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ORIGINAL PAPER

Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features is Rare: A Population Based Study of Incidence

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Abstract

The renaming of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was proposed by a group of experts in 2016 to prevent overtreatment of indolent, low-risk thyroid cancers. The aim of this study was to estimate the incidence and outcome for patients meeting the NIFTP criteria in a well-defined geographic region. Our cohort consisted of 134 patients with papillary thyroid carcinoma from the Region of Southern Denmark (RSD), 2007 to 2011. Patients were retrieved from the Danish Thyroid Cancer (DATHYRCA) Database. All potential NIFTP cases were reviewed by a thyroid pathologist. We identified no cases meeting all diagnostic criteria, but one probable NIFTP case from 2007 to 2011. The patient was treated according to the national guidelines and is alive and recurrence-free after 106 months of follow-up. Molecular testing showed *KRAS* mutation. In a population based set up the incidence rate of NIFTP is very low.

Keywords NIFTP · Incidence · Thyroid · DATHYRCA · Follicular variant of papillary thyroid carcinoma

Introduction

The incidence of thyroid cancer has increased globally over the past 40 years [1, 2], with a substantial rise in the papillary subtype [3]. The follicular variant of papillary thyroid carcinoma (FVPTC) accounts for approximately 20% of all thyroid cancers in Europe and North America [4, 5]. These are known to have an indolent course. To prevent overtreatment, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was proposed by an expert panel in 2015 and enrolled in the WHO Classification of tumors of endocrine organs in the 2017 edition [6].

The diagnosis and classification of thyroid tumors are often dependent on some degree of subjectivity [7–9] NIFTP is by definition a tumor, which is well demarked or has an intact capsule and an (almost) exclusive follicular growth pattern. Similar characteristics applies for follicular adenomas. Hence the only disparity between the two entities is the nuclear features, i.e. whether they are papillary or not [10].

Attempting to minimize this subjectivity nuclear scoring systems have been proposed [11]. The current diagnostic criteria are still debated, and the diagnosis of NIFTP is still evolving, as such it has been proposed to exclude specimens with any true papillae [12, 13]. Only a few studies have surveyed the incidence of NIFTP [14–16], and it has, to the best of our knowledge, never been investigated on a population-based level.

The aim of this study was to investigate the incidence and outcome of NIFTP in a well-defined geographic area.

Materials and Methods

The study design was a population-based cohort study. Most patient and tumor-related data were collected prospectively. Patients diagnosed with papillary thyroid carcinoma (PTC) in RSD (1,220,763 inhabitants as of January 1, 2018) during

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January 2007 to December 2011 were identified in the Danish Thyroid Cancer Database (DATHYRCA Database). RSD is one of five well defined geographic regions in Denmark, containing roughly 20% of the population.

All patients diagnosed with thyroid cancer in Denmark since 1996 have been prospectively registered in the DATHYRCA Database [17]. The validated database consists of systematically registered clinical, surgical, histopathological and follow-up data.

The study was based on data available from the DATHYRCA Database on March 14, 2017.

Patients were classified according to NIFTP criteria (Table 1) [18].

By reviewing pathology reports, patients not compiling with NIFTP criteria were excluded. Patients, who could not be excluded by pathology reports alone, had their original thyroid specimen reevaluated by an experienced thyroid pathologist (SRL).

Our cohort consisted of 134 patients. Of these, 108 patients were excluded after reviewing pathology reports, i.e. if dominant papillary growth pattern or invasiveness was described. After evaluation of the remaining 26 specimens, 25 patients were excluded (Fig. 1). One case complied with almost all of the NIFTP criteria, except for having the whole capsular area represented on the slide (Fig. 2).

The nuclear features were evaluated and scored according to the three-point nuclear scoring system (Table 2) [11].

