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Cytological and Histopathological Evaluation of Thyroid Swellings with Special Reference to Agnor.

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ABSTRACT

Background: Disorders of the thyroid are exceedingly common in clinical practice and these include developmental, inflammatory, hyperplastic and neoplastic disorders. Generally, disorders of thyroid present as enlargement of gland which may be diffuse or nodular in the form of single nodule. Fine-needle aspiration of thyroid gland is now accepted as an important aid in the investigation of thyroid swellings. The ease and safety with which material can be obtained and the low cost of the technique ensues a place of fine-needle aspiration in the diagnostic armamentarium (Solomon, 1982). Fine-needle aspiration alone is not able to differentiate between follicular adenoma and follicular carcinoma. So, histopathological examination is the only tool to reach the final diagnosis. Interest now a days is focused to distinguish the non-neoplastic, benign and malignant neoplasms by counting argyrophillic nucleolar organizing regions (AgNOR). Nucleolar Organizing Regions are loops of DNA present within nucleolus (Crocker et. al., 1987) which encode for ribosomal RNA production (Smith et. al., 1988). The number and frequency of NORs per nucleus, may partly reflect cell ploidy (Giri et. al., 1989). Nucleolar organizing regions are readily demonstrated by the argyrophilia of their associated proteins, using the AgNOR technique (Egan et. al., 1992). The silver binding is attributed to acidic nonhistone nucleolar proteins which are referred to as Nucleolar Organizing Region Associated Proteins (NORAPs). With these considerations, the present study was undertaken with the following aims: 1.To evaluate the efficiency of fine-needle aspiration cytology in the diagnosis of thyroid lesions and to highlight it's limitations and diagnostic pitfalls. 2. To study Nucleolar Organizing Regions to differentiate benign and malignant lesions of thyroid. 3. To evaluate the correlation between histopathological/ cytological diagnosis and hormonal assay. **Methods:** The present study was conducted in the department of pathology Chintpurni Medical College, Bungal, Pathankot in collaboration with Puri diagnostic centre, PURI HOSPITAL, SUJANPUR. Total 863 cases of thyroid lesion were studied, out of which 796 cases were studied on fine needle aspiration smears and 191 cases on histology sections. Cyto-histological correlation was done 124 cases. Argyrophillic nucleolar organizing regions were studied by using silver colloidal staining technique in both cytology and histology. Along with this routine investigations such as hemoglobin estimation, blood sugar and serum cholesterol estimation and hormonal assay were also done. **Results:** In this study the cytological evaluation showed that the most frequent lesion were hyperplastic disorders (82.79%) followed by inflammatory disorders (11.3%), neoplastic disorders (4.9%), development disorders (0.88%).The age range of these patients was from 03-76 years and most of the patients were in the age group 20-39 years (59.79%) followed by age group 40-59 years (21.57%) and females significantly outnumbered the males with a M:F ratio of 1:6.2.Argyrophillic Nucleolar Organising Regions were demonstrated and counted in thyroid gland lesions in 120 cases of fine needle aspiration smears and 36 cases of histopathological sections.In the non-neoplastic lesions of thyroid gland single dot/cell was observed in more number of cells whereas 2-4dots/cell were counted in more number of cells in follicular neoplasm. In malignant neoplastic lesions, the number of dots/cell was>4 in more number of cells. Sensitivity of fine-needle aspiration cytology in the diagnosis of thyroid swellings came out to be 90.62%; specificity 98.91%; predictive value 96.66%; and efficiency 96.77%. **Conclusion:** Based on the observation recorded from the present study, the following conclusions were drawn:- a) Most patients were in the age group 20-49 years of age with a M:F ratio 1:6.2. b) Levels of T3 and T4 were found to be decreased in colloid goitre and increased in cases of toxic goitre. C) Most frequent lesions of thyroid were hyperplastic disorders (82.79%) followed by inflammatory disorders (11.4%), neoplastic disorders (4.96%) and development disorders (0.88%). d) The technique of fine-needle aspiration cytology (FNAC) was found to be simple, quick, economical and with a sensitivity of 90.62%; specificity 98.91%; predictive value 96.66%; and efficiency 96.77%. e) Although fine-needle aspiration is the first investigation of choice but histopathological examination remains the corner stone to make the final diagnosis in certain cases. F) The AgNOR count was found to be of great significance in differentiating benign (goitre, thyroiditis and adenomas) and malignant lesions (thyroid carcinomas). In benign lesions the NORs were closely clustered to from compact, round, central and uniform argyrophillic structures which were less in number (usually less than two). In malignant lesions the NORs were dispered, tiny, irregular in size and shape and multiple in number (usually more than five).

Keywords: Thyroid disorders, Fine needle aspiration cytology(FNAC), Argyrophillic nucleolar organizing regions (AgNOR).

INTRODUCTION

Thyroid gland is the largest of all endocrine glands. It consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx.

The thyroid median anlage develops from the endoderm of the pharyngeal floor as a medial invagination that rapidly proliferates caudally, remaining connected with the oral cavity throw a thin channel, the thyroglossal duct which is later obliterated. Remnants of the thyroglossal duct are identifiable as the pyramidal lobe in approximately 40% adults (Sugiyama, 1971).

Disorders of the thyroid are exceedingly common in clinical practice and these include developmental, inflammatory, hyperplastic and neoplastic disorders. Development disorders include persistence of residual thyroid tissue and thyroglossal cyst. Inflammatory disorders include various thyroiditis as acute suppurative thyroiditis, granulomatous, Hashimoto's, lymphocytic, Riedel's and others. In hyperplastic disorders of thyroid either diffuse or nodular hyperplasia of gland occur leading to clinically detectable enlargement of thyroid known as goitre, these include Dyshormonogenetic, iodine deficient and sporadic goitre. Neoplastic disorders of thyroid may be benign or malignant, majority of the tumours are benign. Malignant tumours of the thyroid have a strong predilection for women (60%-70%). They run the gamut of behavior from extremely indolent and highly curable papillary carcinoma to rapidly growing and inexorably fatal anaplastic carcinomas.

Generally, disorders of thyroid present as enlargement of gland, which may be diffuse or nodular in the form of single nodule.

Fine-needle aspiration of thyroid gland is now accepted as an important aid in the investigation of thyroid swellings. The ease and safety with which material can be obtained and the low cost of the technique ensues a place of fine-needle aspiration in the diagnostic armamentarium (Solomon, 1982).

Fine-needle aspiration is particularly useful in the screening and selection of the patients with thyroid swelling for surgery (Atkinson, 1988). It is used to distinguish between Hashimoto's thyroiditis and simple colloid goitre in diffuse thyroid enlargements. In clinically obvious malignancies a distinction between anaplastic carcinoma and differentiated carcinoma can be of crucial importance in deciding the therapy. A more critical analysis of the cost effectiveness of fine-needle aspiration as a screening method for selecting cases for surgery has been undertaken (Silverman et. al., 1986).

