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Research Article

Clinical and Pathological Features of Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features: A Case Series of Nine Patients

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Abstract

Introduction: Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) is a recently reclassified thyroid entity that aims to reduce overtreatment of indolent tumors previously diagnosed as Follicular Variant of Papillary Thyroid Carcinoma (FVPTC). Accurate identification is essential due to its excellent prognosis and minimal risk of recurrence or metastasis.

Objective: To describe the clinical, cytological, histopathological, and follow-up findings of nine patients diagnosed with NIFTP, and to assess the diagnostic challenges and management approaches in a real-world clinical setting.

Methods: This retrospective case series includes nine patients diagnosed with NIFTP between July 2022 till July 2024 at Dubai Hospital, Dubai Health. Clinical presentation, imaging features, cytology (Bethesda classification), histopathological evaluation, surgical management, and follow-up outcomes were analyzed.

Results: All our patients were female except for one male patient .All patients patients had us thyroid that was reported as TIRAD'D 2, 3 and 4. Patients having TIRAD'S 3 and 4 underwent FNAC and majority were reported as Bethesda iv with few Bethesda 3 and one Bethesda 2. All patients underwent surgical excision total /hemithyroidectomy after MDT decision .Patient with Bethesda 2 was having large goiter with compression symptoms so underwent total thyroidectomy . Final histopathology for all showed NIFTP based on strict diagnostic criteria. During a mean follow-up of one year no recurrences or complications were observed.

Conclusion: NIFTP represents a low-risk thyroid neoplasm with an indolent course. Accurate diagnosis based on histological criteria is crucial to avoid overtreatment. Awareness of its features can help clinicians make appropriate management decisions, particularly regarding the extent of surgery and need for postoperative surveillance.

Introduction

Thyroid nodules are a common clinical finding, and while most are benign, a subset represents differentiated thyroid carcinomas, including the Follicular Variant of Papillary Thyroid Carcinoma (FVPTC). In recent years, growing evidence has demonstrated that a specific subset of encapsulated FVPTCs behaves in an indolent, non-invasive manner and carries an extremely low risk of recurrence or metastasis [1,2]. This observation led to a landmark reclassification in 2016, when an international panel of experts proposed the term Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) to replace these tumors. The goal was to reduce overtreatment and alleviate the psychological impact of a cancer diagnosis in patients with tumors that pose minimal clinical risk [3,4]. NIFTP is characterized by a completely encapsulated or well-demarcated lesion, follicular growth pattern, and nuclear features reminiscent of papillary thyroid carcinoma, but without capsular or vascular invasion. Since its redefinition, NIFTP has significantly influenced thyroid pathology and surgical decision-making. However, accurate diagnosis can be challenging, particularly on Fine Needle Aspiration Cytology (FNAC), as its features often overlap with those of other benign or malignant follicular-patterned lesions [5,6]. The diagnostic criteria for NIFTP have evolved since the original 2016 reclassification. The American Thyroid Association (ATA) and subsequent expert consensus groups have refined the histopathological criteria to improve diagnostic accuracy and ensure the indolent nature of NIFTP is preserved [5-8] (Table 1).

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (years)	22	69	57	39	35	50	31	72	33
Gender	M	M	M	M	M	M	M	M	F
Symptoms	Neck swelling	MNG increasing in size	MNG increasing in size	Hypothyroidism with neck swelling	Neck swelling	MNG	MNG with neck swelling	MNG	Dysphagia
Family History of Thyroid Cancer	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
FNAC Result	Suspicious for follicular lesion, features concerning NIFTP	Suspicious for follicular lesion, features concerning NIFTP/FVPTC	Bilateral benign follicular	Suspicious for PTC	Follicular neoplasm	Bilateral AUS/FLUS	AUS/FLUS	Left: Follicular cells with atypia; Right: Non-diagnostic	Benign follicular
Bethesda Category	IV	IV	Bilateral II	V	NA	Bilateral III	III	L: V / R: I	II
Type of Surgery	Left hemithyroidectomy	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy	Left hemithyroidectomy	Total thyroidectomy	Total thyroidectomy	Left hemithyroidectomy	Left hemithyroidectomy
Coexisting Cancer	No	No	No	No	No	No	No	No	No
Postoperative Complications	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil

Table 1: Demographics and Tumor Characteristics of Patients with NIFTP.

Updated Diagnostic Criteria for NIFTP (Based on ATA and Recent Expert Guidelines)

According to the most recent guidelines and expert consensus updates endorsed by the American Thyroid Association, Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) must fulfill strict histopathological criteria to ensure its low-risk biological behavior. The revised criteria are as follows [8-10]:

1. Encapsulation or Clear Demarcation

The tumor must be completely encapsulated or clearly demarcated from surrounding thyroid parenchyma.

