REVIEW

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a review for clinicians

Pedro Wesley Rosario and Gabriela Franco Mourão

Santa Casa de Belo Horizonte, Minas Gerais, Brazil

Correspondence should be addressed to P W Rosario: pedrowsrosario@gmail.com

Abstract

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or clearly delimited, noninvasive neoplasm with a follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC). It is considered a 'pre-malignant' lesion of the RAS-like group. Ultrasonography (US), cytology and molecular tests are useful to suspect thyroid nodules that correspond to NIFTP but there is wide overlap of the results with the encapsulated follicular variant of PTC (E-FVPTC). In these nodules that possibly or likely correspond to NIFTP, if surgery is indicated, lobectomy is favored over total thyroidectomy. The diagnosis of NIFTP is made after complete resection of the lesion by observing well-defined criteria. In the case of patients who received the diagnosis of FVPTC and whose pathology report does not show findings of malignancy (lymph node metastasis, extrathyroidal invasion, vascular/capsular invasion), if the tumor was encapsulated or well delimited, the slides can be revised by an experienced pathologist to determine whether the diagnostic criteria of NIFTP are met, but special attention must be paid to the adequate representativeness of the capsule and tumor. Since NIFTP is not 'malignant', tumor staging is not necessary and patients are not submitted to thyroid cancer protocols or guidelines. We believe that patients with NIFTP without associated malignancy and without nodules detected by US of the remnant lobe (if submitted to lobectomy) can be managed like those with follicular adenoma.

Key Words

- ▶ noninvasive follicular thyroid neoplasm
- ▶ follicular adenoma
- ▶ papillary thyroid cancer

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Definition

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an encapsulated or clearly delimited, noninvasive neoplasm with a follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC), but without well-formed papillae or psammoma bodies and without typical findings of the aggressive subtypes of PTC or poorly differentiated carcinoma (Nikiforov *et al.* 2016, 2018, Lloyd *et al.* 2017). It is considered a 'borderline' or 'pre-malignant' lesion (Lloyd *et al.* 2017).

The change from the noninvasive encapsulated follicular variant of PTC (E-FVPTC) to NIFTP

When Nikiforov *et al.* (2016) proposed the term NIFTP, it was already known that encapsulated/well-delimited tumors of FVPTC without vascular/capsular invasion had an excellent prognosis after complete resection, even when treated only with lobectomy (Liu *et al.* 2006, Rivera *et al.* 2010, Rosario *et al.* 2014, Ganly *et al.* 2015). In the largest series published so far (Rosario *et al.* 2014), we reported no case of recurrence after 1–10 years (median 7 years)

of follow-up among 108 patients with this tumor, all of them >1 cm. None of the patients received radioiodine or TSH suppression and 57 were treated with lobectomy. Some guidelines already recommended more conservative treatment for this histological subtype (Perros *et al.* 2014, Haugen *et al.* 2016).

Nevertheless, that publication (Nikiforov *et al.* 2016) had a strong impact in clinical practice. First, the absence of metastases in 109 patients with tumors >1 cm treated without radioiodine and followed up for at least 10 years reported in the multicenter study (Nikiforov *et al.* 2016) reinforced the excellent prognosis of this neoplasm after its complete resection. Second, removal of the term 'cancer' itself probably (i) reduces the negative psychological impact on the patient and relatives; (ii) increases the physician's safety to opt for conservative treatment and less intense follow-up and (iii) increases patient acceptance of less aggressive therapy and less frequent follow-up. Third, clear diagnostic criteria were established since variations existed in the definition of E-FVPTC. Indeed, this attempt to standardize the diagnostic criteria, in which pathologists from several countries participated, was an important contribution. Until then, different definitions, especially of the nuclear alterations sufficient to characterize PTC, resulted in a significant interobserver variation in the final diagnosis of follicular thyroid neoplasms. A detailed review of this aspect was recently published in this journal (Amendoeira *et al.* 2018). Fourth and probably the most important, in addition to the name change from noninvasive E-FVPTC to NIFTP, the nature of the lesion was altered, which was no longer classified as 'malignant'. This proposal was subsequently endorsed by the World Health Organization (WHO) in the 4th edition of the classification of endocrine tumors (Lloyd *et al.* 2017).

