Coming to Terms with Diagnosis “Non-Invasive Follicular Neoplasm with Papillary Like Nuclear Features (NIFTP)”: Practice Changer in Endocrine Pathology

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Abstract

This review summarizes the history and development of the concept of noninvasive follicular thyroid tumor with papillary like nuclear features (NIFTP). The salient histopathologic features of this lesion are discussed with emphasis on inclusion and exclusion criteria in light of available data. Immunohistochemical and molecular profiles are presented. The authors also provide their own point of view regarding the practical issues and concerns that are known to surface based on the diagnosis of NIFTP. This discussion also includes the re-review of lesions that once were classified as carcinoma.

Keywords: Thyroid, follicular thyroid carcinoma, papillary thyroid carcinoma, non-invasive carcinoma, NIFTP

Describing Present and Future in View of the Past

Prior to the 1960s, the distinction between papillary and follicular thyroid carcinoma was predicated on the percentage of follicular pattern of growth. Thus the Armed Forces Institute of Pathology fascicle indicated that, if a thyroid tumor showed greater than 50% follicular pattern, it should be diagnosed as “follicular thyroid carcinoma”, and those lesions with more than 50% papillary pattern were “papillary carcinoma” (1, 2).

Beginning in the 1960s with the suggestion that nuclear features predicted biological behavior in follicular patterned thyroid tumors, the concept of the follicular variant of papillary carcinoma arose. In 1977, Chen and Rosai named these lesions, but the seven cases they reported were all infiltrative neoplasms (3). Such neoplasms recapitulated the biological behavior of classic papillary carcinoma with “multifocal” lesions in the thyroid, lymphatic invasion in the gland and extra thyroidal soft tissue and proclivity for regional lymph node metastases. Distant metastases were quite rare.

Over the last quarter of the 20th century and into the 1st decade of the 21st century, lesions which were encapsulated, follicular patterned but with papillary cancer nuclei were recognized and diagnosed as “follicular variant of papillary carcinoma”. When invasive, such lesions however followed a clinical pathway resembling follicular carcinoma since when there was invasion of these lesions either of the tumor capsule or vessels within the tumor capsule or in the adjacent thyroid parenchyma, hematogenous metastasis to bones and brain were common. Nodal metastases were unusual. However, when there was no invasion in a well sampled and studied lesional capsule and if there were no papillae (hybrid of papillary and follicular growth patterns) or psammoma bodies, such lesions appeared on follow-up to behave in a benign fashion, follicular adenoma or follicular patterned adenomatoid nodule. Studies published from Europe, Asia and the United Stated segregated those encapsulated lesions with no invasion from those with invasion and indicated the former group were indolent lesions clinically (4-6). Hence it appeared that there exist two major categories of follicular variant of papillary carcinoma - the infiltrative type and the encapsulated type.

Problems arose in the diagnosis of follicular variant of papillary thyroid carcinoma-encapsulated type since even the “experts” in endocrine pathology showed very poor agreement among themselves in defining the diagnostic nuclear features of papillary carcinoma (7-12). The study by Lloyd et al. evaluating the interobserver variability showed that a concordant diagnosis of follicular variant of papillary thyroid carcinoma was made by all ten reviewers with a cumulative frequency of only 39% (7). An interesting study by Hirokawa et al. of the encapsulated follicular patterned thyroid lesions examined by four American and four Japanese pathologists showed unanimous agreement among all pathologists in two (10%) cases. Interestingly, the American pathologists frequently made the diagnosis follicular variant of papillary thyroid carcinoma as compared to Japanese pathologists (25% vs. 4%) (8). Thus, most experts agreed that this variability in the diagnosis of follicular variant of papillary thyroid carcinoma is due to the lack of agreement on the minimal diagnostic criteria (7, 12). As afore-mentioned, the diagnosis of papillary cancer is made by examining the tumor cell nuclei. Most cytopathologists will not render the diagnosis of papillary carcinoma in thyroid fine needle aspiration (FNA) specimens until all major diagnostic features are presentable. Most FNA specimens that reviewers with a clinical background will accept the diagnosis of follicular variant of papillary carcinoma (13, 14). Numerous studies from various academic and non-academic centers have shown that the rate of malignancy in cases classified as follicular thyroid carcinoma is below 5% and interestingly, most cases on histologic examination are found to be follicular variant of papillary thyroid carcinoma (14, 15).

