

Research

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Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

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IMPORTANCE Although growing evidence points to highly indolent behavior of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), most patients with EFVPTC are treated as having conventional thyroid cancer.

OBJECTIVE To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.

DESIGN, SETTING, AND PARTICIPANTS International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. Review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A series of teleconferences and a face-to-face conference were used to establish consensus diagnostic criteria and develop new nomenclature.

MAIN OUTCOMES AND MEASURES Frequency of adverse outcomes, including death from disease, distant or locoregional metastases, and structural or biochemical recurrence, in patients with noninvasive and invasive EFVPTC diagnosed on the basis of a set of reproducible histopathologic criteria.

RESULTS Consensus diagnostic criteria for EFVPTC were developed by 24 thyroid pathologists. All of the 109 patients with noninvasive EFVPTC (67 treated with only lobectomy, none received radioactive iodine ablation) were alive with no evidence of disease at final follow-up (median [range], 13 [10-26] years). An adverse event was seen in 12 of 101 (12%) of the cases of invasive EFVPTC, including 5 patients developing distant metastases, 2 of whom died of disease. Based on the outcome information for noninvasive EFVPTC, the name "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was adopted. A simplified diagnostic nuclear scoring scheme was developed and validated, yielding a sensitivity of 98.6% (95% CI, 96.3%-99.4%), specificity of 90.1% (95% CI, 86.0%-93.1%), and overall classification accuracy of 94.3% (95% CI, 92.1%-96.0%) for NIFTP.

CONCLUSIONS AND RELEVANCE Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.

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The increasing incidence of cancer worldwide is multifactorial, attributable to population longevity, changing environmental and lifestyle factors, and increased surveillance. Thyroid cancer is a prime example for which intensified surveillance has resulted in an increasing incidence of early cancers with indolent behavior,^{1,2} a phenomenon commonly described as cancer “overdiagnosis.”³ The increasing incidence is solely attributable to papillary thyroid carcinoma (PTC), a tumor named for its papillary growth pattern, although the defining diagnostic criteria are actually the nuclear features of neoplastic cells.⁴ Aside from the enhanced screening, another important factor contributing to this phenomenon is the increase in diagnosis of a variant of PTC known as the follicular variant of PTC (FVPTC).⁵

The follicular variant of PTC was broadly recognized in the mid-1970s as a tumor composed of neoplastic follicles rather than papillae, but with follicular cells showing nuclear features characteristic of PTC.⁴ Two main subtypes are known to occur: infiltrative (or nonencapsulated) and encapsulated.^{6(pp100-109)⁷} Encapsulated FVPTC (EFVPTC) has increased in incidence by an estimated 2- to 3-fold over the past 2 to 3 decades and makes up 10% to 20% of all thyroid cancers currently diagnosed in Europe and North America (eTable 1 in the Supplement).^{5,8}

Encapsulated FVPTC is a challenging and controversial diagnosis in thyroid gland pathology. In those tumors that have no invasion, the diagnosis of cancer rests exclusively on finding the characteristic nuclei, assessment of which in many cases is subjective and even contentious, leading to consistently high interobserver variability.⁹⁻¹¹ Furthermore, studies over the past decade have demonstrated that FVPTC overall,¹² and particularly EFVPTC, has an indolent behavior and is genetically distinct from infiltrative tumors.^{7,13-17} Yet, most patients with EFVPTC continue to be treated similarly to those with conventional PTC. Aside from the stigma of a “cancer” diagnosis and the morbidity of aggressive treatment for PTC, patients and health care professionals have to cope with the rapidly increasing costs of care for patients with thyroid cancer, which were estimated to exceed \$1.6 billion in 2013 in the United States alone.¹⁸

Recognizing the problem of overdiagnosis and overtreatment of indolent cancers in many organs, the National Cancer Institute convened in 2012 a conference to evaluate this problem. Following the conference, a statement from a number of participants emphasized the need to revise terminology, replacing the word “cancer” when data emerge to support a more indolent designation.¹⁹ The goal of the current project was to assemble an international group of expert pathologists and clinicians to reexamine the entity currently known as EFVPTC through a review of a set of cases with long follow-up to (1) establish standardized diagnostic criteria and (2) identify terminology that would appropriately address the biological and clinical characteristics of this lesion.

Methods

Working Group

The Endocrine Pathology Society working group included 24 experienced thyroid pathologists (representing 7 countries and 4

Key Points

Question Do clinical outcomes of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) warrant reclassification of this tumor as nonmalignant?

