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Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): An Update

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Abstract
Based on evidence accumulated over the past three decades showing that noninvasive encapsulated follicular variant of papillary thyroid carcinoma has an indolent clinical behavior and a RAS-like molecular profile similar to follicular adenoma, the Endocrine Pathology Society working group in 2016 proposed to rename this entity as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)" in order to eliminate the term "carcinoma" from the diagnosis. It is a major evidence-based attempt initiated by an international group of endocrine pathologists to tackle the epidemic of thyroid cancer overdiagnosis and overtreatment. However, its creation and continuous existence are not without controversies. NIFTP has sparked a wave of follow up studies aiming to decipher the exact nature of this new entity. In this review, we summarize the rationale, diagnostic criteria, controversies and subsequent changes to the NIFTP concept, and their impact on patient care and pathology practice.

Keywords Thyroid · Follicular variant of papillary thyroid carcinoma · Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) · *BRAF* · *RAS*

Introduction

The term FVPTC was coined by Stuart Lindsay in 1960 in a book entitled "Carcinoma of the thyroid gland" [1]. In his article, he described these tumors as having a follicular growth pattern and nuclear features similar to the one seen in papillary carcinoma. In 1977, Chen and Rosai reported the first detailed clinico-pathologic analysis on FVPTC and concluded that it is a tumor that "resembled papillary carcinoma in its biologic behavior and all morphologic features with the exception that papillae were not present" [2]. In this small series of six patients, where all tumors were infiltrative and lacked complete encapsulation, five individuals developed nodal metastasis and two died of or with disease.

Since that seminal article, FVPTC has gained in popularity among practicing pathologists, and the diagnosis of papillary thyroid carcinoma (PTC) became an exercise based largely on identifying the nuclear features of PTC regardless of architectural pattern, encapsulation and invasive status. Consequently, the diagnosis of papillary carcinoma follicular variant began to prevail, and FVPTC, including the encapsulated noninvasive form, became one of the most common subtype of PTC [3–5].

In 2000s, emerging molecular studies shed light on the nature of FVPTC. As a whole, FVPTC shows a molecular profile similar to follicular adenoma and follicular carcinoma, characterized with high frequency (approximately 43%) of *RAS* mutations [6–8]. The encapsulated form of FVPTC is characterized by the lack of *BRAF* mutations, a high prevalence of *RAS* mutations, and in some instances the presence of *PAX8-PPARG* rearrangement [9, 10]. In 2014, The Cancer Genome Atlas (TCGA) reported a comprehensive molecular profile of 496 PTCs, confirming that FVPTC has frequent *RAS* mutation and a RAS-like molecular signature, unlike classic and tall cell variants of PTC with a $BRAF^{V600E}$-like profile [11].

Within the same period, several studies have investigated the clinical behavior of FVPTC. Liu et al. showed that the clinical behavior and outcome of encapsulated and infiltrative FVPTC were drastically different: while infiltrative

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FVPTC are akin to classic PTC with a propensity to spread to regional lymph nodes, encapsulated FVPTC, in particular the noninvasive form, behaved like follicular adenoma with negligible risk of nodal metastasis and recurrence [12]. Multiple additional studies have further confirmed that encapsulated FVPTC carries no risk of recurrence or death when capsular or vascular invasion is carefully excluded by adequate tumor capsule sampling [5, 13–18].

In 2016, a working group of 28 international experts, including 24 experienced thyroid pathologists, critically re-examined the entity using a cohort of 109 patients with noninvasive encapsulated FVPTC who had at least 10-year follow up and did not receive post-operative radioactive iodine (RAI) treatment. None (0%) developed recurrence [19] As a result of this endeavor, a consensus statement was published advocating for a nomenclature change from noninvasive encapsulated FVPTC to NIFTP with a fundamental aim to avoid the term "carcinoma" [19]. Soon after, NIFTP has been adopted by mainstream clinical management guidelines, including the American Thyroid Association (ATA) [20], the National Comprehensive Cancer Network (NCCN) [21] and the American Head and Neck Society (AHNS) guidelines [22].

