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Head and Neck Cancer

Incidence and Malignancy Rates in Thyroid Nodules in North-East Indian Population by Bethesda System: A Single Institutional Experience of 3 Years

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Abstract

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Introduction Goiter is one of the most common conditions encountered clinically (up to 60% of population) with thyroid malignancy being one of the most common endocrine malignancies. The American Thyroid Association has advocated the need for validation of the Bethesda system of fine needle aspiration cytology (FNAC) in each center. The risk of malignancy (ROM) for Bethesda categories in the Indian population is limited.

Objective As there are variations in the effectiveness of FNAC, this study aims to study the role of FNAC in evaluating thyroid nodules, estimating the risk of malignancy in thyroid nodules in the North-East Indian population, and correlating the FNAC findings with HPE (histopathological examination).

Materials and Methods A total of 110 patients with thyroid nodules had visited the Department of Otorhinolaryngology during 2017–2020. Case records were retrieved, out of which only 66 patients had both FNAC and HPE reports. The FNAC of 66 patients were studied.

Statistical Analysis Data were analyzed using STATA V14. Fischer's exact test was used to determine the association of Bethesda system in diagnosing thyroid malignancy. The percentage agreement between the FNAC and HPE was calculated using the Kappa statistics. The diagnostic validity of FNAC in the diagnosis of malignant thyroid nodule was reported.

Results The sensitivity, specificity, PPV, and NPV of FNAC in diagnosing thyroid malignancy were 52%, 94.3%, 89%, and 69% respectively. The risk of malignancy (ROM) for Bethesda I to VI categories in our study was 20%, 25%, 67%, 40%, 78%, and 100% respectively (p-value < 0.001, Fischer's exact test).

Keywords

- biopsy
- cytodiagnosis
- fine needle
- goiter
- thyroid neoplasms
- thyroid nodule

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Conclusion A specificity of 94.3% and PPV of 89% of FNAC makes it a good reliable tool in ruling in malignancy in our population. The higher ROM in indeterminate categories necessitates the need to consider thyroidectomy with or without intraoperative frozen section analysis in our population. Similar higher ROM has been reported in a few other Indian studies. These findings may suggest an increased ROM for Bethesda categories III and IV in the Indian population; however, the statement needs further validation from large multicentric studies with research to find the reason for the increased risk.

Introduction

Enlargement of the thyroid gland or goiter is one of the commonest conditions encountered clinically and can be present in up to 60% of the population.[1] Although most of the cases are of benign nature and can be treated in a conservative manner, the need to exclude malignancy is an onus on the treating physician. Thyroid malignancy is one of the most common endocrine malignancies and it most commonly presents as a solitary thyroid nodule.[2] Among various investigations that are available for the evaluation of thyroid nodules, fine needle aspiration cytology (FNAC) is considered a cost-effective tool in the evaluation of thyroid nodules.[3] FNAC is considered as one of the first-line investigations; however, the nondiagnostic or inadequate rate can be as high as 28%. The success of FNAC depends on the adequacy and quality of the sample taken and the technique used.[1] FNAC is useful for malignancy screening. Multiple methods have been used to improve the sensitivity and specificity of the FNAC. As there are variations in the effectiveness of FNAC in diagnosing the thyroid nodules, this study aims to determine the sensitivity and specificity of FNAC in the North-East Indian population in a tertiary care hospital. There are several national and international guidelines that will affect the incidence and prevalence of thyroid cancer from region to region due to underdiagnosis or over diagnosis. The risk of malignancy for each Bethesda category also varies from region to region. Moreover, the American Thyroid Association has advocated the need for validation of the Bethesda system in each center.[4] Hence, population-based studies are needed to see the impact of any clinical guidelines and to compare the prevalence rates to decide on interventions.

Aims and Objectives

Aim: To study the role of FNAC in evaluating thyroid nodules in the North-East Indian population in a tertiary care hospital.

Objective: To estimate the risk of malignancy in thyroid nodules in the North-East Indian population.

To correlate the FNAC findings with HPE (Histopathological examination) findings of thyroid nodules.

Materials and Methods

A study on the diagnostic validity of FNAC in diagnosing thyroid malignancy was conducted using the case records of patients with thyroid nodules in the Department of Otorhinolaryngology after obtaining NSAC and institutional ethics committee approval.

