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ORIGINAL ARTICLE

Noninvasive follicular thyroid neoplasm with papillary nuclear characteristics: Clinicopathologic features and follow-up

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Abstract

Introduction: A lesion structurally encapsulated or with noninfiltrating expansive edges, follicular pattern growth, <1% of papillary formation, no psammoma bodies, <30% of trabecular and/or insular solid growth, nuclear score 2-3, no invasion of the tumor capsule or the peritumoral vessels, no tumor necrosis and without high mitotic activity, was once called "papillary thyroid carcinoma (PTC) encapsulated follicular variant" and became "noninvasive follicular thyroid neoplasm with papillary nuclear features" (NIFTP). **Objective:** To review the operated follicular variant PTC. **Materials and Methods:** The cases were adapted to the new classification and the clinicopathologic and follow-up features in our patients with and without NIFTP were described. **Results:** In the follicular variant PTC, 19.3% (21/107) were NIFTP. The range of NIFTPs was between 5 and 50mm; mean ± ESM: 21.8 ± 3.5 mm; 3 NIFTP were larger (>40 mm). All were treated with total thyroidectomy and 20/21 received an ablative dose of I^{131}. At the follow-up (>5 years on average), there were no cases of local, regional or systemic, biochemical or structural recurrences. Comparing the NIFTP and non-NIFTP, similar tumor features were found for the age, gender, maximum tumor dimension, surgical extension, and iodine ablation, median follow-up and recurrent events; p>0.05, without statistical significance. **Conclusion:** Twenty percent of follicular variant papillary carcinomas now reclassified as NIFTP were overtreated and overcontrolled as if they were PTC; no recurrent events or deaths were detected. We cannot distinguish whether the good prognosis is due to the nature of these neoplasms or to overtreatment.

Keywords: papillary thyroid carcinoma; noninvasive follicular thyroid neoplasm with papillary nuclear features; recurrent tumor; overtreatment; over following-up.

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Introduction

In the recent years, thyroid pathology investigations have been focused mainly on the review of encapsulated follicular variant papillary carcinomas (PTC) without capsular and/or vascular invasion.

The process of reclassification of this type of tumors was promoted by the pathologist Yuri Nikiforov (2016), who was the precursor of a new investigation, inviting pathologists, endocrinologists, thyroid surgeons, and even a psychiatrist[1].

It was established that a lesion structurally encapsulated or with noninvasive expansive edges, with follicular pattern growth, with <1% papillary, without

psammoma bodies, <30% of solid growth, trabecular, insular, nuclear score 2-3, without capsular invasion neither the vessels, without tumor necrosis and without high mitotic activity, changes its name from "*encapsulated follicular variant papillary thyroid carcinoma*" to "*noninvasive follicular thyroid neoplasm with papillary nuclear features*" (NIFTP), with the word "carcinoma" disappearing from such technical nomenclature (Figures 1 and 2).

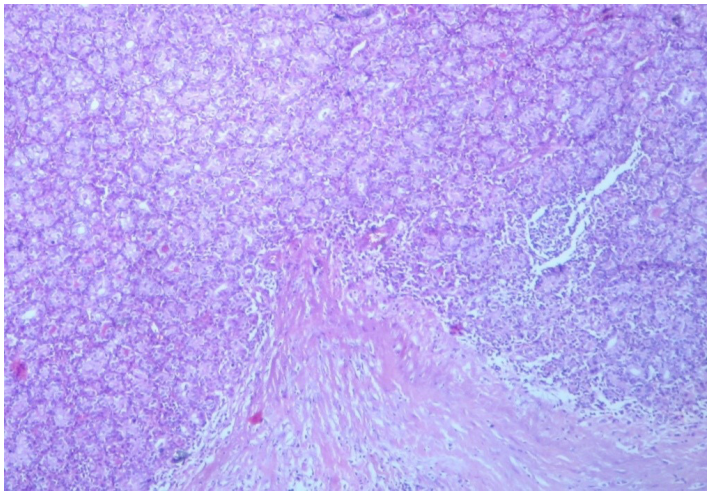

Figure 1. Noninvasive follicular thyroid neoplasm with papillary nuclear characteristics. Hematoxilin and Eosin. Magnification 40X.

