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REVIEW

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Non-invasive follicular thyroid neoplasm with papillary-like nuclearfeatures (NIFTP): a review and update

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Abstract

Background The nomenclature "Non-invasive Follicular Neoplasm with Papillary-like Nuclear Features (NIFTP)" was introduced in 2016. While NIFTP differs from classic papillary thyroid carcinoma (PTC) in imaging, cytomorphology, histology, molecular profile, treatment, follow up, outcome, and behavior, it largely overlaps with follicular variant of PTC at imaging and cytomorphology. Herein, we review the literature for better understanding NIFTP, and its impact on patient care.
Methods The English literature was thoroughly evaluated with the key word of "Noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP)".
Observations NIFTP presents as a thyroid nodule. On imaging, it is a round-to-oval, well circumscribed mass with solid internal content. Aspirated material shows a microfollicular pattern with focal nuclear features of PTC mostly reported in categories 3–5 of the Bethesda System for Reporting Thyroid Cytology (TBRSTC). NIFTP has decreased risk of malignancy in TBRSTC categories 3–6. Histologic examination of NIFTP reveals an encapsulated neoplasm with follicular pattern and nuclear features of PTC with no capsular or vascular invasion. No papillary structure, atypia, or mitosis is present. In contrast to PTC, only 4% of NIFTP cases harbor a *BRAF* mutation. Because NIFTP carries an excellent prognosis and indolent behavior, the tumor behavior was changed from malignant to a neoplasm with tumor with extremely indolent behavior. The recommended treatment is lobectomy with no further ablation therapy. Until better understanding of NIFTP, patient's follow up should be occasionally performed by neck ultrasonography and serum thyroglobulin measurement.
Conclusion NIFTP carries an excellent prognosis. It is critical for both clinicians and patients to be aware of extremely indolent behavior of NIFTP in order to prevent unnecessary, aggressive treatment.

Highlights

- Non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) refers to a subset of encapsulated thyroid neoplasms that was recently reclassified from malignant to tumor with extremely indolent behavior.
- The tumor behavior and molecular profile differ from papillary thyroid carcinoma and it is treated with lobectomy with a favorable outcome.

Keywords NIFTP · Thyroid · Fine needle aspiration (FNA) · TBRSTC · Cytology · Review

Introduction

The first description of encapsulated non-invasive follicular thyroid neoplasm with papillary like nuclear feature was made in 2016 [1]. However, there was a long history before establishment of this entity. The former nomenclature of follicular variant of papillary thyroid carcinoma (FVPTC) was introduced in mid-1970 [1, 2]. This term was widely used for over several decades. However, a subset of FVPTC were encapsulated or well-demarcated and revealed

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different molecular profile from those of classic papillary thyroid carcinoma (PTC). This encapsulated variant of FVPTC showed a very similar behavior to follicular adenoma. However, the suffix of carcinoma conveyed a malignant nature of these neoplasms and majority of the patients carrying this diagnosis were treated with total thyroidectomy [3]. The above observations resulted in evolving the term "noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)", which has an indolent behavior and requires less aggressive treatment [4]. This nomenclature revision had also an impact on the cytology criteria and definitions in the Bethesda System for Reporting Thyroid Cytology (TBSRTC) [5, 6]. Herein, the published literature about NIFTP, this newly described terminology, will be reviewed including its histology, cytomorphology, its impact on TBSRTC and the associated risk of malignancy (ROM) for each category, molecular findings, imaging studies, treatment, and outcome.

Material and methods

The review was performed by searching all the search engines of the English literature mainly consisting of "PubMed", "google scholar", "Scopus", and "google".

The key words were "Non-invasive Follicular neoplasm with papillary like nuclear features", "Encapsulated Follicular neoplasm with papillary like nuclear features", "Encapsulated non-invasive follicular neoplasm with papillary like nuclear features" and NIFTP.

Nomenclature of NIFTP

Although the term NIFTP is novel and was proposed in 2016, the concept of this entity is not new [7]. The terminology was started with the term follicular variant of papillary carcinoma (FVPTC), which was divided as infiltrative follicular variant of papillary carcinoma and non-infiltrative encapsulated follicular variant of papillary thyroid carcinoma, both of which displayed the typical nuclear features of papillary carcinoma with follicular pattern and no papillary architecture [8]. The former variant was similar to classic papillary thyroid carcinoma regarding the outcome and molecular profiling, but the latter was behaved more like a benign adenoma with no or very low potential for metastasis or invasion. The nomenclature indicates that NIFTP has follicular pattern of growth, with nuclear features of papillary carcinoma and no invasive or infiltrative behavior [7, 9, 10]. The World Health Organization (WHO) of Tumors has reclassified NIFTP under "other encapsulated follicular patterned thyroid tumors with unspecified, borderline, or uncertain behavior with ICD-O (International classification of Diseases for Oncology) code of 8349/1 [11].