Inclusion criteria: Case records of patients with FNAC and HPE reports from 2017 to 2020 were included in the study.

Exclusion criteria: Case records of patients who did not have FNAC or HPE reports were excluded.

Sample Size

From 2017 to 2020, 110 patients with thyroid nodules had visited the Department and the study was intended to include case records of all patients with FNAC reports and HPE reports.

Study Procedure

The case records of patients which satisfied the inclusion criteria were selected. The details of the patients such as age, gender, FNAC report, type of surgery done, and HPE report were collected. The Bethesda system was used to categorize the FNAC reports. In our center, the reporting of each FNAC and biopsy was done by a team of pathologists (senior resident doctor and faculty consisting of Professor, Associate Professor, and Assistant professor). The data collection of FNAC was done with blinding from the final HPE report.

Operational Definitions

The Bethesda system of thyroid cytopathology used in our study was as follows[5]:

Bethesda I-Nondiagnostic or unsatisfactory
Bethesda II-Benign
Bethesda III-Atypia of undetermined significance or follicular lesion of undetermined significance
Bethesda IV-Follicular neoplasm/suspicious for follicular neoplasm
Bethesda V-Suspicious for malignancy
Bethesda VI-Malignant

The risk of malignancy (ROM) in each Bethesda category was calculated by the formula:

Number of malignant cases in each category on HPE $\times$ 100%.

Total number of cases in the corresponding Bethesda category.

Kappa statistics: Cohen's kappa was used to measure the interrater reliability testing. Cohen's kappa value of ≤ 0 indicates no agreement, 0.01 to 0.20 indicates none to slight, 0.21 to 0.40 indicates fair, 0.41 to 0.60 indicates moderate,

0.61 to 0.80 indicates substantial and 0.81to 1.00 indicates almost perfect agreement.[6]

Statistical Tools

Data were analyzed using STATA V14. Categorical variables are presented as frequency and percentages. Continuous variables are presented as mean and standard deviation (SD). The HPE report was considered as the gold standard. Considering the implied risk of malignancy in the Bethesda system, the categories I, II, III, and IV were considered as FNAC benign and categories V and VI were considered as FNAC malignant.[7] Fischer's exact test was used to determine the association of the Bethesda system in diagnosing thyroid malignancy. The percentage agreement between the FNAC and HPE was calculated using the Kappa statistics. The diagnostic validity of FNAC in the diagnosis of malignant thyroid nodule was reported using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A p value of < 0.05 was considered statistically significant.

Results

A total of 110 patients with thyroid nodules had visited the Department in 2017–2020. Case records were retrieved, out of which only 66 patients had both FNAC and HPE reports. Our center is a tertiary care center situated in the North-East India and all 66 patients included in the study were from North-East India. Of 66 patients, female patients constituted 58 (88%) and male patients 8 (12%). The mean $\pm$ SD in our study was 39 ± 13 years. ►Table 1 depicts the clinic-radiological features of the thyroid nodules in the study population. Complete ultrasonography (USG) features could be retrieved for only 26 patients from the case records (►Table 1).

USG guided FNAC was done in four patients (6%). Bethesda II was the most common Bethesda category seen in our study constituting 32 (48%) of patients. Next, common categories were Bethesda V and VI constituting 9 (14%) each (►Fig. 1).

Table 1 Clinico-radiological findings of thyroid nodules in the study population

Clinical diagnosis ($N = 66$)	***n***
STN	56 (84%)
MNG	10 (15%)
Clinical features ($N = 66$)	***n***
Age in years	
10–20	4
21–30	16
31–40	14
41–50	22
51–60	6
> 60	4
Clinical size of swelling	
≤ 2 cm	3
2–4 cm	18
5–10 cm	42
11–20 cm	3
Duration of disease	
< 1 year	15
1–5 year	37
6–10 years	11
11–20 years	3
USG features ($N = 26$)	
Nodule size	
< 2 cm	8
2– 4 cm	9
> 4 cm	9
Echogenicity	
Anechoeic	2
Hypoechoeic	18
Isoechoeic	3
Hyperechoeic	3
Composition	
Cystic	2
Solid cystic	8
Solid	16
Margin	
Smooth	22
Irregular	3
ETE	1
Shape	
Taller than wide	0
Wider than tall	26
Vascularity	
No vascularity	2
Normal vascularity	13
Increased vascularity	11
Calcification	
No calcification	16
Microcalcification	7
Macrocalcification	3
Abnormal LN	
Yes	2
No	24

