Pattern of Thyroid Cancer in Wad Medani Teaching Hospital and National Cancer Institute

By

*Mohamed Mustafa Ali Mohamed*

MBBS, Sinnar University, (2005).

A Dissertation
Submitted in Partial Fulfillment of the Requirements
for the Degree of Medical Doctorate
in
General Surgery

Department of Surgery
Faculty of Medicine
University of Gezira

Supervisor   Co/Supervisor
Prof. Mohamed Elimam Mohamed   Dr. Mustafa Idris Mohamed

February 2013
Pattern of Thyroid Cancer in Wad Medani Teaching Hospital and National Cancer Institute Gezira University.

By

Mohamed Mustafa Ali Mohamed

Examination Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Mohamed El Imam Mohamed</td>
<td>Chairman</td>
<td></td>
</tr>
<tr>
<td>Dr. Awad Rahmatulla Abdalla Mohamed</td>
<td>External Examiner</td>
<td></td>
</tr>
<tr>
<td>Dr. Faisal Abdelgalil Nugud</td>
<td>Internal Examiner</td>
<td></td>
</tr>
</tbody>
</table>

Date of Exam: 10.2.2013
Dedication

- To my father the soul & heart of my family may God rest his soul in peace.

- To my mother who made sure I reached up to this level.

- To my fiancé for her patients & support.

- To my brother & sister.
Acknowledgement

Now that years of hard work have been embodied in this thesis, I would like to thank with all my heart all the beloved people who have helped me to reach this moment.

I would extend my great appreciation to all my colleagues in the Department of Surgery. Thanks to MR. MAJD EL DEN AHMED who always was available whenever I needed help; I deeply thank my advisor and supervisor, PROF. MOHAMED EL IMAM whose help, advice and supervision was invaluable; thanks to MR. MUSTAFA IDRIS who supported me.

Finally, I would like to thank all members of the NCI.
Abstract

Thyroid cancer is the most common endocrine neoplasm, with a rising incidence. The reasons for the increased incidence are unclear, with potential explanations including increased screening, more widespread diagnostic testing of asymptomatic thyroid nodules, changing demographics, and changing environmental risk factors. This is a prospective, cross sectional and hospital based study which was carried out at Wad Medani Teaching Hospital (WMTH) and National Cancer Institute (NCI) during the period from Jan 2010 to Dec 2012. To study the pattern of thyroid cancer, A number of 60 patients with thyroid carcinoma were enrolled in this study. The overall female to male ratio was 3.3:1.0 with overall mean age (49.9±14), Follicular carcinoma was the commonest (40%) followed by papillary (35%) and anaplastic (18.3%). Goitre was the main presenting symptom (100%) followed by hoarseness of voice. Fine needle aspiration cytology is a sensitive diagnostic tool with a sensitivity rate 91.67% and specificity 88.95%. Most patients presented with advanced (48.3%) disease limiting the option of total thyroidectomy. A high index of clinical suspicion is needed in areas of endemic goitres in order that selected cases can be subjected to surgery at an earlier stage of the disease. Health professionals should be aware to suspect carcinoma in a solitary thyroid nodules and clinically hard glands so that they can be evaluated at an earlier stage of the disease.
الملخص

