"A CROSS SECTIONAL STUDY TO DETERMINE THE ROLE OF FINE NEEDLE ASPIRATION CYTOLOGY IN THYROID SWELLINGS"

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Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. S.
in
GENERAL SURGERY

Under the Guidance of

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BELGAUM, KARNATAKA

MAY - 2012

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ACKNOWLEDGEMENT

I take this opportunity to express my respect and heartfelt gratitude to all my teachers.

First and foremost I would like to express my sincere gratitude and appreciation for my guide **Dr. P. S. Pattanshetti** $_{\text{MS,}}$ Professor, Department of Surgery, for his constant guidance, valuable suggestions, unparalleled encouragement and co-operation provided to me throughout the course of study. It has been a great pleasure and privilege to work under him. Without his immense professional insight and guidance I could have not completed this study.

I avail this opportunity to thank **Dr. V. M. Uppin** $_{\text{MS}}$ Professor and Head, Department of Surgery for his keen interest, unparalleled encouragement and co-operation.

I express my sincere gratitude to **Dr. V. D. Patil** $_{\text{MD, DCH}}$ Principal, J. N. Medical College, Belgaum, **Dr. M. V. Jali** $_{\text{MD}}$ Director and Chief Executive, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum for allowing me to utilize the facilities in above institution for the dissertation.

I express my sincere gratitude to **Dr. A. S. Godhi** $_{\text{MS, FICS,}}$ **Dr. S. M. Uppin** $_{\text{MS, FICS,}}$ **Dr. M. S. Sangolli** $_{\text{MS}}$ **Dr. S. S. Shimikore** $_{\text{MS}}$ **Dr. S. C. Metgud** $_{\text{MS}}$ **Dr. A. S. Gogate** $_{\text{MS}}$ **Dr. A. C. Pangi** $_{\text{MS}}$ **Dr. R. R. Rao** $_{\text{MS}}$ **Dr. B. M. Kajagar** $_{\text{MS}}$ **Dr. S. N. Halbhavi** $_{\text{MS}}$ **Dr. R. S. Koujalagi** $_{\text{MS}}$ **Dr. V. M. Patanshetti** $_{\text{MS}}$ **Dr. Manoj Togale** $_{\text{MS}}$ **Dr. A Mahajan** $_{\text{MS}}$ **Dr. Rahul K** $_{\text{MS}}$ for their valuable support and guidance during the course of the study. I thank them for their inspiration and moral support.

I sincerely thank my post graduate colleagues **Dr. Chandrashekhar M, Dr. Abhay Agrawal, Dr. Chetan Hoskatti, Dr. Vasant Teggimani, Dr. Chintan Soni, Dr. Rohit Muvva, Dr. Manohar S, Dr. Yogesh J K, Dr. Shawn Thomas, Dr. Amit Nagpure,** and **Dr. Allamprabhu** for their kind help rendered throughout the course of my study.

I sincerely thank all the **Technical Staff** at Clinical Laboratory, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum for their kind support and timely help during the study.

This would have not been possible without the co-operation and understanding of all the **Patients** involved in the study. I also thank the authors of numerous publications whose knowledge have been freely utilized in the preparation.

With deep sense of gratitude and affection, I am very thankful to my parents **Mr. P. C. Chacko** and **Mrs. Leela Chacko** who always have been a pillar of strength for me.

I thank my beloved brother **Arjun and** sister **Anu** for their continuous support they have rendered, not only during course of this study, but in my life as well.

Last but not the least; I would be failing in my duty if I don't thank our ward **Nursing Staff** without whose co-operation this study would not have been completed.

Finally, I thank the **ALMIGHTY** for all the blessings.

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LIST OF ABBREVIATIONS USED

AntiTG	-	Antithyroglobulin
AntiTPO	-	Anti thyroid peroxidase
DIT	-	Di iodo tyrosine
FNA	-	Fine needle aspiration
FNAB	-	Fine needle aspiration biopsy
FNNAB	-	Fine needle non aspiration biopsy
FNAC	-	Fine needle aspiration cytology
FTI	-	Free thyroxine index
HT	-	Hemithyroidectomy
MIT	-	Mono iodo tyrosine
MNG	-	Multi nodular goiter
NTT	-	Near total thyroidectomy
PBI	-	Protein bound iodine
RLN	-	Recurrent laryngeal nerve
STT	-	Sub total thyroidectomy
T_3	-	Tri iodo thyronine
T_4	-	Thyroxine
TBG	-	Thyroxine binding globulin
TBPA	-	Thyroxin binding prealbumin
TRH	-	Thyrotropin releasing hormone
TSH	-	Thyroid stimulating hormone
USG	-	Ultrasonography
WHO	-	World health organization

ABSTRACT

Background and Objectives

Thyroid nodular (TN) lesions are a common clinical problem in the world. A solitary thyroid nodule is a palpable swelling in thyroid gland that has otherwise a normal appearance. A variety of tests have been employed to separate benign from malignant thyroid nodules. These tests include isotope scanning and FNAC. Combined use of isotope scanning, fine needle aspiration cytology, and histopathology of thyroid offers the best diagnostic strategy. The present study was undertaken to assess the accuracy of Fine needle aspiration cytology in patients presenting with thyroid swelling.

Methodology

The present one year cross sectional study was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. A total of 70 patients with thyroid swelling were studied. The correlation of FNAC diagnosis with HPR findings was analysed by calculating sensitivity, specificity, positive predictive value and negative predictive value.

Results

Total number of patients were 70 of which 62 (88.57%) were females and 8 (11.43%) were males. The mean age was 44.93 ± 13.58 years with range being with 20 to 78 years. All the patients (100%) presented with swelling. Majority presented with bilateral and left sided swelling of the thyroid (34.29%). All (100%) reports were benign with FNAC reports showing colloid material in majority and remaining being follicular neoplasm. HPR, which is the gold standard reported Multi nodular goiter in 46 cases, Colloid goiter in 13 cases, Follicular adenoma in 10 cases and remaining one being Hurthle cell adenoma with Hishimotos thyroiditis.

Conclusion and interpretation

The Sensitivity and Specificity of FNAC in predicting diagnosis was 90.91% and 100% respectively. Similarly the Positive predicative value and Negative predicative value for the same was 100% and 98.33% respectively.

Keywords

Fine needle aspiration cytology; Thyroid nodules; Thyroid swelling;

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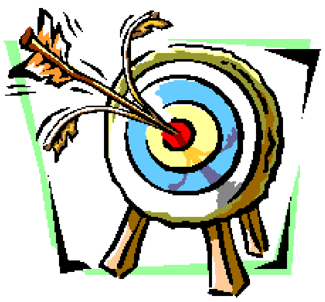

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INTRODUCTION

Thyroid nodules are common clinical findings and have a reported prevalence of 4% to 7% in the adult population.[1-3] Discrete thyroid swellings are common and are present in 3-4% population in UK and USA.[4,5] Thyroid swellings are four times more common in females.[6] The incidence increases with age, a history of radiation exposure and diet containing goitrogens.[3] Thyroid swellings can be isolated or dominant. True incidence of thyroid nodularity is less apparent on clinical classification. When such glands are exposed at operation, clinically impalpable nodules are often detected.[7] The usual presentation of thyroid disease is with swelling, pressure symptoms or signs of toxicity.[8] Importance of discrete thyroid nodule lies in the risk of neoplasia as compared to other thyroid swellings. Fifteen percent of isolated swellings are malignant.[9]

The vast majority of these nodules are non neoplastic lesions or benign neoplasms. However, the distinction of these benign lesions from a malignant nodule cannot be based reliably on the clinical presentation alone. Complications of surgery are possible injury to the recurrent laryngeal nerve, hypoparathyroidism and thyroid hormone dependence.

The available tools to know the nature of a thyroid nodule are thyroid function tests, thyroid antibody titers, isotope scans, ultrasonography and fine needle aspiration cytology.[10] Several diagnostic tests such as scintigraphy (with $I^{1,2,3}$ or 99mTC pertechnetate), ultrasonography and fine needle aspiration cytology (FNAC) have been used to differentiate benign from malignant thyroid disease pre operatively. FNAC has now supplanted most of the other tests for pre-operative evaluation of thyroid nodules.[11-13]

Due to its simplicity, low cost and absence of major complications, this procedure is being performed on an increasing number of patients, which has led to the detection of thyroid cancers at earlier stages, resulting in better outcome of patients.

FNAC is an integral part of selected patient management but comprises only part of overall evaluation.[14] FNAC is usually performed in clinically palpable nodules. If nodules are not palpable, then this procedure can be performed under ultrasound guidandance.[15] Overall diagnostic efficacy of FNAC is 94.2%. However, only limitation is to differentiate between follicular adenoma and carcinoma. Major load of unnecessary surgery can be avoided by perfection and routine use of FNAC in solitary thyroid nodules.[16] FNAC is a simple and cost effective biopsy technique that can be performed on out-patient basis.

Practice guidelines set forth by the American thyroid Association and National Comprehensive Cancer Network state that FNA should be used as the initial diagnostic test because of its superior diagnostic reliability and cost effectiveness before both thyroid scintigraphy and ultrasonography.[17]

Although several studies have been done to prove the efficacy of FNAC in diagnosing thyroid swelling, the sensitivity of studies done to assess the efficacy of FNAC ranges from 65% to 98% and specificity ranges 72% to 100%.[18]

Nevertheless, like any other test FNAC has its limitations. The reported pitfalls are those related to specimen adequacy, sampling techniques, the skill of the physician performing the aspiration, the experience of the pathologist interpreting the aspirate and overlapping cytological features between benign and malignant follicular neoplasm.[19-21]

Because of this discrepancy in the result and the fact that no similar studies were conducted in our setup in recent and past, the present study was undertaken to assess the accuracy of Fine needle aspiration cytology in patients presenting with thyroid swelling.

OBJECTIVES

The objective of the present study was to find out the sensitivity, specificity, positive predictive value and the negative predictive value of FNAC by comparing FNAC report with HPR in patients presenting with thyroid swelling.

REVIEW OF LITERATURE

Historical aspects[22,23]

The thyroid gland was previously referred to as a laryngeal gland and was subsequently named thyroid by Wharton in 1645. Existence of thyroid gland was known to Galen (2 A.D), who thought that it provided fluid for lubrication of larynx.

Sir Astley Cooper (1768-1841) said it has the function of secretion. Thyroxine (T_4) was isolated by Kendall in 1965 and it was synthesized by the Harrington and Banger in 1927. In 1953 the important discovery of 3, 5, 3 Tri-iodothyronine was made by Cross and Pitt-rivers and by Roche, Liesitsky and Michel simultaneously. This was proved to be more effective than thyroxine itself. With the introduction of radioactive iodine in 1934, it was possible for the clear understanding of thyroid physiology.

In 1986 Bouman discovered Iodine in considerable amount in thyroid gland. Iodine was first identified by French Chemist Courtisis in 1812 who found it in ash of burnt seaweed. But Chatin during 1850-1876 was the first to conclude iodine deficiency as a principle cause of goitre. Experimental goitre was produced by Chesney (1888) in John Hopkins University in Rabbits, by feeding them with cabbage and established cabbage as one of the goitrogenic agents. Potassium thiocyanate was found to produce goitre, in some of the hypertensive patients.

Paracelsus (1492-1541) showed relationship between endemic goitre and cretinism. In 1850 Curling, a Surgeon at London hospital, gave account of cretinism in two children and recorded complete absence of thyroid gland at postmortem in both the cases. Gull in 1874 described cretinoid change in adults. In 1878 Ord suggested the term Myxoedema to describe the condition occurring after total or partial thyroidectomy.

Early operations

The first credible account of thyroid surgery was given in 1170, by Roger Frugardi of Salerno, in the Bamberg manuscripts. Goitres which failed to respond were removed by finger dissection, insertion of setons, ligation enmasse, and application of caustic powder. All such procedures were liable to major complications and increased mortality.

The first well-documented partial thyroidectomy was undertaken in Paris in 1791 by Pierre Joseph Desault (1744-1795), during the terror of French Revolution.

Guillaume Dupuytren (1777-1835) also in Paris, undertook total thyroidectomy in 1808 for a Goitre weighing 1.2 kgs, but the patient died. In 1821, Johann Hedenus (1760-1836) of Dresden, successfully removed six “suffocating goitre”, by dissection and ligation of all the arteries. This achievement was not equalled for next forty years. The results of most thyroid operations were disastrous until the second half of 19th century. Bleeding, which could not be controlled, and sepsis, cause of which was not known, often proved fatal.

By the 19th century the usual indications for surgery were suffocation and dysphagia. The overall mortality was over 40% and many surgeons advised against operating on goiters and considered it as one of the most thankless, undertakings. The advances, which followed the advent of general anaesthesia (1840's), antisepsis (1860's) and haemostasis (1870's), enabled surgeons to undertake more thyroid operations, and device new ones, with greatly reduced mortality. Between 1850 and 1977, the world wide operative mortality fell to around 20%.

The leading thyroid surgeons at this time were Theodor Kocher (1841-1917) and Theodor Billroth (1829-1894). Both of them performed thousands of thyroidectomies, with progressively better results. By 1883, operative mortality had fallen to 12% and by the end of the century to 3%.