The potential NIFTP case was subsequently tested for mutations by next generation sequencing (NGS). DNA was extracted from 10 µm paraffin slides using GeneRead DNA FFPE kit (Qiagen, Germany) according to manufacturer's instructions, and quantified using an RNase P TaqMan Copy Number Reference Assay performed on a QuantStudio 12K Flex Real-Time PCR System (Applied Biosystems, Foster City, CA). NRAS, KRAS and BRAF hotspot mutations were investigated using Ampliseq Colon and Lung Cancer NGS Panel v2. Libraries were prepared using the Ion AmpliSeq Library Kit 2.0 and Ion Xpress Barcode Adapters 1–16 Kit

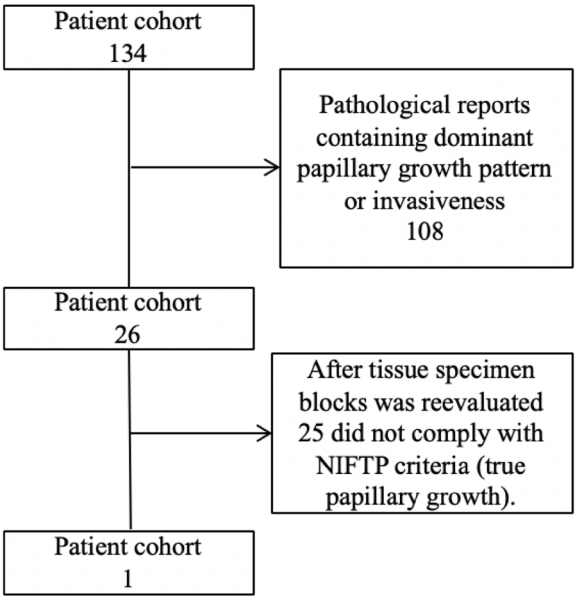

Fig. 1 Flow diagram showing reasons for exclusion

in 10 µL reaction volume with 5 ng template DNA. Library quantitation was performed using the Ion Library Quantitation Kit. Sample preparation was performed using the Ion PGM Template Hi-Q View OT2 Kit on the Ion OneTouch 2 and Ion OneTouch ES instruments. Sequencing was performed using the Ion Torrent PGM System with Ion PGM Sequencing Hi-Q View Sequencing Kit and Ion 318 Chip Kits v2. Data analysis, including base calling, quality scoring, trimming, demultiplexing, and alignment, was performed using standard Torrent Suite v5.4 workflows. All NGS related kits and instruments were supplied by Life Technologies, USA.

To determine outcome, follow-up data from the DATHYRCA Database was used and supplemented by review of medical records. Data of the population of RSD were retrieved from StatBank Denmark [19]. The project was

Table 1 Criteria for Noninvasive follicular thyroid neoplasm with papillary-like nuclear features

1.	Well demarcated/encapsulated follicular patterned tumor
2.	Nuclear cytology of PTC. (i.e. nuclear score of 2–3)
3.	Noninvasive characteristics
	a. No tumor capsule invasion or invasion into the surrounding thyroid parenchyma
	b. No lymphovascular invasion
4.	NIFTP predominantly shows a follicular growth pattern. However, the presence of $<1\%$ papillary structures and $\leq 30\%$ of solid growth pattern (by area) is allowed (papillary structures are hallmark features of conventional carcinoma)
5.	No tumor necrosis
6.	No high mitotic activity three or more mitotic figures in ten consecutive high-power fields exclude the diagnosis of NIFTP (this criterion requires future clinicopathologic validation)

