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The Rate Of Differentiated Thyroid Carcinoma Among Patients With Goiter Referred To Diwaniya Teaching Hospital

A thesis
Submitted to The Council of the College of Medicine/ University of AL-Qadisiyah in a Partial Fulfillment of the Requirement for the Degree of Higher Diploma Equivalent to Master Degree in Family Medicine

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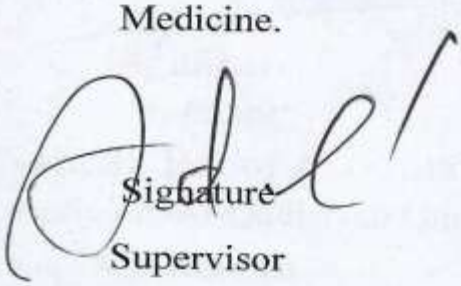

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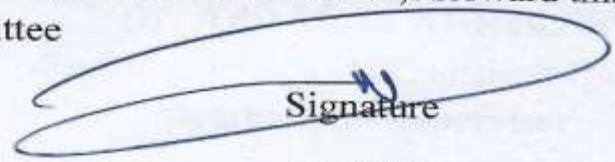

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Dedication

To my Mother and Father

To my Husband

To my lovely children (Fatima and Mohammad)

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List of Abbreviations

MNG	Multinodular goiter
FNA	Fine needle aspiration
PTC	Papillary thyroid carcinoma
FTC	Follicular thyroid carcioma
ATC	Anaplastic thyroid carcinoma
DTC	Differentiated thyroid carcinoma
MTC	Medullary thyroid carcinoma
RLN	Recurrent laryngeal nerve
STA	Superior thyroid artery
ITA	Inferior thyroid artery
MTV	Middle thyroid vein
SLN	Superior laryngeal nerve
EBSLN	External branch superior laryngeal nerve
IBSLN	Internal branch superior laryngeal nerve
T3	Tri-iodothyronin
T4	Tetra -iodothyronin
TBG	Thyroxin-binding globulin
TBPA	Thyroxin-binding prealbumin
TSH	Thyroid-stimulating hormone
TRH	Thyrotrophin –releasing hormone
CLT	Chronic lymphocytic thyroditis
IFT	Invasive fibrous thyroditis
DTH	Diffuse toxic hyperplasia
TSHR	Thyroid-stimulating hormone receptor
FA	Follicular adenoma

FC	Follicular carcinoma
PDC	Poorly differentiated carcinoma
PTL	Primary thyroid lymphoma
LN	Lymph node

Abstract

Background

The thyroid cancer is the most frequent cancer of the endocrine system, and it is rapidly increasing in incidence due to availability of diagnostic tools . It occur more often in people who live in areas with excessive exposure to radiation and excessive use of x-ray which can be considered as an important risk factors . There is a great controversy about the incidence for thyroid gland carcinoma.

The Aim of study

Evaluation of the prevalence of thyroid cancer among patients with goiter that are referred from private clinic to Al Diwanya teaching hospital and to evaluate the histological variants and possible risk factors.

Patients and methods

We randomly select 74 patients (19 male ,55 female) with goiter(33 solitary nodule ,41 MNG) ,from different age groups , evaluate them by history ,examination and investigation , prospectively study them regarding the presence or absence of cancer ,and also the histological type of cancer (papillary or follicular) .

History includes the most important risk factors questionnaire (family history ,exposure to radiation especially x-ray), personal history and all the details regarding their illness.

Physical examination was done to every patient in form of general examination and examination of the thyroid gland.

Also investigations were done for them in form of routine investigation and investigations of the thyroid .

Ultrasound and fine needle aspiration (FNA) also was done .We have followed the patients cases to obtain the results of histological examination .

Results

The collected data reveal that the most frequent ages presented with goiter are between 45-60 y. ,female represented 74.3% of patients, with 55.4% of patients presented with MNG and 44.6% presented with solitary nodule .Family history of goiter was positive in 24.4% and negative in 75.6% of patients. History of x-ray exposure were positive in 59.4% and negative in 40.6% of patients.

The histological results reveal that the papillary cancer represent 14.8% and the follicular cancer represent 6.7% of all patients with goiter with no significant difference between solitary and MNG regarding the type of cancer. The most common surgical procedure was total thyroidectomy (71%) while lobectomy had done in 29% of patients. In our study the x-ray exposure before 5 years age was a significant risk factor for both types (papillary and follicular) of cancer, (p- value is 0.02).Also the positive family history was another significant risk factor for both types of cancer (p-value is 0.001) and females are the most frequently present with goiter and cancer.

Conclusion

Thyroid cancer is not a rare tumor in our region .Better diagnostic tools should be used to reach the diagnosis . The positive family history and the history of x-ray exposure are important risk factors . We really need the activation of registration center of cancer to assess the problem in our country.

CHAPTER ONE

INTRODUCTION

THE AIMS OF STUDY

INTRODUCTION

The thyroid gland is an endocrine gland of a butterfly shape located in the lower front of the neck. The job of the thyroid is the synthesis of thyroid hormones ,which regulate the metabolism in the body.[1]

The thyroid gland is not palpable normally ,the term (goiter) is used to define the generalized increase in the size of it and it may be diffuse or multi nodular. The nodule is a discrete swelling in the gland and it may be isolated(when other sites are normal) or dominant (when other sites are nodular). Goiter is classified functionally as :simple ,toxic (diffuse ,MNG ,or toxic adenoma) ,neoplastic ,and inflammatory [2].Endemic goiter is the presence of goiter in more than 10 % of the people [3].Most countries in the world have one or more areas where endemic goiter is present [4].Iraq is an endemic area with goiter [5] and the incidence increase with age and they are 4 folds more in females than males [6,7].

Cancer is a type of diseases occurs due to uninhibited cells proliferation. These resultant cells are able to invade another organs through direct metastasis of cells or by the blood or lymphatic vessels [8]. More than 200 types of cancer are present that take the name of the organ of their origination [9]. Cancers are found anywhere in the world but the rate differs depending on the variability and density of the relevant reasons[10]. Commonly, there is no worldwide typical standards for the prevalence or incidence of cancer which differ from country to another. In our country, people suffer from a different types of cancer particularly in the last 10 years [11].

Thyroid cancer is the most common malignancy of endocrine system and it rises in its incidence [12]. The increasing incidence is partially due to early detection of asymptomatic small cancer due to availability of screening tools

[13]. Most of thyroid cancers show an indolent phenotype and have a very good prognosis with survival rates of > 95% at 20 years but the recurrence or persistence rate remain elevated [14]. The incidence of thyroid cancer is about 3-4 times higher among women than men ,(6th cancer in women).It occurs at any age but it is rare in children. Most tumors are diagnosed during 3rd -6th decade of age[15]. The thyroid cancer in Iraq represents the 2nd cancer in women and the 8th cancer in men. [16]

Thyroid cancer can arise from either follicular or non-follicular thyroid tissue. Follicular carcinoma includes papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), poorly differentiated and undifferentiated(anaplastic) thyroid cancer (ATC). PTC and FTC together represent the large proportion of thyroid cancer and both called differentiated thyroid cancer (DTC). Subtypes of DTC, include :Hurthle, tall cell, columnar and insular, which are more aggressive. Medullary thyroid carcinoma (MTC) arises from non-follicular thyroid cells called calcitonin-making cells (C cells)[17].The risk factors of thyroid cancer are:

1. Radiation: The thyroid gland exposed to radiation more due to its position in the body. [18]
2. TSH Levels and Iodine deficiency :Low level of Iodine causes an increase level of (TSH), a main growing factor for follicular cells of thyroid.[19]
3. Autoimmune Thyroid disease .[20]
4. Thyroid nodules.[21]
5. Body weight and insulin resistance :There is a strong relation between obesity and risk of cancer.[22]Analysis of five studies prospectively shows that also the risk of thyroid cancer is higher in obese people.[23]
6. Environmental exposure :The most important environmental factors are ionizing radiation and dietary iodine consumption .Others like Solvent

occupational exposure like benzene and formaldehyde(in the shoemaking) , fungicides such as dioxin, and highly consumption of green tea are all associated with thyroid cancer but the evidence of these still contradictory.[24,25] Some studies show a high incidence of thyroid cancer in volcanic areas.[26]

7. Familial or genetic factors: About 5–10 % of thyroid cancers are familial and the vast majority are sporadic. [27]
8. Female gender: The relation between menstruation and reproductive factors with thyroid cancer has been studied , but the studies show a mixed results.[28]
9. Cowden's syndrome and other rare syndromes .[29]

The Aims of Study

The aims of study is to assess the differentiated thyroid carcinoma rate among patients with goiter that are referred to Al Diwaniya teaching hospital and the evaluation of the possible risk factors that may lead to this condition .

CHPTER TWO

REVIEW OF LITRATURE

Review of Literature

2.1 Embryology

The thyroid gland is the first endocrine organ to form. It begins its development during the 3rd week of gestation. It arises from the fusion of 2 structures: medial and lateral thyroid anlages. The medial thyroid anlages arise from the primitive pharynx. The lateral thyroid anlages arise from neural crest cells that form a transient structures called the ultimobranchial bodies. Parafollicular(C cells)arise from the paired ultimobranchial bodies and secrete the calcitonin.(30,31,32,33)

The medial thyroid anlages make most of the size of the thyroid gland, the paired lateral thyroid anlages contribute to a small but important portion of the thyroid gland. During the 5th week of gestation, at the level between the 4th and 5th pharyngeal pouches, cells detach from the wall of the pharynx and fuse with the posterior part of the main body of the thyroid gland as it descends into the neck. These cells differentiate into the parafollicular (C cells).(31) Finely, the fusion between the medial thyroid anlages and the paired lateral thyroid anlages produces thickenings called the tubercles of Zuckerkandl which serve as a landmarks for the recurrent laryngeal nerve (RLN), which runs medial and deep to it on each sides.(34)

The follicles of the thyroid begin to form at 8 weeks of gestation from epithelial plates. By the 4th month follicles can be seen at various stages of development, and at this time they increase widely in number. Colloid is seen at the 12th week of gestation. Iodide is enter to the follicles to start the synthesis of thyroid hormones, which is secreted into the fetal blood.(32,35)