سرطان الغدة الدرقية هو من أكثر سرطانات الجهاز الصمالي شيوعا وقد زاد تردده في الأعوام الأخيرة. الأسباب لزيادة التردد غير واضحة، ولكن توجد عدّة تعليلات تتضمن زيادة المسح لسرطان الغدة الدرقية، انتشار وسائل التشخيص في العقيدة الوحيدة، تغيير في عوامل الخطر المناخي والبيئي. هذه دراسة استطلاعية إجريت في مستشفى ومدني التعليمي والمعهد القومي للسرطان بودمدني في الفترة من يناير 2012 إلي ديسمبر 2012، لدراسة خصائص سرطان الغدة الدرقية، تم دراسة حالة 60 مريض مصاب بسرطان الغدة الدرقية، و أظهرت النتائج أن الغالبية العظمى منهم من النساء نسبة النساء إلى الذكور 3:1، وأن الغالبية العظمى منهم كان العدد العذرية لهم هو (49.9±14) السرطان الجريبي كان الأكثر شيوعا ويمثل نسبة 40% ويليه السرطان الحليمي ويمثل 35% ثم السرطان الكشمي الذي يمثل 18.3%. تضخم الغدة كان الأكثر شيوعا في الاعراض ويمثل نسبة 100% يليه بحة الصوت. الخزعة الرشفية بالابره وسيلة تشخيصية فعالة حيث بلغت نسبة الحساسية 91.67% و الفعالية 88.95%. الغالبية العظمى من المرضى حضروا في مرحلة متقدمة من المرض، 48.3% حال دون خيار استئصال الغدة التام. سرطان الغدة الدرقية يحتاج إلى نسبة عالية من الشك السريري وخاصه في المناطق المتوطنة بتضخم الغدة الدرقية، المختصين بالحقال الصحي يجب أن تكون لديهم دراية في توقع السرطان في العقيدة الوحيدة و الغدة الصلبة بحيث يمكنهم من تقييم المرض في المرحلة الأولى.
# CONTENTS

**Dedication**
II

**Acknowledgement**
III

**Abstract**  
- English  
  IV  
- Arabic  
  V

**List of Figures & Tables**
VII

**Abbreviations**
VIII

## Chapter 1

1-1 Introduction  
1  
1-2 Literature Review  
24  
1-3 Justification and Objectives  
32

## Chapter 2:

2-1 Patients and Methods  
33

## Chapter 3

3-1 Results and Analysis  
37  
3-2 Discussion  
47

## Chapter 4

4-1 Conclusions  
55  
  Recommendations  
56  
4-2 References  
57

Questionnaire  
63
List of Figures and Tables

- Age group and sex distribution 37
- Type of thyroid surgery 43
- The histopathological type 44
- Comparison of fine needle aspiration cytology
  Diagnosis with histopathology diagnosis 45
- Adjuvant therapy 46

Figures

- Types of symptoms 38
- Size of thyroid swelling 39
- Site of thyroid swelling 39
- Consistency of thyroid swelling 40
- Tenderness in thyroid swelling 40
- Mobility of thyroid swelling 41
- Cervical lymph node 41
- Thyroid scan 43
- Fine needle aspiration cytology 43
- Stage of presentation 46
### ABBREVIATION

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMTH</td>
<td>WAD MADANI TEACHING HOSPITAL</td>
</tr>
<tr>
<td>NCI</td>
<td>NATIONAL CANCER INSTITUTE</td>
</tr>
<tr>
<td>TC</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>FA</td>
<td>Follicular adenoma</td>
</tr>
<tr>
<td>PTC</td>
<td>Papillary thyroid carcinoma</td>
</tr>
<tr>
<td>FTC</td>
<td>Follicular thyroid carcinoma</td>
</tr>
<tr>
<td>ATC</td>
<td>Anaplastic thyroid carcinoma</td>
</tr>
<tr>
<td>RNA, mRNA</td>
<td>Ribo-nucleic acid, messenger RNA</td>
</tr>
<tr>
<td>TSH, TSHR</td>
<td>Thyroid stimulating hormone, thyroid stimulating hormone receptor</td>
</tr>
<tr>
<td>Tg</td>
<td>Thyroglobulin</td>
</tr>
<tr>
<td>WHO</td>
<td>World health organization</td>
</tr>
<tr>
<td>DTC</td>
<td>Differentiated thyroid carcinoma</td>
</tr>
<tr>
<td>FNAC</td>
<td>Fine needle aspiration cytology</td>
</tr>
<tr>
<td>RAI</td>
<td>Radio Iodine therapy</td>
</tr>
<tr>
<td>NIS</td>
<td>Sodium iodide symporter</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
</tbody>
</table>
CHAPTER ONE
Introduction and Literature Review

1.1. Introduction

Thyroid carcinoma (TC) is a fascinating tumor for multiple aspects. First, from a biological point of view, TC has many intriguing aspects. Recent insights into the pathogenesis of TC have revealed a clear picture of the relation between genetic alterations and the different subtypes of TC that all arise from the thyroid epithelium. These insights not only have added to the understanding of the pathogenesis of TC, but have also provided new candidate targets for therapy.