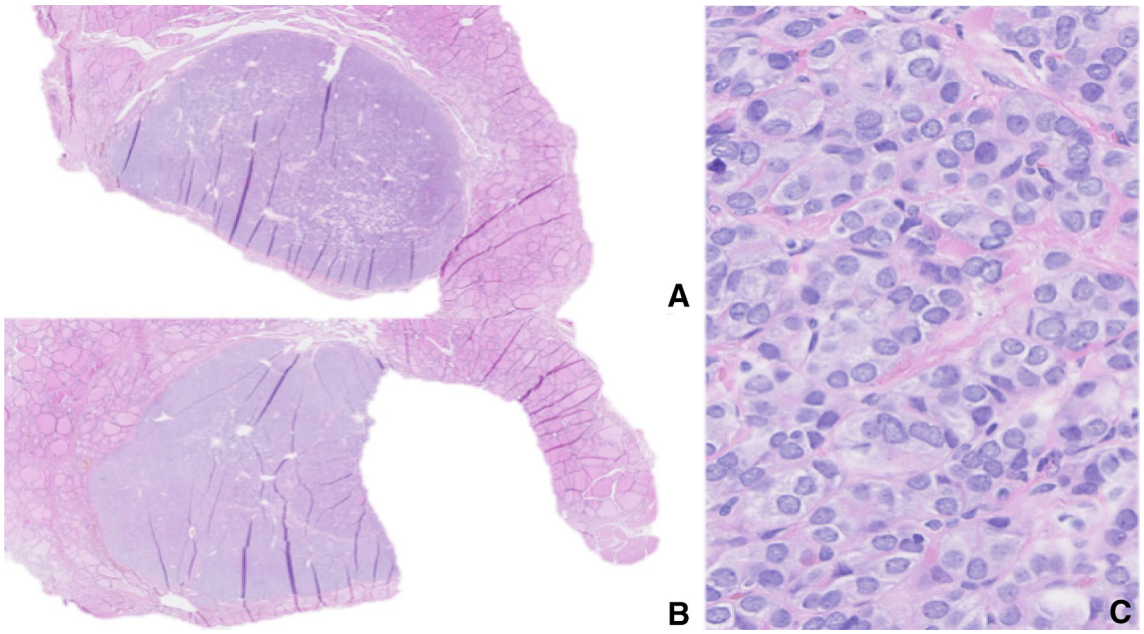

Fig. 2 Probable NIFTP case: **a**, **b** two different sections showing a well demarked, encapsulated tumor. **c** Nuclear score 2

Table 2 Nuclear score (Table 2) was calculated from the sum of three features (each 0 or 1)

1.	Size and shape:
	a. Enlargement
	b. Elongation
	c. Overlapping
2.	Membrane irregularities:
	d. Irregular contours
	e. Grooves
	f. Pseudoinclusions
3.	Chromatin characteristics:
	g. Chromatin clearing
	h. Margination of chromatin to membrane
	i. Glassy nuclei

Score will vary between 0 and 3, and a total score of 2 or 3 is required for a diagnosis of NIFTP

approved by the Regional Ethics Committee (S-20160178) and by the National Danish Data Protection Agency (17/6146).

Results

Incidence

We found one probable case of NIFTP in RSD in the period 2007–2011. The patient was female, aged 55. The lesion (Fig. 2) was well demarked and encapsulated, and all though completely submitted, the lesion was not fully represented on the slide, probably due to fragmentation during tissue preparation. Because capsular invasion in this particular area cannot be evaluated, the case would be excluded as NIFTP using strict criteria (or in a clinical setting). The tumor was discovered incidentally using a MRI scan for diagnosing neck pain. Two FNA was done, the first with suspicion of follicular neoplasm and the second with suspicion of adenoma. Even though most pathologist do not suggest the diagnose of adenoma by FNA, because the diagnosis requires histologic evaluation of the capsule.

The lesion measured $17 \times 10 \times 10$ mm showed follicular growth pattern and no tumor necrosis or high mitotic rate was observed. No capsular- or vascular invasion was found. The cells had enlarged, elongated nuclei with thickened membranes and scored 2 points in nuclear score. By NGS KRAS mutation was identified.

Outcome

The patient was, in accordance with guidelines at the time, treated with total thyroidectomy and subsequently received ablative radioiodine treatment [20]. The patient was alive without sign of recurrence after 106 months of follow-up.

Discussion

In this population based study we reviewed all patients treated for papillary thyroid carcinoma in a well-defined geographical region (RSD) over a 5-year period to estimate the incidence of NIFTP. Of 134 patients, 1 probable NIFTP case was found.

The strength of this study is the prospective patient collection through the DATHYRCA database with a very high degree of completeness [17] and the unique personal identity number for Danish citizens ensuring a high quality in follow-up data and the possibility for searches throughout governmental registries. The Danish Pathology Register has registered diagnosis of pathological specimens in Denmark since September 1968 (http://www.patobank.dk). Registration became mandatory in 1997, with registration of all histological and cytological reports [21]. DATHYRCA database is an established and validated thyroid cancer database and is routinely checked for completeness and missing cases in correlation with the governmental registries [17]. As data are retrieved from the national database selection bias is reduced, and it is also unbiased by social class. Further all cases in our study were reviewed by an experienced thyroid pathologist (SRL).

One might question whether the presented case actually represents a NIFTP. The first inclusion criteria state "Well demarcated/encapsulated follicular patterned tumor" has to be present for a tumor to be classified as NIFTP. In our case the whole tumor was not fully represented on the slide. Therefore one could argue the number of cases found is zero. We opted to include the case to show a "best-case" scenario for NIFTP incidence in RSD. Our patient cohort consisted of patients diagnosed with PTC. One could argue we should have included follicular adenomas and other benign tumors to increase the amount of possible NIFTP cases found. We do, however, believe this would be counterproductive as this would increase number of patients receiving a "pre-malignant" diagnosis, something the diagnosis was introduced to prevent. Extensive studies have already been done to show the change in risk of malignancy for FNA after the NIFTP diagnosis was introduced [22–24].