Clinical presentation of NIFTP

Clinical presentation of NIFTP is nonspecific and similar to other thyroid neoplasms. Either it is detected as a thyroid nodule or it is discovered incidentally during imaging of the neck for other reasons. NIFTP rarely grows large enough to cause pressure effect in the adjacent organs to produce symptoms such as dysphonia, or globous sensation [9].

Imaging findings of NIFTP

Gray-scale ultrasound (US) is the widely accepted, standard imaging modality for the evaluation of thyroid nodules. US findings of NIFTP include a round-to-ovoid shape mass with a well circumscribed margin, solid internal content, parallel orientation, and absence of halo and smooth isoechogenicity [12]. Overall, a non-invasive thyroid nodule is mostly in favor of a benign condition.

US findings of thyroid malignancy including marked hypoechoicity, taller-than-wide shape, micro-calcifications, and blurred or micro-lobulated margins are all against the diagnosis of NIFTP [13].

US findings are very important in the diagnosis of NIFTP by exclusion of invasion [14]. Other imaging modalities have not been recommended for the routine evaluation of thyroid nodules [12–14].

Cytomorphologic findings of NIFTP

Thyroid fine needle aspiration cytology is the method of choice for preoperative evaluation of thyroid nodules.

Microscopic examination of NIFTP in aspirated material show clusters of cells with microfollicular arrangement. The microfollicular pattern is different from follicular neoplasm since they are not discrete and repetitive. It means that the pattern of growth is follicular. No papilla is present, either [15]. Other important criteria are the nuclear features, which are subtle. Some of the nuclear features PTC may be present but they are focal and patchy. In PTC, nuclear features characteristics of PTC including nuclear grooves and pseudo-inclusions are present in large number of cells. In contrast, nuclear pseudo-inclusions are inconspicuous and rare in NIFTP and some studies have suggested to a cut-off number of less than 3 pseudo-inclusions per specimen [16].

A scoring system for nuclear features has been suggested to differentiate between PTC and NIFTP. Three nuclear features including irregular contours, grooves, and pseudo-

inclusions are evaluated. The higher the score, the more likely the diagnosis would be PTC rather than NIFTP [17]. A definitive diagnosis of NIFTP requires surgical excision and histologic examination of the thyroid nodule [18].

In differential diagnosis between NIFTP and other thyroid lesions, there are no specific diagnostic features to look for. Instead, multiple cytomorphologic features should be evaluated [19]. Cytomorphologic features which are in favor of classic PTC and against the diagnosis of NIFPT are microfollicles in sheet-predominant architectural pattern, presence of true papillae and psammomatous calcifications, and easily identifiable nuclear pseudo-inclusions [20–22]. In histologically proven cases of NIFTP, the cytology diagnosis of corresponding cases according to TBSRTC were AUS/FLUS (Atypical cell of undetermined significance/follicular lesion of undetermined significance), FN/SFN (follicular neoplasm/suspicious for follicular neoplasm) or SFM (suspicious for malignancy) [23, 24].

Impact of reclassification of NIFTP on the Bethesda system for reporting thyroid cytopathology (TBSRTC)

The reclassification of NIFTP from "malignant" to "non-malignant" has had a significant impact on ROM on TBSRTC. A large multi-institutional cohort consisting of 6943 thyroid nodules indicated that reclassification of NIFTP had a significant impact on the ROM in all 3 indeterminate categories of TBSRTC. The AUS/FLUS category had a decrease of 5.2% to 13.6%, the FN category had a decrease of 9.9% to 15.1%, and the SM category had a decrease of 17.6% to 23.4% ($P < .05$), whereas the benign and malignant categories had decreases of 0.3% to 3.5% and 2.5% to 3.3%, respectively [24]. ROM changes in a retrospective study was reported as follows: non-diagnostic, no change, benign 5.5% to 2.5%, AUS/FLUS, 42.3% to 22.3%, FN/SFN, 48.7% to 17.9%, SFM, 93.6% to 61.7% and positive for malignancy, 100% to 97%. Decreased ROM was most significant in AUS/FLUS category [25]. A multi-institutional study in five Asian countries on 2044 thyroid nodules with surgical follow up showed 2.9% (59 cases) of all excised nodules were diagnosed NIFTP. Preoperative cytology diagnosis for NIFTP on TBSRTC were as follows: non-diagnostic, 10.2%, benign 18.6%, AUS/FLUS, 22.0%, FN/SFN, 32.2%, SM, 11.9%, and malignant 5.1%. This study showed a relative reduction in ROM of greater than 20% in FN/SFN category [26]. Another study reported a relative decrease in ROM in AUS/FLUS (25.8%) and FN/SFN (22.3%) categories [27]. The incidence of NIFTP in 244 surgically excised thyroid nodules with cytology diagnosis of AUS/FLUS was as follows: 18% for AUS with nuclear atypia, 18% for AUS with a microfollicular pattern, 9% for AUS with nuclear atypia and a microfollicular pattern, 3% for AUS with Hürthle cells and 0% for AUS not otherwise specified. The reclassification of NIFTP as non-malignant has significantly decreased risk of malignancy (ROM) on histology follow up of AUS/FLUS nodules from 43 to 26% for AUS with nuclear atypia, and from 29 to 10% for AUS with a microfollicular pattern [28]. Regarding reclassification of NIFTP and its impact of TBRSTC, the 2017 TBRSTC by Cibas and Ali shows no change in ROM in non-diagnostic and benign categories. However, ROM in other categories shows reduction as follows: from 10–30% to 6–18% in AUS/FLUS, from 25–40% to 10–40% in FN/SFN, from 50–75% to 45–60% in SM, and from 97-99% to 94-96% in malignant [29].

