SIGNIFICANCE OF HURTHLE CELLS IN THYROID CYTOLOGY

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CERTIFICATE

This is to certify that this dissertation entitled "**SIGNIFICANCE OF HURTHLE CELLS IN THYROID CYTOLOGY**" is a bonafide work done by Dr.V.ESWARI, in partial fulfillment of regulations of the **TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY, Chennai**.

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DECLARATION

I declare that this dissertation entitled **"SIGNIFICANCE OF HURTHLE CELLS IN THYROID CYTOLOGY**" has been conducted by me under the guidance and supervision of **Prof. Dr.Shanta Ravisankar, M.D.,D.C.P.,** in the Institute of Pathology and Electron Microscopy, Madras Medical College. It is submitted in partial fulfillment of the requirements for the award of the M.D. Pathology, September 2006 examination to be held under Dr.M.G.R.Medical University, Chennai. This has not been submitted by me for the award of any degree or diploma from any other University.

Dr.V.Eswari

INTRODUCTION

Thyroid gland is unique among endocrine organs. It is the largest of all the endocrine glands. Because of its superficial location, it is the only gland that is amenable to direct physical evaluation, cytological evaluation and histopathological study.

The modern procedure of Fine needle aspiration cytology has found world wide acceptance in clinical use as a quick and reliable diagnostic modality. The method is applicable to lesions that are easily palpable. For ex. Superficial growths of the skin, subcutis, soft tissues and organs such as the thyroid, breast, salivary glands and lymph nodes.

The technique is relatively painless produces a speedy result and is cost effective. It is less complicated than surgical biopsy and so is very suitable for practice in countries with limited resources. The low risk of complications is an additional advantage which allows Fine needle aspiration cytology to be performed as an out patient procedure.

Fine needle aspiration cytology has become an area for research both fundamental and clinical. One can visualize the increasing use of Electron microscopy and immuno cytochemistry of Fine needle aspiration samples and smears. It has been established that morphometric technique applied to Fine needle aspiration preparations can aid not only

in diagnosis of malignancy but also in assessing prognosis and selection of appropriate therapy.

Fine needle aspiration cytology of the thyroid gland is firmly established as a first line diagnostic test for the evaluation of goiter and the single most effective test for the preoperative diagnosis of a solitary thyroid nodule.

The main indications for Fine needle aspiration are

1. The diagnosis of diffuse non toxic goiter.

2. The diagnosis of the solitary or dominant thyroid nodule.

3. Confirmation of clinically obvious thyroid malignancy

4 To obtain material for special laboratory investigations aimed at defining prognostic parameters.

The experience as well as the expertise of the cytopathologist is critical in avoiding pitfalls. Determining the adequacy of an aspirate, cellular atypia, application and interpretation of immunostains and differentiation of lymphocytic thyroiditis from lymphoma are but a few of these problems.

Hurthle cells are of uncertain significance in thyroid disease and this study tries to clarify the meaning and predictivity of Hurthle cells in Fine needle aspirartion cytology for thyroid nodular disease.

AIM OF THE STUDY

There has been renewed interest in the diagnosis and treatment of Hurthle cell lesions because of the increasing use of fine needle aspiration biopsy in the preoperative diagnosis of thyroid nodules.

The aim of our study are

1. Significance of Hurthle cells in the thyroid cytology.

2. Cytologic features that would differentiate reliably between Hurthle cell neoplasm and non - neoplastic Hurthle cell lesions.

3. To aid in decision of therapeutic management of patients with Hurthle cells in cytology.

MATERIALS AND METHODS

The present study was under taken in the Department of pathology Madras Medical College, Tamil Nadu, India and Department of Surgical Endocrinology, Govt. General Hospital Chennai for a period of one year from Jan 2005 -Dec 2005.

The cytological materials were obtained in the form of smears which were fixed in 95% alcohol for Haematoxylin and Eosin stain and methanol for May Grunwald Giemsa stain. The aspiration syringes used were 5ml and the needle size between 22-23 gauges.

Procedure

The thyroid gland is palpated carefully and the nodule(s) to be biopsied identified. The procedure is explained to the patient carefully. The patient is placed supine with the neck hyperextended to expose the thyroid. For support a pillow is placed under the shoulders. The patient is asked not to swallow, talk or move during the procedure. After the aspiration firm pressure is maintained on the biopsy site. The patient is asked to sit for a few minutes. Occasionally patients complain of dizziness or pain. It is best to observe the patients for a few minutes.

Usually 2-3 aspirates and preferably the aspirates should be obtained from the peripheral areas and different parts of the nodule in a

sequential manner to ensure representative sampling. For cystic lesions the fluid should be aspirated and fine needle aspiration cytology attempted on residual tissue[16].

Haematoxylin and Eosin Stain[35]

Fix in 95% alcohol for 20 minutes.

Stain in Haematoxylin for 5 minutes. Wash in water.

Dip in 0.5% acid alcohol for a few seconds.

Blueing in tap water for 20 minutes.

Dip in Eosin stain for 1 minute. Wash in water.

Dry and mount the slide.

May Grunwald Giemsa Stain

May Grunwald - Giemsa both comes as a solution. Before use for. May Grunwald stain dilute with equal volume of buffer water (pH 6.8) for Giemsa Dilute one part of stain with 9 parts of buffer water.

Fix in methanol 15 minutes.

Stain in May Grunwald 10 minutes

Stain in Giemsa 15 minutes

Rinse in Buffer water PH 6.8 for 5 - 7 minutes and allow it to dry.

Buffer Water Preparation

A buffer is a solution which tends to keep its original pH even on addition of small amounts of either acid or alcohol.

Solution No.1

Sodium Hydroxide 8g

Distilled Water 1,000 ml

Solution No. 2

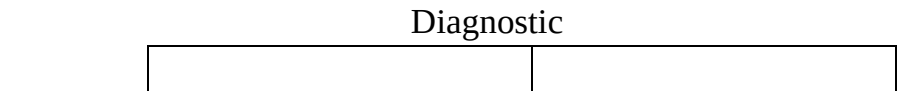
Potassium dihydrogen phosphate 27.2g

Distilled Water 1,000 ml

Take 23.7 ml of solution No.1 and add it to 50ml of solution No.2 Add 20ml of the above mixed buffer solution to 1,000 ml of distilled water. Check the pH. This should have a pH of 6.8. Label the bottle and use this for the diluting with the blood film staining.

For tissue sections the specimens were fixed in formalin. After paraffin embedding 4 micron thick sections were made and stained with Haematoxylin and Eosin[35].

Results of Fine needle aspiration may be grouped as diagnostic (satisfactory) or non diagnostic (unsatisfactory)



Benign	**Malignant**	**Indeterminate**
Colloid Nodules	Primary thyroid cancer	
Benign Cysts	Metastatic malignancy	
Hashimoto's thyroiditis		
Granulomatous thyroiditis		

The indeterminate category includes smears with features suggestive of but not diagnostic for malignancy. Aspirates with too few follicular cells or only degenerative foam cells are labelled non - diagnostic.

For assessing cellularity, the rule of thumb of six groups of normal - appearing thyroid epithelial cell should be well fixed and well stained, appear unremarkable and benign and should not be excessively degenerated. A group is defined as 15 -20 thyroid epithelial cells in a sheet or follicular group. For assessing the adequacy of specimens, degenerative foam cells are not counted because they are encountered in both benign and malignant (especially papillary) conditions.

DEVELOPMENTAL BIOLOGY AND ANATOMY OF THE THYROID

Structural Embryology

The human thyroid anlage is first recognizable about 1 month after conception when the embryo is approximately 3.5 - 4 mm in length. The primordium begins as a thickening of epithelium in the pharyngeal floor, which later forms a diverticulum. With continuing development, the median diverticulum is displaced caudad and the primitive stalk connecting the primordium with the pharyngeal floor elongates (thyroglossal duct). During its caudal displacement the primordium assumes a bilobate shape coming into contact and fusing with the ventral aspect of the fourth pharyngeal pouch.

Normally the thyroglossal duct undergoes dissolution and fragmentation by about second month after conception, leaving at its point of origin a small dimple at the junction of the middle and posterior thirds of the tongue the foramen caecum. Cells of the lower portion of the duct differentiate into thyroid tissue forming the pyramidal lobe of the gland. Concomitantly histological alterations occur throughout the gland. Complex interconnecting cord like arrangements of cells interspersed with vascular connective tissue replace the solid epithelial mass and

becomes tubule like structures at about the third month of fetal life. Shortly thereafter follicular arrangements devoid of colloid appear and eventually follicles fill with colloid[33].

Functional Ontogeny

The ontogeny of thyroid function and its regulation in the human fetus are fairly well defined. Future follicular cells acquire the capacity to form thyroglobulin as early as the 29th day of gestation, whereas the capacities to concentrate iodide and synthesize T4 are delayed until about the eleventh week. Radio active iodine inadvertently given to the mother would be accumulated by the fetal thyroid soon thereafter.

Because the capacity of the pituitary to synthesize and secrete TSH is not apparent until the 10th 12th weeks early growth and development of the thyroid do not seem to be TSH dependent. Subsequently rapid changes in pituitary and thyroid function takes place. Probably as a consequence of hypothalamic maturation and increasing secretion of thyrotropin releasing hormone the serum TSH concentration increases between 18 - 26 weeks of gestation.

Thyroxine binding globulin is detectable in the serum by 10th gestational week. There is progressive increase in T4 concentration during second and third trimesters[33].

Anatomy of the thyroid gland

Following the work of bartholomaeus Eustachius of Rome in the 1700s, the gland acquired the name " Glandulum Thyroideam' (Latin for shield shaped)[7].

The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx. Normal variations in the structure of the thyroid gland include the presence of a pyramidal lobe, a remnant of the thyroglossal duct above the isthmus.

