Journal of the American Society of Cytopathology (2019) 8, 1–4

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/

EDITORIAL

How is noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) shaping the way we interpret thyroid cytology?

Received 9 October 2018; received in revised form 13 October 2018; accepted 15 October 2018

Over the past several decades, the term "follicular variant of papillary thyroid carcinoma" (FV-PTC) has encompassed a broad range of thyroid tumors with a follicular growth pattern and the nuclear atypia of papillary carcinoma. FV-PTCs with grossly infiltrative growth into the adjacent thyroid parenchyma (infiltrative FV-PTC) share molecular and clinical similarities to classical papillary thyroid carcinomas (cPTC), demonstrating an association with *BRAF*-like genetic alterations and a predilection for spread to regional lymph nodes.[1-4] In contrast, encapsulated FV-PTCs are well-circumscribed and/or surrounded by a fibrous capsule, driven by *RAS*-like genetic alterations, and can be further risk-stratified based on assessment of invasion: those with capsular or vascular invasion (invasive encapsulated FV-PTC) have increased risk for distant metastasis similar to follicular thyroid carcinomas,[5] whereas noninvasive encapsulated FV-PTC have very low malignant potential, approaching that of follicular adenomas.[4-12]

Until recently, distinguishing FV-PTC from cPTC on preoperative fine-needle aspiration (FNA) cytology specimens—much less identifying any cytologic differences among these FV-PTC subclasses—was not a priority, as they were all treated as cancer. Both histologically and cytologically, nuclear atypia of PTC was emphasized as one of the defining features of malignancy, recognition of which had generally prompted total or near-total thyroidectomy in tumors larger than 1 cm.[13] However, the diagnosis and management of thyroid cancer has become more refined in recent years, with incorporation of more conservative treatment options for carefully selected thyroid tumors with a low risk of metastasis or recurrence.[14-16] The recent introduction of the term "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) to replace "noninvasive encapsulated FV-PTC" follows in the same vein.[9,17] By substituting the word “neoplasm” for “carcinoma”, the NIFTP terminology conveys its indolent clinical behavior and encourages a more measured treatment approach. Lobectomy is required for diagnosis and is considered adequate treatment for NIFTP, without the need for completion thyroidectomy or adjuvant radioactive iodine therapy.

In the 2.5 years since publication of the seminal study proposing the NIFTP nomenclature change,[9] many authors have examined its implications on thyroid cytology. The studies by Legesse et al[18] and Zhang et al[19] in this issue of the Journal represent 2 recent efforts in this regard. Collectively, these and other retrospective studies have largely focused on two related topics: (1) the cytomorphologic features of NIFTP and (2) the impact of the NIFTP reclassification on cancer-risk estimates associated with each of the interpretive categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Does NIFTP have distinctive features on FNA cytology?:

Because of the implicit changes in treatment associated with the NIFTP reclassification, early cytomorphologic studies examined whether FNA cytology could distinguish NIFTP from its malignant counterparts. From a cytoarchitectural standpoint, aspirates of NIFTP produce a predominantly microfollicular pattern, in contrast with the papillary groups and crowded monolayers seen in aspirates of cPTC. Aspirates of NIFTP also demonstrate milder degrees of nuclear atypia compared with that of cPTC.[20-22] Specifically, intranuclear inclusions, which represent a severe form of nuclear contour irregularity, are characteristic of cPTC but rare or absent in most aspirates of NIFTP.[21] The

E-mail address: mnishin1@bidmc.harvard.edu.

https://doi.org/10.1016/j.jasc.2018.10.002

analysis by Legesse et al and Zhang et al echo these findings.

