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RESEARCH ARTICLE

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in Mureș County, Romania: Incidence and impact of reclassification over a six-year period (2016-2021)

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Objective: In 2016 a group of expert endocrine pathologists proposed a new terminology, NIFTP (Non-invasive follicular thyroid neoplasm with papillary-like nuclear features) for a histological subtype of thyroid carcinoma (encapsulated follicular variant of papillary thyroid carcinoma, non-invasive type). In this study, we aimed to assess on a retrospective basis the epidemiological trend and overall incidence of NIFTP in Mureș county, Romania, over a six-year period (2016-2021). **Methods**: All NIFTPs registered between 2016-2021 in Târgu-Mureș Pathology Departments were reevaluated. NIFTP's incidence was calculated by dividing the number of NIFTPs with the number of papillary thyroid carcinomas (PTCs). Further on, we compared NIFTP's incidence between 2016-2018 with NIFTP's incidence between 2019-2021, as the diagnostic criteria of NIFTP were revised in 2018. **Results**: Forty-six cases of NIFTP were registered in our departments between 2016-2021, resulting in an overall NIFTP incidence of 17.9 % [CI (95%): 7.6-32.5] among the 257 PTCs. When we compared the NIFTP' incidence between the two study periods (2016-2018 versus 2019-2021), our data revealed that the NIFTP's overall incidence has dropped from 21.4 % [CI (95%): -14.5-60.1] to 15% [CI (95%): -8.2-43] in the second evaluated period (p=0.034). **Conclusion**: The overall NIFTP incidence was low in our departments between 2016-2021. Moreover, NIFTP's incidence decreased after 2018, following revision of the diagnostic criteria. Our results highlight that very stringent morphologic criteria need to be apply when making a diagnosis of NIFTP, in order to avoid a misdiagnosis and/or an overtreatment of a tumor with indolent behavior.

Keywords: NIFTP, incidence, impact, reclassification

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Introduction

In 2016 a working group of endocrine pathologists critically re-examined encapsulated follicular variant of papillary thyroid carcinomas (EFV-PTC). They suggested reclassification the non-invasive type of EFV-PTC as a neoplasm with "very low malignant potential". A new terminology was proposed for these tumors: "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) [1]. The primary aim of this reclassification was to avoid the term carcinoma and the consequent risk of overtreatment of noninvasive tumors that have an indolent clinical course. At that time, it was estimated that more than 45000 patients worldwide would be affected by this reclassification each year, thereby significantly reducing the clinical and psychological consequences associated with the diagnosis of cancer [1].

NIFTP is now considered a distinct category in the WHO (World Health Organization) Classification of *Tumors of Endocrine Organs* [2]; it belongs to a "borderline" tumor category, together with follicular tumor of uncertain malignant potential (UMP) and well-differentiated tumor of UMP.

The terminology and the pathologic criteria were revised in 2018 [3]. NIFTP is referred to as a noninvasive, encapsulated or well-demarcated neoplasm, with follicular architecture and papillary-like nuclear features. Well-formed papillae, psammoma bodies, typical findings of the aggressive subtype of PTC or poorly differentiated carcinoma, *BRAF* mutations are all lacking [3].

Seven years after its introduction, this new entity still attracts considerable interest. No doubt, NIFTP represents a significant paradigm shift in thyroid pathology. Nevertheless, the precise amount of its impact is directly influenced by the incidence of NIFTP in each population [4].

In this study, we aimed to assess on a retrospective basis the epidemiological trend and overall incidence of NIFTP in Mureș county, Romania, over a six-year period (2016-2021).

Methods

Case selection

We performed a 6-year retrospective study including all NIFTP and PTC cases registered in Târgu-Mureș Pathology Departments, Emergency and County Mureș Hospitals, respectively, between 2016 and 2021.

The Ethics Committee of the "George Emil Palade" University of Medicine, Pharmacy, Sciences and Technology of Târgu-Mureș approved the study (Letter of approval no.36/07.03.2017).

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Pathological data

Demographic and pathological data were obtained from original pathological reports and institutional database registries. The following data were used in the study: age at diagnosis, gender, surgical procedure (lobectomy ± isthmectomy/total thyroidectomy/total thyroidectomy with lymph node dissection) and tumor histological sub-type.

