Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features in the Pediatric Age Group

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BACKGROUND: The most common malignant thyroid neoplasm in children is papillary thyroid carcinoma (PTC). In 2015, the Endocrine Pathology Society introduced the terminology "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) to replace the noninvasive follicular variant of PTC. The objective of the current study was to evaluate previously diagnosed PTC in the pediatric population, reappraise it for NIFTP, and discuss the impact of NIFTP on the risk of malignancy (ROM) for each The Bethesda System for Reporting Thyroid Cytopathology category in the pediatric population. **METHODS:** The electronic databases of both study institutions were searched for all thyroidectomy specimens in patients aged <19 years from June 1, 2001 through June 1, 2016. The patient's age, sex, diagnosis, previous fine-needle aspiration cytology diagnosis, and follow-up were tabulated. Slides for available cases were reviewed and cases qualifying as NIFTP were separated. **RESULTS:** The cohort included 101 resected nodules; cytological diagnoses were available for 95 cases. These cases included diagnoses of nondiagnostic (5 cases; 5.2%), benign (21 cases; 22.1%), atypia/follicular lesion of undetermined significance (9 cases; 9.5%), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) (25 cases; 26.3%), suspicious for malignancy (7 cases; 7.4%), and malignant (28 cases; 29.5%). On the histological follow-up, 50 cases (49.5%) were benign, 49 cases (48.5%) were malignant, and 2 cases (1.9%) were NIFTP. These NIFTP cases originally were diagnosed as FNs on fine-needle aspiration cytology. The average ROM for FNs with and without NIFTPs was 28% and 25%, respectively **CONCLUSIONS:** According to our rate of 1.9% for NIFTPs on reappraisal for resected nodules, this entity is likely to be less frequent in the pediatric population due to the higher prevalence of PTCs and/or more aggressive variants. NIFTPs do not appear to affect the ROM for The Bethesda System for Reporting Thyroid Cytopathology categories in the pediatric population. However, large-scale studies are necessary to determine whether NIFTPs could affect the pediatric population. ***Cancer Cytopathol* 2018;126:27-35.** *© 2017 American Cancer Society.*

KEY WORDS: *BRAF* mutation; noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); noninvasive follicular variant of papillary thyroid carcinoma; pediatric thyroid lesions; thyroid carcinoma.

INTRODUCTION

It is well known that well-differentiated carcinoma of the thyroid and specifically papillary thyroid carcinoma (PTC) and its variants are among the most common endocrine malignancies in both adult and pediatric patients.[1–14] Several publications have demonstrated that thyroid lesions in childhood have a 1.6-fold higher

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cancer risk compared with those noted in adulthood.[4–6] According to the data from the World Health Organization, PTC accounts for approximately 90% of all cancers, and for the most part are diagnosed as the classic variant of PTC, especially in children aged >12 years. However, in these last decades, several authors have demonstrated that the follicular variant of PTC (FVPC) includes both encapsulated/noninvasive (NI-FVPCs) and invasive FVPCs (I-FVPCs), which have a different prognosis and molecular findings.[15–34] In fact, several publications concluded that I-FVPCs are associated with more aggressive features characterized by lymph node metastases, disease recurrence, and the prevalence of genetic alterations whereas NI-FVPCs, which encompass 50% to 70% of FVPCs, have a less aggressive outcome.[24]

In 2015, the Endocrine Pathology Society introduced the term "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) to replace NI-FVPC. Not only did the introduction of this entity with a set of specific morphological features impact on histology, but it also involved both the cytological diagnosis and the categories of thyroid lesions.[24] Since then, the majority of published articles regarding NIFTPs have included series of thyroid lesions in adulthood.[15–34] To the best of our knowledge, the incidence of NIFTPs in pediatric patients is not exactly known. Nonetheless, it stands to reason that, especially in a pediatric population, the correct management and treatment rely on an accurate cytological diagnosis. Given that, the evaluation of the allocation of NIFTPs in the different cytological categories and the impact on the risk of malignancy (ROM) in the different diagnostic categories is crucial for specifying some diagnostic criteria that would lead to appropriate management. In this context, the application of the criteria used for identifying NIFTPs in adult thyroid lesions should be adopted for pediatric thyroid nodules.