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It would be unrealistic to assume that cytological diagnosis of thyroid swelling is simple and absolutely infallible. Although cancer cells of thyroid are abnormal, they often lack fully developed malignant cytological features (Suen, 1983). While reviewing the cases with suspicious cytological findings, Gharib et. al., (1984), concluded that 20% of the cases will have suspicious cytological findings and of these, 20% may be malignant. False negative as well false positive cyto-diagnosis are encountered from time to time.

Fine-needle aspiration alone is not able to differentiate between follicular adenoma and follicular carcinoma. It is recommended that both these tumours be put under the blanket heading of "Follicular neoplasms" (Lowhagen, 1984). So, histopathological examination is the only tool to reach the final diagnosis.

Hormonal-assays _including T3, T4 and TSH) are the important supportive measures, which help in diagnosis and follow-up of the cases.

Interest now a days is focused to distinguish the non-neoplastic, benign and malignant neoplasms by counting argyrophillic nucleolar organizing regions (AgNOR). Nucleolar Organizing Regions are loops of DNA present within nucleolus (Crocker et. al., 1987) which encode for ribosomal RNA production (Smith et.al., 1988). The number and frequency of NORs per nucleus, may partly reflect cell ploidy (Giri et. al., 1989). Nucleolar organizing regions are readily demonstrated by the argyrophilia of their associated proteins, using the AgNOR technique (Egan et. al., 1992). The silver binding is attributed to acidic nonhistone nucleolar proteins which are referred to as Nucleolar Organizing Region Associated Proteins (NORAPs)

With these considerations, the present study was undertaken with the following aims:

1. To evaluate the efficiency of fine-needle aspiration cytology in the diagnosis of thyroid lesions and to highlight it's limitations and diagnostic pitfalls.
2. To study Nucleolar Organizing Regions to differentiate benign and malignant lesions of thyroid.
3. To evaluate the correlation between histopathological/ cytological diagnosis and hormonal assay.

MATERIALS AND METHODS

The present study was conducted to evaluate the correlation of fine needle aspiration cytology with histopathology in the diagnosis of thyroid lesions and to study Nucleolar Organizing Regions (AgNOR count) to differentiate benign and malignant lesions of thyroid in the Department of Pathology, Chintpurni Medical College, Bungal, Pathankot in collaboration with Puri diagnostic centre, PURI HOSPITAL, SUJANPUR. Study was done on the patients with thyroid swellings attending Surgery/ENT/Medicine departments of both hospitals.

After the proper workup of the patients, including detailed clinical history, examination and investigations, fine-needle aspiration was done and obtained smears were examined. Cytological diagnosis was correlated with the histopathology wherever possible.

Clinical History

A detailed clinical history was taken with special reference to features of toxicity and duration of swelling, progression, presence of pain and tenderness, anxiety, palpitations, diarrhea, constipation.

Investigations

Haemoglobin estimation (By Sahli's method and cyanmethaemoglobin method).
Estimation of blood sugar (By Chem-7, glucose test kit using GOD-POD method).
Estimation of cholesterol (By Chem-7, cholesterol test kit using Wybenger and Pileggi-one step method).
Estimation of T3, T4 and TSH: Hormonal assay was done by LUMAX, Based on chemiluminiscence.

Fine-Needle Aspiration Cytology

Equipments

1. 20 c.c. disposable syringe.
2. 23 gauze disposable needle.
3. Sterile gauge pieces, cotton and spirit.
4. Coplin jar.
5. 95% methanol.
6. Glass slides, spreader and cover slips.
7. Tincture benzoin.

Aspiration procedure

Patient was made to lie in supine position with relaxed neck muscles. After local preparation with spirit, the swelling was palpated by index and middle fingers of left hand, by standing on the side opposite to that of the nodule. Now the needle was pushed into the swelling by the right hand holding the piston. Once the needle is in the swelling suction was done by retraction of the plunger of the syringe. Needle was then moved back and forth in different directions, inside the swelling, to collect small fragments of tissue. Suction was released and then the needle was taken out of the syringe which was then filled with air. Needle was reattached and the air of the syringe was used to expel the sample from the needle to a glass slide. Ideal amount from a solid lesion is 1-2 drops. A smear is immediately made before the material clots as cellular details and architecture are lost if cells are trapped in clotted blood. In case of cystic lesion material was collected in test tube and smear was prepared from centrifused sediment.
After this, few of the smears were air dried and some were fixed in the 95% methanol solution at least for 10 minutes and following stains were used:

1. Leishmann's stain
2. May-Grunwald Giemsa stain (MGG)
3. Papanicolaou stain

Histological Studies

Received tissue was fixed in 10% formalin for histopathological examination. After fixation each gland was grossly palpated for suspicious nodules and gross examination regarding shape, colour, consistency and size was done. Each thyroid tissue was sectioned at 1 cm distance and on an average 4-5 tissue pieces were processed for paraffin embedding.
Sections of 4-5 micron in thickness were cut from paraffin blocks and subjected to following:
1. Haematoxylin and eosin staining (Clayden, 1971).
2. AgNOR staining (Chiu et al., 1988).

Improved Silver Techniques For Staining Of Nors (Chiu et. al., 1989)
Solutions required
I. Silver colloid solution
-2gm/dl gelatin dissolved in 1 g/dl aqueous formic acid.
-The above mentioned solution was mixed just before staining in a ratio of 1:2 volumes
with 20gm/dl aqueous silver nitrate solution.
II. Celloidin solution
-Celloidin 1 gm
-Ethanol 50 ml
-Ether 40 ml

Procedure

- Sections were dewaxed in xylene and transferred to absolute alcohol.
- Treated with acetic acid ethanol mixture (1:3) for 5 minutes.
- Then rinsed with absolute alcohol.
- Celloidin was then poured over the sections for one minutes.
- Excess celloidin was drained off and then 10% ethanol was poured on to harden the celloidin.
- Washed thoroughly with deionised water.
- Then freshly prepared silver colloid solution was poured on the sections and incubated at 45˚c for 30-40 minutes.
- Sections were washed with deionized water.
- Dehydrated by passing through 3-4 baths of absolute alcohol.
- Cleaned in xylene.
- Mounted in DPX.

RESULTS

AgNORs were visualized as dark brown to black dots within the nuclei against the yellowish background. The impurities retained in the colloidin are focused at different levels and therefore do not affect the interpretation.

Counting procedure

The number of AgNORs present in each nuclei were counted using an oil immersion lens. Counts were made in 100 cells and results expressed as the mean number of NORs per nucleus. To avoid biased results, counts were done by 2 different observers.

Sensitivity

It is the ability of the test to correctly identify the true positives, i.e. it gives very few false negative results.