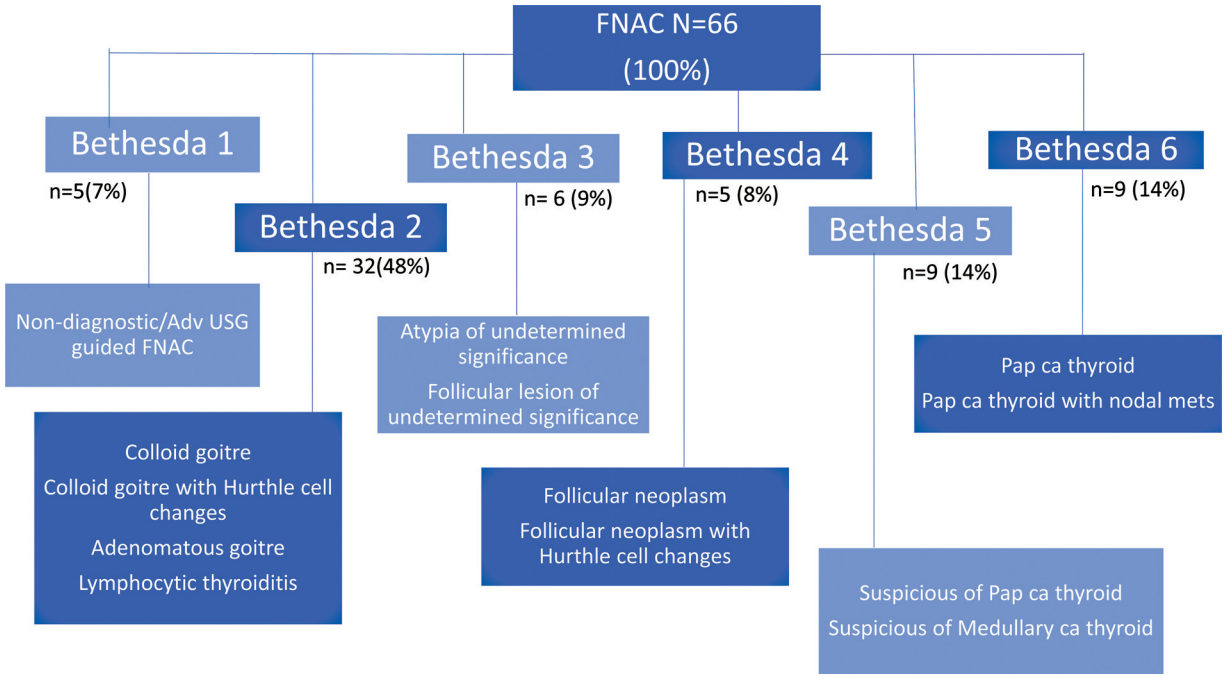

Fig. 1 Distribution of various Bethesda categories in the study.

In FNAC, the most common diagnosis made was colloid goiter in 26 (39.5%), followed by papillary carcinoma thyroid (PCT) in 9 (14%). Hemithyroidectomy was performed in 36 patients (54%), total thyroidectomy was performed in 21 patients (32%), and total thyroidectomy with neck dissection was performed in 9 patients (14%). One patient underwent completion thyroidectomy after frozen section analysis. In HPE, the most common diagnosis made was PCT in 28 (42%), followed by MNG (multinodular goiter) in 17 (25%) patients (►**Table 2**).