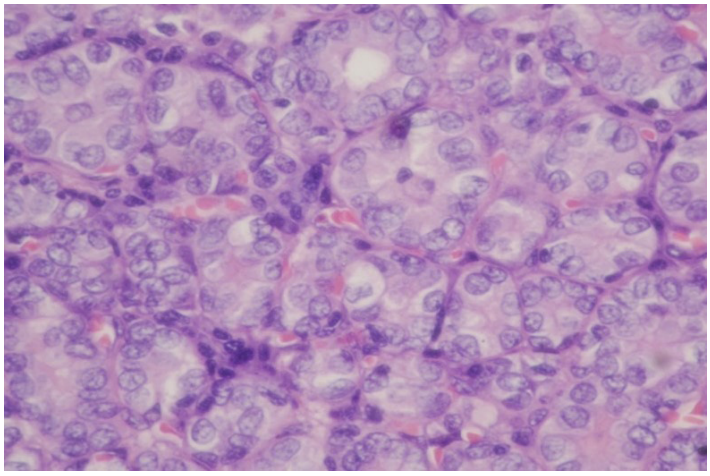

Figure 2. Noninvasive follicular thyroid neoplasm with papillary nuclear characteristics. Hematoxilin and Eosin. Magnification 100X.

The new name for this entity will be included in the endocrine tumor classification system of the WHO[2]. The name change was one of the main news, both in the medical community and in the media[3-5].

ATA has also reviewed this new classification and recommended in 2017 to differentiate encapsulated follicular variant of papillary tumors from nonencapsulated follicular variant of papillary tumors, suggesting that retrospective studies on PTC in recent years should be reviewed and the

results of these subgroups of patients should be observed[6]. Thus, the recommendation motivated the review of operated follicular variant PTC in our patients.

The reclassification of the NIFTPs was introduced to emphasize the low biological potential of these tumors and to reduce the overtreatment and over following-up of these indolent tumors, treating them as a benign neoplasm instead of a carcinoma[7].

The capsule or the expansive edge of the tumor must be examined entirely under a microscope to exclude infiltration, differentiating a NIFTP from a non-NIFTP. That is, a histopathological classification criterion[8].

This study aimed to review the encapsulated follicular variant PTC in our patients in order to adapt them to the new classification, describe their clinicopathologic features, and evaluate the follow-up of patients with and without NIFTP.

Methods

We initially selected cases operated due to PTC, described as encapsulated variant of follicular papillary carcinoma in the histological report. Patients who had a minimum of 5 years of follow-up (surgeries before 2013) were included.

There were 137 cases in the period. Thirty of these cases, who had invasion of the thyroid capsule, were excluded and the remaining 107 cases underwent an anatomopathological review to identify the NIFTP.

In the new review, we identified 21 NIFTPs and compared with the 86 non-NIFTPs.

All surgeries were performed by the same surgeon (JLN) and all histological studies were performed by the same pathologist (OB).

In the statistical analysis, the age and postoperative follow-up between the NIFTP and non-NIFTP groups were compared using the Mann-Whitney test. The chi-square or Fisher test was applied with the rest of the variants, as appropriate. All tests considered $p<0.05$ as statistically significant.

Results

Those NIFTPs originally diagnosed as encapsulated follicular variant PTC represented 19.6% (21 cases).

The average size of the 21 NIFTPs was 21.8 ± 3.5 mm; half of these tumors measured 20mm (range: 5-50 mm). The larger NIFTPs (>40mm) were only 14% (3 cases), without preponderance by gender (2 and 1), and operated at 34, 42 and 55 years old, respectively.

No cases of metastatic lymph node involvement were recorded at the time of diagnosis in any of the patients, even in the 4/21 cases in which the surgical treatment included the central compartment dissection.

These 21 cases were treated with total thyroidectomy. Only one patient did not receive an ablative dose of I^{131} (NIFT of 12 mm). In those who received (94%)

the doses, the doses varied between 100 μC (NIFTP between 5 and 30 mm) and 150 μC (NIFTP between 20 and 26 mm).