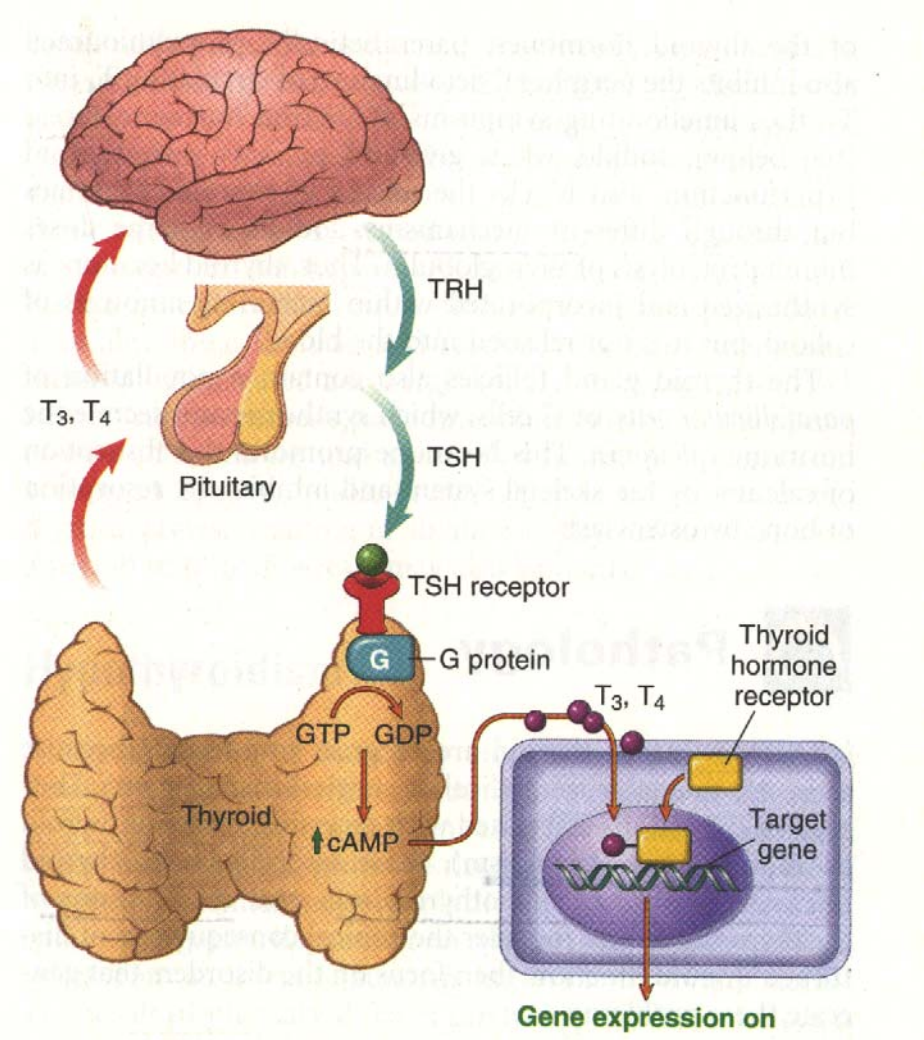
The weight of the normal adult thyroid is approximately 15 - 25gm. The thyroid has a rich intra glandular capillary network that is supplied by the superior and inferior thyroidal arteries. Nerve fibres from the cervical sympathetic ganglia indirectly influence thyroid secretion by acting on the blood vessels[3].

Physiology

Homeostasis in the hypothalamus - pituitary - thyroid axis and mechanism of action of Thyroid hormones.

Secretion of thyroid hormones is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary. Decreased

levels of T3 and T4 stimulate the release of thyrotropin releasing hormone from the hypothalamus and thyroid stimulating hormone from the pituitary causing T3 T4 levels to rise.



Elevated T3 and T4 levels inturn suppress the secretion of both thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). This relationship is termed negative feed back loop. TSH binds to the TSH receptor on the thyroid follicular epithelium which causes activation of G proteins and cyclic AMP mediated synthesis and release of thyroid hormones. In the periphery T3 and T4 interact with the thyroid hormone receptor to form a hormone receptor complex that translocates to the nucleus and binds to so called thyroid response elements on target genes initiating transcription[3].

Light microscopic appearance

Microscopically the thyroid is divided into lobules composed of about 20 - 40 follicles. It is estimated that approximately three million follicles are present in the thyroid of an adult man. Each lobe or lobule is supplied by an intra lobular artery and vein. The follicles are lined by epithelial cells which surround central deposits of colloid. In general the follicles range from uniform to variable size however the plane of section may give the appearance of small follicles interspersed with larger ones. In the interfollicularstoma and occasionally abutting between the epithelial cell are individual or small groups of Para follicular `C' cells[40].

Thyroid function test

Methods for evaluating thyroid function have been divided by Cavalieri into

a) Those which measure effects of thyroid hormone such as basal metabolic rate.

b) Those measuring thyroid iodine metabolism.

c) Those which measure circulating thyroid hormones.

d) Those which assess feed back and control mechanisms.

Thyroid Iodine Metabolism

Radionuclide Uptake

Radio active iodine injected into an individual will be preferentially trapped by the thyroid gland. Measurement of radio activity over the thyroid several time intervals allows an estimation of the ability of the thyroid to trap iodine, organify it and accumulate isotope presumably producing T4 and T3.

Measurement of Circulating Thyroid hormones

Free T4 and Free T3

Normal values include free T4 of 2.0ng/dl and Free T3 of 0.33 ng/dl. These hormones are elevated in 95 - 100% of hyper thyroid patients. T4 is decreased in all hypothyroid individuals whereas T3 may be normal in about 30%.

Tests of Feed back mechanisms

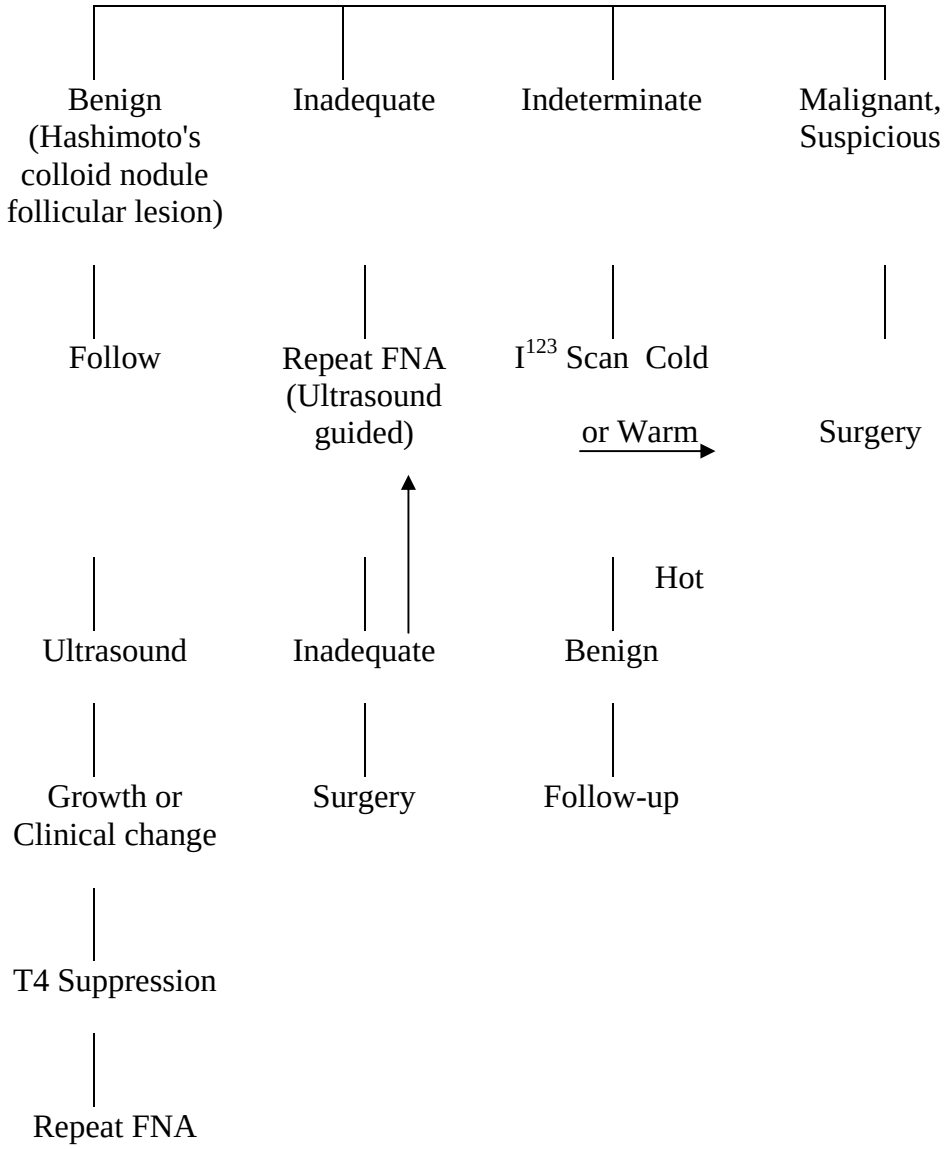
Measurements of TSH by radio immuno assay has become a useful diagnostic tool. Normal range is approximately 0.5 - 50 mu/L. Elevated

levels of this hormone are often found in hypothyroid states. TSH levels rise early in hypothyroidism and this test in exquisitely sensitive as the initial indicator of hypofunction.

The TRH stimulation test - TRH, the tripeptide hypothalamic hormone can be injected to test the integrity of the hypothalamic - pituitary axis. This test may be helpful in the distinction of primary from secondary hypothyroidism. If a hypothyroid patient with a non - elevated TSH level shows a brisk risk in TSH after TRH administration, the pituitary is intact, on the other hand if TSH response is blunted the results suggests an intrinsic pituitary abnormality as the cause of hypothyroidism[40].

[11]Algorithm for the evaluation of the thyroid nodule

FINE NEEDLE ASPIRATION



REVIEW OF LITERATURE

"Diagnosis by Aspiration is as reliable as the combined intelligence of the clinician and pathologist makes it".