Absence of infiltrative growth pattern is mandatory.

2. Follicular Growth Pattern

The tumor must show a pure follicular architecture. No true papillae are allowed. Presence of less than 1% papillae may be considered in exceptional cases by some pathologists, but current trend discourages any papillary formation.

3. Papillary-like Nuclear Features

Nuclear features of PTC must be present, including:Enlarged nuclei,Irregular nuclear contours,Chromatin clearing,Nuclear grooves and occasional pseudoinclusions .These features should be diffuse and convincing, not focal.

4. Absence of Invasion

There must be no capsular or vascular invasion.Entire capsule must be submitted for microscopic evaluation to confidently exclude invasion.

5. Absence of High-Risk Features

No necrosis.,No high mitotic activity (should be <3 mitoses per 10 high-power fields) and No solid/trabecular/insular growth pattern involving >30% of the tumor.

6. Optional Immunohistochemistry or Molecular Testing

While not required for diagnosis, absence of high-risk mutations such as BRAF V600E and TERT promoter mutations supports the diagnosis.RAS-like mutations are more commonly associated with NIFTP. These refined criteria emphasize complete histological evaluation, especially thorough sampling of the tumor capsule, to avoid misclassification. The aim is to maintain a highly specific definition that ensures all NIFTP cases are truly indolent, thus supporting conservative management and avoiding overtreatment [11,12]. These refined criteria emphasize complete histological evaluation, especially thorough sampling of the tumor capsule, to avoid misclassification. The aim is to maintain a highly specific definition that ensures all NIFTP cases are truly indolent, thus supporting conservative management and avoiding overtreatment [12].

Methods

Study Design and Setting

This is a retrospective case series conducted at Dubai hospital , Dubai Health, UAE.The study included patients who underwent thyroid surgery and were diagnosed with Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) on final histopathology between July 2022 till July 2024.

Inclusion Criteria

Patients were included in the study if they met the following criteria:

1. Age ≥ 18 years

2. Histopathological diagnosis of NIFTP based on updated diagnostic criteria (ATA 2016 and recent consensus refinements)

3. Availability of complete clinical, cytological, and histopathological records

Data Collection

Clinical and pathological data were retrieved from hospital medical records and pathology archives. The following variables were collected:

Demographics: age, sex

Clinical presentation: symptoms, nodule size, location

Preoperative imaging: ultrasound findings, TI-RADS category if available

Cytology: FNAC results reported according to the Bethesda System

Surgical details: type of surgery (lobectomy vs total thyroidectomy)

Histopathology: tumor size, encapsulation, nuclear features, presence of invasion,

presence of papillae, mitotic activity, necrosis

Follow-up: All patients had follow up for one year or more .

All histopathological slides were reviewed by experienced endocrine pathologists to confirm the diagnosis of NIFTP according to the most recent diagnostic criteria, including complete encapsulation, absence of invasion, follicular growth pattern, and nuclear features of PTC.

Results

A total of nine patients were diagnosed with Non-Invasive

Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP). The mean age at diagnosis was 45.3 years (range: 22–72 years). Eight patients (88.9%) were male and one patient (11.1%) was female. The most common presenting symptom was neck swelling, reported either alone or in the context of a Multinodular Goiter (MNG). One patient presented with dysphagia, and another was newly diagnosed with hypothyroidism. None of the patients had a family history of thyroid cancer. Preoperative fine needle aspiration cytology (FNAC) varied, with results ranging from benign (Bethesda II) to suspicious for papillary thyroid carcinoma (Bethesda V). Most cases fell into Bethesda categories III to V. One case was non-diagnostic (Bethesda I) on one side. Five patients underwent total thyroidectomy, while four underwent left hemithyroidectomy. Final histopathology confirmed NIFTP in all cases based on strict diagnostic criteria. There was no evidence of capsular or vascular invasion, and no coexisting thyroid malignancy was found in any patient. All patients had an uneventful postoperative course, with no reported complications.

Ultrasound Characteristics

Preoperative neck Ultrasound (US) was performed for all patients and revealed thyroid nodules ranging in size from 0.9 cm to 5.8 cm. The number of nodules varied, with six patients having multinodular goiter, while three had solitary nodules. Most nodules were located in the left lobe (5/9); two were bilateral and two on the right (Table 2).

