ORIGINAL RESEARCH PAPER

Volume-8 | Issue-5 | May-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL MANAGEMENTS RECOMMENDED BY THE REVISED BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY REDUCED INDICATIONS FOR THYROID SURGERY AND HONED THE DIAGNOSTIC ACCURACY OF MALIGNANT NODULES

Medicine

Ricardo Torres Da Silveira Ugino	Medical School, Federal University of Parana, Curitiba, PR, Brazil
Victor Hugo Granella	Medical School, Federal University of Parana, Curitiba, PR, Brazil
Thayse Graciella Batisti Lozovoy	MD, SEMPR, Endocrine Division, Department of Internal Medicine, University Hospital, Federal University of Parana, Curitiba, PR, Brazil
Teresa Cristina Santos Cavalcanti	MD, Department of Pathology, University Hospital, Federal University of Parana, Curitiba, PR, Brazil
Hans Graf	MD, PhD, SEMPR, Endocrine Division, Department of Internal Medicine, University Hospital, Federal University of Parana, Curitiba, PR, Brazil
Cleo Otaviano Mesa Júnior	MD, PhD, SEMPR, Endocrine Division, Department of Internal Medicine, University Hospital, Federal University of Parana, Curitiba, PR, Brazil
Gisah Amaral De Carvalho	MD, PhD, SEMPR, Endocrine Division, Department of Internal Medicine, University Hospital, Federal University of Parana, Curitiba, PR, Brazil

ABSTRACT

This study aimed to evaluate the influence of The 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Data were collected from 2002-2007 with an indeterminate cytological report, and from 2010-2017 with a cytological report including categories III, IV and V of TBSRTC. Subsequently, both groups were compared regarding the established management, surgical incidence, and rate of malignancy. Among the 1458 patients who underwent fine-needle aspiration from 2002-2007, 154 (10.6%) had an indeterminate cytological report, while from 2010-2017, 138 out of 1147 (12%) had a cytological result compatible with categories III, IV and V. After further exclusion, of a total 135 cases pertaining to the pre-Bethesda group, 126 (93.3%) versus 94 out of 135 cases (69.6%) of the Bethesda group were referred for surgery ($p<0.001$). Restricted to the patients who underwent surgery, the malignancy rate before and after TBSRTC was 28.4% versus 55.3%, respectively ($p=0.001$). The malignancy rate within categories III, IV and V was 15/37, 10/20 and 17/19, respectively. The revised TBSRTC reduced the rate of unnecessary surgeries and honed the diagnostic accuracy for the detection of malignant nodules.

KEYWORDS

fine-needle aspiration; Bethesda system; thyroid nodules; thyroidectomy;

INTRODUCTION

The introduction of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), following the "National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference" held in Bethesda, MD, in 2007, enabled the establishment of a uniform six-tiered reporting system for thyroid fine-needle aspiration (FNA). For each of the six diagnostic categories, TBSRTC defined an implied risk of malignancy and recommended clinical management based on the literature. TBSRTC not only described uniform and non-controversial categories, such as benign and malignant thyroid lesions, in FNA specimens but also suspicious ones often diagnosed as "indeterminate for malignancy (called the gray zone)", which represented a major challenge for physicians in diagnosis and management. The latter was subdivided into the following categories: Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS; III), Suspicious for a Follicular Neoplasia or Follicular Neoplasm (SFN/FN; IV), and Suspicious for Malignancy (SM; V)(1). In 2017, TBSRTC was revised and updated, considering "Noninvasive Follicular Thyroid Neoplasm with Papillary-like features" (NIFTP) on the risks of malignancy and molecular testing as an option for the management of AUS/FLUS and SFN/FN.

However, the recommendations for Bethesda category III and IV are debatable and include repeating FNA after 3-6 months, molecular testing or lobectomy. The difficulty in establishing the risk of malignancy underlies in the fact that a minority of patients undergo a thyroidectomy, even though the current literature estimates a malignancy rate of 10-40% in such cases(2).

