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Research Article

Rate of Malignancy in Thyroid Nodules Having Atypia of Undetermined Significance on FNAC

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Abstract

Introduction & Background: The global incidence of thyroid cancer is rapidly increasing largely due to incidental thyroid nodules being found on ultrasonography. Fine Needle Aspiration Cytology (FNAC)is not only a reliable screening test, but also a reliable and cost-effective method for the differential diagnosis of a thyroid nodule. Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS) is one of the six diagnostic categories of the Bethesda System for Reporting Thyroid Cytopathology. The prevalence of malignancy among Bethesda category III cytology is variable, ranging from 5% to 37% in the literature.

Objective: To determine the rate of malignancy in atypical thyroid nodules.

Methods: Records of 120 patients who underwent thyroidectomy from Jan 2018 till July 2021 were retrospectively reviewed and out of these only 23 patient who had pre operative FNAC findings of atypia of undetermined significance were included in study . Comaparsion was done between pre operative FNAC and post operative histopathology and it was found that 57.% of these atypical nodules were actually malignant on final histopathology.

Conclusion;Risk of malignancy in atypical thyroid nodules is significantly high so these patients should be offered diagnostic lobectomy.

Keywords: Atypia of undetermined significance; Classifications of thyroid nodules on FNAC; Rate of malignancy in thyroid nodules

Introduction

The incidence of thyroid cancer is increasing globally mainly because of finding incidental thyroid nodules on ultrasonography. These Nodules are seen in 50% of patients aged 50 years. However, the risk of malignancy in these nodules is 5% to 7%. Most commonly used preoperative diagnostic tool is Fine-Needle Aspiration Cytology (FNAC) for cancer risk stratification in thyroid nodules weather palpable or image detected [1,2]. In the year 2007, the National Cancer Institute (NCI), Bethesda, Maryland, United States, organized the NCI Thyroid Fine Needle Aspiration State-of-the-Science Conference, and an initiative was undertaken to publish an atlas and guidelines using a standardized nomenclature for the interpretation of thyroid fine needle aspirates (FNAs), known as the Bethesda system for reporting thyroid cytopathology [3]. The atlas describes six diagnostic categories of lesions: Non-diagnostic/unsatisfactory, benign, atypical follicular lesion of undetermined significance (AFLUS), "Suspicious" for Follicular Neoplasm (SFN), Suspicious for Malignancy (SM), and malignant [4]. The six diagnostic categories of the Bethesda system have individual implied risks of malignancy that influence management paradigms.

Out of all these 6 categories ,it is type 3ie atypical nodules (AUS/FLUS) that pose management challenges. Bethesda system recommends a repeat follow-up FNA biopsy for cases of thyroid nodules with AUS/FLUS. Reports indicate that about 30% of such cases were still diagnosed as being cytologically indeterminate thyroid nodules despite a repeat FNA biopsy [5]. It makes treatment decisions difficult for clinicians concerned with the optimal management of thyroid nodules. To overcome this problem, several modalities other than repeat FNA have been proposed, such as Core Needle Biopsy (CNB) [6], gene expression classifier test [7], and multi-gene next-generation sequencing assay [8]. Diagnostic accuracy of these modalities is questionable and moreover they are either not available or are very expensive . Since its advent, FNAC became a routine practice for thyroid nodule assessment, and the role of intraoperative frozen section biopsy has been debated. Few authors advocate the use of frozen section because of the very low false positive rates and the high specificity, of up to 90% [9,10]. However, several recent series report very low sensitivities, ranging from 22% to 51% [11,12].

Actually Not all of these patients with atypia of thyroid nodules on FNAC under go surgery because of many patient and clinician related factors so it is difficult to actually calculate the risk of malignancy in these nodules .