All nodules were well-defined on US. Common sonographic features included:

US Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Size (cm)	4.2×3.4×2.2	2.4×1.5	R: 5.8×3.8 L: 2.8×2.2	3.8×1.7	1.8×0.9 3.3×1.8	1.5×0.8 3.2×1.8	L: 1.4×1.2 R: 0.9×0.8	3.38×2.1	2.3×3.0
Number of Nodules	1	1	2	1	2	2	2	1	1
Site	Left	Left	Bilateral	Right	Left	Bilateral	Bilateral	Left	Left
Intralesional Vascularity	No	No	Yes	Yes	Yes	No	No	No	No
Perilesional Vascularity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calcifications	No	No	No	No	No	No	No	No	No
Halo Around	No	No	No	No	No	No	No	Yes	No
Echogenicity	-	Iso	Iso	Iso + Hyperechoic	Hypoechoic + Iso	Iso	Iso + Hyperechoic	Iso	Iso
Heterogeneous	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Cystic Degeneration	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Solid Component	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Margins	Well-defined	Well-defined	Well-defined	Well-defined	Well-defined	Well-defined	Well-defined	Well-defined	Well-defined
TIRADS Classification	3	3	3	3	4	3	3	2	3
Increase in Size	No previous US	-	Yes (20%)	No previous US	No previous US	No previous US	-	Yes (50%)	No previous US

Table 2: Ultrasound Features of Suspicious Nodules in NIFTP Cases.

1. Solid component in all nine cases
2. Heterogeneous echotexture in 6 cases (66.7%)
3. Cystic degeneration in 6 cases (66.7%) Perilesional vascularity was present in all cases
4. Intralesional vascularity was noted in 3 cases
5. No calcifications were seen in any patient Only one nodule showed a halo sign
6. Nodules were mostly isoechoic (7/9)
7. TIRADS 3 was the most common classification (6/9), while one nodule each was categorized as TIRADS 2 and 4
8. Histopathological Findings

All nine patients in the series were confirmed to have Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) on final histopathological evaluation. The tumor size ranged from 0.6 cm to 5.7 cm, with a mean size of 2.3 cm. Each tumor was well circumscribed with no ill-defined margins, and all had free surgical margins. Capsular and lymphovascular invasion were absent in all cases, consistent with the strict diagnostic criteria for NIFTP. All specimens demonstrated papillary-like nuclear features, such as nuclear enlargement, irregular contours, and chromatin clearing. Eight tumors were unifocal, while one (Case 2) was multifocal. All were of the low-risk follicular cell-derived histological subtype (Table 3).

Feature	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9**
Final Diagnosis	NIFTP	NIFTP	NIFTP	NIFTP	NIFTP	NIFTP	NIFTP	NIFTP	NIFTP
Tumor Size (cm)	2.9	0.9	0.85	4	2.3	2.1	0.6	5.7	2.3
Well Defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ill-Defined	No	No	No	No	No	No	No	No	No
Lymphovascular Invasion	No	No	No	No	No	No	No	No	No
Capsular Invasion	No	No	No	No	No	No	No	No	No
Margin Status	Free	Free	Free	Free	Free	Free	Free	Free	Free
Unifocal	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Multifocal	No	Yes	No	No	No	No	No	No	No
Papillary-like Nuclear Features	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Histological Type	Low-risk, follicular cell-derived	Same	Same	Same	Same	Same	Same		

Table 3: Histopathological Characteristics of NIFTP Tumors.

Combined Summary of Findings

A total of nine patients were diagnosed with Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) at our institution. The mean age was 45.3 years (range: 22–72), with a striking male predominance (8 males, 1 female), in contrast to previous reports suggesting a female predilection. The most common presenting complaint was neck swelling, either isolated or as part of a multinodular goiter. One patient presented with dysphagia, and another had newly diagnosed hypothyroidism. All patients underwent preoperative ultrasound, which demonstrated well-defined nodules with solid components in all cases. Most nodules were isoechoic, heterogeneous, and showed cystic degeneration. Perilesional vascularity was noted in all patients, while intralesional vascularity was present in three cases. No calcifications were observed. Nodules were mostly classified as TIRADS 3, with one case each classified as TIRADS 2 and TIRADS 4. FNAC findings were variable and fell across multiple Bethesda categories, with most falling into Bethesda III to V. Only one case had a non-diagnostic result on one side, and two cases were categorized as Bethesda II. This variation highlights the

difficulty in distinguishing NIFTP preoperatively using cytology alone. Surgically, five patients underwent total thyroidectomy, while four had left hemithyroidectomy, reflecting variable initial diagnostic impressions. No patient had a coexisting thyroid malignancy, and none experienced postoperative complications. On final histopathological examination, all tumors met the strict diagnostic criteria for NIFTP:

1. All were well-circumscribed, with no capsular or lymphovascular invasion

2. Tumor size ranged from 0.6 to 5.7 cm (mean: 2.3 cm)

3. All tumors exhibited papillary-like nuclear features

4. Eight tumors were unifocal, and one was multifocal

5. All had free surgical margins and were classified as low-risk, follicular cell-derived neoplasms

These findings support the indolent nature of NIFTP and emphasize the importance of strict histological evaluation for accurate diagnosis. The wide range of cytological and sonographic features further underscores the current limitations of preoperative prediction and highlights the role of thorough postoperative pathological review in preventing overtreatment.