In this retrospective study, including 2 different institutions, the objective was to evaluate the previously diagnosed PTCs in our pediatric cohorts. Herein, we report the potential impact of a NIFTP diagnosis on the associated ROM for each category of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

MATERIALS AND METHODS

A retrospective, computerized search of all thyroid fine-needle aspiration cytology (FNAC) cases recorded between January 2001 and December 2016 at the Agostino Gemelli Hospital of Catholic University in Rome (CU) and at the Loyola University Medical Center (LUMC) in Chicago was performed. A subset of the CU cases also were discussed in a previous publication.[11] The institutional electronic medical record systems (Sunquest CoPathPlus [version 6.0; Sunquest Information Systems Inc, Tucson, Arizona] at LUMC and Armonia-Metafora [Metafora, Rome, Italy] at CU) were searched for thyroidectomy specimens in the pediatric age group (aged < 19 years). The patient's age, sex, diagnosis, previous FNAC diagnosis, and follow-up information were tabulated. All available thyroidectomy slides were reviewed. In both institutions, the majority of nodules were evaluated and biopsied under ultrasound guidance by clinicians and radiologists. All FNAC specimens from CU were processed with liquid-based cytology (LBC) using ThinPrep 5000 processing (Hologic Inc, Marlborough, Massachusetts) and Papanicolaou staining, whereas at LUMC, they were processed through the standard smear and respective staining methods (air-dried Diff-Quik smears, alcohol-fixed Papanicolaou-stained smears). In addition, LBC was performed if the initial evaluation indicated low cellularity.

All FNAs (2 to 4 passes for each lesion) were performed with 25-gauge to 27-gauge needles at both institutions. The cases from CU were collected using 2 passes without rapid on-site evaluation for LBC. At LUMC, rapid on-site evaluation is performed on all pediatric thyroid FNAC specimens that are obtained by radiologists.

At both institutions, the parents of the patients had been appropriately informed regarding the procedure and written informed consent was provided by them. The study was independently evaluated and approved by the institutional review boards of both institutions. All details regarding the LBC method and ancillary techniques have been described in our previous articles.[11,12,14,35–37]

The adequacy was reported accordingly to the classification system of the UK Royal College of Pathologists and Gollner parameter; the lower limit for the adequacy for each sample was established in 6 groups of thyroid follicular epithelial cells within the submitted slide and each of these groups had at least 10 well-visualized epithelial cells.[38]

Specifically, the cytological cases in the reference period were revised and all were classified according to TBSRTC.[39] As reported in TBSRTC, the categories are defined as follows: nondiagnostic (ND), which includes inadequate and cystic-hemorrhagic lesions; benign lesions

(BLs), which include benign follicular nodules, lymphocytic thyroiditis, etc; atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); follicular neoplasm (FN); suspicious for malignancy (SM); and positive for malignancy (PM).

In the 2 institutions, all cytological and histological sections were evaluated by cytopathologists and pathologists with experience in diagnosing thyroid pathology. Those cases in which the interpretation was equivocal were submitted to the diagnostic judgment of the other pathologists until a final agreement was achieved.

Molecular Analysis

Molecular analysis was only performed for 73 of the 95 cases from CU.

