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Case Series

Non Invasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features- A Case Series from Tertiary Care Centre In Wayanad

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ABSTRACT

Background
NIFTP is a recently introduced entity in the WHO classification of tumours of endocrine organs. It is a diagnosis made exclusively on histopathological examination of thyroid lesions. However a preoperative suspicion can be made correlating with the ultrasonographic and cytological findings. Most of these cases may be over diagnosed in cytological evaluation as Papillary thyroid carcinoma or as a Follicular variant of Papillary thyroid carcinoma. A thorough histopathological examination of all thyroidectomy specimens is the key to diagnosis of NIFTP and thus we undertook this study.

Methods
A retrospective analysis of thyroidectomy specimens with a histopathological diagnosis of NIFTP was done from May 2022 to May 2024, of two years duration which were received in the Department of Pathology in our Tertiary care centre at Wayanad. The slides were retrieved from the archives and the clinical, radiological and cytology evaluation data was collected from the HIS (Hospital Information System). All 7 cases were compared with their cytology reports. Statistical quantitative analysis was conducted for demographic, ultrasound findings, cytology and histopathological diagnosis. Results were presented as frequency/percentage for categorical variables. Qualitative analysis examined with detailed descriptions of cases.

Results
Of these cases, about 71% were females, most of them above 40 years and ultrasound diagnosis of about 57.1% cases were TIRADS III. Cytological evaluation had 42.8 % cases with Bethesda category II and 28.5% Suspicious for Malignancy.

Conclusion
NIFTP may not be conclusively diagnosed or suspected in a preoperative radiological or cytological evaluation. Histopathologically it may be an incidental finding in a benign multinodular goitre. So

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surgeons might need to have a high index of suspicion for cases of benign, solitary or multinodular thyroid lesions.

Keywords: NIFTP, FVPTC, Encapsulated FVPTC, Papillary Thyroid Carcinoma.

INTRODUCTION

Non invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a recently introduced entity in The World Health Organization, Classification of Tumours of Endocrine Organs. NIFTP is a borderline thyroid tumour formerly known as Noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC). Papillary Thyroid Carcinoma(PTC) has one among its many variants which is the follicular variant of papillary thyroid carcinoma (FVPTC) and it is the second most common histological variant PTC [1]. Two types of FVPTC has been identified, non-encapsulated (infiltrative) and encapsulated. Many of the encapsulated variant of FVPTC exhibits features of vascular or capsular invasion and individual forms also differ in their molecular profile, clinical behaviour and prognosis [2, 3].

A subset of encapsulated FVPTCs has shown to have an extremely indolent behaviour and good prognosis. Because of this indolent nature of a subset of EFVPTC, The Endocrine Pathology Society working group proposed a new terminology “Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” in 2016 [4]. This entity was introduced to avoid overdiagnosis and unnecessary and financial burden on both clinicians as well as patients. The advent of this new terminology has brought up certain issues pertaining to a proper diagnostic criteria, preoperative cytological diagnosis and clinical impact of this neoplasm.

NIFTP cases may present as thyroid nodules that are usually detected by physical examination or ultrasonography [5]. However, ultrasound does not allow identification or in diagnosis of NIFTP [6]. All NIFTP are diagnosed on histopathology after fulfilment of a set of criteria on the resected specimen. The most recent diagnostic criteria for diagnosis of NIFTP is based on 2022 World Health Organization (WHO) Classification of Tumours of Endocrine organs. As per WHO, the essential criteria are, 1. Encapsulation or clear demarcation 2. Follicular growth pattern with < 1% true papillae, No psammoma bodies, < 30% solid/trabecular/insular growth, 3. Nuclear score of 2–3, 4. No vascular or capsular invasion, 5. No tumor necrosis, 6. Low mitotic count (<3 mitoses/2 mm^2 , 7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant [7].

MATERIALS & METHODS

We report a case series of 7 retrospective cases of NIFTP from our tertiary care center, DMMC in Wayanad. All the cases were diagnosed over 2 years, from May 2022 to May 2024, after the introduction of the term NIFTP by WHO. This report is in line with the updated PROCESS guidelines [8].