These above-mentioned studies attest to the fact that there is significant inter- and intra-observer variability in the diagnosis of follicular variant of papillary thyroid carcinoma, which often created treatment dilemmas among clinicians, i.e. whether to treat or not, i.e. completion thyroidectomy (in cases where lobectomy is done as the initial procedure) and/or radioactive iodine ablation.
Thus the international panel after long discussion and multiple candidate nomenclatures developed the diagnostic term “noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)” (29). This term, although probably grammatically not sound, avoids the words “carcinoma”, “cancer”, “malignant” and “uncertain”, and applies to these tumors a definitive clinicopathologic designation. It stresses the features of the lesion, i.e. “noninvasive”, “follicular”, “neoplasm”, and gives attribution to the nuclei. It is important to include the “nuclear cytology” in NIFTP, because still on FNA some of these will show atypical nuclear features suggestive or suspicious for papillary thyroid carcinoma. Studies have shown that majority of these will be diagnosed on FNA as atypia/follicular lesion of undetermined significance, follicular neoplasm, and suspicious for papillary thyroid carcinoma.

What’s in the Name?

The descriptive terms of NIFTP “fit” the lesion.

“Noninvasive”: Many of these lesions are encapsulated (Figure 1A) but some are not and are only circumscribed. The histologic feature of no invasion is critical for the diagnosis. Invasion of the capsule may be focal; in non-encapsulated tumors, spread or infiltration of neoplastic follicles into the surrounding thyroid may be subtle and some have recommended immunostaining with HBME-1 as a marker to highlight these invasive follicles (Seethala personal communication). The importance of the noninvasive description is paramount and hence requires histological examination of the entire capsule or the entire lesional edge at the tumor and surrounding thyroid parenchyma interface in order to assure an accurate diagnosis.

Additionally, since most of these nodules have been biopsied (either FNA or core biopsy), it is extremely important to distinguish needle biopsy tracts from true tumor capsule invasion. Helpful hints include the geographic (linear) nature of the needle tract, and the association with inflammation and hemosiderin (30, 31).

“Follicular”: The growth pattern of the lesion is predominantly or exclusively follicular (Figure 1B). The majority of examples show a diffuse or multifocal “microfollicular” growth. Some lesions show admixtures of macrofollicles as well. Often, the macrofollicles are found interspersed among the macrofollicles and contain atypical nuclei. Although areas of solid growth are permissible, the panel felt that this should not exceed 30% of the lesion; in such cases careful evaluation for necrosis and mitotic figures should be given so as to rule out a poorly differentiated carcinoma. In addition, no papillary pattern should be allowed (the criteria allow for less than 1% papillae); as a corollary, no psammoma bodies (the ghosts of dead papillae) should be found (29).

“Neoplasm”: These lesions are neoplasms. The preliminary data of molecular analysis suggest that these are clonal neoplasms often harboring mutations in RAS gene, often the NRAS (29, 32). They do not represent hyperplastic or adenomatous nodules; as well, they are often encapsulated, hypercellular and monotonous in their cellular composition histologically.

“Papillary like nuclear features”: The distinction of these tumors from follicular adenoma is the presence of nuclear features of papillary carcinoma (Figures 1C and 1D). The original evaluation of these tumors included an elaborate nine-point grading scheme (subsequently reduced to three grades), which assessed the following nuclear parameters: shape and size, membrane irregularities and chromatin features (29).
Fig. 1: A case of non-invasive follicular neoplasm with papillary like nuclear features (NIFTP). Low power showing a follicular patterned lesion well demarcated at its periphery (1A, 10x), the medium power showing a mixed pattern consisting of small and medium size follicles some with thick eosinophilic colloid (1B, 20x), and the high power showing follicles lined by cells with atypical nuclear cytology (cytologic features of papillary thyroid carcinoma) (1C and 1D, 40x). Hematoxylin and eosin stain.

The nuclear features can be diffuse or multifocal and can show gradations of nuclear parameters in different areas of the lesion. As with invasive encapsulated tumors or infiltrative varieties, the nuclei show most of the features of those in classic papillary carcinoma except that intranuclear inclusions are rare and the nuclei often are more rounded than oval.

**Immunostains:** Special stains for various markers (CK19, Galectin 3) as with most papillary carcinomas are not often helpful (29). However, HBME-1 does show membrane staining in about 60-70% of these lesions. The staining may be focal, and in our experience tends to be concentrated in the areas of microfollicular growth (33).

