

# Non-invasive follicular neoplasm with papillary-like nuclear features: a challenging and infrequent entity in Argentina

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# Abstract

**Purpose:** Non-invasive encapsulated follicular variant of papillary thyroid cancer was reclassified as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). These neoplasms have an extremely low malignant potential. The aim of this study was 1) to assess the prevalence of NIFTP in patients with papillary thyroid carcinoma, 2) to evaluate their outcomes and 3) to determine their molecular profile.

**Methods:** Multicenter, descriptive, retrospective study. Patients with papillary thyroid cancer diagnosed from January 2006 to December 2016 from 11 referral centers were included. Diagnosis of NIFTP was based on criteria described by Nikiforov *et al.* in 2018. At least two pathologists agreed on the diagnosis. Two thousand six hundred and seventy-seven papillary thyroid cancer patients were included; 456 (17%) of them were follicular variant papillary thyroid cancer, and 30 (1.12%) fulfilled diagnostic criteria for NIFTP.

**Results:** Each of the 30 included patients underwent a total thyroidectomy, and 50% were treated with radioiodine (median dose 100 mCi). After a median follow up of 37 months, 84% of patients had an excellent response, 3% had an indeterminate response and data was missing in the remaining 13%. No metastatic lymph nodes, distant metastases or recurrences were found. *RAS* mutations were detected in 4 patients (13%).

**Conclusion:** The prevalence of NIFTP in our series is amongst the lowest reported. Excellent outcomes of patients underscore their low malignant potential. Molecular findings differ from other series, probably related to environmental or ethnic features of our population and the meticulous criteria for diagnosing NIFTP.

## Introduction

Follicular variant of papillary thyroid carcinoma (FVPTC) was described in 1977, as a tumour composed by neoplastic follicles with cells showing nuclear features characteristics of papillary thyroid cancer (PTC) [1–2]. According to the morphology and behaviour, three different subtypes of FVPTC were described: infiltrative and encapsulated, with or without invasion [3]. Over the last decades, FVPTC incidence increased to comprise 10-20% of all differentiated thyroid cancer [4]. Encapsulated, non-invasive variant of FVPTC has an indolent biology, which led to an international expert panel (composed of pathologists, endocrinologists, surgeons) to reassess the features of this neoplasm aiming to establish and standardize diagnostic criteria and nomenclature which would better reflect clinical and biological characteristics of this tumor [1]. After this meeting, it was reclassified as non-invasive follicular neoplasm with papillary-like nuclear features (NIFTP). This new designation aimed to promote a more conservative treatment for these patients, to avoid the psychological burden of a cancer diagnosis and to reduce management associated costs [1].

Subsequently, several publications confirmed the indolent clinical course of NIFTP, its very low risk of recurrence and nearly non-existent risk of mortality [5].

Diagnosis of NIFTP is based on specific histomorphologic features, such as the presence of a capsule or a clearly delimited nodule, a follicular growth pattern and the nuclear features found in PTC. Invasion of the capsule and other exclusion criteria should be carefully ruled out [6]. In 2018, the diagnostic criteria for NIFTP were modified establishing that no true papillary structures should be present, and that if molecular studies were performed, high-risk alterations (ie: *BRAF V600E* and *TERT* mutations or *RET/PTC* rearrangements) should be absent, as well [6].

The aim of this study was a) to retrospectively assess the prevalence of NIFTP on a population of PTC patients, b) to describe their clinical and cytological characteristics c) to determine their outcomes, and d) to evaluate the molecular profile found in this neoplasm.

## Materials And Methods

A multicenter, observational study was performed. Patients older than 18 years, treated in eleven centers from Argentina, from January 2006 to December 2016 were included. Slides from 2677 patients with PTC diagnosis were reviewed; among them, 456 (17%) were FVPTC. Each histopathological sample was re-examined by at least two experienced pathologists from different centers. Clinical records were also reviewed to determine: cytological reports, type of initial surgery, treatment with radioiodine, initial response to treatment and the outcomes at the end of follow-up.

### Inclusion criteria

NIFTP was diagnosed according to criteria defined by Nikiforov *et al.* [6] and it was confirmed by at least two pathologists. Criteria required for diagnosis were encapsulation or clear demarcation, a follicular growth pattern (no true papillary structures, no psammoma bodies, <30% solid/trabecular/insular growth pattern), and a nuclear score 2-3b.

### Exclusion criteria

were presence of *BRAF V600E* mutation detected by molecular assays or immunohistochemistry (if molecular testing was performed), true papillae, psammoma bodies, lympho-vascular or capsular invasion, tumoral necrosis, high mitotic activity, cytologic/morphologic characteristics corresponding to other variants of PTC or poorly differentiated thyroid cancer.

