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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Effect of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) on Malignancy Rates in Thyroid Nodules: How to Counsel Patients on Extent of Surgery

Brenessa M. Lindeman, MD, MEHP[1], Matthew A. Nehs, MD[2], Trevor E. Angell, MD[2], Erik K. Alexander, MD[2], Atul A. Gawande, MD, MPH[2], Francis D. Moore Jr., MD[2], Gerard M. Doherty, MD[2], and Nancy L. Cho, MD[2]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]Brigham and Women's Hospital, Boston, MA

ABSTRACT

Purpose. To investigate the impact of the nomenclature change to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) on reported malignancy rates following thyroidectomy.

Methods. Retrospective cohort study of patients with thyroid nodules sampled preoperatively with fine-needle aspiration (FNA) and subsequently removed at one tertiary-care hospital from 4/2016 to 2/2017. Surgical procedure, anatomic pathology, thyroid cytopathology classification, and demographic characteristics were recorded.

Results. Thyroidectomy was performed in 353 patients. Twenty-six patients (7.3%) had NIFTP on anatomic pathology. Preoperative FNA demonstrated atypia of undetermined significance (AUS/Bethesda III) in 13 (50%), suspicious for malignancy (SUS/Bethesda V) in 6 (23%), suspicious for follicular neoplasm (SFN/Bethesda IV) in 4 (15%), benign/Bethesda I in 2 (8%), and malignant/Bethesda VI in 1 (4%). Invasive malignancy rates across cytologic categories changed as follows: benign ($n = 74$) from 4 to 1%, AUS ($n = 85$) from 33 to 18% ($p < 0.05$), SFN ($n = 58$) from 29 to 22%, SUS ($n = 33$) from 91 to 73% ($p < 0.05$), and malignant ($n = 99$) from 99 to 98%. Overall decrease in invasive malignancy was 7.3% for the entire population and 13.1% for indeterminate preoperative FNA cytology (Bethesda III–V). Among 26 NIFTP patients, 17 had thyroid lobectomy (TL) and 9 underwent total thyroidectomy (TT). Eight of the nine patients with TT could have been definitively treated with TL, an 89% decrease.

Conclusions. The NIFTP nomenclature change led to an overall decrease in the malignancy rate at our institution, especially for Bethesda III–V categories. Patients may be counseled toward more conservative surgical options if NIFTP is in the differential.

The incidence of papillary thyroid carcinoma (PTC) has continued to rise steadily over the last several decades with 63,000 new cases diagnosed in 2014 compared with just over 37,000 in 2009, but rates of disease-specific mortality have remained relatively stable over that same period.[1] This has led many experts to speculate about the indolent nature of many of these tumors, particularly the encapsulated, noninvasive follicular variant of papillary thyroid carcinoma (NFVPTC or eFVPTC).[2–4]

Correspondingly, a landmark study was published by Nikiforov et al. in April 2016 that proposed a nomenclature revision for noninvasive follicular variant of papillary thyroid carcinoma, previously considered a malignancy, to now be termed "noninvasive follicular thyroid neoplasm with papillary-like nuclear features," or "NIFTP," which can be treated as an indolent tumor, albeit still with surgical resection.[5] This study defined reliable inclusion criteria for this diagnosis, which falls within a continuum between follicular adenomas (FA) and PTC, having encapsulation like FAs but "papillary-like" nuclear features that might be observed in PTC.

Although the diagnosis of NIFTP can only be made on surgical pathology through histologic evaluation of the entire nodule capsule,[5] a determination about further

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N. L. Cho, MD
e-mail: nlcho@partners.org; nlcho@bwh.harvard.edu

clinical management is routinely made using results of fine-needle aspiration (FNA) biopsy. The Bethesda System for Reporting Thyroid Cytopathology (TBS)[6] provides estimated malignancy rates for cytology results within each category. For indeterminate cytology results associated with a malignancy rate less than 30% (Bethesda III–IV), patients are often counseled to pursue thyroid lobectomy for diagnostic purposes; for cytology results associated with a malignancy rate of 60% or more (Bethesda V–VI), many patients and providers elect up-front total thyroidectomy. While some studies have reported decreased rates of malignancy among noninvasive follicular variant of PTC reclassified as NIFTP[7–9] or prospectively after adoption of the NIFTP definition,[10,11] examination of how surgeons and endocrinologists should counsel patients about the relative risks and benefits of surgery balanced against the possibility of malignancy has not been well defined. This study examines preoperative thyroid nodule FNA cytology diagnoses that were ultimately found to be consistent with NIFTP, as well as the procedure that the patient underwent.