The risk of malignancy in Bethesda-III category ranges from 12% to 69% in the resected specimens [13-16]. This wide variation could be partly explained due to interobserver variability both at the time of obtaining the specimen and during the cytological interpretation. Moreover, the prevalence of malignancy in the population could influence the percentages of malignancy in the resected specimens. However, eliminating the AUS/FLUS category decreases the FNAC sensitivity and increases the rates of false negative and false positive results [17]. Therefore, it has been suggested that institution-specific and local data should guide the subsequent management of indeterminate nodules. This study was conducted to calculate the risk of malignancy in atypical thyroid nodules in our institute to have institute specific data to help us in making guide lines for management of indetermined nodules. Future studies can be conducted with multiple institutes to get local data for entire community.

Objective

To determine the rate of malignancy in thyroid nodules having atypia of undetermined significance by comparing pre operative FNAC with post thyroidectomy histopathology.

Operational Definitions

Atypia of Undetermined Significance

Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS) is one of the six diagnostic categories of Bethesda system for reporting thyroid cytopathology and fits in to Bethesda category (III).

Details of Bethesda classification are given in introduction.

The prevalence of malignancy among Bethesda III category is variable, ranging from 5% to 37 % in the literature [18].

Materials and Methods

Ethical approval was taken from Dubai Scientific Research Ethics Committee (DSREC) before starting the study. Since it was a retrospective cross sectional/observation study so patients consent was not taken

Setting: Department of General Surgery Dubai Hospital.

Duration of Study: jan 2018 till July 2021.

Sample Size: total 136 patients underwent thyroidectomies during the study period .

Sampling Technique: continuous sampling

Sample Selection

a. Inclusion Criteria: Patients who underwent thyroidectomies in specified duration with pre operative FNAC

showing atypia of undetermined significance (AUS/FLUS) were recruited for inclusion in the study.

b. Exclusion Criteria: Patients whose FNAC results were other than AUS/FLUS and those who did not undergo surgical intervention were excluded.

Study Design: retrospective cross sectional.

Data Collection: Data was collected retrospectively using electronic record system of hospital

Data Analysis

All analysis was done using the Statistical Package for Social Sciences (SPSS) version 28.

The variables included were age, sex, pre operative FNAC and post operative histopathology.

Records of all patients who under went thyroidectomies from jan 2018 till July 2021 were reviewed and out of these patients those who had pre operative FNAC showing atypia of undetermined significance were included in study . The pre operative FNAC of these patients was compared with post operative histopathology to see how many of these patients actually had malignancy.

Results

Over the period of 1.6 years, preoperative FNAC was performed in 120 patients who underwent thyroid surgery.

The mean age was 49.9 years.

Age distribution is shown in Figure 1 and 2.

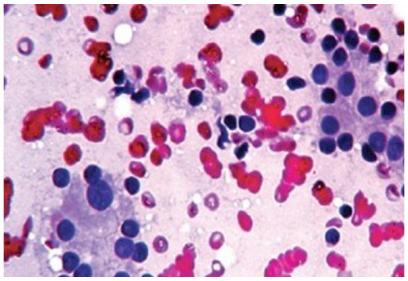

Figure 1: Microphotograph of a smear categorized as AFLUS, showing predominantly benign thyroid follicular cells in sheets, with some cells showing anisonucleosis and forming microfollicles.

AGE

AGE Stem-and-Leaf Plot

Frequency	Stem & Leaf
3.00	1 . 677
6.00	2 . 113344
10.00	2 . 5677889999
18.00	3 . 011112222233334444
19.00	3 . 5555677777788889999
16.00	4 . 0011112222333344
16.00	4 . 5556777788999999
14.00	5 . 01112333334444
7.00	5 . 5678889
8.00	6 . 00122233
1.00	6 . 8
.00	7 .
1.00	7 . 6
1.00 Extremes	(>=81)

Stem width: 10
Each leaf: 1 case(s)

Figure 2: Age Distribution.

90/120 were female while 30 patients were male.

In atypical category 7/21 (33.3 %)were Fmale while 14/21 (66.6) were Male patients.

Sex distribution is shown in Figure 3 and 4.

