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# Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP): Report of an Institutional Experience with 86 Cases

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## Abstract

**Background**: It was recently proposed that noninvasive follicular variant of papillary thyroid carcinomas (PTCs) should be reclassified as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) and treated conservatively. As this is a recent definition, limited data exist about NIFTP. The objective of this study was to report our institutional experience with NIFTP.

**Materials and Methods**: Retrospective study from 2005 to 2015 of all patients with PTCs meeting the histological criteria to be reclassified as NIFTP. We collected information regarding patient demographics, clinical presentation, ultrasound, FNA results, nodule size, multifocality, pathological stage, type and extent of surgery, radioactive iodine treatment, lymph node and systemic metastases, and follow-up.

**Results**: Eighty-six patients (67 women and 19 men, aged 17-83 years (median: 49.5 years)) with NIFTP (median size: 2.5 cm; range: 1.0-5.5 cm) were identified, representing 13.8% of all cases formerly diagnosed as PTC. NIFTP frequently exhibited indeterminate FNA results (71.4%, including suspicious for malignancy (42.9%), follicular neoplasm (20.6%), and AUS/FLUS (7.9%)), while benign (11.3%) and malignant (6.3%) results were less common. Treatment consisted of total thyroidectomy ($n$ = 42), staged total thyroidectomy ($n$ = 33) or lobectomy ($n$ = 11), combined with prophylactic cervical lymph node dissection ($n$ = 14; all pN0) and post-operative radioactive iodine with 30 mCi ($n$ = 34) or 100 mCi ($n$ = 28). All patients were without evidence of disease after a median follow-up of 3.1 years (range 1-11 years).

**Conclusions**: NIFTP represents a significant fraction of cases previously diagnosed histologically as PTC. They were typically diagnosed cytologically as indeterminate and managed like PTCs. None of our patients developed metastases or recurrences. The new NIFTP terminology will have significant impact on the management of patients at our Center.

**Keywords**: Thyroid, cytology, noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP), follicular variant, papillary thyroid carcinoma

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## Introduction

Noninvasive encapsulated (or well-demarcated) follicular variant of papillary thyroid carcinoma (NI-FVPTC) is a controversial entity that was considered and managed as thyroid carcinoma for the last 30 years (1, 2). While relatively rare in the past, its prevalence increased steadily over time, representing the most common subtype of FVPTC (50-75%) (2-4). Historically, the diagnosis of NI-FVPTC was mainly based on the detection of nuclear features of PTC, which are often more subtle than in conventional PTC. This proved to be challenging due to considerable inter-observer variability and lack of consensus, even among experts (1, 2). Greater insight into the molecular alterations of these tumors has revealed that NI-FVPTC is actually closer to the follicular thyroid adenoma/carcinoma (FTA/FTC) group than the conventional PTC group, and frequently harbors genetic alterations associated with follicular-pattern thyroid tumors (5-13). Similarly, in the absence of capsular or vascular invasion, this type of tumors has a very low risk of recurrence or metastasis, even in patients treated by lobectomy alone (5-12). Therefore, experts have recently proposed to rename a carefully defined subset of NI-FVPTC as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), using strict histological inclusion and exclusion criteria, in order to limit overdiagnosis of thyroid malignancy (5, 12). NIFTP is considered a low-risk neoplasm and/or a precursor lesion, rather than a true malignant tumor. This paradigm shift in thyroid tumor classification is expected to have significant impact on thyroid cytology and on the clinical management of patients. At the same time, it may also provide additional insight into so-called indeterminate thyroid cytology. It has been shown that thyroid tumors at an early stage of carcinogenesis (precursor lesions) such as NIFTP have a higher probability of being classified into the indeterminate diagnostic categories due to their less well-developed morphological features of malignant tumors (14-27). Conversely, thyroid cancers in the indeterminate categories have also been shown to be biologically indolent (low stage and low risk) by several researchers, with a significant proportion of FVPTC or NIFTP (28-32).

Herein, we present our institutional experience with 86 cases of NI-FVPTC/NIFTP (henceforth referred to as NIFTP) based on a retrospective study spanning the years 2005-2015 at Geneva University Hospitals, Switzerland. We also discuss our perspectives on NIFTP and how we handle this tumor in our practice.