Specificity

It is the ability of the test to correctly identify the true negatives, i.e. it gives very few false positive results.

Predictive value

It reflects the diagnostic power of the test. It expresses true positives as a proportion of all positives.

Efficiency of the test

It represents the overall true diagnosis (true positive and true negative) out of total cases. The relationship of these measures are shown below:

Result	True diagnosis malignant	Benign	
positive	a (True positive)	b (Falsa positive)	(a+b)
Negative	c (Falsa positive)	d (True Negative)	(c+d)
Total	a+c	b+d	a+b+c+d

Sensitivity	a / a+c
Specificity	d / b+d
Predictive	a / a+b
Efficiency	a+d / A+b+c+d

The present study was conducted in the department of Pathology, Chintpurni Medical College, Bungal, Pathankot in collaboration with Puri diagnostic centre, PURI HOSPITAL, SUJANPUR. The cases consisted of patients who came to the outpatient departments of Surgery/ENT/Medicine of both hospitals.

Total number of cases studied was eight hundred and sixty three, in which fine-needle aspiration was done in seven hundred ninety six cases, histopathological examination alone in sixty-seven cases. Out of seven hundred ninety six cytologically diagnosed cases, hundred twenty-four cases were also examined histologically.

Study of Cytologically Diagnosed Cases

The age of these patients ranged from three to seventy-six years. The youngest patient in this study was three years old and the oldest patient was seventy-six years old. The maximum number of patients (29.79%) belonged to age group 20-29 years of life, followed by age group 30-39 years (28.66%). Minimum number of the patients were in the age group of >70 years (0.52%) and 0-9 years (1.27%).

Table 1: Distribution of Thyroid Swelling Cases According To Age And Sex.

Age group (in years)	Number of cases				Total number of cases	Percentage (%)
	Female	%	Male	%		
0-9	7	0.89	3	0.38	10	1.27
10-19	109	13.69	14	1.76	123	15.45
20-29	213	26.77	24	3.02	237	29.79
30-39	198	24.88	30	3.78	228	28.66
40-49	94	11.81	6	0.76	100	12.57
50-59	51	6.42	23	2.89	74	9.31
60-69	12	1.52	8	0.91	20	2.43
>70	2	0.26	2	0.26	4	0.52
Total	686	86.24	110	13.76	796	100.00

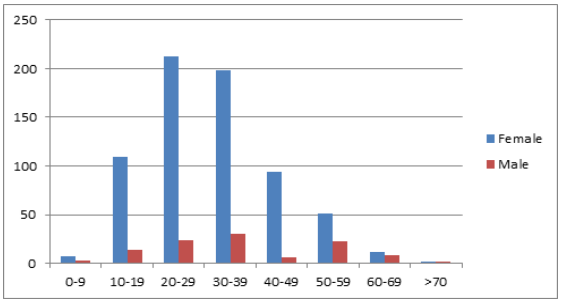

Figure 1: Distribution Of Cases According To Age And Sex

There was definite female predominance (686 females and 110 males) with male to female ratio 1:6.2. majority of the females (66.23%) were below forty years and majority of the males (8.94%) were below forty years of age.

The range of duration was very long, between less than 6 months to 30 years, but majority of the cases (63.61%) presented with duration ranging from 0-1 year.

Table 2: Distribution Of Thyroid Swellings According To Duration.

Duration of swelling	Number of cases	Percentage (%)
0-6 months	402	50.55
6 months – 1 years	104	13.06
1 - 1 ½ years	30	03.76
1½ – 2 years	71	08.91
2 – 3 years	31	03.89
3 – 4 years	73	09.17
4 – 6 years	16	02.01
6 – 8 years	12	01.50
8 – 10 years	06	0.75
10 – 30 years	51	06.40
Total	796	100.00

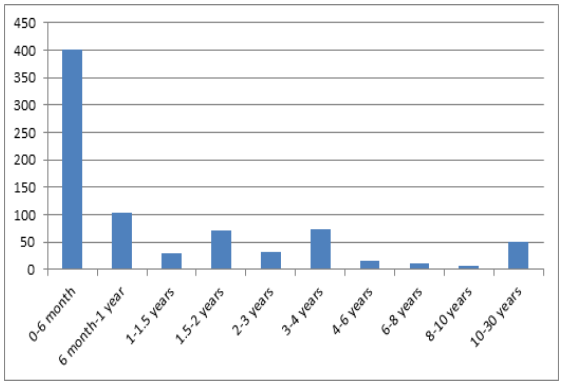

Figure 2: Distribution Of Thyroid Swellings According To Duration

Swelling in front of neck was the most common presenting feature seen in all patients. Other symptoms were anxiety, nervousness (183 patients- 23%), palpitation (191 patients- 24%), heat intolerance (193 patients- 24.24%), cold intolerance (215 patients- 27%), excessive sweating (120 patients- 15%), diarrhea (103 patients- 13%), and constipation (135 patient- 17%). Signs of toxicity such as tremors and tachycardia were seen in 88 (11.10%) and 137 (17.21%) respectively. Change in voice (96 patients- 12%), swelling increasing in size and pain was observed in 175 (21.98%) and 122 (15.33%) patients respectively.

Less common presenting symptoms were loss of appetite, increase in appetite, loss of weight and least common presenting symptoms was bony pain, seen in six cases only.

The hyperplastic disorders were the commonest (82.79%) of all the thyroid disorders, followed by inflammatory (11.30%) and neoplastic disorders (4.90%), developmental disorders (0.88%) and others (0.13).

[Table 3] shows the frequency of various thyroid lesions. As it is evident from the table that colloid goitre was the most common benign lesion seen in 292(36.68%) patients, which was followed by, colloid goitre with cystic chance, toxic goitre, nodular colloid goitre and thyroiditis. Of the total 90 patients (11.31%) of thyroiditis, lymphocytic thyroiditis was seen in 43 (5.40%) patients, Hashimoto's thyroiditis in 28(3.52%) patients, granulomatous thyroiditis in 15(1.88%) patients and 4(0.50%) cases of suppurative thyroiditis were seen. Next in order were follicular neoplasms and malignant tumours. Out of these malignant tumours papillary carcinoma was the commonest. Of the 16 cases of papillary carcinoma, there was only one case of clear cell variety. Other malignant tumours were medullary carcinoma, poorly differentiated carcinoma and anaplastic carcinoma.

Seven cases (0.88%) of thyroglossal cyst were seen and one case of neurilemmoma thyroid, a very rare mesenchymal tumour of thyroid was also found.