Theodor Kocher was Professor of Surgery in Berne, Switzerland. Kocher operated on more than 500 patients. He advocated gentle meticulous surgery that spared yet to be discovered parathyroid glands and anatomical appreciation of recurrent laryngeal nerve. With application of these principles, mortality of thyroid surgery decreased from more than 59% to approximately 0.2%. Even more important was the discovery by Kocher that total thyroidectomy was followed by development of myxoedema and he demonstrated that this complication could be prevented by subtotal thyroidectomy. For this work in medical understanding and care in diseases of thyroid gland Kocher was awarded Nobel Prize in 1909. Thoder Kocher is regarded as father of thyroid surgery.

Because operations were now safe, many goiters were removed mainly for cosmetic reasons. Usually general anaesthesia with ether or chloroform was used, but local anaesthesia with cocaine was sometimes used. The Collar incision introduced by Tules Boeckel (1848-1927) of Strasbourg was adopted widely.

Europe was the Cradle of thyroid Surgery in 19th century. In 1890’s American Surgeons visited the main European centres and began to make important contributions in the early twentieth century. Notable among these were Halsted, Charles Maya (1865-1939) and George Crile (1864-1943). The indications of operation were extended to include the prevention of complications, especially in patients with thyrotoxicosis and thyroid cancer. The latter was sometimes an unexpected discovery after operation. For this reason total lobectomy with removal of the isthmus and pyramidal lobe came to be used.

This reduced the need for further operations when malignancy was found. The first transplantation of thyroid was recorded by Payr in 1906. He transplanted a portion of the thyroid gland from a woman into the spleen of her myxoedemic daughter.

Following the development of non-surgical measures to manage most cases of hyperthyroidism and colloid goitre due to availability of radioactive iodine, antithyroid drugs and iodination of salt, surgical attention was directed to nodules, both benign and malignant but with emphasis on the latter.

In the 1940’s and 1950’s, attempts were initiated to determine the frequency of carcinoma producing thyroid nodules and criteria for operation for thyroid nodules. Thyroid scans using ^{131}I became available and assumed a frequently used role in identifying hypo functional nodules. However it soon became evident that this procedure was of little help in separating the malignant from the numerous benign thyroid nodules.

With the development of techniques such as FNAC and ultrasound, the performance of thyroidectomy has become selective, unlike in the past when surgery was recommended for nearly all Multinodular goitres.

Surgical anatomy

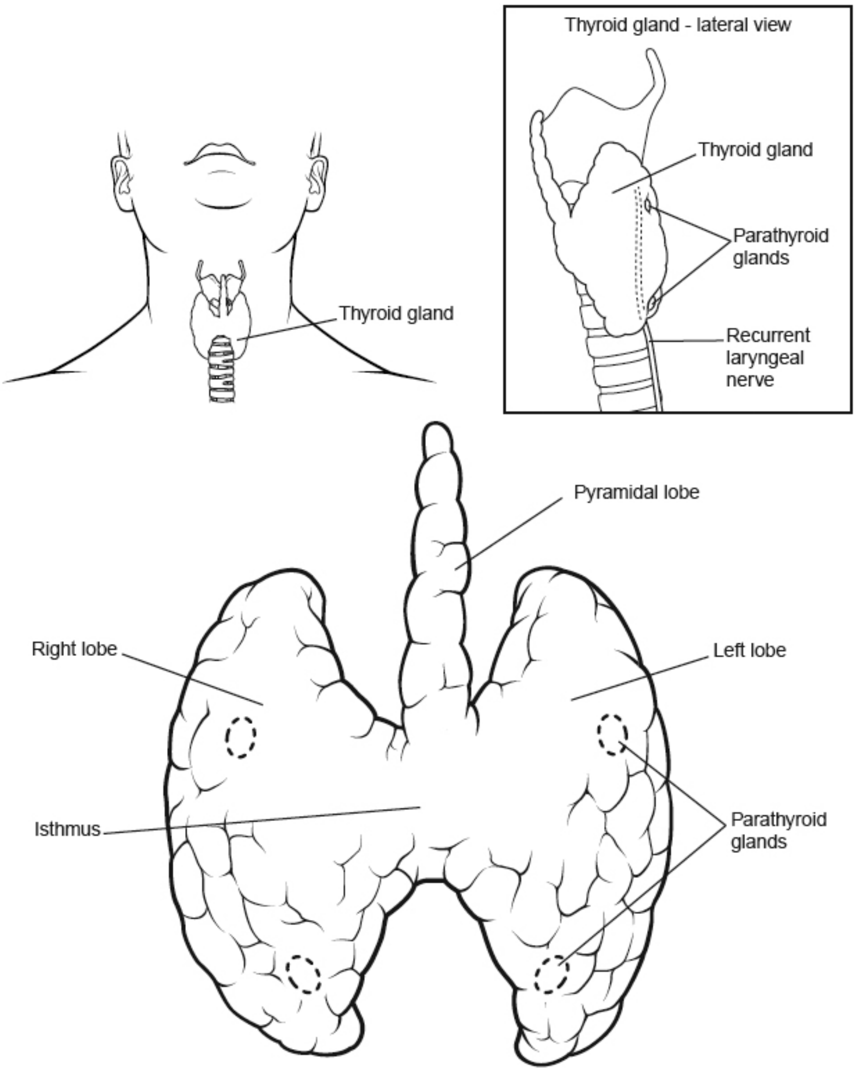


Figure 1. Thyroid gland, anterior and lateral view

The thyroid is a highly vascular, brownish-red gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic. The gland varies from an H to a U shape and is formed by two elongated lateral lobes with superior and inferior poles connected by a median isthmus, with an average height of 12 to 15 mm, overlying the second to fourth tracheal rings. Occasionally, the isthmus is absent, and the gland exists as two distinct lobes.[25,26]

Although thyroid weight varies, it averages 20 gm in adults (it is slightly heavier in women). Remnants of the thyroglossal duct may persist as accessory nodules or cysts of thyroid tissue between the isthmus and the foramen caecum of the tongue base. Usually, two pairs of parathyroid glands lie in proximity to the thyroid gland.

Innervation of the thyroid

Principal innervation of the thyroid gland derives from the autonomic nervous system. Parasympathetic fibers come from the vagus nerves, and sympathetic fibers are distributed from the superior, middle, and inferior ganglia of the sympathetic trunk. These small nerves enter the gland along with the blood vessels. Autonomic nervous regulation of the glandular secretion is not clearly understood, but most of the effect is postulated to be on blood vessels, hence the perfusion rates of the glands.

Structure

Under the middle layer of deep cervical fascia, the thyroid has an inner true capsule, which is thin and adheres closely to the gland. Extensions of this capsule within the substance of the gland form numerous septae, which divide it into lobes and lobules. The lobules are composed of follicles, the structural units of the gland, which consist of a layer of simple epithelium enclosing a colloid-filled cavity.

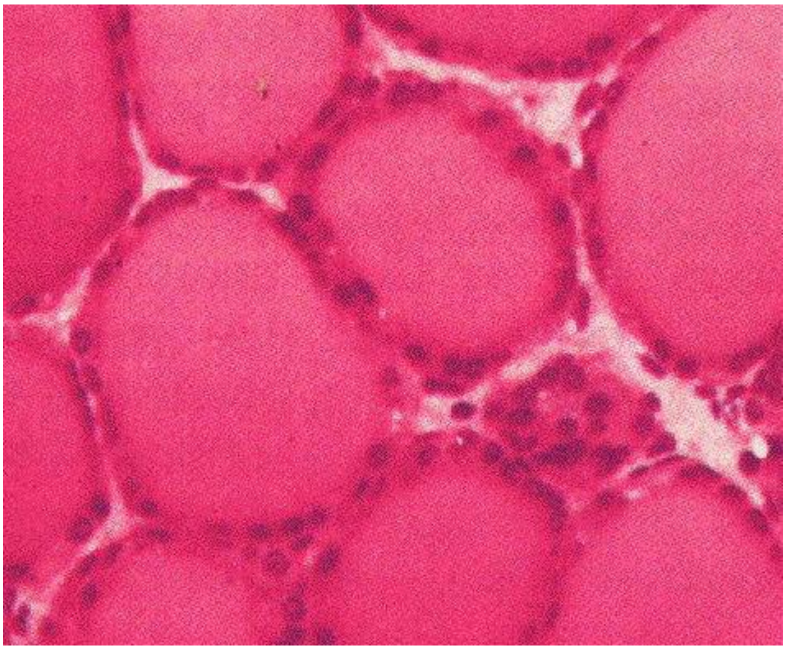


Figure 2. Follicles of the thyroid gland, consisting of a layer of simple epithelium enclosing a colloid-filled cavity

The colloid (pink on hematoxylin and eosin) contains an iodinated glycoprotein, iodothyroglobulin, a precursor of thyroid hormones. Follicles vary in size, depending upon the degree of distention, and they are surrounded by dense plexuses of fenestrated capillaries, lymphatic vessels, and sympathetic nerves.

Epithelial cells are of 2 types: principal cells (follicular) and parafollicular cells (C, clear, light cells). Principal cells are responsible for formation of the colloid (iodothyroglobulin), whereas parafollicular cells produce the hormone calcitonin, a protein central to calcium homeostasis. Parafollicular cells lie adjacent to the follicles within the basal lamina.

Fascia and Ligament

The thyroid gland is ensheathed by the visceral fascia, a division of the middle layer of deep cervical fascia, which attaches it firmly to the laryngoskeleton. The anterior suspensory ligament extends from the superior-medial aspect of each thyroid lobe to the cricoid and thyroid cartilage. The posteromedial aspect of the gland is attached to the side of the cricoid cartilage, first and second tracheal ring, by the posterior suspensory ligament (ie, Berry ligament). This firm attachment of the gland to the laryngoskeleton is responsible for movement of the thyroid gland and related structures during swallowing.

On its way to the larynx, the recurrent laryngeal nerve usually passes deep to the Berry ligament or between the main ligament and its lateral leaf. Deep to the ligament, but lateral to the nerve, is a posteromedial portion of the thyroid lobe, which may be overlooked during thyroidectomy.

Strap Muscles

The lateral surface of the thyroid is covered by the sternothyroid muscle, and its attachment to the oblique line of the thyroid cartilage prevents the superior pole from extending superiorly under the thyrohyoid muscle. More anteriorly are the sternohyoid and superior belly of the omohyoid muscle, overlapped inferiorly by the anterior border of the sternocleidomastoid muscle. The sternohyoid and sternothyroid muscles are joined in the midline by an avascular fascia that must be incised to retract the strap muscle laterally in order to access the thyroid gland during thyroidectomy. If strap muscles are to be transected for better exposure, do so high in the neck, because the motor nerve supply from the ansa cervicalis enters these muscles inferiorly.

Vascular Anatomy and Laryngeal Innervation

The arterial supply to the thyroid gland comes from the superior and inferior thyroid arteries and, occasionally, from the thyroidea ima. These arteries have abundant collateral anastomoses with each other, ipsilaterally and contralaterally. The thyroid ima is a single vessel that, when present, originates from the aortic arch or the innominate artery and enters the thyroid gland at the inferior border of the isthmus.

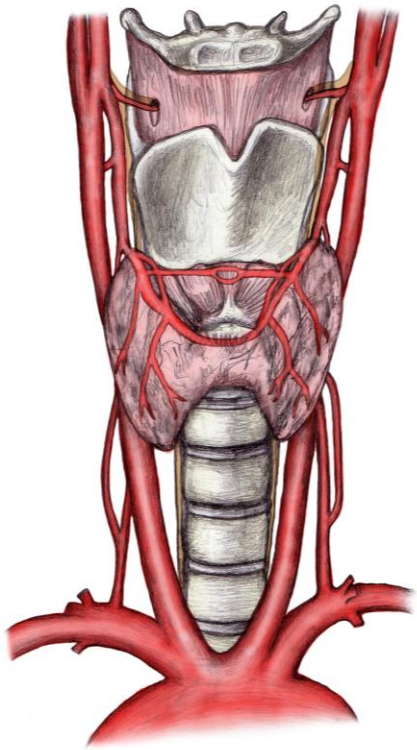


Figure 3. Distribution of thyroid arteries with associated laryngeal nerve, anterior view.

Superior thyroid artery and superior laryngeal nerve

The superior thyroid artery is the first anterior branch of the external carotid artery. In rare cases, it may arise from the common carotid artery just before its bifurcation. The superior thyroid artery descends laterally to the larynx under the cover of the omohyoid and sternohyoid muscles. The artery runs superficially on the anterior border of the lateral lobe, sending a branch deep into the gland before curving toward the isthmus, where it anastomoses with the contralateral artery.

Cephalad to the superior pole, the external branch of the superior laryngeal nerve runs with the superior thyroid artery before turning medially to supply the cricothyroid muscle. High ligation of the superior thyroid artery during thyroidectomy places this nerve at risk of inadvertent injury, which would produce dysphonia by altering pitch regulation. The cricothyroid artery, a potentially bothersome branch of the superior thyroid artery, runs cephalad to the upper pole and runs toward the midline on the cricothyroid ligament. This vessel can be lacerated during emergent cricothyroidotomy.[26]

Inferior thyroid artery and recurrent laryngeal nerve

The inferior thyroid artery arises from the thyrocervical trunk, a branch of the subclavian artery. It ascends vertically and then curves medially to enter the tracheoesophageal groove in a plane posterior to the carotid sheath. Most of its branches penetrate the posterior aspect of the lateral lobe.