This study aimed to evaluate the influence of the revised TBSRTC on patients included in categories III, IV and V for the pre-surgical diagnosis, analyzing the established management, the surgical incidence and the rate of benign nodules mistakenly resected.

METHODS

The study was conducted from January 2016 to March 2019 in the Endocrine Division (SEMPR) of the Department of Internal Medicine and in the Department of Pathology of the University Hospital of the Federal University of Paraná (HC-UFPR), a tertiary university-affiliated medical center part of the Brazilian Unified National Health System. This report describes a retrospective and prospective, longitudinal and observational analysis. The study was approved by the Human Research Ethics Committee of the aforementioned institution. The inclusion criteria, data collection, surgery indication and malignancy criteria, and statistical analysis are described as follows. Molecular testing was not considered in this study because our institution does not perform this test for clinical purpose.

Inclusion criteria

All cytopathological reports of FNA performed between January 2002 and December 2007, classified as "indeterminate", "suspected for malignancy", or another definition of similar significance, and those from January 2010 to May 2017, classified as Bethesda III, IV and V, were included in the study. When the patient was referred for more than one FNA procedure or had more than one cytological classification at different thyroid sites, the diagnosis with a higher malignant potential was used for data computation. The cytopathological reports of FNA with a diagnosis of benign, malignant or unsatisfactory sample, including categories I, II and VI of the Bethesda System, were excluded because there were no significant changes before and after implementation of TBSRTC within those categories. For the purpose of the current study, we reconstructed the diagnostic categories of thyroid FNA before implementation of TBSRTC in our institution to closely match the TBSRTC diagnostic categories.

Data collection

The medical records of the selected patients were analyzed in the Medical File Service (SAME) of HC-UFPR and the following information were collected: date of birth, sex, thyroid stimulating hormone (TSH) and free thyroxine levels (T4) in the preoperative period, maximum diameter of the nodule on ultrasonography, surgical indication and histopathological report. After collection, both groups were compared regarding the established management (surgery indication or clinical and ultrasonography follow-up), the surgical incidence and the rate of unnecessary surgeries (resection of benign nodules).

Surgery Indication criteria

Before implementation of the Bethesda System, our institution indicated surgery for almost all thyroid nodules classified as 'indeterminate' in the cytopathological report, which was a recommendation of the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologist (AACE) ——(35). Despite these recommendations, other factors such as clinical features, US features and patient preferences were also taken into consideration in the treatment decision. In the post-Bethesda group, thyroid nodules pertaining to categories SFN/FN and SM received surgery indication. With respect to category AUS/FLUS, our institution requires the repetition of FNA in 3 to 6 months for initial cases. Patients were referred for surgery only if their FNA specimens were reclassified as AUS/FLUS or a category with higher malignancy (SFN/FN; SM; M) in a second cytopathological report. If patients were found to be non-diagnostic after repeated FNA, it is either recommended that FNA should be repeated or a surgical excision be performed. Patients without surgery indication received clinical and ultrasonography follow-up.

Malignancy criteria

Incidental papillary microcarcinomas (those measuring less than 10 mm detected incidentally at surgery, not as the FNA-targeted mass) and other classic benign thyroid lesions noted on final histopathology were classified as benign lesions. In addition, NIFTP was also considered to be a benign lesion, because a recent revision on thyroid tumor nomenclature suggested that this subcategory carries a very low risk of adverse outcome (6). For a diagnosis of NIFTP, all surgical pathology specimens diagnosed as papillary thyroid carcinoma (PTC) were retrospectively reviewed and reclassified by one experienced pathologist according to the proposed criteria for reclassification as detailed in the initial nomenclature revision article (6). PTC, follicular carcinoma, medullary carcinoma, Hürthle cell carcinoma and other classic malignant thyroid lesions were classified as malignant lesions.