Table 3: Distribution Of Cases According To Cytological Diagnosis

Sr. No.	Cytological diagnosis	Number of cases			
		Female	Male	Total	%
1	Thyroglossal	5	2	7	0.88
2	Colloid goitre	249	43	292	36.68
3	Nodular colloid goitre	72	10	82	10.30
4	Colloid goitre with cystic change	119	19	138	17.34
5	Nodular colloid goitre with cystic change	17	3	20	2.52
6	Toxic colloid goitre	113	14	127	15.95
7	Suppurative thyroiditis	3	1	4	0.50
8	Granulomatous thyroiditis	13	2	15	1.88
9	Hashimoto's thyroiditis	24	4	28	3.52
10	Lymphocytic thyroiditis	38	5	43	5.40
11	Follicular neoplasm	8	3	11	1.38
12	Hurthle cell neoplasm	3	-	3	0.38
13	Papillary carcinoma	14	2	16	2.01
14	Medullary carcinoma	4	1	5	0.63
15	Poorly diff. carcinoma	1	1	2	0.25
16	Anaplastic carcinoma	2	-	2	0.25
17	Neurilemmoma thyroid	1	-	1	0.13
		686	110	796	100.00

Table 4: Distribution Of Thyroid Swelling Cases According To Age And Sex

Age group (in years)	Number of cases				Total number of cases	Percentage (%)
	Female	%	Male	%		
0-9	02	1.04	01	0.52	03	1.57
10-19	24	12.56	04	2.09	28	14.66
20-29	51	26.70	07	3.66	58	30.37
30-39	45	23.56	09	4.71	54	28.27
40-49	19	9.94	03	1.57	22	11.52
50-59	12	6.28	06	3.14	18	9.43
60-69	03	1.57	03	1.57	06	3.14
>70	01	0.52	01	0.52	02	1.04
Total	157	82.19	34	17.81	191	100.00

All the hyperplastic disorders, colloid goitre, nodular colloid goitre, colloid goitre with cystic change, nodular colloid goitre with cystic change and colloid goitre with toxic change were common in the age group 20-39years.

While suppurative thyroiditis was common at the two extremes of the age. Lymphocytic thyroiditis

was more common in the age group 20-39 years while Hashimoto's thyroiditis was more common in the age group 30-49 years.

Papillary carcinoma were common in the age group 40-59 years , while medullary carcinoma and poorly differentiated carcinomas were more common in the age group 50-69 years.

The table-4 shows that all thyroid lesions were more common in the females with a F:M ratio of 4.6:1. Thyroid disorders were most common in the age group 20-29 years (30.37%) followed by 30-39 years (28.27%), 10-19 years (14.66%) and 40-49 years (11.52%).

The [Table 5] shows that hyperplastic disorders were most common (57.06%), followed by neoplastic disorders (25.14%), inflammatory disorders (15.71%) and others (0.52%).

Table 5: Distribution Of Thyroid Lesions According To Type Of Disorder

S. N.	Type of disorder	Female patients		Male patients		Total cases	%
		Number	%	Number	%		
1.	Development disorder	02	1.04	01	0.52	03	1.57
2.	Hyperplasic disorder	94	49.21	15	7.85	109	57.06
3.	Inflammatory disorder	23	12.04	07	3.66	30	15.71
4.	Neoplastic disorder	37	19.37	11	5.75	48	25.14
5.	Others	01	0.52	-	-	01	0.52
	Total	157	82.19	34	17.81	191	100.00

The [Table 6] shows that there was a clear cut female preponderance in cases of follicular adenoma and hurtle cell adenoma and both were common in age group 30-49 years.

Table 6: Distribution of benign tomours according to age and sex

Age group	Follicular adenoma						Hurthle cell adenoma					
	F	%	M	%	T	%	F	%	M	%	T	%
0-9	-	-	-	-	-	-	-	-	-	-	-	-
10-19	-	-	-	-	-	-	-	-	-	-	-	-
20-29	-	-	1	5.8	1	5.8	-	-	-	-	-	-
30-39	6	35.3	2	11.7	8	47.0	2	50	1	25	3	75
40-49	4	23.5	1	5.8	5	29.4	1	25	-	-	1	25
50-59	2	11.7	-	-	2	11.7	-	-	-	-	-	-
60-69	1	5.8	-	-	1	5.8	-	-	-	-	-	-
≥70	-	-	-	-	-	-	-	-	-	-	-	-
Total	13	76.4	4	23.6	17	100	3	75	21	25	4	100

As evident from the [Table 7] that thyroid carcinomas were more common in females (77.7%) as compared to males (22.3%).

Table 7: Sex Wise Distribution Of Malignant Tumours

S. N.	Type of carcinoma	Female patients		Male patients		Total	%
		Number	%	Number	%		
1.	Papillary carcinoma	11	40.7	03	11.1	14	51.8
2.	Follicular carcinoma	05	18.5	01	3.7	06	22.3
3.	Medullary carcinoma	02	7.4	01	3.7	03	11.1
4.	Poorly diff. carcinoma	02	7.4	-	-	02	7.4
5.	Undiff./anaplastic carcinoma	01	3.7	01	3.7	02	7.4
	Total	21	77.7	06	22.3	27	100.00

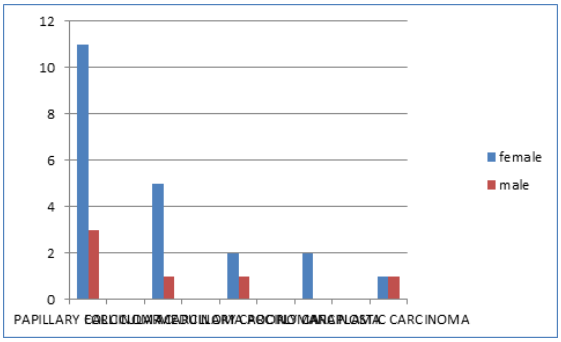

Figure 3: Sex Wise Distribution Of Malignant Tumours

Majority of the patients presented with anemia of mild grade 168 (46.1%), followed by moderate 116 (32.2%) and severe anemia in 72 (20.5%) patients.

Blood sugar above 120 mg% was recorded in 75 patients of toxic goitre, 15 patients colloid goitre, 10 patients of thyroiditis and 10 patients of tumours.

Serum cholesterol level above normal limit was recorded in 40 patients of colloid goitre and 25 patients of thyroiditis. Serum cholesterol levels were below normal limit in 35 patients of toxic goitre and 30 patients of tumours.

T3 level above 187ng/dl was recorded in 08 patients of colloid goitre, 84 patients of toxic goitre. T3 level was within normal limit in 28 patients of toxic goitre indicating they were non toxic.

T4 level above 12ug/dl was recorded in 04 patients of colloid goitre and 64 patients of toxic goitre. Highest value recorded was 18.3ug/dl in case of toxic goitre. Lowest value recorded was 4.0g/dl in case of thyroiditis.

Highest TSH value was in a patient of thyroiditis, lowest 0.6iu/ltr. was observed in a case of toxic goitre.