- Fred W. Stewart (1933)

There is nothing new under the sun. During medieval times the Arabian physician Abul Casim described the needle puncture of the thyroid to diagnose different types of Goitre (Anderson). Needle aspiration biopsy was recorded by Kun in 1847. There was a brief flowering of interest in cytologic techniques in the late 1920s and early 1930s as reported in the classic papers of Dudgeon and Patrick from England who used cytologic scrape preparations of excised tissue.

In the United States Hayes Martin, a head and neck surgeon, Edward Ellis and Fred Stewart reported the use of 18 gauge needles to obtain biopsy specimen from patients. In 1923 Papanicolaou presented his 'New Cancer Diagnosis' later known as 'Pap Smear'.

After world war II Scandinavian and North American workers used the designation 'Fine needle aspiration biopsy' or 'aspiration biopsy cytology' for both the act as a whole and for the operative procedure[38].

Thomson preferred the term ‘Thin needle selective sampling’[39]. Zajdela who introduced non-aspiration technique called it ‘Fine needle sampling’[43].

Svante R. Orell, stated that the ‘Fine needle aspiration cytology’ is still an acceptable description of the whole of the act inspite of the facts that aspiration is not always used. They referred the material expressed from the needle as samples, smears or aspirates[38].

Today because of its numerous advantages fine needle aspiration biopsy is widely used and has a proven track record as a safe and reliable method of making a morphologic diagnosis.

Fine needle aspiration biopsy is best viewed as a chain of events in which the biopsy itself is only one link and not the first on the road to a proper diagnosis. The procedure actually begins well before the biopsy is performed. Clinical information is crucial in the evaluation of a biopsy specimen to arrive at the proper clinico pathologic diagnosis.

Thyroid nodules are more common in women (4:1), oldage, history of radiation exposure and a diet deficient in iodine. The prevalence of thyroid nodules steadily increases with age beginning in childhood. New nodules become clinically detectable at a rate of about 0.1% per year.

Since it would be impossible to operate on every patient with a goitre to find the few with cancer various clinical parameters are used to

define low and high risk groups for cancer (Green span 1974, Thomas 1976, De Groot 1983). These parameters include history, physical examination, diagnostic imaging, laboratory findings particularly 'fine needle aspiration biopsy'[9,19].

Numerous scientific articles and reviews attest to use of fine needle aspiration biopsy of the thyroid as

- **S**imple
- **A**ccurate
- **F**ast
- **E**conomic

as well as SAFE method of diagnosis of thyroid disorders[1]. (Abu Nema 1987, J. Anderson, Baskin, Bodo).

Depending on the patient population, approximately 60-75% of fine needle aspiration biopsies are diagnosed as benign, approximately 5-10% as malignant and the remainder as suspicious.

Gharib et al in 1988 studied the diagnostic accuracy can be as high as 95% or better for satisfactory specimens.

Frable in 1980, 1986, La Rossa 1991 et al studied the positive predictive values ranging from 89-98% and negative predictive values

94-99%. Its potential to reduce unnecessary operations is significant. The greatest risk of false negative diagnosis is in relation to cystic neoplasms mainly cystic papillary carcinomas[14,26].

La Rossa et al found a false negative rate of 6.4% for cystic nodules, whereas it was only 1.4% for solid nodules. False negative diagnosis also arise from inadequate samples, geographic misses of the lesion, dual pathology and errors in interpretation. Clinical and radiologic findings must be taken into account. Repeated fine needle aspiration biopsy sampling over a period of time to reinforce a benign diagnosis or in indeterminate cases particularly if ultra sound guidance is used reduces the false negative rate[26].

Cytology of normal thyroid:

1) Follicular epithelial cells are fragile and bare nuclei are common. These are similar in size and shape to normal lymphocytes. The nuclei are rounded or slightly oval with a smooth outline.

2) Colloid stains blue - purple and forms a thin membrane like coat often with folds and cracks.

Hurthle cells:

The Hurthle cell is a cell in the thyroid which has been associated with debate and confusion. The debate surrounds several aspects of the

cell including its origin, its functional state and the clinical implications of nodules composed of these cells.

Oncocytes from the Greek word ‘swell’ also known as Hurthle cells, Oxyphilic cells or Askanazy cells are characterized by abundant granular cytoplasm due to abundant accumulation of mitochondria. This is a phenomenon of metaplasia and indicates degenerated follicular epithelial cells that occurs in inflammatory disorders such as thyroiditis or situations that results in stress. ‘Proliferation of oncocytes gives rise to hyperplastic and neoplastic nodules’.

Oncocytic cells in the thyroid are often called Hurthle cells. However this is a misrepresentation. Cells of these features were discovered by Askanazy in 1898 in patient with Grave’s disease. In 1936, Eisen studied the characteristic cytoplasmic appearance is due to increased number of mitochondria in a patient with Riedel’s thyroiditis.

In 1919, James Ewing described two patients with adenocarcinoma of the thyroid made of large finely granular eosinophilic cells and suggested that they might represent ‘Hypertrophic Hurthle cells of the thyroid alveoli’. Since that time the term Hurthle cell is used in the world literature to identify the cells that Max Askanazy originally described. The cells that Hurthle described were infact ‘C’ cells[31].

Hurthle cells are found in a wide variety of conditions affecting the gland and there fore they cannot be considered specific for any disease entity[40].

Occurrence of Hurthle Cells

Non-Neoplastic	Neoplastic
1) Chronic Lymphocytic Thyroiditis and variants. **2)** In nodular goitre **3)** In diffuse toxic goiter **4)** Post irradiation **5)** Post chemotherapy 6) As aging process	Follicular Hurthle cell adenomas and Carcinomas. Rare variants of papillary and medullary Carcinomas.

Kauffmann et al studied the significance of Hurthle cells in thyroid nodule fine needle aspiration cytology samples. He concluded that density of Hurthle cells in FNAC ranged from 20-100% the presence of more than 50% Hurthle cells in FNAC correlated with benign or malignant Hurthle cell neoplasm. Hurthle cell carcinomas displayed more than 90%. Hurthle cells in FNAC and surgery is indicated for all nodular lesions with more than 50% Hurthle cells[24].

Kumar et al in their study " Aspiration Cytology of Hashimoto's thyroiditis in an endemic area" has pointed out that fine needle aspiration plays a significant role in the diagnosis of thyroid lesions due to its simplicity and low cost. Hashimoto's thyroiditis is the second most common thyroid lesion next to endemic goitre diagnosed on fine needle aspiration in iodine deficient areas.

Presentation as a nodular thyroid is common. Diagnosis of Hashimoto's thyroiditis is likely to be missed in smears showing cytological evidence of hyperplasia or abundant colloid. Careful screening for Hurthle cell change and lymphocytic infiltration into follicular cells should be carried out. In equivocal cases multiple punctures and immunological investigations are helpful. In antibody negative cases repeat fine needle aspiration at follow-up useful. Marked lymphocytic infiltration and Hurthle cell change may indicate a hypothyroid state but hormonal levels are required for management[25].

Hurthle cells with associated lesions.

Laurie Mac Donald and Hossein M. Yazdi determined the accuracy of cytologic interpretation in the diagnosis of Hashimoto’s Thyroiditis. The results supported the value of fine needle aspiration biopsy in the

diagnosis of Hashimoto's thyroiditis. Two main sources of diagnostic error were the presence of hyperplastic follicular cells and sampling error.

The presence of hyperplastic follicular cells in fine needle aspiration biopsy samples from Hashimoto's Thyroiditis may mimic follicular neoplasm. Adequate sampling is important when there is an associated lesion. The diagnosis of lymphocytic thyroiditis should not be made when only a few lymphocytes are seen. Pleomorphic Hurthle cells may be present in aspirates from Hurthle cell neoplasm[27].

Esther Ravinsky et al refined the cytodiagnostic criteria for distinguishing Hashimoto's thyroiditis from thyroid neoplasms.

Diagnostic criteria separating Hashimoto's thyroiditis from thyroid neoplasms[12].

	Hashimoto's thyroiditis	**Thyroid neoplasms**
Cell arrangements	Flat sheets and clusters with a few single cells. Cohesive tissue fragments with cells well oriented one to the other.	Syncytial type loosely cohesive tissue fragments with cells poorly oriented one to the other as well as isolated single cells.
Nuclear chromatin pattern	Bland and even	Finely granular, coarsely granular or clumped
Nucleoli	Identifiable	Macro nucleoli in Hurthle cell neoplasms.

Giorgadze T, Rossi Ed et al studied the risk of malignancy in cases diagnosed as Hurthle cell neoplasm and identified clinical features that may help in predicting malignancy in patients with fine needle aspiration diagnosis of Hurthle cell neoplasm. The risk of malignancy was greater in nodules measuring more than 2 cm, in patients who were are more than 40 yrs old and was found greater in male patients, than in female patients. However the difference was not statistically significant. The diagnosis Hurthle cell neoplasm / follicular neoplasm with oncocytic features carries a higher risk of malignancy as compared with a diagnosis of follicular lesion / neoplasm. Clinical features including size of the nodule, age and possibly sex of the patient can be a part of the decision analysis in selecting a patient for surgery[18].

Thompson et al called attention to large pyknotic nuclei in Hurthle cells in non-neoplastic Hurthle cell nodules[37].

Sudha R. Kini studied the difficulties in making the cytologic differentiation between surgical and non-surgical Hurthle cell lesions and had enlisted the following criteria[37].

Cytomorphology of Hurthle cell Tumours[37].

1.	Monomorphic cell population.
2.	Cells oval-polygonal with abundant granular cytoplasm that stains eosinophilic, cyanophilic or amphophilic.
3.	Nucleus slightly eccentric, small round to oval with finely granular chromatin.
4.	Prominent macro nucleolus.
5.	Cells mostly in isolated or in loose groups, occasionally sheets or follicles.
6.	Scanty colloid.
7.	Tissue fragments with marked nuclear pleomorphism suggest malignancy. Must be differentiated from auto immune thyroiditis.
8.	No inflammatory cells in the background.