Statistical analysis

The results were described by means, medians, minimum values, maximum values and standard deviations (quantitative variables) or by frequencies and percentages (categorical variables). For the comparison of the pre-Bethesda group (classification of nodules before the implementation of the Bethesda system) and Bethesda group (classification by the Bethesda system), in relation to quantitative variables, Student's t-test or the non-parametric test of Mann-Whitney were used for independent samples. The normality condition of the quantitative variables was evaluated by the Kolmogorov-Smirnov test. In regard to categorical variables, the comparison was made using Fisher's exact test. Values of $p<0.05$ indicated statistical significance. The data were analyzed using IBM SPSS Statistics v.20.0. Armonk, NY: IBM Corp.

RESULTS

A total of 3315 thyroid FNAs obtained from 2605 patients were evaluated at our institution during the study period. A total of 1458 patients underwent FNA from 2002 to 2007, of which 154 (10.6%) had an indeterminate cytological result, while in the period from 2010 to 2017, 1147 patients were referred for FNA, of which 138 (12%) had a cytological result corresponding to Bethesda III, IV and V. Of the 154 medical records within the pre-Bethesda group, five were unavailable in the HC-UFPR Medical Archive Service and fourteen were incomplete; therefore, data regarding surgical indications could not be obtained and they were excluded from the study. In the Bethesda group, of 138 cases, three patients were excluded from the study due to two misdiagnoses of thyroid disease (parathyroid and lymph node samples), and one medical record was unavailable for data extraction of the surgical indication.

Demographic and clinical variables

The analysis presented below is based on data from 135 cases of the pre-Bethesda Group and 135 cases of the Bethesda group. The epidemiological profile of the studied population was similar in regards to age, sex and nodule size, presenting a worthy correspondence against these variables. The TSH and free T4 levels in the pre-surgical period were also compared (Table 1). There was no difference in TSH levels between the pre-Bethesda and Bethesda groups with a mean of 2.52 mU/L and 2.33 mU/L (p=0.899), respectively. Conversely, the pre-surgical free T4 levels were higher in the pre-Bethesda group (1.54 mg/dl) compared with the Bethesda group (1.12 mg/dl, p=0.002).

Table 1 Demographic profile, TSH and free T4 levels of the study population

	pre-Bethesda group (n=135)	Bethesda group (n=135)	p-value
Age (years)			0.123
Mean age	51.1 ± 16.3 (range 7.9–87.6)	54.4 ± 18.1 (range 9–83)	
Median	52.6	59	
Sex			0.238
Women	124 (91.9%)	117 (86.7%)	
Men	11 (8.1%)	18 (13.3%)	
TSHa			
Mean	2.52 ± 2.95 (range 0–17.20)	2.33 ± 2.18 (range 0.01–11.38)	0.899
Median	1.59	1.89	
FT4b			
Mean	1.54 ± 1.35 (range 0.01–10.60)	1.12 ± 0.23 (range 0.54–1.71)	0.002
Median	1.24	1.12	
Nodule size(cm)			0.326
Mean	2.81 ± 1.78 (range 0.40–7.50)	2.86 ± 1.61 (range 0.60–10)	
Median	2.44	2.40	

a TSH, Thyroid-Stimulating Hormone
b FT4, Free Thyroxine Hormone

Comparison of groups in relation to surgical indication

The number of surgical indications was significantly higher in the pre-Bethesda period ($p<0.001$) (Table 2). Of the 135 cases evaluated for this variable, 126 (93.3%) had a surgical indication in the pre-Bethesda group. The remaining 9 cases did not receive a surgery indication because two had poorly controlled severe systemic disease and 7 presented benign US features, thereby clinical and ultrasonographic follow-up were opted in such cases. In the Bethesda group, 94 (69.6%) out of 135 cases received a surgery indication. Of the remaining 41 cases who did not receive surgery indication, 23 were reclassified as Bethesda II in a second FNA after being first classified as AUS/FLUS, and 18 AUS/FLUS were waiting for a second FNA in order to define the final management.

