American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features


American Thyroid Association (ATA) leadership asked the ATA Thyroid Nodules and Differentiated Thyroid Cancer Guidelines Task Force to review, comment on, and make recommendations related to the suggested new classification of encapsulated follicular variant papillary thyroid carcinoma (eFVPTC) without capsular or vascular invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The task force consists of members from the 2015 guidelines task force with the recusal of three members who were authors on the paper under review. Four pathologists and one endocrinologist were added for this specific review. The manuscript proposing the new classification and related literature were assessed. It is recommended that the histopathologic nomenclature for eFVPTC without invasion be reclassified as a NIFTP, given the excellent prognosis of this neoplastic variant. This is a weak recommendation based on moderate-quality evidence. It is also noted that prospective studies are needed to validate the observed patient outcomes (and test performance in predicting thyroid cancer outcomes), as well as implications on patients’ psychosocial health and economics.

INTRODUCTION

A m erican Thyroid Association (ATA) leadership asked the ATA Thyroid Nodules and Differentiated Thyroid Cancer Guidelines Task Force to review, comment on, and make recommendations related to the suggested new classification of encapsulated follicular variant papillary thyroid carcinoma (eFVPTC) without capsular or vascular invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (1). The task force consists of members from the 2015 guidelines task force with the recusal of three members who were authors on the paper under review. Four pathologists and one endocrinologist were added for this specific review.
**ATA Task Force recommendation statement**

The histopathologic nomenclature for eFVPTC without invasion may be reclassified as NIFTP, given the excellent prognosis of this neoplastic variant. Prospective studies are needed to validate the observed patient outcomes (and test performance in predicting thyroid cancer outcomes), as well as implications on patients’ psychosocial health and economics.

*(Weak recommendation, moderate-quality evidence)*

It is important to highlight that the proposed change is in our view primarily semantic in nature, and intended to change nomenclature for this low-risk neoplasm that is more accessible, reassuring, and understandable to non-experts and patients. The proposed reclassification should not be interpreted as indicative of a changed risk profile of an inherently low-risk neoplasm, or as supporting a nonsurgical approach to these neoplasms, as accurate preoperative identification of NIFTP has not yet been demonstrated. Furthermore, the proposed change to NIFTP does not, in our opinion, affect recommendations in the 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (2), as discussed below.

**Scientific study**

As a primary scientific study, the authors retrospectively collected pathology slides from 268 patients at 13 institutions with eFVPTC (1). The patients were divided into eFVPTC without tumor capsule or vascular invasion \((n = 138)\) or with invasion \((n = 130)\). Ultimately, there was consensus by >50% of pathologists for 109 surgical pathology specimens without invasion and 101 with invasion. Those without invasion needed to have clinical follow-up for at least 10 years (median 13 years; range 10–26 years). Another criterion for inclusion was that none of the patients without tumor capsule invasion could have received therapeutic radioiodine. This was a retrospective two-arm comparative study (analogous to case-control study) design to compare noninvasive eFVPTC not treated with radioiodine (61% had lobectomy only) with invasive eFVPTC (86% thyroidectomy, 80% radioiodine). The patients were selected on retrospective review of pathology records from 13 different institutions, but it is not clear that all consecutive or random patients meeting eligibility criteria were selected, which raises concern for selection bias.

The authors found that all of the patients with noninvasive eFVPTC were alive without evidence of disease or a recurrence after the median 13-year follow-up, although the specific follow-up criteria to determine disease-free status were not fully defined. Conversely, of the 101 patients with invasive eFVPTC, 12 had noted “adverse events” (seven with persistent/recurrent disease, five with biochemical evidence of disease), five had distant metastases, and there were two deaths attributed to thyroid cancer, despite a shorter median (3.5 years) follow-up. There was no formal statistical comparison of adverse events in the invasive versus noninvasive eFVPTC groups, which is a minor methodologic concern.