Descriptives

			Statistic	Std. Error
AGE	Mean		41.98	1.143
	95% Confidence Interval for Mean	Lower Bound	39.71	
		Upper Bound	44.24	
	5% Trimmed Mean		41.75	
	Median		41.00	
	Variance		156.663	
	Std. Deviation		12.517	
	Minimum		16	
	Maximum		81	
	Range		65	
	Interquartile Range		18	
	Skewness		.358	.221
	Kurtosis		.041	.438

Figure 3: Age Distribution.

SEX

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	MALE	30	25.0	25.0	25.0
	FEMALE	90	75.0	75.0	100.0
	Total	120	100.0	100.0	

Figure 4: Sex Distribution.

64/120 under went hemi thyroidectomy while 56/120 underwent total thyroidectomy .

107 patients had open surgery while 13 underwent minimal acess thyroidectomy **.** minimal acess procedures included trans oral as well as trans axillary approaches.

Procedure types are explained in Figure 5 and 6.

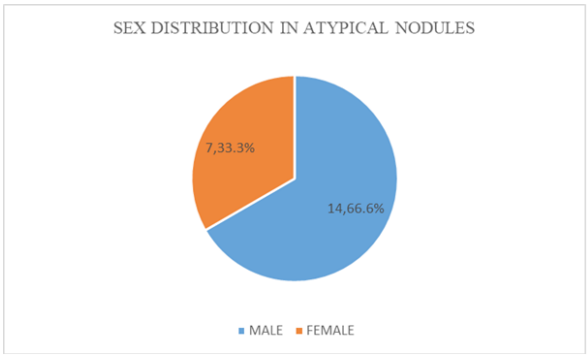

Figure 5: Sex Distribution.

PROCEDURE

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	HEMITHYROIDECTOMY	64	52.5	52.9	52.9
	TOTAL THYROIDECTOMY	56	46.7	47.1	100.0
	Total	120	99.2	100.0	
Missing	System	0	0		
Total		120	100.0		

Figure 6: Procedures Performed.

Pre op FNAC showed benign lesion for 76,atypia for 21 and malignancy for 22 cases ,Shown in Figure 7.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	OPEN	107	89.2	89.2	89.2
	MINIMAL ACESS	13	10.8	10.8	100.0
	Total	120	100.0	100.0	

Figure 7: Type Op Procedure.

Correlation between different FNAC and post op histopatholgies is explained in Figure 8 and 9.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	BENIGN	76	63.3	63.9	63.9
	ATYPIA	21	17.5	17.6	81.5
	MALIGNANT	22	18.3	18.5	100.0
	Total	119	99.2	100.0	
Missing	System	1	.8		
Total		120	100.0		

Figure 8: Fnac Results.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	BENIGN	85	70.8	71.4	71.4
	MALIGNANT FOLLICULAR	4	3.3	3.4	74.8
	PAPILLARY CANCER	29	24.2	24.4	99.2
	OTHER CANCERS	1	.8	.8	100.0
	Total	119	99.2	100.0	
Missing	System	1	.8		
Total		120	100.0		

Figure 9: Histopathology Results.

Pre op FNAC of patients having atypia of undetermined significance was compared with post operative histology which showed that out of all 120 patients only 21 had pre operative fnac finding of atypia and out of these 21 patient with pre op atypia only 13 (57.1 %) were found to have actual malignancy on post operative histopathology ,8 of them were papillary variant of thyroid cancer while 4 had follicular cancer 9/21 (42.9%) patients with atypia had benign histopathology ,shown in Figure 9-11.

			HISTOPATHOLOGY BENIGN	MALIGNANT FOLLICULAR	MALIGNANT PAPILLARY	OTHER MALIGNANCIES	Total
FNAC	BENIGN	Count	72	0	3	1	76
		% within FNAC	94.7%	0.0%	3.9%	1.3%	100.0%
	ATYPIA	Count	9	4	8	0	21
		% within FNAC	42.9%	19.0%	38.1%	0.0%	100.0%
	MALIGNANT	Count	4	0	17	0	21
		% within FNAC	19.0%	0.0%	81.0%	0.0%	100.0%
Total		Count	85	4	28	1	118
		% within FNAC	72.0%	3.4%	23.7%	0.8%	100.0%

Figure 10: FNAC * Histopathology Crosstabulation.