Table 2 Various FNAC diagnoses and HPE diagnoses made in our study

Cytological and histopathological diagnoses			
FNAC diagnoses with Bethesda categories (*N* = 66)	***n***	**HPE diagnoses with staging (*N* = 66)**	***n***
Non-diagnostic (I)	5 (7.5%)	Colloid goiter Colloid goiter with Hashimoto's thyroiditis	7 (11%) 1 (1.5%)
Colloid goiter (II)	26 (39.5%)	Adenomatoid goiter	1 (1.5%)
Adenomatous goiter (II)	5 (7.5%)	MNG MNG with Hashimoto's	15 (22%) 2 (3%)
Hashimoto's thyroiditis (II)	1 (1.5%)	Hashimoto's thyroiditis	2 (3%)
Atypia of undetermined significance (III)	5 (7.5%)	Follicular adenoma	6 (9%)
Follicular lesion of undetermined significance (III)	1 (1.5%)	Hurthle cell adenoma	1 (1.5%)
Follicular neoplasm (IV)	4 (6%)	Classical PCT Classical PCT with Hashimoto's (Classical PCT Stage I – 15 cases; Stage II – 11 cases)	19 (29%) 7 (11%)
Follicular neoplasm with Hurthle cell changes (IV)	1 (1.5%)	Follicular variant of PCT (Stage II)	1 (1.5%)
Suspicious of PCT (V)	8 (12%)	Oncocytic variant of PCT (Stage II)	1 (1.5%)
Suspicious of medullary ca thyroid (V)	1 (1.5%)	Medullary Ca thyroid (Stage II)	1 (1.5%)
PCT (VI)	9 (14%)	Follicular Ca Hurthle cell variant (Stage II)	1 (1.5%)
		Anaplastic Ca (Stage IVb)	1 (1.5%)

Abbreviations: Ca, carcinoma; MNG, multinodular goiter; PCT, papillary carcinoma thyroid.

Table 3 Risk of malignancy (ROM) for each Bethesda category in our study

Bethesda category ($N = 66$)	*n*	Benign	Malignant	ROM
Bethesda I	5 (7%)	4 (80%)	1 (20%)	20%
Bethesda II	32 (48%)	24 (75%)	8 (25%)	25%
Bethesda III	6 (9%)	2 (33%)	4 (67%)	67%
Bethesda IV	5 (8%)	3 (60%)	2 (40%)	40%
Bethesda V	9 (14%)	2 (22%)	7 (78%)	78%
Bethesda VI	9 (14%)	0	9 (100%)	100%

p-Value of < 0.001 by Fischer's exact test.

In FNAC, Hashimoto's thyroiditis was diagnosed in 1 (1.5%) patient, whereas, in HPE it was diagnosed in 12 (18%) patients. Hashimoto's thyroiditis in isolation was seen in two (3%) patients. Hashimoto's thyroiditis in the background of colloid goiter in one (1.5%) patient, MNG in two (3%) patients, and PCT in seven (11%) patients.

The diagnosis of a malignant thyroid nodule was made in 18 patients (27%) by FNAC and in 31 patients (47%) by HPE. The diagnosis of benign thyroid nodule was made in 48 patients (73%) by FNAC and in 35 patients (53%) by HPE.

►Table 3 shows the distribution of benign and malignant diagnoses made in each Bethesda category after HPE. In Bethesda VI, all nine patients (100%) were diagnosed with malignancy.

The overall sensitivity of FNAC in diagnosing thyroid malignancy was 52%.

The overall specificity of FNAC in diagnosing thyroid malignancy was 94.3%.

The positive predictive value was 89%.

The negative predictive value was 69%.

The agreement statistics (Cohen's kappa) = 47.0% (moderate agreement) (►Table 4).

The ROM for Bethesda I to VI categories in our study was 20%, 25%, 67%, 40%, 78%, and 100%, respectively. This relationship was statistically significant by Fischer's exact test with a *p*-value of < 0.001.

Table 4 Diagnostic accuracy of FNAC in diagnosing thyroid malignancy

		HPE		Total
		Malignant	Benign	
FNAC	Malignant	16	2	18
	Benign	15	33	48
		31	35	66

Agreement statistics (Cohen's kappa) = 47.0% (moderate agreement).
Sensitivity = 52%.
Specificity= 94.3%.
PPV = 89%.
NPV = 69%.

