Diagnostic Accuracy of Fine Needle Aspiration Cytology and the Significance of Bethesda Category III in Thyroid Neoplasia

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ABSTRACT

BACKGROUND

Fine Needle Aspiration Cytology (FNAC) plays a pivotal role in the diagnosis of thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has improved the quality of cytology reporting. Bethesda category III or Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance (AUS / FLUS) has been a challenge to pathologists and our objective is to study the significance of Bethesda classification and assess the malignancy risk in AUS / FLUS to plan subsequent management strategy.

METHODS

The study comprised of 133 patients who underwent fine needle aspiration followed by surgery from January 2012 to June 2013 in our institution. Cytology smears were evaluated and reported according to Bethesda system of reporting thyroid cytopathology. Fine needle aspiration cytology diagnosis was compared with the histopathology reports.

RESULTS

On evaluating cytopathology reporting as per Bethesda system, highest number of cases was in the "suspicious for follicular neoplasm / follicular neoplasm category". Incidence of AUS / FLUS was 17.3 %, and the malignancy rate in this category was 60 % which is the highest reported, compared to other similar studies. The most common malignancy was papillary carcinoma.

CONCLUSIONS

Fine Needle Aspiration Cytology (FNAC) is still the most cost effective minimal invasive technique in the diagnosis of thyroid neoplasm. The higher malignancy rate in AUS / FLUS in the present study warrants early surgical intervention as the appropriate management, than the current strategy of "repeat FNAC" in this category. The current study also showed definite correlation between histopathology and FNAC in the diagnosis of thyroid malignancy.

KEYWORDS

Fine Needle Aspiration Cytology (FNAC), Thyroid Nodule, AUS / FLUS, Bethesda System, Malignancy

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BACKGROUND

Globally there is a steady increase of thyroid cancer cases.[1] Since many reports are from developed countries, it is considered as an issue of such countries. On the other hand, the low and middle income countries has controlled the communicable diseases and experiencing more chronic non-infectious diseases.[2] Now the low and middle income countries suffer the burden of heart diseases, cancer, diabetes etc. In these countries the developing health care facility prompt early diagnosis and a large number of preclinical thyroid cases are diagnosed. This phenomenon can be called as overdiagnosis.[3] FNAC has largely facilitated in the diagnosis of thyroid diseases.

Thyroid swellings are a significant problem especially in India which has a prevalence of 40 % goiter.[4] Regional Cancer Centre, Thiruvananthapuram has reported 8.8 % of thyroid cancer which is the highest in the country (National Cancer Registry Program Reports 2018).[5] This center has recorded 17.1 % of thyroid cancers in the pathology department among females in 2018. The preoperative cytological diagnosis of thyroid neoplasia is important because of its treatment implications. The advantages of FNAC are its diagnostic reliability, cost-effectiveness, simplicity, absence of major complications and that it can be done as an outpatient procedure.[6] The routine use of FNAC has significantly reduced the incidence of thyroid surgery for benign diseases of the thyroid; it has also increased the yield of malignancy in thyroidectomy specimens from 5 – 10 % to 30 - 50 % in the recent years.[7]

To standardize FNAC interpretation and reporting a new concept of "The Bethesda System for Reporting Thyroid Cytopathology" (TBSRTC) was introduced in 2009.[8] There are six cytological diagnostic categories, each with different suggested treatment modalities. There is no disputes regarding the malignancy rates and management in Bethesda categories I, II, IV, V, VI. However there are controversial data regarding the risk of malignancies and clinical management in the Atypia of Undetermined Significance (AUS) and Follicular Lesion of Undetermined Significance in thyroid neoplasia (FLUS) grouped under Bethesda category III. The present study was conducted to assess the diagnostic accuracy of FNAC [9] and to study the rate of malignancy in Bethesda category III in this institution.