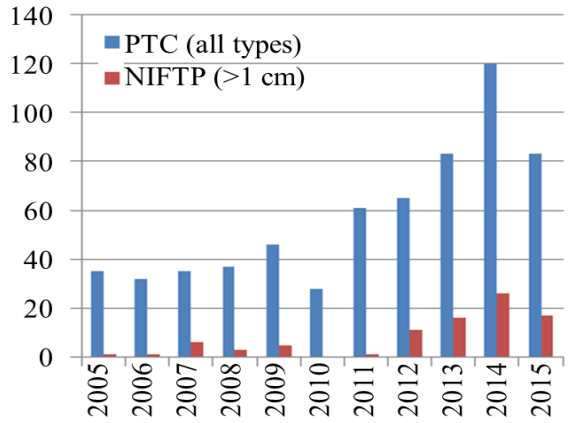


Fig. 1: The prevalence of NIFTP among PTC cases during the years 2005-2015. Y-axis shows the absolute number of cases.

## Material and Methods

We performed a retrospective computerized search of patients who underwent thyroid surgery at Geneva University Hospitals, Switzerland, from January 2005 to December 2015 and harbored a histological diagnosis of PTC. The cytological and surgical pathology reports as well as pertinent clinical history and radiographic results were reviewed. Because the diagnoses for all of these tumors were rendered prior to the proposed nomenclature revision, 5 cases that met current diagnostic criteria of NIFTP were identified among cases diagnosed as NI-FVPTC (>1 cm) based on the final pathological report. Our pathology reports include a detailed histological description of tumors, thus facilitating the retrospective identification of NIFTP cases. When there was ambiguity in the reports about the presence or absence of diagnostic criteria for NIFTP, the histological slides were reviewed by the local dedicated thyroid pathologist (MP). For patients with a diagnosis of NIFTP, we collected information regarding patient demographics, clinical presentation, ultrasound, fine needle aspiration (FNA) results, nodule size, multifocality, pathological stage, type and extent of surgery, radioactive iodine (RAI) treatment, lymph node and systemic metastases, and follow-up. Ultrasound-guided thyroid FNA was performed by endocrinologists or radiologists with 22- to 27- gauge needles with 3 or 4 passes. Rapid on site cytological evaluation was performed for the majority of cases. Ethanol-fixed Papanicolaou-stained direct smears were prepared from the thyroid aspirates on site for the vast majority of cases. All aspirates were also processed using the Thin Prep technique (Hologic, Inc., Marlborough, Massachusetts). Thyroid FNAs performed after 2009 were classified according to The Bethesda System to Report Thyroid Cytopathology (TBSRTC) (33). Thyroid FNAs performed before 2009 were reclassified according to TBSRTC based on the cytologic description (e.g., microfollicular lesion, nuclear features of PTC, etc.) and the original diagnosis available from the cytologic reports. This retrospective study was approved by the Swiss Ethics and Research Committee (Study No: 2017-00162), and was performed in accordance with the guidelines of the Helsinki II declaration. Informed consent was waived.

## Results

Table 1. Clinical data of NIFTP and cytological categorization of FNAB

| | |
|---|---|
| Total No. of cases | 86 |
| Sex | |
| Female | 67 |
| Male | 19 |
| Age (mean; range) | 50.6 years; 17-83 years |
| Size (mean; range) | 2.8 cm; 1-5.5 cm |
| **Cytological diagnostic categories according to the Bethesda System** | |
| Total No. of cases (%) | 63 (73.3) |
| Nondiagnostic (%) | 4 (6.3) |
| Benign (%) | 7 (11.3) |
| AUS/FLUS (%) | 5 (7.9) |
| FN/SFN** (%) | 13*(20.6) |
| FN/SFN oncocytic variant (%) | 2 (3.2) |
| SusM** (%) | 27 (42.9) |
| PTC | 9 |
| FVPTC | 18 |
| Malignant (%) | 4 (6.3) |
| PTC | 2 |
| FVPTC | 2 |

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance. FN/SFN: follicular neoplasm or suspicious for follicular neoplasm; SusM: suspicious for malignancy; PTC: papillary thyroid carcinoma; FVPTC: follicular variant of papillary thyroid carcinoma; NIFTP: noninvasive follicular neoplasm with papillary-like nuclear features; FNAB: fine needle aspiration biopsy. *Including 3 cases with the specific note "rule out FVPTC". **One case was "suspicious" not otherwise specified.