Discussion

Among the endocrine malignancies, thyroid malignancy is the most common. Globally, the incidence of thyroid cancer in 2020 was 5,86,202 contributing to 3% of all cancers. The incidence of thyroid cancer is three times more in females compared with males globally.[8] The thyroid gland evaluation consists of clinical, radiological, cytological, and histopathological analysis with the final aim of diagnosing thyroid cancers at an early stage. Many classification systems have been developed for reporting thyroid cytology to minimize interobserver and intraobserver variations. The Bethesda system of thyroid cytopathology was developed in 2007 and is widely accepted in the United States of America, India, and many other parts of the world. It underwent several changes in the subsequent years.[2] It has been reported that the experience and skill of the aspirator and the cytopathologist affects the outcome of the FNAC.[1,3] Due to this operator dependency, the utility of FNAC widely varies with a sensitivity of FNAC ranging from 65 to 98%, a specificity of 72 to 100%, a false positive rate of 1 to 8% and a false negative rate of 1 to 11% in diagnosing thyroid malignancy.[1]

The incidence and prevalence of thyroid cancer vary from region to region. The highest incidence in decreasing order is reported from North America, Eastern Asia, and Australia. In North America, the incidence was 6.3 per 100,000 males and 18.4 per 100,000 females in 2020.[8] In India, thyroid cancer constitutes around 0.1 to 0.2% of all cancers with an incidence of 1 per 100,000 males and 1.8 per 100,000 females.[2]

In our study, female patients constituted 88% of the study population. This was the similar finding reported in other studies. Thewjitcharoen et al studied the Bethesda system in their center and reported female patients constituting ~89.8% of the study population.[9] Gautam et al in their study also reported similar finding of female patients constituting ~86.6%.[10]

In our study, Bethesda II category of patients constituted 48% followed by Bethesda V and VI each constituting 14%. Mahajan et al in their study reported Bethesda II to be constituting the major part of the study population (79.6%), followed by 9.8% of Bethesda VI patients.[11] These findings were similar to our study. However, in their study, the indeterminate categories of Bethesda III and IV were 2.5% and 3.9%, respectively. This was in contrast to our study, wherein the Bethesda III and IV constituted 9% and 8%, respectively.

The rates of nondiagnostic study in thyroid FNAC should be less than 10% as reported by Ali in his study.[12] Bhartiya et al in their study reported nondiagnostic rate of 5.88%.[13] In our study it was 7.5% and is within the acceptable range.

In cytological diagnosis colloid goiter was the most common diagnosis made, contributing to 39.5% followed by PCT of 14% and suspicious of PCT 12%. In a study by Gautam et al, colloid goiter constituted 61% followed by follicular neoplasm 16% and adenomatous hyperplasia 10%.[10]

Hashimoto's thyroiditis constituted 18% of the cases in our study. Bhartiya et al reported 2.8% of the cases with Hashimoto's thyroiditis.[13] Pasha et al reported that 3.6% of the

Table 5 Comparison of risk of malignancy for Bethesda categories in various studies

Bethesda category	Our study	Implied risk as per TBSRTC[7]	Swati Mahajan et al 2017[11]	Shipra Agarwal et al 2017[2]	Thewjitcharoen et al 2019[9]	Paricha Upadhyaya et al 2019[5]
Bethesda I	20%	1–4%	50%	6–24%	20%	33.3%
Bethesda II	25%	0–3%	7.8%	2–4%	4%	1.49%
Bethesda III	67%	5–15%	50%	23–45%	9%	–
Bethesda IV	40%	15–30%	23.6%	15–36%	24%	7.60
Bethesda V	78%	60–75%	75%	55–84%	57%	80.00
Bethesda VI	100%	97–99%	85.4%	89–98%	90%	95.23

Abbreviation: TBSRTC, Thyroid Bethesda system for reporting thyroid cytology.

cases with Hashimoto's thyroiditis.[14] In a study by Rout et al Hashimoto's thyroiditis constituted around 11% of cases.[15] These findings were in contrast to our findings. Hashimoto's thyroiditis, being an autoimmune disorder, is common in developed countries and is the leading cause of hypothyroidism in developed countries. In rest of the world, especially in developing countries, iodine deficiency is the leading cause of hypothyroidism.[16]

The sensitivity, specificity, PPV, and NPV of FNAC in diagnosing thyroid malignancy in our study were 52%, 94.3%, 89%, and 69%, respectively. The specificity and PPV in our study were comparable to other studies and within the recommended limits.[1] In a study conducted by Bhartiya et al correlating FNAC with histopathological examination of 105 patients, it was found that the Bethesda system had sensitivity of 75% and specificity of 98.9% and diagnostic accuracy of 97.1%.[13]

In a study by Pasha et al, the sensitivity, specificity, PPV, and NPV of FNAC were 81.30%, 77.06%, 57.14%, 91.64%, respectively.[14] Our study had higher specificity and PPV but lower sensitivity and NPV.