The Original Diagnostic Criteria of NIFTP and Their Evolution

The original diagnostic criteria of NIFTP proposed by the consensus statement are summarized in Table 1. Although a diagnosis of NIFTP should be considered in any noninvasive encapsulated/well-demarcated follicular-patterned lesion with nuclear atypia, there are several exclusion criteria that need to be applied, namely psammoma bodies, > 30% solid growth, > 1% true papillae with fibrovascular cores lined by cells with PTC nuclear features, a mitotic rate of ≥ 3/10 high power fields, and/or features of other PTC variants, e.g. tall cell variant [19]. The nuclear score is determined by a 3-point system: (1) nuclear size and shape; (2) nuclear membrane irregularity; and (3) chromatin characteristics. A nuclear score of 2 or 3 (i.e. the presence of at least 2 of the above-mentioned nuclear features) is required for a diagnosis of NIFTP.

Table 1 Consensus diagnostic criteria of noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), adapted from Nikiforov et al. [19]

Encapsulated or clear demarcation
Follicular growth pattern
Nuclear score 2–3
No vascular or capsular invasion
Absence of all the following features
> 1% papillae
Psammoma bodies
> 30% solid/trabecular/insular growth patterns
Tumor necrosis
High mitotic activity (≥ 3 per 10 high power fields)
Cell/morphologic characteristics of other variants of PTC, e.g. tall cell and cribriform morular variants

Since the consensus statement of 2016, multiple subsequent retrospective NIFTP studies have been published [5, 23–31]. In accordance with the findings from the NIFTP consensus cohort, most studies using the original NIFTP diagnostic criteria have reported negligible risk of nodal metastasis and/or recurrence as well as a molecular profile characterized by mutations in *RAS* and absence of $BRAF^{V600E}$ mutations [5, 23-28]. However, three studies, one by Parente et al. from Canada [30] and two by Kim et al. [29] and Cho et al. [31] from Korea, have found up to a 6% rate of metastasis (predominantly nodal) in NIFTP patients, particularly in lesions containing a small percentage (< 1%) of true papillae. Even in tumors without any papillae, the metastatic risk was reported at 2–5% in these three studies. However, the studies reported by Kim et al. and Cho et al. included tumors with synchronous papillary microcarcinoma in the specimens and none of the above three studies compared the molecular profile of NIFTP with the metastasis. Therefore, one cannot exclude with confidence the possibility that the nodal metastasis observed in these patients were associated with a separate papillary microcarcinoma, a well-reported and documented possibility [32–35]. Additionally, since metastatic nodal and even distant disease has been reported in total thyroidectomy specimen negative for carcinoma and entirely submitted for microscopic examination [36, 37], the metastatic deposits seen in these three articles may have even originated from separate infiltrative small carcinomas embedded in the paraffin block or which had undergone regression.

Nevertheless, because of the results of these studies, members of the NIFTP consensus group subsequently published two commentaries proposing to revise the diagnostic criteria from < 1% of papillae to no true papillae allowed [38, 39]. This revision practically means that the finding of a single true papillae in an otherwise noninvasive follicular-patterned lesion with nuclear score of 2 or 3 will lead to a diagnosis of cancer.

Exactly how many papillae are required for an encapsulated lesion to acquire the potential to develop lymph node metastasis? We have addressed this question in a large cohort of 235 unifocal encapsulated papillary thyroid carcinoma and NIFTP [40]. In noninvasive tumor, nodal metastasis was only observed in neoplasms containing at least 10% of papillae (Fig. 1), whereas in the entire cohort (invasive and non-invasive), nodal disease could be seen in tumors with 1% or more papillae. No nodal metastasis was