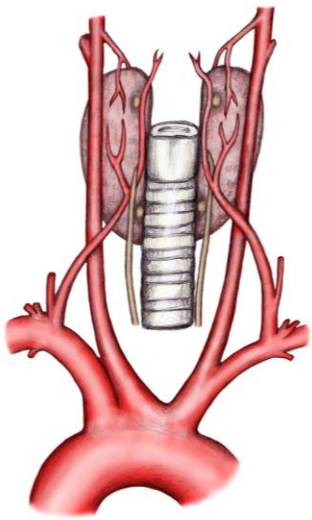


Figure 4. Distribution of thyroid arteries with associated laryngeal nerve, posterior view

The inferior thyroid artery has a variable branching pattern and is closely associated with the recurrent laryngeal nerve. The latter also ascends in the tracheoesophageal groove and enters the larynx between the inferior cornu of the thyroid cartilage and the arch of the cricoid. The recurrent laryngeal nerve can be found after it emerges from the superior thoracic outlet, in a triangle bounded laterally by the common carotid artery, medially by the trachea, and superiorly by the thyroid lobe.

The relationship between the nerve and the inferior thyroid artery is highly variable, as demonstrated by the classic work of Reed, who in 1943 described 28 variations in this relationship. The nerve can be found deep to the inferior thyroid artery (40%), superficially (20%), or between branches of the artery (35%).[27] Significantly, the relationship between nerve and artery on one side of the neck is similar to that found on the other side in only 17% of the population. Furthermore, at the level of the inferior thyroid artery, branches of the recurrent laryngeal nerve that are extralaryngeal may be present (5%). Preservation of all of those branches is important during thyroidectomy.

Another hint to the location of the recurrent laryngeal nerve is the Zuckerkandl tubercle, an extension of the thyroid, which is close to the Berry ligament.[28] On rare occasions, the recurrent laryngeal nerve may pass directly from the vagus to the larynx, close to the superior thyroid vessels. This formation is nearly always observed on the right side and is associated with a retroesophageal subclavian artery. However, the formation can occur on the left side in cases of transposition of the great vessels.

Venous Drainage and Lymphatics

Three pairs of veins provide venous drainage for the thyroid gland. The superior thyroid vein ascends along the superior thyroid artery and becomes a tributary of the internal jugular vein. The middle thyroid vein follows a direct course laterally to the internal jugular vein. The inferior thyroid veins follow different paths on each side. The right passes anterior to the innominate artery to the right brachiocephalic vein or anterior to the trachea to the left brachiocephalic vein. On the left side, drainage is to the left brachiocephalic vein. Occasionally, both inferior veins form a common trunk called the thyroid ima vein, which empties into the left brachiocephalic vein.

Lymphatic drainage of the thyroid gland is extensive and flows multidirectionally. Immediate lymphatic drainage courses to the periglandular nodes; to the prelaryngeal (Delphian), pretracheal, and paratracheal nodes along the recurrent laryngeal nerve; and then to mediastinal lymph nodes. Regional metastases of thyroid carcinoma can also be found laterally, higher in the neck along the internal jugular vein. This can be explained by tumor invasion of the pretracheal and paratracheal nodes causing an obstruction of normal lymph flow.

Physiology[29,30]

The primary function of thyroid gland is the production of sufficient thyroid hormones for proper regulation of cellular metabolism throughout the body.

Iodine metabolism

Iodine is taken in the form of Iodides sea fish; egg and milk are good dietary source of iodide. Dietary iodide is absorbed from upper gastrointestinal tract and carried as inorganic iodide in plasma. Normally thyroid, salivary glands and kidney compete for iodide but thyroid and kidney are the principal organs that compete for iodide.

The adult man requires 0.14 mg of iodide per day and an adult female requires 0.10 mg. Growing children, pregnant and lactating women require more. The daily requirement is met by balanced diet and drinking water, exception being hilly areas where food and water may be deficient in iodine.

Synthesis and secretion of thyroid hormones[31]

The synthesis of thyroid hormones is divided into four steps:

Iodine trapping

The thyroid traps the plasma iodine in the inorganic form. It is essentially an active process and stimulated by TSH. It is competitively inhibited by Thiocynates and perchlorates.

Iodine binding

The inorganic iodide is oxidized to inorganic iodine at the thyroid follicular cells with the help of an enzyme peroxidase. Iodine combines with amino acid tyrosine in the globulin molecule within the follicular cells to form monoiodotyrosine and diiodotyrosine (MIT and DIT) process is inhibited by Thiouracil group of antithyroid drugs and by PAS and chloroquine.

Coupling

Thyroxine (T_4) is formed by coupling of two molecules of DIT and Triiodothyronine (T_3) by coupling of one molecule of each MIT and DIT. The coupling reaction occurs at the Thyroglobulin molecule. They are oxidative reactions and need peroxidase enzyme.

Hormonal release

Thyroglobulin is first taken up by thyroid follicular cells. Under the influence of TSH a protease acts on thyroglobulin to release T_4, T_3, MIT and DIT. MIT and DIT are de-iodinated within the cell and iodine is reutilized for iodinating globulin. From the follicular cells T_4 and T_3 directly enters the circulation. On entering the circulation the thyroid hormones are largely bound to specific protein called thyroxine-binding globulin (TBG), thyroxine binding albumin and thyroxine binding prealbumin (TBPA).

This protein has got more affinity to Thyroxine than to the tri-iodothyronine. The protein bound iodine (PBI), which is about 4-8 g per 100 ml mainly, reflects plasma T_4 level. A small amount of hormone remains free in the serum in equilibrium with the protein bound hormone and is biologically active. The free hormone is physiologically active and protein bound fraction acts as a reserve. Thyroid hormones are disposed by de-iodination 80% and 20% excreted in the stools. About 40% of circulating T_4 is converted to T_3 peripherally called "Reverse T_3". This is inhibited by propranolol and glucocorticoids.

Differences between T_3 and T_4

T_3 has quicker onset of action and is effective in very small doses. The onset of action of T_3 is within 6-8 hours and that of T_4 is 4-14 days. After cessation of therapy the hormonal effect lasts for several days with T_4 but vanishes quickly with T_3. T_3 is the more important physiological hormone and is also produced in the periphery by conversion from T_4. Reverse T_3 is an inactive form of T_3.

Mechanism of action of thyroid hormones[32]

In normal levels, the thyroid hormones act at chromatin of molecules and stimulate synthesis of mRNA molecules. These later synthesize protein molecules including enzymes at cytoplasm, which has anabolic, growth promoting, and calorigenic actions.

But in unphysiological higher concentrations they act at mitochondria and uncouple oxidative phosphorylation. Thus oxygen consumption and heat production is increased.

Effects of thyroid hormone on metabolic processes

Effect on calorigenesis

One classic action of thyroid hormones is their stimulating effect on calorigenesis. This response occurs after a latent period of several hours or days and is evident most of the times. T_3 causes a more prompt but somewhat short-lived effect than does T_4. The precise mechanism of calorigenic effect of thyroid hormones is uncertain. Other responses of thyroid hormones such as increased heart rate decreased cardiac glycogen content and increased sensitivity to lipolytic effect of epinephrine precedes the induction of metabolic action.

Effect on protein metabolism

Thyroid hormones stimulate protein synthesis and thus increased protein synthesis may be fundamental to many of the metabolic actions of the hormone. Thyroid hormones also increase overall growth rate in young individuals. In thyrotoxicosis urinary nitrogen excretion is increased, whereas in hypothyroidism there is a decreased rate of protein synthesis.

Effects on carbohydrate metabolism

Virtually thyroid hormones affect all aspect of carbohydrate metabolism. Many of their influences are dependent upon or modified by other hormones, in particular catecholamines and insulin. Thyroid hormones increase glycogen synthesis and peripheral utilization of glucose and thus potentiate in this respect. Thyroid hormones also increase absorption of glucose and galactose and potentiate epinephrine. Overall in thyrotoxic patients, there is hyperglycemia and diminished sensitivity to exogenous insulin and converse changes occur in hypothyroidism.

Effect on lipid metabolism

Thyroid hormones appear to stimulate all aspects of lipid metabolism including synthesis, metabolism and degradation. In general, degradation is affected more than synthesis, the net effect in state of hormone excess being a decrease in store of most lipids and their concentration in plasma. This is true for triglycerides, phospholipids and cholesterol. Reverse changes are seen in states of thyroid hormone deficiency. A classic effect of thyroid hormones is to lower the concentration of cholesterol in plasma.

Effect on vitamin metabolism

In hyperthyroidism, the requirement of water-soluble vitamins such as Thiamine, Vitamin B12 and vitamin C are increased and their tissue concentrations are reduced. Thyroid hormones are also required for synthesis of vitamin A from carotene. In hyperthyroidism requirement of vitamin A is increased. Vitamin D and E appear to be deficient in hyperthyroid animals.

<u>Theories concerning the mechanism of action of thyroid hormones</u>

- Uncoupling of oxidative phosphorylation at mitochondria.
- Increased activity of Na^+, K^+ dependent ATPase.
- Increased synthesis of specific enzymes.
- Stimulation of adenyl cyclase at plasma membrane.

Regulation of thyroid function

Thyroid function is regulated by two mechanisms, namely suprathyroid and intrathyroid. The suprathyroid regulation is by thyroid stimulating hormone (TSH) released from basophilic cells of the anterior pituitary. TSH stimulates thyroid hypertrophy and hyperplasia. All steps in the synthesis and secretion of thyroid hormones are enhanced and the synthesis of thyroglobulin is increased. These actions of TSH are due to binding of hormone to receptors on thyroid follicular cell membrane. Regulation of TSH secretion is by two opposing mechanisms.

The thyrotrophic-releasing hormone (TRH) of hypothalamic origin stimulates synthesis and secretion of TSH and thyroid hormones. TRH is synthesized in the hypothalamus, reaches anterior pituitary by portal blood system and binds to receptor on thyrotrophic cells. This is called pituitary – thyroid axis. The intrathyroidal regulation is also called autoregulatory mechanism, but this is not to mean that thyroid controls hormone production in the absence of TSH stimulation. The gland reduces the iodine trapping mechanism whenever there is sudden increase in the supply of iodide and this occurs without the negative feedback mechanism.

Thyroid stimulating antibodies

A family of IgG immunoglobulins bind with TSH receptor sites (TRAbs) and activate TSH receptors on the follicular cell membrane. They have a more protracted action than TSH (16-24 hours versus 1.5-3 hours) and are responsible for virtually all cases of thyrotoxicosis not due to autonomous toxic nodules. Serum concentrations are very low and not routinely measured.

Thyroid nodules

Nodular disease of the thyroid gland is prevalent in the United States. The lifetime risk for developing a palpable thyroid nodule is estimated to be 5-10%, and the condition affects more women than men.[33]

In general, nodular disease of the thyroid is common; however, malignancy of the thyroid occurs in only 0.004% of the American population annually (12,000 new cases per y). Roughly 5% of thyroid nodules are malignant; the remainder represent a variety of benign diagnoses, including colloid nodules, degenerative cysts, hyperplasia, thyroiditis, or benign neoplasms. A rational approach to management of a thyroid nodule is based on the clinician's ability to distinguish the more common benign diagnoses from malignancy in a highly reliable and cost-effective manner.[34]

In a study of 261 patients undergoing surgical evaluation for thyroid disease, Mazzaglia investigated whether office-based, surgeon-performed ultrasonographic examination significantly effected operative treatment of the patients even though all of these individuals had previously undergone ultrasonographic thyroid examination. Mazzaglia reported that treatment plans for 46 patients (17.6%) were altered because of significant differences between outside and surgeon-administered ultrasonograms. In 12 patients, for example, previously unidentified nonpalpable, enlarged lymph nodes were found in the surgeon-administered ultrasonograms, with biopsy revealing metastatic thyroid cancer in 3 of these patients. Mazzaglia concluded that surgeon-performed ultrasonographic examinations can be used to make necessary changes in surgical treatment and to avoid unnecessary surgery.[33]

Epidemiology

Approximately 1.1% of all cancers arise from the thyroid and 1.7% of cancers in women compared with 0.5% in men are primary thyroid cancers. Thus, thyroid cancer is about three times more common in women. This gender difference is found in almost all countries. One exception to the gender difference occurs in prepubertal children, in whom the incidence in boys and girls is about equivalent. The average age of the patient with differentiated thyroid cancer is 35–40 years. The peak incidence at about 40 years is different from most malignancies that are more prevalent with advancing age. Hispanic men are the exception to the relatively young median age and their highest incidence is more than 70 years and the frequency is 9.2 per 100,000.[34]

Reasons for the increasing incidence include a true increase that might in part be caused by radioactive fallout from atomic bomb testing and from medical radiation. Alternatively, physicians might be identifying small cancers that would have been overlooked in earlier decades and the almost stable death rate supports this point of view.[35]

Small papillary cancer makes up almost all of the increase in cases. The prognosis is good and 6% of patients die from the cancer but the genders are more equally represented with about 850 women and 650 men expected to die annually (43,000 die of road traffic accidents and 30,000 from gunshots in US annually). Less than 0.5% of all cancer deaths are from carcinomas of the thyroid. Because the large majority of patients who are diagnosed with thyroid cancer have an excellent prognosis, there are several hundred thousand people in the US who are living with a diagnosis of thyroid cancer.[34]

There are substantial differences in the prevalence of thyroid cancer among ethnic groups. In women, the lowest incidence is 3.3 cancers per 100,000 in African Americans. By comparison, women from Hawaii, Vietnam, and the Philippines represent 9.1, 10.5, and 14.6 cases per 100,000.[36]