Gross and histologic findings of NIFTP

Grossly, NIFTP appears well circumscribed. The tumor capsule should be entirely sectioned and microscopically examined. Microscopically, the tumor is encapsulated with no capsular or vascular invasion showing a discrete interface with the surrounding thyroid parenchyma. The capsule can be thin or thick [30–32]. Those tumors that are partly encapsulated or unencapsulated and still are well delineated from adjacent thyroid parenchyma can be categorized as NIFTP [33–35]. Diagnosis of NIFTP is based on the combination of architectural, stromal, and nuclear characteristics [35]. Strict histologic criteria should be applied for a definitive diagnosis of NIFPT. Histologically, the tumor is predominantly follicular pattern either macrofollicular or microfollicular with nuclear features of PTC. (Figs. 1–4). Nuclear features of NIFTP are typically more subtle than those in PTC, and they range from focal to diffuse to patchy

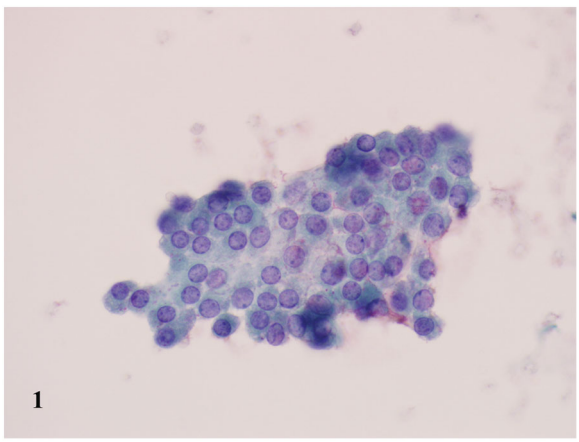

Fig. 1 NIFTP, ultrasound guided aspirated material of a 5 cm thyroid nodule shows a fragment of follicular cells with focal follicular pattern. The nuclei are round to oval and relatively uniform. The chromatin is pale and powdery with rare small nucleoli. The cytology diagnosis was suspicious for a follicular neoplasm (X400, Papanicolaou stain)

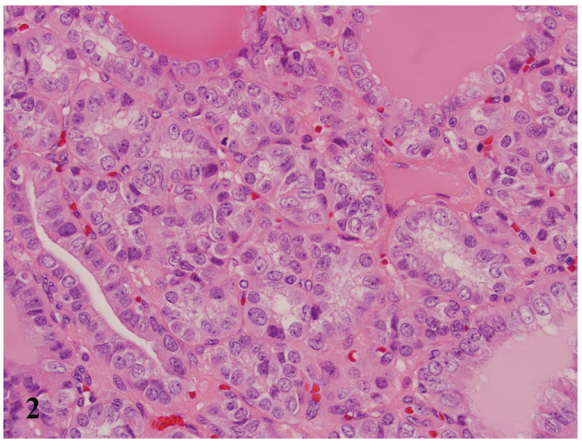

Fig. 2 NIFTP, histologic examination of the above resected nodule showed an encapsulated mass with follicular pattern and nuclear features of papillary thyroid carcinoma. There was no evidence of capsular or vascular invasion (×200, H&E stain)

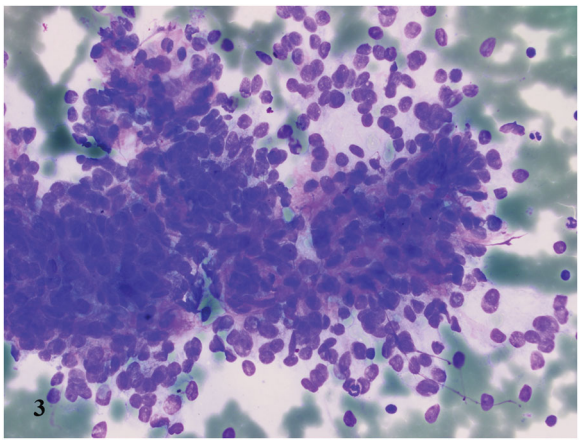

Fig. 3 NIFTP, ultrasound guided aspirated material of a 1.5 cm thyroid nodule shows a fragment of follicular cells with nuclear atypia including nuclear enlargement, elongation, and overlap. The cytology diagnosis was atypia of undetermined significance (×400, Diff-Quik stain)

and multifocal (so-called sprinkling sign). These nuclear features are more prominent at the periphery of the tumor (subcapsular area) and in the more cellular, or microfollicular areas. In NIFTP, colloid may be variable from dense and hypereosinophilic in microfollicular areas to watery in macrofollicular areas [35]. The diagnosis of NIFTP is excluded when there is solid growth pattern in 30% or more of the tumor, high-grade features such as high mitotic rates (>= 3 per 10 high power field), or tumor necrosis. It is recommended to examine 10 consecutive high-power fields for evaluation of mitosis, rather than counting "hot spots", which may be prone to over-estimate of the number of mitosis [34, 35]. In the initial description of NIFTP, the presence of >1% papillae was a criterion for exclusion [1], now it has been suggested that any papillae