During the follow-up of these patients (more than 5 years on average), there were no cases of local, regional or systemic, biochemical or structural recurrent events.

Table 1 shows the statistical significance of the comparison of the clinical, pathological, therapeutic and follow-up features between the NIFTP and non-NIFTP groups.

Table 1. Comparison of the clinical, anatomopathological, therapeutic and follow-up features of the NIFTP and non-NIFTP.

Variables	NIFTP (n = 21)	Non-NIFTP (n = 86)	p
Age (years old)			
Mean ± SD	43.9 ± 0.7	42.8 ± 3.5	p = 0.87 (NS)*
Median (range)	45 (16-70)	41 (18-72)	
< 55	76.2%	72%	p = 0.70 (NS)**
≥ 55	23.8%	28%	
Gender			
Female	71.4%	85%	p = 0.14 (NS)**
Male	28.6%	15%	
Tumor size (mm)			
0-10	14.3%	28.2%	
11-20	42.8%	33.3%	p = 0.48 (NS)**
21-40	28.6%	32.1%	
>40	14.3%	6.4%	
Type of Surgery			
< T.Total	-	18%	p = 0.11 (NS)**
T.Total	100%	82%	
Iodine			
Yes	94.4%	81%	p = 0.32 (NS)**
No	5.6%	19%	
Follow-up (in months)			
Mean ± SD	64.9 ± 6.2	60.5 ± 6.8	p = 0.43 (NS)*
Median (range)	58.3 (0.7-156.8)	34.1 (0.1-268.4)	
Recurrences	0%	0%	-

NS = not significant; SD = Standard Deviation. *Mann-Whitney test; **Chi-square or Fisher test, as appropriate.

The evidence suggested similar tumor features in age, gender, tumor size, surgical range, and iodine ablation; p> 0.05, without statistical significance.

The median follow-up was similar. No recurrent events were recorded in both compared groups.

Discussion

This paper was carried out to review the encapsulated follicular variant PTC and identify the NIFTP; it is a thyroid tumor that, despite the evidence of its indolent behavior, was classified as cancer. Although the ATA and the WHO have already expressed their opinion, it is presumed that, due to its behavior of benign thyroid pathology, the best option is to stop considering it an oncological entity and assign it the new name.

In our experience, NIFTPs were almost 20% of the encapsulated follicular variant PTC. In the experience of Nikiforov et al.[1], they reclassified NIFTP to 100 cases out of a total of 210 patients with follicular variant PTC (47.6%). They reported that patients who had encapsulated lesions did not have recurrent events of the tumor in a period of ten years. On the other hand, the other patients had suffered some recurrent events[1]. Previously, similar behavior was shown by Piana et al.[9].

Xu et al.[10] followed up 79 large NIFTPs (between 4 and 8cm). Half of these patients had not received an ablative postoperative dose. They did not observe recurrent events throughout the cohort, with more than 11 years of follow-up in some cases[10]. Ganly et al.[11] with similar follow-up and without ablative doses had not recorded recurrent events. Recently, Pitoia et al.[12] reported 1/46 patients classified as low risk and 1/17 patients with intermediate recurrent event risk were reclassified as NIFTP. They suggested that a detailed histological report of the PTC features could give more certainty to the risk classification and better estimate of the response rate to treatment[12].

Have we overtreated patients with NIFTP? It is important to remember that these tumors were treated as carcinomas according to the current protocol (surgery and subsequent ablation in most cases). In our experience, all NIFTPs were treated with total thyroidectomy. We even performed central compartment dissection in 4/21 patients, operated on between 2002 and 2006. At that time, the therapeutic approach in the case of a PTC was to perform total thyroidectomy and prophylactic ipsilateral anterior compartment dissection. We have reviewed the clinical history of these four cases, also proving that one of the patients had a history of a breast tumor that would surely irradiate, and in another, the tumor was larger than 40 mm. Also, in our experience, almost 95% of the NIFTPs received an ablative dose.

Have we exaggerated in following them up? In more than 5 years of follow-up, we have not recorded recurrent events.