METHODS

This was an observational study comprising of 133 patients who underwent FNAC for thyroid nodule and who subsequently underwent thyroidectomy between January 2012 and June 2013 in this tertiary care centre. Patients who did not undergo thyroidectomy after FNAC were excluded. Ethical clearance was obtained from the ethical committee. The study was conducted with the written consent of the patients. A detailed clinical examination of the neck swelling was done on all patients in order to accurately localize the site for aspiration. Under aseptic precautions direct FNAC was carried out using a 23 gauge needle. A minimum of six slides were smeared with the aspirate, two for Leishman stain (air dried) and two each for Haematoxylin and Eosin (H & E) and Papanicolaou (Pap) stains (wet smears). Smears to be stained with H&E and pap were fixed in 80 % Isopropyl alcohol for 10 - 15 mins. Whenever fluids was obtained, all the contents were aspirated and centrifuged at 3000 rpm for 15 minutes. The sediment was taken, and three slides were stained with H & E, pap and Leishman stain. Stained smears were studied under light microscopy. The smears were evaluated and reported according to the criteria laid down by Bethesda system for reporting thyroid cytopathology. The adequacy of the smears were determined by the presence of five to six groups of follicular cells, with each group containing 10 or more cells on at least two slides from different passes were considered as adequate aspirate.

Bethesda System for Reporting Thyroid Cytopathology Recommended Diagnostic Categories[8]

1. Nondiagnostic or unsatisfactory - cyst fluid only virtually acellular specimen other (obscuring blood, clotting artifact, etc.
2. Benign - Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc), Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context, Consistent with granulomatous (subacute) thyroiditis and others.
3. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance.
4. Follicular Neoplasm or Suspicious for a Follicular Neoplasm Specify if Hurthle cell (oncocytic) type.
5. Suspicious for Malignancy - Suspicious for papillary carcinoma, Suspicious for medullary carcinoma, Suspicious for metastatic carcinoma, suspicious for lymphoma and other.
6. Malignant - Papillary thyroid carcinoma, Poorly differentiated carcinoma, Medullary thyroid carcinoma, Undifferentiated (anaplastic) carcinoma, Squamous cell carcinoma, Carcinoma with mixed features (specify), Metastatic carcinoma, Non-Hodgkin lymphoma and other.

Criteria for Cytopathological Diagnosis of Thyroid Lesions According to Bethesda System[8]

Nondiagnostic or Unsatisfactory Criteria - Specimens are considered unsatisfactory either if the number of follicular cells is inadequate for reporting or if the morphology of the smears is altered by drying artefact or the presence of blood.

Benign Criteria - If there is adequate number of benign follicular cells along with colloid arranged in microfollicular or macrofollicular pattern or if a definite diagnosis can be made in the presence of proper clinical setting (e.g.: lymphocytic thyroiditis or granulomatous thyroiditis).

Atypia of Undetermined Significance or Follicular Lesions of Undetermined Significance Criteria - If there is predominant population of follicular cells arranged in micro follicles but does not fulfill the criteria for follicular neoplasm / suspicious for follicular neoplasm; or if there is sparsely cellular aspirate with mainly Hurthle cells; or if a benign - appearing sample show focal features suggestive of papillary carcinoma or if a cyst lined by cells showing atypical features like nuclear grooves/prominent nucleoli; or if there is focal atypical lymphoid infiltrate.

Follicular Neoplasm or Suspicious for a Follicular Neoplasm Criteria - Smears show high cellularity with follicular cells arranged in microfollicular or trabecular pattern in a background of scanty colloid. Follicular cells are enlarged and show crowding and overlapping. No nuclear atypia or mitosis.

Suspicious for Malignancy Criteria - If there is only small number of abnormal cells or smears showing only focal nuclear atypia or architectural changes are classified as suspicious for malignancy.

Malignant Criteria - This category is used whenever the architectural pattern and the cytological features are conclusive of malignancy.

