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Evaluating the projected impact of reclassifying noninvasive encapsulated follicular variant of papillary thyroid cancer as noninvasive follicular thyroid neoplasm with papillary-like nuclear features

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Abstract

Background—The reclassification of noninvasive encapsulated follicular variant of papillary thyroid cancer (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) will reduce non-efficacious and potentially harmful care. Reclassification is estimated in 18.5% of PTC patients; we aimed to quantify the implications of this change.

Methods—Pathology reports from 4/2006–4/2016 were reviewed to isolate cases that would have been designated as NIFTP. Of the 1335 cases of PTC, 194 cases (14.5%) met criteria. Cases in which NIFTP was found in combination with other thyroid malignancies (n=25) and cases of prior thyroid lobectomy (n=5) were excluded. Demographic, pathological, treatment, and follow-up data were assessed for the remaining 164 potential NIFTP cases. Logistic regression analysis was performed to evaluate association between fine needle aspiration (FNA) result and index procedure.

Results—Of the 164 patients with tumors meeting NIFTP criteria, FNA results were nondiagnostic (2%), benign (18%), atypia/follicular lesion of undetermined significance (26%), follicular neoplasm (FN) or suspicious for FN (20%), suspicious for malignancy (19%), malignant (6%), and not obtained (9%). Eighty-five (52%) of patients underwent total thyroidectomy. A “suspicious for malignancy” FNA result was associated with undergoing total thyroidectomy

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versus thyroid lobectomy ($p = 0.006$). Thyroid lobectomy was the index procedure for 79 patients (48%); of these patients, 54% ($n=43$, 3.2% of all PTC patients) underwent subsequent total thyroidectomy and 24% received post-op RAI treatment. There were no recurrences among the 125 patients with >3 months follow-up.

Conclusion—The reclassification of noninvasive EFVPTC as NIFTP will decrease non-efficacious treatment and reduce costs. However, the impact of this change with regard to extent of surgery was limited to 3.2% of patients with PTC compared to the projected potential impact on 18.5%.

Key terms

Papillary thyroid cancer; thyroid cancer; NIFTP; FVPTC; EFVPTC; encapsulated follicular variant

Introduction

Thyroid cancer is the most rapidly increasing cancer in the United States, with an increased incidence rate of 5.1% per year from 2003 to 2012, and over 64,000 new patients expected to be diagnosed in 2016.¹ Considering that most people diagnosed with thyroid cancer will not become symptomatic or die from their disease, with 5-, 10- and 15-year survival rates above 95%,¹ emphasis has been placed on understanding the extent of overdiagnosis in thyroid cancer and weighing the benefits of our interventions against undue harm.^{2,3} This acknowledgement has led to strategies to mitigate overtreatment.

The increase in incidence of thyroid cancer is largely attributable to an increase in diagnosis of small papillary thyroid carcinomas (PTC)^{4,5} and specifically, an increase in diagnosis of a variant of PTC known as the follicular variant of PTC (FVPTC) which comprises over 25% of all PTCs.^{6,7} Two main subsets of FVPTC include infiltrative FVPTC, which are more likely to harbor *BRAF* mutations and have a higher prevalence of lymph node metastasis and local recurrences,⁸ and encapsulated FVPTC (EFVPTC), which are more likely to have mutations in the *RAS* family of oncogenes and have a low recurrence rate in the absence of capsular or vascular invasion.⁹ Over the past decade, multiple studies have demonstrated that noninvasive EFVPTC has an indolent course and is genetically distinct from infiltrative tumors,^{8,10–13} yet it had been treated similarly to conventional PTC.

A landmark study published in April 2016 proposed that PTCs thus far diagnosed as noninvasive EFVPTC now be entitled noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), reclassifying a cancer as a indolent tumor.¹⁴ This reclassification intends to reduce non-efficacious and potentially harmful treatments and follow-up, as well as reduce the psychological burden associated with a cancer diagnosis.¹⁴ It is estimated this reclassification would affect more than 46,000 patients, or 18.5% of the 250,000 patients diagnosed with papillary thyroid cancer (PTC) worldwide each year¹⁴ and about 10,000, or 15.4% of the nearly 65,000 thyroid cancer patients a year in the United States.¹⁵ Theoretically, the reclassification of noninvasive EFVPTC to NIFTP should result in fewer total thyroidectomies since thyroid lobectomy alone is sufficient in the work-up and management of NIFTP given the indolent nature of these lesions. However, the surgical

impact is largely only relevant when the indication for surgery is the NIFTP itself, rather than when NIFTP is found incidentally and when thyroid surgery is performed for other reasons. In our study we aimed to help quantify the implications of the reclassification of noninvasive EFVPTC to NIFTP by examining 10 years of thyroid cancer data from a single academic medical center. Our center is equipped to do this retrospectively given that our pathologists have been reporting noninvasive EFVPTC for the duration of the study by systematically analyzing the tumor capsule. Given that a significant number of patients with NIFTP undergo total thyroidectomy as their index procedure (rather than thyroid lobectomy) for various reasons, we hypothesized that the impact of this reclassification on extent of surgery in our cohort would be less than previously projected.

