Background: The introduction of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been shown to decrease the risk of malignancy (ROM) in The Bethesda System for Reporting Thyroid Cytopathology. This knowledge may alter the management of patients with thyroid nodules.

Objectives: To correlate cytological diagnosis with histological diagnosis for establishing the ROM of all Bethesda system categories after the introduction of NIFTP.

Methods: This was a retrospective cohort study. All consecutive fine-needle aspiration cytology (FNAC) specimens collected from January 1, 2013, to December 31, 2017, at King Abdullah Medical City, Jeddah, Saudi Arabia, were assessed, and patients who underwent surgical excision of thyroid nodules were further analyzed. The ROM and overall ROM for each Bethesda category were calculated with and without considering NIFTP as a malignant tumor.

Results: Overall, 1066 FNAC specimens were collected, of which 281 had a surgical correlation. Our cases included 18 (6.4%) non-diagnostic (ND), 109 (38.8%) benign, 28 (9.9%) atypia/follicular lesion of undetermined significance (AUS/FLUS), 39 (13.8%) follicular neoplasm or suspicion for follicular neoplasm (FN/SFN), 20 (7.1%) suspicion for malignancy (SM), and 67 (23.8%) malignant (POM) cases. After considering NIFTP diagnosis on resection specimens, the ROM decreased as follows: ND, 38.8% to 27.7% (P = 0.2388); benign, 21.1% to 11.9% (P = 0.0343); AUS/FLUS, 50% to 39.2% (P = 0.2089); FN/SFN, 53.8% to 33.3% (P = 0.0336); SM, 85% to 75% (P = 0.2147); POM, 95.5% to 88% (P = 0.0582).

Conclusion: The introduction of NIFTP would significantly decrease the ROM of thyroid FNAC in both benign and FN/SFN categories of the Bethesda system.

Keywords: Carcinoma, cytology, fine-needle aspiration, NIFTP, thyroid

Address for correspondence: Dr. Hatim Al-Maghrabi, King Abdullah International Medical Research Center, National Guard Health Affairs, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Riyadh, Saudi Arabia.
E-mail: drpathology@gmail.com

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INTRODUCTION

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been proposed as a replacement for non-invasive follicular variant of papillary thyroid carcinoma (N-FVPTC). The follicular variant of papillary thyroid carcinoma (FVPTC) is a tumor that has a follicular histological architecture with some nuclear features that resemble the typical characteristics of papillary thyroid carcinoma (PTC). It is the second most common histological subtype of PTC, representing 9–22.5% of all cases. However, multiple studies have shown that NIFTP is an indolent “pre-malignant” lesion. Nikiforov et al., in their multicenter international study, found that all 109 patients included were alive and had no evidence of disease at the final follow-up that ranged from 10 to 26 years. Furthermore, molecular analysis has shown that NIFTP is more closely related to follicular adenomas and more frequently harbors RAS mutations than classic PTC. In addition, BRAF V600E mutations and PD-L1 expression, which are present in classic PTC, are absent in NIFTP. The recent introduction of NIFTP as an indolent tumor of low-malignant potential would likely affect the risk of malignancy (ROM) of different categories in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). For example, Strickland et al. reported that the ROM for each fine-needle aspiration cytology (FNAC) diagnostic category when considering NIFTP as non-malignant would be as follows: non-diagnostic (ND), 17.0% (a 10% relative decrease); benign, 5.4% (a 59% relative decrease); atypia/follicular lesion of undetermined significance (AUS/FLUS), 21.6% (a 45% relative decrease); follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN), 37.5% (18% relative decrease); suspicious for malignancy (SM), 45.7% (a 48% relative decrease); and malignant cases (POM), 93.6% (a 59% relative decrease).

The introduction of NIFTP could potentially have a great impact on cytological and histological diagnosis and management decisions. These tumors may have been overtreated by extensive surgery. Due to limited data on the recent category of NIFTP, this study aimed to evaluate our institutional FNAC performance by calculating the ROM within the Bethesda system categories under two conditions: Prior to the introduction of the term NIFTP and after the application of diagnostic criteria for NIFTP in our cohort.

METHODS

This was a retrospective cohort study conducted at King Abdulaziz Medical City (KAMC), Jeddah, Saudi Arabia, and was approved by the associated Institutional Review Board. KAMC is a 750-bed capacity tertiary care center. All consecutive FNAC specimens obtained from January 1, 2013, to December 31, 2017, were assessed, and patients who underwent surgical excision of thyroid nodules were analyzed. Therefore, at least 3 years of follow-up data were available for this study.