The histological type of the tumor was established according to 2017 WHO Classification of Tumors of Endocrine Organs [2]. The diagnosis of PTC relied on characteristic, papillary-type nuclear features (enlargement, overlapping, irregularity of the nuclear contours, grooves, nuclear pseudoinclusions, ground glass or clearing appearance) and confirmation of either papillary pattern or follicular architecture with invasive characteristics. Tumors defined as NIFTP had to meet strict inclusion and exclusion criteria. Inclusion criteria consisted of encapsulation or clear tumor demarcation, follicular growth pattern, PTC nuclear features. Exclusion criteria were the following: vascular or capsular invasion, papillae, psammoma bodies, high mitotic activity, tumor necrosis, >30% solid/trabecular/insular growth pattern.

Statistical analysis

Statistical Package for Social Sciences (SPSS, version 20, Chicago, IL, USA) was used for all statistical analysis. Data were categorized as nominal or quantitative variables. Number and percentages were used to express nominal variables; they were compared using the chi-squared test or Fisher's exact test.

Kolmogorov-Smirnov test was applied to test for normality of distribution of quantitative variables, graphically confirmed with a histogram; quantitative variables were described by mean ± standard deviation or median and percentiles (25; 75%), whenever appropriate. To compare continuous values with Gaussian distribution, the student's t test was used.

Linear regression was used to calculate the linear relationships between dependent (Y - number of thyroid surgical specimens) and independent variables (X - number of PTCs, and NIFTPs, respectively) . To describe the dependent variable, a linear regression model was applied, using a straight line, defined by the $Y = a + b \times X$ equation (Y - intersection of the line, b – the slope of the line).

NIFTP's incidence was calculated by dividing the number of NIFTPs with the number of PTCs.

Further on, we compared NIFTP's incidence between 2016-2018 with NIFTP's incidence between 2019-2021, as the diagnostic criteria of NIFTP were revised in 2018.

The level of statistical significance was defined as $p<0.05$.

Results

Patient's characteristics

Two hundred and fifty-seven (n=257) PTCs and 46 NIFTPs were registered in our departments between April 2016 and December 2021. **Table 1** summarizes the frequencies of these two histological types of thyroid tumors, along with their corresponding demographic data. For both PTCs and NIFTPs, more than half of the patients were younger than 55 years-old (n=163, 63.4% and n=31, 67.4% respectively) and the majority were women (n=207, 84.4% and n=43, 93.5% respectively). Lobectomy was performed in 42.8% (n=110) and 41.3% (n=19) cases of PTC and NIFTP, respectively. Total thyroidectomy was a little more prevalent for both PTC (n=134, 52.1%) and NIFTP (n=27, 58.7%) cases. Total thyroidectomy with lymph node dissection was performed in 13 cases of PTC (5.1%).

Prevalence trend of NIFTP and PTC along the study period

Figure 1 and **Figure 2** demonstrate an increasing trend in the annual rate of PTC over the study period (from 42 cases in 2016 to 62 cases in 2021), irrespective of the number of thyroid surgical specimens (R^2-0.00019, p=0.08). NIFTPs were less numerous; we observed a slightly increasing tendency in the annual prevalence of NIFTPs at the beginning of the study period, followed by a constant trend thereafter. The number of NIFTPs was slightly dependent on the number of surgeries (R2 =0.249, p=0.03).

Table 1. Clinical data for PTC and NIFTP study cases

	PTC (n=257)	NIFTP (n=46)	p
Factors			
Age at surgery (mean±SD, years)	48.9 ± 13.7	47.7 ± 13.1	0.609
Age (n, %)			
< 55 years	163 (63.4)	31 (67.4)	0.606
≥ 55 years	94 (36.6)	15 (32.6)	
Gender (n, %)			
female	217 (84.4)	43 (93.5)	0.106
male	40 (13.2)	3 (6.5)	
Type of surgery (n, %)			
Lobectomy	110 (42.8)	19 (41.3)	0.264
Total thyroidectomy	134 (52.1)	27 (58.7)	
Total thyroidectomy with lymph node dissection	13 (5.1)	0	
Period (n, %)			
2016-2018	117 (45.5)	25 (54.3)	0.336
2019-2021	140 (54.5)	21 (45.7)	

PTC: papillary thyroid carcinoma; NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features; p<0.05.