Case Presentation

Case 1

A 43 year old female with no known comorbidities with c/o swelling in front of the neck for 25 years which increased in size for past 1 year. She had difficulty in swallowing. No significant past history or family history. A 5x2cm, non mobile, firm swelling was noted extending from midline to right sternocleidomastoid. It moved with deglutition. No local rise in temperature or tenderness noted. Ultrasound of neck had multiple well defined, predominantly solid, wider than taller isoechoic lesions

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in thyroid gland- TIRADS III. A Fine needle aspiration cytology (FNAC) was performed and had thyroid follicular cells clusters as macro- and microfollicles admixed with plenty of cyst macrophages against an abundant colloid background. The diagnosis made was Benign Follicular Lesion with Cystic changes (The Bethesda System of Reporting Thyroid Cytopathology - Category II). Total thyroidectomy was done. Per operatively it was multinodular goitre with dominant nodule in the right lobe and had significant retrosternal extension. Pathological examination of resected thyroid was done. The larger lobe measured 6.5x6.5x4cm. Cut surface multiple colloid nodules, largest measuring 3.5x3cm. Other lobe, tagged as left lobe, measured 3.5x3x2cm, cut surface of which showed a gray white area measuring 0.7x0.5cm which was reaching upto the thyroid capsule. Sections were taken from both lobes and small gray white area. On microscopy there were varying sized and cystically dilated thyroid follicles filled with colloid. Areas of follicular hyperplasia, hurthle cell change, lymphocytic infiltration and hemorrhage noted. The gray white area was composed of microfollicles with focal nuclear overlapping, overcrowding and nuclear clearing. Nuclear score: 2. Papillae <1%. No necrosis/mitoses identified. Nodule showed a thin capsule. No capsular or vascular invasion identified. A diagnosis of Non Invasive Follicular Thyroid Neoplasm with Papillary Nuclear Features (NIFTP) measuring 0.7x0.5cm was made.

Case 2

A 65 year old female presented with complaints of swelling in front of neck for past 30 years. Swelling was of insidious onset, non progressive in nature. She also developed difficulty in swallowing. Type2 diabetes mellitus was newly diagnosed and was on medication.Local examination of neck showed a swelling of 3x4cm, firm, in left lobe of thyroid. On Ultrasound guided FNAC, sheets and macrofollicles of thyroid follicular cells with a few cells exhibiting mild cytological atypia, occasional nuclear groves, nuclear irregularity and intranuclear psuedoinclusions were noted. Scanty colloid and mainly blood was present in the background. A diagnosis with suspicion of malignancy, possibly Papillary carcinoma of Thyroid- TBSRTC Category V was made. Intraoperative findings were enlarged right lobe and isthmus with multiple nodules, largest measuring 3x4cm. Gross examination of total thyroidectomy specimen received showed right lobe measuring 4.5x2.5x2cm, left lobe measured 4x1.5x2cm and isthmus 3x2x1.5cm. Cut section of right lobe had a gray white area of 0.8x0.5x0.5cm, about 0.4cm away from the thyroid capsule. Isthmus showed another gray brown to gray white area measuring 2x1x1.2cm, which was at a distance of 0.1cm from the thyroid capsule. Sections from all lesions were taken for histopathological examination. On Microscopy, right lobe showed an encapsulated nodule with focal areas of overcrowded microfollicles exhibiting nuclear clearing, overcrowding and occasional intranuclear psuedoinclusions. Nuclear score of 2. No psammoma bodies/necrosis/mitoses seen. No papillae(<1%). Larger grey brown to grey white nodule showed oncocytic adenomatoid nodule. A final diagnosis of Non Invasive Follicular Thyroid Tumour with Papillary like Nuclear Features measuring 0.8x0.5x0.5cm- Subcentimeter NIFTP was made.

Case 3

A 64 year old male presented with a very insidious and gradually progressive swelling in front of neck of 4 years duration. No other specific complaints was there in this patient. On examination the swelling was of size 4x4cm, oval, firm and mobile. Pemberton's sign was negative. Ultrasound study showed a few large well defined, wider than taller echoic ,solid and cystic lesions in the right lobe of thyroid-TIRADS IV. An FNAC performed had cellular, cohesive clusters and cells in papillary pattern with occasional bizzare cells. There were nuclear overcrowding, overlapping, irregular nuclear borders with some nuclear grooves. No pseudoinclusions noted. A diagnosis of Suspicious for Malignancy-

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Suspicious for Papillary Carcinoma Thyroid – TBSRTC V was made. Total Thyroidectomy was done and specimen sent for pathological study. On gross examination larger lobe measured 6.5x5x4cm and smaller lobe, 5x3x1.5cm. Cut section had cystic areas in larger lobe with some projections in its wall. Microscopic examination showed nodule with sprinkling of thyroid follicles with focal nuclear overcrowding, overlapping and mild nuclear membrane irregularities. Focal areas of calcification, fibrosis, cholesterol clefts and multinucleate giant cell reaction was also noted. No papillae or psammoma bodies identified. With these findings, a diagnosis of NIFTP was made.

