Original Article

Non-invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) Lowers the Risk of Malignancy in the Bethesda System for Reporting Thyroid Cytopathology Diagnostic Categories

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Abstract

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

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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).[1-3] 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.[4] However, multiple studies have shown that NIFTP is an indolent "pre-malignant" lesion.[5-7] 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.[8] Furthermore, molecular analysis has shown that NIFTP is more closely related to follicular adenomas and more frequently harbors RAS mutations than classic PTC.[7,9] In addition, BRAF V600E mutations and PD-L1 expression, which are present in classic PTC, are absent in NIFTP.[6,7,10]

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 5% relative decrease).[3]

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.[11]

To calculate the ROM for each category in TBSRTC, two methods used in previous studies were used.[2,12] 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.

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.

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 (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% ($P = 0.24$).

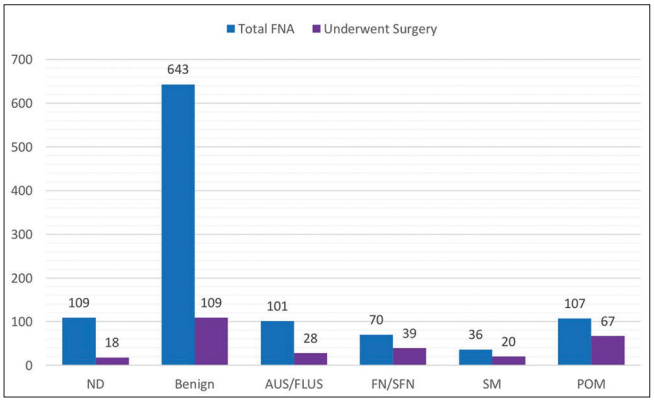

Figure 1: Total number of fine-needle aspiration cytology and surgical cases for each Bethesda category

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[a]	10 (3.6)
Mean surgical tumor size[b] (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)

[a]Others include completion thyroidectomy and debulking excision, [b]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	0.03[a]	0.20	0.03[a]	0.21	0.05
OROM including NIFTP in malignant cases (%)	6.4	3.5	13.8	30	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	0.04[a]	0.26	0.05	0.31	0.24

[a]Statistically 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

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.[13,14] 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.[13,14] 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,[1,3,12] as its incidence has also increased over the past decade.[5,15-23] With a <1% risk of recurrence, NIFTP has been extensively re-evaluated to prevent overtreatment and refine management algorithms for thyroid cytopathology.[3,5,8,12,15,16] Multiple studies have demonstrated that NIFTP has a significant change in the ROM of indeterminate categories, that is, AUS/FLUS, FN/SFN, and SM.[3,12,24-27] 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.[3] Similarly, Faquin *et al.* evaluated thyroid cytology data across five large institutions and observed a significant decrease in all three indeterminate categories.[12]

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.[28] 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.[12,24,25]

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

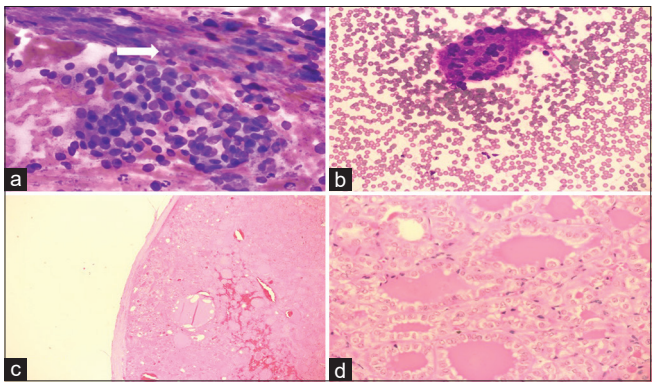

Figure 2: Case #1: (a) Fine-needle aspiration cytology shows pseudoinclusions, elongation, enlargement, overlapping, and nuclear groves (Diff-Quik stain, ×400). (b) Presence of a multinucleated giant cell (arrow) (Diff-Quik stain, ×200). (c) The histopathology on low magnification of the case after resection shows a tumor with a follicular growth pattern surrounded by an intact capsule (H and E stain, ×100). (d) Higher magnification of the histopathology showing nuclear features of papillary thyroid carcinoma including pseudoinclusions, nuclear enlargement and clearing, and nuclear groves. This case was diagnosed as NIFTP (H and E stain, ×400)