Methods

Study cohort and inclusion criteria

A natural language search of pathology reports from 4/2006–4/2016 from a single academic medical center, Massachusetts General Hospital, was performed to identify cases of noninvasive EFVPTC that would have been designated as NIFTP. Of the 1335 cases of PTC, there were 279 cases of EFVPTC of which there were 76 cases of infiltrative EFVPTC and 203 cases on noninvasive EFVPTC. Of the 203 cases of noninvasive EFVPTC, 194 cases met established pathological NIFTP criteria [(i) thick, thin or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue; (ii) follicular growth pattern; (iii) unequivocal nuclear changes of PTC; (iv) absence of capsular or vascular invasion, and (v) capsule submitted in its entirety]. Tumors with insufficient nuclear changes for the diagnosis of PTC did not receive the diagnosis of noninvasive EFVPTC, as they would not have met criterion (iii) above. Cases in which NIFTP was found in combination with other thyroid malignancies (n=25) and cases of prior thyroid lobectomy (n=5) were excluded. Cases meeting inclusion criteria were confirmed by an endocrine pathologist (PMS).

Covariates and data analysis

Clinical information was abstracted retrospectively from the electronic medical record in compliance with the medical center's Institutional Review Board. The following information was collected for the 164 potential NIFTP cases: patient demographic information (including sex and age at time surgery in years as a continuous variable); pre-operative FNA diagnosis [as classified by the Bethesda System for Reporting Thyroid Cytopathology FNA as (i) non-diagnostic, (ii) benign, (iii) follicular lesion or atypia of undetermined significance (FLUS and AUS), (iv) follicular neoplasm (FN) or suspicious for FN, (v) suspicious for malignancy and (vi) malignant]; procedure type (total thyroidectomy versus thyroid lobectomy); and tumor characteristics (including size in centimeters as a continuous variable, Afirma Gene Expression Classifier testing when available, and tumor focality as a categorical variable categorized as unilateral tumors, multiple unilateral tumors, or bilateral tumors). Additionally, we collected data on follow-up interventions including completion thyroidectomy (if a patient had thyroid lobectomy as their index procedure) and post-operative radioactive iodine (RAI) treatment status (both binary variables), median follow-up times from index surgical procedure (in months as a continuous variable), and recurrence

status (binary variable). We defined recurrence of disease as new, structural PTC verified by cytology of an FNA biopsy or on formal surgical pathology in a previously treated patient, with a clinical disease-free interval (i.e. physical exam, neck ultrasound).

Continuous variables were reported as mean $\pm$ standard deviation or median with interquartile range and categorical variables were reported as percent frequency (%). Univariate analysis of whether index procedure was associated with FNA result, sex, age, and tumor size was performed, using the appropriate test (Student *t* test and Fisher exact test) when comparing group means or frequencies. In order to evaluate whether FNA result was associated with undergoing total thyroidectomy as the index operation, a multivariable logistic regression was performed with a benign result as the reference group. Additional covariates included age as a continuous variable and tumor size as a continuous variable. A *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using STATA version 12 (STATA Corp., TX, USA).

Results

Cohort characteristics are outlined in Table 1. Of the 164 patients with tumors meeting NIFTP criteria, 130 (79%) were women. The mean age of patients was 50 ± 15 years and the mean index tumor size was 2.0 ± 1.5 cm. The American Joint Committee on Cancer 7th edition Tumor-stage of these tumors included: 1a (33%), 1b (23%), 2 (34%), and 3 (10%). Most had solitary tumors ($n=143$), while 21 patients had multifocal NIFTP (12 ipsilateral, 9 bilateral). As per the Methods, 25 cases in which NIFTP was found in combination with other thyroid malignancies were excluded; thus, these cases were not counted in the multifocal NIFTP group.