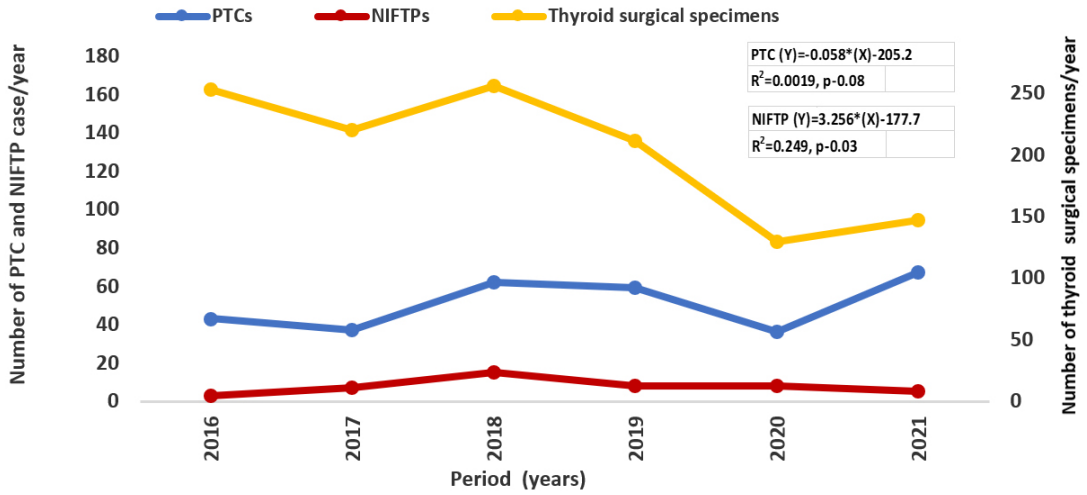

Fig. 1. Prevalence rate of NIFTP and PTC cases over the study period, with respect to the number of thyroid surgical specimens. PTC: papillary thyroid carcinoma; NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features; p<0.05.

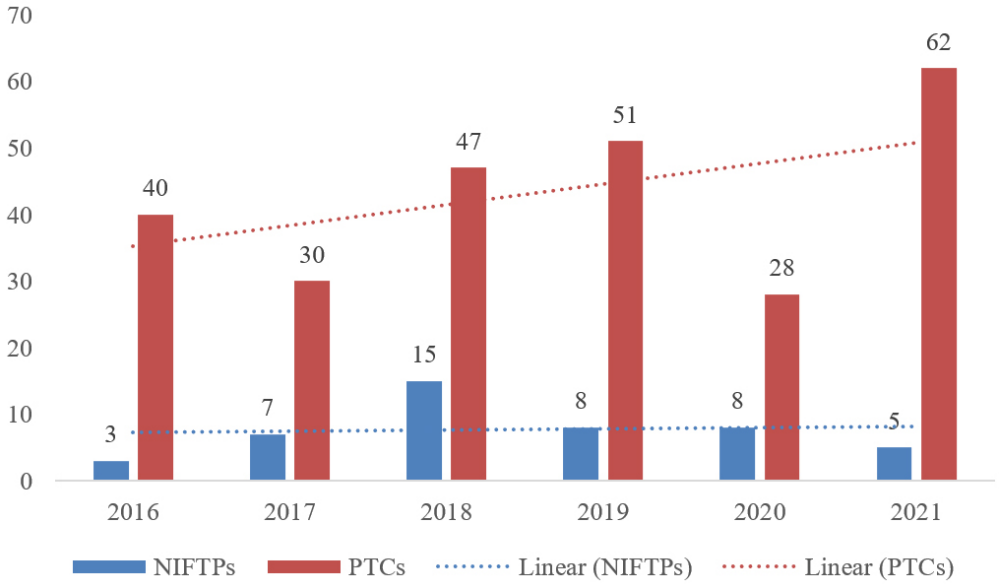

Fig. 2. Annual rate of NIFTP and PTC cases over the study period. PTC: papillary thyroid carcinoma; NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features.

Incidence of NIFTP

Forty six (n=46) cases of NIFTP were identified along the study period , with an overall NIFTP incidence of 17.9 % [CI (95%): 7.6-32.5] among 257 PTCs. When we compared the NIFTP' incidence between the two study periods (2016-2018 *versus* 2019-2021), our data revealed that the NIFTP's overall incidence has dropped from 21.4 % [CI (95%): -14.5-60.1] to 15% [CI (95%): -8.2-43] in the second evaluated period (p=0.034).