Retrieved cases were categorized using TBSRTC as follows: ND, benign, AUS/FLUS, FN/SFN, SM, and POM. Each case was reviewed by at least one board-certified pathologist with experience in cytopathology. A correlation was then made between the FNAC specimen results and histopathological diagnosis after surgical follow-up.

Collected data included age, sex, FNAC site, documented FNA diagnostic category in TBSRTC, type of operation (total thyroidectomy, hemithyroidectomy, completion thyroidectomy), location of surgical excision, size of the tumor, and histological specimen diagnosis. Thyroid nodules reported as incidental microcarcinomas were excluded. Furthermore, the specimen was excluded if the reported FNAC site was different from the reported surgical excision. If a patient had multiple FNAC, only that with the highest ROM was included. All cases reported as NIFTP or N-FVPTC were analyzed. A patient is diagnosed with NIFTP on thyroid resection specimens if the following criteria by Nikiforov et al. were met. Firstly, the nodule must be fully or partially encapsulated or unencapsulated but well circumscribed. Secondly, the predominance of the follicular pattern with no well-formed papillae and/or psammoma bodies and <30% of solid, trabecular, or insular growth patterns. Thirdly, the presence of nuclear features of PTC. Lastly, no vascular or capsular invasion, tumor necrosis or high mitotic activity.

To calculate the ROM for each category in TBSRTC, two methods used in previous studies were used. In the first method, ROM is calculated by dividing the number of malignant cases in the histopathology of surgical specimens for each Bethesda category, by the total number of surgical resections in the same category. This method may overestimate the ROM in the benign category because the usual management of such cases does not require surgery. The second method of calculating the ROM involves using the overall ROM (OROM), in which the denominator is replaced by all original FNAC cases for each Bethesda category. The ROM and OROM for each Bethesda category were calculated with and without considering NIFTP as a malignant tumor.
### RESULTS

A total of 1066 FNAC specimens were collected between January 2013 and December 2017. Of the 1066 FNAC cases, 109 (10.2%) were ND, 643 (60.3%) were benign, 101 (9.5%) were AUS/FLUS, 70 (6.5%) were FN/SFN, 36 (3.4%) were SM, and 107 (10%) were POM [Figure 1].

The overall number of patients who underwent surgical follow-up was 281 [Table 1]. In these cases, patients’ ages ranged from 11 to 95 years, with a mean age of 42.9 years, and there was a female predominance (83%). Further, 18 (6.4%) were of the surgical cases were ND, 109 (38.8%) were benign, 28 (10%) were AUS/FLUS, 39 (13.9%) were FN/SFN, 20 (7.1%) were SM, and 67 (23.8%) were POM [Figure 1]. Of all surgical resections, 60.1% were initial total thyroidectomies. The mean size of the resected nodules was 3.5 cm in maximum dimension. Histopathological diagnosis of these cases uncovered 116 (41.3%) malignant cases. Of all malignant cases, PTC was the most common diagnosis, with 96 (82.8%) cases.

Table 2 summarizes the changes in ROM and OROM before and after the introduction of NIFTP. Compared to the before values, the ROM significantly decreased after the introduction of NIFTP for the benign category (21.1% vs. 11.9%, \( P = 0.03 \)) and FN/SFN (53.8% vs. 33.3%; \( P = 0.03 \)) categories, and nonsignificantly for all other TBSRTC categories: ND, 38.8% vs. 27.7% (\( P = 0.23 \)); AUS/FLUS, 50% vs. 39.2% (\( P = 0.20 \)); SM, 85% vs. 75% (\( P = 0.21 \)), and POM, 95.5% vs. 80% (\( P = 0.05 \)). Similarly, the OROM decreased significantly after the introduction of NIFTP for the benign category (3.5% vs. 2%; \( P = 0.04 \)), and nonsignificantly for all other categories: ND, 6.4% vs. 4.5% (\( P = 0.27 \)); AUS/FLUS, 13.8% vs. 10.8% (\( P = 0.26 \)); FN/SFN, 30% vs. 18.5% (\( P = 0.05 \)); SM, 47.2% vs. 41.6% (\( P = 0.31 \)); POM, 59.8% vs. 55.1% (\( P = 0.24 \)).