Findings This study evaluates cases of encapsulated follicular variant of papillary thyroid carcinoma to establish consensus diagnostic criteria and develop new nomenclature. Among 109 patients with noninvasive EFVPTC, most of whom were treated with lobectomy only and none with radioiodine, all were alive with no evidence of disease at a median follow-up of 13 years.

Meaning Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed “noninvasive follicular thyroid neoplasms with papillary-like nuclear features” (NIFTP).

continents), 2 endocrinologists, 1 surgeon, and 1 psychiatrist. In addition, a molecular pathologist, a biostatistician, and a thyroid cancer survivor/patient advocate participated in the study.

Study Cohorts

For this retrospective study, a total of 268 tumors diagnosed as EFVPTC using current histologic criteria were contributed by working group pathologists from 13 institutions (eMethods in the Supplement) for inclusion into 2 groups. Potential cases for group 1 included noninvasive EFVPTC with no radioiodine (RAI) treatment and at least 10 years of follow-up (n = 138). Potential cases for group 2 included EFVPTC with vascular invasion and/or tumor capsule invasion and at least 1 year of follow-up (n = 130). Shorter follow-up for group 2 was accepted so as not to miss distant spread or recurrence within the first years following diagnosis. The coded slides were digitized into whole-slide images using the Aperio platform and placed on a server accessible to the entire group (<http://image.upmc.edu:8080/NikiForov%20EFV%20Study/view.apml>). The study was performed under institutional review board/ethics committee approval at 11 institutions, with exemption at 2 institutions, with a waiver of informed consent because the study was based on retrospective analysis of existing materials.

Histologic Review and Discussions

Twenty-four working group pathologists independently reviewed the scanned slides and provided their diagnoses in accordance with the existing criteria (eMethods in the Supplement). The diagnoses were tabulated and the initial findings were presented at the initiation of an 8-week series of weekly teleconferences aimed at refining groups 1 and 2 and achieving consensus. At a face-to-face conference in Boston, Massachusetts, on March 20 and 21, 2015, the findings of the study, together with related molecular and clinical outcome information, were discussed and the new nomenclature was established by consensus (eMethods in the Supplement). A nuclear scoring scheme was subsequently developed and validated as detailed in the eMethods in the Supplement.

Molecular Analysis

Molecular analysis was performed on 37 cases initially submitted for inclusion into group 1 on which paraffin blocks were avail-

able, and on 26 new cases of EFVPTC used as a validation set for the nuclear score selected from the files of the Department of Pathology, University of Pittsburgh. Total nucleic acids were isolated from formalin-fixed and paraffin-embedded tumor tissue following manual microdissection. Molecular analysis was performed using ThyroSeq v2 panel as previously described.²⁰ The assay uses targeted next-generation sequencing analysis for detecting point mutations and indels in 14 genes (*AKT1*, *BRAF*, *CTNNB1*, *GNAS*, *HRAS*, *KRAS*, *NRAS*, *PIK3CA*, *PTEN*, *RET*, *TP53*, *TSHR*, *TERT*, *EIF1AX*) and 42 gene fusion types involving the *RET*, *BRAF*, *NTRK1*, *NTRK3*, *ALK*, *PPARG*, and *THADA* genes. Samples that showed more than 5% of mutant alleles (corresponding to 10% of cells with heterozygous mutation) for point mutations or more than 100 high-quality reads crossing the fusion point of the transcript were considered positive. The minimum depth of coverage for each gene was 500×.

Statistical Analysis

Data analyses were divided into a training phase and testing or validation phase. In the training phase, 23 pathologists, blinded to molecular diagnosis, provided a 3-point nuclear score (range, 0-3 per case) for each of 13 cases. With the molecular data serving as the reference standard, a random-effects logistic regression model was fitted to predict molecular diagnosis based on molecular status and individual pathologist's nuclear score. The logistic model accounted for correlation among pathologists evaluating the same case. The predicted probability of calling a case positive was computed and the cutoff providing the most accurate decision was ascertained. This method detected minimal impact of individual pathologist, and therefore a simplified decision rule that ignored the individual pathologist was also calculated. This simplified rule was selected for validation. Validation of the simplified rule was tested in a second cohort of 26 patients with molecular diagnoses. Once again, pathologists (N = 22) blindly scored each case with a 3-point nuclear score. Treating the 22 test pathologists as independent and combining their evaluations, the decision rule from the training phase was then summarized by computing sensitivity, specificity, positive predictive value, and accuracy.