Previous studies [14–16] have also examined the incidence of NIFTP, these however are from selected populations which may have affected the results. One article reports 2.1% in a study population of 4790 PTC cases [15] while another study found 7% out of 200 patients [14]. The former is closer to the 0.75% of NIFTP cases in our patient cohort. An Asian study examined the incidence across six countries and found the incidence at 1.6% (95% CI 0.9–2.5%; 7 studies) among 26.604 PTC patients. The incidence of NIFTP was initially reported as high as 13.6–25% among PTC patients at different institutions [4, 25, 26]. These rates would indeed prove the need for a reclassification of the diagnosis. However, a NIFTP incidence of approximately 1/5 of PTC cases was something we could not confirm in our study. We speculate that the difference in incidence could stem from subjectivity in interpretation of nuclear features. Maybe in RSD the threshold for naming a lesion true papillary is higher, hence a lesion might be called a follicular adenoma instead of NIFTP or perhaps the diagnostic thresholds for "when something is papillary enough" have differed between North America, and elsewhere over the years. This hypothesis is shared by Poller et al. who discusses that the majority of NIFTP lesions in the United Kingdom would previously have been diagnosed as follicular adenomas, reflecting different thresholds for papillary type nuclei [27].

As thyroid pathologists know, it is not always easy to decide, whether papillary characteristics are present or not. In some cases, it is obvious, as all the classical features are present. In other cases only, some of the features are present or the nuclear changes are more subtle. In these cases, one pathologist might call a tumor PTC and another find that criteria are not sufficient for such a diagnosis. In these cases, if the tumor is encapsulated and with follicular growth pattern one pathologist might diagnose NIFTP and another follicular adenoma. Alternatively, NIFTP is simply a rare entity in RSD.

The scoring system is an attempt to unify diagnostic criteria and thereby minimize subjectivity when diagnosing PTC [4]. The scoring system is kept at a low level of complexity to reduce mistakes and subjectivity. In our opinion whether nuclear features are sufficient to meet criteria and obtain sufficient score to diagnose PTC and thus also NIFTP, is still heavily dependent on subjectivity. This uncertainty and subjectivity are described both in literature and clinical practice [8]. A multi-institutional review article remarks, "the nuclear scoring scheme may allow for a more systematic approach to classification, but does not entirely remove the issues of interobserver variability" [28]. Another study showed the interobserver variability when reviewing benign nodules vs. carcinomas in thyroid specimens, was approximately 10% for expert reviewers [29].

Many attempts have been made to distinguish thyroid nodules by molecular testing. Something that is gaining a bigger role, in some countries in the differential diagnosis and managing of thyroid nodules, especially regarding fine needle biopsies [30]. Still a genetic mutation alone cannot classify a thyroid nodule nor be used as a prognostic marker. But the presence of a mutation can in some instances help to classify a lesion. Also, a genetic mutation is much less prone to subjectivity. As such we reviewed our case for mutations.

Molecular tests have previously confirmed that NIFTP not only looks and behaves as follicular adenomas but also

share similar genetic mutations [10]. NIFTP's are therefore most often found with RAS mutations, whereas BRAF V600E mutations are more likely to be found in classic PTC or in the invasive follicular variant of PTC [30, 31]. In our case, we identified a *KRAS* mutation, which is most often seen in follicular adenomas [10].

Previously genetic similarity between NIFTP and follicular adenomas has been described by Johnson et al. who concluded that NIFTP is an indolent neoplasm that is similar to follicular adenomas and speculate that NIFTP is a pre-invasive neoplasm that can transform into carcinomas [10]. This also applies for follicular adenomas as both can contain RAS mutations. If one were to identify a *BRAF* V600E mutation in a possible NIFTP case that might indicate a potential for invasive behavior. Previous studies have found a similar invasive behavior in NIFTP tumors. Parente et al. demonstrated malignant behavior in 6% of patients classified as NIFTP [15] and a Korean study presented similar data with 3% of NIFTP cases presenting with micrometastatic disease in the central neck lymph nodes [32].

Conclusion

In a population based set up the incidence rate of NIFTP is very low.

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Compliance with Ethical Standards

Conflict of interest No competing financial interests exist.

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