Bahaj et al conducted a population-based study evaluating the role of FNAC and reported a sensitivity, specificity, PPV, and NPV of 79.8%, 82.1%, 74.8% and 85.9% respectively.[17] Higher specificity and PPV were noted in our study. Sensitivity and NPV were less in our study. Chaudhary et al conducted a study and found FNAC to be having a sensitivity, specificity, PPV, and NPV of 92.31%, 45.45%, 85.71% and 62.50% respectively.[18] Our study had similar PPV and NPV. However, the sensitivity was less and specificity was more in our study.

The sensitivity and NPV of FNAC in diagnosing thyroid malignancy in our study were relatively less compared with other studies. This can be explained by many factors. First is that the sample size was relatively small in our study. Second, FNAC may have been taken from nonrepresentative areas for malignancy. Third, some cytological features can mimic both benign and malignant conditions. Hyperplastic changes with increased cellularity, pale chromatin, occasional nuclear grooves, occasional nuclear inclusions, round nucleus in large sheets of follicular cells can be seen in nodular goiter or Hashimoto's thyroiditis. These cytological changes can also give the impression of PCT leading to misdiagnosis of malignancy. Similarly, scant cellularity in slides, absence of nuclear inclusion or grooving, may lead to diagnosis of cystic degeneration of colloid goiter and any occasional atypical histiocytoid cells can be missed out in slides. These changes can lead to misdiagnosis or underdiagnosis of malignancy.[5]

The ROM for Bethesda I to VI in our study was 20%, 25%, 67%, 40%, 78% and 100% respectively. It correlates with the implied ROM for Bethesda categories of V and VI but our study has higher than the implied risk for categories I,II, III, and IV.[7] However, similar higher ROM has been reported in other studies for categories I, II, and III and IV[2,5,9,11] (►Table 5).

The possible explanation is that all patients of Bethesda I, II, III and IV identified in our study and previous studies were subjected to thyroidectomy, leading to the overdiagnosis of thyroid malignancy. The patients in our study in Bethesda I, II, III, and IV underwent surgery based on clinico-radiological suspicion for malignancy and patient preference for surgery.

The Thyroid Bethesda system for reporting thyroid cytology (TBSRTC) in 2017 advocated that the Bethesda III category should be within 10% of all the thyroid FNACs in a center.[19] Bethesda III and IV categories constituted 9% and 8% respectively in our study. The TBSRTC in 2017 also revised the risk of malignancy for Bethesda III and IV as 10 to 30% and 25 to 40%, respectively.[20] It has been reported in the literature that the malignancy rates are inconsistent for Bethesda III and IV categories ranging from 15.7 to 54.7% and 16.8 to 72.4% respectively with Western studies reporting around 25 to 28%.[19,21] In our study, the malignancy rates in above categories were 67% and 40% respectively. Studies from the Indian population on the risk of malignancy is scarce. On literature search, only three other Indian studies were found on risk of malignancy, which reported a similar higher risk of malignancy for Bethesda categories III and IV. Swati et al reported a risk of 50% and 24% respectively for Bethesda III and IV in their study.[11] Chakravarthy et al reported ROM for Bethesda III category as 69%.[4] Chirayath et al reported ROM for Bethesda III and IV as 54.6% and 72.4% respectively.[19] These findings may suggest an increased ROM for Bethesda categories III and IV in the Indian population; however, the statement needs further validation from large multicentric studies with research to find the reason for the increased risk.

The limitations of the study are the retrospective design and the relatively small sample size. Hence, it may not be representative of the entire general population of the region.

Conclusion

Overall, a specificity of 94.3% and a PPV of 89% of FNAC makes it a good and reliable tool to help in ruling in malignancy in our population. Our study has a higher risk of malignancy for all Bethesda categories compared with the Bethesda system's implied risk of malignancy. The relatively lower sensitivity in our study needs attention and steps such as ultrasound-guided FNAC should be considered to improve the same. The relatively large proportion of indeterminate categories in our study is a concern, and refined criteria or methods are needed to categorize them into definitive categories. The higher ROM in indeterminate categories necessitates the need to consider thyroidectomy with or without intraoperative frozen section analysis in our population. Although molecular markers have been studied and advocated for indeterminate categories, it is expensive and not widely available for use especially in developing countries or remote center like ours. The use of FNAC and Bethesda system is highly recommended in our population. However, we recommend large sample-sized institutional studies or audits to update their clinical guidelines according to the risk of malignancy and compare the prevalence rates for targeted intervention.