White and Hispanic women have similar incidences of 6.5 and 6.2 cancers per 100,000. When age is also considered, Filipino women between 55 and 69 years have an incidence of 32.5 cancers per 100,000. Filipino men also have a higher incidence of thyroid cancer with 4.1 per 100,000 compared with 1.4 per 100,000 for African Americans. A multiethnic study in the San Francisco Bay area tried to answer whether there were environmental differences, but no compelling factor was identified.[34]

The five year survival for white Americans over time has been 92% (1974–1976), 94% (1980–1982), and 95% (1989–1995); in contrast, the outcomes for African Americans were 88%, 94%, and 89%. The incidence in the United Kingdom (UK) (1000 new cases annually) is proportionately about one fi fth of that of the US based on the respective populations. There are 2.3 thyroid cancers per 100,000 women and 0.9 per 100,000 men. Two hundred fi fty (25%) die annually in the UK (25%) and the 5-year survival for women and men is 75%

and 64%.4 The lower incidence and higher mortality in the UK might be attributable to delayed diagnosis.[34]

Thyroid cancer is not common and there are significant differences in the incidence based on ethnicity. It is not clear whether the increasing incidence is attributable to diagnosis of earlier cases, or a true increase attributable to environmental factors. The use of a staging system such as tumor, node, metastasis of every new case would allow this point to be resolved. Within one country, the survival is also dependent on ethnicity. The five year survival for white Americans was 95% for the period 1989–1995. Over the same time, the outcome for African Americans was lower at 89%.[34]

Etiology[34]

Radiation and genetics are two important causal factors. Radiation causes mutations that can be carcinogenic. There are also familial thyroid cancers that are associated with genetic abnormalities. This is best understood for familial medullary cancer and multiple endocrine neoplasia (MEN 2) syndromes. There is increasing evidence that some cancers of follicular cells are also familial. Varying doses of radiation to the thyroid have different effects, with intermediate doses (10–1000 rad or 0.1–10 Gy) to tissues being carcinogenic and high doses causing death of cells and hypothyroidism. For many years, the majority of data supported that external radiations, predominantly X-rays, were more likely to induce thyroid cancer. The increased incidence of thyroid cancer in children who were exposed to internal radiation at the time of the Chernobyl incident has altered this concept.

Pathophysiology

Clinical outline[37]

A comprehensive history and physical examination provides the foundation for decision making in the management of thyroid nodules. A number of features in the patient's history and physical examination significantly influence the statistical probability of malignancy in a thyroid nodule.

Factors suggesting a malignant diagnosis include the following:

- Age younger than 20 years or older than 70 years
- Male sex
- Associated symptoms of dysphagia or dysphonia
- History of neck irradiation
- Prior history of thyroid carcinoma
- Firm, hard, or immobile nodule
- Presence of cervical lymphadenopathy

Factors suggesting a benign diagnosis include the following:

- Family history of autoimmune disease (eg, Hashimoto thyroiditis)
- Family history of benign thyroid nodule or goiter
- Presence of thyroid hormonal dysfunction (hypothyroidism, hyperthyroidism)
- Pain or tenderness associated with nodule
- Soft, smooth, and mobile nodule

Of importance, these factors are only guidelines to assist in decision-making, and they do not provide absolute diagnostic information.

Diagnostic Workup

Laboratory evaluation

The most important laboratory test is a sensitive thyroid-stimulating hormone (TSH) assay, which is used to screen for hypothyroidism or hyperthyroidism. In addition, obtaining serum thyroxine (T4) and triiodothyronine (T3) levels may be helpful (when TSH levels are low-normal or high-normal). In most cases of solitary thyroid nodules, the TSH level is normal. In cases of a solitary thyroid nodule with a normal TSH value, no additional laboratory studies may be required in the diagnostic evaluation unless autoimmune disease (Hashimoto thyroiditis) is suspected.

When the patient's history and physical findings reveal a family history or raise clinical suspicion for Hashimoto thyroiditis, obtain serum antithyroid peroxidase (anti-TPO) antibody and antithyroglobulin (anti-Tg) antibody levels. A diagnosis of Hashimoto thyroiditis does not exclude the possibility of malignancy.

Additional laboratory studies are unnecessary in the routine initial diagnostic evaluation of a solitary thyroid nodule.

Imaging studies

Thyroid scintigraphy

In most centers, the routine initial diagnostic evaluation of a solitary thyroid nodule no longer includes imaging studies. In the past, radionuclide scanning was an important imaging study performed routinely in the initial assessment of a thyroid nodule. Nuclear imaging can be used to describe a nodule as hot, warm, or cold on the basis of its relative uptake of radioactive isotope. Hot nodules indicate autonomously functioning nodules, warm nodules suggest normal thyroid function, and cold nodules indicate hypofunctional or nonfunctional thyroid tissue. (Examples of hot and cold nodules are seen in the image below.) Hot nodules are rarely malignant; however, 5-8% of warm or cold nodules are malignant.[38]

Ultrasonography

Because of advances in technology, ultrasonography is highly sensitive in determining the size and number of thyroid nodules. By itself, ultrasonography cannot reliably be used to distinguish a benign nodule from a malignant nodule. However, combining high-resolution sonography with Doppler and spectral analysis of the vascular characteristics of a thyroid nodule holds promise as a useful tool in screening thyroid nodules for malignancy. Studies have shown that the risk of malignancy is lower in nodules with a predominantly perinodular pattern than in nodules with an exclusively central vascular pattern. Furthermore, if the vascular characteristics of thyroid nodules are combined with their ultrasonographic parameters, including a halo, microcalcifications, cross-sectional diameter, and echogenicity, the predictive value of this imaging approach may increase.[38-41]

A study by Sun et al found that osteopontin expression has a role in the microcalcification found in papillary thyroid carcinoma that is reflected on ultrasonography.[42]

Thyroid ultrasonography can be helpful in certain cases when it is used to guide fine needle aspiration biopsy (FNAB). Data have suggested that ultrasonography-guided FNAB may be preferable to palpation-guided FNAB.[43] Although sensitivity and specificity are not clearly and significantly between the approaches to FNAB, many authors consider image-guided FNAB to hold certain advantages. For example, image-guided FNAB may be particularly helpful in the assessment of nonpalpable or small nodules, nodules with cystic components, or nodules that are difficult to access (posterior or substernal nodules). Ultrasonography-guided FNAB, combined with on-site cytologic verification of the adequacy of the specimen by a cytotechnologist or pathologist, may likely provide the highest sensitivity and specificity. Whether this is the most cost-effective approach for all thyroid nodules remains an issue.

Computed tomography (CT) scanning, magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning

CT scanning or MRI is generally not cost-effective in the initial evaluation of solitary thyroid nodules. Such studies may be useful in the assessment of thyroid masses that are largely substernal. Also, in some cases CT scan–guided FNAB may be helpful. PET scanning with 18F-fluorodeoxyglucose is at present primarily an investigational tool, but it might have some role in thyroid imaging in the future, particularly in the evaluation of metastatic disease.[44]

In the past, nuclear imaging studies of the thyroid, often combined with ultrasonography, were routinely performed in initial assessment of thyroid nodules. Because only 10% of solitary thyroid nodules are hot and because 90% of cold nodules are not malignant, nuclear imaging with or without ultrasonography typically offers a low yield of cancer diagnoses in surgical specimens when their results are used as the main guides for referral to a surgeon.

Fine-needle aspiration cytology (FNAC)

Fine-needle aspiration cytology has emerged as the most important step in the diagnostic evaluation of thyroid nodules.[45] Data from numerous studies have established FNAC as highly accurate, with mean sensitivity higher than 80% and mean specificity higher than 90%. The accuracy of FNAC in diagnosing thyroid conditions highly depends on the cytopathologist's expertise and experience and the technical skill of the physician performing the biopsy. In addition, FNAC is highly cost-effective compared with traditional workups that heavily depended on nuclear imaging and ultrasonography. Routine use of FNAC in the evaluation of thyroid nodules can reduce the need for diagnostic thyroidectomy by 20-50% while increasing the yield of cancer diagnoses in thyroid specimens by 15-45%.

Provided that adequate cellular material is available, FNAC of thyroid nodules can be used to categorize tissue into the following diagnostic categories: thyroiditis, follicular neoplasm, or malignant, benign, suspicious, or nondiagnostic tissue. In the malignant category, FNAC can be used to distinguish papillary carcinoma, medullary carcinoma, anaplastic carcinoma, and carcinoma metastatic to the thyroid gland, and it can be used to distinguish malignant lymphoma from other disease.[39] FNAC can also help in reliably diagnosing colloid nodules, Hashimoto thyroiditis, and subacute thyroiditis.

The main weakness of FNAC involves hypocellular aspirates and aspirates with high follicular cellularity. Hypocellular aspirates may be observed in cystic nodules, or they may be related to biopsy technique. The addition of ultrasonography to guide FNAC sometimes reduces technical errors. In addition, on-site verification of the adequacy of the specimen by a cytotechnologist or a pathologist is likely to reduce the rate of nondiagnostic specimens.

Aspirates characterized by high follicular cellularity suggest follicular neoplasm; however, FNAC cannot be used reliably to distinguish a benign follicular neoplasm from a malignant neoplasm. In addition, aspirates that are highly cellular with Hürthle cells can be observed with benign or malignant Hürthle-cell neoplasms and with some cases of Hashimoto thyroiditis.[46]

Advances in cytologic analysis may increase the predictive value of FNAC of thyroid nodules in the future. For example, the incorporation of immunocytochemical studies, as well as genetic and molecular profiling of aspirates, may improve the accuracy of minimally invasive diagnostic techniques.

An Italian study[47] compared the effectiveness of FNAC with that of fine-needle nonaspiration biopsy (FNNAB) in the evaluation of thyroid nodules. The 2 techniques were performed on the same 104 patients, who were known to have a uninodular or multinodular goiter. No statistically significant difference was found between the adequacy of samples obtained through FNAC and those collected through FNNAB in the diagnosis of colloid, follicular, or malignant nodules. The only significant difference was in the percentage of samples yielding inadequate results (16.3% and 5.8% for FNAC and FNNAB, respectively). The authors suggested that the frequency of inadequate samples was lower for FNNAB because the technique allows better-quality specimens to be collected. Otherwise, the investigators found both techniques to be useful and cost-effective.

Role of FNA biopsy

Depending on the nature of the thyroid nodule, FNA biopsy can function as a diagnostic test or a trage tool.[48-50] As a diagnostic test, FNA biopsy can be used to diagnose papillary carcinoma, poorly differentiated carcinoma, medullary carcinoma, anaplastic carcinoma, metastatic malignancy, thyroiditis, and most benign nodular goitres and cysts. However, follicular adenoma, well-differentiated carcinoma indistinguishable on FNA cytology.

As a triage tool, FNA biopsy can be used to distinguish thyroid nodules that might have a higher risk of malignancy (neoplasms), and would thus require surgical excision, from goitrous nodules or thyroiditis, which can be managed medically. Although FNA cytology can reduce the number of diagnostic thyroidectomies by identifying benign lesions that need not be removed, it does not and cannot eliminate all diagnostic operations.[48-50] Some patients with thyroid nodules who are referred for operation after FNA biopsy are actually found to have benign disease, because of our inability to distinguish accurately between follicular adenoma, well-differentiated carcinoma on FNA.

Indications for FNA biospy

Traditionally, the main indication for FNA biopsy of the thyroid has been the presence of a solitary nodule. It has been taught that the risk of cancer in a multinodular goitre is much less than that in a solitary nodule. However, recent literature indicates that if a nodule in a multinodular goitre has grown steadily, become distinctly dominant or changed in consistency, its risk of malignancy is the same as that for a solitary nodule.[51,52] Under these circumstances, FNA investigation is indicated. In autoimmune thyroid diseases, such as Graves' disease and Hashimoto's thyroiditis, a dominant localized abnormality in the thyroid gland is an indication for FNA.[53] FNA biopsy is also required for a diffuse, rapidly growing thyroid enlargement to rule out anaplastic carcinoma or lymphoma, especially in patients over 50 years of age.

Management of Thyroid Nodules

The most important routine aspects of the diagnostic evaluation of solitary thyroid nodules include thorough history taking and physical examination, measurement of the serum TSH level, and FNAB of the nodule if the patient has access to an experienced cytopathologist. Subsequent management of a solitary thyroid nodule largely depends on the diagnosis from FNAB. Malignant cytopathology is usually an indication for surgical referral. Exceptions may be made in the case of malignant lymphoma, which is typically not managed surgically, and in cases of anaplastic carcinoma, in which surgical intervention may be futile.[54]

Most thyroid nodules associated with benign cytopathology on FNAC can be managed without routine surgical referral, provided that adequate follow-up is possible. Although the incidence of false-negative results with FNAC is low, most physicians recommend repeat FNAC for confirmation 6 to 12 months after an initial diagnosis of a benign lesion or if the characteristics of the nodule change on follow-up examination.