Fine needle aspiration (FNA) results from the primary tumor focus (Table 2) were nondiagnostic (2.4%), benign (18.3%), atypia/follicular lesion of undetermined significance (25.6%), follicular neoplasm (20.1%), suspicious for malignancy (18.9%), malignant (5.5%), and absent (9.2%). Patients who did not undergo pre-operative FNA were those who underwent surgery primarily for symptomatic multinodular goiter ($n = 13$) or hyperthyroidism ($n = 2$), and thus in these cases, NIFTP was essentially found incidentally.

Total thyroidectomy was performed in 30% of those with a benign FNA (Table 3); in these cases, surgery was performed primarily for an enlarging nodule or symptomatic multinodular goiter. Total thyroidectomy was also performed in 19/42 patients with AUS or FLUS samples (45.2%), 13/33 patients with FN or suspicious for FN samples (39.4%), 22/31 patients with samples suspicious for malignancy (71%), and 9/9 patients with FNA samples demonstrating definitive malignancy (Table 3). On unadjusted analysis, differences in age and index tumor size were statistically significant between those who underwent thyroid lobectomy versus total thyroidectomy as the index procedure (46.6 ± 14.0 years versus 53.6 ± 15.2 years and 2.4 ± 1.4 versus 1.7 ± 1.5 cm, respectively). Index tumor size was smaller in the total thyroidectomy group given that this group included more incidentally-found NIFTPs, frequently when the surgical indication was symptomatic multinodular goiter. Afirma Gene Expression Classifier testing was only recorded for nine patients in the NIFTP cohort; of these patients, one had a benign result and eight had a

suspicious result. Of the eight patients with a suspicious result, five patients underwent total thyroidectomy and three patients underwent thyroid lobectomy.

A multivariable logistic regression was performed in order to evaluate whether FNA result was associated with a patient undergoing total thyroidectomy (versus thyroid lobectomy) (Table 4). After adjusting for age and tumor size, a “suspicious for malignancy” FNA result (versus a benign result) was found to be independently predictive of undergoing total thyroidectomy versus thyroid lobectomy (OR 4.90, $p = 0.006$).

Overall, of the 1335 patients diagnosed with PTC from 4/2006–4/2016, 79 NIFTP patients (6%) underwent thyroid lobectomy and 85 NIFTP patients (6.4%) underwent total thyroidectomy as their index procedure (Figure 1). Of the 79 patients who underwent thyroid lobectomy as their index procedure (48% of cohort), 54% ($n=43$) underwent subsequent total thyroidectomy and 24% ($n= 19$) received post-operative RAI treatment after completion thyroidectomy. Thus, of the 1335 patients with PTC, 43 patients (3.2%) would have had the potential for less extensive surgery after the reclassification of noninvasive EFVPTC to NIFTP. Of those who underwent thyroid lobectomy as their index procedure, 15 (19%) underwent this procedure for a reason other than FNA findings, including lobectomy for multinodular goiter or symptomatic mass, parathyroid adenoma exploration, and thyroid lobectomy in the setting of surgery for thyroglossal duct cyst excision.

Eighty-five NIFTP patients underwent total thyroidectomy as their initial procedure (Figure 1); of these patients, 29 (34%) underwent this procedure for a reason other than FNA findings (i.e. patient had a benign FNA but patient had a symptomatic multinodular goiter). Twenty-four percent of the total thyroidectomy group underwent post-operative RAI treatment. There were no cases of recurrence among the 125 patients with >3 months follow-up (median follow-up = 24 months [IQR 12–49]).

Discussion

In 2016, it was proposed that noninvasive EFVPTCs no longer be classified as “cancer” and instead be called NIFTP.¹⁴ It is projected that this name change will affect more than 46,000 patients, or 18.5% of the 250,000 patients diagnosed with PTC worldwide each year¹⁴ and about 10,000, or 15.4% of the nearly 65,000 thyroid cancer patients a year in the United States.¹⁵ In this study we aimed to help quantify the implications of this change in terms of extent of surgery by examining 10 years of thyroid cancer data from a single academic medical center. In our cohort, given that only half of patients underwent lobectomy as their index procedure, and only half of these patients underwent subsequent completion thyroidectomy, the potential impact of this change with regard to extent of surgery was limited to approximately 3.2% of patients with PTC compared to the projected potential impact on 18.5% of all patients with PTC worldwide.