DNA was extracted from LBC samples stored in PreservCyt solution (Hologic Inc) and from paraffin-embedded tissues. LBC samples were centrifuged and the supernatant fluid was discarded and the cellular pellet processed. The pellet was incubated at 56 °C for 3 hours in 180 µL of ATL lysis buffer and 20 µL of proteinase K (20 mg/mL) from the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). For histological samples, 10 µm of slide tissue was deparaffinized and, after ethanol treatment, was incubated at 56 °C overnight in 180 µL of ATL lysis buffer and 20 µL of proteinase K (20 mg/mL) from the QIAamp DNA mini kit (Qiagen). DNA was extracted following the manufacturer's protocol, and we spectrophotometrically assessed the quantity and quality of the DNA (A260, A260/280 ratio, spectrum 220-320 nm; Biochrom, Cambridge, UK) and by separation on an Agilent 2100 Bioanalyzer (Aligent, Santa Clara, California). Low purity or insufficient DNA samples were extracted a second time. After a first amplification on a Rotor-Gene Q polymerase chain reaction cycler (Qiagen), the mutational analysis of BRAF was achieved using Anti-EGFR MoAb Response (BRAF status) kit (Diatech Pharmacogenetics, Diatech Pharmacogenetics srl, Jesi, Italy) by pyrosequencing via the PyroMark Q96 ID system (Qiagen). The sensitivity of this method was found to be 5% in the CU laboratory.[40] The exon 15: ACAGT/AGAAA sequence was analyzed. The percentage of disease-specific cells for molecular analysis was at least 50% in all LBC samples.

Histology

All surgical specimens were fixed in 10% buffered formaldehyde and embedded in paraffin. The 5-µm-thick sections were stained with hematoxylin and eosin. All tumors were submitted entirely for microscopic examination. The perithyroid adipose tissue, if present, was submitted and examined for lymph node research. The diagnosis of PTC was based on the presence of true papillary structures and distinctive nuclear features, whereas the diagnosis of FVPC relied on the detection of entire follicular architecture and the nuclear features of PTC in multiple foci. Encapsulated tumors with either lymphovascular invasion (within the capsule or beyond) or capsular penetration were diagnosed as invasive FVPCs. All cases were classified according to the seventh edition of the American Joint Committee Cancer TNM staging system.[41] The histological diagnosis of NIFTP was rendered according to the criteria described in the recent article by Nikiforov et al.[24] However, in the study institutions, the NIFTP terminology was used for FNs without any overt papillary structures. The diagnosis of follicular adenoma (FA) was based on evidence of a capsulated nodular lesion with typical follicular cells.

Statistical Analysis

Descriptive statistical analysis (including sex, age, laterality, size of the nodule, type of surgery, and histologic diagnosis) was performed using a commercially available statistical software package (SPSS version 23.0; IBM Corporation, Armonk, New York) for Windows (Microsoft Corporation, Redmond, Washington). The histological diagnoses were considered to be the gold standard for the statistical analysis. Comparison of categorical variables was performed using the Z Test Calculator for 2 population percentages using a 2-tailed hypothesis test. A $P < .05$ was considered statistically significant.

RESULTS

The study cohort included 101 surgical cases (73 from CU and 28 from LUMC) and corresponding cases with cytological samples (73 from CU and 22 from LUMC) obtained between January 2001 and December 2016. The entire series included 83 female and 18 male patients with ages ranging from 9 to 18 years (mean, 15 years). For the reference period, the entire pediatric cytological series (100 cases from CU and 80 cases from LUMC) included the following distribution of thyroid diagnoses: 2.8% were ND (ND plus cystic cases), 60.5% were BLs, 4.8% were AUS/FLUS, 12.5% were FN/SFN, 5.7% were SM, and

TABLE 1. Clinicopathological Features in the Current Series

Clinical features	Goiter	FA	NIFTP	I-FVPC	PTC	FC/PDC	MTC
Sex							
Male	2	8	1	0	7	0/0	0
Female	11	30	1	5	30	4/1	1
Nodule size, cm							
<2	6	25	1	3	21	3	1
>2	7	12	1	2	16	2	0
Cytology (BSRTC)[a]							
Inadequate/cystic (5 cases)	2	3	0	0	0	0	0
Benign (21 cases)	8	12	0	0	1	0/0	0
AUS-FLUS (9 cases)	1	7	0	0	0	1/0	0
FN-OFN (25 cases)	1	17	2	1	1	2/1	0
SM (7cases)	0	0	0	3	4	0/0	0
PM (28 cases)	0	0	0	1	26	0/0	1
T classification							
I-II	0	0	0	4	32	3/0	1
III-IV	0	0	0	1	5	1/1	0
N classification							
N0	-	-	2	4	13	4/0	0
N1	-	-	0	1	14	0/1	1
BRAF[b]							
V600E mutation	0	0	0	0	4	0	0
Wild-type	7	37	2	5	15	2	1