### Table 1: Demographic and surgical data of thyroid resections (\( N = 281 \))

| Parameter | Value |
|-----------|-------|
| Mean age (years) | 42.9 (range: 11–95) |
| Gender (%) | |
| Female | 233 (83) |
| Male | 48 (17) |
| Tumor location (%) | |
| Right thyroid | 125 (44.5) |
| Left thyroid | 118 (42) |
| Isthmus | 3 (1) |
| Bilateral | 35 (12.5) |
| Type of operation (%) | |
| Initial total thyroidectomy | 169 (60.1) |
| Hemithyroidectomy | 102 (36.3) |
| Other* | 10 (3.6) |
| Mean surgical tumor sizea (cm) | |
| Malignant | 3.3 (1–9) |
| Benign (excluding NIFTP) | 4.3 (1–10) |
| NIFTP | 3.4 (1.2–7) |
| Overall | 3.5 (1–10) |
| Number of surgical cases (%) | |
| Malignant | 116 (41.3) |
| Benign (excluding NIFTP) | 135 (48) |
| NIFTP | 30 (10.6) |

*aOthers include completion thyroidectomy and debulking excision, size in maximum dimension. NIFTP – Noninvasive follicular thyroid neoplasm with papillary-like nuclear features

### Table 2: Change in risk of malignancy after the introduction of noninvasive follicular thyroid neoplasm with papillary-like nuclear features

| Parameter | ND | Benign | AUS/ FLUS | FN/ SFN | SM | POM |
|-----------|----|--------|------------|--------|----|-----|
| Malignant surgical follow-up | 5 | 13 | 11 | 13 | 15 | 59 |
| Benign surgical follow-up | 11 | 86 | 14 | 18 | 3 | 3 |
| NIFTP surgical follow-up | 2 | 10 | 3 | 8 | 2 | 5 |
| ROM including NIFTP in malignant cases (%) | 38.8 | 21.1 | 50 | 53.8 | 85 | 95.5 |
| ROM after excluding NIFTP from malignant cases (%) | 27.7 | 11.9 | 39.2 | 33.3 | 75 | 80 |
| P | 0.23 | 0.20 | 0.20 | 0.21 | 0.21 | 0.05 |
| OROM including NIFTP in malignant cases (%) | 5.4 | 3.5 | 13.8 | 17 | 47.2 | 59.8 |
| OROM after excluding NIFTP from malignant cases (%) | 4.5 | 2 | 10.8 | 18.5 | 41.6 | 55.1 |
| P | 0.27 | 0.26 | 0.05 | 0.31 | 0.24 |

*aStatistically significant P-value. AUS/FLUS – Atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN – Follicular neoplasm/suspicious for follicular neoplasm; ND – Nondiagnostic, NIFTP – Noninvasive follicular thyroid neoplasm with papillary-like nuclear features, ROM – Risk of malignancy; OROM – Overall ROM, SM – Suspicious for malignancy; POM – malignant

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**Figure 1:** Total number of fine-needle aspiration cytology and surgical cases for each Bethesda category

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Statistical analysis

Microsoft® Excel software (Microsoft Corporation, Redmond, USA) was used as the datasheet for extraction and for all statistical analyses. \( P \) value for each category in the TBSRTC was calculated using the one-tailed z-test, and a \( P \) value of <0.05 was considered statistically significant.
By reviewing the seven NIFTP cases in our institution that were SM or POM in FNAC, in view of previously reported cytological features of NIFTP, no case had a predominance of tumor sheets or papillae that would be associated with classic PTC. By contrast, two cases demonstrated the presence of intranuclear cytoplasmic pseudoinclusions [Figures 2 and 3]. Two other cases had a predominance of microfollicles, which has been reported to be associated with NIFTP. The presence of transgressing vessels was also noted on the cytology of some cases [Figure 3].

**DISCUSSION**

The risk stratification of preoperative cytological evaluation of thyroid nodules has been impacted since the definition of NIFTP, as its incidence has also increased over the past decade. With a <1% risk of recurrence, NIFTP has been extensively re-evaluated to prevent overtreatment and refine management algorithms for thyroid cytopathology. Multiple studies have demonstrated that NIFTP has a significant change in the ROM of indeterminate categories, that is, AUS/FLUS, FN/SFN, and SM. Strickland et al. evaluated 655 FNA specimens in their institution and found that the greatest impact of NIFTP was in the SM category, with a relative reduction of 48% in the ROM. Similarly, Faquin et al. evaluated thyroid cytology data across five large institutions and observed a significant decrease in all three indeterminate categories.