The determination of NIFTP still requires examination of the entire tumor capsule. Moreover, patients still require at least a thyroid lobectomy for diagnosis. Therefore, the impact of a NIFTP diagnosis will largely be borne out of less extensive surgery, namely thyroid lobectomy versus total thyroidectomy. Rosario *et al.* performed a retrospective

study¹⁶ examining potential NIFTP cases at a single institution. In their study of 129 potential NIFTP patients, approximately 50% underwent thyroid lobectomy as their index procedure, similar to our rate of 48%. This again highlights that even if NIFTP is diagnosed on final pathology, the potential to avoid further surgical intervention may only impact approximately half of patients. In our study, of the 48% of patients who underwent thyroid lobectomy as the index procedure, only about half underwent subsequent total thyroidectomy; in most of these cases, patients were counseled on the low-risk nature of their tumors and patients ultimately opted for lobectomy alone with surveillance. This trend toward more conservative surgical treatment is in line with the 2015 American Thyroid Association thyroid nodule and differentiated thyroid cancer management guideline recommendations which suggest lobectomy alone as a reasonable surgical approach to low-risk PTC.¹⁷ With regard to the other half of patients who underwent total thyroidectomy as their index procedure, it was clear that patients undergo total thyroidectomy initially for a variety of reasons that will not be impacted by the nomenclature change to NIFTP. In our cohort, 34% of patients who underwent total thyroidectomy underwent the procedure for a reason other than a concerning FNA result, such as for symptomatic multinodular goiter, compressive symptoms, other nearby head and neck cancer, and Grave's disease. Thus, because NIFTP is often found incidentally on final pathology after a total thyroidectomy, it is important not to include these patients in the projected surgical impact of the nomenclature change, as these patients would have received the same operation regardless of the NIFTP diagnosis.

We acknowledge that the impact of this reclassification, and consideration of a once-cancer as now an indolent tumor, extends beyond saving patients from undergoing completion thyroidectomy after thyroid lobectomy. For one, we found that 39 patients in our cohort (24% of our NIFTP patients) underwent post-operative RAI treatment. RAI carries with it its own expense and complications,^{18–20} and eliminating the use of this treatment in this population will be significant. Other considerations include the psychological impact of a cancer diagnosis^{21,22} and the cost and toll associated with long-term clinical follow-up given that recurrence of PTC can occur up to 30 years after diagnosis.²³ In fact, Likhтеров *et al.* found that the total direct and indirect costs of surveillance of a patient with EFVPTC in 2015 approximates \$4,388 for the first year after surgery and \$3,884 for each subsequent year of surveillance.²⁴ At the same time, we must also consider the immediate logistical cost of disclosure to many patients that their malignant pathology has been reclassified as “non-malignant,” and consider the cost of reevaluating the pathologic slides of those patients at risk to ensure that the invasive nature of the tumor is comprehensively evaluated before notifying a patient of a change in diagnosis.²⁴ In many cases, this reclassification may not be possible if the capsule was not entirely submitted for evaluation initially and if slides are not available for review, and may carry medical-legal considerations. A future comprehensive direct and indirect comparative effectiveness analysis of the change in thyroid nodule management, after the nomenclature change to NIFTP, will be especially important to further quantify the overall impact to patients, clinicians, and society.

This study has inherent limitations secondary to the retrospective nature of its design. We utilized pathology reports of FVPTC alone in identifying patients for the study. There is, therefore, the potential for misdiagnosis. Prospective data collection and analysis after the

April 2016 change will be important as we continue to better understand the implications of this reclassification. Second, we did not routinely perform molecular tests on our pathology samples; this information would have been instructive as previous studies have shown that mutations in *BRAF* are not expected in NIFTP, while mutations in *RAS* are common.¹⁴ While Afirma Gene Expression Classifier testing was only performed for 9 patients in our proposed NIFTP cohort; of these patients, a majority (8/9) had a suspicious result, consistent with prior research demonstrating that noninvasive FVPTCs are often categorized as suspicious by Afirma Gene Expression Classifier testing.²⁵ This highlights that, to date, pre-operative Afirma Gene Expression Classifier testing and FNA do not aid in diagnosing NIFTP. A suspicious result on Afirma Gene Expression Classifier testing may, in fact, lead surgeons and patients to choose total thyroidectomy as the initial procedure. In terms of FNA results, in our cohort, a “suspicious for malignancy” result (versus a benign result) was found to be independently predictive of undergoing total thyroidectomy versus thyroid lobectomy. While this will vary with institution, surgeon, and over time with changing guidelines and shift to less aggressive therapy, many surgeons will treat “suspicious for PTC” as malignant and perform total thyroidectomy per usual care. This is underscored by the finding that all patients with malignant FNA underwent total thyroidectomy in our cohort. Lastly, while there were no cases of recurrence among the patients in our cohort, our median follow-up time was only two years. This short median follow up time was due to a number of factors, including the number of patients in our cohort being diagnosed and treated in the last 5 years as well as patients re-locating or becoming lost to follow up in our system. It will be important to continue to track long-term recurrence rates of NIFTP moving forward.