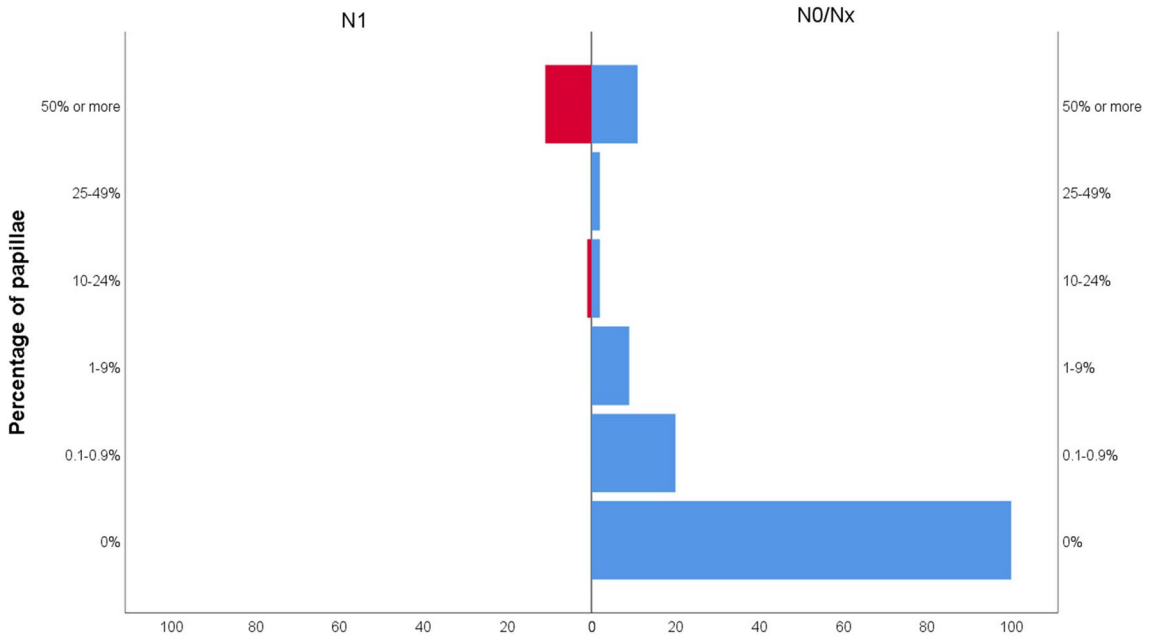

Fig. 1 Regional lymph node metastatic status according to percentage of papillae in 156 unifocal non-invasive encapsulated papillary thyroid carcinoma. Patients with < 10% papillae do not have any lymph node metastasis. Vertical axis represents percentage of papillae in the tumor while horizontal axis represents number of patients. Left red bars indicate patients with N1 (lymph node metastasis) and right blue bars patients with no nodal disease (N0/Nx). From reference [40]

observed in 127 patients without any true papillae and 31 patients with < 1% of true papillae [40]. The discrepancy between our study and most of the published literature on NIFTP on one side and those of Parente et al. [30], Kim et al. [29] and Cho et al. [31] on the other could be due to differences in defining or quantifying papillae. Whatever the reason for these discordant results, our findings indicate that the original criterion of 1% papillae may still be sound for the diagnosis of NIFTP. Future studies with larger number of encapsulated tumors with rare papillae (< 1%) will further help solve this controversy. Finally, in regard to the assessment of invasion, the original publication stated that it "requires adequate microscopic examination of the tumor capsule interface" [19]. There is now a general consensus that the whole tumor capsule should be submitted for histologic examination to exclude any invasion which is the most crucial defining feature of NIFTP [39].

Expansion of the Concept of NIFTP: Subcentimeter, Large (at Least 4 cm), Oncocytic Lesions and Lesions in Pediatric Patients

As the cohorts studied by the NIFTP consensus conference [19] and in previous reports [12, 17] did not include or specifically address subcentimeter lesions and oncocytic lesions, practice varies when such noninvasive lesions are encountered.