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; BSRTC, Bethesda System for Reporting Thyroid Cytopathology; FA, follicular adenoma; FC/PDC, follicular carcinoma/poorly differentiated carcinoma; FN/OFN, follicular neoplasms/oncocytic follicular neoplasms; I-FVPC, invasive follicular variant of papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PM, positive for malignancy; PTC, papillary thyroid carcinoma; SM, suspicious for malignancy.
[a] Cytology was available for 95 of 101 cases.
[b] *BRAF V600E* mutation was performed on the 73 cases from the Catholic University.

13.7% were PM. The size of the lesions ranged from 0.4 cm to 6.0 cm in greatest dimension. All subcentimeter lesions were discovered during radiologic screening for causes unrelated to the thyroid glands. There was no significant difference in the size observed among the diagnostic entities.

The clinicopathologic data, including the cytological diagnoses, are summarized in Table 1.

Histologic diagnoses were rendered as benign in 49.5% of cases and malignant in 48.5% of cases with the exclusion of 1.9% of NIFTP cases (Table 2). The surgical pathology follow-up of the 50 BLs included goiter (8 cases), Graves' disease (2 cases), hyperplastic oncocytic nodules in Hashimoto thyroiditis (3 cases), FA (35 cases), and Hurthle cell adenoma (2 cases). The 51 cases with malignant histological diagnoses included 37 PTC cases, 5 I-FVPC cases, 2 NI-FVPC (NIFTPs) cases, 5 follicular carcinomas (FC) cases, 1 medullary thyroid carcinoma case, and 1 poorly differentiated carcinoma case. Specifically, the 37 PTC cases included 30 classic variant, 2 solid variant, 3 diffuse sclerosing variant, 1 macrofollicular variant, and 1 columnar variant. Table 3 outlines the distribution of the histological variants of PTC among the cytological categories diagnosed according to TBSRTC.

We also evaluated the different cytological categories for these 95 cases including 5 ND cases (5.2%), 21 BLs (22.1%), 9 AUS-FLUS cases (9.5%), 25 FN cases (26.3%), 7 SM cases (7.4%), and 28 PM cases (29.5%); the cytohistological correlation of the 95 cases is depicted in Table 2. The 5 ND cases included 2 goiters and 3 hyperplastic adenomas with Hashimoto thyroiditis, whereas the 21 BLs with surgical pathology follow-up included 8 goiters, 12 FAs, and 1 classic variant of PTC. The 9 AUS/FLUS cases were 1 goiter, 7 FAs, and 1 FC. The 25 FNs were subclassified as 20 FNs and 5 oncocytic FNs (OFN). The former included 1 hyperplastic oncocytic nodule, 10 FAs, 2 OFNs, 2 NIFTPs (Figs. 1 and 2), 1 I-FVPC, 1 macrofollicular variant of PTC, 2 FCs, and 1 poorly differentiated carcinoma. The 5 OFN cases were 3 FAs and 2 OFNs. Seven cases diagnosed as SM underwent surgical resection; all of them had malignant follow-up, including 3 I-FVPCs, 2 classic variant of PTC, 1 diffuse sclerosing variant of PTC, and 1 columnar variant of PTC. Surgical pathology follow-up was available for 28 cases classified as PM on FNAC; all were found to be malignant. The most frequent malignant diagnoses were classic variant of PTC (22 cases), solid variant of PTC (2 cases), diffuse sclerosing variant of PTC (2 cases), 1 case of I-FVPC, and medullary

TABLE 2. Cytohistological Correlation of 95 Thyroid FNAC Specimens at 2 Institutions