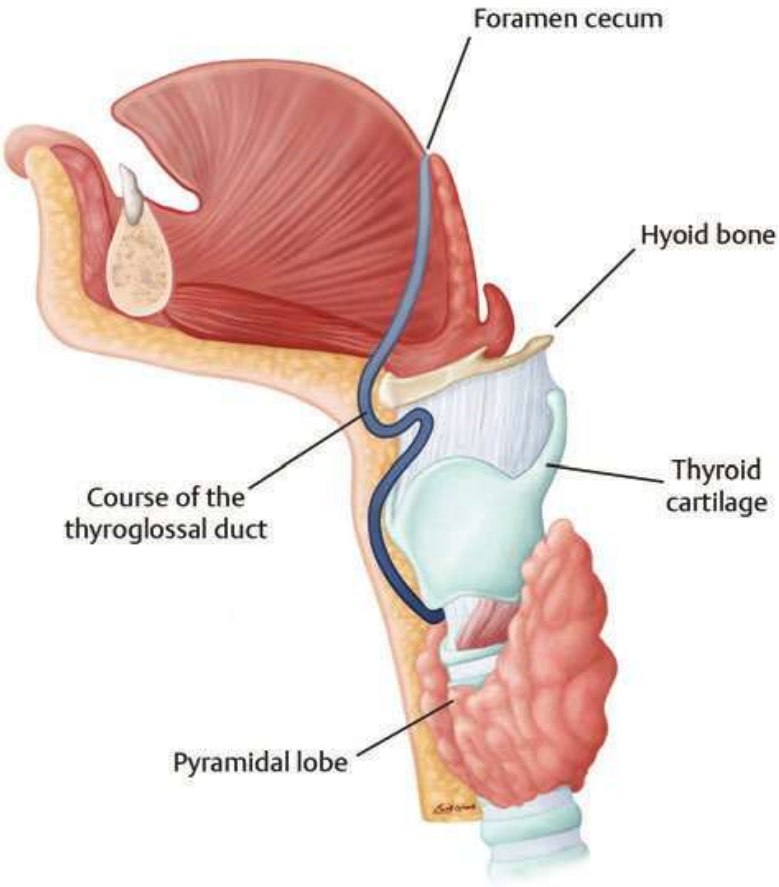

Figure 2.1 The pathway of descend of thyroid gland from the embryological origin at the foramen cecum to its final position. [35]

2.2 Anatomy

The normal thyroid gland of adult weighs about 10 - 20 g and is located anterior to trachea ,midway between the thyroid cartilage and the suprasternal notch. A capsule formed from fibrous tissue developed from the deep cervical fascia cover it by dividing in to an anterior and a posterior sheath. The thyroid gland is further covered at anterior side by superficial cervical fascia, strap muscles, and the platysma. At lateral side, the deep cervical fascia is loosely attach to the thyroid gland. On the posterior part of the thyroid gland, the deep

cervical fascia thickened to form a thick suspensory ligament (ligament of Berry), which causes the thyroid gland to be fixed to the trachea and larynx strongly. This ligament is responsible for the movement of the gland during swallowing. The final thyroid gland consists of two lobes, on each sides of trachea, with a midline isthmus connect the 2 lobes. The lobes are 4 cm from upper to below, 2 cm wide, and 2-4 cm in thick. The isthmus is about 1.25 cm. Thyroid disease change these measures. A pyramidal lobe is present in about 50% of population and is connecting to the isthmus or one of lobes .[33]

2.3 Congenital Thyroid Anomalies

2.3.1 Ectopic thyroid tissue

It is a functional thyroid tissue exists at any site along the way of migration . The majority of it occurs in the midline of neck along thyroglossal tract. Lateral site is rare. Women have a higher incidence for ectopic thyroid tissue than men.[36,37]

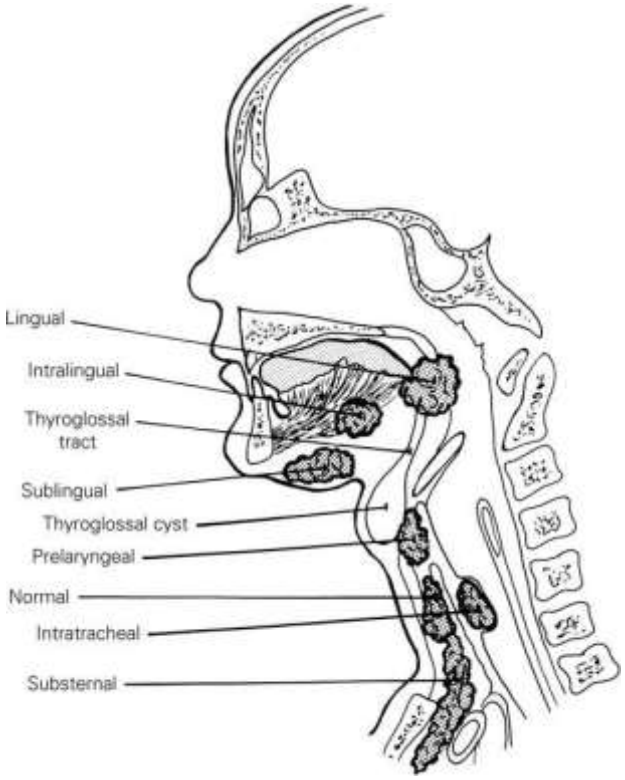

Figure 2.2 Abnormal Locations of Thyroid Tissue. [37]

2.3.2 Lingual Thyroid

It is relatively rare and usually asymptomatic, so the true incidence is unknown. It accounts for 90% of thyroid ectopic tissue .[37] It results when the medial thyroid anlage fails to migrate downward. In 70% of cases, it is associated with the absence of the normal thyroid gland. If both locations are present (cervical and lingual), lingual thyroid usually is the only functioning tissue. Usually the patients complain of asymptomatic mass at the back of tongue.[33,36,37] . It is usually associated with hypothyroidism and increase size from TSH stimulation which may lead to dysphagia, dysphonia, dyspnea, or a sensation of choking. So, asymptomatic lingual thyroid can be left without need for surgery. It has a low risk of malignant change, with papillary thyroid carcinoma is the most often to develop.[38]

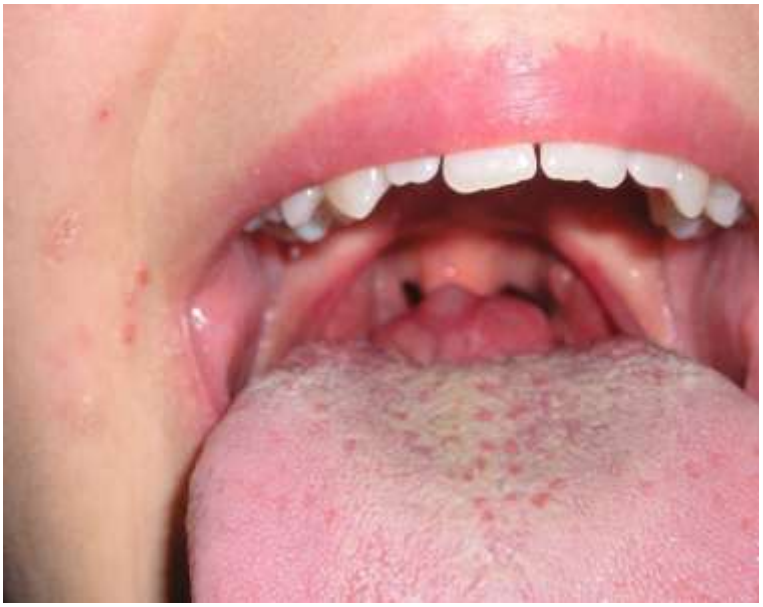

Figure 2.3 Lingual Thyroid .[38]

2.3.3 Thyroglossal Duct Remnant

The thyroglossal duct usually obliterates by the 8th week of gestation, but remnants of it can persist later in life[39]. These may present as a cyst or a sinus which can develop anywhere along the way of descent of the thyroid anlage. It is the most common cause of congenital neck masses in childhood. The most common symptom of presentation is a painless palpable neck mass[40]. It usually occur in the midline or near the midline between the hyoid bone and isthmus of the thyroid gland and measure about 2.5 to 3 cm[39] .The cyst may not be seen until it has infection or rupture spontaneously after upper respiratory tract infection. There is no gender predilection, and most patients present before age 20 year[39]. It is firmly attach to the hyoid bone and tongue musculature ,so swallowing will classically raise it in a predictable fashion[40]. Thyroid cancer can develop within it, so all specimens should send for histology .

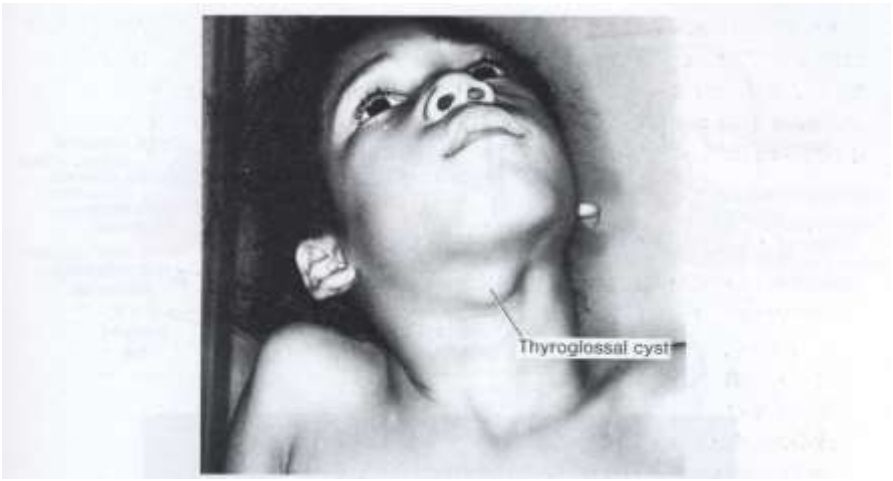

Figure 2.4 Thyroglossal cyst. [40]

2.4 Thyroid Gland Vasculature

The thyroid gland is a very vascular gland. Its arterial supply of blood is mainly by the superior thyroid artery(STA) and inferior thyroid artery(ITA). The origin of STA is variable but usually from the external carotid artery[33,41]. It may also arise from the bifurcation of the common carotid artery and internal

carotid artery, but this is less commonly occur[41] .The STA run along the external aspect of the inferior constrictor muscle and enter into the gland posteromedially near the upper part[33,42]. The artery may branch before entering the gland. There is classification of STA branching ways: type I (2 major branches), type II (trifurcation of artery), and type III (not branch)[41].

The ITA has a variable distribution and prior to entering the gland, it divides into an upper and a lower branch [42].The upper branch goes to the posterior part and the lower branch to the lower part of the gland.

The aberrant ITA (thyroid ima artery) arising from the aortic arch or the brachiocephalic, Right Common carotid, or internal thoracic artery. When it is found, it usually emerges on the right side[33].

On each side of the gland , there are 3thyroid veins : the superior(STV), middle(MTV), and inferior(ITV). The STV, drains the upper 2/3 of the ipsilateral lobe, accompanies its corresponding artery and arise from the upper part of the gland. It empties into the internal jugular; but, sometimes it will end into the linguofacial trunk and common facial vein[43].

The MTV is mostly present in patients with thyrotoxicosis and large goiters. Like the STV, the MTV usually drains the upper 2/3 of the gland into the internal jugular v[44].

The 2 inferior thyroid vein(ITV) arise from the lower part of the gland . This plexus of veins in the pretracheal fat is usually the source of hemorrhage during and after anterior neck operation[45].There may be a number of branches (1-5) from the ITV, and these branches can end into the left brachiocephalic vein, the right brachiocephalic vein, or both[43,45].

2.5 Lymphatic Drainage :

The efferent lymphatic vessels run along with the venous vessels. There are specific drainage patterns for the upper, lateral, and lower parts of the gland. The lymphatic vessels from the upper part and isthmus go to the Delphian, or

prelaryngeal lymph nodes and the jugular lymph node. The lymphatic vessels from the lateral part drain along with the middle thyroid vein. The lymphatic vessels that drain the lower part follow the inferior thyroid vein and drain to pretracheal, paratracheal , and lower jugular regions as well as other nodes in the anterior mediastinum .

The thyroid gland also has an intraglandular lymphatic vessels that connects the 2 lobes of the gland and it facilitates the spread of cancer within it[33].