Since NIFTP is not 'cancer', tumor staging (e.g., TNM/AJCC) is not necessary and patients with this diagnosis do not need to be submitted to protocols or

guidelines for differentiated thyroid carcinoma. Compared to data that include it as 'malignant' tumor, with NIFTP no longer being considered 'cancer', a reduction in the risk of 'malignancy' is observed in thyroid nodules with the features shown in Table 1, which are more frequently found in lesions corresponding to NIFTP. This fact has possible implications for the predictive value for 'malignancy' of ultrasonography (US) (Chaigneau *et al.* 2018, Rosario *et al.* 2018a,b), cytology (Cibas & Ali 2017, Rocha *et al.* 2018), molecular tests (Sahli *et al.* 2017) and fluorodeoxyglucose positron emission tomography (FDG-PET) (Rosario *et al.* 2019). Tumors that nowadays correspond to NIFTP were included in the group of low-risk PTC (Wong *et al.* 2017, Rosario 2019a), that is, tumors restricted to the thyroid without vascular invasion or typical components of aggressive subtypes, in the absence of the *BRAFV600E* mutation (Haugen *et al.* 2016). Thus, a slight increase in the recurrence rate may occur after the exclusion of NIFTP from this group. Clearly, all these impacts depend on the prevalence of NIFTP in the population studied and the diagnosis of NIFTP is less often made in Asian populations (Bychkov *et al.* 2018).

Preoperative suspicion of NIFTP

Although the preoperative diagnosis is not possible, knowledge of thyroid nodules that possibly or likely correspond to NIFTP is important. In these nodules, if surgery is indicated, lobectomy is recommended, except if the choice for total thyroidectomy were due to reasons other than the risk of malignancy of the nodule or to concern about another nodule.

Ultrasonography (Hahn *et al.* 2017, Rosario 2017a, Yang *et al.* 2017), cytology (Rosario 2017a, Bongiovanni *et al.* 2018) and molecular tests (Nikiforov 2017) are useful for suspecting NIFTP. Some results render NIFTP unlikely (Table 1) and are more characteristics of classical

Table 1 Data that lead to the reasonable possibility of a thyroid nodule corresponding to NIFTP.

Clinical examination	Absence of clinically apparent or known metastasis of thyroid origin ^a
Ultrasonography	Absence of LNM ^a Nodule without the following findings: extrathyroidal extension, microcalcification, taller-than-wide shape, spiculate/microlobulate/ill-defined margin, high suspicion of malignancy
Fine-needle aspiration	Category III, IV or V cytology of the Bethesda system ^b Nodule without mutations or with <i>RAS</i> or other <i>RAS</i> -like mutations (e.g., <i>PAX8/PPARG</i> rearrangement) ^c

^aThe presence excludes NIFTP or indicates associated thyroid malignancy; ^bfollicular pattern, no papillae, no psammomatous calcifications, no florid nuclear features of papillary thyroid carcinoma, no necrosis or mitoses; ^cNIFTP is virtually excluded in the case of a nodule with *BRAFV600E* or other *BRAFV600E*-like mutations (e.g., *RET/PTC* fusions), or high-risk mutations (e.g., *TERT* promoter, *p53*).

PTC, infiltrative FV and aggressive subtypes. In contrast, these tumors less frequently exhibit the typical findings of nodules that correspond to NIFTP (Table 1). However, the findings of NIFTP and E-FVPTC, especially with lower invasion, widely overlap. The Doppler vascularization pattern (Hahn *et al.* 2017, Yang *et al.* 2017, Rosario 2018b), histogram analysis of greyscale sonograms (Kwon *et al.* 2018) and uptake of FDG on PET (Rosario 2018d) have been studied but do also not distinguish NIFTP from E-FVPTC.