PATIENTS AND METHODS

A retrospective review was conducted of all adult patients at one tertiary-care hospital who underwent either thyroid lobectomy or total thyroidectomy from April 2016 to February 2017, with at least one nodule sampled preoperatively by FNA. All surgical pathology was reviewed by dedicated endocrine pathologists who started including NIFTP as a diagnosis after the April 2016 guidelines were published.[5] Our predictor variables were surgical procedure and Bethesda FNA cytology category.[6] The outcome variables measured were presence of NIFTP and invasive malignancy on surgical pathology.

The majority of FNA specimens were obtained at Brigham and Women's Hospital (BWH) by an attending endocrinologist under ultrasound guidance in our Thyroid Nodule Clinic. Preoperative ultrasound was performed by an attending radiologist using a 5- to 17-MHz transducer. Ultrasound was used to guide the needle tip into the nodule and ensure an accurate specimen. All aspirations were processed using the Thin Prep technique (Hologic, Inc., Marlborough, MA) as previously described.[12] All cases were reviewed by dedicated thyroid pathology subspecialists. All outside cases were reviewed at our institution to confirm cytologic diagnosis. Surgery was performed by one of five endocrine surgeons at the institution (G.M.D., F.D.M, A.A.G, N.L.C., and M.A.N.).

We examined the effect of the nomenclature change (before and after NIFTP definition) on malignancy rates within the same cohort of patients using McNemar's test for paired categorical variables, using Stata 11 (StataCorp, College Station, TX). Significance was defined as $p < 0.05$. The study protocol was approved by the Institutional Review Board by Partners Healthcare.

RESULTS

A total of 427 patients underwent thyroidectomy at our institution between April 2016 and February 2017. Those without a preoperative FNA result were excluded (Graves' disease, symptomatic goiter, large nodules > 4 cm), leaving 353 for the study population. Demographic characteristics of our study population are presented in Table 1, with median patient age of 51 years (interquartile range 40–61 years), nodule size of 1.9 cm (interquartile range 1.1–3.0 cm), and 78% female. Approximately half (49.8%) of the cohort underwent an operation for indeterminate Bethesda FNA cytology. The most common indication for thyroidectomy in the study population was malignant (Bethesda VI) cytology ($n = 99$). Among patients with benign cytology ($n = 74$), the most common indication for surgery was symptomatic nodules.

A total of 26 cases of NIFTP were identified in our study population (7.3%) (Table 2). Though cytology diagnoses were notably diverse throughout the entire cohort, the majority of NIFTP were diagnosed in patients who had atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda III) on FNA cytology ($n = 13$). The next most common FNA cytology associated with NIFTP was the suspicious for malignancy (Bethesda V) group ($n = 6$). For all patients who underwent preoperative FNA sampling, those in the Bethesda V group were most likely to be diagnosed with NIFTP on surgical pathology (18.1%) relative to other Bethesda categories.

TABLE 1 Study population demographic characteristics

Characteristic	Total ($n = 353$)
Age, median (IQR)	51 (40–61) years
Nodule size (IQR)	1.9 (1.1–3.0) cm
Sex (%)	
Female	276 (77.8)
Male	79 (22.3)
Bethesda FNA category (%)	
Benign	74 (21.0)
Atypia of undetermined significance	85 (24.1)
Suspicious for follicular neoplasm	58 (16.4)
Suspicious for malignancy	33 (9.3)
Malignant	99 (28.0)

IQR interquartile range, *FNA* fine-needle aspiration

TABLE 2 NIFTP cases by preoperative FNA cytology category

Bethesda category	Number (n = 26)	% NIFTP by category
Bethesda I: Nondiagnostic	0	0% (0/0)
Bethesda II: Benign	2	2.7% (2/74)
Bethesda III: AUS/FLUS	13	15.3% (13/85)
Bethesda IV: SFN/SHCN	4	6.8% (4/58)
Bethesda V: Suspicious for malignancy	6	18.1% (6/33)
Bethesda VI: Malignant	1	1.0% (1/99)

AUS atypia of undetermined significance, *FLUS* follicular lesion of undetermined significance, *SFN* suspicious for follicular neoplasm, *SHCN* suspicious for Hurthle cell neoplasm