2.6 Nerve Supply :

The gland receive sympathetic nerve supply from the superior , middle and inferior cervical ganglion of the sympathetic trunk and receive parasympathetic nerve supply from superior laryngeal and recurrent laryngeal nerve.

2.6.1 Recurrent Laryngeal Nerve (RLN):

Identification of RLN and SLN is a main principle during neck operation. An understood of these nerves and relation to other structures is important to avoid injury that may cause temporary or permanent results, like dysphonia, dysphagia, and dyspnea.

After Origination from the medulla oblongata, the vagus nerve starts its course by exiting from skull through jugular foramen. When the vagus nerve traverses the neck, the SLN (superior laryngeal nerve) and the RLN emerge to supply the larynx. On the right side, the recurrence of the nerve loops around right subclavian artery then ascends the neck to supply the larynx[33].

The left RLN emerge from the vagus when it enters the chest. It go either to the trachea, or in the nearby fatty tissues and connective tissue.[33,46]

The RLN enters the larynx posterior to the cricothyroid joint and provides motor, sensory, and parasympathetic innervation. Motor innervation is provided by the anterior branch of the RLN, which innervates the thyroarytenoid, lateral

cricoarytenoid, posterior cricoarytenoid, and transverse arytenoid muscles. The only laryngeal muscle not innervated by the RLN is the cricothyroid muscle. Sensory innervation is provided by the posterior branch of the RLN, which supplies sensation to the vocal cords and to the subglottic region[47].

The relation of the RLN to the ITA is used when we need to identify the nerve, although there is a great variability in this relation. The artery usually run lateral to nerve and then medial to thyroid gland[47].

2.6.2 Superior Laryngeal Nerve (SLN):

The vagus nerve exits the jugular foramen, one of its 1st branches is the SLN. The SLN arise from the nodose ganglion and run inferiorly posterior to the internal carotid artery .About 1.5 cm inferior to the bifurcation of the common carotid artery, the SLN divides into an internal branch (IBSLN) and an external branch (EBSLN) .The Internal branch has been pass to the larynx and give sensation to the part of larynx superior to the vocal folds. The external branch give motor supply to cricothyroid muscle, which make a rocking motion at the cricothyroid joint, increasing the vocal pitch, so the damage of it causes subtle change in vocal pitch and decreases the vocal range .

Documentation of the external branch during operation can avoid injury and reduce the rate of permanent voice changes[48].

2.7 Parathyroid glands :

Normally they weigh55-60 mg., about 3-8 mm. They are oval shaped yellow-brown color. Blood supply of them usually from ITA .They are usually symmetrical [49] .

2.8 Physiology of thyroid gland

Tri-iodothyronine(T3) and thyroxin(T4) has been linked to thyroglobulin in the gland .Many steps involved :

1- Tricking of inorganic iodide from the blood stream.

2-Oxidation of iodide to iodine.

3-Connecting of iodine with tyrosine to make iodotyrosine

4-Monoiodotyrosines and di-iodotyrosines are coupling to make T4 and T3.

When these are needed, the complex is resorbed to the cell and thyroglobulin is breaking down. T4 and T3 are released , arrive the blood, when it bind to serum proteins: albumin thyroxin-binding globulin and thyroxin-binding prealbumin .A small amount of hormones remain free and active.

T3 is the more important physiological hormone and is also produced in the periphery by conversion from T4. T3 is quick acting (within a few hours), whereas T4 acts more slowly (4–14 days). Synthesis and release of these hormones is controlled by TSH from the anterior Pitutary gland . Secretion of TSH. depends upon the level of T3 and T4, and is modified in a negative feedback mechanism. In thyrotoxicosis TSH is decreased, whereas in decease thyroid function it is increased. TSH secretion is regulated by the action of thyrotrophin-releasing hormone TRH made in hypothalamus.[(2)]

2.9 Diseases of the thyroid gland

2.9.1 Thyroiditis

2.9.1.1Chronic Lymphocytic Thyroiditis CLT (Hashimoto's or Autoimmune Thyroiditis) :

It is an autoimmune disease and the common and important type of thyroiditis. It is characterized by damage of follicular cells results in hypothyroidisms. Cellular -mediated and humoral mechanisms seem to be involved .It may be caused by genetic and environmental factors [(50)].It cause diffuse goiter, 2-4 times normal size of gland. Variants of it include fibrous, fibrous atrophy, toxic, and juvenile, so most types of it have mild - moderate

fibrosis. which is limited to the gland, in contrast to the extrathyroidal fibrosis of Riedel's thyroiditis[51]. CLT may be associated with increase thyroid function (hashitoxicosis) which is the early phase of Hashimotos thyroiditis[52].

2.9.1.2 Subacute Granulomatous Thyroiditis (De Quervain's Thyroiditis):

Inflammation of thyroid gland following attack with Coxsackie ,mumps or adenoviruses. Its clinical features are pain, tender large thyroid and systemic upset. Affect women aged 20-40 year[53] . The initial stage , usually is hyperthyroid stage because the thyroid gland shows follicular destruction. Acute and chronic inflammatory cells are present . With time granulomatous and chronic inflammation with various grades of fibrosis predominate[54] .

2.9.1.3 Acute Thyroiditis

It is a suppurative, inflammation of thyroid and is characterized by a mainly neutrophilic inflammatory infiltrate. It is a rare type of thyroiditis, usually due to bacterial infection occur anywhere in the neck. In children, it is frequently associated with a pyriform sinus fistula[55].

2.9.1.4 Invasive Fibrous Thyroiditis (Riedel's Thyroiditis)

Also called fibrosing, or sclerosing thyroiditis ,it is a rare disease considered as advanced fibrosis of the thyroid gland . The diseased glands are very firm and attached to perithyroidal tissues due to that the fibrosis spreading outside the gland. FNA is usually not diagnostic due to acellular or paucicellular samples[56].

2.9.2 Goiter

Goiter is a general term means expansion of the thyroid gland and includes MNG, endemic, dyshormonogenetic, diffuse toxic, and amyloid goiter. These objects, except of amyloid goiter, are linked with hyperplastic changes of the follicles.

2.9.2.1 Multi nodular Goiter (Nodular Hyperplasia) :

MNG is a common condition considered as enlargement of the thyroid gland with various amounts of nodules. It is also called nodular hyperplasia or nodular goiter.

Endemic goiter is frequently due to lack of dietary iodine[57]. Sporadic cases have a number of probable pathogenic ways, include individual lacking of dietary iodine , excessive consumption of goitrogenic diet, drugs, increased TSH level, and the activation of thyroid gland cells due to mutations of the TSH receptor gene[58]. Identification of the exact cause may be difficult, if not impossible, due to that most cases of it seem to be due to difficult interaction between many genetic and environmental reasons.

It is described as thyroid enlargment that range from mild – severe, mostly has many nodules seen obviously, but early cases may lack apparent nodularity or only has a solitary grossly seen nodule. Goiter may be symmetrical or asymmetrical. The cut surfaces usually have a nodular, heterogeneous appearance. Some parts have a semi-translucent look because of copious colloid, while other foci show bleeding , fibrosis, cystic degeneration, and/or calcification. Nodules may seem partly encapsulated by fibrous tissue. Follicles may contain papillary-like folding of epithelium, occasionally look like papillary carcinoma. Focus of hemorrhage and fibrosis is common and may be occur with dystrophic calcification[59].

2.9.2.2 Endemic Goiter

Endemic goiter is the enlargement of thyroid gland that occurs in a significant portion of region or population. The usual criteria is 5% or more of children aged 6 to 12 have goiter or in 10% of population[59].

2.9.2.3 Dyshormonogenetic Goiter

Numerous autosomal recessive defects in the synthesis of thyroid hormones have been described , usually results from lack of intra-thyroidal peroxidase enzyme. Homozygotes patients present with congenital decrease in thyroid function while the heterozygotes present in the first 2 decades of life with goiter ,normal level of hormones and elevated TSH [53] .

2.9.2.4 Toxic MNG

Toxic MNG is a complication of MNG in which one or more nodular collections of follicular cells secrete an excessive amount of thyroid hormones. Final diagnosis depends on clinical and laboratory findings of hyperthyroidism.

2.9.2.5 Diffuse Toxic Hyperplasia (Graves' Disease) DTH

It is an autoimmune disorder characterized by excessive production of thyroid hormones and diffuse hyperplasia with goiter. It is associated with extra-thyroidal lesion, comprising inflammation of the orbit tissues, (exophalmous and ophthalmopathy), and too much accumulation of glycosaminoglycans in the skin,(myxedema). It is caused by autoantibodies linked to the TSH receptor (TSHR) on follicular cells causing activation the receptor and stimulate the synthesis and secretion of thyroid hormones and proliferation of the follicular epithelium. It may be caused by genetic and environmental factors[50].

There is mild – moderate symmetrical goiter.

Some types of treatment precedes removal of gland in most cases, leading to decrease of the hyperplasia and an elevated level of colloid. Nodular lesions are present in 10 to 25% of glands with DTH, mostly they are benign with features of follicular hyperplasia or colloid nodule. However, about 10 - 20% of nodules may have carcinoma (PTC), and the incidence of cancer linked with DTH is in the 1 to 9% range[60,61].

2.9.3 Congenital thyroid diseases

A-Congenital thyroid anomalies (mentioned previously)

B-Dyshormonogenesis (mentioned previously)

C-Thyroid hormone resistance : rare disease in which the pituitary and hypothalamus are unaffected by feedback suppression of TSH because of mutations in thyroid gland hormones receptors or by defects monodeiodinase activity , all these lead to elevation of TSH ,T4 and T3 with moderate enlargement of gland usually not noted till adulthood . Other tissues may also have resistance to thyroid hormone and there may be a thyrotoxicosis . This may be hard to be differentiated from TSH-producing pituitary gland tumor but giving TRH result in elevation of TSH in thyroid hormone resistance but not in TSH-producing tumor but MRI is needed to exclude a macroadenoma [(53)].

2.9.4 Iodine –associated thyroid diseases

A-Iodine deficiency : which cause endemic goiter in mountainous part of the world . Mostly the patients have normal T3 andT4 with normal or raised TSH, but hypothyrodism can occur in severe cases .

B- Iodine-induced thyroid dysfunction :Iodine have a complex outcome on thyroid gland function . Excessive consumption of iodine decrease the hormone discharge and this is the cause for iodine use in management of thyroid storm and prior to operation . Iodine initially enhances but then inhibits , iodination of tyrosine .

C-Amiodarone : It is anti-arrhythmic drug has a structure analogous to T4 and contain high amount of iodine , it also takes a cytotoxic effect on the thyroid gland and inhibit the change of T4 toward T3 . So 20 % of the patients with amiodarone will have hypothyroidism or thyrotoxicosis [(53)].

2.9.5 Thyroid tumors

Thyroid tumors by world health organization (2004).

1. Non-epithelial

- Primary lymphoma and plasmacytoma
- Angiosarcoma
- Teratoma
- Smooth muscle tumors
- Peripheral nerve sheath tumors
- Paraganglioma
- Solitary fibrous tumor
- Follicular dendric cell tumor
- Langerhans cell histiocytosis
- Rosai-Dorfman disease
- Granular cell tumor

2. Epithelial

A. Follicular cell derived

1) Benign

- Follicular adenoma

2) Uncertain malignant potential (UMP)

- Hyalinization trabecular tumor

3) Malignant

- Papillary carcinoma
- Follicular carcinoma
- Poorly-differentiated carcinoma
- Un-differentiated (Anaplastic) carcinoma

B. C-cell derivative

- Medullary ca.