### Demographics

Eighty-six cases of NIFTP were identified in a total of 625 patients harboring PTC on final pathology. The prevalence of NIFTP among PTC cases during the years 2005-2015 was 13.8%. Interestingly, the prevalence of NIFTP among PTC was 6.2% during the years 2005-2011 and rose up to 20% during the years 2012-2015 (Figure 1).

### Clinical Findings

There were 67 females and 19 males (male to female ratio = 1/3.5), ranging from 17 to 83 years (median: 49.5 years; mean 50.6 years) (Table 1). Fifty three patients (61.6%) presented with a single nodule and 30 patients (34.9%) presented with multinodular goiter. Two patients presented with 2 nodules and one with toxic goiter.

### Pre-operative Cytology

Sixty three patients (73.3%) had undergone pre-operative FNA. The most common FNA diagnoses (Table 1) were “suspicious for malignancy” or SusM (*n* = 27, 42.9%) including suspicious for FVPTC (*n* = 18) or suspicious for PTC (*n* = 9), followed by “suspicious for follicular neoplasm” or FN/SFN (*n* = 13, 20.6%, including 3 with a specific note “rule out FVPTC”), “benign” (*n* = 7, 11.3%), “atypia/follicular lesion of undetermined significance” or AUS/FLUS (*n* = 5, 7.9%), “malignant” (*n* = 4, 6.3%) including FVPTC (*n* = 2) and PTC (*n* = 2) (Figure 2), and “suspicious for oncocytic/Hürthle cell neoplasm” (*n* = 2, 3.2%). One case was “suspicious” not otherwise specified. Four samples (6.3%) were nondiagnostic. Twenty three patients (26.7%), including 17 with multinodular goiter, one with toxic goiter and five with a single nodule, did not have pre-operative FNA performed.

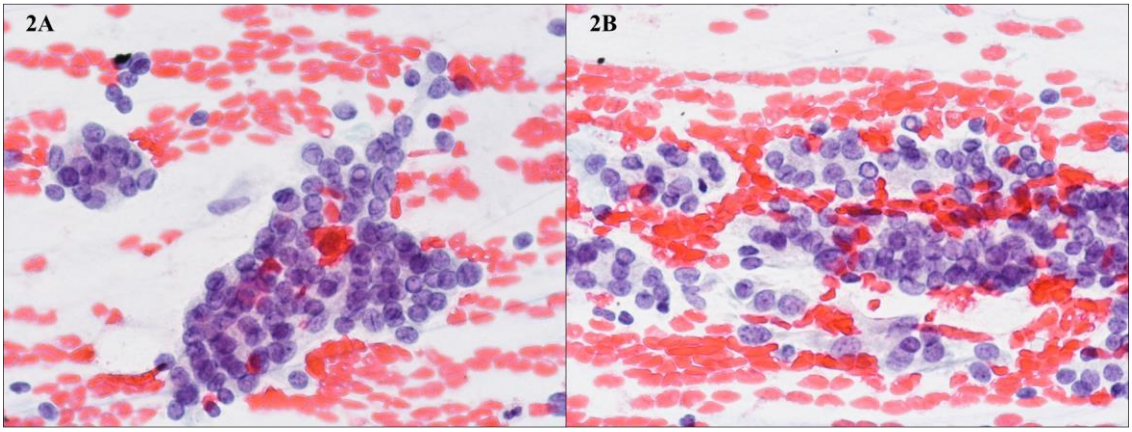


Fig. 2: A-B: a case of NIFTP that was diagnosed cytologically as Malignant-PTC. The tumor cells are arranged in a microfollicular pattern with nuclear overlapping. There are many nuclear grooves as well as several cytoplasmic intranuclear pseudoinclusions. However, neither papillary structures nor psammoma bodies were found in this case. (Papanicolaou stained smears 400x).