Case 4

45 year old female had complaints of swelling in front of neck since 3 years and it was gradually progressive and increasing in size. She had a mild difficulty in breathing over few months. An ultrasonography of neck showed features of multinodular goitre with a dominant nodule in the left lobe- TIRADS III and IV nodules. FNAC diagnosis was Benign follicular nodule- TBSRTC II. Post surgical examination of thyroid gland showed a larger lobe of size 8x5x5cm and a smaller lobe of size 7x3x2.5cm. Cut section of the larger lobe revealed a well circumscribed nodule measuring 5.5x5x5cm and a small gray white area measuring 0.5cm, situated 0.7cm away from the larger nodule. The microscopic findings of larger nodule showed a well encapsulated lesion composed of closely packed follicles and small follicles devoid of colloid. Small pockets of follicles had nuclear clearing, nuclear grooves, overcrowding and overlapping. Occasional nuclear psuedoinclusions noted. No well defined papillae could be identified. The smaller grey white area also showed sprinkling sign with nuclear clearing, overcrowding and grooves. Features were consistent with a diagnosis of NIFTP, measuring 5.5x5x5cm.

Case 5

A 41 year old female had an swelling in the front of neck over past 3 years. It was of insidious onset. She had no other specific complaints. No difficulty in breathing or swallowing. On examination, the swelling was firm, moved with deglutition and multiple nodules was palpable. Ultrasound findings showed multiple nodules, isoechoic with solid and cystic areas with TIRADS III nodules. Cytology of thyroid gland studied was benign follicular nodule -TBSRTC Category II. Total thyroidectomy received in the department of pathology was evaluated. Right lobe was of size 5.5x3.5x3cm, left lobe and isthmus together measured 3.5x3.5x1cm. Cut section of larger right lobe had large nodule filled with colloid, cystic and yellowish areas. Rest of the thyroid was grey brown. On microscopic examination, an area of clear demarcation composed of follicular growth pattern was identified with <1% papillae. Nuclear crowding and overlapping with sprinkling sign noted. Adjacent thyroid showed calcification, cholesterol clefts and areas of hemorrhage. No psammoma bodies or necrosis or mitoses seen. A diagnosis of NIFTP was made and a strict follow up was advised.

Case 6

A 22 year old female presented with a diffuse and nodular swelling in front of neck for past 4 years. She had difficulty in swallowing food and mild dyspnoea. On local examination, the swelling was firm with multiple palpable nodules on both right and left lobes of thyroid. A video laryngoscopy was performed and showed normal, mobile bilateral vocal cords. An ultrasound of neck was performed which revealed multiple isoechoic nodules on right and left lobes of TIRADS II and TIRADS III. After all laboratory investigations and pre anaesthetic evaluation, a Total thyroidectomy was done. The resected specimen studied at the Pathology department showed an enlarged right lobe measuring 7x6x5cm, Left lobe and isthmus measuring 5x2x2cm. Cut section of left lobe showed a circumscribed

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grey brown to grey white nodule measuring 2x1cm. Rest of the thyroid cut section showed multiple colloid nodules. Microscopic examination of right lobe showed multiple large colloid filled follicles of varying sizes along with hemorrhage and odema. Sections from left lobe showed a well defined nodule with thick encapsulation, composed of micro and macrofollicles. The cells had moderate cytoplasm with uniform mildy enlarged nucleus, some showing nuclear clearing (nuclear score 2). No papillae or psammoma bodies identified. There was no capsular or vascular invasion noted. With these findings a diagnosis of NIFTP with multinodular goitre was made.