It was observed that of the 126 patients in the pre-Bethesda group who had a surgical indication, 95 (75.4%) underwent surgery. The remaining patients did not undergo surgery because 27 lost to follow-up and 4 refused to undergo surgery. In the Bethesda group, 76 patients out of 94 (80.8%) underwent surgery. Of the remaining 18 cases, 8 were in the surgery waiting list, 3 had a poorly controlled severe systemic disease, 3 lost to follow-up and 4 refused to undergo surgery.

Table 2 Comparison of the groups regarding surgical indication and rate of malignancy

Surgical indication	pre-Bethesda group	Bethesda group	p-value
No	09 (6.7%)	41 (30.4%)	<0.001
Yes	126 (93.3%)	94 (69.6%)	
Total	135	135	
Histological classification			
Malignant	27 (28.4%)	42 (55.3%)	p=0.001
Benign	68 (71.6%)	34 (44.7%)	
Total	95	76	

Comparison of groups in relation to malignancy

Restricted to the patients who underwent surgery, there was a significant difference between the groups in relation to the rate of

malignancy, with percentages of 28.4% versus 55.3% being observed (p=0.001) in the pre-Bethesda and Bethesda groups, respectively (Table 2). Of all PTC cases that were retrospectively reviewed to detect NIFTP, none of them fulfilled its criteria. The pathological results of all surgically resected nodules are represented in Table 3.

Table 3 The pathological results of all surgically resected nodules

Histological classification	pre-Bethesda group	Bethesda Group
Malignant diseases	27 (28.4%)	42 (55.3%)
Papillary carcinoma (classic, follicular and oncocytic variants)	19	32
Follicular carcinoma	7	6
Medullary carcinoma	1	2
Clear cell carcinoma	-	2
Benign diseases	68 (71.6%)	34 (44.7%)
Adenomatous hyperplasia	-	4
Follicular adenoma	18	11
Hashimoto's thyroiditis	11	3
Colloid nodular goiter	9	6
Multinodular goiter	17	6
Papillary microcarcinoma	3	-
Riedel thyroiditis	1	-
Follicular adenoma (oncocytic variant)	9	4

Cytological classification in the Bethesda group

After implementation of the Bethesda System, categories III, IV and V included 84 (62.2%), 29 (21.5%) and 22 (16.3%) of the 135 patients. The prevalence of each category amongst all 1549 FNAs in the post-Bethesda period was 6.32%, 2% and 1.42%, respectively. Considering the cases that underwent surgery and had a final histopathological report, the malignancy rate of each category was 15/37 (40.5%), 10/20 (50%) and 17/19 (89.5%), respectively (Table 4).

Table4 Cytological classification and its histological correspondence post- surgery in the Bethesda group

	Cytological classification		
Histological classification	III	IV	V
Malignant	15 (40.5%)	10 (50%)	17 (89.5%)
Benign	22 (59.5%)	10 (50%)	2 (10.5%)
Total	37	20	19

DISCUSSION

Before implementation of TBSRTC, we followed the recommendations of the ATA/AACE, which recommended that virtually all thyroid FNA specimens compatible with the nomenclature "indeterminate for malignancy" were formally indicated for surgery, provided the patient had a satisfactory clinical condition to undergo the procedure. However, in many cases, the histological results post-operatively were benign. After implementing TBSRTC, we reduced the percentage of patients with indeterminate samples indicated for surgery (combining the three indeterminate subcategories of the Bethesda System) from 93.3% to 69.6%. An explanation for the difference is the repetition of FNA in subcategory III of TBSRTC, which recategorized 23 patients as benign, altering the clinical management of their thyroid nodules. Analyzing a larger cohort of indeterminate thyroid nodules, two studies conducted at the same institution found similar results, showing a lower rate of thyroidectomies performed in the post-Bethesda era with a higher frequency of cancer found after resection (7,8). Conversely, other studies have reported conflicting results (9,10), suggesting that a reevaluation and perhaps an improvement in the Bethesda system is of paramount relevance, particularly regarding AUS/FLUS specimens, a controversial subcategory likely to be fragmented due to its different cytological interpretations.