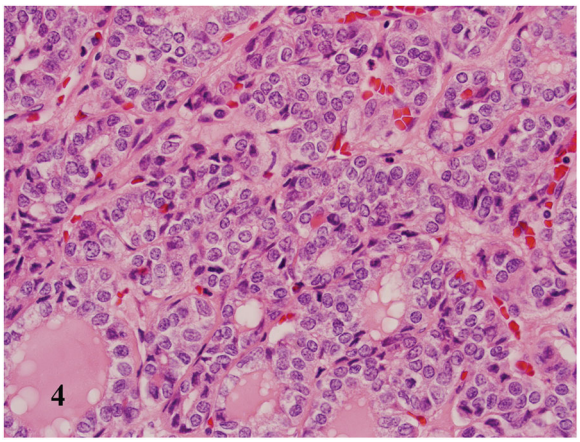

Fig. 4 NIFTP, histologic examination of the above resected nodule showed an encapsulated mass with follicular pattern and nuclear features of papillary thyroid carcinoma. There was no evidence of capsular or vascular invasion (×200, H&E stain). Note, the histomorphologic overlap of these two nodules while they present different cytomorphology on the smears

should preclude a NIFTP diagnosis [10]. Presence of tall cells, columnar cells, or cribriform pattern all excludes the diagnosis of NIFTP [35]. A scoring system is proposed to differentiate NIFTP from PTC and other thyroid neoplasms using nuclear features [30].

The scoring system evaluates the nuclei for (1) nuclear size and shape including nuclear enlargement, overlapping, crowding and elongation, (2) nuclear membrane including irregular contours, grooves and pseudo-inclusions, and (3) chromatin characteristics including clearing with margination, and glassy nuclei. The tumor will receive one point for each feature. Tumors with a score of zero or 1 with a growth pattern similar to NIFTP should be considered benign, follicular adenoma or adenomatous nodule, whereas those with a score of 2 or 3 are most consistent with NIFTP. This scoring system is not mandatory to diagnose NIFTP in routine daily practice, but it makes the diagnosis more objective and potentially more accurate [35]. Nuclear pseudo-inclusions are uncommon in NIFTP and psammomatous calcifications should also be absent in NIFTP [31]. Neoplasms with follicular architecture and nuclear features of PTC with unencapsulated, infiltrative growth pattern are best characterized as infiltrative FVPTC and should not be categorized as NIFTP [32, 33]. Invasion precludes a diagnosis of NIFTP. Criteria for capsular invasion or infiltrative border is similar to those in diagnosis of follicular thyroid carcinoma [35].

For encapsulated NIFTP tumors, capsule penetration by tumor cells precludes the diagnosis of NIFTP. For NIFTP cases without a fibrous capsule, infiltration of tumor cells into adjacent uninvolved parenchyma is adequate for exclusion of NIFTP and it does not require "mushroom like" growth pattern [34, 35].

Table 1 The diagnostic criteria for non-invasive follicular thyroid neoplasm with papillary like nuclear features

	Cytomorphology	Histology
Inclusion criteria for diagnosis of NIFTP	Predominance of microfollicles	Predominantly follicular pattern
	Nuclear enlargement, elongation, and overlapping	Nuclear features of papillary thyroid carcinoma
	Nuclear grooves	Encapsulated or well-demarcated
	Nuclear pseudoinclusions	
	Irregular nuclear contour	
Exclusion criteria for diagnosis of NIFTP	Tall cell or columnar cell features	>30% solid, insular or trabecular pattern
	Papillary pattern	Tumor necrosis >3 mitosis/10 high power field
	Psammoma bodies	Tall cell or columnar cell features
		Papillary pattern
		Psammoma bodies
		Capsular invasion
		Invasion of tumor cells into adjacent uninvolved parenchyma
		Lymphatic invasion
		Vascular invasion

The diagnosis of lymphatic and/or vascular invasion is defined by presence of the tumor cells within an endothelial lined space, or in the vessels outside the tumor mass showing wall attachment and not just free-floating tumor. Perineural invasion and extra-thyroidal extension also exclude the diagnosis of NIFTP [30–35]. NFITP with foci of spindle cell metaplasia is a rare finding, which can be a diagnostic challenge [36, 37]. Overall, a diagnosis of NIFTP should not be rendered if there is difficulty in evaluating the growth pattern [38]. A recent study suggests that even the tumors <1.0 cm can be included in the NIFTP category, although the NIFTP proposal study did not include tumors less than 1 cm [3, 39]. Moreover, NIFTP tumors measuring 4 cm or greater are associated with an extremely low risk of recurrence, even when treated with surgical excision without radioiodine therapy [40]. The entire capsule should be carefully evaluated by histopathologic examination to exclude any invasive process [39]. Table 1 demonstrates the inclusion and exclusion criteria for diagnosis of NIFTP.

