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Evaluating the projected surgical 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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Background. The reclassification of noninvasive encapsulated follicular variant of papillary thyroid cancer to noninvasive follicular thyroid neoplasm with papillary-like nuclear features will reduce nonefficacious and potentially harmful care. Reclassification is estimated in 18.6% of patients with papillary thyroid carcinoma; we aimed to quantify the implications of this change.

Methods. Pathology reports from April 2006 to April 2016 were reviewed to isolate cases that would have been designated as neoplasm with papillary-like nuclear features. Of the 1,335 cases of papillary thyroid carcinomas, 194 cases (14.5%) met criteria. Cases in which neoplasm with papillary-like nuclear features was found in combination with other thyroid malignancies (n = 25) and cases of prior thyroid lobectomy (n = 5) were excluded. Demographic, pathologic, treatment, and follow-up data were assessed for the remaining 164 potential neoplasm with papillary-like nuclear features cases. Logistic regression analysis was performed to evaluate association between fine-needle aspiration result and index procedure.

Results. Of the 164 patients with tumors who met neoplasm with papillary-like nuclear features criteria, fine-needle aspiration results were nondiagnostic (2%), benign (18%), atypia/follicular lesion of undetermined significance (26%), follicular neoplasm or suspicious for follicular neoplasm (20%), suspicious for malignancy (19%), malignant (6%), and not obtained (9%). Eighty-five (52%) patients underwent total thyroidectomy. A "suspicious for malignancy" fine-needle aspiration result was associated with undergoing total thyroidectomy versus thyroid lobectomy (P = .006). Thyroid lobectomy was the index procedure for 79 patients (48%); of these patients, 54% (n = 43, 3.2% of all patients with papillary thyroid carcinomas) underwent subsequent total thyroidectomy, and 24% received postoperative radioactive iodine treatment. There were no recurrences among the 125 patients with >3 months of follow-up.

Conclusion. The reclassification of noninvasive encapsulated follicular variant of papillary thyroid cancer as neoplasm with papillary-like nuclear features will decrease nonefficacious treatment and reduce costs. However, the impact of this change with regard to extent of surgery was limited to 3.2% of patients with papillary thyroid carcinomas compared with the projected potential impact on 18.6%. (Surgery 2017;160:XXX-XXX.)

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 >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 >95%,[1] emphasis has been placed on understanding the extent of overdiagnosis in thyroid cancer and weighing the benefits of interventions against undue harm.[2,3] This acknowledgement has led to strategies to mitigate overtreatment.

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The increase in the incidence of thyroid cancer is attributable largely to an increase in the diagnosis of small papillary thyroid carcinomas (PTC)[4,5] and specifically to an increase in diagnosis of a variant of PTC known as the follicular variant of PTC (FVPTC), which comprises >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] Throughout 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 should 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 nonefficacious and potentially harmful treatments and follow-up and to reduce the psychologic burden associated with a cancer diagnosis.[14] It is estimated this reclassification would affect >46,000 patients, or 18.6% of the 250,000 patients diagnosed with papillary PTC worldwide each year,[14] and about 10,000 (15.4%) of the nearly 65,000 thyroid cancer patients per year in the United States.[15]

Theoretically, the reclassification of noninvasive EFVPTC to NIFTP should result in fewer total thyroidectomies because 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 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 because 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 April 2006 to April 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 1,335 cases of PTC, there were 279 cases of EFVPTC; of these, there were 76 cases of infiltrative EFVPTC and 203 cases of noninvasive EFVPTC. Of the 203 cases of noninvasive EFVPTC, 194 cases met established pathologic NIFTP criteria [(1) thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue; (2) follicular growth pattern; (3) unequivocal nuclear changes of PTC; (4) absence of capsular or vascular invasion, and (5) capsule submitted in its entirety]. Tumors with insufficient nuclear changes for the diagnosis of PTC did not receive the diagnosis of noninvasive EFVPTC because they would not have met criterion (3). 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 that met the inclusion criteria were confirmed by an endocrine pathologist (P.M.S.).

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); preoperative FNA diagnosis [as classified by the Bethesda System for Reporting Thyroid Cytopathology FNA as (1) nondiagnostic, (2) benign, (3) follicular lesion or atypia of undetermined significance [FLUS and AUS, respectively], (iv) follicular neoplasm [FN] or suspicious for FN, (5) suspicious for malignancy, and (6) 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 postoperative 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 (ie, on physical examination, neck ultrasound).

Continuous variables were reported as mean ± 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. 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. Statistical analysis was performed using STATA version 12 (STATA Corp., TX).

Results

Cohort characteristics are outlined in Table I. 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

Table I.
Cohort demographics and tumor characteristics

Characteristic	NIFTP ($n = 164$)
Female sex, *n* (%)	130 (79.3)
Age (±SD), y	50 ± 15
Tumor size (±SD), cm	2.0 ± 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)

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