	Benign Histology Follow-Up (CU/LUMC)	Malignant Histology Follow-Up (CU/LUMC)
Total FNAC (95 cases)	51 (46/5)	44 (28/16)
Inadequate FNAC (5 cases)	5 (5/0)	0 (0/0)
Benign FNAC (21 cases)[a]	20 (16/4)	1 (0/1)
Goiter	17 (13/4)	1 (0/1)
Hyperplastic nodules	3 (3/0)	0 (0/0)
Indeterminate lesions (41 cases)	26 (25/1)	15 (13/2)
AUS/FLUS (9 cases)	8 (8/0)	1 (1/0)
FN/OFN (25 cases)[a]	18 (17/1)	7 (5[a]/2)
SM (7 cases)	0 (0/0)	7 (7/0)
Malignant (28 cases)	0 (0/0)	28 (15/13)

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; CU/LUMC, Catholic University (Rome)/Loyola University Medical Center (Chicago); FN/OFN, follicular neoplasms/oncocytic follicular neoplasms; FNAC, fine-needle aspiration cytology; SM, suspicious for malignancy.
[a] The 2 cases of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) were included in the malignant FNs.

TABLE 3. Distribution of the Histological Variants of PTC Among the Cytological Categories Diagnosed According to The BSRTC

Histology Cytology	CPTC	I-FVPC	DSPTC	Col-PTC	MPTC	SPTC
ND	0	0	0	0	0	0
BL	1	0	0	0	0	0
AUS/FLUS	0	0	0	0	0	0
FN/OFN	0	1	0	0	1	0
SM	2	3	1	1	0	0
PM	22	1	2	0	0	2

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; BL, benign lesion; BSRTC, Bethesda System For Reporting Thyroid Cytopathology; Col-PTC, columnar variant of papillary thyroid carcinoma; CPTC, classic variant of papillary thyroid carcinoma; DSPTC, diffuse sclerosing variant of papillary thyroid carcinoma; FN/OFN, follicular neoplasms/oncocytic follicular neoplasms; I-FVPC, infiltrative follicular variant of papillary thyroid carcinoma; MPTC, macrofollicular variant of papillary thyroid carcinoma; ND, nondiagnostic; PTC, papillary thyroid carcinoma; SM, suspicious for malignancy; SPTC, solid variant of papillary thyroid carcinoma; PM, positive for malignancy.

thyroid carcinoma (1 case). In the current series, we had only 2 NIFTPs with preceding FNA diagnoses of FN.

Based on the histopathologic follow-up, there were 2 false-negative results and no false-positive cases. The global evaluation of the 3 indeterminate subcategories (AUS/FLUS, FN/OFN, and SM) demonstrated 13 malignant diagnoses (31.7%), whereas for each subcategory the ROM was 11.1%, 20%, and 100%, respectively, with the exclusion of NIFTPs. The inclusion of NIFTPs slightly increased the ROM for the FN category from 25% to 28%.

The evaluation of $BRAF^{V600E}$ analysis demonstrated that the quality and quantity of DNA obtained from LBC stored material was sufficient for an adequate molecular evaluation and we obtained molecular yields from all the analyzed cases. Specifically, the 2 NIFTPs were wild-type whereas 4 of the 19 PTCs (21%) had $BRAF^{V600E}$ mutations. In addition, a retrospective evaluation of *RAS* mutations was performed on both LBC stored material and histological slides from the 2 NIFTPs. These 2 cases were both found to be wild-type for *RAS* mutations.

The statistical analysis was performed with and without the inclusion of NIFTPs in the malignant category. The first scenario demonstrated a sensitivity of 77.7%, a specificity of 100%, a negative predictive value of 82%, a positive predictive value of 100%, and a diagnostic accuracy of 89%, whereas the second scenario resulted in a sensitivity of 81.3%, a specificity of 100%, a negative predictive value of 85.4%, a positive predictive value of 100%, and a diagnostic accuracy of 91.1%.