Results

Consensus Diagnostic Features of Encapsulated FVPTC

Review of representative digital and still images and subsequent discussions identified a list of major and minor diagnostic criteria for EFVPTC used by the majority of thyroid pathologists participating in the study (Box 1, Figure 1, and eFigure 1 in the Supplement). Furthermore, as a result of the discussion, consensus exclusion criteria for EFVPTC were accepted (Box 1). The initial review and rereview of cases in both groups was conducted in a blinded fashion, ie, without knowledge of follow-up.

Results of Initial and Subsequent Reviews of Cases in Group 1

The initial review of 138 potential cases for group 1 (noninvasive EFVPTC) resulted in 105 (76%) cases having the diagnosis of EFVPTC rendered by 12 or more (≥50%) pathologists and only 1 case with a concordant diagnosis of a benign nodule rendered

Box 1. Consensus Diagnostic Criteria for the Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (EFVPTC)

Major Features

- Encapsulation or clear demarcation
- Follicular growth pattern
- Nuclear features of papillary thyroid carcinoma (PTC)^a:
 - Enlargement, crowding/overlapping
 - Elongation
 - Irregular contours
 - Grooves
 - Pseudoinclusions^b
 - Chromatin clearing^c

Minor Features

- Dark colloid
- Irregularly shaped follicles
- Intratumoral fibrosis
- "Sprinkling" sign^d
- Follicles cleft from stroma^d
- Multinucleated giant cells within follicles

Features Not Seen/Exclusion Criteria

- "True" papillae^e >1%
- Psammoma bodies
- Infiltrative border
- Tumor necrosis
- High mitotic activity^f
- Cell/morphologic characteristics of other variants of PTC^g

^a In a tumor with multifocal presence of PTC, most pathologists do not require a specific minimal percentage of the tumor nodule to demonstrate these features.

^b A major and helpful diagnostic feature for all variants of PTC, although uncommon in EFVPTC.

^c Effacement of normal chromatin distribution with margination of chromatin to membrane also known as "glassy nuclei" or "Orphan Annie" nuclei.

^d As described and illustrated by Vanzati et al.²¹

^e True papillae are defined as complex, arborizing papillae with fibrovascular cores, lined by cells with nuclear features of PTC, and not associated with a fine-needle aspiration area.

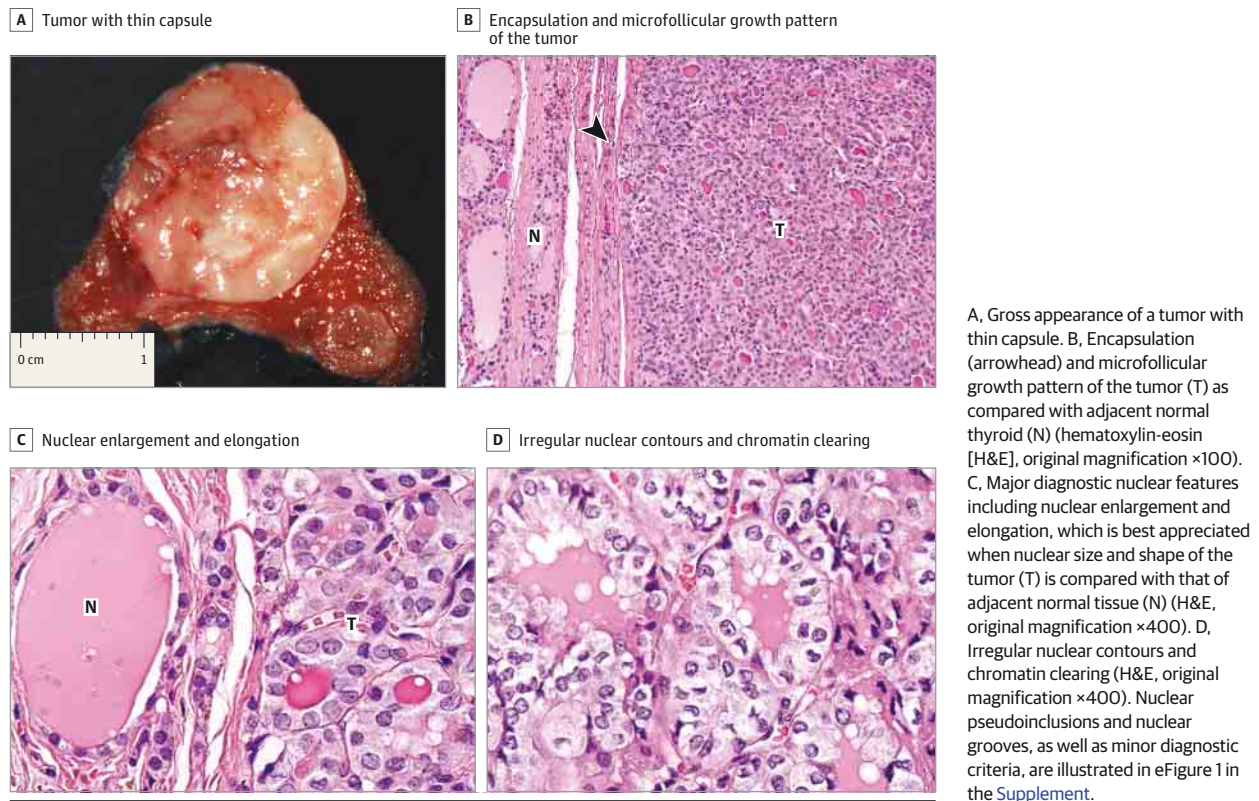
^f At least 3 per 10 high-power fields (×40).