Molecular analysis: For the evaluation of molecular alterations, a panel assessing 6 genes was performed in 19 patients (63%): mutations in *BRAF* (exon 15), *K/H/N-RAS* (exons 2 and 3), *RET/PTC1* and *PAX8/PPAR-Gamma* fusions. DNA purification from paraffin blocks was optimized with High Pure PCR Template Preparation KIT (Roche); RNA was purified with a modified protocol of TRIzol (Tripure Isolation Reagent). Point mutations were studied with RT qPCR followed by high resolution melting (HRM). Analysis of HRM was performed comparing curves of positive and negative controls. Samples with

altered or positive findings were sequenced by Sanger (Macrogen, Seoul, Korea). Gene fusions were studied by reverse transcription followed by RT PCR and visualized in agarose gel.

Statistical analysis Categorical values were presented as percentages and numerical values as median (25th–75th percentile).

## Results

Out of 2677 PTC patients, 456 (17%) were FVPTC and 30 fulfilled diagnostic criteria for NIFTP (1.12% of all PTC and 6.57% of all FVPTC).

Table 1 describes the clinical characteristics of the study population. Fine needle thyroid aspiration (FNA) was performed before surgery in 25 patients (83%): in 10 patients (33%) results were classified as suspicious for malignancy (Category V, according to the Bethesda system for reporting cytology) and in 10 (33%) as malignant (Category VI). (cita Bethesda)

Table 1  
 Characteristics of thirty patients with a diagnosis of NIFTP

<b>Age at diagnosis (years)</b>	<b>53 (44.7-61.2)</b>
Gender (Female/male)	25/5
Categories of TBSRTC	0 (0%)
I	2 (7%)
II	2 (7%)
III	1 (3%)
IV	10 (33%)
V	10 (33%)
VI	5 (17%)
Incidental finding	
Tumor >4cm	3 (10%)
Metastatic lymph nodes	0%
Distant metastases	0%
Tumor diameter (mm)	14.5 (6.7-22.2)
Follow-up (months)	37 (22.5-82.5)
Categorical values were presented as percentages and numerical values as median (25th–75th percentile).	
TBSRTC: The Bethesda system for reporting thyroid cytology	

All patients underwent total thyroidectomy, and 15 (50%) were treated with radioiodine with a median dose of 100 mCi <sup>131</sup>I. No metastatic lymph node or distant metastases were found at diagnosis.

After a median follow-up of 37 months (22.5-82.5), 25 patients (84%) showed no evidence of disease, one patient (3%) with initially undetectable anti-thyroglobulin antibodies developed detectable anti-thyroglobulin antibodies during follow up and data was missing for the remaining 4 (13%). During follow-up, none of the patients had a structural incomplete response nor required additional therapies.

Genetic studies were performed in 19 tumours (63%) and molecular alteration were found in only 5: in 2/19 an exon 3 *N-RAS Q61K* (c.181 C<A) was found and in 2/19 a mutation of exon 3 *H-RAS Q61R* (c.182 A<G). *BRAF K601E* mutation was found in 1 patient (Table 2). No *RET/PTC1* and *PAX8/PPAR-Gamma* fusions were detected (Figure 1).

Table 2  
Molecular alterations found in 19 patients diagnosed with NIFTP

	Patients with molecular alterations
<i>PAX8/PPAR-Gamma fusions</i>	0
Exon 2 and 3 <i>K-RAS</i> mutations	0
Exon 2 <i>N-RAS</i> mutation	0
Exon 3 <i>N-RAS Q61K</i> mutation (c.181C>A)	2
Exon 2 <i>H-RAS</i> mutation	0
Exon 3 <i>H-RAS Q61R</i> mutation (c.182A>G)	2
<i>BRAF K601e</i> mutation	1
*NIFTP: Non-invasive follicular neoplasm with papillary-like nuclear features	

## Discussion

Encapsulated non-invasive follicular variant of PTC was reclassified as NIFTP in 2016 [1], and was included in the WHO Classification of Tumours of Endocrine Organs in 2017 [7] as a separate entity, acknowledging its very low malignant potential. However, Ferris et al [8] recommend considering NIFTP as a preneoplastic lesion. Therefore, and considering that the reclassification is a recent event, strict follow-up is endorsed until further evidence is gathered. (aca necesitamos una cita)

Prevalence of NIFTP in our series was 1.12%, (30/2677), thus being among the lowest reported. Similar findings were found in Korea (0.18% (2/1411 PTC), Japan (0.5% (54/10176) and Canada (2.1% (102/4790) [9, 10, 11]. In a multi-institutional series from Southern Europe, the rate was 5.2%, but was highly variable in neighbouring institutions, ranging from 0 to 12.1%, suggesting pathologist's interpretation of nuclear alterations as the main cause of these differences [12]. A meta-analysis including seven series showed that the incidence of NIFTP was 1.6% in different Asian populations. This is significantly lower than the incidence found in non-Asian series, which can be as high as 15% [13]. Dissimilarities may be due to environmental and ethnic differences, as well as the thorough examination and strict criteria for diagnosing NIFTP that the samples in our series were submitted to. Also, in some countries, fear of malpractice claims can modify the histological thresholds, leading many pathologists to diagnose malignancy in equivocal lesions [14],