In Table 4, we compared the findings of the current study regarding NIFTPs with those of studies published from adult cohorts.[27–29,31,42] We compared the rate of NIFTPs for the entire FNAC series and for the PTC cases. The figures assessed much higher NIFTP rates in adult populations compared with the pediatric cohort herein.

DISCUSSION

In the current study, we aimed to evaluate the prevalence of the new entity of NIFTP in the pediatric population.

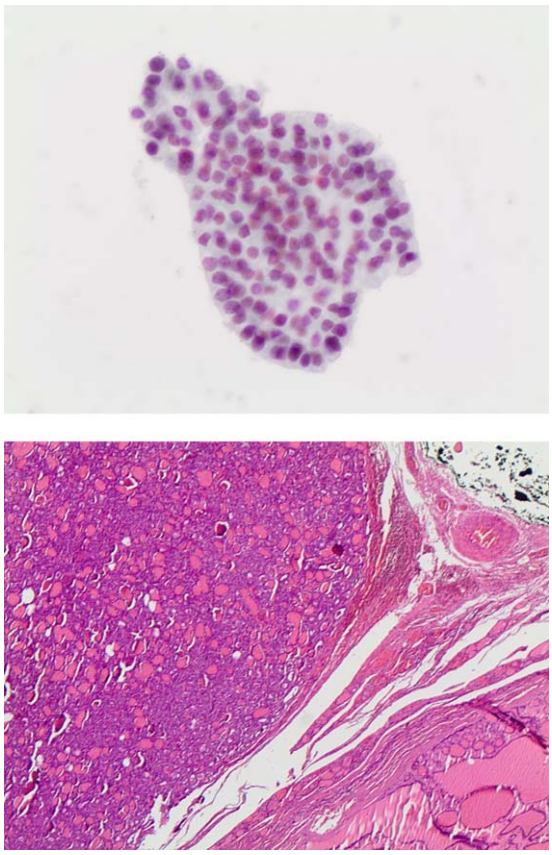

Figure 1. (*Top*) Cytological features of a case of a follicular neoplasm (liquid-based cytology, H & E; original magnification × 400) (*Bottom*) diagnosed on histology as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (H & E, original magnification × 40).

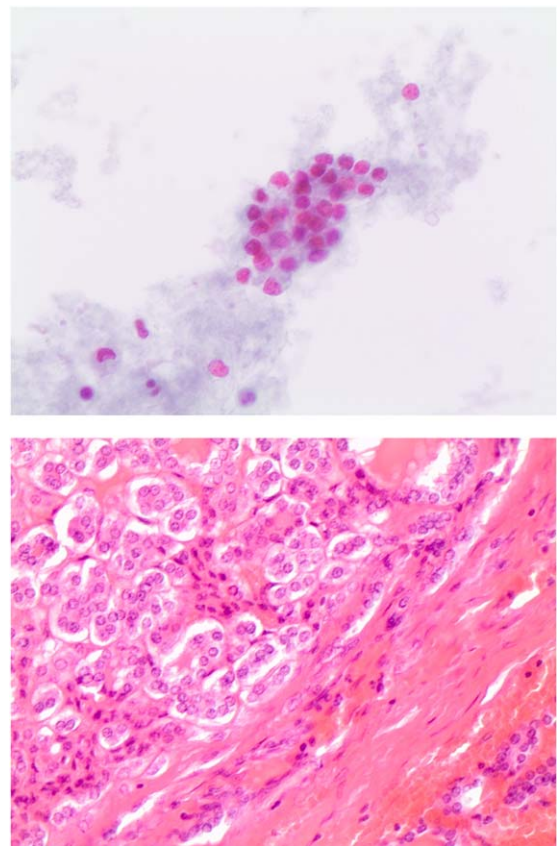

Figure 2. (*Top*) Cytological features of a follicular neoplasm diagnosed as noninvasive follicular thyroid neoplasm with papillary-like nuclear features on histology (liquid-based cytology, H & E; original magnification × 400). (*Bottom*) Some histological details of the nodule are shown (H & E, original magnification × 1000).