Table 2. Results of intra-operative examination of NIFTP cases and extent of initial surgery

| | | Results of intra-operative examination | | Extent of initial surgery | |
|---|---|---|---|---|---|
| | | Conclusive for FVPTC | Not conclusive for malignancy* | Total thyroidectomy | Lobectomy |
| Preceding cytologic diagnosis | | | | | |
| None | 4 | 0 | 4 | 0 | 4 |
| Non diagnostic | 4 | 0 | 4 | 0 | 4 |
| Benign | 1 | 0 | 1 | 0 | 1 |
| FN/SFN | 2 | 0 | 2 | 1 | 1 |
| SusM | 20 | 10 | 10 | 15** | 5 |
| Total No. of cases (%) | 31 (36) | 10 (32.3) | 21 (67.7) | 16 | 15 |

*Including microfollicular/follicular nodule/proliferation with or without atypia, Hashimoto thyroiditis and multinodular goiter;
**Combined with central lymph node dissection in 7 patients

**Initial Treatment**

Forty two patients underwent upfront total thyroidectomy, including 38.5% ($n$ = 5) of patients with a preceding FN/SFN diagnosis and 69% ($n$ = 20) of patients with a preceding SusM diagnosis. Among this group, 16 patients had intra-operative examination (see below). Thirty three patients underwent staged surgery (i.e., lobectomy followed by completion thyroidectomy a few weeks/months thereafter, after the final diagnosis of FVPTC was obtained), including 53.8% ($n$ = 7) of patients with a preceding FN/SFN diagnosis and 17.2% ($n$ = 5) of patients with a preceding SusM diagnosis. Eleven patients underwent lobectomy only. Fourteen patients (16.5%) also had prophylactic central lymph node dissection. Patients with pre-operative "benign" FNA cytology underwent surgery mostly for compressive symptoms or concern for malignancy due to large nodule size.

**Intra-operative examination**

Intra-operative evaluation of the thyroid nodule, using a combination of cytological smear and frozen section, was performed in 31 cases (36%), including 27 patients with the preceding FNA diagnosis of SusM (PTC or FVPTC) ($n$ = 20), nondiagnostic ($n$ = 4), FN/SFN ($n$ = 2) or benign ($n$ = 1), and 4 patients who did not have pre-operative FNA (Table 2). In 10 cases, all with a SusM preceding diagnosis, the intra-operative diagnosis was conclusive for FVPTC, resulting in the immediate completion of thyroidectomy. In 21 cases, the intra-operative diagnosis was not conclusive for malignancy (Table 2). In six of these cases, including five with a SusM preceding diagnosis, an immediate total thyroidectomy was performed because of the presence of bilateral nodules.

**Tumor Characteristics**

The median tumor size was 2.5 cm (mean: 2.8 cm; range: 1.0-5.5 cm). Ten tumors were bifocal and 31 tumors had one or several papillary microcarcinomas (<1 cm) in the same lobe and/or in the contralateral lobe. Molecular testing was performed in 5 cases (5.8%), including 4 for *BRAF* mutation only on cytological material and one for *BRAF* and *H-*, *N-*, and *K-RAS* mutations on histological material. In the latter, a *N-RAS* Q61R mutation was found. No *BRAF* mutations were found. There were no lymph node metastases (pN0) in 12 patients (14%) with lymph node sampling (mean number of lymph nodes: 6.75, range: 2-11). The remaining patients (86%), including two with only one lymph node in the sampling, were staged pNx.

**Clinical Treatment and Patient Outcome**

Sixty two patients (72.1%) received radioactive iodine ablation (RAI) treatment, with a dose of either 30 mCi ($n$ = 34) or 100 mCi ($n$ = 28). There were 79 out of 86 patients (91.9%) who had follow-up with no evidence of recurrence, based on biochemical or structural disease, nor death at last follow-up: median 3.1 years (mean: 3.8 years; range 1-11 years). In 7 patients, there was no data on follow-up, either because they were lost to follow-up or because the recommended RAI therapy was refused by the patient.