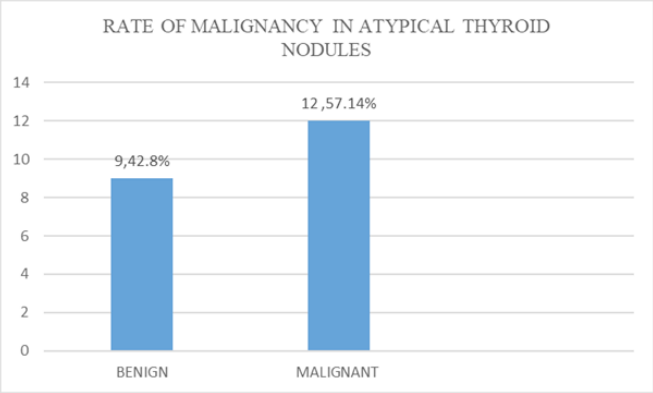

Figure 11: Rate of Malignancy in Atypical Thyroid Nodules.

We must highlight that we have only reviewed the cases submitted to surgical intervention. This would yield a malignancy risk closer to the upper bound estimate which might be a slight overestimation of the actual risk.

Result Statatics

Discussion

There is heterogenisity in prevalence, utilization, interpretation, and management of atypical thyroid nodules within and across different specialities [19]. There is controversy in using combination of different diagnostic tests ,biopsy practices,use of ultrasound and pathology reporting system and availability and utilization of frozen section .Although most of clinicians follow Americal thyroid association guide lines there is deviation from guidelines because management is individualized depending on availability of resources, patient's preferences as well as clinical and ultrasonic features [19]. Repeat FNAC is also not reliable as incidence of atypia on repeat cytology is 30% [5] leading to management challenge and leading back to square zero. Even if repeat FNAC comes as benign these patients need to have follow up and repeat ultrasound after 3-6 months and ultrasound finding of suspicious nodule will again require FNAC leading to wastage of resources and patient's anxiety along with management challenge for surgeons. If repeat FNAC is malignant patient anyways needs lobectomy after a delay of 3 months. Frozen section biopsy has sensitivity and specificity of 21-55 % and can easily miss carcinoma in atypical nodules so should not be done for atypical nodules [11,12].

Najah and Tresallet [20] concluded that frozen section contributed little to the diagnosis of undetermined thyroid nodules due to their low sensitivity and high false negative rates. They suggested that tumor capsular invasion, which is the hallmark to diagnose malignancy, could not be evaluated on FSs(frozen section), and was only possible on permanent sections. In fact, frozen section jeopardize the detection of capsular invasion because of the fragmentation of the specimen during the process [14].

Our histopathology department is not recommending to go for frozen section as the definitive histopathology is often different than frozen section diagnosis so we don't use it any more for atypia and further more follicular carcinoma still can be missed on frozen section biopsy so its risky to take decision on basis of frozen section. The rate of malignancy in atypical nodules in our study is 57.14% which is very high and based on these figures we recommend to go for diagnostic lobectomy for all patients having atypia of undetermined significance on FNAC in as institute specific approach is favored based on institute specific data. This rate might not be the true representative because of small sample size but since there is no institute specific data this can be used to carry out large studies in future to make the results more generalized .

Conclusion

Based on high rate of malignancy in atypical thyroid nodules as is evident from our study (57.14%) ,all patients presenting with atypia of undetermined significance should straight away be offered diagnostic lobectomy.

Although the rate of malignancy as per our study is very high another study with larger sample size can be conducted to further analyze the results and then to implement the guidelines.

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