For studies that evaluate whether NIFTP can be cytologically distinguished from FV-PTC, the results appear to be mixed. Most authors report that cytologic features cannot reliably separate NIFTP from FV-PTC.[1,3,22-24] Similar to the follicular adenoma/carcinoma distinction, the diagnosis of NIFTP is based on the histologic exclusion of invasive growth. Invasion takes different forms for FV-PTC, however, and the distinction between infiltrative FV-PTC and invasive encapsulated FV-PTC is not consistently made in cytology studies. Predominance of infiltrative FV-PTC and possibly even cPTC among study samples likely accounts for some of the reported cytologic differences between NIFTP and FV-PTC.[25] As a case in point, Legesse et al report that the presence of irregular branching sheets and linear arrangement of tumor cells on direct smears favors "invasive FV-PTC" over NIFTP. However, both of these cytoarchitectural features are thought to be correlates of papillary architecture, suggesting that cPTCs with predominantly follicular architecture may be included among their cases of invasive FV-PTC.

Altogether, these studies suggest that FNA cytology can potentially distinguish NIFTP from many cases of cPTC (and possibly some cases of infiltrative FV-PTC), but not from invasive encapsulated FV-PTC. These cytomorphologic studies reinforce the concept that thyroid nodules with exclusively microfollicular architecture on FNAs, including those with moderate levels of nuclear atypia, often rely on ancillary molecular testing and/or subsequent resection for further classification. In keeping with these observations, aspirates of NIFTP have been predominantly classified in one of the indeterminate categories of TBSRTC: atypia/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), or suspicious for malignancy (SUS).[3,24,26-40] Table 1 summarizes the distribution of NIFTP among TBSRTC categories in published studies to date.

The proportion of NIFTPs that have been classified as malignant on FNA cytology has been small, constituting approximately 8% of NIFTPs among published series (Table 1). To the extent that a malignant FNA diagnosis for NIFTP can be considered an overdiagnosis, some authors have advocated for strict cytologic criteria for malignancy. For aspirates with the nuclear atypia of PTC, Krane et al recommend limiting the cytologic diagnosis of malignancy to those with features of classical or tall-cell variant PTC, recognized by the presence of papillary architecture, psammoma bodies, or frequent intranuclear pseudoinclusions.[41] These strategies aim to amplify the cytologic separation of cPTC from NIFTP on FNA specimens, during the stage when different surgical approaches are still routinely advocated for these tumors (ie, total thyroidectomy for cPTC, lobectomy for NIFTP). If the emerging trend towards lobectomy as the initial surgical approach for clinically low-risk thyroid cancer achieves wider support,[16] it is possible that the need to distinguish

Table 1 Cytologic classification of NIFTP among the diagnostic categories of The Bethesda System for Reporting Thyroid Cytopathology in published studies.

Study	NIFTP (n)	Number of NIFTP in each TBSRTC category					
		NonDx	Benign	AUS/FLUS	FN/SFN	SUS	Malignant
Bychkov et al, 2018 (India)[a,26]	15	0	0	6	9	0	0
Bychkov et al, 2018 (Japan)[a,26]	9	2	1	0	4	1	1
Bychkov et al, 2018 (Korea-1)[a,26]	6	0	1	3	0	2	0
Bychkov et al, 2018 (Korea-2)[a,26]	6	0	0	1	1	2	2
Bychkov et al, 2018 (Taiwan)[a,26]	11	1	3	3	3	1	0
Bychkov et al, 2018 (Thailand)[a,26]	12	3	6	0	2	1	0
Canberk et al, 2016[27]	94	13	15	14	23	17	12
Faquin et al, 2016[28]	173	1	15	54	46	42	15
Glass et al, 2016[29]	37	0	2	13	15	6	1
Kiernan et al, 2018[30]	17	0	1	5	2	7	2
Kim et al, 2018[31]	25	1	5	14	2	3	0
Lastra et al, 2018[32]	119	1	7	51	37	19	4
Lau et al, 2018	87	0	5	35	24	15	8
Layfield et al, 2017[34]	16	0	2	2	2	5	5
Legesse et al (current issue)[18]	35	0	11	12	3	4	5
Li et al, 2018[35]	17	0	3	8	4	1	1
Maletta et al, 2016[24]	96	0	0	14	54	26	2
Ohori et al, 2017[b,36]	11	.	.	.	.	10	1
Pusztaszeri et al, 2017[37]	62	4	7	5	15	27	4
Rosario et al, 2016[38]	126	1	10	25	53	32	5
Strickland et al, 2015[39]	85	1	13	17	7	39	8
Zhang et al, (current issue)[19]	55	0	3	5	34	10	3
Zhao et al, 2017[3]	50	3	2	14	13	9	9
Zhou et al, 2018 (Institution A)[a,40]	68	0	3	20	26	15	4
Zhou et al, 2018 (Institution B)[a,40]	69	0	6	26	16	14	7
Zhou et al, 2018 (Institution C)[a,40]	10	0	0	5	4	0	1
TOTAL	1311	31	121	352	399	308	100
% (of NIFTP)[c]		2%	9%	27%	30%	23%	8%