Discussion

Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) is a relatively new pathological entity introduced to reduce overtreatment of indolent thyroid tumors previously classified as non-invasive Follicular Variant of Papillary Thyroid Carcinoma (FVPTC) [5]. The reclassification, first proposed by Nikiforov et al. in 2016, was based on a consensus that encapsulated follicular-patterned lesions with papillary-like nuclear features but lacking invasive characteristics behave in an indolent manner [6]. Our case series of nine patients contributes to the growing clinical experience with NIFTP, highlighting the challenges in preoperative diagnosis and reinforcing its favorable post-surgical outcomes. In our study, the mean age was 45.3 years, which is consistent with the age distribution reported in other studies, typically involving middle-aged adults [2]. However, we observed a male predominance (88.9%), in contrast to the literature, where NIFTP is more frequently reported in females 333. This gender disparity may reflect regional variation, small sample size, or selection bias and warrants further investigation.

Most patients presented with neck swelling or multinodular goiter, which is consistent with common presentations of indolent thyroid neoplasms 444. Ultrasound findings were largely nonspecific: all nodules were well-defined, with solid components, and many demonstrated cystic changes and heterogeneous echotexture. No case exhibited calcifications, which is typical of NIFTP and may help distinguish it from classic Papillary Thyroid Carcinoma (PTC) [5]. All nodules had perilesional vascularity, but intralesional flow was limited to three cases, supporting prior reports that NIFTP often lacks aggressive vascular patterns on imaging [6]. The TIRADS classification in most cases was TIRADS 3, suggesting a low-to-intermediate suspicion. Only one case was classified as TIRADS 4. This reflects a diagnostic gray zone, as many NIFTP cases fall within TIRADS 3–4, overlapping with benign and malignant categories [7]. FNAC results spanned Bethesda categories II to V, with most in category III (AUS/FLUS) or IV (follicular neoplasm/suspicious for follicular neoplasm). This variability is in line with previous studies, which report that NIFTP commonly falls into Bethesda III–V, making definitive cytological diagnosis challenging 888. Notably, NIFTP cannot be definitively diagnosed on cytology alone; it requires full histopathological evaluation, including submission of the entire capsule to rule out invasion [1,9]. Surgical management varied in our series: five patients underwent total thyroidectomy, and four underwent hemithyroidectomy. Since NIFTP carries a negligible risk of recurrence or metastasis, lobectomy is generally considered sufficient 101010. In retrospect, many of the total thyroidectomies may have been avoided with greater preoperative confidence in the indolent nature of these lesions. Histopathologically, all tumors were well-circumscribed, with no capsular or vascular invasion, and all showed papillary-like nuclear features. These are the core criteria for NIFTP and were consistently met in our cohort. One patient had a multifocal tumor, which is rarely reported but has not been associated with increased risk of recurrence [1,2,5]. None of the patients experienced postoperative complications, and no recurrences were observed during follow-up, further supporting the excellent prognosis of NIFTP when correctly identified and managed conservatively [1,3,5].

Clinical Implications

Our findings reinforce the need for:

1. Meticulous histological examination to ensure accurate diagnosis

2. Judicious surgical decision-making, favoring lobectomy where appropriate

3. Enhanced radiological and cytological awareness of NIFTP patterns to avoid overtreatment

Limitations

This study is limited by its retrospective nature, small sample size, and short-term follow-up. Larger, prospective studies with molecular profiling may provide additional insights into risk stratification and preoperative diagnostic accuracy.

Conclusion

NIFTP is a low-risk, indolent thyroid neoplasm with favorable outcomes. Although preoperative diagnosis remains a challenge due to overlapping cytologic and ultrasound features, strict application of histopathological criteria ensures proper classification and prevents unnecessary aggressive treatment. Continued education and awareness among clinicians and pathologists are essential to fully realize the benefits of this reclassification.

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Statement of Ethics: This case series is conducted in accordance with The World Medical Association (WMA) Declaration of Helsinki and obtaining Informed consent from all the patient for this case series.

Ethical Approval: The Institutional Review Board (IRB) at Dubai Health has reviewed and approval is granted

Patient Informed Consent Statement: Written Patient Informed Consent was obtained from all the Patient to publish their case and any accompanied images.

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