Case 7

A 56 year old man with Type 2 diabetes mellitus came to OPD with complaints of swelling in front neck for 1 month duration. He had noticed a rapid increase in size towards the left side of the swelling. He also had weight loss. No dysphagia or dyspnoea. USG ahowed TIRADS 3 and TIRADS 4nodules in the left lobe of thyroid. Cytological diagnosis was Atypia of undetermined significance- TBSRTC Category III. Total thyroidectomy was done and on gross examination of resected specimen, right lobe measured 5.5x1.7x2cm, left lobe 6x4x3cm and isthmus 2x1x0.8cm. The right lobe and isthmus on cut section had diffuse colloid filled areas. Left lobe had a well circumscribed nodule with colloid, areas of hemorrhage and calcification. On histopathology, the left lobe showed a poorly encapsulated lesion composed of microfollicles and sheets of colloid follicles. No papillae noted.Cells having mildly enlarged nucleus, focal irregular nuclear membranes and margination of chromatin was noted. Nuclear score was 2. No capsular or vascular invasion seen. Areas of cystic degeneration and hemorrhage was found. A diagnosis of NIFTP in a background of multinodular goitre was given.

RESULTS

Of the seven cases of NIFTP diagnosed, 5 out of 7 were females which accounts for 71%. Most of our patients were above the age of 40 years. The ultrasound impression were of TIRADS III (57.1%) , TIRADS II (28.5%) and one case with TIRADS V (14.2%). Cytological evaluation in these cases diagnosed as Benign Follicular Nodule, TBSRTC Category II in 42.8%. Atypia of Undetermined significance, TBSRTC Category III, was given as diagnosis in two patients(28.5%). Two cases were reported cytologically Suspicious for Papillary Carcinoma, TBSRTC Category V which accounted to 28.5%.

Table.1 Demographic, Ultrasound and cytology of 7 cases

Sl No	Age	Sex	USG score	FNAC
1.	64	M	TIRADS IV	Suspicious for PTC – TBSRTC Category V
2.	65	F	TIRADS II	Suspicious for PTC – TBSRTC Category V
3.	22	F	TIRADS II and III	Atypia of Undetermined Significance - TBSRTC Category III
4.	43	F	TIRADSIII	Benign Follicular Nodule - TBSRTC Category II
5.	41	F	TIRADS III	Benign Follicular Nodule - TBSRTC Category II
6.	56	M	TIRADSIII and IV	Atypia of Undetermined Significance - TBSRTC Category III
7.	45	F	TIRADSIII	Benign Follicular Nodule - TBSRTC Category II

M-male, F-Female, TIRADS- The Thyroid Imaging Reporting and Data System, TBSRTC- The Bethesda System of Reporting Thyroid Cytopathology.

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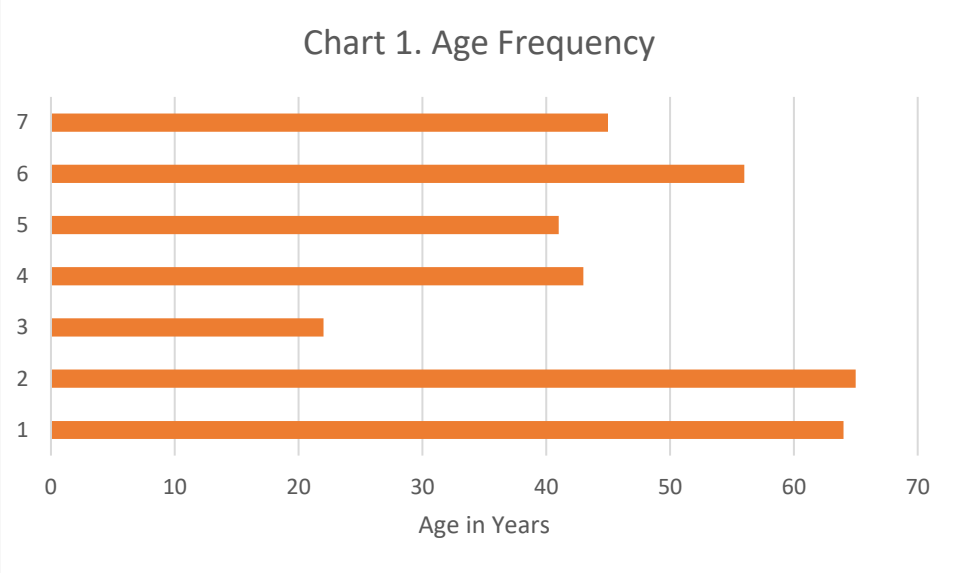