Diagnosis of NIFTP

At present, the diagnosis of NIFTP can only be made after complete resection of the lesion observing the following criteria (Nikiforov *et al.* 2016, 2018, Lloyd *et al.* 2017): (i) encapsulation or clear demarcation from adjacent thyroid parenchyma; (ii) follicular growth pattern with no well-formed papillae, no psammoma bodies and <30% solid/trabecular/insular growth pattern; (iii) nuclear features of PTC (nuclear score 2–3); (iv) no vascular or capsular invasion; (v) no tumor necrosis or high mitotic activity. Molecular tests are helpful but not required for NIFTP diagnosis. When obtained, *BRAFV600E* or other *BRAFV600E*-like mutations (e.g., *RET/PTC* fusions) or high-risk mutations (e.g., *TERT* promoter, *p53*) are absent in NIFTP (Nikiforov *et al.* 2018). The initial criteria (Nikiforov *et al.* 2016) were revised in 2018 (Nikiforov *et al.* 2018). In the presence of true well-formed papillae, even if accounting for <1% of the tumor, the latter is no longer considered NIFTP (Nikiforov *et al.* 2018). Tumors with papillae have been associated with a non-negligible frequency of the V600E mutation in the *BRAF* gene (Cho *et al.* 2017, Kim *et al.* 2018b,c, Rosario 2019b), lymph node metastases (Cho *et al.* 2017, Kim *et al.* 2018c, Rosario 2019b), and even a case of distant metastasis (Cho *et al.* 2017). If exuberant nuclear alterations of PTC (score 3) are present, comprehensive revision of the entire tumor capsule interface is recommended in order to identify invasion and of the entire tumor in order to identify structural components of PTC (Nikiforov *et al.* 2018).

When morphological criteria are strictly observed, the finding of the *BRAFV600E* mutation in NIFTP is very unlikely and most studies show its absence (Nikiforov *et al.* 2016, Johnson & Sadow 2018, Johnson *et al.* 2018, Jung *et al.* 2018, Kim *et al.* 2018a). We reviewed studies that reported exceptional cases of NIFTP with the *BRAFV600E* mutation. Cho *et al.* (2017) and Kim *et al.* (2018b) found this mutation in 10/105 and 3/43 cases, respectively,

but all 13 tumors had papillae. Lee *et al.* (2017) reported the mutation in 5/24 cases. When four of these five cases were revised, papillae were found in one case, capsular invasion in another and inadequate representativeness of the tumor in the other two (Kakudo *et al.* 2018). In the series of Kim *et al.* (2018c), 9/73 NIFTP carried the mutation: four tumors with well-formed papillae, four with abortive papillae and one result was false-positive because of adjacent *BRAF*-positive PTC. Zhao *et al.* (2017) found 1/48 NIFTPs with the *BRAFV600E* mutation, but the authors recognize that the lack of examination of the entire tumor may have failed to detect the components of classical PTC.

Despite the small number of reported cases, the diagnosis of NIFTP also applies to children and adolescents and the absence of metastases has been demonstrated in this age group (Chereau *et al.* 2019, Rosario & Mourão 2018).

The size of the tumor does not constitute a criterion for the diagnosis of NIFTP (Nikiforov *et al.* 2018), although some cases require greater care and time-consuming evaluation to ensure the absence of excluding findings. Reviewing 250 patients with subcentimeter NIFTP from nine studies (Thompson 2016, Can *et al.* 2017, Hahn *et al.* 2017, Kwon *et al.* 2017, Johnson & Sadow 2018, Mainthia *et al.* 2018, Rosario 2018c, Shafique *et al.* 2018, Xu *et al.* 2018), without associated PTC, we found only two patients with micrometastases <2 mm in a single lymph node in the central compartment, none with distant metastases and no case of recurrence. In addition, reviewing 265 patients with NIFTP ≥4 cm (Thompson 2016, Golding *et al.* 2017, Kwon *et al.* 2017, Rosario 2017b, Xu *et al.* 2017a, Chereau *et al.* 2019, Kim *et al.* 2018b, Mainthia *et al.* 2018, Parente *et al.* 2018), excluding cases with associated PTC, we did not identify any patients with lymph node metastases (LNM), only one with pulmonary metastases and no case of recurrence.