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda-III); FN/SFN, follicular neoplasm/suspicious for follicular neoplasm (Bethesda-IV); NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; NonDx, nondiagnostic (Bethesda-I); SUS, suspicious for malignancy (Bethesda-V); TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.

[a]Data for each institution are listed separately for multi-institutional studies that provided this information.

[b]This study included analysis of only SUS and malignant cases.

[c]Percentages represent the sum of NIFTPs in each Bethesda category divided by the total number of NIFTPs in this analysis (n = 1311).

these tumors on FNA cytology will be mitigated once again.

How has NIFTP changed estimates of cancer risk associated with TBSRTC categories?:

One of the central features of TBSRTC is its stratification of cytomorphology-based categories by approximate risk of malignancy (ROM), which in turn helps guide management options for thyroid nodules after the FNA. ROM calculations reflect the prevalence of histologically proven cancer among nodules classified in each TBSRTC category. Accordingly, changing the histologic classification of a tumor from a cancer (noninvasive encapsulated FV-PTC) to a premalignant neoplasm (NIFTP) reduces the ROM estimates of TBSRTC categories, particularly for the 3 indeterminate categories to which NIFTP aspirates are most often classified.

For aspirates classified as AUS/FLUS or FN/SFN, the decrease in ROM brought about by the NIFTP reclassification may have only a negligible effect on existing management recommendations. Repeat FNA (for AUS/FLUS) and/or ancillary molecular testing (for AUS/FLUS and FN/SFN) continue to be common management options following FNA in the NIFTP era. When surgery is considered for solitary nodules in these lower-risk indeterminate TBSRTC categories, diagnostic lobectomy is generally recommended.[16] This conservative surgical approach is compatible with current treatment recommendations for NIFTP.

Historically, both lobectomy and total thyroidectomy have been recommended for nodules following a SUS interpretation on FNA biopsy, based on a 60% to 75% ROM.[13,42] The NIFTP reclassification and the ensuing decrease in ROM (45% to 60%) for the SUS category may ultimately shift the balance towards diagnostic lobectomy as the preferred surgical procedure for this category, especially for cases with low-risk clinical, molecular, and sonographic features (eg, intrathyroidal tumors smaller than 4 cm with no evidence of nodal metastasis) and/or the cytologic features suggestive of NIFTP or FVPTC.

The NIFTP reclassification is a part of a broader effort to promote treatment for thyroid tumors that is commensurate with its risk of recurrence and metastasis. For thyroid FNAs that demonstrate nuclear atypia, recognition and reporting of cytologic features that point towards NIFTP—together with the adjustment in ROM for the indeterminate TBSRTC categories—may help curb the rate of total thyroidectomy for cases where lobectomy may suffice. At the same time, these studies serve as a reminder that a nodule's TBSRTC category is just one of many factors that influence treatment decisions after FNA. In this age of personalized medicine, integration of cytologic, molecular, and clinical features (the latter of which includes nodule size, sonographic features, presence of nodules in the opposite lobe, clinical risk factors, patient comorbidities) is expected play a growing role in informing clinical judgment and patient preferences for treatment.

Michiya Nishino, MD, PhD*
Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Harvard Medical School, Boston, Massachusetts

* Corresponding author: Michiya Nishino, MD, PhD, Department of Pathology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215; Tel.: (617) 667-5731; Fax: (617) 667-7120.