Although widespread adoption of the new NIFTP terminology was anticipated, reports of NIFTP on cancer registries failed so far to confirm this. Kitahara et al. [15] in 2017 informed that the observed number of NIFTPs recorded in SEER-18 accounted for only 1.3% of the number of total PTCs, much lower than the estimated proportion predicted by Nikiforov *et al.* (18.6%). Furthermore, a recent study including 3368 pathology reports from six countries found that the prevalence of NIFTP among papillary thyroid cancer

cases was 4.8%. No substantial changes in the frequency of diagnosis of NIFTP were found from 2016 to 2019 [16].

Regarding cytological evaluation of NIFTP, it was suggested that there are certain characteristics, such as hypercellularity, sheet-like architecture, follicular pattern, follicular microarchitecture and nuclear score that point towards the diagnosis [17, 18]. However, in order to establish an accurate diagnosis of NIFTP, the indemnity of the tumor capsule needs to be fully assessed and lympho-vascular invasion should be ruled out, and this cannot be estimated exclusively on the information yielded by FNA [19]. Additionally, even if psammoma bodies and papillae are exclusive of PTC, other nuclear features are shared between NIFTP and PTC [7, 18, 20]. In our series, only 9% of the cases had cytologic diagnosis corresponding to the categories III and IV of the BSRC. This is in contrast with other results, showing that the prevalence of these categories may reach to 58% [20]. The impact of changes in the predictive value for malignancy of ultrasonography, cytology, molecular tests or even fluorodeoxyglucose positron emission tomography (FDG-PET) depend on the prevalence of NIFTP in the population [22]. As we found only 1.12% of NIFTP in our multicentric study in Argentinian patients, no substantial changes on the relative malignancy rate of each of the Bethesda system for reporting thyroid cytology (TBSRTC) categories should be expected with the introduction of NIFTP in the classification of thyroid tumors in Argentina.

All of the patients included in this series were treated with total thyroidectomy. Over half of them also were submitted to radioiodine ablation, according to usual practices before the reclassification of these tumors as NIFTP [23, 24]. Currently, radioiodine ablation in NIFTP is not recommended. Surgery remains the therapy of choice, as NIFTP is considered a preneoplastic lesion, and definitive diagnosis needs the complete histologic assessment of the tumor. Hemithyroidectomy is the preferred surgical approach, providing there are no lesions in the contralateral lobe, as recommended by the American Thyroid Association guidelines [23]. However, Katsakhyan *et al.* [25] did not find significant changes in the number of total or partial thyroidectomies performed as initial surgeries comparing a pre- to a post-NIFTP cohort. Perhaps more time is needed to show changes, as a significant increase in the rate of hemithyroidectomies was found when comparing surgical treatment of thyroid cancer before or after the release of the 2015 American Thyroid Association Guidelines [26].

As for follow up, since NIFTP was only recently established as a diagnostic entity, it was suggested that an occasional neck ultrasound and annual measurements of thyroglobulin and anti-thyroglobulin antibodies should be performed until more clinical experience is obtained [8]. In contrast, Rosario argues that if patients with NIFTP continue to be followed up like those with low risk PTC, the practical impact promoted by these changes would have been minimal or none [22].

Molecular biology studies were performed in 19 cases (63%). *RAS* mutations were the most frequent finding and were identified in 4 tumors (13%). This is in coincidence with other studies, in which overall prevalence of *RAS* mutations ranges from 10-67% [1, 27, 28]. This genetic profile is similar to the one found in other follicular lesions (such as PVCPT, follicular adenoma and follicular carcinoma), and differs from the usual molecular findings in classic PTC, further warranting the reclassification of NIFTP as a

different entity. In our series, *HRAS* and *NRAS* mutations were equally frequent (6.5% each), in contrast with other reports, in which *HRAS* mutations comprise between 25-50% of cases [1, 27–34] being *NRAS* mutations the most usual [27, 28, 35, 36].

The original diagnostic criteria for NIFTP were proposed in 2016 [1], and then modified in 2018 [6] stating that the presence of any true papillary structure would rule out the diagnosis of NIFTP. In addition, if molecular testing (which is not mandatory) is performed, the presence of high-grade mutations, such as *TERT*, *BRAF V600E*, or *RET/PTC* rearrangements would exclude the diagnosis of NIFTP. This item raises the practical question of whether NIFTP can be diagnosed without molecular biology techniques, which are not routinely available in Argentina.

