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PRACTICE GUIDELINES

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AHNS Series: Do you know your guidelines? AHNS Endocrine Section Consensus Statement: State-of-the-art thyroid surgical recommendations in the era of noninvasive follicular thyroid neoplasm with papillary-like nuclear features

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Abstract

The newly introduced pathologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) will result in less bilateral thyroid surgery as well as deescalation in T4 suppressive and radioactive iodine treatment. Although, NIFTP is a nonmalignant lesion that has nuclear features of some papillary malignancies, the challenge for the surgeon is to identify a lesion as possibly NIFTP before the pathologic diagnosis. NIFTP, due to its reduction of overall rates of malignancy, will result in the initial surgical pendulum swinging toward lobectomy instead of initial total thyroidectomy. This American Head and Neck Society endocrine section consensus statement is intended to inform preoperative evaluation to attempt to identify those patients whose final pathology report may ultimately harbor NIFTP and can be offered a conservative surgical plan to assist in cost-effective, optimal management of patients with NIFTP.

KEYWORDS
lobectomy, RAS mutations, surveillance, thyroid cancer, ultrasound

1 | INTRODUCTION

The purpose of this consensus statement through the AHNS endocrine section, which is the largest U.S. Surgical Society relating to thyroid cancer treatment, is to synthesize a collaborative, state-of-the-art guideline regarding noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and its implications for surgical planning through review and interpretation of the recent multidisciplinary literature. Many of the members of the author panel have contributed substantially to this literature. Ultimately, these guidelines promote best uniform practices and encourage safe and successful outcomes. These state-of-the-art recommendations are intended to help guide surgeons in the clinical decision-making process when managing NIFTP and lesions of similar cytological and histological milieu and, at their core, these guidelines are quality driven and focused on cost-effective, safe, and effective management. It is our hope that these guidelines translate the available world literature and significant clinical experiences of the AHNS endocrine section toward best practices, and in doing so will reduce treatment variation and improve overall quality for our endocrine surgical patients. In our opinion, this monograph represents the best contemporary surgical care for this patient population. The evidence-based literature analysis derives from PubMed searches from 2000 to 2017. Key search words included follicular variant of papillary thyroid carcinoma (encapsulated and invasive varieties), and NIFTP, augmented by additional references supplied by the author panel.

1.1 | Definition

The histologic entity NIFTP is defined by the World Health Organization as a noninvasive tumor of thyroid follicular cells with a follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC).[1] It is considered a neoplasm with extremely low malignant potential and is best considered a premalignant lesion rather than a benign lesion. This nomenclature was introduced in 2016 to reclassify a specific subtype of low-risk PTC known at that time as noninvasive encapsulated follicular variant of PTC (noninvasive EFVPTC).[2] This new nomenclature was introduced to better optimize patient care without the stigma of malignancy and to deescalate such patients' treatment and follow-up.

The diagnosis of NIFTP is based on the finding of an encapsulated or clearly demarcated nodule with a follicular growth pattern and cells revealing nuclear features of PTC with complete lack of invasive characteristics, papillary structures or psammoma bodies, significant solid growth, tumor necrosis, or high mitotic rate. Because a diagnosis of NIFTP can be made only after exclusion of invasion, a complete histologic examination of the entire tumor capsule and tumor interface is required. This has implications on retrospective diagnostic attempts, which will be discussed.

1.2 | Noninvasive follicular thyroid neoplasm with papillary-like nuclear features and presurgical evaluation

The paradigm shift in terminology presented by NIFTP, will affect clinical management with deescalation of postoperative thyroid hormone suppression of thyroid-stimulating hormone and radioactive iodine therapeutic modalities, and allow for increased intervals between follow-up appointments. The challenge, however, is how to provide the surgeon with reliable and actionable information before the histological diagnosis in order to optimally enlighten initial

surgical planning. Inevitably, the emergence of NIFTP, due to its depression of ultimate rates of malignancy, will result in the initial surgical pendulum swinging to some degree toward more conservative options in the form of lobectomy as opposed to initial total thyroidectomy. The degree to which the pendulum will swing is yet to be determined and will be affected by many factors. This section is intended to increase the acuity of the surgical preoperative evaluation in an attempt to identify those patients whose final pathology report may ultimately denote NIFTP and can, therefore, be offered a conservative surgical plan in the form of a lobectomy as opposed to total thyroidectomy.

1.3 | Noninvasive follicular thyroid neoplasm with papillary-like nuclear features cannot be definitively diagnosed preoperatively

The ability to detect NIFTP preoperatively is clearly challenging as it is a histologic diagnosis; predicting its presence preoperatively relies on preoperative informed speculation and is not a perfect endeavor.