The overall low mortality associated with thyroid cancer should be complemented by minimal morbidity from diagnosis and treatment. In this vein, the recent reclassification of noninvasive EFVPTC to NIFTP will likely improve the quality of thyroid cancer care, quality of life of the affected patients, and reduce costs. However, this impact may be more limited than previously predicted. In our cohort, given that only 48% of patients underwent lobectomy as their index procedure, and only half of these patients underwent completion thyroidectomy, the potential impact of the nomenclature change with regard to extent of surgery was limited to approximately 3.2% of all patients with PTC compared to the projected potential impact on 18.5% of patients with PTC. Future studies that characterize the molecular and clinical features of NIFTP and further evaluate the impact of this reclassification on overall treatment, surveillance, and quality of life, will be instructive.

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Figure 1.
Treatment and postoperative management.

Table 1

Cohort demographics and tumor characteristics.

Characteristic	NIFTP (n=164)
Female sex, n (%)	130 (79.3)
Age (years $\pm$ SD)	50 $\pm$ 15
Tumor size (cm $\pm$ SD)	2.0 $\pm$ 1.5
Tumor Focality	
Solitary tumor, n (%)	143 (87.2)
Multiple unilateral, n (%)	12 (7.3)
Multiple bilateral, n (%)	9 (5.5)
Pathologic T-stage (TMN)	
T1a, n (%)	51 (31.1)
T1b, n (%)	40 (24.4)
T2, n (%)	56 (34.2)
T3, n (%)	17 (10.4)

Table 2

Preoperative fine need aspiration cytology results.

FNA cytology results	NIFTP (n = 164)
Bethesda category	
(i) non-diagnostic, n (%)	4 (2.4)
(ii) benign, n (%)	30 (18.3)
(iii) AUS or FLUS, n (%)	42 (25.6)
(iv) suspicious for FN or FN, n (%)	33 (20.1)
(v) suspicious for malignancy, n (%)	31 (18.9)
(vi) malignant, n (%)	9 (5.5)
No FNA performed, n (%) *	15 (9.2)

AUS, atypia of undetermined significance; *FLUS*, follicular lesion of undetermined significance; *FN*, follicular neoplasm

* Patients who did not undergo pre-operative FNA were those who underwent surgery for symptomatic multinodular goiter (n = 13) or hyperthyroidism (n = 2).

Table 3

Univariate analysis of undergoing thyroid lobectomy versus total thyroidectomy as index procedure.

	NIFTP		
	Thyroid lobectomy (n = 79)	Total thyroidectomy (n = 85)	p-value
Bethesda category			
(i) non-diagnostic, n (%)	3 (3.8)	1 (1.2)	0.353
(ii) benign, n (%)	21 (26.6)	9 (10.6)	0.009
(iii) AUS or FLUS, n (%)	23 (29.1)	19 (22.3)	0.372
(iv) suspicious for FN or FN, n (%)	20 (25.3)	13 (15.3)	0.122
(v) suspicious for malignancy, n (%)	9 (11.4)	22 (25.9)	0.027
(vi) malignant, n (%)	0 (0)	9 (10.6)	0.003
No FNA performed, n (%)	3 (3.8)	12 (14.1)	0.029
Female sex, n (%)	65 (82.3)	65 (76.5)	0.442
Age (years $\pm$ SD)	46.6 $\pm$ 14.0	53.6 $\pm$ 15.2	0.003
Index tumor size (cm $\pm$ SD)	2.4 $\pm$ 1.4	1.7 $\pm$ 1.5	0.005

AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm

Table 4

Adjusted logistic regression model evaluating odds of total thyroidectomy as index procedure based on FNA among NIFTP patients.

Covariate	OR	95% CI	<i>p</i> -value
Bethesda category			
(i) non-diagnostic	0.65	0.06–7.40	0.725
(ii) benign	Ref	Ref	Ref
(iii) AUS or FLUS	1.76	0.64–4.88	0.276
(iv) suspicious for FN or FN	1.44	0.48–4.30	0.502
(v) suspicious for malignancy	4.90	1.58–15.22	0.006
(vi) malignant	*	*	*
Age	1.02	0.99–1.05	0.222
Index tumor size	0.80	0.62–1.04	0.091

OR, odds ratio; *CI*, confidence interval; *AUS*, atypia of undetermined significance; *FLUS*, follicular lesion of undetermined significance; *FN*, follicular neoplasm

* Given that all patients with malignant FNA cytology results underwent total thyroidectomy, these patients (n=9) were omitted from the model