## Discussion

**Epidemiology of NIFTP**

Our data show that the prevalence of NIFTP, formerly classified as NI-FVPTC, has increased significantly over the last decade (2005-2015) and accounts for 13.8% of all diagnosed PTCs, and seems to increase over time in our center for an unknown reason (Figure 1). For comparison, other studies have shown that NIFTP was relatively uncommon in the past, comprising 5% of PTCs from 1979 to 2004 in the study by Piana *et al*. (34) from Italy and 6% of PTCs from 1990 to 2009 in the study by Liu *et al*. from Japan (35). In contrast, NIFTP comprised approximately 15-30% of all tumors previously classified as thyroid malignancies on histology in more recent studies from several European countries and North America (14-22). It has been hypothesized that this increased incidence is due mainly to a shift over time in pathological criteria for diagnosis of thyroid cancer, along with an increased awareness of FVPTC (2, 3). Interestingly, the prevalence of NIFTP appears to be lower in Asia (<5%). These differences between eastern and western countries may be partially explained by different diagnostic criteria for the diagnosis of borderline lesions such as NIFTP and/or well differentiated tumor of undetermined malignant potential (WDT-UMP) and a more conservative management (i.e., clinical follow-up without immediate surgical treatments when no other clinical tests indicate high-risk malignant features) for cases which are suspicious for NIFTP/WDT-UMP in the East (36).

**Cytological Diagnosis of NIFTP using TBSRTC**

NIFTP is often associated with more subtle nuclear features than conventional PTC and invasive FVPTC, but with more abnormalities than benign nodules including FTA (14-20). Thus, recent studies have shown that cytology samples of NIFTP are typically diagnosed as indeterminate, including SusM (18-35%), FN/SFN (25-56%) or AUS/FLUS (10-35%) (14-22). For example, the NIFTP cases in Maletta's study were preceded by FNA diagnoses of AUS/FLUS (15%), FN/SFN (56%), SusM (27%) and Malignant (2%). Similarly, our data show that more than 2/3 of NIFTP are cytologically diagnosed as indeterminate and mostly as SusM (47%, including 69% for a follicular variant), although our rates of FN/SFN (21%) and AUS/FLUS (8%) diagnoses were lower than in other studies.

Based on a combination of cytological features including microfollicular architecture and nuclear atypia, the cytopathologist can raise concern for the diagnosis of NIFTP. The definitive diagnosis, however, can only be made after complete histological examination of the tumor and its capsule, taking into account all the different inclusion and exclusion criteria that define NIFTP (including exclusion features such as >1% papillae or >30% solid areas) (5). In terms of the implied risk of malignancy (ROM) and initial management, this situation becomes analogous to the FN/SFN category, in which the cytopathologist raises concern for FTC but the distinction between FTA and FTC must be made at the histological level. Therefore, although NIFTP is no longer considered a malignant entity, a diagnostic and therapeutic lobectomy is still warranted for NIFTP, first because it cannot be diagnosed with certainty on FNA and second because it is a very low risk neoplasm that likely represents a pre-invasive stage of FVPTC (5, 23, 37).

**Impact of NIFTP on the ROM of TBSRTC Diagnostic Categories**

In a previous retrospective multi-institutional study that included our Institution, it was shown that the NI-FVPTC/NIFTP reclassification as a nonMalignant entity would have a significant impact on the ROM of all diagnostic categories of TBSRTC, especially for the three indeterminate categories (AUS/FLUS, FN/SFN, SusM) (15). Specifically, at our Institution, during the time frame of that study (from January 2013 to July 2014; 18 months) with the highest incidence of NIFTP (23 cases in total), the ROM decreased from 100% to 85.7% in the Malignant, 79.3% to 37.9% in the SusM, 24.2% to 14.5% in the FN/SFN, and 20.8% to 16.7% in the AUS/FLUS categories. The most drastic drop was in the SusM category, consistent with the fact that most NIFTP are diagnosed in this cytological category. Several other studies have shown similar results for the ROM in the three indeterminate categories (AUS/FLUS, FN/SFN, SusM) of TBSRTC (14, 16-20, 23). This impact, however, is likely to be influenced by demographics and the institutional proportion of NIFTP cases, which may vary depending on the time frame, as shown in the current study (15, 23).