When a benign diagnosis is confirmed, referral to a surgeon is reasonable for patients with symptoms, such as dysphagia or discomfort, or concerns about cosmesis. Patients with suggestive or follicular cytopathology on FNAC should be referred to a surgeon because 20 to 30% of such nodules are malignant. When findings from the aspirate are nondiagnostic, repeat the aspiration, possibly with ultrasonographic guidance. Nodules for which aspirates are repeated nondiagnostic may ultimately require surgical management.[55]

Literature review

A comparative study[56] between FNAC and thyroid scan used to diagnose the solitary thyroid nodule and histopathology was used as gold standard to compare the results of both modalities hypothesized that FNAC and thyroid scan diagnose solitary thyroid nodule (STN) as accurately as histopathology on 50 patients with STN. These patients underwent FNAC in the department of Pathology and surgery in Mayo Hospital. The cases were operated and evaluated for histopathological changes. On thyroid scan, 40 patients (80%) having cold nodule were labeled as suspicious 10 patients (20%) had hot nodule. On FNAC 23 patients (46%) had benign lesion, 22 patients (44%) had indeterminate lesion and 5 patients (10%) had malignant lesions. On histopathology, 45 patients (90%) were confirmed to have benign lesions and 5 patients (10%), malignant lesions. After comparison of results of thyroid scan and FNAC with histopathology, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of thyroid scan were 80%, 20%, 10%, 90% and 26%, respectively whereas those of FNAC were 80%, 97.7%, 80%, 97.7% and 96%, respectively. The study concluded that, FNAC was a significantly better predictor of malignancy than thyroid scan and resulted in a smaller proportion of excisions for benign nodules.

Another study[57] reported that, the major categories of thyroid abnormality in such patients include cysts, adenomas, thyroiditis, and cancer. Although radionuclide scans, ultrasound examination and computer tomography have all been employed in the assessment of thyroid nodules, and thyroid stimulating hormone assay is useful for confirming a euthyroid state, fine needle aspiration biopsy (FNAB) has proved to be the most efficient diagnostic tool. The findings from FNAB allow avoidance of operative treatment for a large portion of these patients with palpable thyroid nodules, but a diagnosis of “follicular neoplasm” on FNAB usually requires operation, despite the fact that many such patients do ultimately prove to have a benign lesion. The extent of operation in patients undergoing surgery will depend on the diagnostic findings before operation, but unilateral thyroid lobectomy is the minimum procedure when surgery is required.

The diagnostic accuracy of fine needle aspiration cytology (FNAC) was evaluated in thyroid nodules in 100 consecutive cases, who subsequently underwent thyroidectomy between the years 1989–1991. FNAC as a diagnostic test for thyroid nodules demonstrated an accuracy of 90.9%, a sensitivity of 76.5%, a specificity of 95.9% with a false positivity of 2%, false negativity of 4%, positive and negative predictive values of 86.7% and 92.2%, respectively. A correct classification of the carcinoma type on the basis of FNAC was possible only in 69% patients. As a result, FNAC is the first line of investigation in most nontoxic nodular goiters and often the only procedure necessary to obtain an accurate diagnosis. However, it is recommended only as an adjunct to clinical judgment and is not intended to replace it.[58]

Another study[59] to determine the efficacy of fine needle aspiration cytology in diagnosis and management of thyroid nodules evaluated the predictive value of pre-operative fine needle aspiration cytology (FNAC) in surgical decision making, by comparing the final pathological diagnosis with the initial FNAC result. All patients who underwent thyroidectomy between 1999 and 2003 were analysed. One hundred and sixty patients who underwent pre-operative FNAC were included in this study. Fine needle aspiration was accurate in 119 (74.3%) patients. Fine needle aspiration cytology and histology did not correlate in 32 (20%) patients and FNAC was inadequate in nine (5.6%) cases. Failures were mainly noted in cases of follicular neoplasm. Our results indicate that FNAC is helpful in the diagnosis of thyroid pathology. However, complete histopathological analysis is essential to distinguish follicular adenoma from follicular carcinoma. From this study, it can be concluded that FNAC is a cost-effective method of evaluating thyroid pathology pre-operatively and plays a useful role in planning the surgical management of thyroid nodules. However, results must be interpreted with the clinical picture in mind.

Fine-needle aspiration (FNA) of thyroid is a cost-effective and simple diagnostic tool in the initial screening of patients with thyroid nodules. But, its role in a clinically normal thyroid or a minimally enlarged thyroid in a symptomatic patient suspected of having thyroid dysfunction is unknown.[60]

A study[60] from Bangalore, India with 2 year experience in a setup of a tertiary health care hospital, aimed to implement a management protocol using FNA thyroid done without ultrasound guidance and TSH estimation done during the same visit in symptomatic patients suspected of having thyroid pathology but presenting with no goiter or having minimally enlarged thyroid with no palpable nodules. The thyroid enlargement in 172 cases were graded with the criteria endorsed by WHO, Pan American Health Organization, and International Council for Control of Iodine Deficiency Disorders into grade 0, 1, and 2. The cases were evaluated cytologically and correlated with TSH values according to the algorithm formulated by the authors. FNA was diagnostic in 86.6, 98, and 100% in grade 0, 1, and 2 goiters, respectively. 52.3% (n=90), 19.8% (n=34), 16.9% (n=29) of cases were diagnosed as Hashimoto's thyroiditis (HT), colloid goiter (CG), and lymphocytic thyroiditis (LT). Sixteen had a combination of LT and CG (n=6), HT and CG (n=6), papillary carcinoma (n=2), and diffuse hyperplasia (n=2). No statistically significant difference (p=0.4586) was noted between the groups of patients with grade 0 and grade 1 to 2 goiter, who underwent FNAC. 38.95% of patients (n=67) with TSH values greater than 10 μIU/ml and considered hypothyroid showed features of HT/LT at FNA. 23.83% (n=41) having TSH values between 5 and 10 μIU/ml (subclinical hypothyroidism) also showed features of HT/LT at FNA. Both groups were treated with thyroxine. 35.46% (n=61) of cases with TSH values within normal range (0.5 to 5.1 μIU/ml) and considered euthyroid showed a spectrum of lesions at cytology other than HT and LT. They are being followed up to detect them at an early stage of subclinical hypothyroidism. Only 13 cases (7.5%) who were serologically euthyroid showed HT/LT and are being followed-up. Thus, the authors advocate FNA of the thyroid as a single simple cost-effective office procedure in the medical management of all nonpalpable/minimally enlarged thyroid in patients suspected of having thyroid pathology and/or in combination with TSH values. FNA helps in early detection of subclinical hypothyroidism, which is of utmost importance in pregnant women and further makes possible availability of baseline values for future reference. With the implementation of this protocol of FNA thyroid without imaging, authors affirmed that, the practice of cytology which differs in different geographic areas and from country to country depending on economy and availability of infrastructure can be made more user-friendly.

The application and reliability of fine-needle aspiration (FNA) biopsy in community hospitals may be less efficacious in the clinical assessment of patients with thyroid nodules than in tertiary referral centers.[61]

In a retrospective review[61] of community teaching hospital on 183 patients who underwent thyroidectomy after FNA biopsy, thyroid cancer was confirmed postoperatively in 70 patients (38%). An FNA biopsy diagnosis of papillary carcinoma (in 29 patients) correlated with a predictive accuracy of 93%

(27 patients). Suspicious for papillary carcinoma (n=14) correlated with malignancy in 8 patients (57%). Indeterminate follicular lesion (n=60) correlated with malignancy in 18 patients (30%), of whom 16 (89%) had papillary carcinoma (10 patients had follicular variant) and 2 (11%) had follicular carcinoma. Indeterminate Hürthle cell lesion (n=20) correlated with malignancy in 7 patients (35%). Atypical cell clusters (n=5) did not correlate with malignancy. Benign FNA biopsy findings (n=44) in patients who underwent thyroidectomy for other clinical features correlated with malignancy in 8 (18%). Of 11 patients who underwent thyroidectomy for insufficient number of cells after repeated FNA biopsy attempts, 2 (18%) had carcinoma. Study concluded that, accuracy of an FNA biopsy of thyroid nodules in a community hospital setting is comparable to results from major endocrine referral centers. An indeterminate follicular lesion was the most common FNA biopsy indication for thyroidectomy and correlated with the presence of differentiated thyroid cancers in 18 (30%) of 60 patients.

Fine-needle aspiration cytology is the single most important diagnostic test for the evaluation of patients with thyroid nodules. Prerequisites for attaining high degrees of diagnostic accuracy include adherence to the appropriate methods of specimen procurement and processing and exposure to a significant volume of cases.

METHODOLOGY

The present study was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010.

Study design

A one year cross sectional study.

Place

The present study was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

Study period

One year from January 2010 to December 2010.

Source of data

Patients with thyroid swelling having clinical and sonological indication for FNAC and subsequent thyroid surgery admitted in the wards of Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the study period.

Sample size and method

A total of 70 patients with thyroid swelling were studied.

Sampling procedure

The sample size was calculated by using the formula as below.

$$n = 4pq/d^2$$

Where,	p	-	Prevalence of disease (50%)
	q	-	100-p
	d	-	Absolute error (12%)

Selection criteria

Inclusion

- All the patients with thyroid swelling and clinical and sonological indication for FNAC and subsequent thyroid surgery.
- Patient of all the age groups, sex and demographic distribution.
- Patient with normal thyroid function test (TFT).

Exclusion

- Patients with abnormal TFT.
- History of previous surgery in thyroid and parathyroid region.
- History of irradiation to head and neck in the past.
- Diffuse goiter with no clinical indication for FNAC.
- All cases of clinically diagnosed physiological goiter.

Procedure

Ethical clearance for the study was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum. Based on the selection criteria patients with thyroid swelling having clinical and sonological indication for FNAC and subsequent thyroid surgery admitted in the wards of Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the study period were screened for eligibility. The eligible patients were briefed about the nature of the study and a written informed consent (Annexure I) was obtained from the selected patients. Thorough history was taken and clinical examination was done for all patients and findings were recorded on predesigned and pretested proforma (Annexure II).

The patients underwent fine needle aspiration cytology to establish pre operative tissue diagnosis. Prior to the surgery following routine investigations were done:

- Hemoglobin, Total Leukocyte Count, Differential Count.
- Blood grouping and cross matching with one pint of blood reserved for operation.
- Urine routine examination and microscopic examination.
- X-ray chest posterior-anterior view if the patient is over 40 years of age or if there is any suspicion of chest infection or other chest abnormalities.
- ECG if the patients was over forty years of age or in case of doubt of any cardiac abnormalities.

- Platelets count, BT, CT, PT and APTT in cases of suspected bleeding disorder.
- Thyroid Function tests.

Further the patients underwent surgery as per clinical and FNAC diagnosis. After the surgery, excised specimen obtained was sent for histopathology examination. The FNAC reports were compared with histopathological report which is gold standard for the diagnosis.

Statistical Analysis:

Data obtained was tabulated and expressed as rates, ratios and percentages. The correlation of FNAC diagnosis with HPR findings was analysed by calculating sensitivity, specificity, positive predictive value and negative predictive value as below.

- Sensitivity = a/(a+c)x100
- Specificity = d/(b+d)x100
- Positive predictive value = a/(a+b)x100
- Negative predictive value = d/(c+d)x100

  Where,
  - a = true positive (FNAC correctly diagnoses the case as malignant or neoplastic)
  - b = false positive (FNAC diagnoses falsely as neoplastic or malignant)
  - c = false negative (FNAC diagnoses falsely as not having malignant or neoplastic lesions)
  - d = true negative (FNAC correctly diagnoses the case as benign)

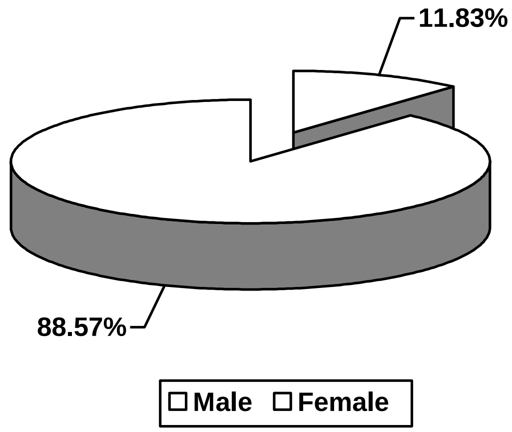
RESULTS

The present one year cross sectional study was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. Data obtained was tabulated analysed as below.

Table 1. Sex Distribution

Sex	**Distribution (n=70)**	
	Number	**Percentage**
Male	8	11.43
Female	62	88.57
Total	**70**	**100.00**

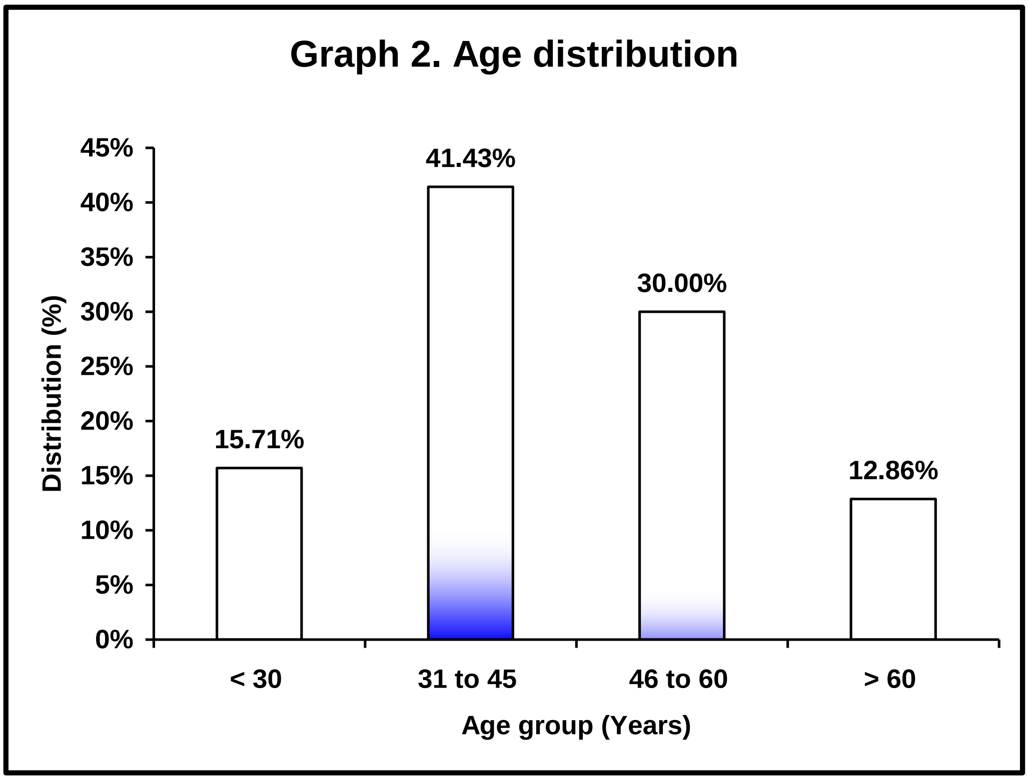
Graph 1. Sex Distribution



Total no of patients were 70 of which 62 (88.57%) were females and 8 (11.43%) were males.