Danielle D, Elliott in their study " Fine needle aspiration Biopsy of Hurthle cell lesion of the thyroid gland" concluded, that fourteen cytologic features were examined and 6 were found to be statistically significant in identifying Hurthle cell neoplasm. The following four features when found in combination were found to be highly predictive of Hurthle cell neoplasm[8].

* Non macro follicular architecture
* Absence of colloid
* Absence of inflammation
* Presence of transgressing blood vessels

Jorge L. Gonzalez et al studied many statistically significant cytological differences between Hurthle cell Tumour and non-neoplastic Hurthle cell lesions, statistically significant features are

1) A high percentage of >90% Hurthle cells
2) Single Hurthle cells >10%
3) Cellular dyshesion
4) Large nucleoli
5) Significant nuclear enlargement absence of plasma cells, macrophages and few lymphocytes[22].

The majority of fine needle aspirates of the thyroid that demonstrate a predomnance of Hurthle cells are diagnosed as suspicious for Hurthle cell neoplasm. Only a minority of these patients are found to have carcinoma at the time of resection. Renshaw AA attempted to define criteria that were more specific for Huirthle cell carcinoma without a loss in sensitivity.

Hurthle cell carcinomas could be identified using a total of five criteria. Predominantly Hurthle cells and scant colloid and atleast one of either small cell dysplasia (cytoplasmic diameter less than twice the nuclear diameter with often quite bland cells), large cell dysplasia (greater than twice the variation in nuclear diameter) large cells typically demonstrate prominent nucleoli and irregular nuclear outline, crowding (Nuclei touching) and dyshesion (single cells).

He concluded that by focusing on criteria for Hurthle cell carcinoma rather than all Hurthle cell neoplasm criteria can be developed that improve the specificity without a loss of sensitivity[34].

Dr. Gita Jayaram in ‘Problems in the interpretation of Hurthle cell populations in Fine needle aspirates’ had cases with Hurthle cell population showing features of pleomorphism in the presence of a scant number of lymphocytes. Such cases needed to be evaluated very carefully with the help of antibody tests in order to distinguish Hurthle cell lesions requiring surgical intervention from those that do not[21].

Diya I. Aladeen et al studied the predominance of Hurthle cells in Fine needle aspiration biopsy ‘A predominance of Hurthle cells was defined by a smear in which Hurthle cells comprised greater than 50% of the cellular content’. As a result thyroidectomy is recommended for all patients with a thyroid nodule and a predominance of Hurthle cells on Fine needle aspiration biopsy specimen[10].

Gia Khanh Nguyen et al concluded that Tumour cells with ill defined cytoplasm and prominent nucleoli in syncytial clusters and abundant naked tumour cell nuclei in the Fine needle aspirate of a thyroid nodule should alert the observer about the strong possibility of an Hurthle cell carcinoma[17].

Sudha R. Kini et al has pointed out that ‘Horn in 1951 stated that the papillary or follicular cancers composed of Hurthle cells do not

behave differently from the usual follicular or papillary carcinomas. He felt that the architectural pattern rather than the cell type predicted the behaviour of the tumour[37].

Role of Morphometry in the diagnosis of Hurthle cell Neoplasm.

Stefan E. Pambucian et al studied that nucleolar features such as size, variation in size and roundness may be more effective than cellular or nuclear features in differentiating Hurthle cell Adenomas and Hurthle cell carcinomas in Fine needle aspiration cytology smears[36].

"Morphometric studies on Nuclei in smears of Fine needle aspiration from oxyphilic tumours of the thyroid gland" by Lennart Bondeson et al also concluded that mean nuclear size and or degree of anisokaryosis is of no practical value in distinguishing between benign and malignant thyroid neoplasms of the oxyphilic type[5].

Andrew flint in "Cytophotometric measurements of Hurthle cell Tumours of the thyroid gland stated that statistically significant association was found between aneuploidy and tumour invasion. However measurement of the percentage of cycling tumour cells as well as nuclear size and shape were not useful in separating benign from malignant neoplasms[2].

Heppe H, Armin et al reviewed 34 patients treated between 1972 and 1984. On the basis of strict histopathologic criteria 14 patients with

Hurthle cell hyperplasia, 10 with Hurthle cell Adenoma and 10 with Hurthle cell carcinoma were identified. Lobectomies were performed in patients with tumours considered histopathologically benign and total thyroidectomy in patients with histologically malignant lesions.

Therefore appropriate treatment for Hurthle cell Adenoma and nodular hyperplasic is a lobectomy. Total thyroidectomy is reserved for Hurthle cell carcinoma primarily because of the high incidence of bilateralism[20].

Wasvary H, Ezako. P also concluded unilateral thyroid lobectomy is adequate therapy for the treatment of Hurthle cell Adenoma with total thyroidectomy reserved for patients with histologically proven carcinoma[42].

Caplan RH, Abellera RM et al reviewed the pathology and clinical follow-up of 26 patients with Hurthle cell adenomas and three patients harboring Hurthle cell carcinomas. Although benign lesion could not be distinguished from malignant tumours by cytologic features alone, other pathologic features allowed differentiation. A total thyroidectomy was performed in only one patient the remaining patients were treated by less extensive operations. None of the patients with benign adenomas including those tumours greater than 2cm in diameter experienced recurrent or metastatic disease. The period of observation varied from 2 - 22 yrs. They concluded that lobectomy is a satisfactory operation for

removal of Hurthle cell adenoma and reserve total or near- total thyroidectomy for cases displaying pathologic evidence of malignancy[6].

Nesland JM et al Studied `Ultra Structural features of Hurthle cells in neoplastic and non - neoplastic lesions'. The presence of distinct smooth surface cells interspersed with cells with many microvilli is almost a pathgnomonic scanning electron microscopic feature of benign and malignant Hurthle cell lesions. Most Hurthle cells stained positively for thyroglobulin in all cases but no immuno reactivity for CEA and calcitonin was found[30].

Pisani T, Pantellini F et al studied the immuno cytochemical expression of Ki67 and laminin in Hurthle cell adenomas and carcinomas. Benign Hurthle cell lesions with a higher cellular proliferation associated with an increased laminin expression could define a subset of lesion prone to malignant transformation. Conversely all cases with low expression of both laminin and Ki 67 always correspond to adenomas. The different expression of these two antibodies on FNAC can provide a further tool for the pre operative identification of lesions at low risk of malignancy thus avoiding unnecessary surgery[32].

Kanthan R, Radhi JM, et al Studied " The immuno histochemical analysis of thyroid adenomas with Hurthle cells" Their aim was to elucidate the relation ship between the normal uninvolved thyroid and the

adenoma and also to evaluate the role of histo chemical studies in adenomas with Hurthle cell changes.

A panel of 9 antibodies directed against thyroglobulin, high molecular weight keratin, low molecular weight keratin, P - 53, bcl - 2, Epithelial membrane antigen carcino embryonic antigen, S 100 and HMB - 45 were used, Majority of Hurthle cells and adenomas with predominant Hurthle cells had an increased percentage of P - 53 staining[23].

Zeppa P, Ferrara G, " L - Thyroxine effects on thyreocytes and Hurthle cells in nodular hyper plastic goitre on Fine needle aspiration samples".

A morpho metric study was performed on thyreocytes and Hurthle cells. Results suggest that morphometry may be useful in the follow-up of nodular hyperplastic goitre to evaluate the effects of L - Thyroxine and that this therapy reduces the size of thyreocytes. However the therapy has little value or no effect on Hurthle cells[44].

"Hurthle cell tumours of the thyroid. A flow cytometric DNA analysis" by A.K - el - Naggar J.G. Batsakis has shown that nuclear DNA ploidy alone does not distinguish benign from malignant Hurthle cell tumour. Diploid DNA Hurthle cell carcinomas behave far less aggressively than aneuploid Hurthle cell carcinomas and all patients with

aneupolid carcinomas died of their disease or are alive with persistent carcinoma[29].

Wallin G, Backdhal, M, Lundell G, Auer G in their study " Nuclear DNA content and prognosis in Hurthle cell tumours of the thyroid gland". Concluded that DNA measurement in morphologically identified single tumour cells performed either on fine needle aspiration biopsy material or on histological sections from the primary tumours identifies those patients with a good versus a bad prognosis. These results correlate well with the findings in earlier studies about paprillary, follicular and medullary thyroid tumours[41].

Bronner MP, Clevenger CV et al examined paraffin embedded surgical biopsy material from 17 Hurthle cell tumours of the thyroid for DNA content by flow cytometry to assess the diagnostic and prognostic utility of ploidy determinations in these rare tumours. Both adenomas and carcinomas were studied. As a control for methods, ten randomly selected normal autopsy thyroids were analyzed all of which demonstrated normal diploid DNA content. The findings demonstrated the limited value of aneuploidy or polyploidy as diagnostic features for maligrancy in Hurthle cell tumours of the thyroid. As for prognosis there does not appear to be any for unfavourable prognostic significance for abnormal DNA content in histologically benign Hurthle cell tumours treated by surgical excision because no metastases or recurrences occured in this group. Preliminary data suggest that aneuploidy may however have an important prognostic

value for histologically defined Hurthle cell carcinomas because the only patient to die from the tumour in this series had an aneuploid Hurthle cell carcfinomas[4].

McIvor NP, Freeman JL et al studied the "Value of fine needle aspiration in the diagnosis of Hurthle cell neoplasms". They concluded that aspiration cytology can differentiate non - neoplastic from neoplastic Hurthle cell lesions with high accuracy, but that the differentiation between benign and malignant lesions is less reliable[28].