C. Mixed-follicular and C-cell derivative

- Mixed medullary and follicular ca.
- Mixed medullary and papillary ca.

D. different or uncertain cell derived

- Mucoepidermoid carcinoma
- Sclerosing mucoepidermoid ca. with eosinophilia
- Squamous-cell ca.
- Mucinous-ca.
- Spindl cells tumor with thymus-like differentiation (SETTLE)

- Ca. show thymus-like differentiations (CASTLE)

- Ectopic-thymoma

II. Secondary (metastatic)

2.10 Papillary thyroid carcinoma(PTC)

It is a major differentiated type which consists 90% of thyroid cancer and showing papillary proliferation , mostly has good prognosis but about 10% of it may recur such as LN recurrence and lung metastasis, usually affect the age of >45 years. It is characterized by a large size of tumor , invasion outside the gland , distant metastasis, with blood vessel invasion and poor histological features are negative prognosis factors [(62)].

Usually showing papillary growth pattern but the nuclear features are the most important diagnostic features . The nucleus looks of PTC are pure, ground glass, or Orphan-Annie eyed . These features are not specific as chronic thyroiditis commonly shows the same intra nuclear inclusions or nuclear grooves as well as follicular adenoma [(62)].

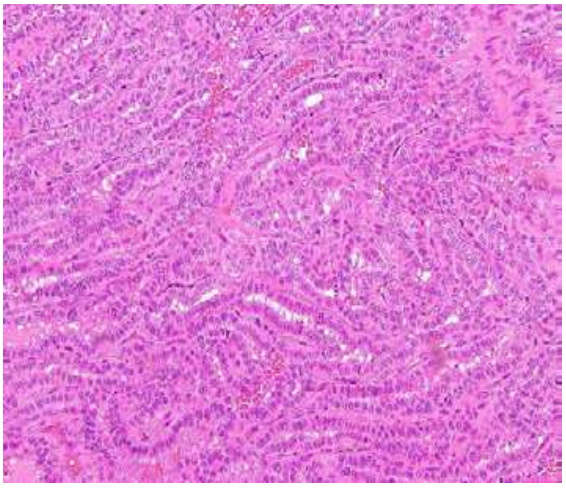

Figure 2.5 Microscopical features of PTC .[(62)]

The papillary growth pattern is often seen but it is not needed for diagnosis[63].

Usually it is sporadic ,only a small part is due to mutations[64]. Pre-existing solitary nodules or adenomas and MNG are risk factors for it[65].

Most of the PTCs seem as a separate but ill-defined nodule with irregular borders. A capsule is classically not present but some may be well delineated or encapsulated, except the follicular variation. It varies in look from tan-brown to gray-white and from firm and solid to more friable with cystic spaces[66].

Lymphatic invasion is commonly seen, while vascular invasion is rare[67].

Extensive extrathyroidal invasion be associated with a poor prognosis[68]

Variants of Papillary Carcinoma : More than 10 different variants, most of which are rare. The most common is microcarcinoma, defined by WHO as PTC, which is both ≤1 cm in diameter and found incidentally[69]and they can show papillary, follicular, or a mixed pattern.

Follicular variant PTC (FVPTC) is a common type characterized by a limited or mainly follicular pattern, absence of well-forming papilla, and the presence of diagnostic of nuclear features of PTC. This is a discrete variant of PTC , some of its features overlap with FTC. It is normally well bounded and sometimes encapsulated. Most of the nuclear features of PTC are existing. Immunohistochemical staining, may help to distinguish FVPTC from a FTC or adenoma[70].

The tall cell variation is characterized by a (> 50%) of tumor cells with a tallness at least 3times the width . It has a poor prognosis with a high rate of LN and distant metastases and lower 5-year survival[71,72].

Extra variants consist of solid, diffuse sclerosing, columnar cell, oncocytic, Warthin-like, clear cell, cribriform-morular, and those with prominent hobnail cells or fasciitis-like stroma[73]. The solid variant occur when solid growth signifies >50% of tumor ,it is frequently seen in child and frequently related to

PTC patients after Chernobyl nuclear accident[74] , lymphatic and vascular invasion are often detected and some studies informed that it may associated with poorer prognosis[75,76] . The diffuse sclerosis variation is 3%of PTC which penetrate all the gland and is related with young age [77] and it show extension outside the gland and regional LN metastasis at diagnosis leading to increase recurrence but mortality rate is low [78]. Columnar cell variant is an aggressive form of PTC . The cribriform-morular variant usually associated with familial adenomatous polyposis[73].

2.11 Follicular Adenoma (FA) and Carcinoma (FC)

FA it is a benign, condensed, not invasive tumor creating from thyroid gland follicular cells, and FC is a malignant, good differentiated tumor of follicular cells with absence of the nuclear features of PTC, mostly they are solitary nodules that obviously delineated from the adjacent cells by a fibrous capsule. Carcinoma is distinguished from FA by aggressive progress through capsule or to vascular system . One of them is enough criteria for cancer . Invasion is not obviously recognizable in a majority of circumstances. When invasion is obviously distinguishable, it can be focal or extensive in a tumor that has slight or no capsule .FC may be more cellular than adenoma, but the cellularity alone is not a distinguishing feature[79].

Valuation for capsular and vascular invasion may be a challenge because of a number of issues, include intermittent foci and a number of actual and not actual aberrations that is similar to invasion. The degree of blood vessel invasion seems to be important due to that invasion of 4 or more blood vessels is linked to an elevated degree of recurrences or mortality rate[80,81]. The poor prognosis features are distant metastasis, age>45 year, big size of tumor, wide blood vessel invasion, extension outside the thyroid , and extensively aggressive cancer[82].

FAs and FCs has a number of microscopic variations. Hürthle cell is common and described by cells that are bigger than classic neoplasm cells and has

granular eosinophilic cytoplasm due to copious mitochondria .A minimum of 75% of the cells must be oncocytic to diagnosed as this type. The word (oncocytic) is suggested in place of Hürthle cell[83]. Other variants of follicular neoplasm include clear, mucinous, and signet ring cells.

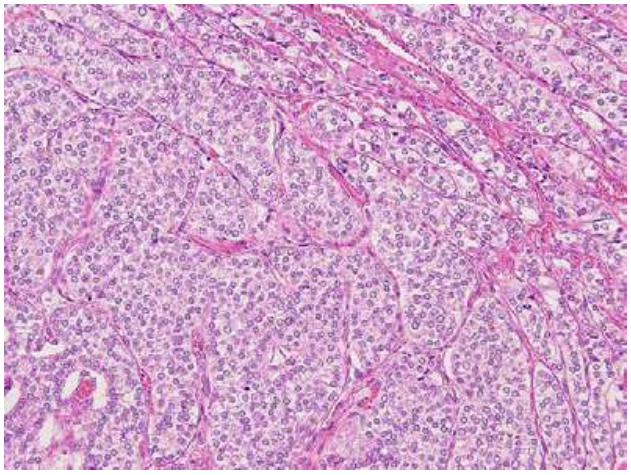

Figure 2.6 follicular thyroid cancer (microscopic features). [79]

2.12 Poorly Differentiated Carcinoma PDC :

PDC is a malignancy of follicular origin that found in intermediate position between well differentiated and anaplastic thyroid carcinoma. The 2004 WHO organization distinguishes PDC as a specific entity characterized by solid, trabecular, or insular architecture; infiltrative growth; necrosis; and blood vessels invasion[83] .

It characteristically displays obviously evident penetration, frequently with extension outside the thyroid. Some of these display incomplete capsulation, but whole and complete capsule is rare. The cutting surface is hard, tan to white-tan, and often multicolored due to focuses of bleeding and necrosis. Regions of well-differentiated FC or FC can be seen in stability with PDC [83].

2.13 Anaplastic (Undifferentiated) Carcinoma :

It is a very aggressive undifferentiated type, with nearly 100%mortality rate[84],represent around 40% thyroid cancer death and merely <2% of thyroid cancer. The average survival rate from diagnosis is about 6 month[85]. It widely attacks nearby organs, and remote metastases are noted at diagnosis in 1/3 of patients. Highest age of patients is more than that of DTCs and >70% of patients are females [86]. About 50% of patients have previous or coexisting DTC. It is proposing that ATC arises as a consequence of de-differentiation of DTC. As compare to DTC, ATC typically does not uptake iodine, leading to refractory against radioiodine therapy. Though clinical obvious ATCs are typically unresectable, intrathyroidal ATCs are resectable and this essential removal offers well results[87] .

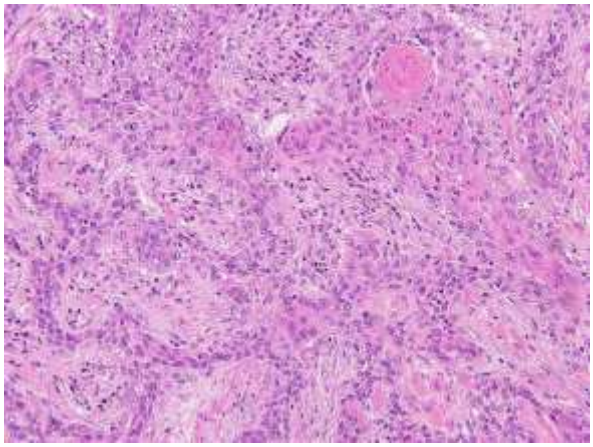

Figure 2.7 Anaplastic thyroid carcinoma. [87]

2.14 Medullary thyroid Carcinoma (MTC) :

It is a malignant tumor that displays C-cell variation. MTC represent about <5% of thyroid cancer[65]. About 75% of cases are sporadic, and the rest are genetic because of a mutation of RET (rearranged during transfection) gene[88].The 3 types of genetic disease are involved by multiple endocrine neoplasm type 2A (MEN2A), multiple endocrine neoplasm type 2B (MEN2B),

and familial medullary thyroid carcinoma (FMTC). MEN2A is the most frequent of the 3 types, representing about 75 - 90% of hereditary cases, with FMTC and MEN2B represent about 15% and 5% of cases, respectively[88,89]. Peak age of hereditary MTC is young (about 35 y.) while that of sporadic MTC (40-60 y.). The 5-year survival with MTC is 86%. Poor predictive factors are old age, progressive stag, the occurrence of LN metastasis at the time of diagnosis, and *RET* mutation[90]. Sporadic MTC is usually solitary but most of hereditary MTC display bilateral, multi-centric focusing.

MTCs classically display gray-tan color, firm, solid tumors and do not have a well-formed capsule[91] .