T3,T4, TSH hormone assay in case of colloid goitre, correlated with cytological findings in 112 cases out

of 120 cases in which hormone assay was done. Out of 112 cases of toxic goitre hormone levels were consistent in 84 cases, 28 cases on Radioimmunoassay were non-toxic.

Table 8: Correlation of Cytological Finding With T3, T4 And Tsh Values

S.N.	Cytological diagnosis	T3, T4, TSH	Consistent	Inconsistent	Result
1.	Colloid goitre	120	112	08	Toxic
2.	Toxic goitre	112	84	28	Non-toxic
3.	Thyroiditis	24	20	04	

Agnors In Thyroid Lesions

Argyrophillic Nucleolar Organizing Regions were demonstrated and counted in thyroid gland lesions in 120 cases of the fine needle aspiration smears and 36 cases of histopathological sections.

AgNOR counts were performed in oil immersion (x100) in multiple areas on histological sections and fine needle aspiration smears. AgNORs were counted in a minimum 100 cell nuclei each in the epithelium. Inflammatory cells were not counted. Mean AgNOR counts/nucleus were then determined in each case and the range of AgNOR values and mean ±SD computed. The AgNORs that were in aggregates, morphologically inseparable or clustered, were recorded as one, the precise number with in the aggregate could not be counted.

In the non-neoplastic lesions of thyroid gland single dot/cell was observed in more number of cells whereas 2-4dots/cell were counted in more number of cells in follicular neoplasm. In malignant neoplastic lesions, the number of dots/cell was>4 in more number of cells.

Table 9: Agnor Count of Cells in Different Thyroid Lesions On Cytology

S.N.	Thyroid gland lesion	No & % of cells having AgNOR		
		Single dot/ cell % of cells	2-4dots/ cell % of cells	>4dots/ cell % of cells
1	Colloid goiter	78	22	-
2	Nodular colloid goiter	73	27	-
3	Toxic colloid goiter	77	23	-
4	Hashimoto's thyroiditis	68	30	02
5	Lymphocytic thyroiditis	70	30	-
6	Granulomatous thyroiditis	70	29	-
7	Follicular neoplasm	38	51	11
8	Papillary carcinoma	17	21	62
9	Medullary carcinoma	11	21	68
10	Poorly diff. carcinoma	10	26	64
11	Undiff./anaplastic carcinoma	07	24	69

Table 10: Agnor Counts In Different Thyroid Lesions on Cytology

S.N.	Thyroid lesions	Mean AgNOR count/nucleus	S.D.
1	Colloid goiter	1.37	0.53
2	Nodular colloid goiter	1.41	0.68
3	Toxic colloid goiter	1.36	0.24
4	Hashimoto's thyroiditis	1.47	0.92
5	Lymphocytic thyroiditis	1.52	0.81
6	Granulomatous thyroiditis	1.46	0.69
7	Follicular neoplasm	3.46	0.48
8	Papillary carcinoma	5.23	1.03
9	Medullary carcinoma	5.69	0.94
10	Poorly diff. carcinoma	6.24	0.64
11	Undiff./anaplastic carcinoma	6.91	0.72

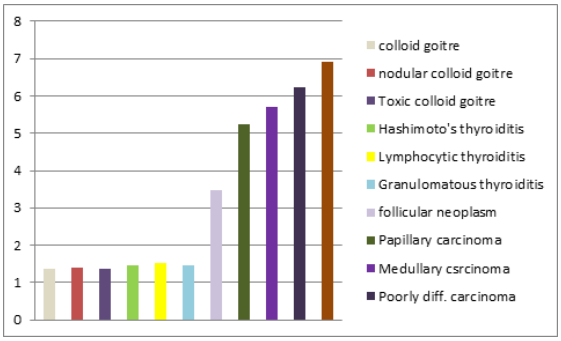

Figure 4: Agnor Counts In Different Thyroid Lesions On Cytology

Table 11: Agnor Counts In Different Thyroid Lesions on Histopathology

S.N.	Thyroid lesions	Mean AgNOR count/nucleus	S.D.
1	Colloid goiter	1.41	0.24
2	Nodular colloid goiter	1.39	0.43
3	Toxic colloid goiter	1.53	0.58
4	Hashimoto's thyroiditis	1.48	0.22
5	Lymphocytic thyroiditis	1.54	0.63
6	Granulomatous thyroiditis	1.57	0.55
7	Follicular neoplasm- benign Malignant	2.72 4.67	1.21 0.74
8	Papillary carcinoma	4.81	0.82
9	Medullary carcinoma	5.72	0.69
10	Poorly diff. carcinoma	6.81	0.81
11	Undiff./anaplastic carcinoma	6.43	1.08

As evident from the table-9 that the AgNOR count differed significantly in malignant group from that in the benign and non-neoplastic group P=0.015(<0.05).

In samples from non-neoplastic and benign lesions the NORs were closely clustered to form one or two compact, round, uniform argyrophillic structure which were more or less central in position. This picture was in thyroiditis, follicular adenoma. The mean AgNOR counts among the non-neoplastic lesions were least in colloid goitre (1.37) followed by nodular colloid goitre (1.41) and granulomatous thyroiditis (1.46).

In malignant lesions the NORs were dispersed in the nucleus. Their number, size, shape and distribution

varied according to the malignancy of the tumour. With the increasing grade of malignancy they appeared as tiny, exceedingly numerous black dots, that were more, irregular in size and shape. In papillary carcinoma the mean AgNOR count was 5.23 followed by medullary carcinoma (5.69), poorly differentiated carcinoma (6.28) and undifferentiated/anaplastic carcinoma (6.91).

The AgNOR count differed significantly in benign and malignant lesions. In follicular adenoma (2.72) it was midway between non-neoplastic and malignant lesions but in follicular carcinoma it is clearly high (4.67) as seen in other carcinomas of thyroid gland.

Table 12: Cyto-Histological Correlation in Thyroid Lesions

S. N.	Cytological diagnosis	Cytology	Histopathology Cons.	Incons.	False Neg.	False Posi.	Accuracy
1	Thyroglossal	03	03	-	-	-	100.0 %
2	Colloid goiter	24	24	-	-	-	100.0 %
3	Nodular goiter	36	33	03	03	-	91.67 %
4	Colloid goiter with cystic change	15	15	-	-	-	100.0 %
5	Toxic goiter	09	09	-	-	-	100.0 %
6	Thyroiditis	07	07	-	-	-	100.0 %
7	Follicular Adenoma Carcinoma	03 05	02 05	01 -	- -	01 -	66.67 % 100.0 5
8	Hurtle neoplasm	03	03	-	-	-	100.0 5
9	Papillary carcinoma	12	12	-	-	-	100.0 %
10	Medullary carcinoma	03	03	-	-	-	100.0 %
11	Poorly diff carcinoma	01	01	-	-	-	100.0 %
12	Undiff./anaplastic carcinoma	02	02	-	-	-	100.0 %
13	Neurilemmoma	01	01	-	-	-	100.0 %
	Total	124	120	04	03	01	

As evident from the [Table 12] that histopathology specimens were available only in 124 cases out of 796 cases of thyroid lesions.