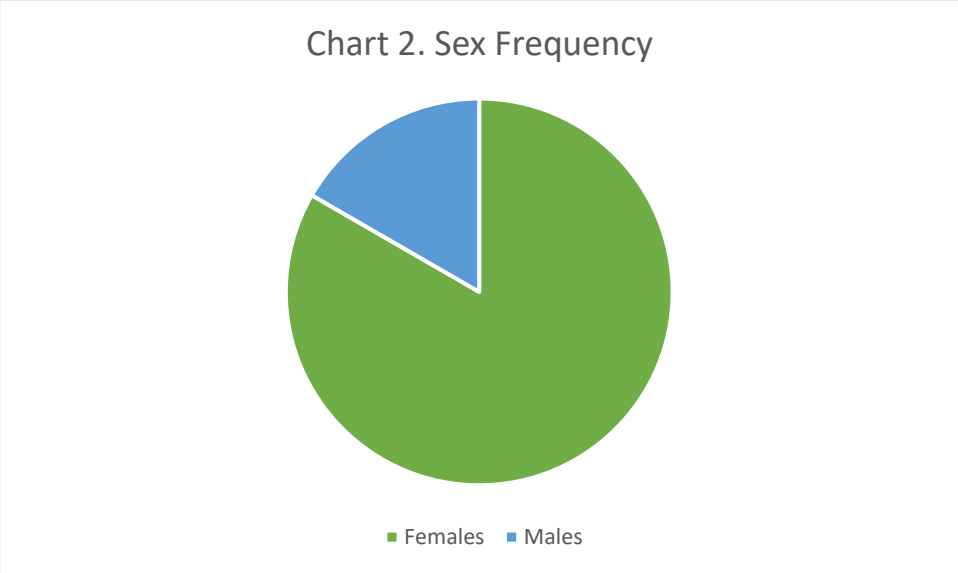

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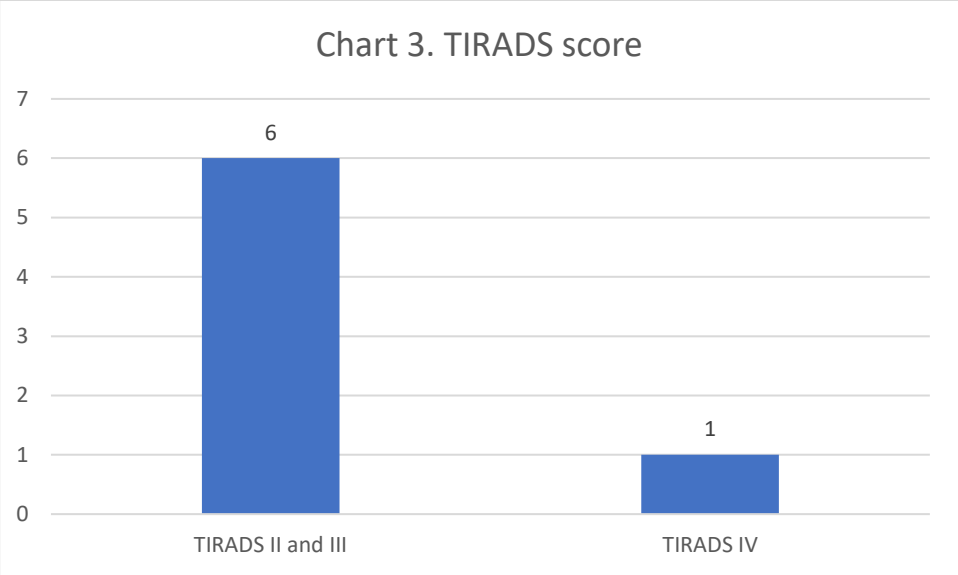