Molecular profile in NIFTP

Molecular alterations have been reported in approximately 78% of the NIFTP cases. NIFTP harbors activating *RAS* mutation in 30–54% of cases including *NRAS*, *HRAS*, and less commonly *KRAS* mutations [1, 31, 41–44]. Non-V600E *BRAF* mutations such as *BRAF* K601E mutation have been found in a subset of NIFTP cases (4%) [1, 31, 45, 46]. BRAF V600E mutations, and less commonly NTRK1 and AGK-BRAF fusion were found in classic PTC and HRAS mutation in NIFTP, respectively [47].Overall, tumors harboring *BRAF* K601E mutation are associated with better outcome than tumors with *BRAF* V600 mutation [46]. In a study by Paulson et al., NIFTP accounted for 59% of *RAS* mutant thyroid tumors [44].

Although NIFTP predominantly harbors *RAS* mutations, a small subset harbor other mutations including *PPARG* and *THADA* mutations [1, 3, 8, 41, 44, 46, 48]. A study of 27 NIFTP cases found molecular alterations in 78% of the cases including 30% *RAS* mutations, 22% *PPRAG* fusion, 22% *THADA* fusion, and 4% *BRAF*- K601E substitution [1, 49].

Borrelli et al. investigated the expression of 798 miRNA in a cohort study. They found that 2 mi-RNAs including miR-10a-5p and miR-320e are able to discriminate between NIFTP and infiltrative FVPTC [49, 50].

ThyroSeq panel and Afirma gene expression classifier (Afirma GEC) are the most well established molecular testings in evaluation of thyroid nodules. In Afirma GEC, mRNA expression of multiple genes, currently 142 genes, is evaluated using microarray technology to classify a nodule either as benign or malignant. Afirma GEC is mostly considered as a test to "rule out malignancy". In contrast, ThyroSeq is designated to identify malignant neoplasms or in other words "to rule in malignancy" [47, 51, 52]. There are very few studies regarding the use of above mentioned molecular testings in NIFTP, most of which confirm high rate of *KRAS* mutation and low frequency of *BRAF* mutation [50, 53–55]. Fu and colleagues investigated programmed cell death-ligand-1 (PD-L1) expression in NIFTP and invasive encapsulated FVPTC [56]. They found cytoplasmic expression of PD-L1 was similar to benign nodules and

cytoplasmic PD-L1 levels were significantly lower in NIFTP compared to encapsulated FVPTC. Moreover, the higher cytoplasmic PD-L1 expression in encapsulated FVPTC was associated with higher risk of capsular invasion [56].

Treatment modalities and follow up of NIFTP

According to current ATA (American Thyroid Association) guidelines, decision for surgery on a thyroid nodule greater than 1 cm should be made based upon cytomorphologic, sonographic, and molecular findings and the patient's preference [57]. Most cases with histologically confirmed final diagnosis of NIFTP have preoperative cytological diagnosis of TBRSTC category III, IV, and or V. For category IV and V, surgical excision is the recommended procedure either lobectomy or total thyroidectomy. For category III, decision and risk stratification should be made based on clinical, sonographic and molecular findings, which can be followed up with repeat FNA, or surgery [57–59]. It is extremely important to understand that NIFTP is not a "benign tumor" but a "low-risk neoplasm" that requires surgical excision for diagnosis and a complete microscopic evaluation of the tumor including the capsule [39]. Radioactive iodine ablation is not recommended in NIFTP. No additional surgery is required if lobectomy is performed and the definitive tissue diagnosis is NIFTP [59].

Periodic serum thyroglobulin (Tg) measurements should be considered in patients with the final diagnosis of NIFTP who are on thyroid hormone therapy and have not treated with radioactive ablation or total thyroidectomy. Until more long-term follow-up data would be available, occasional monitoring with serum thyroglobulin (Tg) and neck ultrasound (US) can be considered depending upon the patient context. Rising Tg level over time is suspicious for growing thyroid tissue or even malignancy [57, 60].

Clinical outcome of NIFTP

NIFTP has an excellent prognosis with extremely low risk of recurrence, even when treated conservatively without RAI (radioactive iodine) therapy. Conservative surgical treatment alone appears to be adequate for NIFTP even when the tumor is large (>4-cm) [40]. Future long-term follow-up studies are necessary on NIFTPs greater than 4 cm for better understanding of their behavior. Clinicians should continue to follow these patients for evaluation of adverse oncologic outcomes [61]. The most important point is sticking to strict criteria for the diagnosis of NIFTP [62]. The reclassification of NIFTP from "malignant" to "a neoplasm with extremely indolent behavior" would also have an impact on patients' health care plans and costs. In fact, it would cost less and patients would have more options to choose.