Histopathology was available in 3 cases of thyroglossal cyst and they were all consistent with the cytological finding.

Histopathology was available in 24 cases of colloid goitre and they were all consistent with the cytological finding.

Histopathological was available in 36 cases of nodular colloid goitre and 33 were consistent with the cytological finding whereas 3 were inconsistent with cytological findings. Three cases on fine needle aspiration cytology were diagnosed as nodular colloid goitre and on histopathology one turned out to be a case of papillary carcinoma and two cases of follicular carcinomas.

One case on fine needle aspiration was diagnosed as follicular adenoma and on histopathology it turned out to be a case of colloid nodular goitre.

Findings were consistent in cases of toxic goitre, thyroiditis and in all other benign and malignant tumours as papillary carcinoma, medullary carcinoma, poorly differertiated carcinoma and undifferentiated/anaplastic carcinoma.

Relationship of Fine Needle Aspiration Cytology and Results of Final Accurate Diagnosis

	True Diagnosis		Total
	Malignant	Nonmalignant	
Positive	A (True positive) 29	B (False positive) 01	(a+b) 30
Negative	C (False negative) 03	D (True negative) 91	C+d 94
Total	a+c 32	b+d 92	a+b+c+d 124

$$\text{Sensitivity} = \frac{a}{a+c} = \frac{29}{32} = 90.62\%$$

$$\text{Specificity} = \frac{d}{b+d} = \frac{91}{92} = 98.91\%$$

$$\text{Predictive value} = \frac{a}{a+b} = \frac{29}{30} = 96.66\%$$

$$\text{Efficiency} = \frac{a+d}{a+b+c+d} = \frac{29+91}{29+1+3+91} = \frac{120}{124} = 96.77\%$$

Sensitivity of this procedure in this series was 90.62%; Specificity was 98.91%; Predictive value was 96.66%; and Efficiency was 96.77%.

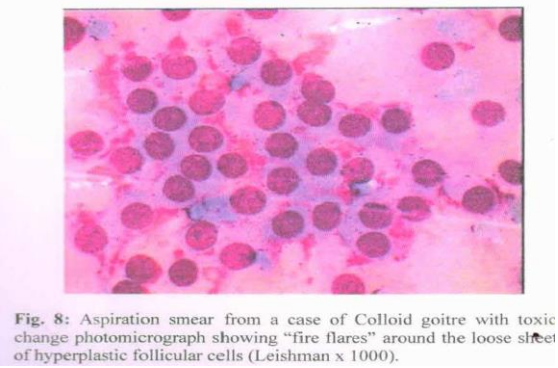

Fig. 8: Aspiration smear from a case of Colloid goitre with toxic change photomicrograph showing "fire flares" around the loose sheet of hyperplastic follicular cells (Leishman x 1000).

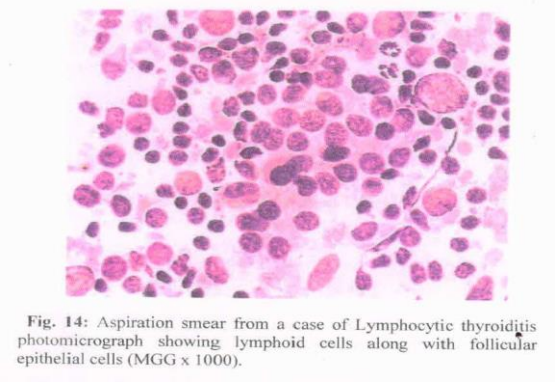

Fig. 14: Aspiration smear from a case of Lymphocytic thyroiditis photomicrograph showing lymphoid cells along with follicular epithelial cells (MGG x 1000).

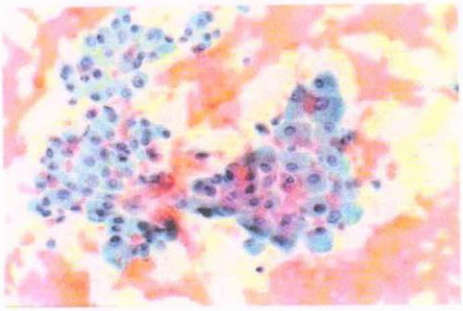

Fig. 19: Aspiration smear from a case of Oxyphil (Hurthle cell) adenoma photomicrograph showing sheets of Oxyphil cells (Papanicolaou x 400).

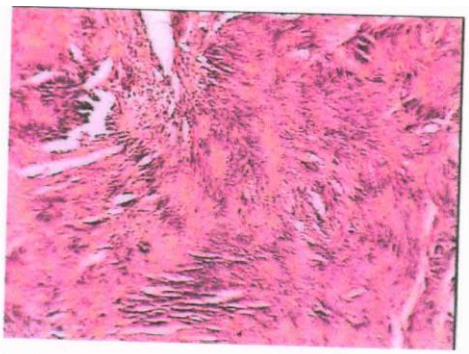

Fig. 51: Tissue section from a case of Neurilemmoma thyroid showing Verocay bodies (H & E x 400).

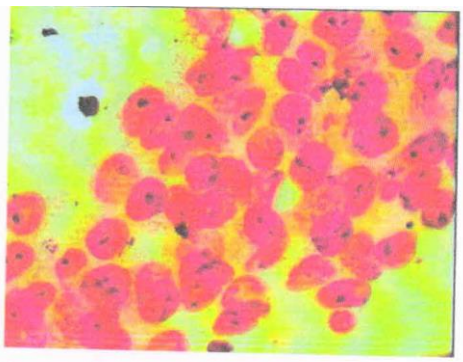

Fig. 54: Aspiration smear from a case of Hashimoto's thyroiditis photomicrograph showing one to two compact, round dots per cell (AgNOR stain x 1000).

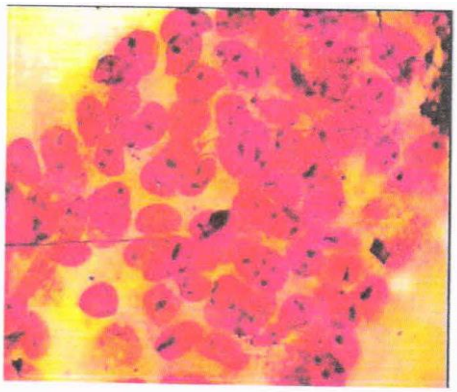

Fig. 58: Aspiration smear from a case of Papillary carcinoma photomicrograph showing five to six tiny, irregular, peripheral dots per cell (AgNOR stain x 1000).