Table 2. Age distribution

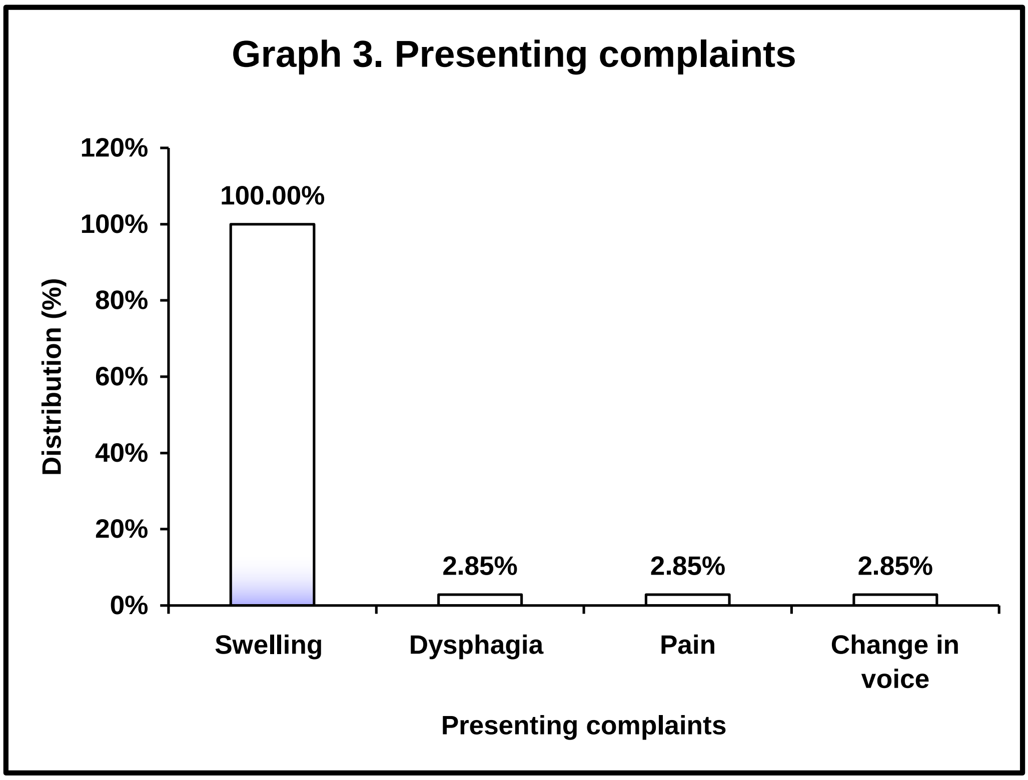
Age group (Years)	Distribution (n=70)	
	Number	**Percentage**
< 30	11	15.71
31 to 45	29	41.43
46 to 60	21	30.00
> 60	9	12.86
Total	**70**	**100.00**



Patient's age ranged from 20 years to 78 years with maximum no of patients being in the age group of 31 years to 45 years. The mean age was 44.93 ± 13.58 years with range being with 20 to 78 years.

Table 3. Presenting complaints

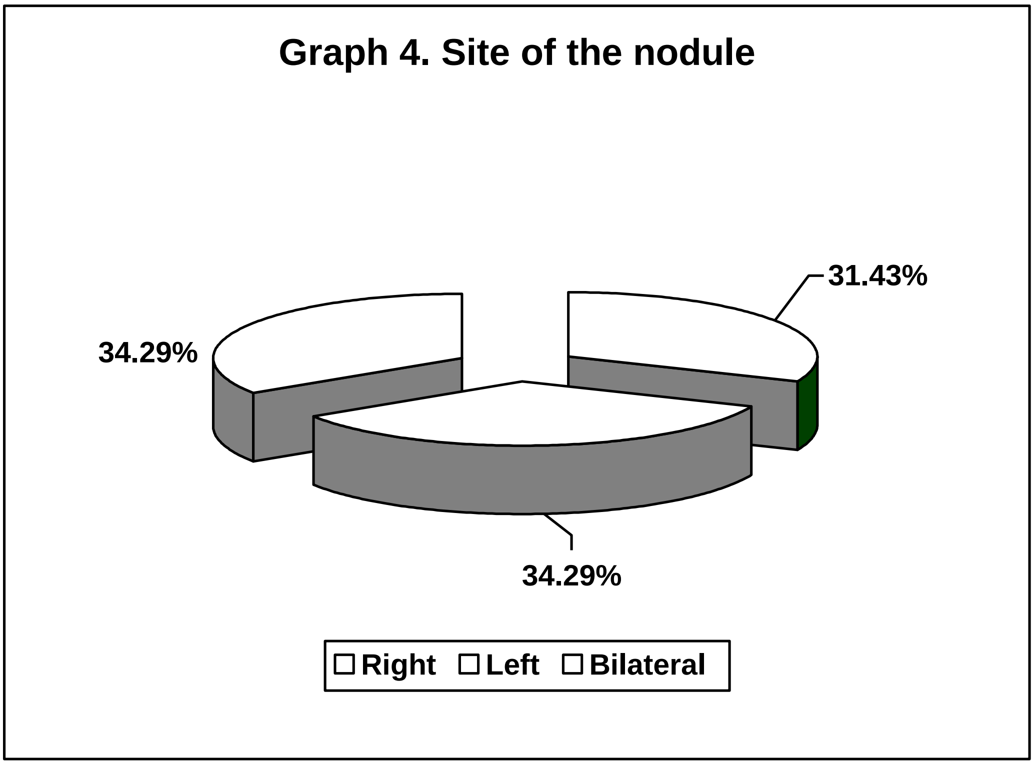
Presentation	Distribution (n=70)	
	Number	Percentage
Swelling	70	100.00
Dysphagia	2	2.85
Pain	2	2.85
Change in voice	2	2.85



All the patients (100%) presented with swelling. Dysphagia, pain and change in voice was noted in 2.85% patients each.

Table 4. Site of the nodule

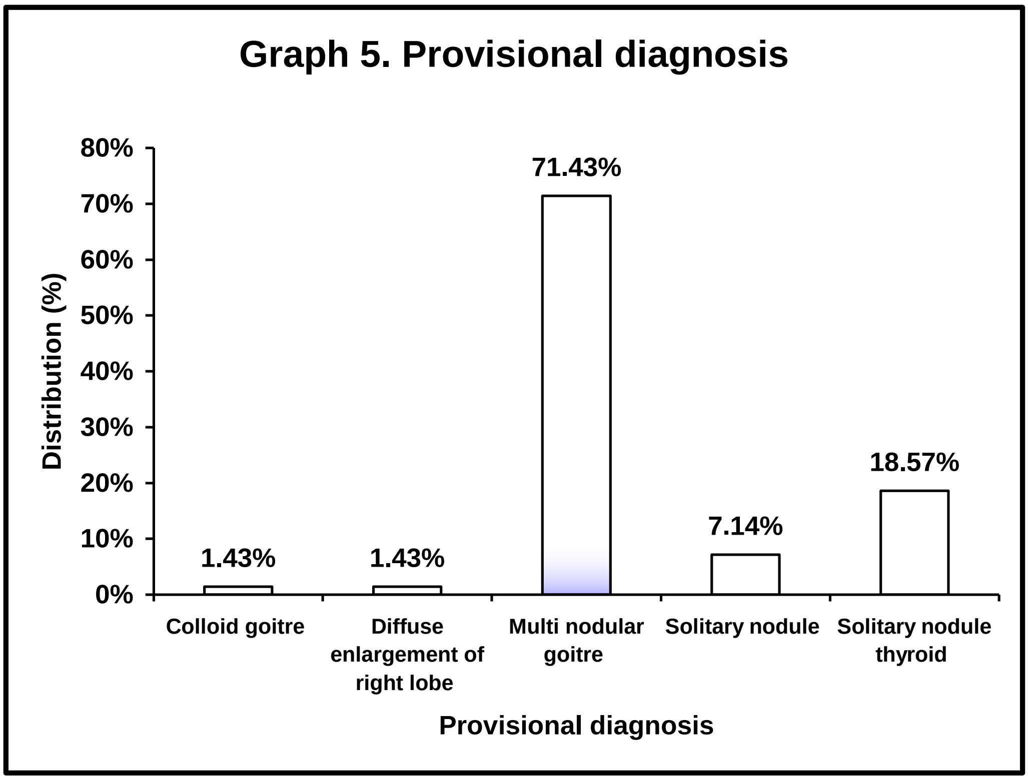
Site	Distribution (n=70)	
	Number	Percentage
Right side	22	31.43
Left side	24	34.29
Bilateral	24	34.29
Total	**70**	**100.00**



Majority presented with bilateral and left sided swelling of the thyroid (34.29%).

Table 5. Provisional diagnosis

Provisional diagnosis	Distribution (n=70)	
	Number	Percentage
Colloid goitre	1	1.43
Diffuse enlargement of right lobe	1	1.43
Multi nodular goiter	50	71.43
Solitary nodule	5	7.14
Solitary nodule thyroid	13	18.57
Total	**70**	**100.00**

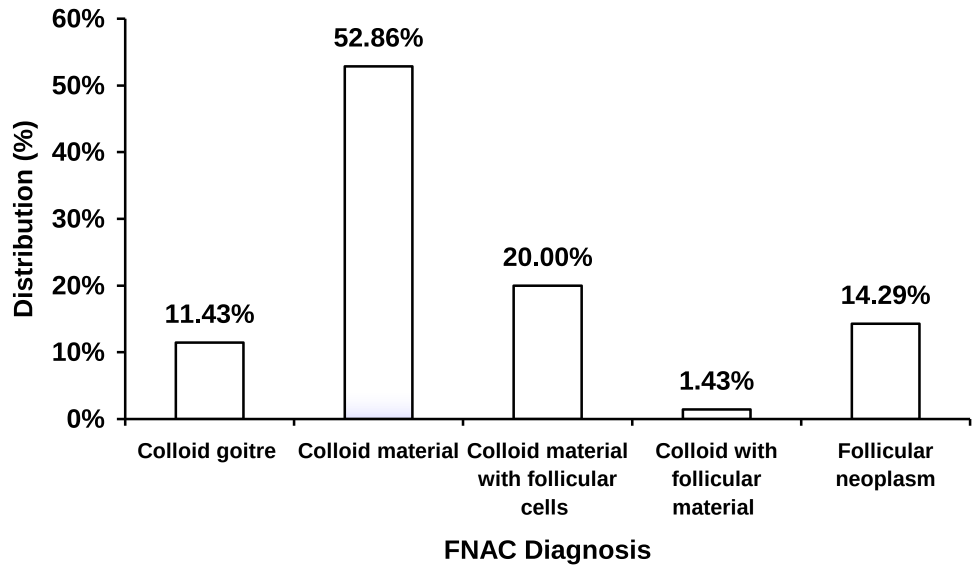


All patients were suspected to have benign disease clinically with majority having diagnosed to have MNG.