^g Such as tall cell features, cribriform-morular variant, solid variant, etc.

by all 24 pathologists. Overall, the degree of expression of nuclear features of PTC correlated with the proportion of pathologists rendering the diagnosis of EFVPTC (eFigure 2 in the Supplement).

Following the acceptance of the aforementioned consensus diagnostic criteria, 30 cases from group 1 with the most disparate diagnoses rendered on the initial review were rereviewed and discussed at teleconferences. As a result, 28 cases were excluded from group 1 because of insufficient diagnostic nuclear features of PTC (n = 14), presence of invasion (n = 6), at least 1% papillary growth consistent with classical PTC (n = 4), or prominent (>30%) solid/trabecular/insular growth pattern consistent with either solid variant PTC or poorly differentiated thyroid carcinoma (n = 4). One case was submit-

Figure 1. Gross and Histopathologic Features of the Tumor Currently Known as Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (EFVPTC)



ted and reviewed twice under different coded numbers; the duplicate was eliminated. This resulted in a total of 109 cases accepted as noninvasive EFVPTC in group 1.

Results of Mutational Analysis of Selected Cases in Group 1

Mutational analysis was performed on 37 cases initially submitted as group 1. The analysis assessed point mutations in 14 genes and 42 types of gene fusions, which are found in approximately 90% of PTC.²² Clonal molecular alterations were detected in 25 (68%) of cases, with RAS mutations being the most common (eTable 2 in the Supplement). None of the 5 cases excluded from group 1 as a result of insufficient nuclear features had identifiable mutations. In contrast, 21 (78%) of genetically characterized lesions remaining in group 1 revealed clonal mutations.

Results of Initial and Subsequent Reviews of Cases in Group 2

A total of 130 cases were submitted as group 2, EFVPTC with invasion. These tumors had the same nuclear features and follicular architecture as group 1 but, unlike group 1 cases, had vascular and/or tumor capsule invasion. Initial review yielded 105 (81%) cases that were diagnosed as EFVPTC with invasion by at least 50% of reviewers, whereas the remaining cases were preferentially called either classic PTC or infiltrative FVPTC (eTable 3 in the Supplement). After review and discussion of 44 cases with the most discrepant diagnoses at teleconferences and application of the consensus diagnostic criteria, 29 cases were excluded from group 2 on the basis of at least 1% papillary growth (n = 17), infiltrative border (n = 8), lack of the nuclear features

of PTC (n = 3), or lack of invasion (n = 2). As a result, 101 cases remained in group 2. This included 80 cases with invasion of the tumor capsule, 12 with vascular invasion, and 9 with both invasion types (eFigure 3 in the Supplement).

Follow-up for Patients in Study Groups

At the face-to-face conference, the follow-up information was provided, as summarized in the Table. In group 1, among 109 patients observed for 10 to 26 years, all were alive with no evidence of disease. Sixty-seven of these patients were treated with lobectomy only, and none of them received RAI. In group 2, among 101 patients, 85 patients were treated with RAI, 15 did not receive RAI, and RAI treatment status in 1 patient was unknown. Patients were observed for 1 to 18 years, and 12 (12%) registered an adverse event. Of those, 5 patients developed distant metastases (lung and/or bone), 2 of whom died of disease. In addition, 1 patient had a lymph node recurrence, 1 had persistent disease, and 5 had detectable serum thyroglobulin and were considered to have either an indeterminate response or biochemically incomplete response to therapy (eTable 4 in the Supplement). Among 5 patients who had distant metastases, at presentation 2 tumors had capsular invasion only, 1 had vascular invasion only, and 2 had both types of invasion.