Note

The article was prepared after obtaining institutional ethics committee approval and in confirmation to the Declaration of Helsinki.

Conflict of Interest

None declared.

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References

1 Scott-Brown's Otorhinolaryngology and Head and Neck Surgery. 8th ed. Routledge and CRC Press; 2018:651–700
2 Agarwal S, Jain D. Thyroid cytology in India: contemporary review and meta-analysis. J Pathol Transl Med 2017;51(06):533–547
3 Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 1993;118(04):282–289
4 Chakravarthy NS, Chandramohan A, Prabhu AJ, et al. Ultrasound-guided fine-needle aspiration cytology along with clinical and radiological features in predicting thyroid malignancy in nodules ≥ 1 cm. Indian J Endocrinol Metab 2018;22(05):597–604
5 Upadhyaya P, Dhakal S, Adhikari P, Adhikari B, Khadka D, Niraula SR. Histopathological review of diagnostic categories of the Bethesda system for reporting thyroid cytopathology – an institutional experience of 5 years. J Cytol 2019;36(01):48–52
6 McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22(03):276–282
7 Al Dawish MA, Robert AA, Muna A, et al. Bethesda system for reporting thyroid cytopathology: a three-year study at a tertiary care referral center in Saudi Arabia. World J Clin Oncol 2017;8(02):151–157
8 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(03):209–249
9 Thewjitcharoen Y, Butadej S, Nakasatien S, et al. Incidence and malignancy rates classified by The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) - an 8-year tertiary center experience in Thailand. J Clin Transl Endocrinol 2018;16:100175
10 Gautam H, Kumar V, Kanaujia S, Maurya D, Singh S. Clinico-cytoradiological correlation of thyroid surgery in patients with thyroid nodule. Ann Indian Acad Otorhinolaryngol Head Neck Surg 2017;1(02):17
11 Mahajan S, Srinivasan R, Rajwanshi A, 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(02):103–110
12 Ali SZ. Thyroid cytopathology: Bethesda and beyond. Acta Cytol 2011;55(01):4–12
13 Bhartiya R, Mallik M, Kumari N, Prasad BN. Evaluation of thyroid lesions by fine-needle aspiration cytology based on Bethesda system for reporting thyroid cytopathology classification among the population of South Bihar. Indian J Med Paediatr Oncol 2016;37(04):265–270
14 Pasha HA, Mughal A, Wasif M, Dhanani R, Haider SA, Abbas SA. The efficacy of Bethesda system for prediction of thyroid malignancies-a 9 year experience from a tertiary center. Iran J Otorhinolaryngol 2021;33(117):209–215
15 Rout K, Ray CS, Behera SK, Biswal R. A comparative study of FNAC and histopathology of thyroid swellings. Indian J Otolaryngol Head Neck Surg 2011;63(04):370–372
16 Mincer DL, Jialal I. Hashimoto Thyroiditis. In: StatPearls. StatPearls Publishing; 2021. Accessed September 15, 2021 at: http://www.ncbi.nlm.nih.gov/books/NBK459262/
17 Bahaj AS, Alkaff HH, Melebari BN, et al. Role of fine-needle aspiration cytology in evaluating thyroid nodules. A retrospective study from a tertiary care center of Western region, Saudi Arabia. Saudi Med J 2020;41(10):1098–1103
18 Chaudhary M, Baisakhiya N, Singh G. Clinicopathological and radiological study of thyroid swelling. Indian J Otolaryngol Head Neck Surg 2019;71(suppl 1):893–904
19 Chirayath SR, Pavithran PV, Abraham N, et al. Prospective study of Bethesda categories III and IV thyroid nodules: outcomes and predictive value of $BRAF^{V600E}$ mutation. Indian J Endocrinol Metab 2019;23(03):278–281
20 Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27(11):1341–1346
21 Zahid A, Shafiq W, Nasir KS, et al. Malignancy rates in thyroid nodules classified as Bethesda categories III and IV; a subcontinent perspective. J Clin Transl Endocrinol 2021;23:100250