Discussions

In 2016, Nikiforov et al. in their seminal article suggested the reclassification of a low-risk thyroid cancer as NIFTP, removing the term "carcinoma /cancer" from the name of the tumor [1]. Immediately, NIFTP was recognized as a hot topic among the scientific community and more than 80 publications reporting their institutional experience with NIFTP were published within less than 2 years thereafter [5–10]. No doubt, NIFTP and its introduction in daily practice represents an important paradigm shift in thyroid pathology, with important consequence for the diagnosis and treatment of thyroid tumors [11].

Nevertheless, the extent of the changes related to NIFTP reclassification is influenced by the incidence of NIFTP in an institution or a particular population [12]. In our departments, 46 NIFTPs were registered over a 6-year period (2016-2021). We observed a slightly increasing trend in the annual prevalence at the beginning of the study period, followed by a constant trend thereafter. The overall NIFTP incidence was 17.9 % [CI (95%): 7.6-32.5] of all PTCs registered in our departments over the study period.

Large variations in NIFTP incidence are reported by different studies. In a meta-analysis performed by Rana C et, the authors have collected data from 50 studies from Europa, America, and Asia [4]. They found that the NIFTP's overall incidence is 6% [CI 4.4-8.2] of all PTCs worldwide. Nevertheless, significant discrepancies were observed between Asian studies that have reported much

lower incidence of NIFTP (2.1% [CI 1.2-3.6]) compared to European (9.6% [CI 5.9-15.3]) and American (9.3% [CI 6.7-12.9] North America and 15% [CI 12.8-17.5]) counterparts. The explanation for this variance is multifactorial. One of the major causes, no doubt, is represented by the different approaches in the histopathological interpretation of the thyroid lesions with follicular arhitecture [9]. In a previous study aiming to assess the epidemiological trend of different types of well-differentiated follicular-cell derived thyroid carcinomas over a 15-year period (2001-2015) in the Department of Pathology, Emergency County Hospital Târgu-Mures, Romania we revised 375 cases of PTC; of these 125 were reclassified as NIFTPs, resulting in a NIFTP overall incidence of 33.3% of all PTCs [13]. Compared to the present study, this study did not include cases of papillary thyroid micro-carcinoma, which could explain the differences in NIFTPS's overall incidence between these two studies. Also, in the abovementioned study, a diagnosis NIFTP was performed on a retrospective basis. Thus, sampling of the tumor capsule entirely , a required criteria for a diagnosis of NIFTP, was not performed as not considered a standard method at that time. This might have led to an overestimation of the NIFTP diagnosis.

After its first description in 2016, the diagnosis of NIFTP has been revised later-on, recommending more precise criteria [3,14–18]. In 2018, a group of expert endocrine pathologists, conducted by Thompson LDR [3] have published a synoptic article, a monograph, serving as a guide for pathologists when dealing with a diagnosis of NIFTP. This article highlights all the details regarding the morphological diagnostic of NIFTP (both inclusion and exclusion criteria), covering also the more recently introduced refined criteria for NIFTP (e.g.<1%papillae substitutes with no papillae). In line with this, studies have shown that with time, especially after 2017, there has been a declining trend in NIFTP rates, particularly in North American and European studies [4]. In the present study, as well, a similar trend was observed. The overall incidence of NIFTP has dropped from 21.4 % [CI (95%): -14.5-60.1] in 2016-2018 to 15% [CI (95%): -8.2-43] in 2019-2021 and the difference was statistically significant (p=0.034). Hence, since the introduction of this new entity, pathologists are getting more versed and are more watchful on NIFTP diagnostic features.

Conclusion

Our data revealed that the overall NIFTP incidence was low in our departments between 2016-2021. When the incidence of NIFTP was compared between the two study periods (2016-2018 *versus* 2019-2021), a significant declining trend in the incidence rates was observed in the second evaluated period. The fact that the incidence decreased after refining the diagnostic criteria in 2018, emphasizes the need to apply very stringent histomorphologic criteria when making a diagnosis of NIFTP, in order to avoid a misdiagnosis and/or an overtreatment of a tumor with indolent behavior.

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Authors' contribution

ANB (Conceptualization, Methodology, Project administration, Writing – original draft);
AC (Data curation, Formal Analysis, Software, Methodology);
EAS (Data curation, Investigation, Visualization);
RC (Data curation, Investigation, Visualization);
AB (Conceptualization, Supervision, Validation, Writing – review & editing).

Conflict of interest

None to declare.

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