Thus, it will be important to monitor regularly both the prevalence of NIFTP and the ROM for the different categories of TBSRTC at each individual Institution, in order to better guide the clinical management of patients. This will also be essential in order to estimate the positive and negative predictive values of any molecular tests that are performed to assist in the clinical management (see below).

Because of NIFTP terminology, there is growing concern in the cytology community that false positive diagnoses and overtreatment may occur, since NIFTP comprises a significant proportion of all thyroid FNAs classified as SusM and a minor variable subset (2-10%) of those classified as Malignant in other retrospective studies (14-22). In our series, 6% were diagnosed as Malignant (FVPTC or PTC) (Table 1 and Figure 2). Because of the subsequent overtreatment and potential medico-legal implications, it is highly desirable to exclude potential NIFTP cases from the malignant category, and even from the SusM category at other Institutions performing upfront total thyroidectomy. It is also important to limit the malignant category to conventional PTC and other variants of PTC (23, 27). While it is too early to know how this will affect TBSRTC (33) and other classification systems (38) in the future and if a specific diagnostic category is necessary for NIFTP, some institutions have already implemented provisional approaches and specific policies for the interpretation and reporting of thyroid FNAs in this new NIFTP era (27, 39). In particular for the FN/SFN, SusM, and Malignant categories, explanatory notes added to the cytologic diagnosis about the possibility of NIFTP on histologic follow-up could be particularly useful in order to support a more conservative clinical management as recommended by the latest American Thyroid Association (ATA) guidelines for low-risk thyroid neoplasms (4, 39). In addition, the diagnostic criteria of FN/SFN and SusM may be refined in order to better accommodate NIFTP. This could include the inclusion of incomplete and/or focal nuclear features of PTC in the FN/SFN category, which is explicitly listed as an exclusion criterion in the current TBSRTC (33). At our Institution, if a

FVPTC or NIFTP is suspected on cytology, we do mention it either in the diagnosis or in a note. The initial management of cases diagnosed cytologically as FN/SFN or SusM is similar at our Institution and consists of diagnostic lobectomy unless total thyroidectomy is required because of other thyroid pathology in the contra-lateral lobe. Nevertheless, intra-operative examination is commonly performed in SusM because of the higher likelihood to find PTC. Based on our results, cases with some degree of nuclear atypia that are suspicious for NIFTP might be better placed in the FN/SFN category than in the SusM category since the latter diagnosis was more often followed by upfront total thyroidectomy than the FN/SFN category (69% *vs*. 38.5%, respectively). However, this difference in the management between FN/SFN and SusM cases in our series was likely the result of intra-operative examination (Table 2) combined with the standard of care in this pre NIFTP era, which included immediate completion thyroidectomy for cases with a conclusive intra-operative diagnosis of FVPTC (see below).

**Ancillary Studies for the Diagnosis of NIFTP**

Ultrasonography and molecular tests can also assist the risk stratification and management at the time of FNA diagnosis (40-45). On ultrasound, most NIFTP are benign-appearing with round-to-oval, circumscribed nodules with a hypoechoic rim (21, 22, 24). However, a highly suspicious ultrasonographic appearance (i.e., thyroid imaging reporting and data system (TIRADS) category 5) can be seen in some cases (21, 22). In order to limit the risk of overdiagnosis, cytopathologists should be cautious before making a definite Malignant-PTC diagnosis in cases that do not have suspicious ultrasonographic features.

At the molecular level, NIFTP show a very high association with other follicular-pattern neoplasms, with *RAS* mutations being the most common (44), followed by *PAX8/PPARγ* translocations, *THADA* fusions, and *BRAFK601E* mutations (5, 13, 23, 42-45). In contrast, *BRAFV600E* mutations and *RET* fusions (common in conventional PTC) are absent in NIFTP (5, 13, 11, 23). Sequencing with large multigene panels may therefore assist in the detection of NIFTP (41, 45). Recent studies have shown the Afirma gene expression classifier test classifies NIFTP cases as "suspicious" (42). MicroRNA based classifiers may also prove to be useful, but further studies are required (43).