Conclusion

NIFTP is an encapsulated or well-defined thyroid neoplasm with predominantly follicular pattern and subtle nuclear features of PTC. *RAS* mutation is shown in 50% of NIFTP cases. Other less common mutations are *PPRAG* fusion, *THADA* fusion, and *BRAF*- K601E substitution. Lobectomy is considered treatment of choice with no further additional completion of total thyroidectomy or radioiodine therapy due to its extremely indolent behavior.

Compliance with ethical standards

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

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References

1. Y.E.S.R. Nikiforov, G. Tallini, Z.W. Baloch, F. Basolo et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol. **2**, 1023–1029 (2016)
2. G. Tallini, R.M. Tuttle, R.A. Ghossein, The history of the follicular variant of papillary thyroid carcinoma. J. Clin. Endocrinol. Metab. **102**, 15–22 (2017)
3. L.D. Thompson, Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features would help prevent overtreatment. Mod. Pathol. **29**, 698–707 (2016)
4. M.M.M. Jaconi, A.I. Pincelli, V. Giardini, M. Scardilli, A. Smith, G. Fellegara, F. Pagni, The impact of the non-invasive follicular thyroid neoplasm with papillary-like nuclear feature terminology in the routine diagnosis of thyroid tumours. Cytopathology **28**, 495–502 (2017)
5. Z.W.S.R. Baloch, W.C. Faquin, M.G. Papotti, F. Basolo et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): A changing paradigm in thyroid surgical pathology and implications for thyroid cytopathology. Cancer Cytopathol. **124**, 616–620 (2016)
6. I.M.T. Amendoeira, M. Sobrinho-Simoes, Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): impact on the reclassification of thyroid nodules. Endocr. Relat. Cancer **25**, R247–R258 (2018)
7. D.E.J.X. Range, An update on noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Curr. Opin. Oncol. **30**, 1–7 (2018)
8. J. Liu, B. Singh, G. Tallini et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer **107**, 1255–1264 (2006)
9. R.J.X. Jug Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: an evidence-based nomenclature change. Pathol. Res. Int. **2017**, 1057252 (2017)
10. R.V.A.S. Lloyd, V.A. LiVolsi, P.M. Sadow, A.S. Tischler, R.A. Ghossein, R.M. Tuttle, Y.E. Nikiforov, The evolving diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Hum. Pathol. **74**, 1–4 (2018)