Table 6. Fine needle aspiration cytology diagnosis

FNAC diagnosis	Distribution (n=70)	
	Number	Percentage
Colloid goitre	8	11.43
Colloid material	37	52.86
Colloid material with follicular cells	14	20.00
Colloid with follicular material	1	1.43
Follicular neoplasm	10	14.29
Total	**70**	**100.00**

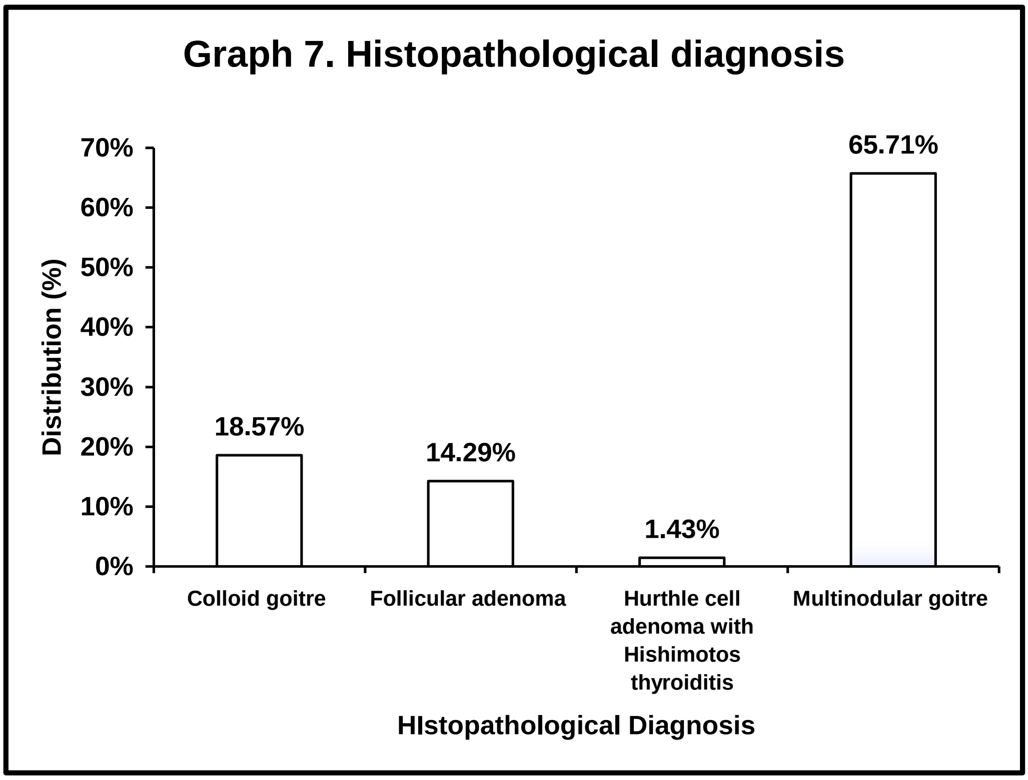
Graph 6. Fine needle aspiration cytology diagnosis



All reports were benign with FNAC reports showing colloid material in majority and remaining being follicular neoplasm.

Table 7. Histopathological diagnosis

Histopathological diagnosis	Distribution (n=70)	
	Number	**Percentage**
Colloid goitre	13	18.57
Follicular adenoma	10	14.29
Hurthle cell adenoma with Hishimotos thyroiditis	1	1.43
Multi nodular goitre	46	65.71
Total	**70**	**100.00**



HPR, which is the gold standard reported Multi nodular goiter in 46 cases, Colloid goiter in 13 cases, Follicular adenoma in 10 cases and remaining one being Hurthle cell adenoma with Hishimotos thyroiditis.

Table 8. Correlation of FNAC and Histopathological diagnosis

True positive (a)	**False positive (b)**
10	0
False negative (c)	**True negative (d)**
1	59

From this table, following values were calculated as -

Sensitivity

$$= \frac{a}{a + c} \times 100 = \frac{10}{10 + 1} \times 100 = 90.91\%$$

Specificity

$$= \frac{d}{b + d} = \frac{59}{0 + 59} = 100\%$$

Positive predictive value

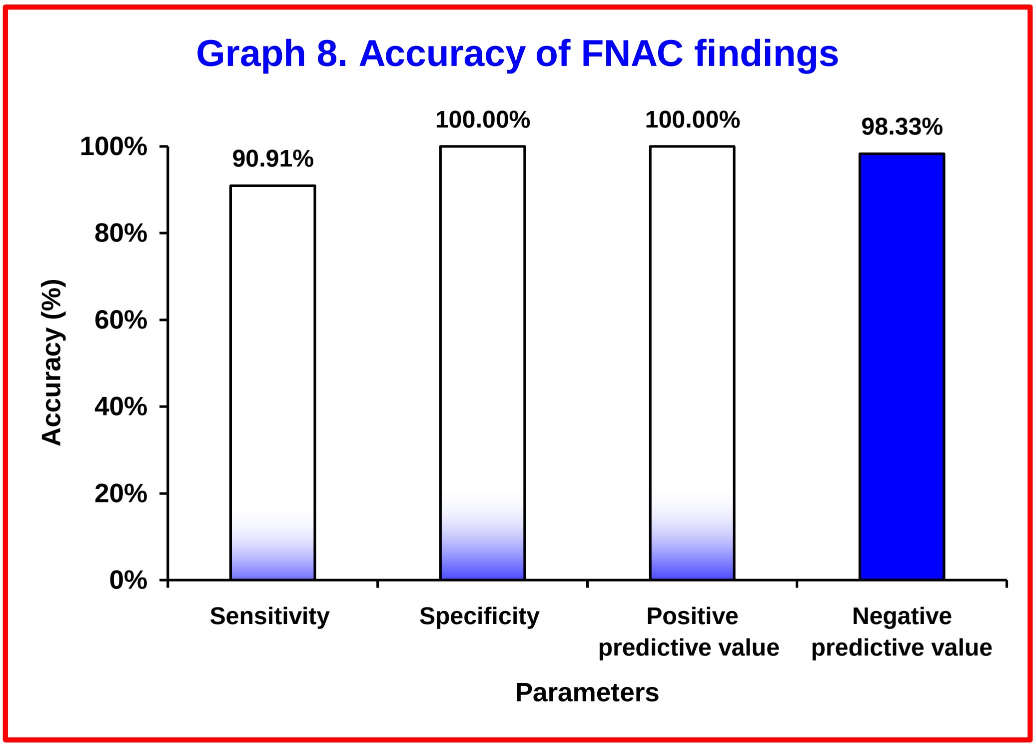
$$= \frac{a}{a + b} = \frac{10}{10 + 0} = 100\%$$

Negative predictive value

$$= \frac{d}{c + d} = \frac{59}{1 + 59} = 98.33\%$$

Table 9. Accuracy of FNAC findings

	Accuracy
Sensitivity	90.91%
Specificity	100%
Positive predictive value	100%
Negative predictive value	98.33%



The Sensitivity and Specificity of FNAC in predicting diagnosis was 90.91% and 100% respectively. Similarly the Positive predicative value and Negative predicative value for the same was 100% and 98.33% respectively.

DISCUSSION

Thyroid nodular (TN) lesions are a common clinical problem in the world. These are more common in women and in areas of iodine deficiency. Exposure to ionizing radiation in childhood and adolescence increases the risk of solitary thyroid nodule and thyroid carcinoma. In the United States, 4 to 7% of the adult population has a palpable thyroid nodule.[56]

A solitary thyroid nodule is a palpable swelling in thyroid gland that has otherwise a normal appearance. The majority of thyroid nodules are asymptomatic and only about 5% of all palpable nodules are found to be malignant. A variety of tests have been employed to separate benign from malignant thyroid nodules.[56]

These tests include isotope scanning and FNAC. Combined use of isotope scanning, fine needle aspiration cytology, and histopathology of thyroid offers the best diagnostic strategy.[56]

Isotope scanning was generally used to classify nodules into nonfunctioning (cold) or functioning (warm or hot) nodules. The scans used either Iodine123 or technetium Tc99m pertechnetate. Only 5 to 15% of the cold nodules are malignant.[56]

Fine needle aspiration cytology of thyroid nodules is the single most sensitive, specific, and cost-effective method of investigation of thyroid nodules. Now it is safely and widely recommended for the preoperative selection of patients. The major pitfall of this procedure is that fine needle aspiration cytology cannot differentiate between follicular adenoma and follicular carcinoma.[56]

Histopathology of the excised specimen showed multinodular goiter as the commonest lesion. In one study, fine needle aspiration cytology and thyroid scan offers the best preoperative assessment of solitary thyroid nodule. Histopathology later on confirms the preoperative diagnosis. As the incidence of solitary thyroid nodule is high in Pakistan, this study will help in early detection of thyroid lesions.[56]

Fine needle aspiration cytology is a well-established technique for preoperative investigation of thyroid nodules. The technique is a noninvasive, cost-effective, and efficient method of differentiating benign and malignant thyroid nodules.[56] Many investigators have shown that fine needle aspiration cytology is the single most sensitive, specific, and cost-effective method in the investigation of solitary thyroid nodules.[62,63]

Despite studies supporting the cost-effectiveness of fine needle aspiration cytology as the diagnostic test of choice, I-131 scintigraphy continues to be used by frontline providers as primary diagnostic tools in the management of patients with nodular thyroid diseases. Justifications for the continued use of this alternative diagnostic strategy usually range from historical practice patterns within institutions to faster turnaround time for results when compared with waiting for FNAC pathology reports. FNAC of thyroid is gaining popularity among pathologists and clinicians all over the world.[56]

Fine Needle Aspiration Cytology is a sensitive and highly specific method of evaluating thyroid nodules for malignancy.[56]

Fine Needle Aspiration Cytology has been used for last four decades in various parts of the world as a diagnostic tool. In later half of the tenth century the famous Arabian physician Abulcasim described needle puncture of the thyroid to distinguish different types of goiter. But the technique was first used for the cytological diagnosis of a thyroid tumor in America in 1930s. Since early1950, FNAC is being used routinely in all forms of thyroid diseases.[64-66]

It is vital to distinguish the types of thyroid nodules as this will help to decide the further line of management. Although most of the thyroid nodules are benign, more than 1000 people die of thyroid cancer each year.[67] According to Anderson and Webb the preoperative identification of thyroid malignancy on the basis of clinical findings, isotope scintigraphy and ultrasonography results in a low percentage of yields of malignant disease.[65]

Moreover scintigraphy and ultrasonography are not affordable by every patients in our country. According to Matheson NA et al the FNAC is easily available, easy to perform and cheap method for the diagnosis solitary thyroid nodule.[68]

In this study a total of seventy patients diagnosed clinically as thyroid swelling were subjected to FNAC followed by surgery during a period of one year. The patients were picked up from the General Surgery and OPD Otolaryngology of Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. FNAC from the thyroid swelling were performed. These patients were operated and the specimen were sent to the department of pathology for histopathological examinations. Correlation between FNAC and histopathological results were done and the efficacy of FNAC for the final diagnosis of thyroid swellings was calculated.

In this study the ages of the patients ranged from 20 years to 78 years with the mean age was 44.93 ± 13.58 years with range being with 20 to 78 years. Majorities of these patients (41.43%) were between 31 to 45 years. 30% being in 46 years to 60 years, 15.71% being less than 30 years and remaining 12.86% more than 60 years.

Mann CV et al has mentioned that the thyroid swellings are said to be more common in female, the ratio being four times more in female.[68] But in our series the swelling were eight times more common in female. Out of these seventy patients, 62 (88.57%) were female and 8 (11.43%) were male. Although this study was performed in tertiary center further study is needed to confirm this higher frequency of thyroid swelling in female in our context.

The chief presenting complaint was swelling in the thyroid region, which was present in all (100%) patients. Two patients each presented with pain discomfort in addition to swellings. Mann CV et al has also mentioned that the commonest presenting complaint is thyroid swelling.[68]

Twenty-one of these patients (42%) 45 presented in months. Another sixteen patients presented in 1 to 2 years of development of swellings. Majority of the patients (76%) in this study presented within two years of appearance the swelling.

FNAC Histopathology

All reports were benign with fnac reports showing colloid material in majority and remaining being follicular neoplasm.

The results of this study was compared with the various previous studies.[20,70] There is great disparity between studies in the clinical nature of the swellings (that is, multinodular, isolated, or dominant) and the numbers of operation. Only in three studies by Al-Sayer HA et al,[20] Bouvet M et al[67] and Cusick et al[69] isolated swellings were identified separately.

This study was similar to that of Al–Sayer HM et al.[20] Total number patients in his study were seventy. The methods of calculations were also similar. But positive predictive value of 66.6% was slightly lower in this study. Our study was similar to that of f Cusick et al[69] but the findings were different from his study. The sensitivity to detect the neoplasm was 76% while in our study it was 90.91%. The overall specificity was 69% in his study but in this series it is 100%.

The sensitivity and specificity for neoplatic lesion were 90.91% and 100% respectively in this series. The positive predictive value was 100% and the negative predictive value being 98.33% in this study.

Every patient in our country does not afford the ultrasonography, computed tomography, scintigrapy and magnetic resonance imaging. Further the thyroid scan is only available in certain Hospitals. The FNAC is accurate, cost effective, safe and easily available method for the diagnosis of thyroid nodule.

Layfield LJ et al[70] have stressed that once an aspiration diagnosis of follicular neoplasm has been made, no other clinical, radiological or laboratory test can differentiate these tumors as benign and malignant nature of these neoplasms. Histopathological examination is required to identify the vascular and/or capsular invasion. No other investigations were performed to differentiate benign from malignant nature of these neoplasms in this study. Histopathological examinations were performed for the final diagnosis.

There were no malignant lesion in this study. The majority being MNG and the rest being colloid goiter, follicular adenoma and one being hurthle cell adenoma with hashimotos thyroiditis.

CONCLUSION

A total of seventy patients diagnosed clinically as Thyroid swelling were subjected to FNAC followed by surgery during a period of one year. These patients were operated and histopathological examinations of these excised nodules were performed and FNAC report was compared with HPR reports. The accuracy of FNAC showed sensitivity of 90.91%, specificity of 100% with positive predictive value of 100% and negative predictive value of 98.33% in diagnosis.

SUMMARY

Thyroid nodular (TN) lesions are a common clinical problem in the world. A solitary thyroid nodule is a palpable swelling in thyroid gland that has otherwise a normal appearance. A variety of tests have been employed to separate benign from malignant thyroid nodules. These tests include isotope scanning and FNAC. Combined use of isotope scanning, fine needle aspiration cytology, and histopathology of thyroid offers the best diagnostic strategy. The present study was undertaken to assess the accuracy of Fine needle aspiration cytology in patients presenting with thyroid swelling.

The present one year cross sectional study was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. A total of 70 patients with thyroid swelling were studied. The correlation of FNAC diagnosis with HPR findings was analysed by calculating sensitivity, specificity, positive predictive value and negative predictive value.