RESULTS AND OBSERVATION

Table - 1: Showing age wise distribution of 180 cases

Age group	No. of cases
10-20	15
21-30	58
31-40	58
41-50	27
51-60	14
61-70	6
Total	178

For 2 cases Age was not recorded

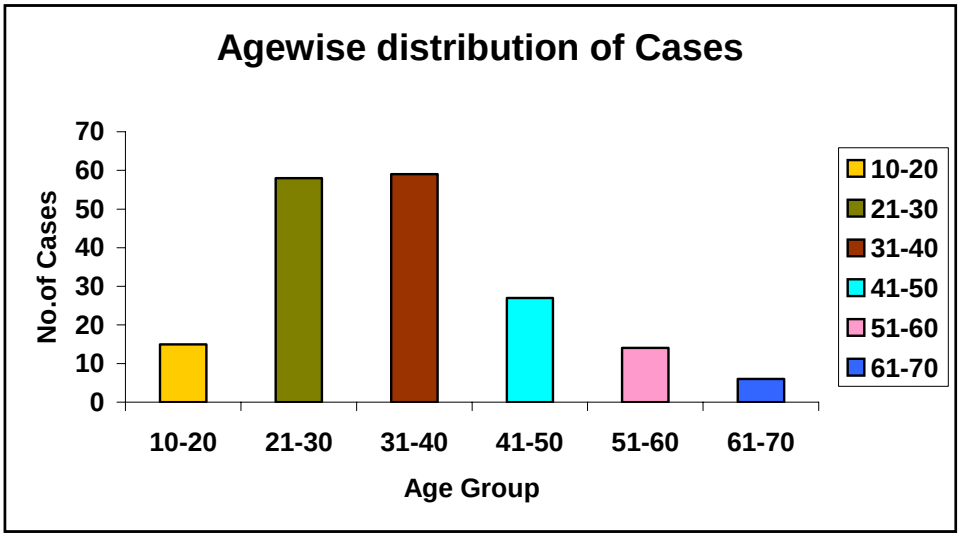


Table - 2: Showing sex incidence

Sex	No. of cases
Males	7
Females	173
Total	180

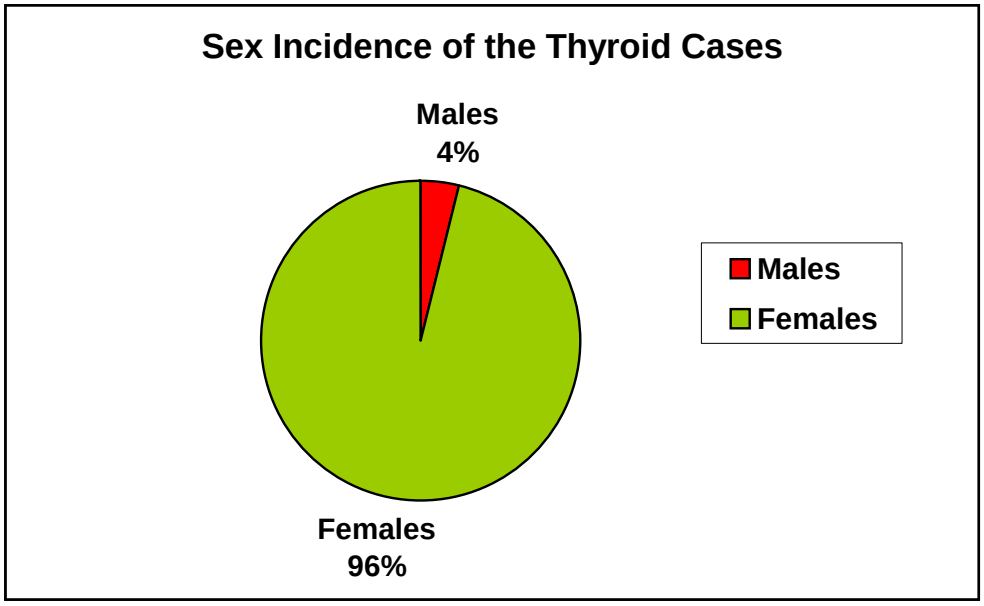


Table - 3: Showing presentation of cases

Anatomical diagnosis	No. of cases
Solitary nodule thyroid	54
Multi nodular goitre	55
Diffuse goitre	71
Total	180

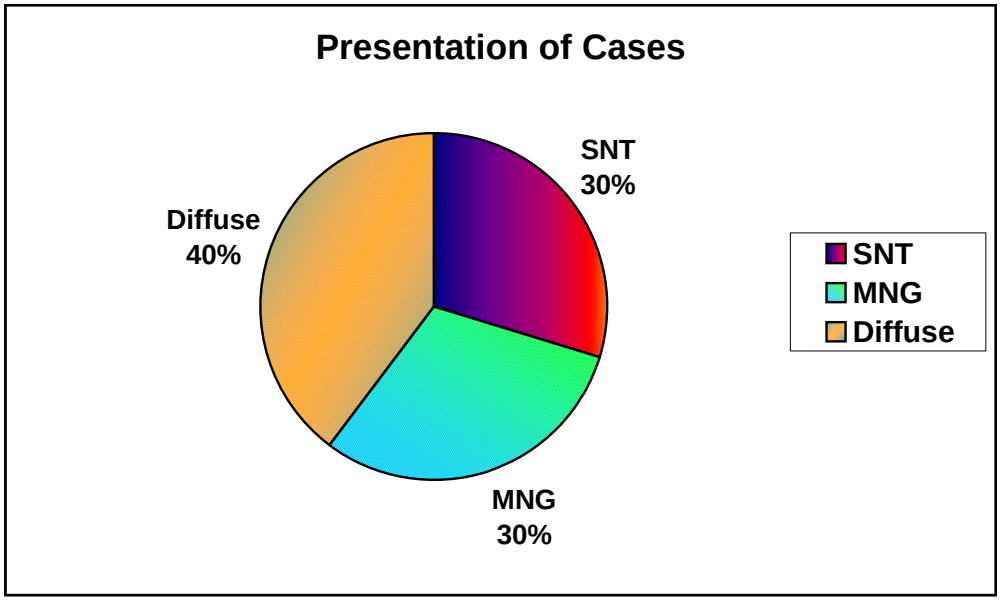
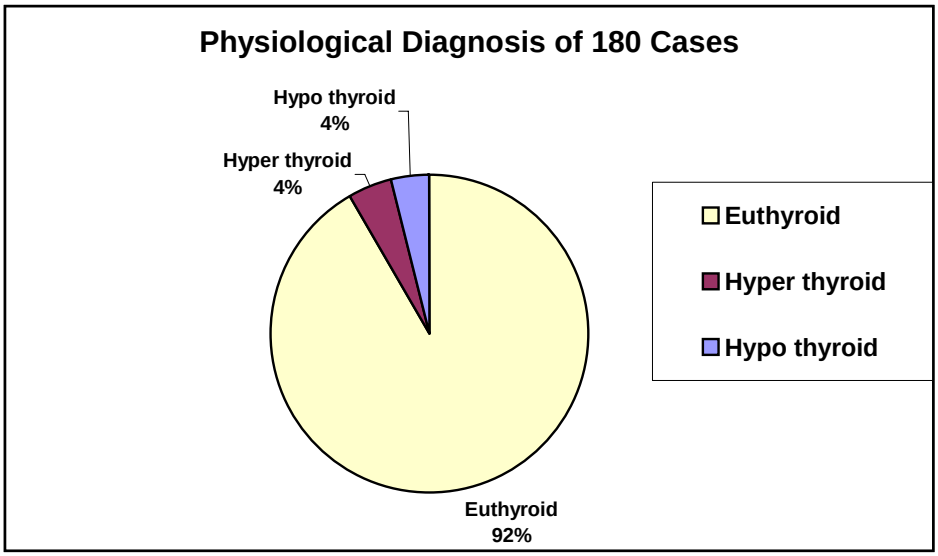


Table - 4: Showing physiological diagnosis of 180 cases

Physiological diagnosis	No. of cases
Eu thyroid	165
Hyper thyroid	8
Hypo thyroid	7
Total	180



In our study of 180 cases of Fine Needle Aspiration of Thyroid, it was found that 73 cases showed a predominance of Hurthle cells.

The sex incidence was found to be 2 males and 71 females that is in the ratio of 1:35.5. The age incidence was found to be between 16 years and 63 years.

The clinical presentation was as follows :

Solitary nodule	12
Diffuse	37
Multiple nodules	24
Total	**73**

The conditions which showed a predominance of Hurthle cells were classified as :-

Non - Neoplastic	
Hashimoto's	59
Nodular Colloid Goitre	10
Toxic Goitre	1
Neoplastic	
Follicular Neoplasm	1
Papillary Carcinoma	1
Hurthle cell Neoplasm	1

The study of the cytological smears was based on the distribution of Hurthle cells, their individual cytomorphology, nuclear features,

cohesiveness associated cells and the study of background in which the cells were distributed.

Of the 73 cases which showed Hurthle cells, surgery was done only for 18 cases. As most of the cases were diagnosed as Hashimoto's thyroiditis and colloidgoitre which did not require surgical intervention we had histopathological correlation only for 18 cases. The results of which were tabulated as follows

Cytohistologic Results in cases where Hurthle cells are prominent

Cytologic Diagnosis	Histologic diagnosis	No.of Cases
Hashimoto's thyroiditis	Hashimoto's thyroiditis	6
Hashimoto's thyroiditis	Nodular colloid Goitre	2
Hashimoto's thyroiditis	Nodular colloid Goitre with thyroiditis	3
Toxic Goitre	Toxic Goitre	1
Nodular colloid Goitre	Toxic Goitre	1
Nodular colloid Goitre	Hashimoto's thyroiditis	2
Hurthle cell Neoplasm	Hurthle cell adenoma	1
Follicular Neoplasm	Follicular Adenoma	1
Papillary carcinoma	Papillary carcinoma	1
Total		**18**

For the rest of the cases, a clinical follow-up was done. Cases diagnosed as Hashimoto's thyroditis proved to the same by Anti body test and cases diagnosed as colloid goitre showed marked improvement with drug therapy.

The cellularity of aspirates from Hashimoto's thyroditis varied from mild - moderate with lymphocytic infiltrate being mild - moderate.