In the last few years, several authors have demonstrated that the majority, if not all, of the patients with encapsulated FVPCs do not develop any disease recurrences and metastases after a follow-up of years and/or decades.[15–24] A multi-institutional series including 109 patients with encapsulated FVPCs (NI-FVPCs) documented that none of these individuals developed any disease recurrence.[24] As a result, the 2015 Endocrine Pathology Society meeting questioned whether these NI-FVPCs warrant a diagnosis of carcinoma and whether to rename them. Based on their yields, the Endocrine International Working Group recommended the reclassification of these NI-FVPCs as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). Specifically, this entity was characterized by a set of morphological findings, including nuclear membrane irregularities, a maximum of 1% papillary architecture, ground glass appearance of the nuclei, nuclear pseudoinclusions, and larger nuclear size in a context of encapsulated follicular tumor. Thus, according to Nikiforov et al, the recent reclassification of NIFTP may have a significant impact on the ROM for indeterminate/follicular proliferations, which represent the most frequent cytological diagnoses of NIFTPs.[24]

In particular, recent articles by authors from different institutions have demonstrated that if NIFTPs were no longer termed "carcinoma," the ROM for these categories would have a significant decrease of between 20% to 48%.[15–34]

A growing number of studies have investigated whether these lesions can be identified and diagnosed on either histology or FNAC and, more specifically, their impact on ROM. Several recent articles have been published regarding NIFTPs in the adult population, even though, to the best of our knowledge, the incidence of NIFTPs in pediatric patients is not exactly known.[15–34,42–44] According to

TABLE 4. Comparison of the Current Pediatric Series With Some Adult NIFTP Series in the Literature (Cytohistological Series)

Study	Total No. of FNAC Cases With Surgical Follow-Up	Total No. of PTC Cases	No. of NIFTP Cases (% in All FNAC Versus % in PTC)
Current pediatric series	95	44	2 (1.9% vs 4.5%)
Strickland 2015[29]	655	346	85 (12.9% vs 24.6%)
Faquin 2016[28]	1827	756	173 (9.4% vs 23%)
Maletta 2016[31]	157	120	96 (61% vs 80%)
Bizzarro 2016[27]	90	77	24 (26.6% vs 31%)
Jiang 2017[42]	302	25	8 (2.6% vs 32%)

Abbreviations: FNAC, fine-needle aspiration cytology; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.

Nikiforov et al[24] and other series, the initial incidence of NIFTP in adults has been reported to be as high as 16% to 23% of all PTC cases (Table 4).[27–29,31,42] In the current series, we reported a rate of 1.9% for the diagnostic category of NIFTP in a pediatric cohort of patients with resected thyroid nodules. However, considering only the PTC cohort, our rate of NIFTPs was 4.5%. These figures are not completely different from new published data from the adult population.[43,44] Not surprisingly, recent series have reported a consistently lower incidence than what was speculated by Nikiforov et al,[24] most likely due to more rigid evaluation criteria for the definition of encapsulation of the tumor.[43,44] In fact, the rates of NIFTP were reported to account for <5% of all PTCs in recent series in which rigid evaluation criteria were the standard of practice.[43,44]

Nonetheless, in this context, the most valid guideline is the application and adoption in pediatric thyroid nodules of the same criteria used for identifying NIFTPs in adult thyroid lesions.