In addition, the pathogenesis of TC has also revealed important knowledge about normal thyroid physiology, in particular the physiology of molecules involved in iodide metabolism, like the sodium iodide symporter (NIS) and thyroid peroxidase (TPO). The defects in iodide metabolism in TC that are present in advanced tumors, offer a model to study the contribution and significance of the components involved in iodine metabolism and may also offer targets for re differentiation approaches. The accomplishments of basic research in these areas may ultimately provide valuable directions for clinical management of TC.

Second, from a clinical point of view, TC is fascinating because the approach to the patient differs essentially from many non-endocrine tumors. The central role of therapy with radioactive iodine is unique for TC. Another special aspect is the fact that despite the good prognosis, a substantial proportion of patients develop metastases, that are not life threatening but may impair quality of life considerably, a situation that is not often encountered in general oncology. The unique features of TC offer opportunities for basic and clinical research and indeed insights
from the pathophysiology of TC have often lead to a broader understanding of biological mechanisms involved in cancer. Despite these fascinating aspects of TC, the diagnosis and therapy remain a challenge to the surgeons. TC has a low incidence and in general an excellent prognosis. Therefore, intervention studies are difficult to perform because to reach relevant endpoints high numbers of patients with long follow-up periods are required. As a result, most protocols are based on retrospective studies. The low incidence logically would require centralized treatment and registration of TC patients in order to develop optimal follow-up protocols. The problem, however, is that treatment of TC is often decentralized, resulting in many different follow-up protocols. A typical example of the decentralized follow-up is the fact that many different staging systems have been developed, which complicates the comparison of treatment results between centers. Fortunately, in recent years, several national and multinational guidelines have become available (published by the British, American and European Thyroid Associations)(1,2). Although these guidelines agree in many aspects, they are still based on moderate evidence levels. The present thesis is focused on several clinical questions involved in gender, age, clinical presentation & histopathology of patients with TC.

1.1.1 basic of thyroid gland:
The thyroid gland is developed from the median bud of the pharynx (the thyroglossal duct) which passes from the foramen caecum at the base of the tongue to the isthmus of the thyroid. The ultimobranchial body, which arises from a diverticulum of the fourth pharyngeal pouch of each side, amalgamates with the corresponding lateral lobe. Parafollicular cells (C-cells) are derived from the neural crest and reach the thyroid via the ultimobranchial body. Recently,
consideration has been given to the possibility that some C-cells are of endodermal rather than neural crest origin. It is doubtful whether the branchial apparatus itself contributes to the thyroid follicular cells.

The normal gland weighs 20-25 grams. The functioning unit is the lobule supplied by a single arteriole and consisting of 24—40 follicles, which are lined by cubical epithelium. The resting follicle contains colloid in which thyroglobulin is stored. The arterial supply is rich, and extensive anastomoses occur between the main thyroid arteries and branches of tracheal and oesophageal arteries. There is an extensive lymphatic network within the gland. Although some lymph channels pass directly to the deep cervical nodes, the subcapsular plexus drains principally to the juxtathyroid nodes, i.e. pretracheal (Delphic) and paratracheal nodes, and nodes on the superior and inferior thyroid veins, and hence to the deep cervical and mediastinal group of nodes.

**Physiology**

The hormones tri-iodothyronine and thyroxine are bound to thyroglobulin within the colloid. Synthesis within the thyroglobulin complex is controlled by several enzymes, in distinct steps:

- trapping of inorganic iodide from the blood.
- oxidation of iodide to iodine, and binding of iodine with tyrosine to form iodotyrosines
- coupling of mono-iodotyrosines and di-iodotyrosines to form $T_3$ and $T_4$
- when hormones are required the complex is resorbed into the cell and thyroglobulin broken down; 13 and 14 are liberated and enter the blood where they are bound to serum proteins. A small amount of hormone remains free in the serum in equilibrium with the protein bound hormone and is biologically active.
The principal metabolic effects of the thyroid hormones are due to unbound free $T_4$ and $T_3$ (0.03—0.04 per cent and 0.2—0.5 per cent of the total circulating hormones respectively). $T_3$ is quick acting (within a few hours) whereas $T_3$ acts more slowly (4—14 days). $T_3$ is the more important physiological hormone and is also produced in the periphery by conversion from $T_4$.