**The Role of Frozen Section in the Era of NIFTP**

With the NIFTP concept and the conservative approach, which is associated with low risk thyroid neoplasms, including also minimally invasive FTC, the controversial role of intra-operative examination (i.e., frozen section) of thyroid nodules may be redefined. It may represent an attractive alternative to molecular testing (e.g., *RAS* or *BRAF* mutations) for detecting low-risk (i.e., encapsulated) thyroid neoplasms and determining the extent of resection. For example, in the SusM category, a conservative management could be proposed for encapsulated follicular neoplasms with or without nuclear features of PTC and without evidence of invasion, while a total thyroidectomy with lymph node dissection could be proposed for cases that show classic and/or infiltrative and/or aggressive PTC features. Before the advent of NIFTP and the revised ATA guidelines, the ultimate goal of intra-operative examination was to identify subtle nuclear features that could allow for the diagnosis of FVPTC in cases diagnosed cytologically as SusM, thereby prompting completion thyroidectomy during the same procedure. Our data show that intra-operative examination actually reached this purpose in 1/3 of cases. There is a paradigm shift: nowadays, we do no longer spend a significant amount of time to determine whether or not there are papillary-like nuclear features in noninvasive follicular lesions, as it does no longer change the initial management. Instead, we focus essentially on architectural features, which have been more strongly associated with tumor behavior than nuclear features (15).

**Avoiding Overtreatment of NIFTP**

In this series of 625 patients diagnosed with PTC, 86 would currently be diagnosed as NIFTP. Up to seventy five of them had "unnecessary" total thyroidectomy (with the need for thyroid hormone replacement therapy and with a small but significant risk of hypoparathyroidism) and 60 of them had "unnecessary" RAI. In our experience, the new NIFTP entity will lead to a more conservative surgery in those patients and will spare RAI with its potential risks and complication in about 10% of all PTC patients.

**Limitations of the Study and Future Directions**

In this retrospective study, the NIFTP cases were identified based on the descriptive surgical pathology reports, and the diagnoses for all of these tumors (i.e., NI-FVPTC) were rendered prior to the proposed nomenclature revision. However, the majority (~85%) of these cases were diagnosed by the same pathologist during the time frame of the study, limiting inter-observer variability for the diagnosis of this entity. Future studies that determine the interobserver variability of this surgical pathology diagnosis will be important. Indeed, some of the histological diagnostic criteria for NIFTP are arbitrary and/or subjective. These include the presence of <1% of papillae and <30% of solid growth. On the other hand, some features such as oncocytic changes, cystic changes or a large tumor size (i.e., >10 cm) are not specifically mentioned as exclusion criteria for NIFTP. A recent study showed that large (i.e., 4-8 cm) NIFTPs apparently also appear to have an extremely low risk of recurrence (46). Further studies, however, are required to assess whether the inclusion and exclusion criteria for NIFTP should be refined.

The true number of NIFTP cases during the time frame of the study may be underestimated as it is possible that a subset of FTA might be currently diagnosed as NIFTP. It would be interesting to verify, in another study, how many tumors formerly classified as FTA would meet the criteria for NIFTP. Additional studies to further explore the prevalence of NIFTP based on strict pathologic criteria will also be important.

The median follow-up of patients is relatively short, and since the majority of them (86%) did not have lymph node dissection, their lymph node status could not be assessed (i.e., pNx). Therefore, we cannot rule out the possibility of lymph node metastases in patients who might have been cured with RAI treatment. Future studies with longer follow-up are needed to confirm and validate conservative surgical approach using intra-operative frozen section to direct the extent of resection and need for prophylactic central neck dissection.

## Conclusions

NIFTP represented a significant fraction of cases previously histologically diagnosed as PTC, which were typically diagnosed cytologically as indeterminate, and thus often managed as PTCs. The prognosis of NIFTP appears to be excellent, regardless of the type and extent of surgery. The new NIFTP terminology will have significant impact on the management of patients in our center. Since the majority of NIFTP cases are diagnosed as SusM or FN/SFN and managed initially with diagnostic lobectomy, there might be a central role for intra-operative examination to determine the extent of surgery. Further studies are required to fully define clinical management and the long-term follow-up of these patients.

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