Revision of Tumor Nomenclature

Based on the outcome information available for tumors diagnosed using standardized criteria, new nomenclature was developed. The goal was to offer a designation for the lesion cur-

Table. Summary of Follow-up Information for Patients in the Study Groups

Characteristic	Group 1 (Noninvasive EFVPTC) (n = 109)	Group 2 (Invasive EFVPTC) (n = 101)
Age, mean (range), y	45.9 (21-81)	42.8 (8-78)
Sex, No. (%)		
Female	91 (83)	71 (70)
Male	18 (17)	30 (30)
Tumor size, mean (range), cm	3.1 (1.1-9.0)	2.5 (0.6-5.5)
Extent of surgery		
Lobectomy	67	15
Total thyroidectomy	42	86
Follow-up, y		
Mean (range)	14.4 (10-26)	5.6 (1-18)
Median	13.0	3.5
Adverse events during follow-up, No. (%)	0	12 (12)

rently known as noninvasive EFVPTC that would reflect the following characteristics:

1. main morphological features, ie, the follicular growth pattern and nuclear features of PTC;
2. lack of invasion, which separates this tumor from invasive EFVPTC;
3. clonal origin determined by finding a driver mutation, which indicates that the lesion is biologically a neoplasm; and
4. a very low risk of adverse outcome when the tumor is non-invasive.

Additional consideration was to use words translatable to other languages without losing their exact meaning. As a result, the term “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) was accepted.

Diagnostic Nuclear Score

To provide simplified and reproducible criteria for the nuclear features that could assist in the diagnosis of NIFTP in routine pathology practice, the 6 main consensus nuclear features (Box 1) were grouped into 3 categories: (1) size and shape (nuclear enlargement/overlapping/crowding, elongation), (2) nuclear membrane irregularities (irregular contours, grooves, pseudo-inclusions), and (3) chromatin characteristics (clearing with margination/glassy nuclei). A 3-point scoring scheme was developed, in which each class of nuclear features was assigned a score of 0 or 1, yielding a range of scores from 0 to 3. Using a visual guide for scoring the nuclear features (eFigure 4 in the Supplement), 30 cases from group 1 were evaluated by 23 pathologists who were blinded to the results of molecular analysis available on 18 of these lesions (eTable 5 in the Supplement). Using a molecular end point as the reference standard separating NIFTP from benign hyperplastic nodules, the scoring scheme delivered the most accurate classification when a score of 0 or 1 was diagnostic of a benign nodule and a score of 2 or 3 was diagnostic of NIFTP. This approach demonstrated a sensitivity of 86.5% (95% CI, 82.7%-90.3%), specificity of 80.8% (95% CI, 73.8%-87.9%), and overall accuracy of 85.0% (82.8%-90.3%). The 3-point scoring scheme was then validated in an independent set of 26 new cases with molecular end points (eTable 6 in the Supplement). Using a 0 to 1 vs 2 to 3 score separation, the

Box 2. Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation^a
2. Follicular growth pattern^b with <1% Papillae
No psammoma bodies
<30% Solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion^c
5. No tumor necrosis
6. No high mitotic activity^d

^a Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.

^b Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid.

^c Requires adequate microscopic examination of the tumor capsule interface.

^d High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×).

3-point scoring scheme showed a sensitivity of 98.6% (95% CI, 96.3%-99.4%), specificity of 90.1% (95% CI, 86.0%-93.1%), and overall classification accuracy of 94.3% (95% CI, 92.1%-96.0%).

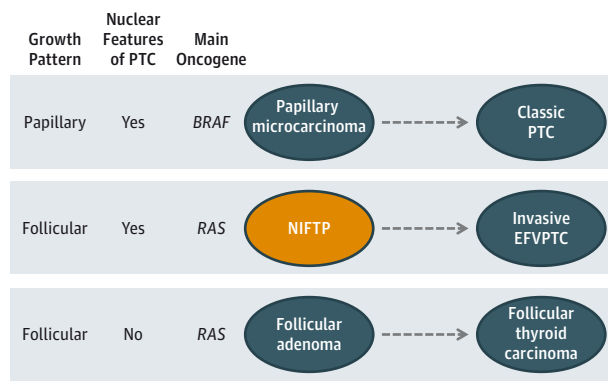
Final diagnostic criteria for NIFTP are summarized in Box 2.