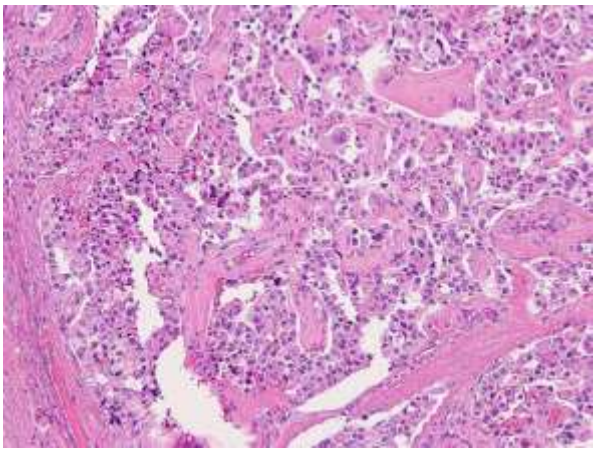

Figure 2.8 Medullary thyroid carcinoma (microscopic features). [91]

2.15 Primary thyroid lymphomas :

They are defined by the absence of systemic disease. Almost all of them arise in the setting of Hashimoto thyroiditis. All of them are B-cell lymphomas[92,93]

2.16 Secondary (Metastatic) Thyroid Tumors :

Secondary, or metastatic, tumors are the result of lymphatic or blood vessel spreading from a remote place, not direct invasion from a neighboring structures. They range from microscopic deposition in lymphatic vascular places

to obviously apparent masses. The kidney (renal cell carcinoma), lung, breast, and GIT are the most common sites of primary lesion[94].

2.17 Symptoms of the thyroid cancer :

Thyroid cancer frequently presenting as a swelling or nodule in the thyroid gland and usually do not causing any symptoms . Blood tests usually do not help to find it and they are typically normal, even when the cancer is existing. Examination of neck is a usual way in which thyroid nodules and cancer are present. Frequently, nodules are exposed by the way on image testing like CT scans and neck US done for other reasons. Rarely, persons find a nodule by observing a bulge in the neck. Seldom, thyroid cancer can cause symptoms. In this case, patients may suffer from pain in neck, jaw, or ear. If a nodule is big sufficiently to pressure on the trachea or esophagus, it may cause dyspnea or dysphagia .Also hoarseness can occurred if the cancer attacks the nerve that supply the vocal cords[1]

2.18 Imaging Modalities of the Thyroid :

A-Ultrasound

In the previous 4 decades, US become the favored diagnostic imaging way to evaluate the thyroid cancer. US provides an accurate assessment of the size and parenchymal homogenicity without radiation or high costs of other modalities .The indications of thyroid US are :palpable neck mass, incidental thyroid abnormality detected in other way of imaging ,screening of high risk patients, evaluation of LN metastasis and screening of thyroid bed in post thyroidectomy patients[95,96] .

B-CT and MRI

CT and MRI have partial capability for evaluation of intrathyroidal diseases because of poor ability to distinguish benign from malignant lesions. Though, CT and MRI have vital adjunctive role to staging of progressive

cancer by documentation of extracapsular invasion of tumor into nearby organs, e.g. the esophagus, trachea, larynx and muscules. They are also vital to evaluate direct invasion of tumor into mediastinum or retrotracheal region, also to recognize both local LN and distant metastasis [97,98]. Contrast-enhanced CT rises the attenuation of the gland due to heavy uptake of iodinated contrast[98].

C-Nuclear Scintigraphy .

It shows a significant role to evaluate the thyroid disease, providing a reflect ion of the functional state of the gland and the biological state of any structure in the gland e.g. a thyroid nodule. Indications include assessment of the size and location of thyroid tissue, thyroid assessment when clinical and laboratory tests propose unusual thyroid job, assessment of persons who are at risk for cancer , valuation of job of a nodules, and assessment of congenital abnormalities[98]. The 2 main isotopes that are used are technetium- 99 m (Tc-99m) and iodine 123 (I-123). Tc- 99 m is trapped by the gland , while I-123 is trapped and organified. One discrete benefit of I-123 over Tc-99 m is in the assessment of thyroid nodules, especially when the nodule seems "warm" by Tc-99 m. If "cold" on I-123, this is thought to be a discordant nodule needing additional checkup and probable fine-needle aspiration (FNA). I- 123 also has an benefit over Tc-99 m in recognizing and focusing ectopic thyroid tissue as there is less background activity within the head and neck when compared to Tc-99 m[97,99,100].

2.19 TNM Classification of Thyroid Cancer [101,102]

*Primary tumor (T)

TX :primary tumor cannot be assessed.

T0 :no evidence of primary tumor is found.

T1 :tumor size < or equal to 2 cm in greatest dimension and is limited to the thyroid T1a :tumor < or equal to 1 cm , limited to the thyroid.

T1b: tumor > 1cm but < or equal to 2cm ,limited to the thyroid.

T2 :tumor size >2cm but < or equal to 4cm ,limited to the thyroid.

T3 :tumor size >4cm , limited to the thyroid or with minimal extrathyroidal extension (e.g. extension to sternothyroid muscle or perithyroid soft tissue.

T4a :moderately advanced disease ,tumor of any size extending beyond thyroid capsule to invade subcutaneous soft tissue ,larynx ,trachea ,esophagus ,or recurrent laryngeal nerve.

T4b: very advanced disease ,tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel .

*All anaplastic carcinoma ATC are considered stage IV :

T4a :intrathyroidal ATC .

T4b : ATC with gross extrathyroid extension.

*Regional lymph nodes (N) :

NX: regional LN cannot be assessed.

N0 : no regional LN metastasis.

N1: regional LN metastasis.

N1a :metastasis to level VI(pretracheal ,paratracheal , and prelaryngeal – Delphian LN) N1b: metastasis to unilateral, bilateral, or contralateral cervical (level I,II,III,IV, or V) or retropharyngeal or superior mediastinal LN (level VII)

*Distant metastasis (M) :

M0 :no distant metastasis .

M1 :distant metastasis .

*Stage grouping :

** Papillary and follicular thyroid cancer , age <45 years :

Stage I : any T ,any N , M0

Stage II : any T ,any N , M1

** Papillary and follicular thyroid cancer ,age >or equal to 45 years :

Stage I : T1 N0 M0

Stage II : T2 N0 M0

Stage III :T3 N0 M0

Stage IVA : T1-3 N1a M0 OR T4a N1b M0

Stage IVB :T4b any N M0

Stage IVC :any T any N M1

** Anaplastic carcinomas : all are considered stage IV:

Stage IVA : T4a any N M0

Stage IVB : T4b any N M0

Stage IVC : any T any N M1

** Medullary thyroid cancer (all age groups) :

Stage I : T1 N0 M0

Stage II : T2,T3 N0 M0

Stage III : T1-T3 N1a M0

Stage IVA :T4a N0 M0 ,,, T4a N1a M0 ,,,T1 N1b M0 ,,, T2 N1b M0 ,,, T3 N1b M0 ,,,T4a N1b M0 ,,, T4a N0 ,N1b MO ,,, T1-T4a N1b M0

Stage IVB : T4b any N M0

Stage IVC : any T any N M1

2.20 Radiation is an important risk factor :

Radiation is a well-recognized carcinogenic, interrelating with DNA to yield many mutations at complex places. Ionizing radiation is the well-recognized risk factor for thyroid cancer especially when the exposure occurs in childhood, when the thyroid gland is very radiosensitive. Most of the reported contact was in the method of radioiodine from the atmosphere or from medical use e.g. CT- scan.

Radioiodine Exposure : It kills the thyroid gland causing thyroid failure. This is the rational when it is used in the treatment for person with thyrotoxicosis and for remaining thyroid cancer. Though, thyroid cancer was established to be more predominant among persons who are heavy exposed to ionizing radiation at the atomic bombings in 1945 [103]. Furthermore, the low dose contact to radiation is related to malignancy changing which become more clear after the Chernobyl disaster in 1986 [104] During that exposure the rise in thyroid cancer, attributed to the actual great quantities of iodine 131 with a strong relation between younger aging on contact and hazard for development of PTC[105].

Direct thyroid gland Exposures : By the use of CT scans and medical and dental X-Rays [106].

Why Children?

The young children is more susceptible to radiation due to an advanced proliferation action of thyroid gland cells [107].

Thyroid Imaging with Radioiodine 131 :The annual number of thyroid examinations using radioiodine is currently five per 1,000 individuals worldwide. However, there are no data suggesting that diagnostic imaging can be correlated with thyroid cancer. There are data from patients receiving larger doses for treatment of thyroid cancer and Graves' disease, which may correlate with long term cancer development in a variety of organs [108,109], but the increased risk appears to be quite small.

2.21 Dietary Iodine Intake

Deficiency of iodine effects the thyroid function , through the reduction in the level of T3,T4 and an increase in TSH secretion, which is a major growth factor for thyroid follicular cells[110,111]. Increasing of investigation and development in the value of diagnosis are the most rational clarification for these data[112].

2.22 Autoimmunity and Thyroid Cancer :

Hashimoto's Thyroiditis :

The incidence of Hashimoto's thyroiditis increases in the last 2 decades, parallel with the increased occurrence of thyroid cancer and women with Hashimoto's thyroiditis suffering thyroidectomy were 30 % more expected to have cancer than predictable.[108]

There is an evidence that the frequency of PTC in person with Hashimoto's autoimmune thyroiditis may be partially due to augmented TSH[113], but there is growing evidence of an association between thyroid lymphocytic and macrophage infiltrations and thyroid cancer, which may apply to both Hashimoto's and Graves' diseases[114] studies based on surgery specimens have shown that raised levels of thyroglobulin antibodies were associated with an augmented risk for thyroid cancer [115,116] and that any nodules present are more likely to be malignant.[117]

2.23 Treatment of thyroid cancer

The primary therapy for thyroid cancer is surgery. The extent of surgery (lobectomy or total thyroidectomy) will depend on the size of the tumor and on whether it is confined to the thyroid. Sometimes findings such as spread of the tumor into surrounding areas or the presence of involved lymph nodes – will indicate a total thyroidectomy . For very small cancers (<1 cm) that are confined to the thyroid, involving only one lobe and without evidence of lymph node involvement a simple lobectomy is sufficient. Recent studies suggest that small tumors(micro papillary cancers) may be observed without surgery depending on the location in the thyroid. Often, thyroid cancer is cured by surgery alone, especially if it is small, but if it is large, spread to lymph nodes or if there is a

high risk for recurrence, radioactive iodine may be used after the thyroid gland is removed.

Most DTC absorb and concentrate iodine, so radioactive iodine can be used to eliminate all remaining thyroid tissue after surgery(radioactive iodine ablation). Since most other tissues do not efficiently absorb iodine,I-131 usually has little or no effect on other tissues. However, in some patients who receive larger doses of I-131,it can affect the glands that produce saliva and result in dry mouth. If higher doses of I-131 are necessary, there may be a small risk of developing other cancers later in life. This is very small, and increases as the dose of I-131 increases.

If the I-131 is recommended, TSH will need to be elevated prior to the treatment, this can be done by stop levothyroxine for 3-6 weeks. This causes high levels of TSH and results in hypothyroidism, which cause symptoms, that can be significant, so we may prescribe T3 that is usually taken after the levothyroxine is stopped until the final 2 weeks before the I-131 treatment. The second way is by injecting TSH as two injections in the days prior to I-131 treatment and stay on thyroid hormone . Also the patient is asked to go on a low iodine diet for 1 to 2 weeks prior to treatment which results in high absorption of I-131 and maximizing the treatment effect.