1.4 | Noninvasive follicular thyroid neoplasm with papillary-like nuclear features is a surgical target

The second important point is that NIFTP is considered a precancerous lesion and is thereby an appropriate surgical target. Although not a cancer, NIFTP requires surgical removal and histologic evaluation. Statistical accuracy assessment of fine-needle aspiration (FNA) varies based on the specific definition of disease, which can be defined as malignancy or simply as disease requiring surgical resection.[3]

The existence of NIFTP results in a decreased rate of thyroid cancer overall and will, therefore, tend to lead to lobectomy versus total thyroidectomy in appropriately selected patients. However, total thyroidectomy remains an acceptable option for some cases ultimately defined as NIFTP.

Given our imperfect ability to preoperatively diagnose NIFTP and a specific patient's other clinical factors that may lead towards more extensive surgery, total thyroidectomy remains a valid, acceptable, and potentially preferable option even when the ultimate pathology report reveals NIFTP. This situation requires thorough preoperative counseling in conjunction with endocrinology.

1.5 | Cytology, fine-needle aspiration, and noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Pre-NIFTP, the likely histologic outcome of a follicular-patterned lesion of the thyroid in an FNA included a hyperplastic/adenomatoid nodule, follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma (FVPTC).[4,5] Before April 2016, the FVPTC diagnosis included encapsulated forms with and without invasion as well as infiltrating FVPTC tumors.[6]

The reclassification of the noninvasive encapsulated FVPTC as NIFTP[7] has significant implications for the practice of thyroid cytopathology.[8] The most significant change will involve a decrease in the implied risk of malignancy, particularly for cases classified into 3 so-called "indeterminate" diagnostic categories of The Bethesda System for Reporting Thyroid Cytopathology: (1) Bethesda class III= atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); (2) Bethesda class IV= follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN); and (3) Bethesda class V= suspicious for malignancy (SFM).[9–11] Recent studies suggest that the decrease in risk of malignancy as a result of NIFTP will be most significant (up to 50%) for thyroid FNA specimens classified as SFM.[9,10] Interestingly, these same studies have shown no appreciable change in the risk of malignancy for FNA specimens classified as "benign" and only a small decrease for the malignant category. Faquin et al[10] reported a collection of 6943 thyroid FNA specimens pooled from 5 institutions and found that 173 (2.5%) were diagnosed as NIFTP in the surgical resection specimens. The preoperative FNA cytological diagnoses for these 173 NIFTPs were characterized as: nondiagnostic (1%), benign (9%), AUS/FLUS (31%), FN/SFN (27%), SFM (24%), and malignant (9%). Given that NIFTPs are considered nonmalignant lesions, the risk of malignancy is decreased by 1.4%, 3.5%, 13.6%, 15.1%, 23.4%, and 3.3%, respectively, in each Bethesda category (I to VI).[10] It is now recommended that NIFTP should be added into the differential diagnosis for cytological specimens classified as AUS/FLUS, FN/SFN, and SFM (PTC).[8]

Some authors have suggested that cytomorphologic criteria can be used to recognize potential NIFTPs in FNA specimens,[12–14] but the data are preliminary, and some authors remain skeptical.[15] Cytopathologic ability to distinguish NIFTP from invasive FVPTC is made difficult as both lesions may demonstrate a microfollicular growth pattern and nuclear features of PTC, including nuclear enlargement, pallor, crowding, and grooves.[12] However cytological features can be used to help exclude a diagnosis of NIFTP in favor of a classical papillary cancer diagnosis. In a review of 52 patients, Strickland et al[9,12] showed that the majority of NIFTPs or other follicular lesions can be distinguished from classical papillary cancer on cytopathology. The NIFTPs tended to exhibit a microfollicular growth pattern, whereas classical papillary cancers tended to demonstrate papillae, pseudoinclusions, or psammomatous calcifications (Tables 1 and 2). Classical papillary cancers were accurately diagnosed preoperatively by cytopathology

TABLE 1 List of cytopathologic features supportive of noninvasive follicular thyroid neoplasm with papillary-like nuclear features versus infiltrative encapsulated follicular variant of papillary thyroid carcinoma, papillary thyroid carcinoma, or follicular adenoma