Prior to the April 2016 introduction of NIFTP into the nomenclature, malignant cytology (Bethesda VI) at our institution was nearly 100% concordant with invasive malignancy on surgical pathology; Bethesda V had a similarly high concordance rate of 91%. After application of the revised diagnostic criteria, however, the rate of invasive malignancy on surgical pathology decreased significantly from 91 to 73% in the Bethesda V group and from 33 to 18% in the Bethesda III group ($p < 0.05$ for both) (Fig. 1). Additionally, rates of invasive malignancy decreased from 4 to 1% for benign disease, from 29 to 22% for SFN, and from 99 to 98% for malignant disease. Overall, the invasive malignancy rate dropped 7.3% for the entire study population and 13.1% for patients with indeterminate preoperative FNA cytology (Bethesda III–V).

In our cohort, 212 patients (60%) underwent total thyroidectomy (TT) with nearly half (44%) of these cases performed for malignant FNA cytology (Fig. 2). For patients with indeterminate FNA cytology (Bethesda III–V), 44% underwent TT, including 73% of the Bethesda V group. Patients with benign FNA cytology who received TT did so for symptomatic nodules, multinodular goiter, or enlarging nodules. Among the 26 NIFTP patients, 17 had thyroid lobectomy (TL) and 9 underwent TT. Eight patients with TT for Bethesda category III–VI nodules could have been definitively treated with TL, an 89% decrease.

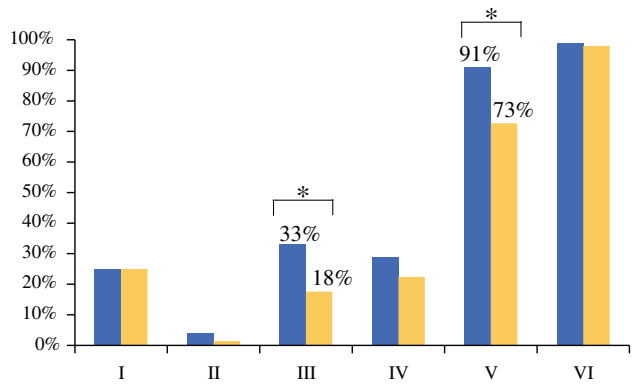

FIG. 1 Change in invasive malignancy rates by Bethesda category before (blue) and after (yellow) implementation of revised NIFTP criteria. Asterisk denotes p value < 0.05

DISCUSSION

Introduction of the term "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" or "NIFTP" decreased the overall rate of invasive thyroid cancers diagnosed on surgical pathology following thyroidectomy in our study population. Our findings are consistent with other studies that have examined change in malignancy rates through reclassification of noninvasive follicular variant of papillary thyroid carcinoma as NIFTP[7–9] and those looking prospectively since the definition of NIFTP.[10,11] Some discussion of this has also been incorporated into the newly published revision of the Bethesda System for Reporting Thyroid Cytopathology in 2017.[13]

No features that decisively differentiate NIFTP from papillary thyroid carcinoma (PTC) or follicular adenoma (FA) have been identified on ultrasound,[14,15] although some features that may be used to distinguish NIFTP on FNA cytology have been recently described.[16,17] As such, the diagnosis of NIFTP must be made on surgical pathology with microscopic examination of the entire nodule capsule.[5] Because of the high rates of malignancy among patients with preoperative Bethesda V FNA cytology, many surgeons have recommended total thyroidectomy up front for these patients. However, this study demonstrates a relatively high rate of NIFTP among patients with indeterminate thyroid nodule FNA results, particularly in the Bethesda V group, which decreased the rate of malignancy among these patients by almost 20%. Taking individual patient preferences, comorbidities, and risk–benefit profiles into account, surgeons could consider performing initial thyroid lobectomy for patients with Bethesda V cytology results, especially when NIFTP features are preoperatively identified on FNA cytology.[16] Consideration for more conservative surgery could also be discussed with patients given the updated guidelines from the American Thyroid