The authors further noted in the discussion: “In the English language literature, only 2 (0.6%) of 352 well-documented noninvasive encapsulated/well-circumscribed FVPTCs recurred.” A recent retrospective surgical review of 77 patients with NIFTP in a large community-based health system showed no structural or biochemical recurrences after a median follow-up of 11.8 years (range 1.2–1.2 years), despite most patients having only thyroidectomy or lobectomy (3). Some of the patients in this study were also in the current study under review (1). This overall summary of multiple nonrandomized studies, together with the data presented in the article under review, is felt to be *moderate-quality evidence* that noninvasive eFVPTC is a very low-risk neoplasm, and the name change to NIFTP is reasonable. There are, however, some limitations causing minor to moderate concern about internal validity of the results, leading to a *weak recommendation* for the name change.

The 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer devotes section B15 and Recommendation 46 (pp 37–40) to the basic principles of histopathologic evaluation of thyroidectomy samples (2). It is noted in Recommendation 46B that “Histopathologic variants of thyroid carcinoma with more…favorable outcomes (e.g., encapsulated follicular variant of PTC without invasion…) should be identified during histopathologic examination and reported.” The discussion further highlights that “A completely excised noninvasive encapsulated follicular variant of papillary carcinoma is expected to have a very low risk of recurrence or extrathyroidal spread, even in patients treated by lobectomy.”

Even before this proposed name change to NIFTP, the guidelines have classified eFVPTC without invasion as a low-risk neoplasm that can be treated with lobectomy alone. Therefore, this new study does not significantly change the 2015 guidelines, other than the proposed name change.

**Position paper**

As a position paper, the authors were justifiably concerned that patients with eFVPTC, and in particular the noninvasive subtype, were classified and at times treated similarly to patients with classical PTC, and that these patients carried the stigma of a “cancer” diagnosis. Based on their own analysis of 109 patients, described in the paragraphs above, and their review of the literature, the authors propose that this neoplasm with very low potential for recurrence after surgery alone (lobectomy or thyroidectomy) should be reclassified as a non-cancer. They propose the name NIFTP in order to incorporate the etiology as a follicular thyroid neoplasm, excluding the term “carcinoma,” and retain the morphologic description papillary-like nuclear features, highlighting the potential overlap with classical nuclear grooves and pseudoinclusions, which have historically been suspicious or diagnostic for PTC.

We feel that this is a reasonable suggestion of name change. However, it is important to have additional studies to explore further the prevalence of this neoplasm subtype based on the strict pathologic criteria, as well as studies that determine the interobserver variability of this surgical pathology diagnosis. This proposed name change may affect how pathologists evaluate and report this subset of thyroid neoplasms. For example, examination of the entire capsule will now be required to rule out any foci of invasion (just as is the current standard of practice for encapsulated follicular lesions). In addition, the strict diagnostic criteria will likely mandate histologic examination of the entire lesion to ensure
absence of any exclusionary criteria such as psammoma bodies or >1% papillae. Finally, this name change presents obvious challenges for cytology, since NIFTP is a surgical diagnosis and requires architecture for the assessment of invasion. It therefore follows that there will be a small increase in false positives in the malignant category of The Bethesda System and a modest decrease in the risk of malignancy for the indeterminate subcategories (4–7). The proposed name change will also affect the performance of molecular tests when applied to patients with indeterminate cytology. For example, neoplasms harboring RAS mutations will likely have a lower positive predictive value (PPV) for malignancy, while nodules with no genetic mutation or a negative gene expression classifier will likely have a slightly higher negative predictive value (NPV). These effects will be dependent on the prevalence of NIFTP in a given population. Since NIFTP, like follicular adenoma, requires surgery for a definitive diagnosis, the changes in PPV and NPV of the molecular tests will not alter the requirement of surgical intervention for these patients. Potential frameworks for addressing cytology and molecular reporting are still evolving.

It is also unclear how these patients should be monitored. Based on the low risk for recurrence DTC recommendations in the 2015 ATA guidelines (lobectomy sufficient—Recommendation 38A and 51B; remnant ablation not recommended—Recommendation 38B; thyrotropin target 0.5–2 mIU/L—Recommendation 59C and 59E), these general recommendations would not be different for patients with tumors classified as NIFTP. American Joint Committee on Cancer/tumor-node-metastasis staging would no longer be necessary. Until more long-term follow-up data are available, occasional monitoring with serum thyroglobulin and neck ultrasound can be considered, depending upon patient context, but this is not mandatory. The length of time between follow-up evaluations in NIFTP is also not yet defined based upon available evidence.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

REFERENCES


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