Although there is no consensus, we believe that tumors composed of cells with oncocytic (Hürthle cells) appearance can be classified as NIFTP if they meet all other diagnostic criteria (Xu *et al.* 2019). We report here the evolution of ten patients with NIFTP with oncocytic features seen at our institution. There were eight women and two men ranging in age from 18 to 72 years. Median tumor size was 2.2 cm (range, 1.1–3.5 cm). Six patients were submitted to total thyroidectomy and four to lobectomy. No LNM were detected at diagnosis. Complete resection of the primary tumor was achieved in all patients. Radioiodine was not administered to any of the ten patients. The patients were followed up for

18–144 months (median 72 months). None of the patients developed structural disease or biochemical recurrence during follow-up.

Outcomes in studies involving patients with NIFTP

Since a greater representativeness (capsule and tumor) than usually obtained in the past is currently required for the diagnosis of NIFTP, we do not believe that the frequency of ‘outcomes’ (i.e., metastases on presentation and recurrences) reported in retrospective studies is underestimated (Rosario & Mourão 2019). On the contrary, it is possible that they diagnosed retrospectively as NIFTP tumors that were PTC; with the current requirement, even better results (in terms of ‘outcomes’) are expected (Rosario & Mourão 2019).

Reviewing studies published since the pioneering article (Nikiforov *et al.* 2016) until December 2018 and excluding patients with known associated PTC or tumors with well-formed papillae (in <1% of the tumor) that are no longer diagnosed as NIFTP (Nikiforov *et al.* 2018), we found no report of death due to NIFTP and only one case of pulmonary metastasis (Parente *et al.* 2018). However, LNM were reported (Jiang *et al.* 2016, Cho *et al.* 2017, Hahn *et al.* 2017, Kwon *et al.* 2017, Kim *et al.* 2018b,c, Parente *et al.* 2018, You *et al.* 2018). Evaluation of these last cases showed that (i) involvement was restricted to the central compartment (N1a) in all patients, (ii) all but one patient had a single lymph node affected, (iii) all but one study reported the size of LNM and all were microscopic (<2 mm) and (iv) no recurrence was reported.

Table 2 lists the studies involving the largest number of patients with NIFTP that reported ‘outcomes’.

The presence of metastases in patients with NIFTP does not necessarily confirm its potential of dissemination. First, insufficient representativeness of the tumor and capsule that fails to detect findings excluding NIFTP cannot be ruled out in some retrospective studies. Second, the capacity of minute microcarcinomas (<3 mm) to metastasize to lymph nodes (Wada *et al.* 2003) and even to distant organs (Xu *et al.* 2017b) is known. Many patients with NIFTP could have these minute microcarcinomas that were not detected by US of the remnant lobe (in patients submitted to lobectomy) or that escaped the slides obtained from the tumor. Another possibility would be regression of the microcarcinoma after it metastasized. The report of dissociation between LNM with mutation in the *BRAF* gene and the primary tumor (NIFTP) negative for this mutation supports the hypothesis of another, although not apparent, metastasis origin (Kim *et al.* 2018b).

Management after resection

In patients with NIFTP, after its complete resection and in the absence of associated malignancy (including microcarcinoma), the need for and protocol of follow-up are matters of debate. There seems to be consensus that suppression of TSH is not necessary. According to the American Thyroid Association, complementary tests (thyroglobulin (Tg), antithyroglobulin antibodies (TgAb), neck US) are not mandatory (Haugen *et al.* 2016), while some authors recommend NIFTP to be monitored in the

Table 2 Outcomes (metastases on presentation or recurrences) observed in studies involving the largest number of patients with NIFTP.

Reference	Number of patients	Length of follow-up	LNM*	Distant metastasis*
Thompson (2016)	77	1.2–12.5 years (median 11.8)	0	0
Nikiforov <i>et al.</i> (2016)	109	10–26 years (median 13)	0	0
Rosario <i>et al.</i> (2016)	129	12–146 months (median 72)	0	0
Xu <i>et al.</i> (2017a)	79	0.3–26 years (median 5.8)	0	0
Kwon <i>et al.</i> (2017)	105	–	2	0
Cho <i>et al.</i> (2017)	95	17–96 months (median 36)	2	0
Parente <i>et al.</i> (2018)	102	0–11 years (mean 5.7)	5	1
Mainthia <i>et al.</i> (2018)	164	IQR 12–49 months (median 24)	0	0
Johnson and Sadow (2018)	130	Mean 1.63 years	0	0
Chereau <i>et al.</i> (2019)	363	IQR 12–146 months (median 55)	0	0
Kim <i>et al.</i> (2018c)	73	0.6–31.9 months (mean 15.5)	2	0

*Diagnosed on presentation or during follow-up in patients with NIFTP according to the current criterion and without associated carcinoma.
IQR interquartile range; LNM, lymph node metastases.

same way as low-risk PTC (Cho *et al.* 2017, Parente *et al.* 2018).