The amount of colloid was scanty in majority of the smears, with oceassional smears showing moderate colloid. There was an admixture of epithelial cells, lymphocytes and plasma cells. The epthelial cells were found to be arranged in monolayered sheets and in small clusters.

In aspirates from Hashimoto's thyroiditis Hurthle cells showed dark nucleus with mild - moderate nuclear polymorphism. The nuclear chromatin pattern was bland and even. This type of atypia is called regressive atypia which is considered to be characteristic of non - neoplastic lesion[12]. Some of the smears stained with Maygrunwald Giemsa showed identifiable nucleoli with few binucleated cells.

The Hurthle cell morphology in aspirates from nodular colloid goitre showed honey comb pattern of arrangement and were interspersed by regular follicular epithelial cells. The differentiating feature between

the Hurthle cells and regular epithelium was increase in size and the presence of abundant granular eosinophilic cytoplasm.

The aspirates of toxic goitre showed features of regular follicular epithelial cells arranged in flat monolayered sheets with cytoplasmic vacoulation with background showing lymphocytes and Hurthle Cells.

In aspirates from thyroid neoplasm the epithelial cellularity was found to be greater than that of Hashimoto's thyroiditis.

In smears from papillary carcinoma, there was high cellularity with flat monolayered sheets of follicular epithelial cells which exhibited nuclear grooves and pseudo nuclear inclusions. Hurthle cells were seen in sheets.

The aspirates from pure Hurthle cell lesion showed a monomorphic population of Hurthle cell arranged both in loose clusters and in singles. There was no colloid or lymphoplasma cytic infiltrate in the background. Such lesion proved to be well encapsulated Hurthle cell adenoma.

Aspirates from follicular neoplasm showed micro follicular arrangement of follicular epithelial cells with a drop of colloid, in a background of Hurthle cells and lymphocytes Histologically also the case was proved to be follicular adenoma with Hurthle cell nodule.

The differentiating features of Hurthle cells in neoplastic and non-neoplastic lesions of thyroid.

Neoplastic lesions	**Non - neoplastic**
A High percentage of Hurthle cells mostly isolated or in loose cohesive sheets	Hurthle cells in flat sheets and clusters with a few single cells.
Monomorphic cell population with cells oval - polygonal with abundant granular eosinophilic cytoplasm, eccentric nuclus with finely granular or clumped chromatic	Nuclear chromatin pattern is bland and even
Prominent macronucleoli	Identifiable nucleoli
No inflammatory cells in the background	Inflammatory cells in the background

DISCUSSION

Hurthle cell nodules of the thyroid can result from non - neoplastic conditions such as Hashimoto's Thyroiditis, adenomatous Goitre and graves disease. Conversely neoplastic nodules may be composed predominantly of Hurthle cells. They are referred to as Hurthle cell tumours and represent approximately 5% of thyroid neoplasms.

Hurthle cell neoplasms in turn can be categorized as adenomas which are usually unilateral and carcinomas which have a high incidence of bilaterality.

Hurthle cell tumours have been a source of controversy for several decades. In terms of behaviour studies support that although Hurthle cell adenomas behave in a benign fashion Hurthle cell carcinomas pursue a much more aggressive course than do follicular carcinomas.

Unequivocal capsular / vascular invasion is the `sine qua non' criterion for the diagnosis of Hurthle cell carcinoma.

Fine needle aspiration of the thyroid is a reliable relatively non - invasive method for identifying Hurthle cell nodules likely to be neoplastic and requiring surgical excision for careful histological evaluation.

The diagnosis of Hashimoto's thyroiditis on fine needle aspiration cytology samples is made when lymphoid and Hurthle cell components are present in varying proportions. Problems may arise when the proportion of these two cell components are markedly deviated.

Fine needle aspiration was successful in detecting Hashimoto's thyroiditis in six cases. In three cases Hashimoto's thyroiditis was diagnosed but did not sample the associated lesioon.

These three cases presented as multi nodular goitre[27]. Sampling error in these cases stresses the importance of adequate sampling from several areas of thyroid lesions especially when there is an associated nodule.

In the remaining two cases of Hashimoto's thyroiditis, histologically nodular colloid goitre was reported. A small population of lymphoid cells from peripheral blood was considered as the source of these cells causing misinterpretation. According to laurie MacDonald, A diagnopsis of lymphocytic thyroiditis should not be made when only a few lymphocytes are present[27].

Dr.Gita Jayaram in "Problems in the interpretation of Hurthle cell populations in fine needle aspirates" have encountered these Hurthle cells showing features of plcomorphism in the presence of scant number of lymphocytes such cases needs to be evaluated very carefully with the help of antibody tests[21].

The aspirates from non - neoplastic Hurthle cell nodules of Nodular goitre tend to exhibit tissue fragments of Hurthle cells that display a `Honey comb' pattern. This is incontrast to Hurthle cell neoplasms in which a dissociated pattern are seen. Also in non - neoplatic lesions, the Hurthle cells less commonly display the characteristic nuclear morphology. Macronucleolus is infrequently seen. Other features that may help in differentiation are the admixture of regular follicular epithelium and the frequent occurence of pyknotic nuclei in Hurthle cells.

In two cases of nodular goitre Hurthle cells are associated with ordinary follicular cells arranged in large sheets macrofollicles and abundant colloid. The amount of colloid is not a statistically significant parameter (Gonzalez et al)[22].

Hashimoto's thyroiditis typically have a scant colloid. But one case which had abundant colloid was histological proved as Hashimoto's thyroiditis. Nodular goitre may also have scant colloid with Hurthle cell. This explains that colloid is not a significant parameter in differentiating Hurthle cell lesion from non - neoplastic Hurthle cell lesion.

According to Gita Jayaram in "Problems in the interpretation of Hurthle cell populations in fine needle aspirates" have encountered these cells in thyrotoxic Goitre, Follicular neoplasms and papillary carcinoma. In these conditions the problem is alleviated by the presence of features specific to the predominant lesion[21].

In the case of follicular neoplasm, the thyroid follicular epithelial cells are seen in clusters and in micro acinar groupings with colloid. Hurthle cells are seen in small groups and in cohesive sheets. Histologically well eneapsulated follicular adenoma with Hurthle cell component are seen.

The presence of Hurthle cells in papillary carcinoma does not change the usual behaviour of papillary carcinoma. The architectural pattern rather the cell type predicted the behaviour of the tumour[37] (Sudha Kini).

The accurate diagnosis of Hurthle cell tumour by fine needle aspirate is very important. The aspirates from Hurthle cell lesion show monomorphic cells with loosely cohesive tissue fragments as well as in singles. The nuclear chromatin is finely granular with prominent nucleoli. There were no inflammatory cells in the background. Histological sections showed an encapsulated lesion with Hurthle cells in trabecular pattern. There was no evidence of invasion.

SUMMARY

The accurate diagnosis of Hurthle cell neoplasm by needle biopsy is very important. Benign hyperplastic nodules of Hurthle cell type were commonly seen in Hashimoto's Thyroiditis and nodular goitre. These nodules may reach a large size and clinically present as a solitary nodule.

From our study a polymorphic cellular pattern containing Hurthle cells, normal follicular epithelium and lymphocytes helped in making a correct diagnosis of Hashimoto's Thyroiditis.

`Regressive atypia' is characteristic of non - neoplastic Hurthle cell lesions.

Frequent occurrence of pyknotic nuclei in Hurthle cells in non - neoplastic conditions is also a helpful differentiating feature.

A diagnosis of Hashimoto's Thyroiditis should not be made when there is a scant number of lymphocytes. Such cases are needed to be evaluated carefully with the help of antibody test.

The following characteristics are helpful in making a diagnosis of Hurthle cell neoplasm.

A high percentage of dyshesive Hurthle cells with macro nucleoli, single Hurthle cells (>10%), absence of inflammatory cells in the background. The amount of colloid is not a significant parameter in

distinguishing Hurthle cell tumor from non - neoplastic Hurthle cell lesion.

The presence of Hurthle cells in follicular adenoma and papillary carcinoma does not alter the behaviour of the tumour. The architectural pattern rather than the cell type predicts the behaviour of the tumour.

CONCLUSION

From our study it was observed that the cytological features of Hurthle cells varied in different lesions of the thyroid, thus enabling us to differentiate between non-neoplastic and neoplastic lesions by way of which we could guide the clinicians regarding further therapeutic management.

As Hurthle cell Tumours are being a source of controversy for several decades, distinction between benign and malignant Hurthle cell tumours is not made out easily by cytology as in the case of Follicular neoplasms.

Our findings indicate that a high percentage of Hurthle cells (>90%) as compared with all follicular cells, with >10% being single exhibiting cellular dyshesion, macronucleoli, nuclear enlargement with pleomorphism and few - no lymphocytes is predictive of Hurthle cell Tumours.