**Molecular analysis:** Nikiforov et al. have shown that those lesions that have been studied may harbor mutations in RAS - 30%, and PPARG or THADA gene fusions - 44%, and only one case showed BRAF K601E mutation (29). In comparison to invasive lesions especially those with vascular invasion, none of the NIFTP cases shows TERT or p53 mutations (29).

**The Buck Doesn’t Stop Here: Future Directions**

**Micro-NIFTP:** The original description of NIFTP included only lesions that measured greater than 1.0 cm or more. Tumors with the appropriate histological characteristics that measure 1.0 cm or less and thus would be microcarcinomas have not been studied in a systematic fashion. Thompson’s series however did include sub-centimeter tumors (smallest was 7 mm) and these seemed to behave in a similar fashion to larger NIFTPs (34). However, until additional data are available for these small tumors, it is recommended that they are diagnosed as “follicular variant of papillary microcarcinoma”.

An additional observation about size of NIFTP is appropriate. In the original series, lesions up to 9.0 cm were encountered and in Thompson’s data one lesion measured 9.5 cm (29, 34). It has been our experience that, although large nodules can represent NIFTP, in many tumors over 4 cm careful histological assessment of the periphery will show foci of invasion thereby indicating the diagnosis of carcinoma. We have identified two recent cases summarized below:

1. 54-year-old woman with 4.5 cm nodule. Originally 8 sections of edge - no invasion was seen (had papillary carcinoma nuclei). Submitted additional -24 sections of which 5 had capsular and transcapsular invasion. Hence this was encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC with invasion (per criteria “Cancer”)).
2. 49-year-old man with 6.9 cm nodule. Original 13 sections of lesional edge - no invasion was seen (showed papillary cancer nuclei). Submitted -49 additional sections of which 4 had capsular
and transcapsular invasion; hence this was diagnosed as EFVPTC with foci of tumor capsule invasion and invasion into surrounding thyroid (per criteria “Cancer”).

In addition, careful histologic examination of the entire lesion may show a focus or tiny foci of papillary growth and despite the absence of invasion, such lesions rarely can metastasize to regional lymph nodes. We have identified such a case:

1. 32-year-old woman with a 2.7 cm circumcised nodule shows no invasion but one 1.3 mm focus of papillary growth. A micrometastasis to a peri-isthmic lymph node was identified; hence this was an encapsulated papillary carcinoma.

**NIFTP with oncocytic cytology**: The presence of foci of or diffuse oncocytic cytology in NIFTP has not been recognized or studied. Since such cytoplasmic change is not uncommon in infiltrative follicular variant of papillary carcinoma, it seems that some NIFTP may show this alteration. Again, no data are available on this feature and this awaits further studies.

**Multifocal lesions in same gland**: Some thyroid glands may contain more than one NIFTP (up to 20% in one series) (34). If so, each needs to be fully examined and the diagnosis confirmed. Each should carry the prognosis of one individual tumor. These cases are interesting as they appear to recapitulate “multifocal” classic papillary carcinomas or papillary microcarcinomas. However, some multifocal papillary carcinomas may represent intrathyroidal lymphatic spread of one tumor, which cannot be true for NIFTP as the latter does not show lymphatic invasion. Molecular analysis of these unusual multifocal cases should clarify if these NIFTPs are indeed independent clonal proliferations.

**Prognosis and treatment**: Based on the available data, one can easily deduce that the great majority of NIFTPs are of low risk and conservative surgical excision is adequate treatment. The evidence so far published indicates that those lesions that are adequately examined microscopically do not recur or metastasize; possible rare exceptions may exist. The one case published by Baloch et al. did not have complete examination of the lesional capsule and bone metastases developed (35). Vivero et al. showed a subsequent recurrence of a case in which the initial lesion was transected preventing the complete evaluation of the tumor periphery for invasive characteristics and subsequently recurred (21).

The case of nodal metastasis described by Valderobano et al. shows that NIFTP has very low but real malignant potential (platform presentation at American Thyroid Association Annual Meeting, Sept. 2016). This was identified in a retrospective case review; it is unclear how adequately the lesional edge was sampled and examined (36).