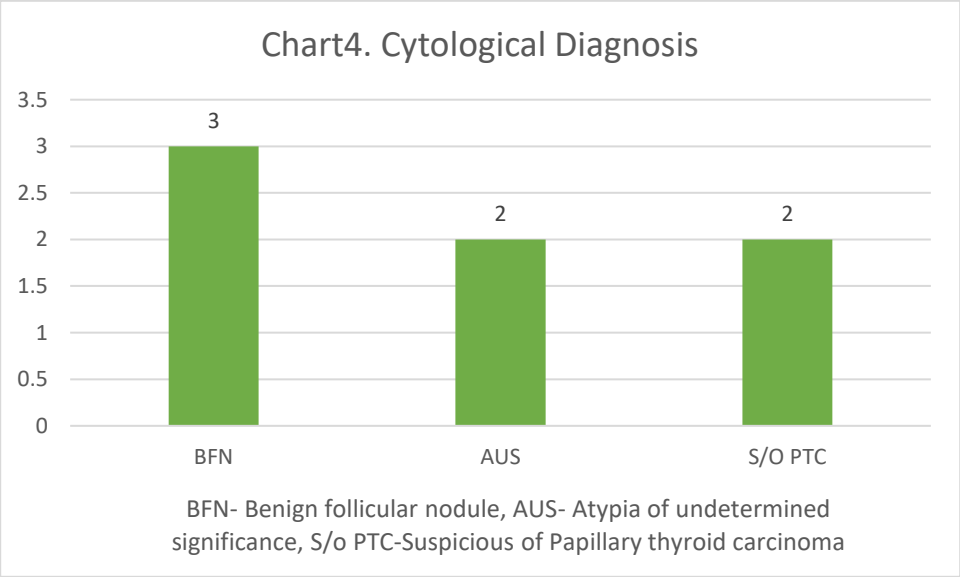

DISCUSSION

NIFTP is a follicular cell-derived non-invasive encapsulated neoplasm having a follicular growth pattern and nuclear features of papillary thyroid carcinoma (PTC) which has an extremely low malignant potential [9]. According to the latest guidelines of the World Health Organization, NIFTP is a solitary, well-demarcated nodule, typically with a thin to moderately thick capsule. The tumours are usually 2–4 cm in size but can be much larger. One of the most common and standard diagnostic tool in evaluation of thyroid lesions is Ultrasonography.

The Thyroid Imaging Reporting and Data System(TIRADS) guidelines is popularly used to categorize thyroid nodules based on sonographic findings as follows: 1, no nodule; 2, benign: spongiform or partially cystic nodule with comet tail artifact or pure cyst; 3, low suspicion: partially cystic or iso-hyperechoic nodule without any of three suspicious ultrasound(US) features (microcalcification, non-parallel orientation/taller than wide, and spiculated/microlobulated margin);

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4, intermediate suspicion: solid hypoechoic nodule without any of three suspicious US features or partially cystic or iso-hyperechoic nodule with any of three suspicious US features; and 5, high suspicion: solid hypoechoic nodule with any of three suspicious US features [10]. A Fine Needle Aspiration Cytology (FNAC) plays a crucial role in preoperative diagnosis in thyroid lesions. FNAs of NIFTP are characterized by a microfollicular architecture of follicles with variable nuclear features of Papillary carcinoma of thyroid, including overcrowding, nuclear membrane and contour irregularities, nuclear grooves and chromatin clearing. However these nuclear features are subtle than in cases of PTC but more prominent than that of benign follicular nodule. For this reason, most NIFTP are diagnosed into one of the indeterminate Bethesda categories: AUS/ FLUS, FN/SFN or SFM [11-18]. Histopathological evaluation based on the recommended criteria by WHO revised in 2022 can be used for an accurate diagnosis, which has an impact on further management and risk assessment of patients.

Compared with European and North American countries, Asian countries generally have reported lower incidence of NIFTPs [19,20,21]. Indeed, results from studies including Asian multi-institutional study performed by Bychkov et al. indicate that magnitude of ROM decrease was slight and not significant [22]. A meta-analysis performed by Vuong et al. [23] compared the Risk Of Malignancy (ROM) in Asian regions to Western counterparts and found that the decrease in ROM in each category is generally lower in Asian countries, with the greatest difference in SM category (5% vs. 18%), followed by AUS/FLUS category (8% vs. 10%).

CONCLUSION

NIFTP can be found as a solitary nodule or as a dominant nodule in Multinodular goitre and either benign or malignant. The Bethesda category plays a significant role in distinguishing between Follicular tumours from Papillary carcinomas and its variant but it is not effective in conclusively distinguishing NIFTP and invasive EFVPTC. A diagnosis of NIFTP should therefore be interpreted in the context of ultrasonographic and cytological features. Years after introduction of NIFTP into clinical practice, the diagnosis of this still poses a challenge for clinicians, radiologists and pathologists. Although the diagnosis is postoperative, accurate preoperative assessment may raise suspicion of NIFTP and indicate a more conservative management.

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