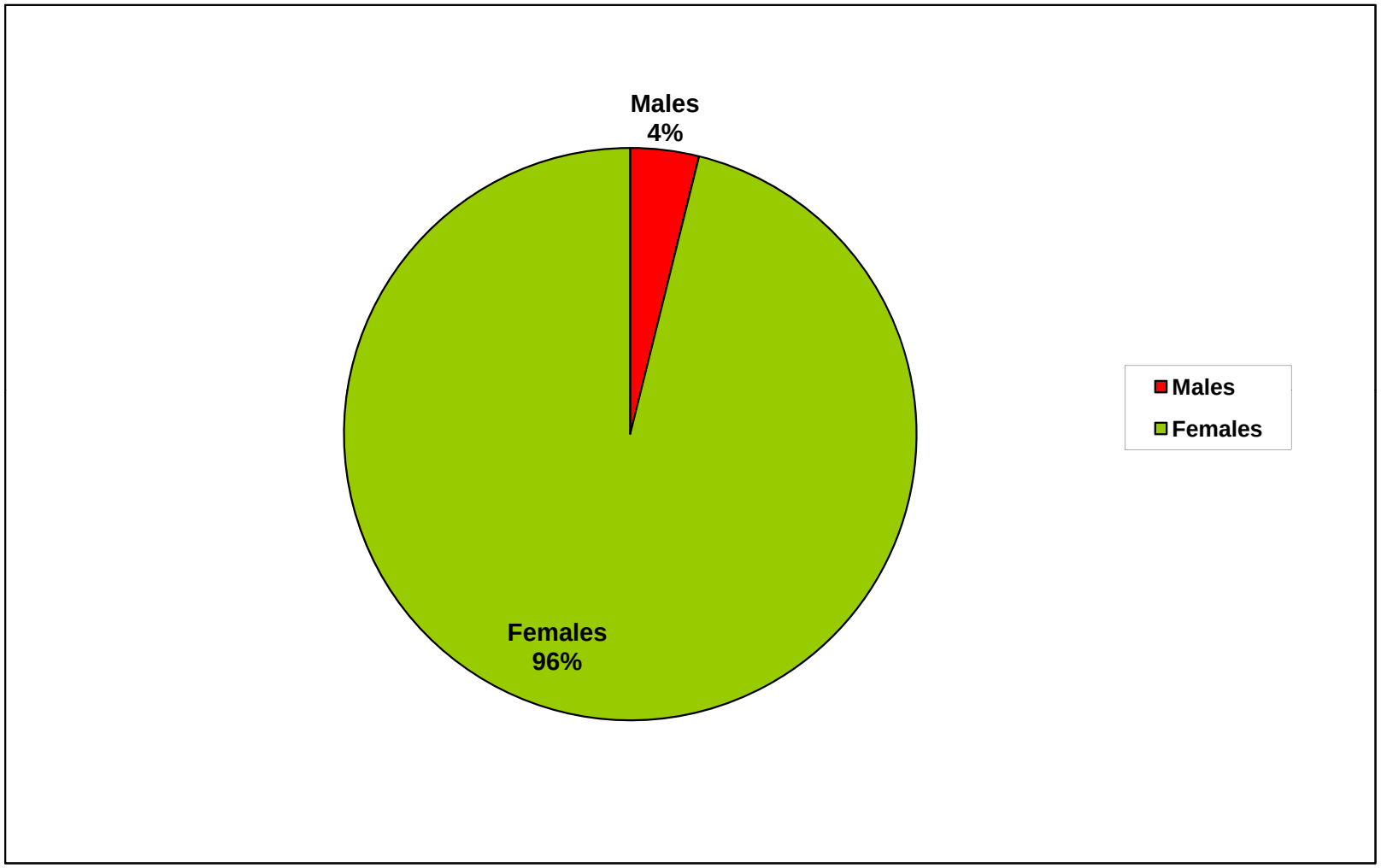
In contrast in non neoplastic lesions Hurthle cells appeared as cohesive clusters or sheets without macronucleoli. In Hashimoto's Thyroiditis there was often a background of chronic inflammatory cells including plasma cells.

In Goitre the Hurthle cells were associated with ordinary follicular cells arranged in large sheets and macrofollicles with abundant collorid.

The amount of colloid in the background is not a significant parameter as we have seen in our study that there were cases of Hashimoto's thryoiditis which showed abundant colloid which is not a feature of Hashimoto's thyroiditis. Likewise there were cases of goitre which showed scant colloid with few lymphocytes, thus explaining why lack of colloid is not a significant parameter in differentiating neoplasms of Hurthle cells from non neoplastic Hurthle cells.

In conclusion, the cytodiagnosis of Hurthle cell lesions of the thyroid by fine needle aspiration cytology is challenging since Hurthle cell neoplasm and non-neoplastic Hurthle cell nodules have some overlapping cytologic features.

When Hurthle cell tumour is suspected, surgical excision of the lesion should be done for histological evaluation.


Males
4%
Females
96%
Males
Females

MASTER CHART

No	Cytology No	Age / Sex	Anatomical Diagnosis	Physiological Diagnosis	Cytological Diagnosis	Histopathological Diagnosis	Biopsy No
1.	300/05	37/F	MNG	Euthyroid	Toxic Goitre	Toxic Goitre	1158/05
2.	501/105	34/F	® SNT	Euthyroid	Colloid Goitre	Nodular Goitre	531/05
3.	675/05	55/F	SNT	Hyper thyroid	Colloid Goitre	Toxic Goitre	634/05
4.	889/05	38/F	MNG	Euthyroid	Colloid Goitre	Hashimoto's thyroiditis	1566/05
5.	981/05	38/F	SNT (L)	Euthyroid	Adenomatous goitre	Nodular Goitre	843/05
6.	1056/05	30/F	SNT ®	Euthyroid	Follicular Neoplasm	Nodular Goitre	895/05
7.	1069/05	32/F	Diffuse	Euthyroid	Colloid Goitre	Nodular Goitre	1030/05
8.	1152/05	48/F	MNG	Hyper thyroid	Toxic Goitre	Toxic Goitre	1237/05
9.	1233/05	45/F	MNG	Hyper thyroid	Adenomatous hyperplasia with toxic	Follicular Adenoma	1345/05
10.	1370/05	19/F	SNT ®	Euthyroid	Nodular Goitre		
11.	1406/05	58/F	MNG	Euthyroid	Nodular Goitre		
12.	1407/05	45/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
13.	1423/05	50/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
14.	1428/05	32/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
15.	1453/05	25/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
16.	1467/05	30/F	MNG	Euthyroid	Nodularcolloid goitre	Pap.CA	1850/05
17.	1473/05	37/F	Diffuse	Euthyroid	Nodularcolloid goitre		
18.	1478/05	50/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
19.	1480/05	33/F	Diffuse	Euthyroid	Hashimoto's thyroiditis	Adenomatous goitre	1683/05
20.	1481/05	20/F	Diffuse	Euthyroid	Lymphocytic thyroiditis		
21.	1496/05	42/F	Diffuse	Euthyroid	Colloid goitre		
22.	1501/05	25/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
23.	1507/05	65/F	Diffuse	Euthyroid	Colloid goitre		
24.	1509/05	32/F	Diffuse	Euthyroid	Hashimoto's thyroiditis	Hashimoto's thyroiditis	1735/05
25.	1527/05	58/M	SNT ®	Euthyroid	Colloid goitre	Colloid goitre	1899/05
26.	1529/05	34/F	SNT ®	Euthyroid	Colloid goitre		
27.	1532/05	37/F	MNG	Euthyroid	Colloid goitre		

28.	1557/05	55/F	Diffuse	Euthyroid	Colloid goitre		
29.	1560/05	45/M	MNG	Euthyroid	Pap.ca thyroid		
30.	1566/05	65/F	MNG	Hypothyroid	Nodular colloid goitre	Nodular colloid goitre	2057/05
31.	1568/05	40/F	SNT	Euthyroid	Hashimoto's thyroiditis		
32.	1570/05	41/F	Diffuse	Euthyroid	Nodular colloid goitre		
33.	1574/05	23/F	Diffuse	Euthyroid	Adenomatous goitre		
34.	1579/05	22/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
35.	1588/05	27/F	Diffuse	Euthyroid	Hashimoto's thyroiditis	Hashimoto's thyroiditis	1898/05
36.	1594/05	33/F	SNT ®	Euthyroid	Nodularcolloid goitre	Nodular colloid goitre	1402/05
37.	1596/05	21/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
38.	1628/05	63/F	SNT	Euthyroid	Hashimoto's thyroiditis		
39.	1648/05	30/F	Diffuse	Euthyroid	Nodularcolloid goitre		
40.	1654/05	27/F	Diffuse	Euthyroid	Nodularcolloid goitre		
41.	1655/05	47/F	Diffuse	Euthyroid	Nodularcolloid goitre		
42.	1660/05	65/F	SNT	Euthyroid	Hashimoto's thyroiditis		
43.	1661/05	40/F	MNG	Euthyroid	Nodularcolloid goitre		
44.	1666/05	28/F	Diffuse	Euthyroid	Nodularcolloid goitre		
45.	1667/05	47/F	MNG	Euthyroid	Nodularcolloid goitre	Nodular colloid goitre	2524/05
46.	1671/05	30/F	Diffuse	Hyper	Nodularcolloid goitre		
47.	1676/05	35/F	SNT®	Euthyroid	Cystic degeneration		
48.	1693/05	32/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
49.	1704/05	28/F	MNG	Euthyroid	Hashimoto's thyroiditis		
50.	1718/05	34/F	Diffuse	Euthyroid	Nodularcolloid goitre		
51.	1719/05	30/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
52.	1726/05	50/F	® SNT	Euthyroid	Nodularcolloid goitre	Nodular colloid goitre	1651/05
53.	1728/05	46/F	SNT ®	Euthyroid	Hashimoto's thyroiditis		
54.	1732/05	16/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
55.	1733/05	32/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
56.	1735/05	18/F	Diffuse	Euthyroid	Nodularcolloid goitre		
57.	1736/05	26/F	Diffuse	Euthyroid	Hyperplastic nodule		
58.	1738/05	21/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
59.	1740/05	26/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		