The advanced cancer that metastasizes outside the neck is rare. Surgery and radioactive iodine remain the best way for treatment . However, for more advanced cancers, or when radioactive iodine therapy is no longer effective, other forms of treatment are needed. External beam radiation directs precisely focused X-rays to areas that need to be treated ,this can kill or slow the growth of tumors. Cancer that has spread more widely requires additional treatment. New chemotherapy agents are becoming more widely available for treatment . These drugs rarely cure advanced cancers but they can slow down or partially reverse the growth of the cancer. These treatments are given by an oncologist.[1]

CHAPTER THREE

PATIENTS AND METHODES

Patients and methods

After we take a permission from ethics committee of Al Qadisiyah university of medical science, ethical consideration and patient agreement ,74 Iraqi patients (55 female,19 male), with ages of more than 5 years , had involved in this study, at the duration from April,2018 to June,2018, in Al Diwanya teaching hospital which is the major referral hospital in our city .

3.1 The design of study :

Is prospective conventional cross sectional study to determine the prevalence of thyroid cancer among patients with goiter referred to AlDiwanya Teaching hospital .

3.2 Inclusion And Exclusion criteria :

Inclusion criteria :

All patients admitted for surgery, referred from the clinic or out patients .

Exclusion criteria :

No patient was excluded from the study.

3.3 Clinical Assessment :

Questionnaire :

Formal questionnaire used for data collection, including : name , Age, Sex.

,and duration of illness

Family history of thyroid diseases (also genetic diseases or syndromes) History of x-ray exposure before 5 years age.

physical examination : including :

Solitary nodule or MNG.

Size of goiter.

Consistency (firm, hard)

Retrosternal extension.

Laboratory investigation:

Lab. Investigations also done for patients in form of:

Routine laboratory investigation like :CBC, LFT,RFT and virology screen (as a preparation for surgery).

T3,T4 ,TSH (toxic or not toxic).

Other data : Which collected after surgery :

If total thyroidectomy or lobectomy done for them .

Results of histological examination

All patients were sent to Al Diwanya hospital lab for investigation, but the biopsies were sent to a different private labratories.

Examination of goiter : It done for all patients which consist of inspection and palpation .

Inspection is done anteriorly and laterally .

Anterior method :

1- the person is sit down in relaxed situation in a nonaligned or mild stretched location.

2- Ask the patient to swallow to view the upward movement of thyroid.

Lateral approach: to view any prominence and measure it.

Palpation was done by anterior approach :

1-Locate the isthmus of thyroid gland by palpate amid way the cricoid cartilage and the suprasternal notch.

2- the sternocleidomastoid muscle is retracted while the other examining hand palpate the thyroid gland .

3-Ask the patient to swallow.

4-Identify the size, number, consistency, mobility ,tenderness ,and regional LN .

3.4 Statistical Analysis

Data has been collect and encompassed in a data grounded system and examined by statistical set of community knowledge ((SPSS, Inc., Chicago, IL, USA)) version 20.

Non-parametric data has been expressed as percentages such as male and female, type of goiter. were analyzed using chi square like in comparison between the types of goiter and its consistence .

Significance was set at the $P \leq 0.05$ level in all analyses.

CHAPTER FOUR

RESULTS

Results

Seventy four patients with goiter were included in this study. These patients aged between 5-70 years with the mean age of patients 43.7 year and the most frequent ages were between 45-60 years. There were 19 males and 55 females patients.

Table 4.1: Gender distribution.

		NO.	%
Gender	male	19	25.7
	female	55	74.3
	Total	74	100%

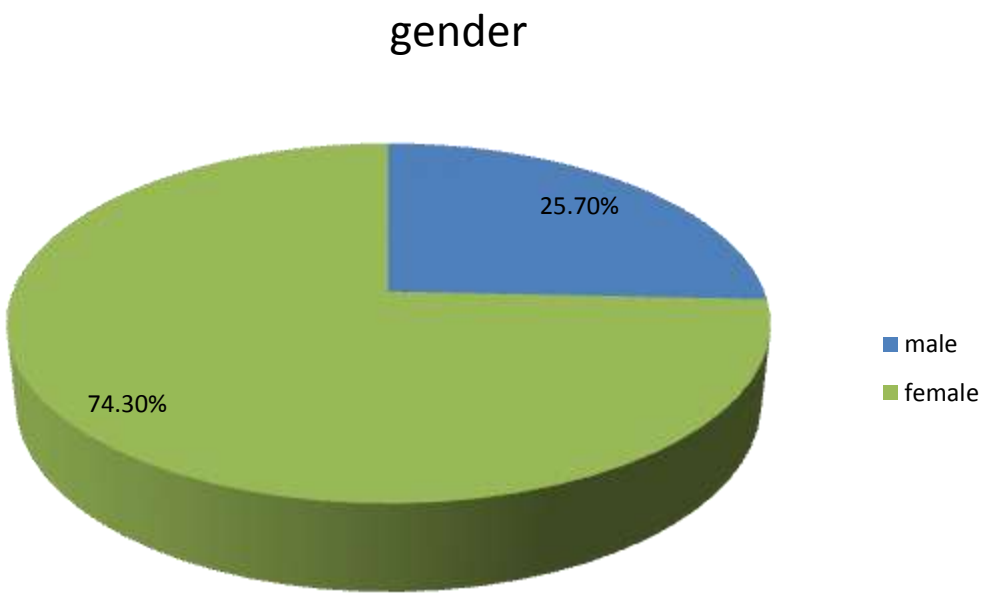

Figure 4.1: Percentages of males and females patients with goiter.

Table 4.2: Age groups of patients with goiter.

Age groups	No.	%
5-14 y	11	15%
15-44 y	15	20%
45-60 y	35	47%
Above 60 years	13	18%
Total	74	100

Table 4.3: Presentation of goiter.

	No.	%
solitary	33	44.6
MNG	41	55.4
Total	74	100

This table shows that the MNG is more frequent.

Table 4.4: Numbers and percentages of solitary and MNG in different age groups.

		Solitary	MNG	Total
Age groups	5-14 y	8(72%)	3(28%)	11
	15-44 y	9(60%)	6 (40%)	15
	45-60 y	11(31%)	24(69%)	35
	Above 60 years	5(38%)	8(62%)	13
	Total	33	41	74

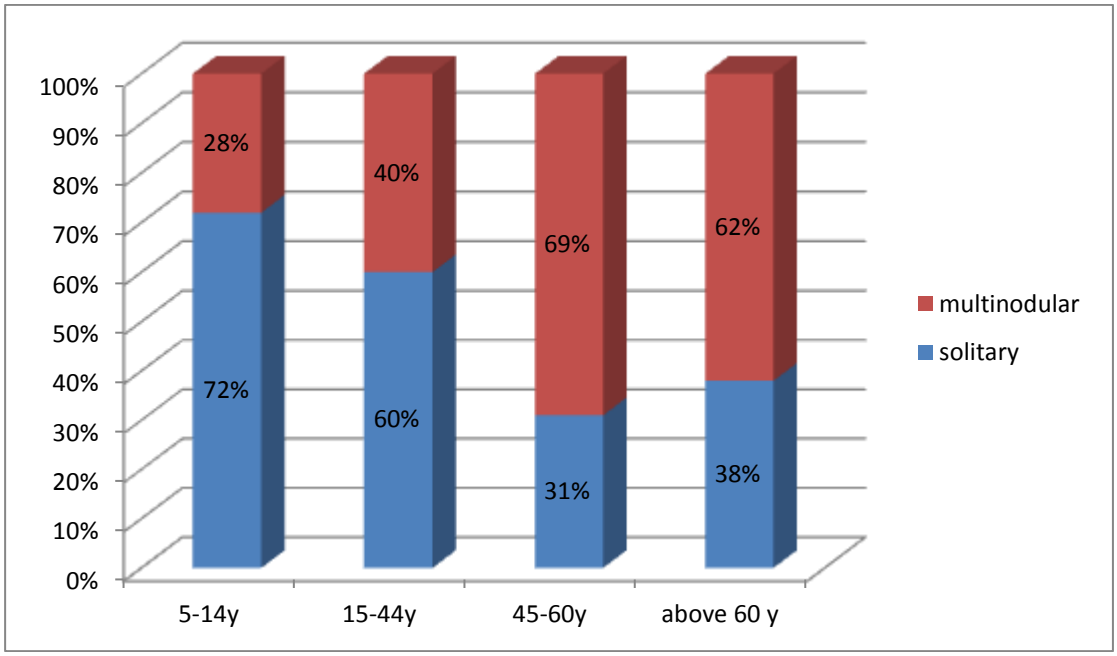

Figure 4.2 :Distribution of goiter according to age groups.

Sixty four percent of goiters were firm in consistency and 36% were hard in consistency as shown in table 4.5 . Family history of goiter presented in 24.4% of patients as shown in table 4.6 .

Table 4.5: Consistency of goiter.

Consistency	No.	%
Hard	27	36%
Firm	47	64%
Total	74	100

Table 4.6: Family history of goiter.

Family history of goiter	No.	%
Positive	18	24.4%
Negative	56	75.6%
Total	74	100

Total thyroidectomy was the most frequent surgical procedure (table 4.7).

Table 4.7: Types of surgery .

Type of surgery	No.	%
Lobectomy	22	29%
Total thyroidectomy	52	71%
Total	74	100

X-ray exposure was positive in 59.4% of patients (table 4.8).

Table 4.8: X-ray exposure.

X-ray exposure	No.	%
Positive	44	59.4%
Negative	30	40.6%
Total	74	100

The MNG is more frequent in females while the solitary nodules are mostly in males and there is no significant difference between males and females regarding the type of goiter (solitary , MNG) as shown in table 4.9 .

Table 4.9: Numbers and percentages of each gender in solitary goiter and MNG and the significance of this.

		No.	%	p-value
Solitary	Male	11	14.8%	0.82
	Female	22	29.7%	
MNG	Male	8	10.9%	0.95
	Female	33	44.6%	

Most of the patients were with no retrosternal extension (table 4.10).

Table 4.10: Retrosternal extension.

Retrosternal extension	No.	Percent
Yes	10	13.5%
No	64	86.5%

In our study, there was no significant difference between solitary and MNG regarding the development of retrosternal extension as shown in table 4.11 .

Table 4.11: Number and percentages of retrosternal extension in solitary and MNG.

	Retrosternal extension				Total	p-value
	Yes		No			
	No.	%	No.	%		
Solitary	3	9	30	91	33	0.63
MNG	7	17	34	83	41	
Total	10		64		74	

The firm consistency is most frequently present in both solitary and MNG with no significant difference between solitary and MNG regarding the type of consistency as shown in table 4.12

Table 4.12 :Distribution of the goiter according to the consistency.

				p-value
		No.	%	
Solitary	Hard	10	13.5	0.4
	Firm	23	31	
MNG	Hard	17	23	0.71
	Firm	24	32.5	
Total		74	100	

The rate of thyroid tumor among patients with goiter in our study was 21.5 % , with 14.8% was papillary carcinoma and 6.7% was follicular carcinoma ,so the papillary carcinoma represents 68% and the follicular carcinoma represents 32% of the total number of patients with thyroid cancer which was 16 patients, as shown in table 4.13.

Table 4.13: Types of thyroid tumor.