Criteria for Papillary Carcinoma - Cells arranged in papillary or syncytial pattern, showing enlarged, oval irregular nuclei with intranuclear grooves and intranuclear cytoplasmic pseudo inclusion. Psammoma bodies and multinucleated giant cells may be present.

Criteria for Medullary Carcinoma - Moderate to markedly cellular smears arranged singly and in syncytial clusters composed of plasmacytoid / polygonal / round or spindle cells. These cells show mild-to-moderate pleomorphism.

Criteria for Poorly Differentiated Thyroid Carcinoma - The cells are arranged either in solid, insular or trabecular pattern having scanty cytoplasm, high nuclear / cytoplasmic (N / C) ratio with variable nuclear atypia scattered mitotic figures or necrosis are often present.

Criteria for Undifferentiated Carcinoma - Moderate to markedly cellular smears with cells arranged singly and / or variable - sized clusters, cells are round to polygonal and / or spindle shaped and show enlarged, irregular, pleomorphic nuclei, clumped chromatin with prominent irregular nucleoli. Intranuclear inclusions, multinucleation, necrosis, numerous mitotic figures, neutrophilic infiltration are seen.

Criteria for Lymphoma Thyroid - Smears are markedly cellular and show non cohesive sheets of round or oval cells with moderate cytoplasm and vesicular nuclei with open chromatin and small nucleoli. numerous lymphoglandular bodies are seen in the background.

The thyroidectomy specimens after surgery were fixed in 10 % formalin overnight. A detailed gross examinations was done, relevant areas were sampled and processed. Five micron paraffin sections were cut and stained by H&E. The sections were studied under light microscopy. The histopathologic diagnosis was compared with Fine needle aspiration cytologic diagnosis according to Bethesda system for reporting thyroid cytopathology.

Statistical Analysis

Numerical variables were expressed as mean and standard deviation. Categorical variables were expressed as frequencies & percentages. To compare the accuracy of FNAC with histopathology diagnostic evaluation method was applied. Chi - square test was used to obtain the association of study variables with histopathology. Data analysis was done using SPSS software version 20.

RESULTS

A total number of 133 cases of thyroid lesion in which FNAC followed by thyroid surgery were analyzed. The age of the subjects ranged from 10 to 80 years with mean age of 39.43 ± 15.26 years. Females formed the predominant group 83.5 % (Table 1).

On cytopathology reporting as per Bethesda system highest number of cases reported in the "suspicious of follicular neoplasm / follicular neoplasm category" accounting for 31.6 % of cases (Table 2), and showed equal number of benign and malignant lesions on histopathology. All the 12 malignant lesions on FNAC proved to be malignant on histopathology also. Out of the 15 "suspicious for malignancy" cases, 11 cases proved to be malignant by histopathology. A benign diagnosis was given by FNAC in 31 cases, out of which 17 turned to be malignant. Of these 17 cases eight cases were papillary carcinoma arising in multi nodular goiter. In AUS / FLUS category eight out of 17 AUS cases and all six FLUS cases were reported as malignant on histopathology and all were papillary carcinomas (Table 3). In ten cases FNAC turned to be non-diagnostic. Among 120 neoplastic lesions papillary carcinoma was 81 cases (67.5 %), follicular adenoma 35 cases (29.17 %) and Hurthle cell adenoma four cases (3.33 %). The remaining 13 cases were multinodular goiter.

The sensitivity was found to be 76.3 % and specificity 27.7 %. Positive predictive value (PPV) was found to be 63.1 % and negative predictive value was found to be 41.9 % for FNAC compared to histopathology findings (p= 0.036 McNemar test).