The pituitary thyroid axis. Synthesis and liberation of thyroid hormones from the thyroid is controlled by thyroid stimulating hormone (TSH) from the anterior pituitary. Secretion of TSH depends upon the level of circulating thyroid hormones and is modified in a classic negative feedback manner. In hyperthyroidism, where hormone levels in the blood are high, TSH production is suppressed whereas in hypothyroidism it is stimulated. Regulation of TSH secretion also results from the action of thyrotrophin releasing hormone (TRH) produced in the hypothalamus$^{(3)}$.

1.1.2. Characterization of thyroid carcinomas

TC has a low incidence, varying from 2-10/100,000 (3-6) with a female to male preponderance of 2:1. In general, 80% of newly diagnosed thyroid carcinomas are differentiated tumors with a median age at diagnosis of 45 to 50 years$^{(4)}$. TC has a relatively favourable prognosis with a 10-yr survival of 90-95% (Table 1)$^{(2)}$. 

- 4 -
<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Prevalence</th>
<th>Sex ratio (female:male)</th>
<th>Age (years)</th>
<th>Lymph-node metastasis</th>
<th>Distant metastasis</th>
<th>Survival rate (5 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid carcinoma</td>
<td>85–90%</td>
<td>2:1–4:1</td>
<td>20–50</td>
<td>&lt;50%</td>
<td>5–7%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Follicular thyroid carcinoma</td>
<td>&lt;10%</td>
<td>2:1–3:1</td>
<td>40–60</td>
<td>&lt;5%</td>
<td>20%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Undifferentiated thyroid carcinoma</td>
<td>2%</td>
<td>1.5:1</td>
<td>60–80</td>
<td>40%</td>
<td>20–50%</td>
<td>1–17%</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>3%</td>
<td>1:1–1.2:1</td>
<td>30–60</td>
<td>50%</td>
<td>15%</td>
<td>80%</td>
</tr>
</tbody>
</table>


This high survival rate is the result of the biological behavior of most of these tumors and the efficacy of primary therapy, consisting of surgery & Radio Iodine (RaI) therapy.

However, when distant metastases occur, the prognosis is worse because the results of (RaI) therapy, which is virtually the only curative treatment option, are moderate.

Although these metastases are rarely life threatening, they may affect quality of life for years depending on the localization and size.

The tumor-node-metastases (TNM) classification system is based primarily on pathologic findings and separates patients into four stages, with progressively poorer survival with increasing stage\(^{(5)}\). Recently, the 7th edition of the TNM system has become available (Table 2)\(^{(6)}\). The most important difference with the 6th edition is the fact that the dimension of T1 has been extended to 2 cm, which has implications for the prognosis of TC \(^{(7)}\). Therefore, some experts propagate to continue the use of the 6th edition\(^{(8)}\). In this thesis the 7th edition of the TNM staging system is used \(^{(6)}\).
T0 No primary tumor
T1 Tumor diameter < 2 cm
T2 Tumor diameter 2- 4 cm
T3 Tumor diameter > 4 cm, limited to the thyroid or with minimal extrathyroid extension
T4a Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
T4b Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
N0 No metastatic nodes
N1a Metastases to level VI (pretracheal, paratracheal and prelaryngeal lymph nodes)
N1b Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal nodes
M0 No distant metastases
M1 Distant metastases
Stage grouping

Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma.