	No.	% (from 74)
Papillary carcinoma	11 (68 %)	14.8%
Follicular carcinoma	5 (32%)	6.7%
Total	16 (100%)	21.5%

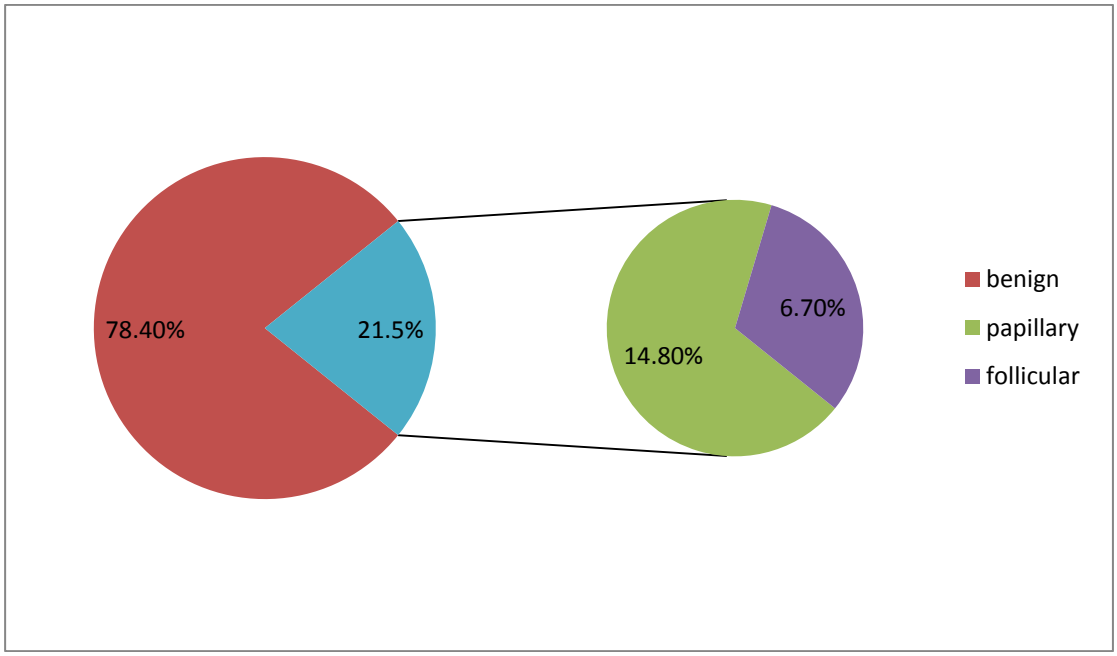

Figure 4.3 :Percentage of thyroid tumor among patients with goiter and the percentage of each type of cancer.

Most of the patients that are discovered to have thyroid cancer were females (56.3 %) while the percentage of males was (43.7%) as shown in table 4.14 .

Table 4.14 :Distribution of the types of thyroid carcinoma according to the gender.

		Papillary	Follicular	Total
Gender	Female	5	4	9(56.3%)
	Male	6	1	7(43.7%)
	Total	11	5	16

The rate of thyroid cancer in solitary nodule was 27% (9 from 33) is more than that of MNG which was 17% (7 from 41) so the thyroid cancer is frequently present with solitary nodule with no significant difference between the types of thyroid carcinoma (papillary ,follicular) as shown in table 4.15 .

Table 4.15: Distribution of thyroid cancer according to the types of goiter.

		No.	% (from 16)	p-value
Solitary	Papillary	8	50%	0.15
	Follicular	1	6.25%	
MNG	Papillary	3	18.75%	0.38
	Follicular	4	25%	
	Total	16	100%	

Most of the thyroid carcinoma present with hard consistency with no significant difference between the papillary and the follicular type , as shown in table 4.16.

Table 4.16: Distribution of the thyroid cancer according to their consistency .

				p-value
		No.	%	
Papillary	Hard	6	37.5	0.7
	Firm	5	31.25	
follicular	Hard	3	18.75	0.3
	Firm	2	12.5	
Total		16	100	

In regard to the risk factors of thyroid cancer ,the relation of x-ray exposure with malignancy there were 87.5 % of malignancy had history of exposure which is statistically significant as shown in table 4.17 .

Table 4.17: The significance of x-ray exposure in the development of thyroid cancer.

	x-ray exposure			p-value
	Positive	Negative	Total	
Malignant	14(87.5%)	2(12.5%)	16	0.02
Benign	30(51.7%)	28(48.3%)	58	
Total	44	30	74	

The family history of thyroid cancer is a significant risk factor for thyroid malignancy ,as shown in table 4.18 .

Table4.18: The significance of family history of thyroid cancer in the development of it .

	Family history			p-value
	Positive	Negative	Total	
Malignant	10(62.5%)	6(37.5%)	16	0.001
Benign	8(13.7%)	50(86.3%)	58	
Total	18	56	74	

The x-ray exposure and the family history of thyroid cancer are a significant risk factors for DTC but with no significant difference regarding the type of DTC as shown in table 4.19 .

Table 4.19: The significance of history of x-ray exposure and the family history in the development of special type of DTC.

		Papillary	Follicular	Total	p-value
x-ray exposure	Positive	10	4	14	0.82
	Negative	1	1	2	
Family history	Positive	6	4	10	0.67
	Negative	5	1	6	

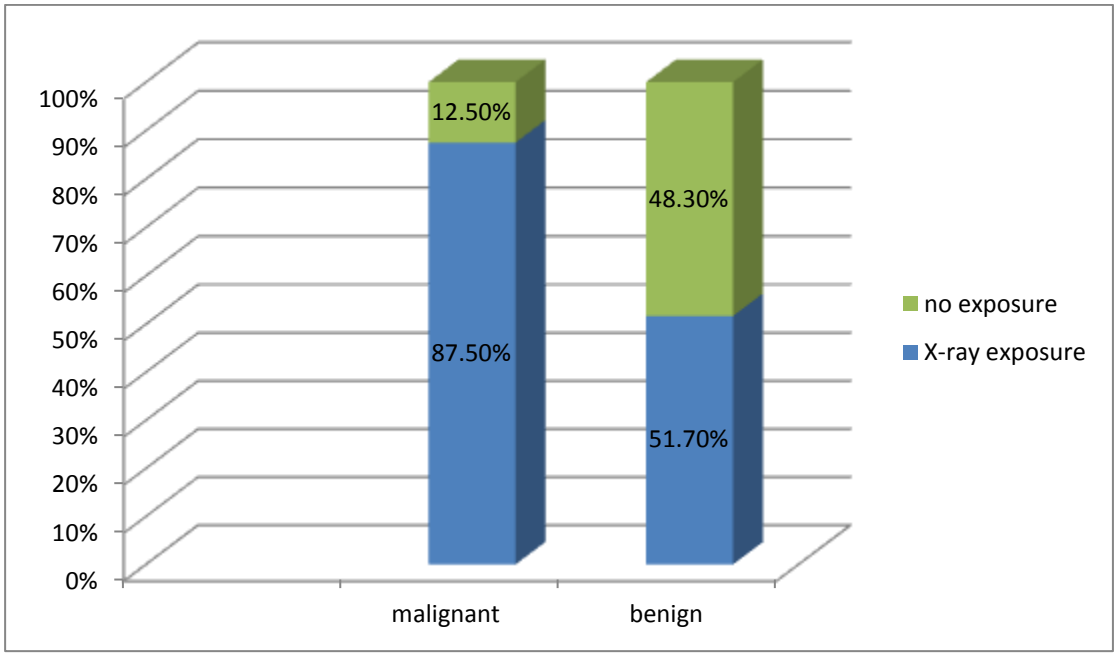

Figure 4.4 : Percentages of patients with or without x-ray exposure.

CHAPTER FIVE

DISCUSSION

Discussion

The rate of the thyroid cancer increased from 3.6/100,000 in 1973 to 8.7/100,000 in 2002, without any change in the mortality rate [118] .

There was obvious changes in the thyroid cancer rates between 1973- 1977 and between 1998-2002 all over the world [118] . Thyroid cancer represent 8.8% of all cancers in 2010, which is very higher than the proportion in the America (2.9%). The rate for women was about 3 times higher than those for men at ages 30–39 year[118].

The incidence of thyroid malignancy has been on rise during the past 60 years [119]. It has been proposed that the availability of more sensitive diagnostic tools might be responsible for the increasing incidence [119] .Thyroid cancer represent < 1% of all malignancies . The rate of thyroid cancer annually vary all over the world from 0.5 - 10 / 100,000 people. It is the most common endocrine malignancy (90%) and is responsible for most deaths than other endocrine malignancies together [120]. The United states cancer Society estimates that 17,000new cases of thyroid cancer are diagnosed every year in the America and that 1,300 thyroid cancer-related deaths occur every year [120].

In our study we found that female is predominant, 74.3% female, 25.57% male, which goes with study by Ali Al Katib in Hilla city in which 75% female [121], in study in Baghdad city found Females are more affected with goiter (82.5%132 patients) than males (17.5% 28 patients) with ratio 4.7/1 female to male[122]. while other study in India was reported 89% female included in study[123]. These findings are in agreement with the findings of study conducted in Iran[124].

The men to women ratio was 1:2.8 which is less than that reported by Ali Al Katib 1/4.8 [121] and YasserA.et.al, of 1/8.4[125].

In our study the mean age of patients was 43.7 year. This is less than that reported by Al Katib[121] 48 year, and more than that reported by Yasser A. of 38.4 year [125], and that reported by Saleh M.et. al (36.7year)[126]. This may be due to lowering of the age of presentation of patients with goiter [123].

The commonest ages at presentation were (45-60 years), which resemble the mean age of our patients, which coincide with study by Fazal Hussain(2013)in saudi Arabia[118], while other study by Al- Katib reported that mostly the patients are in the range (31-40 years), 33.3% ,in study by Seetu Palo (2016) demonstrated majority of the patients were in the 3rd and 4th decade of life[123], same result reported by Ayad J. Matar (2106) in baghdad The most affected patients are in the 4th decade of age[122].

Our result found 44.6% of goiter presented as solitary and 55.4% MNG, these result consisted with result by Albasri 2014 in Saudi Arabia 58% MNG[127] , And Seetu Palo (2016) which reported (57.3%) patients presented with MNG [123], while (42.7%) patients presented with a solitary nodule, and similar to Al-Katib (2009) 57%. In Aldiwanyia by Albaaj (2012) reported 71.5% of patient with MNG[128] , in thiqar 2010 reported 59% MNG[129] , on other hand, these finding higher what recorded by by Saleh 16.5% [126] , and Yasser 42% [125] .

In our study, 60% of patients presented in age group 15-44 years were solitary and 40% MNG , similar result in india by seetu palo, also presented 69% of patient in age group 45-60year were MNG and 31% in same age group were solitary [123] .

In our study thyroid tumor rate was 21.6% from patient with goiter this coincide with study by Seetu Palo (2016) 22% of investigated patients with goiter[123], and in study in Babylon city reported incidence of cancer in thyroid nodule was 11.8% of patients [130] ,which is considered lower than the reported by Yasser A. 14% [125] .

In other study in Aldiwanyia Al-Baaj (2012) reported 8.7% [128] and by Ayad J. Matar(2016) in Baghdad which was 7% thyroid cancer from 200 patient with goiter[122].

According to the 2008 Saudi cancer Registration report, there was a total of 727 case of thyroid cancer; 606 among Saudi people and 121 among non-Saudi people. Among Saudi people, thyroid cancer is about 6.8% of all new cases at this year[118].