In conjunction with the reduction in surgery indications in the post-Bethesda era, the malignancy rate in this same period increased significantly as we had expected (28.4% before versus 55.3% after implementation of TBSRTC). Because the Bethesda system sub-divided the indeterminate category into three new ones, thereby facilitating management decisions in regard to classifying this broad spectrum of lesions, we had hypothesized that the adoption of this system in our institute would be more efficient in detecting malignant thyroid nodules. In summary, the combination of reduction in surgery indication associated with the increase in the malignancy rate after implementation of TBSRTC represented a quantum leap for the clinical practice at institution in the last 10 years.

A study conducted by Rabaglia et al. (11) evaluated whether comparisons between indeterminate samples before implementation of TBSRTC and exclusively category Bethesda III nodules would interfere with the malignancy risk estimates at a large medical academic center. These researchers determined that there was a decreased malignancy rate, which was explained by either an overcall of Bethesda III from previous benign samples and/or an upgrade of cytological specimens with more concerning characteristics into the suspicious by FN category. Likewise, Hirsch et al. (7) reported an improvement in the malignancy detection, concluding that TBSRTC honed the diagnostic accuracy in that studied population. Nevertheless, the results published by Chen et al. (10) , regarding the changes in the overall rate of malignancy, are opposed to ours. A two-fold explanation for that result might be a pool of indeterminate specimens previously presenting with a high rate of malignancy and/or a limited sample size that could have prevented the achievement of a significant result.

We found 10.6% and 12% indeterminate cases in the pre- and post-Bethesda groups, respectively. These similar results, in addition to the difference of the overall malignancy rate before and after implementation of TBSRTC, suggest that the former indeterminate samples were subclassified into the three categories of TBSRTC (III, IV and V) with misclassification of benign, inadequate or malignant samples. Additionally, the subcategory III should be interpreted carefully, and it is recommended that it should not exceed 7% of the total because an inexperienced pathologist could overdiagnose Bethesda III in order to guarantee additional investigation for doubtful cases. In our series, subcategory Bethesda III was found in 6.32% of all FNAs, which is in accordance with this recommendation. Recent studies, however, have reported a highly variable prevalence of Bethesda III, e.g., Dincer et al. (12) (2.7%), Garg et al. (13) (6.5%) and Ho et al. (14) (8%), although most of these reports maintained the < 7% recommendation.

In respect to the rate of malignancy within subcategories III, IV and V, the present study has found a prevalence of 40.5%, 50%, and 89.5%, respectively. These results are higher than the findings published by a meta-analysis conducted by Bongiovanni et al. (15). However, several studies have also observed frequencies higher than the NCI-expected rate for the indeterminate categories and a number of reports have discussed whether these considerations should be strictly pursued (13,14,16). The additional use of clinical and radiologic evaluation in the decision-making process are regarded as factors that may create a "selection bias" by referring to surgery cases with higher risk of malignancy, thereby overestimating the malignancy rate in these categories (17–20).

Considering subcategory III in particular, although its rate of malignancy was supposed to have been underestimated by TBSRTC, recent studies have suggested that specific cases showing the presence of focal nuclear atypia carry a higher risk of cancer than other cases supposedly assigned to AUS/FLUS and fit more appropriately into the category of SM. Conversely, in those cases in which atypical nuclear characteristics are not observed, the risk of malignancy is in accordance with that recommended for the TBSRTC AUS/FLUS categories (21). Owing to their high risk of malignancy, these cases might require further data validation as to whether proceed immediate resection or go straight to repeat FNA for the decision to choose the best management approach. Recent studies have reported predictors of malignancy, including clinical, radiologic and cytopathological features in order to better stratify the cases deserving a surgery indication. Nonetheless, the results demonstrated to be conflicting, indicating that further research to establish a more precisely criteria is required (20,22).