After the name change removing the term 'cancer' (Nikiforov *et al.* 2016), alteration of the nature of the lesion which is no longer 'malignant' (Lloyd *et al.* 2017), and definition of somehow strict diagnostic criteria designed exactly to rule out the possibility of metastases (Nikiforov *et al.* 2018), maintaining patients with NIFTP under a similar follow-up as patients with PTC seems to be little justified (Rosario & Mourão 2019). In our view (Rosario 2018a, Rosario & Mourão 2019), 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 since noninvasive E-FVPTC was known to have an excellent prognosis after lobectomy (Liu *et al.* 2006, Rivera *et al.* 2010, Rosario *et al.* 2014, Ganly *et al.* 2015) and conservative treatment of this histological subtype was already recommended by the available guidelines (Perros *et al.* 2014, Haugen *et al.* 2016).

It is expected that specific protocols or recommendations for selective follow-up of subgroups of patients with NIFTP will be proposed, but they will be empirical and based on the extrapolation of data from patients with 'cancer'. Finally, because of the exceptionality of 'outcomes', performing follow-up similar to that of low-risk PTC to detect an 'eventual' recurrence of NIFTP would require hundreds of tests of Tg, TgAb and US at the end of 10 years, with probably unviable costs and numerous false-positive results and their potential consequences (Rosario *et al.* 2018c).

We believe that patients with NIFTP without associated malignancy and without nodules detected by US of the remnant lobe (if submitted to lobectomy) can be managed like those with follicular adenoma. This management seems to be more harmonic with the current nomenclature (not containing the term 'cancer') and the nature of the lesion (not 'malignant') and is based on (i) the existence of well-defined diagnostic criteria, (ii) molecular signature, (iii) rarity of metastases on presentation, a finding that can even be a coincidence and (iv) the virtual absence of recurrences. These last aspects have been demonstrated in the past for noninvasive E-FVPTC and now using the criteria of NIFTP.

Revision of histology slides

Patients who were diagnosed in the past with FVPTC and whose pathology report did not show findings of

malignancy (LNM, extrathyroidal invasion, vascular/capsular invasion) can have their slides revised by an experienced pathologist if the tumor is encapsulated or well delimited (non-infiltrative) in order to determine whether the diagnostic criteria of NIFTP are met. In this reassessment, special attention must be paid to the adequate representativeness of the capsule and tumor and establishment of the diagnosis of NIFTP is not recommended if it is insufficient unless more sections can be submitted. The diagnosis of NIFTP cannot be based on retrospective interpretation of the original pathology report, especially when this report was obtained before definition of the current diagnostic criteria.

Despite its inclusion in the WHO classification of endocrine tumors (Lloyd *et al.* 2017), it may still take some time until the NIFTP nomenclature becomes routine in all pathology laboratories. During this period of transition, we recommend revision by pathologist in the case of a diagnosis of noninvasive E-FVPTC or FVPTC with the characteristics cited above (neoplasm with capsule or clear delimitation without LNM, extrathyroidal invasion, capsular/vascular invasion) to determine whether the tumor meets the criteria for NIFTP.

In the above situations, molecular tests can be requested if available and feasible, but they do not substitute histology.

Conclusion

Clinicians must be aware of the ultrasonographic, cytological and molecular findings of nodules corresponding to NIFTP since this knowledge influences the definition of the extent of surgery, if indicated, favoring lobectomy. In addition, clinicians and pathologists must be familiar with the histological criteria for the diagnosis of NIFTP to spare patients with this tumor (without associated malignancy) from additional treatment and from the traditional follow-up recommended for differentiated thyroid cancer.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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