The thyroid cancer was found in Arab countries ,the same as that for India in which the thyroid cancer was found to be one of 5 commonest cancer in India study by Kalyani [131] while in Iran, thyroid cancer is the 7th commonest cancer in women, study by Khayamzadeh[132] . And in a study over 25 year about the new cases of commonest cancer in Hong Kong, a number of cancer including thyroid cancer were found to be increasing during the study period which done by Xie [133] . A report from Nepal on head and neck cancer reported that the most common site of primary carcinoma was larynx, followed by the thyroid this study is done by Lasrado[134].

Geographical studies shows marked difference in incidence of thyroid carcinoma ranging for example from 6% of population in Hawaii and Iceland to less than 1.5 in Denmark and England[120].

Thyroid cancer is a significant health care burden for the Iraq, occur anywhere and involve any age . Increasing in incidence due to modern styles of life and urbanization due to development of economics .There is no screening program or good screening tools to detect early thyroid cancer so the patients are diagnosed in the later stages of cancer[127,128].

In our result female were predominant in malignancy 56.3% and male 43.7% these result consisted with study in Babylon city were female 72% of malignant patients[121], also Fazal 2013 in Saudi arabi reported female had rate more than

three times than male[118]. Similar observations were made by Pang and Chung and Nanjappa BA[135].

Thyroid cancer has a higher incidence rate among women in Arab Gulf and is the 2nd commonest cancer among females[127] .

Qatari females have the highest rate of thyroid cancer (ASR 10.9/100,000). The rate of thyroid cancer increase in GCC countries with a 24% increase in men and 63% increase among women over the ten year period[118].

In the United States, thyroid cancer is the 5th commonest cancer among females, while in Saudi Arabia, it is the 2nd commonest cancer among females[120,118]. There are many causes to explain why thyroid cancer is more frequent in females[136] also the higher rate of cancer in females may be due to that there is estrogen receptors in all malignant tissue of thyroid [136] .

The frequency of malignancy was higher in Solitary (27%) as compared to MNG (17%) and Various other investigators have reported similar higher percentage of malignancy in Solitary , study by Seetu palo 2016 38% [123], Anwar et al 24% [137] and Nanjappa et al 23% [138] .

In recent times, other investigators also have noted a rise in the prevalence of cancer in MNG[123,137].

The commonest type of cancer in our patients was PTC 68%,followed by FTC 32%, other studies with the same results of PTC by Al-Katib A.2009 in Babylon 60% [121] , in Thiqar 56% [129], in ALdiwania80% [128] ,in Baghdad (2009) 89% [139] and Baghdad (2016) 85% [122] , and 62% reported by Seetu Palo 2013 in india [123].

In our findings there was a positive association between patient who have malignancy with X-ray exposure and radiation, similar result reported by study down in Kuwait demonstrate that there is association of Dental X-rays with thyroid cancer [140] .This is the same finding from many previous studies, including a case-control study in Sweden (Hallquist and Näsman)[141], and

cohort study in USA also report that workers of x-rays had a higher risk of developing cancer than others, the study by Zabel [142].

Exposure to radiation, especially in children, is an important risk factor for PTC; radioactive fallout, depleted uranium, and Chernobyl disaster are known risk factors for thyroid cancer[142].

According to the Saudi Cancer Registration data, the highest incidence of thyroid cancer and leukemia is in Tabuk and Eastern regions which may indicate a possible relation with depleted uranium (DU) in this area from gulf war [118], these regions are in south border of Iraq may share the same risk factors[129].

Other findings noted that malignancy is more prevalent in those with family history of thyroid tumor, same findings observe in in Saudi Arabia by Fazal Hussain [118] by genetic factor through a mutations may lead to thyroid cancer[122].

These findings are consistent with the study by Iribarren [143] which included 196 incident cases of thyroid cancer, and reported an approximately 2-fold increased risk with a family history of thyroid disease. In addition, a case-control study reported that seventeen cases (5.0%) and 2 controls (0.6%) reported at least one first degree in relation with thyroid cancer thus suggesting that genetic factors are important for thyroid cancer[136]. Another study from Kuwait conducted in 2006 reported association between family history of benign thyroid disease and thyroid cancer [140].

Family history is other risk factor(especially for PTC) and the rate of PTC and cancer of colon among families occur due to familial adenomatous polyposis [131] . New and rare mutations may contribute to risk for progressive thyroid cancer.[139] There is a correlation of family history with thyroid cancer in the Saudi people [131]. The incidence of FTC and breast cancer is higher among patients with Cowden disease [118].

In our study the most common surgical procedure performed was total thyroidectomy (71%), followed by lobectomy (29%), same result demonstrated by Al katib 2009 in Babylon city [121].

CHAPTER SIX

CONCLUSIONS & RECOMENDATIONS

Conclusions :

Thyroid cancer is common among patients with goiter in our region .

The most frequent ages that presented with goiter are between 45-60 year with female predominance .

The most common type of goiter was MNG (55.4%) while the solitary nodule was 44.6%

The family history of goiter was positive in 24.4% of patients and 75.6% were with negative family history .

X-ray exposure was positive in 59.4% and negative in 40.6% of patients with goiter .

There was 13.5% of patients with retrosternal extension and 86.5% with no retrosternal extension.

The papillary carcinoma of thyroid gland was found in (14.8%) of patients with goiter while the follicular carcinoma percent was (6.7%) .

Family history of thyroid cancer was positive in 62.5% of patients with thyroid cancer . X-ray exposure was positive in 87.5% of thyroid cancer patients

In our study, the x-ray and family history were a significant risk factors .

The papillary thyroid carcinoma is more common(14.8%) than follicular thyroid carcinoma(6.7%) among patients with goiter.

Recommendations

1. We need for the activation of the cancer registration center because cancer is very common in our country due to environmental factors .
2. The use of x-ray especially in childhood should be limited and used only when it is indicated .
3. We need a screening program to detect any development of cancer in pre-existing goiter as Iraq is an endemic goiter area .

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APPENDECES

Name

Age

Sex

Duration of illness

Family history of thyroid diseases (also genetic diseases or syndromes)

History of x-ray exposure

Physical examination:

Solitary nodule or MNG
Size of goiter
Consistency (hard, firm)

Lab. Investigation :

Routine (CBC, LFT, RFT)
T3,T4, TSH

Other investigations : US ,FNA

الاسم

العمر

الجنس

مدة المرض

تاريخ العائلة (الامراض الوراثية)

هل تعرض سابقا للاشعة السينية

الفحص السريري :ويشمل :
فحص الغدة الدرقية (الحجم ,القوام)

التحاليل المختبرية :وتشمل
:
التحاليل الروتينية (فحص الدم الشامل ,فحص وظائف الكبد والكلى)

فحص وظائف الغدة الدرقية

الخلاصة

المقدمة :

يعتبر سرطان الغدة الدرقية من اكثر انواع سرطانات الغدد الصم حدوثا وقد ازداد في السنوات الاخيرة بسبب ازدياد وسائل التشخيص المبكر وزيادة التلوث الاشعاعي وعوامل بيئية اخرى.

يحدث عادة بين الناس الذين يتعرضون بشكل متكرر الى الاشعاع (من ضمنها الاشعة السينية) والذي يعتبر هو اهم عامل من عوامل الخطورة.

يوجد اختلاف كبير بين دول العالم في معدل حدوث سرطان الغدة الدرقية.

الهدف من الدراسة :

تقييم نسبة حدوث سرطان الغدة الدرقية المتغايرفي المرضى الذين يعانون من تضخم الغدة الدرقية والذين تم احالتهم الى مستشفى الديوانية التعليمي وتقييم عوامل الخطورة المحتملة .

الطريقة :

تم اختيار 74 مريض يعاني من تضخم الغدة الدرقية بشكل عشوائي من بين المرضى المحالين الى مستشفى الديوانية التعليمي , وكان عمر المرضى يزيد على 5 سنوات .

تم تقييم المرضى عن طريق اخذ التاريخ المرضي (الاسم ,العمر ,التعرض الى الاشعاع والتاريخ الوراثي) وعن طريق الفحص السريري وارسالهم الى التحاليل والسونار.

تم متابعة المرضى الى ما بعد اجراء عملية رفع الغدة الدرقية (بشكل كامل او جزئي) لغرض معرفة نتيجة الفحص النسيجي.

النتيجة :

من خلال المعلومات المتوفرة تم التوصل الى :

اغلب المرضى تتراوح اعمارهم بين 45-60 سنة.

نسبة المرضى النساء المصابات بتضخم الغدة الدرقية اعلى من نسبة الرجال.

نسبة المرضى المصابين بتضخم الغدة الدرقية متعدد العقد اعلى من نسبة المرضى المصابين بتضخم الغدة الدرقية احادي العقدة.

سرطان الغدة الدرقية الحليمي اكثر انتشارا من سرطان الغدة الدرقية الجريبي في المرضى المصابين بتضخم الغدة الدرقية.

التعرض للاشعة السينية يعتبر من عوامل الخطورة لسرطان الغدة الدرقية.

وجود تاريخ عائلي لسرطان الغدة الدرقية ايضا يعتبر من عوامل الخطورة.

الاستنتاج:

سرطان الغدة الدرقية المتغاير ليس نادرا في العراق.

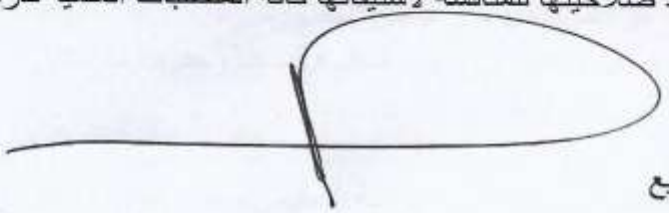
يجب استخدام افضل الوسائل للوصول للتشخيص الصحيح.

التاريخ العائلي والتعرض للاشعة السينية خصوصا في فترة الطفولة هي عوامل خطورة لذلك المرض.

العراق بحاجة الى تفعيل مركز التسجيل السرطاني لتقييم مشكلة السرطان في بلدنا بشكل صحيح.

اقرار المشرف

اني الاستاذ المساعد الدكتور عادل موسى الركابي المشرف على رسالة طالبة الدبلوم العالي المعادل للماجستير هدى غازي هبان قد اطلعت على رسالة الطالبة المذكورة والتي انجزت تحت اشرافي اقر واؤيد صلاحيتها للمناقشة لاستيفائها كافة المتطلبات العلمية لدرجة الدبلوم العالي .



التوقيع

المشرف الاستاذ المساعد الدكتور عادل موسى الركابي

مصادقة

اني رئيس فرع طب الاسرة والمجتمع في كلية الطب جامعة القادسية اصادق على اقرار المشرف على رسالة طالبة الدبلوم العالي (المعادل للماجستير) هدى غازي هبان واعتبر الرسالة صالحة للمناقشة من قبل اللجنة الممتحنة لهذا الغرض .

التوقيع

م.د علي عبد الحسين موسى

رئيس فرع طب الاسرة والمجتمع

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة القادسية
كلية الطب
فرع طب الاسرة والمجتمع

معدل انتشار سرطان الغدة الدرقية المتغاير بين المرضى الذين يعانون من تضخم الغدة الدرقية والمحالين الى مستشفى الديوانية التعليمي

رسالة مقدمة الى مجلس كلية الطب في جامعة القادسية كجزء من متطلبات نيل درجة الدبلوم العالي المعادل للماجستير في طب الاسرة

اعداد
هدى غازي هبان
بكلوريوس طب وجراحة عامة

اشراف
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