**Papillary and follicular thyroid cancer (age < 45y):**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Papillary and follicular; differentiated (age ≥ 45y):**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T1-3</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Anaplastic carcinoma (all anaplastic carcinomas are considered stage IV):**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA</td>
<td>T4a</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Medullary carcinoma (all age groups):**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2, T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1-T3</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0, N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-T4a</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

1.1.3. Pathogenesis of TC

1.1.3.1 Molecular Pathogenesis
Human thyroid tumors originate from epithelial follicular cells or from parafollicular C-cells. Follicular cell-derived tumors represent a wide spectrum of lesions, ranging from benign adenomas to differentiated (follicular and papillary), undifferentiated (anaplastic) and medullary carcinoma, thus providing a good model for finding a correlation between specific genetic lesions and histological phenotype.
Recent developments have provided a detailed map of the role of the genetic alterations involved in the pathogenesis of thyroid neoplasms. The dissection of the genetic alterations has important implications not only for the diagnosis, but also for the understanding of the molecular pathology of thyroid disorders\(^\text{(9-11)}\).
Follicular adenomas and carcinomas frequently have mutations in one of the three RAS genes. The understanding of the molecular pathogenesis of papillary carcinoma (PTC) has improved considerably by the recent identification of mutations in B-RAF, which are present in 40-60% of the carcinomas.
Anaplastic carcinomas are frequently associated with mutations in the p53 tumor suppressor gene\(^\text{(12)}\). This is in contrast with many other tumors in which p-53 mutations play a role early in the process of tumorigenesis.
In the pathogenesis of thyroid carcinoma, it is believed that the genetic alterations lead to both proliferations via multiple pathways, and the loss of thyroid specific protein expression. The disappearance of the functional expression of thyroid specific proteins is a complex chain of events, in which the mechanism is incompletely understood. From many observations, it is believed that there is a sequential disappearance of
specific proteins. The disappearance of thyroid peroxidase (TPO) is believed to be an early event. TSH receptor (TSHR) expression and thyroglobulin (Tg) expression are usually still present in advanced stages\(^{13;14;15}\). The mechanisms involved in the decreased expression of thyroid specific proteins may be genetic, involving the absence of thyroid transcription factors, epigenetic changes (TSHR), mutations (not frequently observed) or by post-translational regulation\(^{16}\).

### 1.1.3.2 Sodium iodide symporter and iodide metabolism

The main treatment option for recurrent or metastatic thyroid carcinoma is therapy with radioiodide (RaI). The discovery and molecular cloning of the rat and later NIS have contributed greatly to the understanding of the pathophysiology of iodide uptake by the thyroid gland\(^{17;18}\). NIS resides at the basolateral membrane of thyroid epithelial cells and is responsible for the uptake of iodide from capillaries into the thyroid epithelial cell. The relation between decreased (RaI) uptake in thyroid carcinoma and decreased NIS activity has been well established. However, controversy exists on the mechanism. There is evidence that genetic alterations in TC lead to decreased NIS mRNA and protein expression\(^{19}\). Indeed, the causal chromosomal rearrangements in PTC have been demonstrated to inactivate NIS expression by decreased expression of the transcription factors\(^{20}\). In other studies however, a defect in targeting of NIS to the cell membrane is reported, which is accompanied by an intra-cytoplasmatic over expression of NIS in about 80% of thyroid tumors\(^{16}\). These differences have important consequences for interventions aimed at increasing NIS expression.

The ultimate dose of radioactivity in thyroid tumors is not only determined by the amount activity of RaI administered to the tumor
(specific activity), the rate of uptake but also by the tumor volume and the effective half life of RaI, which on its turn is determined by the physical half life and the biological half life \(^{(21)}\). The exact mechanism of iodide efflux remains elusive. Although candidate molecules for apical iodide efflux \(^{(22)}\) have been discovered, their exact role in apical iodide transport has not been determined yet. The putative apical iodide symporter \(^{(23)}\) has been proven not to transport iodide \(^{(24)}\).