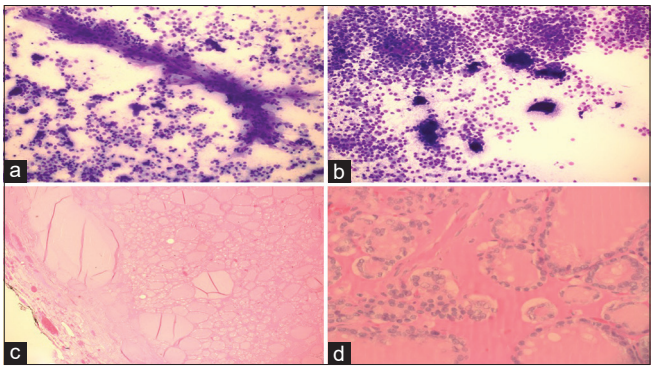

Figure 3: Case #2: (a) Fine-needle aspiration cytology shows the presence of transgressing vessels in a background of a microfollicular cellularity (Diff-Quik stain, ×200). (b) Nuclear features of papillary thyroid carcinoma are also identified, in addition to areas of calcification (Diff-Quik stain, ×200). (c) On low magnification, histopathology of the tumor capsule was intact and surrounded a follicular lesion (H and E stain, ×100). (d) On higher magnification, the follicular cells appear clear and there are many grooves and pseudoinclusions (H and E stain, ×400)

NIFTP ranging from 5% to 13% of resected cases.[3,12,24,25] 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.[2,26,29] The recurrence rate of NIFTP has been shown to be 0–1%.[2,8,26,29] Therefore, there have been suggestions to exclude it from the ROM calculation.[1,8] A proposed modification for TBSRTC was to change the term "risk of malignancy" to "risk of neoplasm" to include NIFTP cases in the calculation.[30] 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.[12,13,31] 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.[13] In addition, papillae and pseudoinclusions were absent in NIFTP. Among all cytological nuclear features of PTC, pseudoinclusions are the most specific but not sensitive.[32] PTC also imposes the formation of the papillae.[32] 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 [Figure 3].

Molecular studies of NIFTP have shown a molecular profile analogous to that of follicular adenoma.[24,33-37] NIFTP has frequent RAS mutations with PAX8/PPARγ rearrangements and CREB3L2-PPARγ gene fusion rather than BRAF V600E mutations, as seen in PTC.[24,33-37] However, invasive encapsulated FVPTC has a molecular profile similar to that of NIFTP.[6,38-40]

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. As 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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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nikiforov YE. Ramifications of new terminology for encapsulated follicular variant of papillary thyroid carcinoma-reply. JAMA Oncol 2016;2:1098-9.
2. Piana S, Frasoldati A, Di Felice E, Gardini G, Tallini G, Rosai J. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. Am J Surg Pathol 2010;34:868-72.
3. Strickland KC, Howitt BE, Marqusee E, Alexander EK, Cibas ES, Krane JF, *et al*. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. Thyroid 2015;25:987-92.
4. Tielens ET, Sherman SI, Hruban RH, Ladenson PW. Follicular variant of papillary thyroid carcinoma. A clinicopathologic study. Cancer 1994;73:424-31.
5. Rosario PW, Mourão GF. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): A review for clinicians. Endocr Relat Cancer 2019;26:R259-66.
6. Howitt BE, Jia Y, Sholl LM, Barletta JA. Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma. Thyroid 2013;23:1256-62.
7. Rivera M, Ricarte-Filho J, Knauf J, Shaha A, Tuttle M, Fagin JA, *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 2010;23:1191-200.
8. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, *et al*. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: A paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016;2:1023-9.