Additionally, an accurate differential diagnosis of NIFTP from encapsulated FVPTC requires, besides routine *BRAF* mutation testing, a complete assessment of the tumour (and not only the capsule) to rule out the presence of papillae [37]. This places higher demands on the pathologists (both in terms of time and expertise), and also may lead to further diagnostic confusion and increasing costs (due to mandatory molecular studies). The benefits are therefore unclear, as both entities share a similar clinical behaviour. Further studies with longer follow up are needed to elucidate these questions.

In conclusion, NIFTP prevalence in this series was among the lowest reported. Excellent response to initial treatment confirms the indolent behaviour of these neoplasms, which will probably lead to a more conservative management, avoiding unnecessary expenses for the health care system, and reducing emotional distress for patients with this diagnosis. Molecular findings differ from other series, which may be related to stringent criteria for diagnosing NIFTP and/or, to environmental or ethnic features of our population.

## Declarations

**Conflict of interest:** The authors declare that they have no conflict of interest.

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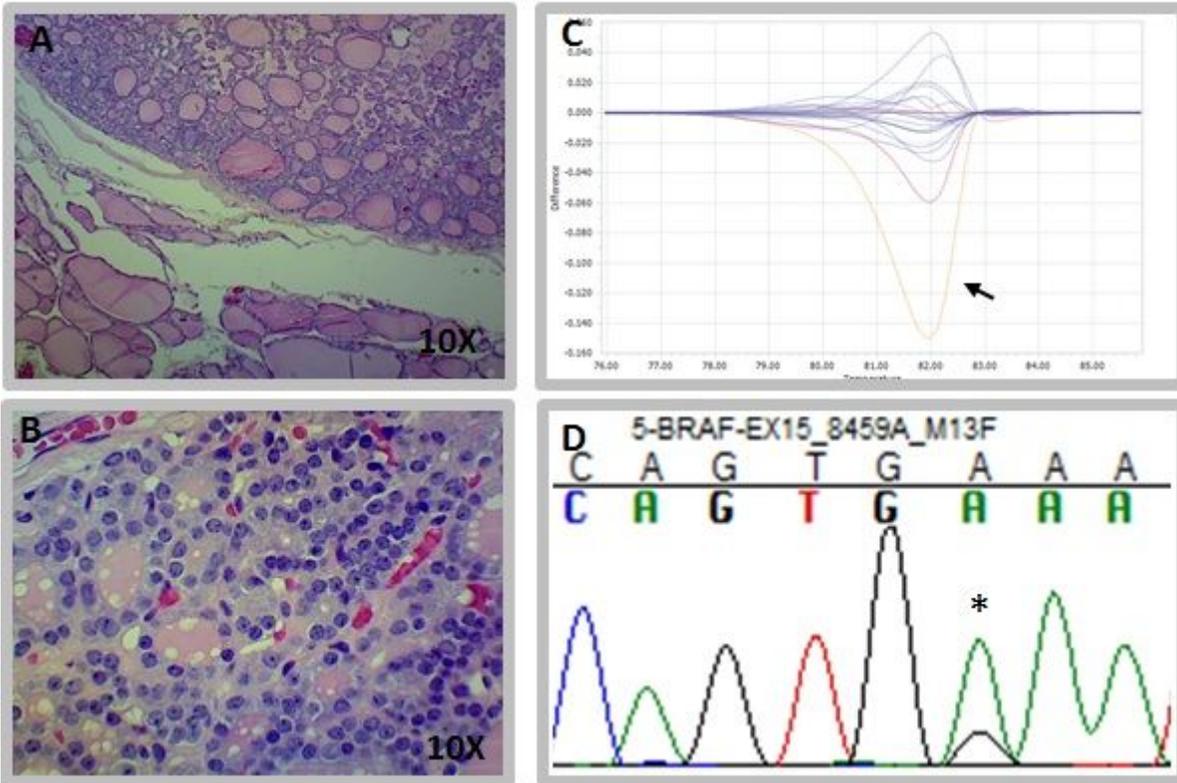
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## Figures

## Histología

## HRM / Secuencia



**Figure 1**

Histology image, HRM and Sanger sequencing. **Panel A** (haematoxylin-eosin, 10x) and **B** (haematoxylin-eosin, 40x) show histologic sections of a non-invasive follicular neoplasm with papillary-like nuclear features. Nuclear characteristics and follicular pattern can be seen in B. This tumor was positive for *BRAF* *K601E* mutation indicated by the arrow on the HRM curve (**C**) confirmed by Sanger sequencing (**D**). Black arrows indicate the curve of the positive sample plus the positive control.

\* in black indicate the base change associated with the mutation. HRM: high-resolution melting