Variables		Total	Benign		Malignant		P Value
			n	%	n	%	
Age (years)	<30	35	16	45.7	19	54.3	0.521
	30-49	70	27	38.5	43	61.5	
	≥50	28	9	32.1	19	67.9	
Sex	Male	22	9	36.4	13	63.6	0.834
	Female	111	44	39.6	67	60.4	

Table 1. Age and Sex Wise Distribution of Histopathologic Findings

Category Bethesda System		FNAC		Histopathology			
		n = 133	%	Benign n = 52	%	Malignant n =81	%
I	Non Diagnostic	10	7.5	4	40	6	60
II	Benign	31	23.3	14	45.2	17	54.8
III	AUS	17	12.8	9	52.9	8	41.1
	FLUS	6	4.5	0	0	6	100
IV	Suspicious of follicular Neoplasm/ Follicular Neoplasm	42	31.6	21	50	21	50
V	Suspicious of malignancy	15	11.3	4	26.7	11	73.3
VI	Malignant	12	9.0	0	0	12	100

Table 2. FNAC - Different Categories and Correlation with Histopathology

Histopathological Findings	AUS n=17		FLUS n=6	
	n	%	n	%
Multinodular goitre	4	23.5	0	0
Follicular adenoma	4	23.5	0	0
Hurthle cell adenoma	1	5.9	0	0
Papillary carcinoma	4	23.5	3	50.0
Papillary carcinoma arising in multinodular goitre	0	0	2	33.3
Papillary carcinoma with invasion into adjacent tissue	0	0	1	16.7
Papillary carcinoma multifocal	2	11.8	0	0
Papillary microcarcinoma arising in multinodular goitre	1	5.9	0	0
Papillary microcarcinoma multifocal	1	5.9	0	0

Table 3. Percentage of Malignancy on Histopathology in AUS and FLUS

Abbreviations

FNAC : Fine Needle Aspiration Cytology
AUS : Atypia of Undetermined Significance
FLUS : Follicular Lesion of Undetermined Significance

DISCUSSION

FNAC is sensitive and specific in triaging neoplastic from non-neoplastic thyroid lesions. The mean age of the population in the present study was 39.43 ± 15.26 and male to female ratio 1 : 5 which is similar to the other reports.[9] Among the neoplastic lesion in the present study papillary carcinoma was the commonest malignancy and accounted for 67.5 % followed by follicular adenoma 29.17 %, which is accordance with other studies.[10] Papillary carcinoma is believed to be an easy diagnosis by FNAC.[11] It is reported that the predictive value of cytological diagnosis is 100 % for papillary carcinoma of thyroid.[12] This is in concordance with the present study where all the 12 papillary carcinoma diagnosed cytologically agreed with the histopathology reports. There are still grey zones of diagnostic difficulty especially in follicular lesions due to overlap of cell pattern, cellular details and background elements.

In the present study 42 cases reported as suspicious for follicular neoplasm / follicular neoplasm showed equal number of benign and malignant lesions on biopsy. Bethesda category -III (AUS / FLUS) has generated much controversy. It included thyroid aspirates that are not sufficient enough for "suggestive of malignancy", but have features which limits their inclusion in benign category.[13,14] In the present study this category III has 17.3 % of total cases. Different studies have reported variable rates of AUS/ FLUS ranging from 0.8 % to 29 %.[15,16,17,18]

TBSRTC has estimated the risk of malignancy to range from 5 % to 15 % in AUS / FLUS category and the recommended management is to repeat FNAC.[8] A study reported surgical confirmed malignancy rate of 28.5% among patients with AUS / FLUS nodules.[19] However, the present study showed a higher malignancy rate of 60 % (14 out of 23), which is very high compared to other studies. This may be either due to overuse of this category or due to inclusion of incidental carcinoma.[14,20] In view of the increased rate of malignancy in AUS / FLUS category, the current management strategy of TBSRTC may need reassessment.

CONCLUSIONS

Current study showed definite correlation between histopathology and FNAC in the diagnosis of thyroid malignancy. Bethesda category III, (AUS / FLUS) showed higher malignancy rate in this study than previously reported. This warrants management by early surgical intervention, than the recommended clinical management by "repeat FNAC" in this category. Further studies with additional multimodal diagnostic techniques are needed to predict malignancy risk and plan appropriate treatment strategy for AUS / FLUS category.

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