References

1. Kim TH, Lee M, Kwon AY, et al. Molecular genotyping of the noninvasive encapsulated follicular variant of papillary thyroid carcinoma. *Histopathology*. 2018;72:648−661.
2. Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct Braf and Ras mutation patterns. *Mod Pathol*. 2010;23:1191−1200.
3. Zhao L, Dias-Santagata D, Sadow PM, Faquin WC. Cytological, molecular, and clinical features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features versus invasive forms of follicular variant of papillary thyroid carcinoma. *Cancer Cytopathol*. 2017;125:323−331.
4. Finnerty BM, Kleiman DA, Scognamiglio T, et al. Navigating the management of follicular variant papillary thyroid carcinoma subtypes: a classic PTC comparison. *Ann Surg Oncol*. 2015;22:1200−1206.
5. Ganly I, Wang L, Tuttle RM, et al. Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant. *Hum Pathol*. 2015;46:657−664.
6. Gupta S, Ajise O, Dultz L, et al. Follicular variant of papillary thyroid cancer: encapsulated, nonencapsulated, and diffuse: distinct biologic and clinical entities. *Arch Otolaryngol Head Neck Surg*. 2012;138:227−233.
7. Howitt BE, Jia Y, Sholl LM, Barletta JA. Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma. *Thyroid*. 2013;23:1256−1262.
8. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. *Cancer*. 2006;107:1255−1264.
9. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol*. 2016;2:1023−1029.
10. Rivera M, Tuttle RM, Patel S, Shaha A, Shah JP, Ghossein RA. Encapsulated papillary thyroid carcinoma: a clinico-pathologic study of 106 cases with emphasis on its morphologic subtypes (histologic growth pattern). *Thyroid*. 2009;19:119−127.
11. Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. *Mod Pathol*. 2016;29:698−707.
12. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. *Thyroid*. 2013;23:273−279.
13. American Thyroid Association Guidelines Taskforce on Thyroid Nodules, Differentiated Thyroid CancerCooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167−1214.
14. Vaisman F, Momesso D, Bulzico DA, et al. Thyroid lobectomy is associated with excellent clinical outcomes in properly selected