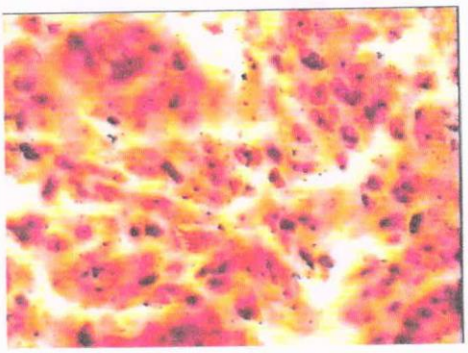

Fig. 62: Section from a case of Medullary carcinoma showing five to seven tiny, irregular, peripheral dots per cell (AgNOR stain x 1000).

DISCUSSION

One can never feel quite sure regarding the nature of thyroid swellings without a biopsy but for the practical reasons excision biopsy is not always possible. These words definitely set forth the importance of technique mentioned.

The study consists of 9028 patients presented with complaints related to thyroid in the surgery, ENT, Medicine and Human metabolism and endocrinology OPDs. FNAC was done in 813 patients. Seventeen cases were excluded from study due to scanty material on aspiration. Histopathology could be done in 191 cases. T3, T4, TSH hormone assay was done in 234 patients. Results of cytological diagnosis were correlated with histopathology in 124 patients.

In the present study, the age of patients varied from 3 to 76 years. The youngest patient was 3 year old and oldest patient was of 65 years. The maximum number of the cases fell between 21-40 year (63.8%) while others had reported the maximum number of cases in 30-50 years age group (Kumar Ahuja, Chattopadhyay, 1992).

In this study range of duration was 6 days to 30 years. Majority of the patient presented within duration of 0-1 year. Several patients with thyroid malignancy had history of more than 3 years (Davidson's, 1994 and Bailey and loves 1995).

Hyperthyroidism patient had symptoms for at least 6 months before presentation there is great individual variation. Initial presentation may be palpitation, diarrhea, weight loss, sign of toxicity, tachycardia, tremors, lid retraction, exophthalmos. Features of hypothyroidism such as weight gain, cold intolerance, hoarseness of voice, constipation have also been mentioned in various textbooks (Davidson's, principles and practice of medicine 16th ED. 1994; Bailey and loves short practice of surgery, 1995).

Majority of the patients presented with anemia of mild grade 168 (46.1%) followed by moderate 116 (32.2%) and severe anemia in 72 (20.5%). The degree of anemia is mild to moderate with a hemoglobin concentration rarely less than 8-9 g/dl.

Although normochromic normocytic anemia must be considered the characteristic form of anemia of hypothyroidism. The most frequent type of anemia observed is a microcytic hypochromic anemia caused by iron deficiency (Bommford, 1938; Larsson, 1967). In hypothyroid women menorrhagia is a frequent complication, and may explain adequately the lack of iron.

In present study, the diagnostic yield was 97.9% which is similar to reported in other series (Collins and wong 1984; Motitch Back, Dreismen, Gottlieb and Boey, Hsu 1984, Parker 1984, AI Sayer, Krukowsk; Wiltiam and Matheson, 1985; Leontsini, Economy, 2003).

The general diagnostic yield in the literature ranges from 90-97% (Gershengorn et. al., 1977; Friedman, Shimaoka, 1978; Boey, Hsu, Collins et. al., 1984 Molitch, Beck et. al., 1998 & Stiarma et. al., 2003).

The minimal criteria for the suitability of the smear for the diagnosis of a benign lesion have been made (Goellner, Gharib, Grant, Johnson, 1987 and Hamburger, Hussain, Nishiyamar et. al., 1989) which suggested at least five or six clusters of benign cells in several slides as reasonable minimal criteria, in addition to abundant colloid to the requirement for the unequivocal diagnosis of benign colloid nodule. Hall et. al., reported high accuracy rate for diagnosis using FNAC, but only if unsatisfactory smears were excluded from study.

In present study 758 (94.5%) were benign lesions, 8 (1.38%) follicular neoplasia and 26 (4.32%) malignant whereas sirpal 1996) reported 96.35% benign lesion, Hussm et. al., (1998) reported 92% benign and 85 malignant lesions. Of the 796 cytologically diagnosed thyroid swellings colloid goitre were 292 (36.68%) colloid nodular goitre 82 (10.30%), colloid goitre with cystic changes 138 (17.34%) colloid nodule goitre cystic change 20 (2.52%), Toxic goitre 127 (15.95%), thyroiditis 90 (11.345), follicular neoplasia 11 (1.38%) and malignant lesion were 26 (5.5%).

Toxic goitre were 127 (15.95%) diagnosed on cytological finding were correlated with T3, T4, TSH radio immune assay. This is comparable to the results of the studies done by Lowhagen et. al., (19930. Lowhagen studied 100 patients and found colloid goitre 41%, colloid goitre with cystic change in 18%, nodular colloid goitre 11%, thyroiditis 12%, follicular neoplasm 2% and malignant lesions 6%.

Fine needle aspiration biopsy of the thyroid gland has become increasingly popular over the last three decades but it's use at present is mostly restricted to the disgnosis of solitary thyroid nodule, confirmation of clinically obvious malignancyand diagnosis of diffuse non-toxic goitre (Einhorn and Franzen, 1962; Parsson, 1968).

Although FNAC is rarely the critical investigation in the diagnosis of hyperthyroidism but in presence of thyroid epithelial hyperplasia in the aspirate, it became a important differential diagnosis (Wolfish, Miskin, Rosen et. al., 1998)

The diagnosis of hyperthyroidism in this study was based on clinical signs and symptoms corroborated by laboratory confirmation by T3,T4 and TSH levels and FNAC of all clinically suspected cases.

Diagnosis findings in this study were blood stained smear, scanty colloid, variable degree of cellularity, some follicular and ring structure, fire flare due to peripheral metachromatic cytoplasmic granules, vacoulations in the cytoplasm and variation in the nuclear size, presence of granules and vacuoles suggested increased secretory activity and increased rate of protein synthesis respectively and these corresponds to dilated cisternae of endoplasmic reticulum (Nilsson, 1992). These findings were indicative of cellular hyperactivity and hyperfunction had correlated very well with level of T3, T4 and TSH. Similar hypothesis had been made by (Soderstorm and Nilsson, 1989) variation in nuclear size was present in this study (Nilsson, 1992).

The aspiration of clinically and defined nodule is more accurate when compared with random aspiration of diffuse process. Diffuse more abundant fibrotic stroma is a real obstacle in obtaining satisfactory material. This explains, why some authors who had reported their experience with needle aspiration in chronic thyroiditis in the large number of cases have obtained very decessive results (Cornillot, Granier et. al., 1998). In diffuse lymphocytic thyroiditis it is more difficult to obtain satisfactory material by fine puncture than in most thyroid diseases (Person, 1988). In this study their was no problem in obtaining material in these cases.