1.1.3.3 Epigenetic Regulation in Thyroid Cancer

Recognizing that DNA is associated with histone proteins to form a condensed structure known as chromatin, research is now investigating how modifications in chromatin structure may contribute to carcinogenesis. Epigenetic modifications refer to heritable alterations of the DNA structure, histones, and/or in nucleosome remodeling, resulting in altered gene expression. Epigenetic changes have been described in thyroid cancer, most notably the altered DNA methylation patterns in the promoters of genes important in normal thyrocyte function such as the sodium-iodide symporter and the TSH receptor. Increased promoter methylation by DNA methyltransferases (DNMTs) leads to gene silencing and further dedifferentiation of the thyroid tumor. DNMT inhibitors such as 5_-azadeoxycytidine are being evaluated as “redifferentiation” agents, thereby allowing tumors to again become more responsive to conventional therapy such as radioactive iodine. Identification of specific methylation patterns may also allow stratifying tumors that may no longer be responsive to thyroid hormone suppressive therapy and I\(^{131}\). Research on how posttranslational modification of histones may influence cancer has recently seen tremendous growth. The nucleosome, or basic structural unit of chromatin, consists of 147 bp of DNA wrapped
around an octamer of core histone proteins. Histone modifications include methylation, acetylation, phosphorylation, and ubiquitination and may act in concert with DNA promoter methylation to modulate gene silencing. Epigenetic drug targets may play a more central role in cancer treatment in the future \(^{(24)}\).

### 1.1.4. Work up

#### 1.1.4.1 History

The most common presentation of thyroid cancer is an asymptomatic thyroid mass, or a nodule, that can be felt in the neck. Record a thorough medical history to identify any risk factors or symptoms. For any patient with a lump in the thyroid that has appeared recently, focus on obtaining history regarding every prior exposure to ionizing radiation, as well as the cumulative lifetime exposure. Consider family history of thyroid cancer. Some patients have persistent cough, difficulty breathing, or difficulty swallowing. Pain seldom is an early warning sign of thyroid cancer. Other symptoms (pain, stridor, vocal cord paralysis, hemoptysis, rapid enlargement) are rare. These symptoms can be caused by less serious problems. At diagnosis, 10-15% of patients have distant metastases to bone and lung and initially are evaluated for pulmonary or osteoarticular symptoms (pathologic fracture, spontaneous fracture) \(^{(25)}\).

#### 1.1.4.2 Physical

Palpate the patient's neck to evaluate the size and firmness of the thyroid and to check for any thyroid nodules. The principal sign of thyroid
carcinoma is a firm and non tender nodule in the thyroid area. This mass is painless.
Some patients have a tight or full feeling in the neck, hoarseness, or signs of tracheal or esophageal compression.
Palpable thyroid nodules are usually solitary, with a hard consistency, an average size of less than 5 cm, and ill-defined borders. This nodule is fixed in respect to surrounding tissues and moves with the trachea at swallowing.
Usually, signs of hyperthyroidism or hypothyroidism are not observed\textsuperscript{(25)}.

1.1.5. Initial diagnosis of TC

1.1.5.1 Fine needle aspiration (FNA)

Despite the increasing standards of imaging techniques like ultrasound, thyroid scan, fine needle aspiration (FNA) is the procedure of choice in patients presenting with thyroid enlargement. The sensitivity of FNA for TC in most series is 90-95\%. The specificity of FNA is lower, 60-80\% when all patients with a non-benign FNA are referred for surgery \textsuperscript{(26)}. As a consequence, the frequency of FTC in hemi-thyroidectomies performed after suspicious results from FNA is only 20-30\%. The problem is that the distinction of benign and malignant follicular neoplasms is difficult to make by FNA, as the crucial criterion for FTC vs. adenoma (FA) is capsular invasion, which cannot be determined by cytology. In addition, the distinction between FA and Follicular carcinoma (FC) is also difficult, because the crucial criterion here is the aspect of the nuclei. The implication is that 70-80\% of the patients with suspicious results from FNA, who undergo thyroid surgery have a benign tumor. Therefore, approaches to improve the accuracy of FNA are warranted \textsuperscript{(27)}. 
1.1.5.2 Thyroid function

Perform complete assessment of thyroid function in any patient with thyroid lumps. Available studies are not specific for FTC. Levels above the reference range of thyroxine (T4; reference range, 4.5-12.5 mcg/dL), triiodothyronine (T3; reference range, 100-200 ng/dL), and TSH (reference range, 0.2-4.7 mIU/dL) may indicate thyroid cancer, usually they are with the normal levels.