Discussion

This study was undertaken to reexamine the clinical and pathologic approach to noninvasive EFVPTC—a thyroid tumor that, despite increasing evidence of its indolent behavior, is nonetheless classified as cancer. The outcome data obtained in this study support renaming this tumor in a manner that more accurately reflects its behavior. Indeed, in our highly curated cohort of more than 100 noninvasive EFVPTCs there were no recurrences or other manifestations of the disease at a median follow-up of 13 years. This finding correlates with previous reports on noninvasive EFVPTC. In the English language literature, only 2 (0.6%) of 352 well-documented noninvasive encapsulated/well-circumscribed FVPTCs recurred.^{14,15,23-27} One of the recurred tumors had been incompletely excised, whereas in the other case the noninvasive nature of the tumor remains questionable. Even if these 2 cases of recurrence are accepted, the combined data suggest that in the absence of invasion this lesion entails a very low risk of adverse outcome and therefore should not be termed cancer.

The new proposed terminology, NIFTP, reflects key histopathologic features of this lesion, ie, lack of invasion, follicular growth pattern, and nuclear features of PTC. Molecular analysis performed in this study on a limited number of samples confirmed previous observations^{16,28} demonstrating that most of these lesions are driven by clonal genetic alterations and are therefore neoplasms rather than hyperplastic proliferations. When defined with strict histopathologic criteria, these tumors are not expected to show molecular alterations associated with classic PTC, such as *BRAF* V600E mutations. Instead, they demonstrate a high prevalence of *RAS* and other mutations, which have been associated with follicular-pattern thyroid tumors, including follicular adenoma (FA), follicular thy-

Figure 2. Putative Scheme of Thyroid Carcinogenesis



EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.

roid carcinoma (FTC), and EFVPTC.^{16,22,29} Furthermore, tumors analyzed in this study also recapitulate the FA to FTC sequence of progression with the capacity for invasion, suggesting that NIFTP likely represents the “benign” counterpart or precursor of the invasive EFVPTC (Figure 2).

We have defined a set of reproducible diagnostic criteria that accurately identify NIFTP. We have also shown that given the metastatic potential of the invasive tumors in group 2, adequate sampling of the tumor capsule interface to exclude invasion is imperative before designating a nodule as NIFTP. To our knowledge, adequacy of tumor capsule sampling has not been discussed in the literature to date with respect to FVPTC. Precedent can be drawn from the approach to the encapsulated FA/FTC tumors, in which histologic assessment of the entire lesion capsule is preferable to exclude a minimally invasive FTC.³⁰ Thus, like FA, NIFTP should undergo extensive review of the tumor capsule interface to exclude invasion.

The results of this study, together with previously reported observations, suggest that when the diagnosis of NIFTP is made on the basis of careful histopathological examination, the tumor will have a low recurrence rate, likely less than 1% within the first 15 years. Of note, most differentiated thyroid carcinomas relapse within the first decade after initial therapy,³¹ although late recurrences and distant spread are documented.³² Importantly, a large proportion of patients with tumors diagnosed as NIFTP in the present study underwent lobectomy only and none received RAI ablation. This suggests that clinical management of patients with NIFTP can be deescalated because they are unlikely to benefit from immediate completion thyroidectomy and RAI therapy. Staging would be unnecessary. In addition to eliminating the psychological impact of the diagnosis of cancer, this would reduce complications of total thyroidectomy, risk of secondary tumors following RAI therapy, and the overall cost of health care.^{33,34} Avoidance of RAI treatment alone would save between \$5000 and \$8500 per patient (based on US cost).³⁵ Decreased long-term surveillance would account for another substantial proportion of cost reduction.

Conclusions

The results of this international and multidisciplinary study establish that thyroid lesions currently diagnosed as noninvasive EFVPTC represent a distinct class of thyroid tumors with very low risk of adverse outcome. These tumors can be diagnosed using a set of reproducible diagnostic criteria and should be termed “noninvasive follicular thyroid neoplasms with papillary-like nuclear features” (NIFTP). We estimate that this reclassification would affect more than 45 000 patients worldwide each year (eTable 7 in the Supplement), thereby significantly reducing the psychological burden, medical over-treatment and expense, and other clinical consequences associated with a cancer diagnosis.

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