The diagnostic role of FNAC in the evaluation of pediatric thyroid lesions has been thoroughly assessed and reported in the literature.[1–14] In fact, numerous articles have emphasized that the majority of thyroid lesions are easily recognized and correctly diagnosed on cytological specimens. For this reason, the objective of the current study was to: 1) appraise the relevance of NIFTPs in a multi-institutional pediatric cytological cohort; and 2) discuss the role of NIFTPs in light of their risk of malignancy and false-negative and false-positive results. To the best of our knowledge, to date TBSRTC and any other thyroid international classification systems have not included any specific evaluation of NIFTPs.[38,39] Regardless of the age of the patients, the majority of FVPCs (including both noninvasive and invasive carcinomas) are diagnosed in the categories of indeterminate proliferations (AUS/FLUS, FN, and SM) due to subtle nuclear/cellular and/or architectural features that do not allow for a conclusive cytological diagnosis of malignancy.[25–34] Faquin et al demonstrated that the highest impact of the reclassification of NIFTPs led to a decrease in the ROM ranging from 13.6% to 23.5%, especially for AUS/FLUS, for which, most likely due to the inclusion of NIFTP, the ROM appears to be slightly higher than that expected from TBSRTC.[28] Analyzing the distribution of NIFTPs among our cytological categories, we estimated a correlation between NIFTPs and indeterminate categories as demonstrated by the fact that our 2 NIFTP cases (1.9%) were diagnosed as FN whereas the majority of I-FVPCs were classified as SM and PM. These data confirmed the results from Maletta et al[31] and Bizzarro et al.[27] In fact, these 2 studies highlighted that indeterminate diagnoses in NIFTPs (including both AUS/FLUS and FN) were twice those found in the I-FVPTCs (54.1% vs 29.2%).[27,31] For this reason, the same authors investigated how some cellular/morphological features are likely to be associated with a diagnosis of NIFTP on FNAC. According to these recent studies, we found that our 2 pediatric NIFTP cases were characterized by 100% microfollicular structures and a nuclear size ranging from 14 to 20 μm; therefore, these morphological recognitions might help to render a cytological diagnosis of "follicular proliferation"/FN, also including a possible NIFTP diagnosis.[25–34]

The comparative analysis between the 2 institutions suggested the low prevalence of NIFTPs in the pediatric population and strongly demonstrated the high diagnostic accuracy of cytology regardless of the cytological methods used, including both conventional and LBC preparations.

The exclusion of NIFTPs from the malignant histological lesions resulted in a malignancy rate of 48.5%, which is in perfect alignment with the statement from the American Thyroid Association Task Force on Pediatric Thyroid Cancer, which reported a malignancy rate between 9.2% and 50% for pediatric thyroid nodules.[7]

Our 2 NIFTP cases also confirmed the lower aggressive behavior reported by Nikiforov et al in their study of NIFTPs[24]; in fact, the 2 NIFTP cases in the current study did not demonstrate any disease recurrences or lymph node metastases during a follow-up period of 7 years. Furthermore, we also found a lack of common somatic mutations (ie, *BRAF*^{V600E} and *RAS*) in the 2 NIFTP cases in the current study. Nonetheless, larger and multi-institutional studies might confirm our preliminary yields.

A limitation of the current study was that it is a retrospective study with a starting point of surgical cases. Another limitation may be the relatively low number of cases compared with similar studies in the adult population, a limitation that is inherent to studies in pediatric populations.

According to the Surveillance, Epidemiology, and End Results program and the World Health Organization, PTC accounts for approximately 90% of all cancers, and is mainly diagnosed as the classic variant of PTC.[1–8] This diagnostic evidence might justify the low prevalence of NIFTPs in pediatric thyroid nodules. For example, according to the literature, the current series included 71.5% of the classic variant of PTC, 11.9% of I-FVPCs, 7.1% of diffuse sclerosing variants, 4.7% of the solid variant, 2.3% of the columnar variant, and 2.3% of the macrofollicular variant.

The results of the current study demonstrate that this new histological entity might be diagnosed in only a few cases among a pediatric series. Even though a definitive diagnosis of NIFTP cannot be rendered on FNAC, we associated these cases with specific cytological features, including a microfollicular pattern and a nuclear size in between those of FAs and invasive PTCs. In pediatric series as well as in adult cohorts, the role of NIFTP in the definition of surgical treatment remains an ongoing concern even though a conservative approach is the best recommended therapy in cases of suspected NIFTP, especially in pediatric patients.

The new terminology of NIFTP might be considered in pediatric series even though further studies, including larger series, are necessary to define the role of this entity in pediatric cohorts, its clinical management, and the long-term follow-up.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

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