Although it is counter-intuitive to label a subcentimeter non-invasive encapsulated follicular patterned lesion with nuclear score of 2 to 3 as carcinoma while a similar histologic lesion that is > 1 cm in size is classified as NIFTP, some continuously label them as papillary microcarcinoma. Two recent studies have addressed this issue and independently demonstrated the highly indolent nature of papillary microcarcinoma, noninvasive encapsulated FVPTC: one included 52 cases with a median follow up of 6.3 years and the other reported 8 cases with a mean follow up of 12 years, all of which showed a negligible risk of nodal metastasis, distant metastasis, and recurrence [24, 28] (Fig. 2).

Large NIFTPs of at least 4 cm in size do exist. Prior to the introduction of NIFTP, these lesions would be staged as pT3a using the 8th edition American Joint Committee on Cancer (AJCC) staging manual [41]. According to the current American Thyroid Association (ATA) guidelines [20], post-operative radioactive iodine treatment would be offered as a management option to this cohort of patients. The implementation of NIFTP would alter the treatment from a total thyroidectomy with possible post-operative radioactive iodine treatment to lobectomy alone. In a recent international collaborative study involving four tertiary hospitals, we studied 79 patients with NIFTP of at least 4 cm in size [25]. All patients were disease free with a median follow up of 6.7 years, including 37 individuals that did not

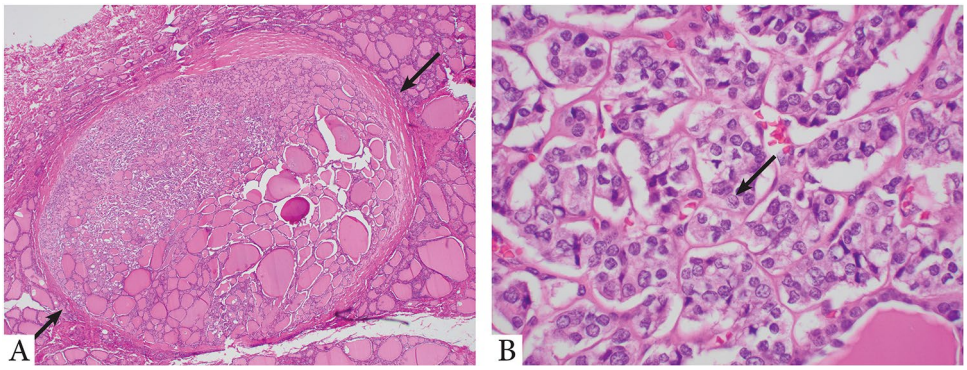

Fig. 2 Forty-nine-year-old female with a 0.35 cm noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) who did not receive radioactive iodine (RAI) therapy. Patient is without nodal disease and no recurrence after 7 years. **a** Low power microscopic view of the tumor which is completely encapsulated (arrows) and non-invasive. **b** High power microscopic view shows enlarged, irregular, overlapping nuclei with chromatin clearing and nuclear grooves (arrow)

receive radioactive iodine therapy. Based on these results, it appears that large NIFTP can be safely and adequately managed by surgical treatment alone as long as the tumor capsule is entirely sampled to exclude invasion.

Similarly, we have recently demonstrated that noninvasive follicular patterned nodules with papillary carcinoma nuclear alterations and oncocytic change (i.e. noninvasive encapsulated oncocytic FVPTC, Fig. 3) follow an indolent clinical course without metastasis and recurrence with a median follow up of 10.2 years in an international multi-institutional cohort of 61 patients [23]. Additionally, noninvasive encapsulated oncocytic FVPTC has a high frequency of *RAS* mutations (being 33%) and lacks $BRAF^{V600E}$ mutation similar to what has been reported in NIFTP [23]. Mariani et al. have also shown that NIFTP may occur in pediatric patients and their NIFTP cases did not recur [26]. However, the pediatric patients in this report were very few in numbers. In regard to multifocal NIFTP, the number of reported cases is also too small to assess their behavior [42].

Taken together, this data provides support for the expansion of the concepts of NIFTP to specific patient populations, e.g. those with large, small or oncocytic tumors.