It is understandable to doubt whether the good prognosis is due to the histological nature of the NIFTP or to the treatment received.

This reclassification into NIFTP and non-NIFTP will lower the incidence of PTC, and by reducing the PTC, the proportion of all the PTC features will increase, and some will be associated with poor prognosis (extrathyroidal invasion, multifocality etc.).

As an example of this the experience, Wong et al.[13] distinguished 94 NIFTP in 348 cases of PTC (27%). When excluding them as carcinomas, the rate of other histological characteristics of PTC was significantly increased in the remaining PTCs, such as extrathyroidal invasion (from 19% to 26%), lymphovascular invasion (from 27% to 37%) and lymph node metastases (from 19% to 26%) (all with $p<0.05$)[13].

The distribution in risk classification of ATA was also modified, especially in the low risk. Although the survival rate of the PTC is very high, the exclusion of the NIFTP in the analysis should not significantly change this prognosis[6].

On the other hand, due to the effects of this reclassification in the rate of malignancy and in the clinical management algorithms, it is imperative to explore whether the fine needle aspiration biopsy (FNA) could differentiate between a NIFTP, a PTC and a follicular adenoma (FA). The FA is an entity that shares a similar histomorphological appearance and molecular genotype as the NIFTP[14].

FA are well divided as partially or totally encapsulated, and composed of follicles that can be organized in several growth patterns (microfollicular, macrofollicular, trabecular, etc.), lacking the nuclear features of PTC[15].

Faquin et al.[16] evaluated the potential impact of NIFTP on the risk of malignancy established by the diagnostic categories of the Bethesda system, studying the proportion of NIFTP in the different categories - 0.2%, 0.4%, 5%, 9.9%, 17.6% and 2.6% for Bethesda I, II, III-AUS, III-FLUS, IV and V-VI, respectively. The authors concluded that this histological reclassification has a significant impact on the risk of malignancy of the indeterminate categories (III) of the Bethesda system[16]. Bizarro et al.[17] also highlighted the fact that this reclassification can have an impact on the diagnosis of the Bethesda system. In their paper, most NIFTPs had lack of nuclear pseudoinclusions and papillary structures, allowing the inclusion in the follicular nodule cases. For these authors, nuclear size and microfollicular clusters could suggest discrimination between NIFTPs and PTC invasive follicular variant[17].

Zhao et al.[18] and Blandler et al.[19] matched the cytological, histological and molecular findings of 97 cases originally diagnosed with PTC. They noted that the Bethesda system did not clearly identify NIFTPs from non-NIFTPs. However, the NIFTPs were mostly classified as Bethesda III (atypia or lesion of undetermined significance) or IV (suspicious of follicular neoplasia) when compared to infiltrative neoplasms, mostly classified with Bethesda V and VI. The authors reported that cytology is not prepared to properly distinguish between an invasive and a noninvasive follicular neoplasm[18,19].

In our study, most of the FNAs did not report the categorization of the Bethesda System (2009); (please consider that we include PTCs operated before 2013).

In the molecular analysis, although the experiences included a limited number of samples, they showed that most of these lesions are driven by clonal genetic alterations and for this reason, they are neoplasms rather than hyperplastic proliferation. When NIFTPs are defined with such strict histopathological criteria, they are not expected to show molecular alterations associated with classical PTCs such as mutations of the BRAF V600E gene. Instead, these tumors were associated with mutations in the RAS gene, which

have been associated with follicular thyroid tumors such as FA, follicular thyroid carcinoma and non-NIFTP[20-22]. No molecular studies were performed on the PTCs of our patients.

Conclusion

We have distinguished 20% of NIFTP originally overtreated and over controlled as cancer; no recurrent events of the disease were detected. We cannot distinguish whether the good prognosis is due to the nature of these neoplasms or to overtreatment. Since the diagnosis of NIFTP is anatomopathological, the entire tumor must be studied. When the preoperative tests and examinations advance in the diagnosis of NIFTP, performing a hemithyroidectomy for a NIFTP will be enough, even for larger tumors (>40 mm). The patient should be informed that the resected tumor is not a carcinoma.

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