differentiated thyroid cancer patients with primary tumors greater than 1 cm. *J Thyroid Res*. 2013;2013:398194.
15. Matsuzu K, Sugino K, Masudo K, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. *World J Surg*. 2014;38:68−79.
16. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26:1−133.
17. Seethala RR, Baloch ZW, Barletta JA, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a review for pathologists. *Mod Pathol*. 2018;31:39−55.
18. Legesse T, Parker L, Heath J, Staats PN. Distinguishing non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) from classic and invasive follicular-variant papillary thyroid carcinomas based on cytologic features. *J Am Soc Cytopathol*. 2018;1.
19. Zhang Z, Chhieng D, Harshan M, Zheng X, Zakowski M. Cytological features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). *J Am Soc Cytopathol*. 2018;1.
20. Howitt BE, Chang S, Eszlinger M, et al. Fine-needle aspiration diagnoses of noninvasive follicular variant of papillary thyroid carcinoma. *Am J Clin Pathol*. 2015;144:850−857.
21. Mito JK, Alexander EK, Angell TE, et al. A modified reporting approach for thyroid FNA in the NIFTP era: a 1-year institutional experience. *Cancer Cytopathol*. 2017;125:854−864.
22. Strickland KC, Vivero M, Jo VY, et al. Preoperative cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a prospective analysis. *Thyroid*. 2016;26:1466−1471.
23. Brandler TC, Zhou F, Liu CZ, et al. Can noninvasive follicular thyroid neoplasm with papillary-like nuclear features be distinguished from classic papillary thyroid carcinoma and follicular adenomas by fine-needle aspiration? *Cancer Cytopathol*. 2017;125:378−388.
24. Maletta F, Massa F, Torregrossa L, et al. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. *Hum Pathol*. 2016;54:134−142.
25. Ibrahim AA, Wu HH. Fine-needle aspiration cytology of noninvasive follicular variant of papillary thyroid carcinoma is cytomorphologically distinct from the invasive counterpart. *Am J Clin Pathol*. 2016;146:373−377.
26. Bychkov A, Keelawat S, Agarwal S, et al. Impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on The Bethesda System for Reporting Thyroid Cytopathology: a multi-institutional study in five Asian Countries. *Pathology*. 2018;50:411−417.
27. Canberk S, Gunes P, Onenerk M, et al. New concept of the encapsulated follicular variant of papillary thyroid carcinoma and its impact on the Bethesda system for reporting thyroid cytopathology: a single-institute experience. *Acta Cytol*. 2016;60:198−204.
28. Faquin WC, Wong LQ, Afrogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in the Bethesda system for reporting thyroid cytopathology. *Cancer Cytopathol*. 2016;124:181−187.
29. Glass R, Kahn L, Khalid K, Siddiqui MT, Cocker R. Predicting histological subtypes of follicular variant of papillary thyroid carcinoma based on cytomorphology. Can cytomorphology optimize use of molecular testing? *J Am Soc Cytopathol*. 2016;5:345−350.
30. Kiernan CM, Weiss VL, Mehrad M, Ely K, Baregamian N, Solorzano CC. New terminology-noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP) and its effect on the rate of malignancy at a single institution. *Surgery*. 2018;163:55−59.
31. Kim M, Kim JE, Kim HJ, Chung YR, Kwak Y, Park SY. Cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and its impact on the risk of malignancy in The Bethesda System for Reporting Thyroid Cytopathology: an institutional experience. *J Pathol Transl Med*. 2018;52:171−178.
32. Lastra RR, Birdsong G, Hwang DH, et al. Preoperative cytologic interpretation of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a 1-year multi-institutional experience. *J Am Soc Cytopathol*. 2018;7:79−85.
33. Lau RP, Paulsen JD, Brandler TC, Liu CZ, Simsir A, Zhou F. Impact of the reclassification of "noninvasive encapsulated follicular variant of papillary thyroid carcinoma" to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" on The Bethesda System for Reporting Thyroid Cytopathology: a large academic institution's experience. *Am J Clin Pathol*. 2017;149:50−54.
34. Layfield LJ, Baloch ZW, Esebua M, Kannuswamy R, Schmidt RL. Impact of the reclassification of the non-invasive follicular variant of papillary carcinoma as benign on the malignancy risk of The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis study. *Acta Cytol*. 2017;61:187−193.
35. Li W, Sciallis A, Lew M, Pang J, Jing X. Implementing noninvasive follicular thyroid neoplasm with papillary-like nuclear features may potentially impact the risk of malignancy for thyroid nodules categorized as AUS/FLUS and FN/SFN. *Diagn Cytopathol*. 2018;46:148−153.
36. Ohori NP, Wolfe J, Carty SE, et al. The influence of the noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) resection diagnosis on the false-positive thyroid cytology rate relates to quality assurance thresholds and the application of NIFTP criteria. *Cancer Cytopathol*. 2017;125:692−700.
37. Pusztaszeri M, Auger M. Update on the cytologic features of papillary thyroid carcinoma variants. *Diagn Cytopathol*. 2017;45:714−730.
38. Rosario PW, Mourao GF, Nunes MB, Nunes MS, Calsolari MR. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Endocr Relat Cancer*. 2016;23:893−897.
39. Strickland KC, Howitt BE, Marqusee E, et al. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. *Thyroid*. 2015;25:987−992.
40. Zhou H, Baloch ZW, Nayar R, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): implications for the risk of malignancy (ROM) in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). *Cancer Cytopathol*. 2018;126:20−26.
41. Krane JF, Alexander EK, Cibas ES, Barletta JA. Coming to terms with NIFTP: a provisional approach for cytologists. *Cancer Cytopathol*. 2016;124:767−772.
42. Burch HB, Burman KD, Cooper DS, Hennessey JV, Vietor NO. A 2015 survey of clinical practice patterns in the management of thyroid nodules. *J Clin Endocrinol Metab*. 2016;101:2853−2862.