Another aspect of this research that should be highlighted is that cases pertaining to NIFTP were considered in this study, although none of the PTC specimens retrospectively reanalyzed matched its criteria. The NIFTP group is believed to follow an indolent course; thus, it has been proposed that this particular subcategory should be considered to be a benign tumor, rather than a carcinoma. As a result, Faquin et al. and Strickland et al. had predicted that considering its reclassification would have a significant impact on the rate of malignancy in further studies (23,24). The incidence of NIFTP has been firstly suggested to be around 16-23% of all PTC cases in North American and European countries (6,25). Nevertheless, we evaluated 51 cases of PTC and none of them fulfilled the established criteria. Recent publications involving

North American, European and Asian populations have found NIFTP incidence as low as <1% (26–29). Geographical and ethnic differences as well as the lack of proper use of strictly diagnostic criteria and inter-observer variation in reporting thyroid tumors are key explanations for these discrepancies.

The limitations of this study are the retrospective design of the data collected before 2017, as well as the small number of samples in categories IV and V, which could have overestimated the malignancy rate within these two TBSRTC categories. Moreover, the results may have also been affected by interobserver variability in the final management decision of indeterminate samples before TBSRTC due to its lack of standardization, but this is a permanent factor of daily clinical practice and would be a shared factor in any other institution.

CONCLUSION

In conclusion, the revised TBSRTC reduced the number of cases with an indication for thyroid surgery and improved the diagnostic accuracy among patients with thyroid nodule cytology corresponding to III, IV and V Bethesda categories compared with the results obtained using the previous method, under which they were classified as follicular lesions. In addition, the introduction of NIFTP did not altered the risks of malignancy in patients with indeterminate thyroid nodule.