11. R.V.O.R. Lloyd, G. Kloppel, J. Rosai. *WHO Classification of Tumors of Endocrine Organs*. 4th edn. (International Agency for Research on Cancer, Lyon, 2017). p. 66–80
12. M.R.S.J. Kwon, S.Y. Hahn, Y.L. Oh, J.Y. Kwak, E. Lee, Y. Lim, Histogram analysis of greyscale sonograms to differentiate between the subtypes of follicular variant of papillary thyroid cancer. Clin. Radiol. **73**(591), e591–591 e597 (2018)
13. G.C.H.F. Yang, KO, Pathologic basis of the sonographic differences between thyroid cancer and noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Ultrasonography **37**, 157–163 (2018)
14. S.Y.S.J. Hahn, Y.L. Oh, T.H. Kim, Y. Lim, J.S. Choi, Role of ultrasound in predicting tumor invasiveness in follicular variant of papillary thyroid carcinoma. Thyroid **27**, 1177–1184 (2017)
15. S.A.S. Mahajan, N. Kocheri, D. Jain, S.R. Mathur, V.K. Iyer, Cytopathology of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: a comparative study with similar patterned papillary thyroid carcinoma variants. Cytopathology **29**, 233–240 (2018)
16. J.B.C.M. Chandler, M.L. Prasad, G.G. Callender, C. Quinn, D. Chhieng, A.J. Adeniran, Identification of distinct cytomorphologic features in the diagnosis of NIFTP at the time of preoperative FNA: implications for patient management. Cancer Cytopathol. **125**, 865–875 (2017)
17. F.M.F. Maletta, L. Torregrossa, E. Duregon, G.P. Casadei et al. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. Hum. Pathol. **54**, 134–142 (2016)
18. G.C.H.F.K. Yang, T. Scognamiglio, Sonographic and cytologic differences of NIFTP from infiltrative or invasive encapsulated follicular variant of papillary thyroid carcinoma: a Review of 179 Cases. Diagn. Cytopathol. **45**, 533–541 (2017)
19. T.C.Z.F. Brandler, C.Z. Liu, M. Cho, R.P. Lau, A. Simsir, K.N. Patel, W. Sun, Can noninvasive follicular thyroid neoplasm with papillary-like nuclear features be distinguished from classic papillary thyroid carcinoma and follicular adenomas by fine-needle aspiration? Cancer Cytopathol. **125**, 378–388 (2017)
20. J.F.A.E. Krane, E.S. Cibas, J.A. Barletta, Coming to terms with NIFTP: a provisional approach for cytologists. Cancer Cytopathol. **124**, 767–772 (2016)
21. B.E.C.S. Howitt, M. Eszlinger, R. Paschke, M.G. Drage, J.F. Krane, J.A. Barletta, Fine-needle aspiration diagnoses of non-invasive follicular variant of papillary thyroid carcinoma. Am. J. Clin. Pathol. **144**, 850–857 (2015)
22. T.M.M. Bizzarro, S. Capodimonti, P. Straccia, C.P. Lombardi, A. Pontecorvi, L.M. Larocca, E.D. Rossi, Young investigator challenge: The morphologic analysis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features on liquid-based cytology: Some insights into their identification. Cancer Cytopathol. **124**, 699–710 (2016)
23. H.B.Z. Zhou, R. Nayar, T. Bizzarro, G. Fadda et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): Implications for the risk of malignancy (ROM) in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Cancer Cytopathol. **126**, 20–26 (2018)
24. W.C.W.L. Faquin, A.H. Afrogheh, S.Z. Ali, J.A. Bishop et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in The Bethesda System for Reporting Thyroid Cytopathology. Cancer Cytopathol. **124**, 181–187 (2016)
25. R.P.P.J. Lau, T.C. Brandler, C.Z. Liu, A. Simsir, F. Zhou, Impact of the Reclassification of "Noninvasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma" to "Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features" on the Bethesda System for Reporting Thyroid Cytopathology: A Large Academic Institution's Experience. Am. J. Clin. Pathol. **149**, 50–54 (2017)
26. A.K.S. Bychkov, S. Agarwal, D. Jain, C.K. Jung et al. Impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on the Bethesda system for reporting thyroid cytopathology: a multi-institutional study in five Asian countries. Pathology **50**, 411–417 (2018)
27. W.S.A. Li, M. Lew, J. Pang, X. Jing, Implementing noninvasive follicular thyroid neoplasm with papillary-like nuclear features may potentially impact the risk of malignancy for thyroid nodules categorized as AUS/FLUS and FN/SFN. Diagn. Cytopathol. **46**, 148–153 (2018)
28. J.F.W.W. Hang, A.G. Zhou, D.S. Cooper, S.Z. Ali, The impact of noninvasive follicular thyroid neoplasm with papillary-like nuclear features on the rate of malignancy for atypia of undetermined significance subcategories. Cancer Cytopathol. **126**, 309–316 (2018)
29. E.S. Cibas, S.Z. Ali, The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid **27**, 1341–1346 (2017)
30. K.P.S.A. du Jour, A.Y. Chen, C.C. Griffith, Application of Strict Criteria for Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features and Encapsulated Follicular Variant Papillary Thyroid Carcinoma: a Retrospective Study of 50 Tumors Previously Diagnosed as Follicular Variant PTC. Endocr. Pathol. **29**, 35–42 (2018)
31. Y.P.B.J. Hung, A user's guide to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Histopathology **72**, 53–69 (2018)
32. K.E.-N.A. Kakudo, S.P. Hodak, E. Khanafshar, Y.E. Nikiforov, V. Nose, L.D.R. Thompson, Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in thyroid tumor classification. Pathol. Int. **68**, 327–333 (2018).
33. L.D.R.P.D. Thompson, K. Kakudo, R. Burchette, Y.E. Nikiforov, R.R. Seethala, An International Interobserver Variability Reporting of the Nuclear Scoring Criteria to Diagnose Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: a Validation Study. Endocr. Pathol. **29**, 242–249 (2018).
34. D.N.N.Y. Poller, Non-invasive follicular thyroid neoplasm with papillary-like nuclei: reducing overtreatment by reclassifying an indolent variant of papillary thyroid cancer. J. Clin. Pathol. **69**, 947–948 (2016).
35. R.R.B.Z. Seethala, J.A. Barletta, E. Khanafshar, O. Mete et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a review for pathologists. Mod. Pathol. **31**, 39–55 (2018)
36. G.P.M. Arnoux, "Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features" With Focal Spindle Cell Metaplasia. Int. J. Surg. Pathol. **26**, 261–265 (2018)
37. M.R.A.A. Haroon Al Rasheed, G. Tarjan, Encapsulated follicular variant of papillary thyroid carcinoma/noninvasive follicular thyroid neoplasm with papillary-like nuclear features with Spindle Cell Metaplasia: case report and review of literature. Pathol. Res. Pract. **213**, 416–421 (2017)
38. K.C.H.B. Strickland, J.A. Barletta, E.S. Cibas, J.F. Krane, Suggesting the cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a retrospective analysis of atypical and suspicious nodules. Cancer Cytopathol. **126**, 86–93 (2018)
39. Z.W.H.R. Baloch, E.M. Brett, G. Randolph, J.R. Garber, A.E.S.S. Committee, C. Thyroid Scientific, American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Commentary: Managing Thyroid Tumors Diagnosed as Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features. Endocr. Pract. **23**, 1150–1155 (2017)