**Treatment**: Treatment for NIFTP is simple lobectomy. In some cases, the thyroid will contain multiple nodules in the opposite lobe or patients who are severely hypothyroid on thyroid replacement therapy and near total or total thyroidectomy is deemed appropriate. When the excised lesion is diagnosed as NIFTP, no further surgery is needed. No postoperative radioactive iodine treatment should be given.

**Preoperative diagnosis**: The preoperative diagnosis of NIFTP is not possible with our current available modalities. The cytologic diagnosis of this entity has been studied in retrospective analyses (37-41). Most of the lesions are diagnosed on aspiration biopsy as “atypia of undetermined significance”, “follicular lesion of undetermined significance”, “follicular neoplasm”, or “suspicious for papillary carcinoma”. A few have been called “malignant-papillary carcinoma”. These diagnostic categories reflect the vagaries of the nuclear changes in the category of NIFTP lesions. (Please see also paper on Cytology in another area of this journal).

**What NIFTP Is and What It Is Not: Personal View and Cautionary Note**

From studies of this lesion, we can claim it is a neoplastic proliferation of thyroid follicular epithelial cells. As noted above, molecular analysis has shown that these are clonal proliferations and share mutational signatures with the family of follicular tumors (follicular adenoma/carcinoma) (18, 20). We also know by follow-up data (clinical, biochemical and radiologic) that these lesions pose very low risk to the patient after their simple but complete removal (6).

**What NIFTP is not** includes a list of other lesions: papillary carcinoma, encapsulated; follicular variant of papillary carcinoma with invasion; solid papillary carcinoma; poorly differentiated thyroid carcinoma; and follicular adenoma.

The major question is in our view: **Is NIFTP carcinoma?** We applaud the report by the NIH committee to reassess low grade lesions of various organs which pose minimal risk to patient survival and yet by diagnosing them as “cancer”, aggressive and unnecessary treatment is given; “the treatment may be worse than the disease” (25). Hence the committee recommended altered terminology for these low risk lesions, avoiding the “carcinoma” word and replacing it with less “toxic” verbiage.

With that approach in mind, we concur with newer diagnostic terms like indolent lesions of epithelial origin (IDLE) in the prostate (25, 42) or NIFTP in the thyroid. However, we believe NIFTP is equivalent to ductal carcinoma in situ of the breast, or carcinoma in situ of the urinary bladder; that is, it is carcinoma that has not obtained the capacity to invade. The panel did not consider diagnosing these lesions as thyroid carcinoma in situ, as to avoid the toxic rubric of “carcinoma” or “cancer”. We believe that, although the risk of recurrence or spread is very low, longer follow-up of well-studied cases is needed. The reportedly rare finding of nodal metastases in women with ductal carcinoma in situ has been correlated with early minimal invasion beyond basement membrane of ducts at the ultrastructural level (43, 44). Hence it is theoretically possible that some similar mechanisms may rarely occur in thyroid encapsulated lesions.

We, however, do not consider NIFTP as equivalent to IDLE (25, 42) in the prostate since those lesions are low-grade but already invasive carcinomas and despite being invasive are associated with excellent prognosis and rare metastatic disease (42).

**Should We Go Back? The Dilemma of Retrospective Review**

The question of reevaluation of slides of nodules removed years before the concept of NIFTP was introduced is a difficult one to answer (45). When the diagnosis of “encapsulated follicular variant of papillary carcinoma” was rendered on these lesions, it was standard of care at that time, also standard was how these were treated.

It is not possible to know in each case how adequately the lesion was pathologically examined and to review the available slides may lead to spurious re-diagnosis. Hence it may be ethically inappropriate to “go back” and reassure the patient of a low risk...
diagnosis from review of incomplete data. NIFTP is a prospective diagnosis and should remain so.

If the future studies indicate that NIFTP harbors a **SPECIFIC** molecular signature that can distinguish it from all papillary carcinomas and can be assayed on existing tissue blocks; then and only then should the diagnosis be changed from carcinoma to NIFTP. However, this is not a reversal of a diagnosis based solely on histopathological review.

**Conclusions**

This paper reviews “non-invasive follicular variant of papillary thyroid carcinoma” now known as “NIFTP” in view of historical perspective; the features of this lesion and the necessity of careful histopathologic evaluation are stressed. The immunohistochemistry and molecular characteristics so far known are discussed as well. Finally, the ethical issue of retrospective diagnosis of such lesions is briefly discussed and the authors provide their opinion on this controversial topic.

**References**

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