In our study, ROM decreased in all TBSRTC categories, with a significant decrease in the benign and FN/SFN categories by a relative reduction of 43.6% and 38.1%, respectively. The former category also had the only significant decrease in OROM, with a relative reduction of 42.8%. When comparing the ROM in all categories before and after NIFTP of our study with the 2017 TBSRTC values, we found that the ROM was higher in all categories except benign, where it was similar, and POM, where it was lower. The 2017 TBSRTC reported a 1–5% absolute decrease in the ROM of the POM category after the introduction of NIFTP, while we found a 15.5% absolute reduction in our cases in this category. These differences could possibly be due to the low number of cases in this study (281).

Most cases of ND and AUS/FLUS do not proceed to surgery unless either suspicious clinical or sonographic features of malignancy were present or if the patient had a persistent ND or AUS/FLUS cytology. This could be attributed to the higher ROM observed in such cases. We used two methods of calculating the ROM for all categories due to the drastically overestimated ROM in the benign category if it was calculated by surgical follow-up alone. This overestimation is because the usual management of such cases is limited to regular follow-ups with no surgical intervention unless there is a persistent nodule or features of malignancy. Thus, some authors relied on the OROM by including all original FNAC cases for the benign category to avoid selection bias.

In our institution, there were 30 cases of NIFTP, representing 10.7% of all resected cases. This is within the reported range in various large institutional studies, with
The diagnosis of NIFTP on cytology is difficult due to the inherent limitations of FNAC in evaluating capsular or vascular invasion, both of which are important features in the definition of NIFTP. The recurrence rate of NIFTP has been shown to be 0–1%. Therefore, there have been suggestions to exclude it from the ROM calculation. A proposed modification for TBSRTC was to change the term “risk of malignancy” to “risk of neoplasm” to include NIFTP cases in the calculation. However, this may inadvertently lead to inclusion of other neoplasms, such as follicular adenoma, in the calculation, although they are benign. This recommendation would most likely reduce the specificity and, therefore, the clinical value of using TBSRTC.

Cytological evaluation could be valuable in preoperatively distinguishing NIFTP from PTC. In another study conducted by Strickland et al., NIFTP was shown to have frequent microfollicular arrangement, while no tumor sheets were present, similar to classic PTC. In addition, papillae and pseudoinclusions were absent in NIFTP. Among all cytological nuclear features of PTC, pseudoinclusions are the most specific but not sensitive. PTC also imposes the formation of the papillae. These characteristics that could aid in identifying NIFTP in cytology correspond to the findings in our cases, except for the presence of microfollicular arrangements and the presence of pseudoinclusions. The presence of transgressing vessels (capillaries in clusters of epithelial cells) was noted in two cases.

Molecular studies of NIFTP have shown a molecular profile analogous to that of follicular adenoma. NIFTP has frequent RAS mutations with PAX8/PPARγ rearrangements and CREB3L2-PPARγ gene fusion rather than BRAF V600E mutations, as seen in PTC. However, invasive encapsulated FVPTC has a molecular profile similar to that of NIFTP.

**Limitations**

The limitation of our study is that it is a single institutional study and future multi-institutional studies with larger number of cases would be needed. Another shortcoming of our study is the lack of molecular profiling studies of thyroid nodules in our patient population. Further studies incorporating molecular studies that analyze the risk of malignancy would further refine the TBSRTC categories.

**CONCLUSION**

The introduction of NIFTP has an impact on the ROM in TBSRTC categories, namely, benign and FN/SFN. TBSRTC is a crucial tool in guiding the management of patients with thyroid nodules, such studies will have a remarkable role in optimizing the preoperative treatment algorithms for patients with thyroid nodules.

**Ethical considerations**

The Ethics Committee of the King Abdullah International Medical Research Center, Jeddah, Saudi Arabia, approved this study (ref. no. JED-19-427780-93727), on June 9, 2019. Requirement for informed consent was waived owing to the retrospective study design. The study adhered to the Declaration of Helsinki, 2013.

**Data availability statement**

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

**Peer review**

This article was peer-reviewed by three independent and anonymous reviewers.

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**Conflicts of interest**

There are no conflicts of interest.

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