Bethesda III, IV, or V with:
Follicular pattern
Hypercellular
Microfollicular architecture
Sheet-like architecture
No papillae
No psammomatous calcifications
No prominent nuclear pseudo-inclusion
No prominent nuclear grooves
No necrosis or mitoses

in 95% of cases. Brandler et al[16] found that when PTC nuclear features and microfollicles are present NIFTP should be considered. Bizzarro et al[13] concluded that NIFTP usually lacks pseudoinclusions and papillary structures; nuclear size and microfollicular clusters may allow differentiation between NIFTP and invasive FVPTC. Howitt et al[17] found statistically significant differences in cytomorphologic features between patients with NIFTP and those with PTC. In their series, among PTC cases, 96% demonstrated tumor sheets, 50% had papillae, 79% had pseudoinclusions, and microfollicles were noted in only 4% of cases. In comparison NIFTP cases demonstrated papillae or pseudoinclusions in 0%, tumor sheets in 36%, and microfollicles in 55% ($p = .0009$). Renshaw and Gould[18] demonstrated that both papillae lined by cells with nuclear features of papillary carcinoma and swirls are highly specific for the diagnosis of PTC and neither are seen in NIFTP. Maletta et al[14] reviewed 96 histologically proven cases of NIFTP and found good correlation ($\kappa = 0.62$) of nuclear features between histological and cytological specimens. They further showed that certain nuclear features of NIFTP (including nuclear size, irregularities of contour, and chromatin clearing) were significantly different from those of benign nodules but not significantly different from those of invasive EFVPTC. They concluded that because of the overlapping nuclear features with invasive EFVPTC, NIFTP cannot be reliably diagnosed preoperatively.[14] Similarly, Zhao et al[15] believe that even though there are differences in the cytological and molecular profiles between NIFTP and infiltrative follicular varient of papillary carcinoma (IFVPTC), the overlap between the two makes it implausible to correctly differentiate between NIFTP and IFVPTC in most cases.

1.6 | Molecular testing and noninvasive follicular thyroid neoplasm with papillary-like nuclear features

The NIFTPs are primarily associated with activating mutations of 1 of the 3 *RAS* genes (*NRAS*>*HRAS*>>*KRAS*) with a frequency of 36%-57%.[7,19,20] The majority of these point mutations lead to codon 61 glutamine substitutions. Other driver mutations identified in NIFTP include *PAX8-PARG* (4%-22%),[1,3] *THADA* fusions (22%), and occasionally $BRAF^{K601E}$ mutations.[7] A distinctive aspect of NIFTP lesions is the absence of $BRAF^{V600E}$, *TERT*, *RET*, and

TABLE 2 Preoperative features that may indicate noninvasive follicular thyroid neoplasm with papillary-like nuclear features diagnosis and are permissive of offering hemithyroidectomy initially

I. Physical examination characteristics

1. No lymph node metastasis
2. No fixation
3. No voice abnormalities
4. No vocal cord paralysis

II. Ultrasound characteristics (see also Table 2)

1. Low and intermediate nodule findings: isoechoic or hypoechoic, oval to round, sharp regular margin, hypoechoic rim
2. Not taller than wide
3. No microcalcifications
4. No contralateral lobe nodules
5. No extrathyroidal extension
6. No posterior abutment
7. No lymph node metastasis
8. No fixation
9. No vocal cord paralysis

III. Cytology characteristics (see also Table 1)

Bethesda III, IV, or V with:

+ Follicular pattern
+ Hypercellular
+ Microfollicular architecture
+ Sheet-like architecture
- No papillae
- No psammomatous calcifications
- No prominent nuclear pseudoinclusions
- No prominent nuclear grooves
- No necrosis or mitoses

IV. Molecular characteristics

1. May have RAS, THADA fusion, or PAX8-PARG
2. Should not have BRAF, RET fusion, TERT promoter, or other high-grade mutation

V. Patient/endocrine characteristics

1. Willing to have second surgery if needed
2. Medically fit for possible second anesthesia
3. Endocrinologist in agreement with initial lobectomy surgery

TABLE 3 Sonographic characteristics of follicular patterned tumors with papillary-like nuclear features[22]

	NIFTP or minimally invasive EFVPTC	EFVPTC – overtly invasive	IFVPTC
Gray-scale ultrasound	Circumscribed oval nodule with a rim Variable echogenicity[a]	Hypoechoic nodule with irregular or lobulated margins	Taller-than-wide hypoechoic nodule with blurred margins
Color Doppler ultrasound	Mostly hypervascular	Mostly hypervascular	Mostly avascular

Abbreviations: EFVPTC, encapsulated follicular variant of papillary carcinoma with capsular/vascular invasion; IFVPTC, infiltrative follicular variant of papillary carcinoma without capsule; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

[a]Hypoechoic for microfollicular nodule, isoechoic for macrofollicular nodule.