The Molecular Profile of NIFTP and Its Impacts on Commercially Available Molecular Platforms

Molecular testing has been adopted by the 2015 ATA guideline [20] as an alternative in managing thyroid nodules with an indeterminate diagnosis on FNA, in particular the atypia of undetermined significance (AUS) and the follicular neoplasm/suspicious for follicular neoplasms (FN/SFN) categories. A number of molecular classifiers have been studied, validated, and are available for clinical usage, with the most common used ones being Thyroseq [43] and Afirma assays [44–46].

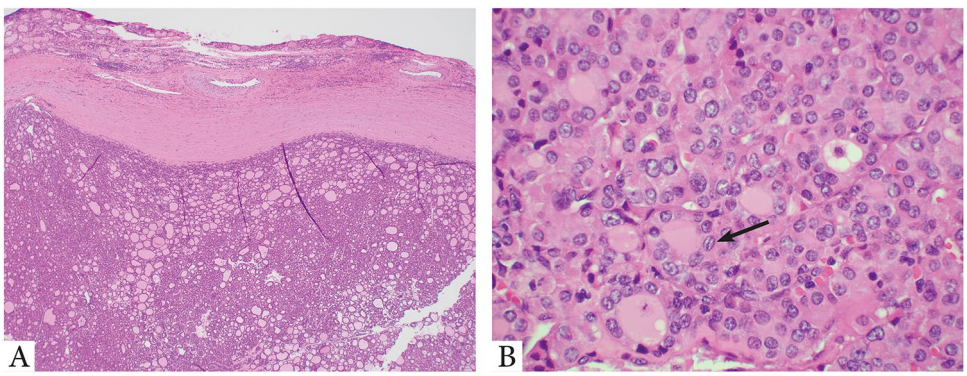

Fig. 3 Forty-eight-year-old female with a 1.3 cm oncocytic noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) treated by lobectomy only. Patient is without nodal disease and no recurrence after 5 years. **a** Low power microscopic view of the tumor which is thickly encapsulated without invasion. **b** High power microscopic view shows enlarged, irregular, overlapping, clear nuclei with grooves (arrow). The tumor cells show oncocytic features with abundant eosinophilic granular cytoplasm

As discussed in the previous section, studies have shown that NIFTP/non-invasive FVPTC is associated with a high frequency of *RAS* mutation [9-11] (Table 2). Similarly, Nikiforov et al. has reported the molecular profile of 27 cases from the consensus NIFTP cohort and detected a high frequency of *RAS* mutation (8/27, 30%) and *PPARG* fusion (6/27, 22%) (19). Other molecular events reported included: *THADA* (thyroid adenoma associated) fusion (6/27, 22%), *EIF1AX* (2/27, 7%, both coexisting with *RAS* mutation), and $BRAF^{K601E}$ (1/27, 4%) [19]. It is evident that all the common mutations and fusions detected in NIFTP can be captured by Thyroseq version 3, a next generation sequencing platform of 112 thyroid cancer-related genes [43]. Hence, it is reasonable to assume that the positive predictive value of Thyroseq in detecting malignancy would decrease, while the positive predictive value to predict neoplasm (i.e. the risk for a "surgically treatable condition") remains unchanged if NIFTP is considered a non-malignant tumor. Indeed, in a large-scale prospective study investigating the performance of Thyroseq version 3 in indeterminate cytologic samples, NIFTP was detected in 11 of 257 cases (4%), all of which had a positive Thyroseq results and a RAS-like signature [43].

Afirma gene expression classifier investigates the mRNA expression profile of 167 genes, and has been shown to be an excellent rule out test with a negative predictive value of 95%, 94%, and 85% for FNA diagnoses of AUS, FN/SFN, and suspicious categories [47]. Hang et al. have investigated 244 thyroid FNAs with a diagnosis of AUS and a suspicious or benign Afirma results. All their cases reclassified as NIFTP were suspicious by Afirma results [48]. In a study comparing Afirma and Thyroseq, all cases meeting the criteria for NIFTP demonstrated either high-risk mutations on Thyroseq or a "suspicious" result on Afirma GEC [49]. In the era of NIFTP, this clearly shows that a "positive" test result for either the Afirma or Thyroseq should not exclude conservative (i.e. lobectomy) surgical management [49].