60.	1774/05	52/F	SNT ®	Euthyroid	Nodularcolloid goitre		
61.	1776/05	35/F	Diffuse	Euthyroid	Nodularcolloid goitre		
62.	1778/05	27/F	Diffuse	Hyperthyroid	Toxic goitre		
63.	1789/05	27/F	SNT ®	Euthyroid	Nodularcolloid goitre	Nodular colloid goitre	3336/05
64.	1790/05	27/F	® SNT	Euthyroid	Adenomatous goitre	Pap.CA	1789/05
65.	1812/05	40/F	® SNT	Euthyroid	Nodularcolloid goitre		
66.	1826/05	35/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
67.	1828/05	M	Diffuse	Euthyroid	Nodularcolloid goitre		
68.	1835/05	30/F	Diffuse	Euthyroid	Nodularcolloid goitre		
69.	1845/05	27/F	MNG	Euthyroid	Nodularcolloid goitre		
70.	1848/05	50/F	SNT ®	Euthyroid	Nodularcolloid goitre		
71.	1849/05	42/F	SNT ®	Euthyroid	Nodularcolloid goitre		
72.	1851/05	35/F	Diffuse	Euthyroid	Nodularcolloid goitre		
73.	1857/05	55/F	MNG	Euthyroid	Papillary Carcinoma		2090/05
74.	1870/05	35/F	Diffuse	Euthyroid	Nodularcolloid goitre		
75.	1872/05	50/F	Diffuse	Hyperthyroid	Toxic goitre		
76.	1884/05	30/F	MNG	Euthyroid	Nodularcolloid goitre		
77.	1887/05	35/F	SNT ®	Euthyroid	Nodularcolloid goitre		
78.	1894/05	45/F	SNT ®	Euthyroid	Nodularcolloid goitre		
79.	1899/05	25/F	MNG	Euthyroid	Nodularcolloid goitre		
80.	1904/05	24/F	SNT ®	Euthyroid	Nodularcolloid goitre		
81.	1906/05	50/F	SNT (L)	Euthyroid	Nodularcolloid goitre		
82.	1909/05	25/F	MNG	Euthyroid	Nodularcolloid goitre		
83.	1985/05	40/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
84.	1986/05	35/F	SNT ®	Euthyroid	Adenomatous goitre		
85.	1987/05	30/F	Diffuse	Euthyroid	Colloid goitre		
86.	1993/05	64/M	SNT®	Euthyroid	Nodularcolloid goitre	Nodular colloid goitre	2235/05
87.	2000/05	50/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
88.	2021/05	58/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
89.	2042/05	25/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
90.	2087/05	25/F	MNG	Euthyroid	Hashimoto's thyroiditis	Hashimoto's thyroiditis	1981/05
91.	2121/05	23/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		

92.	2229/05	40/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
93.	2314/05	32/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
94.	2319/05	50/F	MNG	Euthyroid	Nodular colloid goitre		
95.	2322/05	45/F	MNG	Euthyroid	Nodular colloid goitre		
96.	2323/05	18/F	MNG	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	2472/05
97.	2324/05	40/F	SNT (L)	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	2202/05
98.	2329/05	30/F	SNT ®	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	2064/05
99.	2334/05	29/F	Diffuse	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	2200/05
100.	2346/05	F	MNG	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	2592/05
101.	2355/05	25/F	Diffuse	Euthyroid	Nodular colloid goitre		
102.	2482/05	20/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
103.	2490/05	51/F	SNT ®	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	5619/05
104.	2562/05	66/F	MNG	Euthyroid	Nodular colloid goitre		
105.	2600/05	35/F	SNT ®	Euthyroid	Nodular colloid goitre		
106.	2621/05	40/F	MNG	Euthyroid	Nodular colloid goitre		
107.	2632/05	50/F	MNG	Euthyroid	Pap.CA		
108.	2798/05	25/F	SNT ®	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	4797/05
109.	2800/05	30/F	MNG	Euthyroid	Nodular colloid goitre	Hashimoto's thyroiditis	3800/05
110.	3309/05	32/F	Diffuse	Euthyroid	Hashimoto's thyroiditis	Hashimoto's thyroiditis	6485/05
111.	3353/05	20/F	SNT (L)	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	4104/05
112.	3390/05	40/F	SNT ®	Euthyroid	Hashimoto's thyroiditis	Hashimoto's thyroiditis	4197/05
113.	3438/05	32/F	Diffuse	Euthyroid	Toxic		
114.	3443/05	29/F	SNT ®	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	3025/05
115.	3439/05	37/F	MNG	Euthyroid	Hyperplastic goitre		
116.	3440/05	27/F	MNG	Euthyroid	Adenomatous goitre		
117.	3441/05	60/F	SNT (L)	Euthyroid	Nodular colloid goitre		
118.	3442/05	24/F	Diffuse	Hyperthyroid	Toxic goitre		
119.	3444/05	60/M	SNT (L)	Euthyroid	Follicular neoplasm		
120.	3539/05	19/F	SNT	Euthyroid	Hashimoto's thyroiditis		
121.	3540/05	40/F	MNG	Euthyroid	Hashimoto's thyroiditis		
122.	3541/05	28/F	MNG	Euthyroid	Hashimoto's thyroiditis		
123.	3542/05	40/F	MNG	Euthyroid	Nodular colloid goitre		

124.	3543/05	24/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
125.	3544/05	32/F	MNG	Euthyroid	Hashimoto's thyroiditis		
126.	3612/05	40/F	Diffuse	Hypothyroid	Hashimoto's thyroiditis		
127.	3613/05	20/F	MNG	Euthyroid	Hashimoto's thyroiditis	MNG	5360/05
128.	3614/05	14/F	Diffuse	Euthyroid	Nodular colloid goitre		
129.	3615/05	24/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
130.	3774/05	20/F	SNT	Euthyroid	Hyperplastic goitre		
131.	3775/05	19/F	Diffuse	Hypothyroid	Hashimoto's thyroiditis		
132.	3776/05	25/F	MNG	Hypothyroid	Hashimoto's thyroiditis		
133.	3777/05	42/M	MNG	Euthyroid	Hashimoto's thyroiditis	MNG with Hashimoto's thyroiditis	4807/05
134.	3778/05	48/F	® SNT	Euthyroid	Thyroiditis		
135.	3779/05	26/F	SNT	Hypothyroid	Colloid goitre	Pap.CAwith Hashimoto's thyroiditis	3446/05
136.	3780/05	26/F	Diffuse	Euthyroid	Nodular colloid goitre		
137.	3781/05	15/F	MNG	Euthyroid	Lymphocytic thyroiditis		
138.	3782/05	26/F	Diffuse	Euthyroid	Colloid goitre		
139.	3783/05	25/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
140.	3784/05	22/F	MNG	Euthyroid	Hashimoto's thyroiditis with toxic		
141.	3785/05	26/F	MNG	Hypothyroid	Hashimoto's thyroiditis		
142.	3786/05	22/F	Diffuse	Hypothyroid	Hashimoto's thyroiditis		
143.	3787/05	16/F	Diffuse	Euthyroid	Lymphocytic thyroiditis		
144.	3788/05	16/F	Diffuse	Euthyroid	Lymphocytic thyroiditis		
145.	3868/05	39/F	SNT (L)	Euthyroid	Lymphocytic thyroiditis		
146.	3869/05	21/F	SNT ®	Euthyroid	Nodular colloid goitre		
147.	3870/05	35/F	MNG	Euthyroid	Hashimoto's thyroiditis		
148.	3871/05	19/F	MNG	Euthyroid	Hashimoto's thyroiditis		
149.	3872/05	35/F	MNG	Euthyroid	Pap.CA		
150.	3873/05	45/F	MNG	Euthyroid	Hashimoto's thyroiditis		
151.	3910/05	37/M	MNG	Euthyroid	Hashimoto's thyroiditis	MNG with Hashimoto's thyroiditis	4255/05
152.	3927/05	23/F	MNG	Euthyroid	Pap.CA	Pap.CA	3499/05
153.	3937/05	33/F	MNG	Hyperthroid	Hurthle cell tumour		
154.	3938/05	27/F	MNG	Euthyroid	Nodular colloid goitre		
155.	3939/05	55/F	SNT ®	Euthyroid	Nodular colloid goitre		

156.	3940/05	35/F	MNG	Hypothyroid	Hashimoto's thyroiditis		
157.	3941/05	36/F	Diffuse	Euthyroid	Colloid goitre		
158.	3942/05	26/F	MNG	Euthyroid	Nodular colloid goitre		
159.	3943/05	21/F	SNT	Euthyroid	Hashimoto's thyroiditis	Follicular adenoma	3873/05
160.	3974/05	60/F	SNT ®	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	3326/05
161.	4026/05	46/F	MNG	Hypothyroid	Hashimoto's thyroiditis		
162.	4027/05	32/F	MNG	Euthyroid	Hashimoto's thyroiditis		
163.	4028/05	37/F	SNT	Euthyroid	Nodular colloid goitre		
164.	4029/05	35/F	SNT (L)	Euthyroid	Follicular neoplasm		
165.	4030/05	38/F	Diffuse	Euthyroid	Hashimoto's thyroiditis		
166.	4135/05	57/F	SNT ®	Euthyroid	Nodular colloid goitre	Hashimoto's thyroiditis	5000/05
167.	4230/05	35/F	Diffuse	Euthyroid	Colloid goitre		
168.	4231/05	33/F	SNT ®	Euthyroid	Nodular colloid goitre		
169.	4239/05	15/F	MNG	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	4032/05
170.	4232/05	25/F	MNG	Euthyroid	Adenomatous hyperplasia		
171.	4233/05	33/F	Diffuse	Euthyroid	Colloid goitre		
172.	5178/05	50/F	SNT (L)	Euthyroid	Colloidcyst	Nodular colloid goitre	4254/05
173.	5327/05	52/F	SNT	Euthyroid	Pap.CA	Pap.CA	4932/05
174.	5362/05	40/F	SNT ®	Euthyroid	Nodular colloid goitre	Nodular colloid goitre	4869/05
175.	5660/05	30/F	MNG	Euthyroid	Nodular colloid goitre	Hashimoto's thyroiditis with focal toxic	5002/05
176.	6352/05	32/F	MNG	Euthyroid	Hashimoto's thyroiditis	Nodular colloid goitre with Hashimoto's thyroiditis	5972/05
177.	6632/05	35/F	Diffuse	Euthyroid	Nodular colloid goitre	Hashimoto's thyroiditis	5928/05
178.	6966/05	40/F	MNG	Euthyroid	Hashimoto's thyroiditis	Hashimoto's thyroiditis	5926/05
179.	5605/04	45/F	SNT	Euthyroid	Hurthle cell tumour	Hurthle cell adenoma	6318/04
180.		31/F	SNT (L)	Euthyroid	Pap.CA	Pap.CA	