Incidence of malignancy in present study was 5.5% in cytologically diagnosed cases and 20.82% in histologically diagnosed cases; this discrepancy in results was due to the fact that surgery is usually the treatment of choice in malignancies. Majority of them were in the age group 50-69 years. Among malignant lesions incidence of papillary carcinoma as high as 80% of all thyroid cancers had been reported in other series (Taylor, 1999; Woolbar et. al., 1976, Stewart et. al., 1993; Prakash et. al., 1997; Dave and Patel, 2001; Clark, 2004).

In this study papillary carcinoma was reported in 16 out of total 26 cases of malignancy. So incidence of papillary carcinoma was 51.8% with female to male ratio 3:1.

In this study histopathology was available in 124 cases, cytohistological correlation was there in 120 cases so overall diagnostic accuracy was 89.5%. overall diagnosis accuracy ranging from 75.5-98% have been reported by large number of workers in the past (Walfish et. al., 1993; Talukedar et. al., 1988; Friedman and Geeta, 1979: Kini, Miler et. al., 1980; Kini et. al., 1980; Vergino, 1981).

The results of the accuracy of FNAC vary but in most series overall accuracy rate exceed 90% with 5-

10% frequency of false positive and false negative (Crile, 1976; Freedman et. al., 1983; Ghoshai 1984; Joyaram, 1985; Harsoulis, 1986; Anderson and Weff, 1987; Northen et. al., 1988; hamming et. al., 1990). Sharma et. al., 1990 made correct diagnosis in 93.7% with false positive rate (1.1%) and false negative rate of 92%, sensitivity of FNAC was 93.7% specificity 98.8%.

In the present study sensitivity was 90.62% and specificity was 98.91%. A sensitivity ranging from 82.6% to 95.2% had been reported by a large number of workers (Enharn and Franzen, 1962; Grashgeorn, 1977; Colchio et. al., 1980; Harsoulius et. al., 1986; Anderson and Webb 1987; Hawkins et. al., 1987, Sharma et. al., 1990; Lopez et. al., 1996; Mayor Prez, Mandez et. al., 1997; Sabl and Storan et. al. 1997) and specificity ranging from 77.32%-99.4% had been reported by many workers in the past (Enharn and Franzen, 1962; Grashgeorn, 1977; Colchio et. al., 1980; Harsoulius et. al., 1986; Anderson and Webb 1987; Hawkins et. al., 1987; Sharma et. al., 1990; Lopez et. al., 1996; Mayor, Prez, Mandez et. al., 1997; sabl and Storan et. al.,1997).

Table: Comparison of Diagnostic Accuracy

Authors	Year	No. of aspiration	Diagnosis of accuracy	Specificity	Sensitivity
Enhorn	1974	117	94.4	92.3	95.2
Gershengo	1977	32	81.3	77.3	90.0
Colchio	1988	300	97.3	98.5	82.6
Hasoulis o	1989	1100	94.2	95.4	89.2
Anderson	1996	373	98.4	99.4	83.5
Hawkins	1998	1399	93.7	95.3	86.3
Sharma	2003	140	98.0	98.0	93.7
Present study	2016	796	89.5	98.91	90.62

AgNOR In Thyroid

Argyophilic Nucleolar Organizing Regions were demonstrated and counted in thyroid gland lesions in 120 cases of fine needle aspiration smears and 36 cases of histopathological sections.

In samples from non-neoplastic and benign lesions the NORs were closely clustered to form one or two compact, round, uniform argyrophillic structure which were more or less central in position. This picture was in thyroiditis, follicular adenoma. The mean AgNOR counts among the non-neoplastic lesions were least in colloid goitre (1.37) followed by nodular colloid goitre (1.41) and granulomatous thyroiditis (1.46).

In malignant lesions the NORs were dispered in the nucleus. Their number, size, shape and distribution varied according to the malignancy of the tumour. With the increasing grade of malignancy they appeared as tiny, exceedingly numerous black dots, that were more, irregular in size and shape. In papillary carcinoma the mean AgNOR counts was 5.23 followed by medullary carcinoma (5.69), poorly differentiated carcinoma (6028) and undifferentiated/anaplastic carcinoma (6.91). these results were comparable with the study done by Singh and Agarwal in Lucknow in 1997, Lower counts were recoeded in case of thyroiditis (1.375+/-0.414) where as follicular carcinoma had a higher number of AGNOR counts (5.04+/-0.52). the clusters of AGNOR dots were centrally located in colloid goitre but no cluster arrangement was observed in case of carcinoma. The results were comparable with that of another study by Slowinska-Klencka and Klencki et. al., in 2003, who found that Hurtle cell neoplasms usually had a single and relatively large dot. With respect to diagnosing follicular lesions, they found that the evaluation of the total area of dots in the nucleus seemed to be the most useful for discrimination and analysis of AgNOR may be useful in the diagnosis of thyroid lesions.

Therefore, AGNOR study in thyroid lesions can be used as an additional diagnostic method with cytomorphological features to differentiate benign & malignant follicular neoplasms.

In this study no serious complications were recorded. Patient should be warned not to swallow during aspiration as this cause tearing of tissue with needle inplace. Local hematoma withon gland or adjacent tissue do occur, it is useful to have an assistant to apply pressure to the site rather than except the patient to do so and with correct pressure, heomorrhage or hemotoma are minimized, necrosis of whole nodule, transient laryngeal nerve palsy have been recorded, as have coughing and hemoptysis due to puncture of tracheal wall (Jayaram, 1984: Jones, Pit Man et. al., 1985; Silverman, West, et. al., 1997).

CONCLUSION

Based on the observation recorded from the present study, the following conclusions were drawn:-

a) Most patients were in the age group 20-49 years of age with a M:F ratio 1:6.2.
b) Serum cholesterol levels were below normal limit in majority of cases of thyroid malignancies.
c) Levels of T3 and T4 were found to be decreased in colloid goitre and increased in cases of toxic goitre.
d) Most frequent lesions of thyroid were hyperplastic disorders (82.79%) followed by inflammatory disorders (11.4%), neoplastic disorders (4.96%) and developmental disorders (0.88%)
e) The technique of fine-needle aspiration cytology (FNAC) was found to be simple, quick, economical and with a sensitivity of 90.62%; specificity 98.91%; predictive value 96.66%; and efficiency 96.77%.

f) Although fine-needle aspiration is the first investigation of choice but histopathological examination remains the corner stone to make the final diagnosis in certain cases.

g) The AgNOR count was found to be of great significance in differentiating benign (goitre, thyroiditis and adenomas) and malignant lesions (thyroid carcinomas). In benign lesions the NORs were closely clustered to from compact, round, central and uniform argyrophillic structures which were less in number (usually less than two). In malignant lesions the NORs were dispered, tiny, irregular in size and shape and multiple in number (usually more than five).

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