REFERENCES

1. Ali SZ, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology. 1st ed. New York: Springer. In press;
2. Baloch ZW, Cooper DS, Gharib H, Alexander EK. Overview of Diagnostic Terminology and Reporting. In: Ali SZ, Cibas ES, editors. The Bethesda System for Reporting Thyroid Cytopathology. 2nd ed. Springer, Cham; 2018. p. 1–6.
3. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, et al. AACE/AME Task Force on Thyroid Nodules (2006) American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocr Pract. 2006;12:63–102.
4. Wang HH. Reporting Thyroid Fine-Needle Aspiration: Literature Review and a proposal. Diagn Cytopathol. 2006;34:67–76.
5. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2006;16:109–42.
6. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LDR, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors Yuri. JAMA Oncol. 2016;2:1023–9.
7. Hirsch D, Robenshtok E, Bachar G, Braslavsky D, Benbassat C. The Implementation of the Bethesda System for Reporting Thyroid Cytopathology Improves Malignancy Detection Despite Lower Rate of Thyroidectomy in Indeterminate Nodules. World J Surg. 2015;39:1959–65.
8. Bahar G, Braslavsky D, Shpitzer T, Feinmesser R, Avidan S, Popovtzer A, et al. The Cytological and Clinical Value of the Thyroid "Follicular Lesion." Am J Otolaryngol. 2003;24:217–20.
9. Harvey AM, Mody DR, Amrikachi M. Thyroid Fine-Needle Aspiration Reporting Rates and Outcomes Before and After Bethesda Implementation Within a Combined Academic and Community Hospital System. Arch Pathol Lab Med. 2013;137:1664–8.
10. Chen JC, Pace SC, Chen BA, Khiyami A, McHenry CR. Yield of repeat fine-needle aspiration biopsy and rate of malignancy in patients with atypia or follicular lesion of undetermined significance: The impact of the Bethesda System for Reporting Thyroid Cytopathology. Surgery. 2012;152:1037–44.
11. Rabaglia JL, Kabbani W, Wallace L, Holt S, Watumull L, Pruitt J, et al. Effect of the Bethesda system for reporting thyroid cytopathology on thyroidectomy rates and malignancy risk in cytologically indeterminate lesions. Surgery. 2010;148:1267–73.
12. Dincer N, Balci S, Yazgan A, Guney G, Ersoy R, Cakir B, et al. Follow-up of atypia and follicular lesions of undetermined significance in thyroid fine needle aspiration cytology. Cytopathology. 2013;24:385–90.
13. Garg S, Naik LP, Kothari KS, Fernandes GC, Agnihotri MA, Gokhale JC. Evaluation of thyroid nodules classified as Bethesda category III on FNAC. J Cytol. 2017;34:5–9.
14. Ho AS, Sarti EE, Jain KS, Wang H, Nixon IJ, Shaha AR, et al. Malignancy Rate in Thyroid Nodules Classified as Bethesda Category III (AUS/FLUS). Thyroid. 2014;24:832–9.
15. Bongiovanni M, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for Reporting Thyroid Cytopathology : A Meta-Analysis. Acta Cytol. 2012;56:333–9.
16. Mahajan S, Srinivasan R, Rajwanshi A, Radotra B, Panda N, Dey P, et al. Risk of Malignancy and Risk of Neoplasia in the Bethesda Indeterminate Categories: Study on 4,532 Thyroid Fine-Needle Aspirations from a Single Institution in India. Acta Cytol. 2017;61:103–10.
17. Çuhaci N, Arpaci D, Üçler R, Yazgan AK, Kıyak G, Yalçin S, et al. Malignancy Rate of Thyroid Nodules Defined as Follicular Lesion of Undetermined Significance and Atypia of Undetermined Significance in Thyroid Cytopathology and Its Relation with Ultrasonographic Features. Endocr Pathol. 2014;25:248–56.
18. Nagarkatti SS, Faquin WC, Lubitz CC, Garcia M, Barbesino G, Ross DS, et al. The Management of Thyroid Nodules with Atypical Cytology on Fine Needle Aspiration Biopsy. Ann Surg Oncol. 2013;20:1–13.
19. Park VY, Kim EK, Kwak JY, Yoon JH, Moon HJ. Malignancy risk and characteristics of thyroid nodules with two consecutive results of atypia of undetermined significance or follicular lesion of undetermined significance on cytology. Eur Radiol. 2015;25:2601–7.
20. Hong IK, Kim JH, Cho YU, Park S, Kim SJ. Clinicopathological factors increased the risk of malignancy in thyroid nodules with atypical or follicular lesions of undetermined significance (AUS/FLUS) risk factor of malignancy in thyroid nodule with AUS/FLUS. Ann Surg Treat Res. 2016;90:201–6.
21. Walts AE, Mirocha J, Bose S. Follicular Lesion of Undetermined Significance in Thyroid FNA Revisited. Diagn Cytopathol. 2014;42:18–22.
22. Turkyilmaz S, Ulusahin M, Celebi B, Cekic AB, Mungan S, Kucuktulu U, et al. Thyroid nodules classified as atypia or follicular lesions of undetermined significance deserve further research: Analysis of 305 surgically confirmed nodules. Cytopathology. 2017;(February).
23. 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.
24. 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.
25. Jung CK, Little MP, Lubin JH, Brenner A V., Wells SA, 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(2):276–85.
26. Bychkov A, Jung CK, Liu Z, Kakudo K. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features in Asian Practice: Perspectives for Surgical Pathology and Cytopathology. Endocr Pathol. 2018;
27. Cho U, Mete O, Kim MH, Bae JS, Jung CK. Molecular correlates and rate of lymph node metastasis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features and invasive follicular variant papillary thyroid carcinoma: the impact of rigid criteria to distinguish non-invasive f. Mod Pathol. 2017;30(6):810–25.
28. Parente DN, Kluijfhout WP, Bongers PJ, Verzijl R, Devon KM, Rotstein LE, et al. Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign? World J Surg. 2018;42(2):321–6.
29. Hare KO, Regan EO, Khattak A, Healy ML, Toner M. Reclassification as NIFTP: a Retrospective Review in a Single Institution with an Emphasis on Workload. Endocr Pathol. 2018;