Minimally invasive = undetectable by ultrasound; overtly invasive = detectable by ultrasound.

NTRK fusions and other mutations associated with classical and tall cell variant PTCs. These mutations should not be encountered in appropriately diagnosed NIFTPs.[1–3] It is important to note that none of the mutations present in NIFTPs are pathognomonic of this entity. Thus, although *RAS* mutations are the dominant lesion in NIFTPs, they are also prevalent in follicular adenomas and carcinomas, follicular-variant papillary carcinomas, and poorly differentiated and anaplastic thyroid cancers. Similarly, *PAX8-PPARG* is also found in follicular carcinomas, follicular-variant PTCs and, less frequently, in more advanced tumors.

The presence of RAS mutations may contribute supportive evidence favoring a diagnosis of NIFTP, follicular adenoma, or follicular carcinoma in contrast with $BRAF^{V600E}$ mutations, which are more commonly observed in association with classical PTC. The presence of a $BRAF^{V600E}$ mutation would not be compatible with NIFTP.

The predictive value, reporting schemes, and ultimate clinical utility of currently available molecular tests need to be reassessed in the era of NIFTP. Workers have reviewed results of molecular testing from thyroid nodules subsequently diagnosed as NIFTP on surgical resection and showed that all of the surgically confirmed NIFTPs revealed molecular alterations on both the ThyroSeq version 2.0 and Afirma Gene Expression Classifier. Jiang et al[21] recently investigated molecular features specific to NIFTP and reported that 4 of 8 cases were found "suspicious" using the Afirma Gene Expression Classifier with 4 cases being RAS-positive and concluded that further independent study is warranted for better characterization of the molecular and clinical characteristics of NIFTP. Additional cytology-histology correlative studies are needed to better characterize molecular test performance given our new nomenclature. As RAS mutations are also found in thyroid cancers as well as NIFTP lesions, its presence in a preoperative cytological specimen does not allow for the definitive diagnosis of NIFTP.

1.7 | Ultrasonography and noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Some researchers propose that ultrasound findings coupled with the cytomorphologic features can be used to triage intermediate FNA categories in regard to NIFTP preoperative detection (Tables 2 and 3).[22,23] Yang et al[22] have reviewed 179 cases and have categorized ultrasonography characteristics and cytomorphologic FNA features for different FVPTC categories, as shown in Table 3. Hahn et al,[23] in a multicenter study, demonstrated that NIFTP cases lacked malignant ultrasound features and were better triaged using an ultrasound core biopsy rather than using standard FNA to facilitate the surgical decision making. Yang et al[22] found the ultrasound findings of NIFTP and minimally invasive EFVPTCs were similar and could not be distinguished from each other; both typically exhibited a circumscribed oval or round nodule with a hypoechoic rim and a hypervascular Doppler signal. In contrast, ultrasound findings for overtly invasive EFVPTC typically showed a round or oval nodule with irregular margins and hypervascularity on Doppler. Ultrasound for an invasive FVPTC typically reveals at least one of these features: markedly hypoechoic, taller-than-wide, microcalcifications, or blurred margins with an avascular Doppler pattern.[22]

1.8 | Preoperative clinical patient features and noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Although there are no clinical features established or even suspected that definitively prove the existence preoperatively of a NIFTP, many clinical features available to the astute clinician can be pivotal in making management decisions. Presence of significant contralateral lobe nodules, lymph node metastases, tumor fixation, vocal cord paralysis or voice changes, posterior capsule tumor abutment on imaging, or clear radiographic evidence for extrathyroidal extension should lead toward total thyroidectomy.

Additionally, the patient's willingness to have a second surgery if needed as well as medical fitness for potential completion surgery should also be considered in the initial surgical discussion of hemithyroidectomy versus total thyroidectomy. Furthermore, multidisciplinary preoperative discussion should occur and the team as a whole should also be comfortable with plans for less extensive surgery when NIFTP is suspected preoperatively. Once suspected by cytomorphologic, molecular testing, and ultrasonography, the clinical management of a patient with NIFTP should incorporate these clinical features in discussions between the patient, endocrinologist, and surgeon (Table 2).

1.9 | Suggested follow-up of noninvasive follicular thyroid neoplasm with papillary-like nuclear feature lesions

Cases of NIFTP represent a new thyroid tumor diagnostic category introduced in 2016 and long-term prospective follow-up of patients with these tumors does not exist. Therefore, our clinical suggestions are based in large part on expert opinion and retrospective case-control studies rather than prospective trials.