9. Sahli ZT, Smith PW, Umbricht CB, Zeiger MA. Preoperative molecular markers in thyroid nodules. Front Endocrinol (Lausanne) 2018;9:179.
10. Fu G, Polyakova O, MacMillan C, Ralhan R, Walfish PG. Programmed death-ligand 1 expression distinguishes invasive encapsulated follicular variant of papillary thyroid carcinoma from noninvasive follicular thyroid neoplasm with papillary-like nuclear features. EBioMedicine 2017;18:50-5.
11. Nikiforov YE, Baloch ZW, Hodak SP, Giordano TJ, Lloyd RV, Seethala RR, *et al*. Change in diagnostic criteria for noninvasive follicular thyroid neoplasm with papillarylike nuclear features. JAMA Oncol 2018;4:1125-6.
12. Faquin WC, Wong LQ, Afrogheh AH, Ali SZ, Bishop JA, Bongiovanni M, *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 2016;124:181-7.
13. Strickland KC, Vivero M, Jo VY, Lowe AC, Hollowell M, Qian X, *et al*. Preoperative cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: A prospective analysis. Thyroid 2016;26:1466-71.
14. Howitt BE, Chang S, Eszlinger M, Paschke R, Drage MG, Krane JF, *et al*. Fine-needle aspiration diagnoses of noninvasive follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2015;144:850-7.
15. Liu J, Singh B, Tallini G, Carlson DL, Katabi N, Shaha A, *et al*. Follicular variant of papillary thyroid carcinoma: A clinicopathologic study of a problematic entity. Cancer 2006;107:1255-64.
16. Vollmer RT. Revisiting overdiagnosis and fatality in thyroid cancer. Am J Clin Pathol 2014;141:128-32.
17. Davies L, Welch HG. Thyroid cancer survival in the United States: Observational data from 1973 to 2005. Arch Otolaryngol Head Neck Surg 2010;136:440-4.
18. Jung CK, Little MP, Lubin JH, Brenner AV, Wells SA Jr., Sigurdson AJ, *et al*. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab 2014;99:E276-85.
19. Baloch ZW, LiVolsi VA. Encapsulated follicular variant of papillary thyroid carcinoma with bone metastases. Mod Pathol 2000;13:861-5.
20. Baloch ZW, Shafique K, Flanagan M, Livolsi VA. Encapsulated classic and follicular variants of papillary thyroid carcinoma: Comparative clinicopathologic study. Endocr Pract 2010;16:952-9.
21. Rivera M, Tuttle RM, Patel S, Shaha A, Shah JP, Ghossein RA. Encapsulated papillary thyroid carcinoma: A clinico-pathologic study of 106 cases with emphasis on its morphologic subtypes (histologic growth pattern). Thyroid 2009;19:119-27.
22. Gupta S, Ajise O, Dultz L, Wang B, Nonaka D, Ogilvie J, *et al*. Follicular variant of papillary thyroid cancer: Encapsulated, nonencapsulated, and diffuse: Distinct biologic and clinical entities. Arch Otolaryngol Head Neck Surg 2012;138:227-33.
23. Otto KJ, Lam JS, MacMillan C, Freeman JL. Diminishing diagnosis of follicular thyroid carcinoma. Head Neck 2010;32:1629-34.
24. Li W, Sciallis A, Lew M, Pang J, Jing X. 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 2018;46:148-53.
25. Lau RP, Paulsen JD, Brandler TC, Liu CZ, Simsir A, Zhou F. 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 2017;149:50-4.
26. Vaccarella S, Dal Maso L, Laversanne M, Bray F, Plummer M, Franceschi S. The impact of diagnostic changes on the rise in thyroid cancer incidence: A population-based study in selected high-resource countries. Thyroid 2015;25:1127-36.
27. Pitoia F, Jerkovich F, Urciuoli C, Schmidt A, Abelleira E, Bueno F, *et al*. Implementing the modified 2009 American Thyroid Association risk stratification system in thyroid cancer patients with low and intermediate risk of recurrence. Thyroid 2015;25:1235-42.
28. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. J Am Soc Cytopathol 2017;6:217-22.
29. Hunt JL, Dacic S, Barnes EL, Bures JC. Encapsulated follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2002;118:602-3.
30. Pusztaszeri M, Rossi ED, Auger M, Baloch Z, Bishop J, Bongiovanni M, *et al*. The Bethesda system for reporting thyroid cytopathology: Proposed modifications and updates for the second edition from an international panel. Acta Cytol 2016;60:399-405.
31. Maletta F, Massa F, Torregrossa L, Duregon E, Casadei GP, Basolo F, *et al*. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. Hum Pathol 2016;54:134-42.
32. Canberk Ş, Fırat P, Schmitt F. Pitfalls in the cytological assessment of thyroid nodules. Turk Patoloji Derg 2015;31 Suppl 1:18-33.
33. Ohori NP, Singhal R, Nikiforova MN, Yip L, Schoedel KE, Coyne C, *et al*. BRAF mutation detection in indeterminate thyroid cytology specimens: Underlying cytologic, molecular, and pathologic characteristics of papillary thyroid carcinoma. Cancer Cytopathol 2013;121:197-205.
34. Xu B, Ghossein RA. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): An update. Head Neck Pathol 2020;14:303-10.
35. Nikiforov YE, Yip L, Nikiforova MN. New strategies in diagnosing cancer in thyroid nodules: Impact of molecular markers. Clin Cancer Res 2013;19:2283-8.
36. Nikiforov YE. Molecular diagnostics of thyroid tumors. Arch Pathol Lab Med 2011;135:569-77.
37. Giordano TJ, Beaudenon-Huibregtse S, Shinde R, Langfield L, Vinco M, Laosinchai-Wolf W, *et al*. Molecular testing for oncogenic gene mutations in thyroid lesions: A case-control validation study in 413 postsurgical specimens. Hum Pathol 2014;45:1339-47.
38. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014;159:676-90.
39. Wreesmann VB, Ghossein RA, Hezel M, Banerjee D, Shaha AR, Tuttle RM, *et al*. Follicular variant of papillary thyroid carcinoma: Genome-wide appraisal of a controversial entity. Genes Chromosomes Cancer 2004;40:355-64.
40. Zhao L, Dias-Santagata D, Sadow PM, Faquin WC. 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 2017;125:323-31.