Although almost all studies demonstrated that NIFTP has a *RAS* mutation profile and in general lacks $BRAF^{V600E}$ [50], one study showed a significant number of $BRAF^{V600E}$ mutation (10%) in NIFTP [31]. Other authors have found $BRAF^{V600E}$ mutation but at a much lower rate such as 1 in 50 cases in the article of Zhao et al. [51] In our most recent study, we were surprised to find one out of 50 (2%) NIFTPs positive for $BRAF^{V600E}$ by immunohistochemistry [40]. It was a 0.2 cm well-circumscribed tumor completely devoid of papillae on multiple H&E levels examined. We do not have a clear explanation for this unusual molecular finding. Whatever the reason, we are in agreement with the statement by some of the authors of the NIFTP working group that detection of $BRAF^{V600E}$ by immunohistochemistry or molecular studies should lead to an exhaustive search for papillae and invasion [39]. However, as stated by the same investigators, it cannot be used solely to exclude NIFTP which is a histologic diagnosis [39]. In summary, comprehensive genotypic studies in relatively large series (Table 2) and immunostaining on a large number of cases clearly show that NIFTP has mainly *RAS* mutations, some *PPARG* and *THADA* rearrangements and very rarely $BRAF^{V600E}$ mutation [52, 53].

Conclusions

Based on the clinical and molecular evidences accumulated over the past three decades, the term NIFTP was introduced into the field of thyroid pathology to spare patients afflicted with a very indolent tumor the side effects of completion thyroidectomy, RAI therapy and the psychosocial impact of a cancer diagnosis. Three years after the advent of NIFTP, multiple subsequent studies have been published further supporting the overall excellent prognosis of these lesions. Evidence based studies have suggested that NIFTP can include subcentimeter lesions, large size tumors, as well as nodules

Table 2 Molecular profile of noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP)

References	Detection method	*RAS*	$BRAF^{V600E}$	*PPARG* fusion	*THADA* fusion	*BRAF* other than V600E	*EIF1AX*	*PTEN*	No mutations found
Nikiforov et al. [19]	NGS	8/27 (30%)[a]	0/27	6/27 (22%)	6/27 (22%)	1/27 (4%)	2/27 (7%)[a]	0/27	6/27 (22%)
Zhao et al. [51]	NGS	27/48 (56%)	1/48 (2%)	2/48 (4%)	NA	NA	NA	NA	18/48 (38%)
Brandler et al. [52]	NGS	18/27 (67%)[b]	0/27	3/27 (11%)	3/27 (11%)	1/27 (4%)[c]	1/27 (4%)[c]	1/27 (4%)	1/27 (4%)
Total		53/102 (52%)	1/102 (1%)	11/102 (11%)	9/54 (17%)	2/54 (4%)	3/54 (6%)	1/54 (2%)	25/102 (25%)

NGS next generation sequencing

[a]Two cases had concomitant RAS and EIF1AX mutations

[b]Three of the 18 were associated with concurrent mutations (TP53, n = 1; PTEN, n = 2)

[c]One case showed two mutations EIF1AX and BRAF T599_R603

with oncocytic features. However, the concept of NIFTP was and continues to be controversial, as several studies have implied a small but non-zero risk of nodal metastasis. Additional studies, especially large-scale multi-center well-designed studies with long term follow up are needed to bring the controversies to an end.

Regardless, the introduction of NIFTP brings a shift in the practice of thyroid pathology. As it is now the invasive status that determines a cancer diagnosis, much needed attention has been switched from evaluation of nuclear features to capsular sampling and determination of invasion. Beyond thyroid pathology, the renaming of the non-invasive encapsulated FVPTC into NIFTP represents a road map that can be used to reduce the overdiagnosis and overtreatment of other indolent epithelial neoplasms through a change in nomenclature.

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Compliance with Ethical Standards

Conflict of interest No competing financial interests exist for all contributory authors.

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