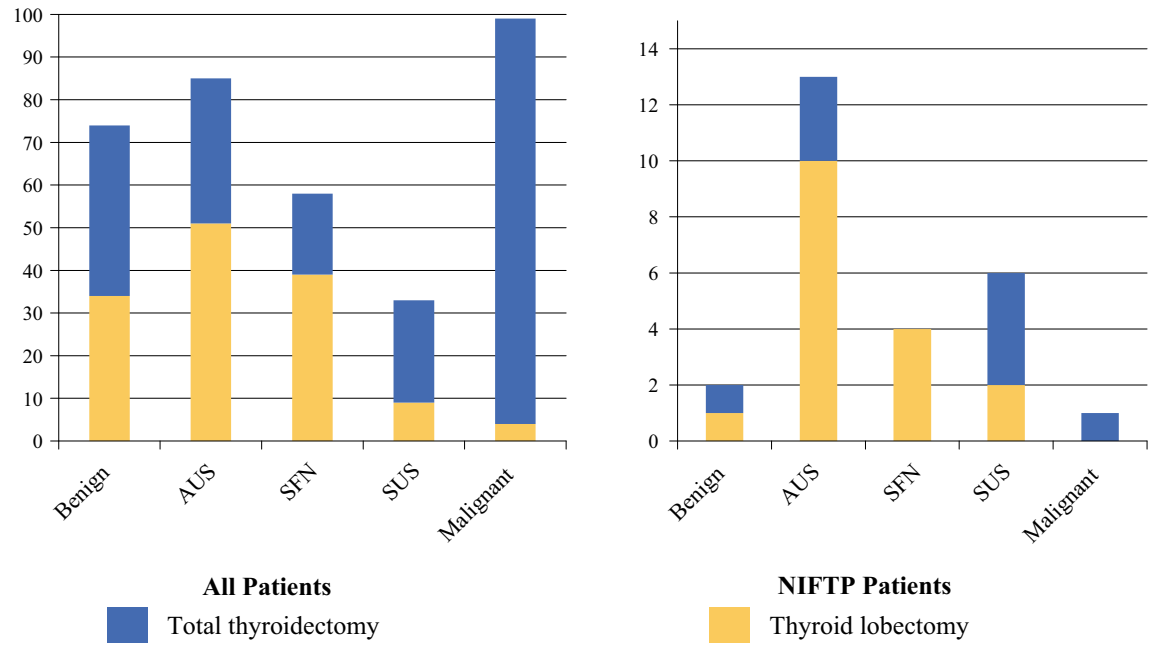

FIG. 2 Extent of surgery for patients undergoing thyroidectomy by FNA category

Association suggesting that thyroid lobectomy alone may be adequate surgery for low-risk carcinomas under 4 cm in size.[18]

Because of the relatively recent introduction of the term NIFTP, ongoing evaluation of all the ways in which this nomenclature change impacts the care of patients with thyroid nodules is warranted. Specifically, examination of the impact on mortality rates of reclassifying a portion of papillary thyroid carcinoma as a very low-risk lesion should be examined, as well as more long-term follow-up of outcomes among patients with NIFTP to lend further validity to the assertion of the neoplasm's indolent behavior.

Our findings should be interpreted in light of our study's limitations. First are those inherent to any retrospective study, including incomplete data capture, bias, and omission of potentially interesting variables. The study was limited to one institution, and the practice patterns of these surgeons and pathologists may or may not be generalizable to other areas; For example, the rates of malignancy for Bethesda III (33%) and V (91%) nodules were higher than generally reported in literature (5–15% and 60–75%, respectively). However, our results are consistent with two separate reports published by pathologists at our institution demonstrating malignancy rates of 39.2% and 87.2% for Bethesda III and V nodules, respectively, over a 22-month period[19] and 27.3% for Bethesda III nodules over a 5-year period.[20] These higher rates of malignancy may reflect selection bias given that the analysis was conducted on a subset of Bethesda III nodules that eventually proceeded to surgery (whether due to clinical or sonographic findings, Afirma results, patient preference, etc.) as opposed to the majority of AUS nodules that are likely benign and treated with surveillance. Taken together, our findings are consistent with those from other authors regarding the impact of NIFTP on rates of malignancy among different categories of thyroid cytopathology, and extend further to suggest that thyroid surgeons could avoid overtreatment by performing thyroid lobectomy for many patients with Bethesda III–V lesions.

CONCLUSIONS

Definition of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" has been shown by this study and others to decrease the rate of invasive carcinoma identified following thyroidectomy. The majority of these lesions were identified in patients with indeterminate preoperative FNA cytology (Bethesda III–V), and surgeons could consider performing an initial diagnostic lobectomy for patients in these groups, especially for smaller lesions or those suggestive of NIFTP on FNA cytology, to avoid overtreatment in patients who are ultimately diagnosed with NIFTP.

DISCLOSURES None.

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