40. B.T.G. Xu, T. Scognamiglio, B.R. Roman, R.M. Tuttle, R.A. Ghossein, Outcome of large noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Thyroid **27**, 512–517 (2017)
41. M. Rivera, J. Ricarte-Filho, J. Knauf et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct BRAF and RAS mutation patterns. Mod. Pathol. **23**, 1191–1200 (2010)
42. B.E. Howitt, Y. Jia, L.M. Sholl, J.A. Barletta, Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma. Thyroid **23**, 1256–1262 (2013)
43. L. Zhao, D. Dias-Santagata, P.M. Sadow, W.C. Faquin, Cytological, molecular, and clinical features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features versus invasive forms of follicular variant of papillary thyroid carcinoma. Cancer Cytopathol. **125**, 323–331 (2017)
44. V.A. Paulson, P. Shivdasani, T.E. Angell et al. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features Accounts for More Than Half of "Carcinomas" Harboring RAS Mutations. Thyroid **27**, 506–511 (2017)
45. D.C.N. Ng, Z.V. Ma, A. van Zante, B. Ljung, E. Khanafshar, Cytomorphologic features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a comparison with infiltrative follicular variant of papillary thyroid carcinoma. J. Basic Clin. Med. **6**, 51–56 (2017)
46. M. Afkhami, A. Karunamurthy, S. Chiosea et al. Histopathologic and clinical characterization of thyroid tumors carrying the BRAF (K601E) mutation. Thyroid **26**, 242–247 (2016)
47. K.C.E.M. Strickland, R. Paschke, T.E. Angell, E.K. Alexander et al. Molecular Testing of Nodules with a Suspicious or Malignant Cytologic Diagnosis in the Setting of Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP). Endocr. Pathol. **29**, 68–74 (2018)
48. M. Vivero, S. Kraft, J.A. Barletta, Risk stratification of follicular variant of papillary thyroid carcinoma. Thyroid **23**, 273–279 (2013)
49. F.M.E. Basolo, C. Ugolini, D.N. Polle, Z. Baloch, The Molecular Landscape of Noninvasive Follicular Thyroid Neoplasm With Papillary-like Nuclear Features (NIFTP): a literature review. Adv. Anat. Pathol. **24**, 252–258 (2017)
50. N.D.M. Borrelli, C. Ugolini, A.M. Poma, M. Miccoli, P. Vitti, P. Miccoli, F. Basolo, miRNA expression profiling of 'noninvasive follicular thyroid neoplasms with papillary-like nuclear features' compared with adenomas and infiltrative follicular variants of papillary thyroid carcinomas. Mod. Pathol. **30**, 39–51 (2017)
51. X.S.H.G. Jiang, M.B. Datto, Young investigator challenge: molecular testing in noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Cancer Cytopathol. **124**, 893–900 (2016)
52. T.H.L.M. Kim, A.Y. Kwon, J.H. Choe, J.H. Kim et al. Molecular genotyping of the non-invasive encapsulated follicular variant of papillary thyroid carcinoma. Histopathology **72**, 648–661 (2018)
53. R.C.D.M. Jug, X.S. Jiang, Molecular testing for indeterminate thyroid nodules: performance of the Afirma gene expression classifier and ThyroSeq panel. Cancer Cytopathol. **126**, 471–480 (2018).
54. Z.T.S.P. Sahli, C.B. Umbricht, M.A. Zeiger, Preoperative molecular markers in thyroid nodules. Front Endocrinol. **9**, 179 (2018)
55. G.V.M. Acquaviva, A. Repaci, K.J. Rhoden, D. de Biase, A. Pession, T. Giovanni, Molecular pathology of thyroid tumours of follicular cells: a review of genetic alterations and their clinicopathological relevance. Histopathology **72**, 6–31 (2018)
56. G.P.O. Fu, C. MacMillan, R. Ralhan, P.G. Walfish, Programmed Death-Ligand 1 Expression Distinguishes Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma from Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features. EBio Med. **18**, 50–55 (2017)
57. B.R.A.E. Haugen, K.C. Bible, G.M. Doherty, S.J. Mandel et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid **26**, 1–133 (2016)
58. B.R.S.A. Haugen, E.K. Alexander, K.C. Bible, P. Caturegli et al. American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features. Thyroid **27**, 481–483 (2017)
59. A.A.R.H. Ghuzlan, M. Schlumberger, Noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Curr. Opin. Endocrinol. Diabetes Obes. **24**, 377–380 (2017)
60. P.W. Rosario, Long-Term Outcomes of Patients with Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) > / = 4 cm Treated Without Radioactive Iodine. Endocr. Pathol. **28**, 367–368 (2017)
61. Z.J.S. Aburjania, C. Montemayor-Garcia, R.V. Lloyd, D.F. Schneider, R.S. Sippel, H. Chen, D.M. Elfenbein, Encapsulated follicular variant of papillary thyroid cancer: are these tumors really benign? J. Surg. Res. **216**, 138–142 (2017)
62. V.A.F.K.K. Alves, V. LiVolsi, R.V. Lloyd, Y.E. Nikiforov, V. Nose, M. Papotti, L.D.R. Thompson, Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP): Achieving Better Agreement By Refining Diagnostic Criteria. Clin. (Sao Paulo). **73**, e576 (2018)