Total no of patients were 70 of which 62 (88.57%) were females and 8 (11.43%) were males. The mean age was 44.93 ± 13.58 years with range being with 20 to 78 years. All the patients (100%) presented with swelling. Majority presented with bilateral and left sided swelling of the thyroid (34.29%). All (100%) reports were benign with FNAC reports showing colloid material in majority and remaining being follicular neoplasm. HPR, which is the gold standard reported Multi nodular goiter in 46 cases, Colloid goiter in 13 cases, Follicular adenoma in 10 cases and remaining one being Hurthle cell adenoma with Hishimotos thyroiditis.

The Sensitivity and Specificity of FNAC in predicting diagnosis was 90.91% and 100% respectively. Similarly the Positive predicative value and Negative predicative value for the same was 100% and 98.33% respectively.

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ANNEXURE I – CONSENT FORM

Title of Research Study: Role of fine needle aspiration cytology in diagnosis of thyroid swelling.

Principal Investigator

Dr. Sidharth Chacko
Post Graduate Student,
Department Of General surgery
J. N. Medical College, Belgaum.

Introduction and purpose

Most definitive diagnosis pre operatively in case of a thyroid swelling is FNAC. This study is being done to assess the accuracy of fine needle aspiration cytology.

Procedure

Fine needle aspiration cytology.

Voluntary participation/withdrawal

I Mr./Ms.________________________ have been explained about the research study, the need of the study, the diagnostic intervention, their risks, benefits and alternatives available in my own vernacular language.

Taking part in this study is voluntary. I may choose not to take part in the study, or withdraw from the study anytime later. My decisions will not change the present or future health care or any service I receive. The study doctor or sponsor may stop my participation in the study without any consent. While taking part in the study I will be told of any important new findings that may change my willingness to continue or take part. If I choose not to take part in the study I will receive the standard treatment for patients with my conditions.

Compensation

In the event that I become injured as a result of taking part in this study, treatment will be offered to me or I will be given information about where to receive medical care: but my insurance company or I will be responsible for the costs. No reimbursement, compensation or free medical care will be given.

Confidentiality

All information collected about me during the course of the study will be kept confidential to the extent, permitted by law. I will be identified in research records by a code number. Information of the study may be published but my identity will be kept confidential in any publication.

Consent to participate in the study

I voluntarily agree to participate in this study by signing up this form below. I may withdraw at any time from this study. I am not giving any of my legal rights by signing up this form. My signature / thumb impression below indicates that I have read or information in the consent been read to me including the risks and benefits and have cleared my doubts. I will be given a copy of this consent form.

In case of any queries, you can contact the following:

Dr. V. D. Patil $_{\text{MD, DCH}}$,
Chairman, College Ethical Dissertation
And Research Committee,
J. N. Medical College,
KLE University, Belgaum – 10.

Dr. P. S. Pattanshetti
Professor
Department of
J. N. Medical College,
KLE University, Belgaum-10

Dr. Sidharth Chacko
Post graduate student,
Department of General surgery
J. N. Medical College,
KLE University, Belgaum – 10.

Signature of the study patient:

Name of the study patient:

Signature of the legally authorized representative:

Relationship to the patient:

Signature of the witness:

Signature of the investigator:

Date:

ANNEXURE II – PROFOMA

History

Name

Age/Sex

Presenting complaints:

History of present illness:

Past history:

Family history:

Personal, social and occupational history:

General Examination

Pulse:

Blood pressure:

Temperature:

Respiratory rate:

Systemic Examination

Cardiovascular System:

Gastrointestinal System:

Respiratory System:

Central nervous system:

Local Examination

INSPECTION:

PALPATION:

PERCUSSION:

AUSCULTATION:

Provisional Diagnosis:

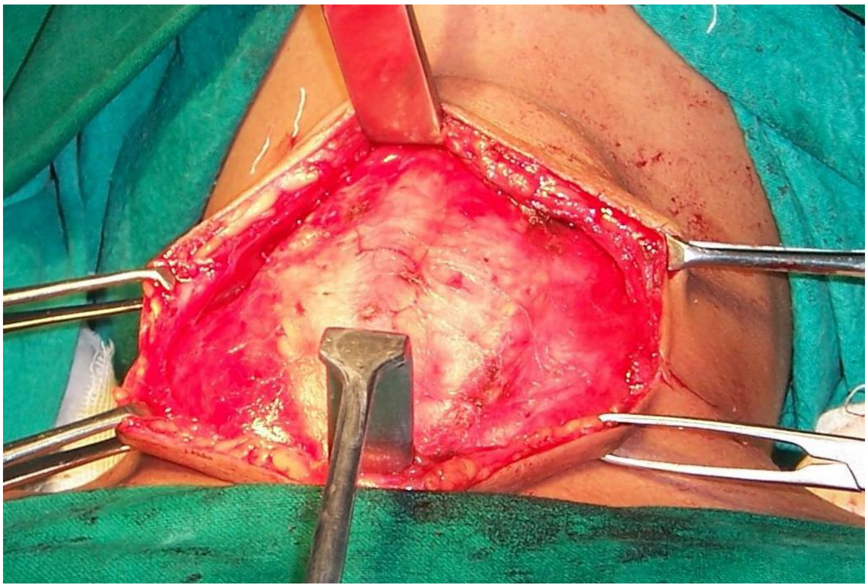
FNAC REPORT:

HPR REPORT:

ANNEXURE III – PHOTOGRAPHS

Photograph 1. Case of multinodular goiter presented with complaints of swelling

Photograph 2. Skin incision for thyroidectomy



Photograph 3. Elevation of flap for thyroidectomy

Photograph 4. Thyroidectomy specimen

ANNEXURE IV - MASTER CHART

Serial Number	In Patient Number	Sex	Age (Years)	Complaints				Site of nodule	Consistency	Provisional diagnosis	FNAC	HPR findings
				Swelling	Dysphagia	Pain	Change in voice					
1	336599	F	38	1Y	1m	-	-	L	FM	MNG	Colloid goitre	MNG
2	336657	F	37	2Y	-	-	-	B	FM	MNG	Colloid material with follicular cells	MNG
3	339585	F	39	5m	-	-	-	B	FM	MNG	Colloid material with follicular cells	MNG
4	340534	M	21	2m	3W	-	-	L	FM	MNG	Colloid goitre	MNG
5	341873	F	64	3Y	-	-	-	R	FM	MNG	Colloid material with follicular cells	MNG
6	344329	F	78	5Y	-	-	1Y	L	FM	Solitary nodule	Colloid material with follicular cells	Colloid goitre
7	344898	F	26	1Y	-	-	-	B	FM	MNG	Colloid material with follicular cells	MNG
8	345296	M	22	2m	-	-	-	R	FM	Solitary nodule	Colloid material with follicular cells	Colloid goitre
9	345663	F	60	6m	-	-	-	R	FM	MNG	Colloid material	MNG
10	347353	F	50	7m	-	-	-	L	FM	MNG	Colloid material	MNG
11	369846	F	35	2Y	-	-	-	B	FM	MNG	Colloid goitre	MNG
12	347741	F	48	1Y	-	1W	-	R	FM	MNG	Colloid goitre	MNG
13	302735	M	38	6m	-	-	-	L	FM	MNG	Colloid goitre	MNG
14	349159	M	25	1.5m	-	-	-	L	FM	Solitary nodule	Colloid material	Colloid goitre
15	352272	F	47	6m	-	-	-	R	FM	Diffuse enlargement of right lobe	Colloid goitre	Hurthle cell adenoma with hashimotos thyroiditis
16	352677	F	28	1Y	-	-	-	R	FM	MNG	Colloid material with follicular cells	MNG
17	354257	F	65	2Y	-	-	-	R	FM	Colloid goitre	Colloid material	Colloid goitre
18	356473	F	35	1Y	-	-	-	B	FM	MNG	Colloid material	MNG
19	355301	F	40	20D	-	-	-	B	FM	MNG	Colloid material with follicular cells	MNG
20	361544	F	40	2m	-	-	-	R	FM	Solitary nodule	Follicular neoplasm	Follicular adenoma
21	365253	F	28	2m	-	-	-	R	FM	MNG	Colloid material	MNG
22	356442	F	45	3m	-	-	-	L	FM	MNG	Colloid material with follicular cells	MNG
23	361521	F	42	6m	-	-	-	L	FM	Solitary nodule thyroid	Follicular neoplasm	Follicular adenoma
24	368797	F	46	7m	-	-	-	R	FM	MNG	Colloid material with follicular cells	MNG
25	369504	F	32	6m	-	-	-	L	FM	MNG	Colloid material	MNG
26	371721	F	30	1Y	-	-	-	R	FM	Solitary nodule thyroid	Colloid goitre	Colloid goitre
27	361374	F	35	3Y	-	-	-	R	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
28	361548	F	29	4Y	-	-	-	L	FM	MNG	Colloid material with follicular cells	MNG
29	289149	F	46	2Y	-	-	-	B	FM	MNG	Colloid material	MNG
30	294727	F	57	4m	-	-	-	B	FM	MNG	Colloid material	MNG
31	296506	F	60	1Y	-	-	-	B	FM	MNG	Colloid material with follicular cells	MNG
32	335072	M	24	3m	-	-	-	L	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
33	373645	F	39	5W	-	-	-	R	FM	MNG	Colloid material	MNG
34	352272	F	47	7m	-	-	-	R	FM	MNG	Colloid material with follicular cells	MNG
35	366612	F	28	2m	-	-	-	L	FM	Solitary nodule thyroid	Colloid material	Colloid goitre

ANNEXURE IV - MASTER CHART

Serial Number	In Patient Number	Sex	Age (Years)	Complaints				Site of nodule	Consistency	Provisional diagnosis	FNAC	HPR findings
				Swelling	Dysphagia	Pain	Change in voice					
36	339230	F	37	5W	-	-	-	R	FM	MNG	Colloid with follicular material	MNG
37	333862	M	70	4Y	-	-	-	B	FM	MNG	Colloid goitre	MNG
38	339232	F	26	1m	-	-	-	L	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
39	332535	F	35	2m	-	-	-	B	FM	MNG	Colloid material with follicular cells	MNG
40	379311	F	55	6m	-	-	-	B	FM	MNG	Colloid material	MNG
41	384635	F	45	3W	-	-	-	L	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
42	388346	F	20	1m	-	-	-	R	FM	Solitary nodule thyroid	Follicular neoplasm	Follicular adenoma
43	356015	F	52	5Y	-	-	-	B	FM	MNG	Colloid material	MNG
44	356477	F	38	3m	-	-	-	L	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
45	356442	M	45	1W	-	-	-	L	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
46	356418	F	45	2Y	-	-	-	B	FM	MNG	Follicular neoplasm	Follicular adenoma
47	356408	F	35	7m	-	-	-	L	FM	MNG	Colloid material	MNG
48	355982	F	52	5Y	-	-	-	R	FM	Solitary nodule	Follicular neoplasm	Follicular adenoma
49	357418	F	50	4Y	-	-	-	B	FM	MNG	Colloid material	MNG
50	357415	F	41	1W	-	-	-	R	FM	MNG	Colloid material	MNG
51	357756	F	49	3W	-	-	-	L	FM	Solitary nodule thyroid	Follicular neoplasm	Follicular adenoma
52	358743	F	72	7Y	-	-	-	B	FM	MNG	Colloid material	MNG
53	359221	F	44	1m	-	-	-	L	FM	MNG	Colloid material	MNG
54	359893	F	60	4Y	-	1W	-	L	FM	MNG	Colloid material	MNG
55	360037	F	55	3Y	-	-	-	R	FM	Solitary nodule thyroid	Colloid material	Colloid goitre
56	360580	F	65	2W	-	-	-	B	FM	MNG	Colloid material	MNG
57	361544	F	40	1Y	-	-	-	B	FM	MNG	Follicular neoplasm	Follicular adenoma
58	361566	M	60	11Y	-	-	-	B	FM	MNG	Colloid material	MNG
59	362212	F	58	1Y	-	-	-	B	FM	MNG	Colloid material	MNG
60	363637	F	72	15Y	-	-	1Y	B	FM	MNG	Colloid material	MNG
61	365580	F	40	3Y	-	-	-	L	FM	MNG	Colloid material	MNG
62	367729	F	54	6m	-	-	-	L	FM	Solitary nodule thyroid	Follicular neoplasm	Follicular adenoma
63	367934	F	43	2m	-	-	-	R	FM	MNG	Follicular neoplasm	Follicular adenoma
64	367887	F	40	2W	-	-	-	L	FM	MNG	Colloid material	MNG
65	370043	F	52	1W	-	-	-	B	FM	MNG	Colloid material	MNG
66	371145	F	45	1W	-	-	-	L	FM	MNG	Colloid material	MNG
67	372201	F	60	5W	-	-	-	R	FM	MNG	Follicular neoplasm	Follicular adenoma
68	373056	F	62	2Y	-	-	-	B	FM	MNG	Colloid material	MNG
69	379939	F	41	3Y	-	-	-	R	FM	MNG	Colloid material	MNG
70	377937	F	63	2W	-	-	-	B	FM	MNG	Colloid material	MNG

ANNEXURE IV – KEY TO MASTER CHART

B	-	Bilateral
F	-	Female
FM	-	Firm
FNAC	-	Fine needle aspiration cytology
HPR	-	Histopathology report
L	-	Left
M	-	Male
m	-	Months
MNG	-	Multi nodular goiter
R	-	Right
W	-	Week
Y	-	Year