The diagnosis of NIFTP should not be based on retrospective interpretation of written pathologic reports created before May of 2016. The pathologic rendering of a diagnosis of NIFTP requires that the entire tumor be available for sectioning and that the whole specimen is evaluated for presence of papillary architecture or evidence of capsular or vascular invasion. Such an evaluation is time-consuming but necessary for accurate diagnosis and meaningful prospective data collection.

The suggestions below are no substitute for the evidence-based, individualized, clinical judgement of a physician caring for a unique patient with thyroid nodular disease.

Based on the significant lack of tumor recurrence in several retrospectively analyzed NIFTP cohorts,[7,24,25] patients with resected solitary NIFTP tumors should require less active follow-up than that recommended for patients with "low-risk recurrence of differentiated thyroid cancer" in the 2015 American Thyroid Association guidelines.[26] Measurement of yearly quantitative thyroglobulin in patients with NIFTP is also appropriate, with expected values 6 weeks after surgery <5 ng/mL for total thyroidectomy patients and levels <30 ng/mL for lobectomy patients, in the absence of thyroglobulin antibodies.[27] Single thyroglobulin measurements are of less value than mapping the thyroglobulin trend over 3 or more data points. Maintenance of thyroid-stimulating hormone in the normal range should be sufficient. If significant thyroid tissue remains in the neck, as documented by a 6-week post-total thyroidectomy serum thyroglobulin concentration in excess of 5, a neck ultrasound examination should be considered every 1 to 2 years for the first decade after surgery to evaluate residual thyroid tissue and lymph node architecture and size.

The NIFTP tumors are currently viewed as thyroid cancer precursors and frequently present with microcarcinomas and macrocarcinomas elsewhere in the thyroid.[28] Therefore, when there is multifocal tumor associated with an NIFTP lesion, follow-up frequency and intensity should be based on the coexisting malignant lesion with the highest risk, as assessed by pathologic evaluation of all excised tissue.

1.10 | Retrospective diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Traditionally, the pathologic diagnosis of EFVPTC was made based upon its follicular growth pattern, encapsulation, and, most importantly, its hallmark nuclear cytology.[29] Section of the tumor capsule, tumor, and the surrounding parenchyma must be sufficient to assess for tumor capsular and/or vascular invasion, as well as lymphatic permeation within the surrounding uninvolved thyroid parenchyma to rule out satellite lesions and extrathyroidal extension.[29] Given the requirement to sample the entire tumor and tumor/parenchymal interface[7] and complete lesional assessment to exclude the presence of true papillary architecture,[7,30] the diagnosis of NIFTP should not be made retrospectively. Despite documentation of gross submission of the entire lesional interface (capsule), complete scrutiny cannot be retrospectively assured.

1.11 | Limitations and future directions

A very low recurrence risk for NIFTP has been established based on a retrospective analysis of 101 tumor cases with 13 years median follow-up in the initial reclassification study and 352 cases reported by 2016 in the literature.[2] However, the indolent nature of this disease should be further confirmed in additional studies, preferably in a prospective series of patients. These studies will also allow a reevaluation of the reproducibility and robustness of the diagnostic criteria for NIFTP. This need is highlighted by 2 recent studies reporting single cases diagnosed as NIFTP with regional lymph node metastasis.[21,23] The NIFTP diagnostic errors may occur in both follicular and papillary lineage directions. The NIFTP is a follicular-pattern neoplasm often driven by RAS-like mutations, and the invasive counterpart of this tumor, invasive EFVPTC, is known to metastasize primarily via a hematogenous route and not to regional lymph nodes. However, their nuclear features have overlap with PTC. Such reports emphasize the need for thorough histopathological examination and following stringent criteria to diagnose NIFTP.

Better understanding is also needed to define whether or not NIFTP lesions of large size have a similarly low risk of

recurrence. A recent study has reported no recurrences in a series of 49 large (≥4 cm) NIFTP cases followed for at least 4 years,[25] although larger series of cases with longer follow-up are needed to define the appropriate monitoring strategies for such patients. Similarly, multifocal and subcentimeter tumors are not well studied, although intuitively, the latter are predicted to be indolent. Additionally, it remains unclear whether tumors composed of cells with oncocytic (Hürthle cell) appearance can be classified as NIFTP if they meet all other diagnostic criteria. Finally, future studies should also investigate if an accurate preoperative diagnosis of NIFTP is possible using cytology with other ancillary techniques, such as molecular testing.

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