Evaluate serum levels of thyroglobulin, calcium, and calcitonin. Determining serum level of carcinoembryonic antigen (CEA) may be helpful; the reference value is less than 3 ng/dL. However, the implications of CEA elevation are not specific because CEA levels are elevated in several cancers, and many healthy people may have small amounts of CEA, especially pregnant women and heavy smokers (28).

TSH suppression test

Thyroid cancer is autonomous and does not require TSH for growth, whereas benign thyroid lesions do. Therefore, when exogenous thyroid hormone feeds back to the pituitary to decrease the production of TSH, thyroid nodules that continue to enlarge are likely to be malignant. However, consider that 15-20% of malignant nodules are suppressible. Preoperatively, the test is useful for patients with nontoxic solitary benign nodules and for women with repeated inconclusive test results (28).

Postoperatively, the test also is useful in follow-up of TC cases.
**PCR**

A prognostic indicator of significant value may be *ras* genotyping by PCR technique, which may help in the clinical and histologic reassessment of these tumors\(^{28}\).

### 1.1.5.3 Imaging study

Ultrasonography is the first imaging study that must be performed in any patient with suspected thyroid malignancy. Ultrasonography is noninvasive and inexpensive, and it represents the most sensitive procedure for identifying thyroid lesions and determining the diameter of a nodule (2-3 mm). Ultrasonography is also useful to localize lesions when a nodule is difficult to palpate or is located deeply. Ultrasonography can determine whether a lesion is solid or cystic and can detect the presence of calcifications. The rate of accuracy of ultrasonography in categorizing nodules as solid, cystic, or mixed is near 90%\(^{29}\).

Ultrasonography may direct a fine-needle aspiration biopsy (FNAB). Disadvantages of thyroid ultrasonography are that the test cannot distinguish benign nodules from malignant nodules, and it cannot be used to identify true cystic lesions. Prior to the introduction of FNAB, thyroid scintigraphy (or thyroid scanning) performed with technetium Tc 99m pertechnetate (99mTc) or radioactive iodine (I-131 or I-123) was the initial diagnostic procedure of choice in thyroid evaluation. Thyroid scanning is not as sensitive or specific as FNAB in distinguishing benign nodules from malignant nodules. The scintigraphy procedure performed with 99mTc has a high error rate because although 99mTc is trapped in the thyroid, as iodide is, it is not
organified there. 99mTc has a short half-life and cannot be used to determine functionality of a thyroid nodule.

Radioactive iodine is trapped and organified in the thyroid and can be used to determine functionality of a thyroid nodule. Iodine-containing compounds and seafood interfere with any tests that use radioactive iodine. Scintigraphic images of the thyroid are acquired 20-40 minutes after IV administration of radionuclide. In more than 90% of cases, clearly benign nodules appear as hot because they are hyperfunctioning and have a high uptake of radionuclide and, physiologically, of iodine. Malignant nodules usually appear as cold nodules because they are not functioning\(^{30}\).

Thyroid scanning is helpful and specific in localizing the tumor preoperatively and residual thyroid tissue immediately postoperatively. It also is used to follow-up for tumor recurrence or metastasis. Thyroid scanning could be useful in diagnosing thyroid tumors in patients with benign lesions (by FNAB) or solid lesions (by ultrasonography)\(^{28}\).

Integrated imaging, using 18F-FDG and coregistered total body PET and CT scan, seems to be effective in improving diagnostic accuracy in patients with iodine-negative differentiated thyroid carcinoma, allowing precise localization of the tumor tissue\(^{30}\). In addition, image fusion by integrated PET/CT offers more information than side-by-side interpretation of single images obtained separately with CT and PET.

Chest radiography, CT scanning, and MRI usually are not used in the initial workup of a thyroid nodule, except in patients with clear metastatic disease at presentation. These tests are second-level diagnostic tools and are useful in preoperative patient assessment.
**Other Tests**

Perform indirect or fiberoptic laryngoscopy to evaluate airway and vocal cord mobility and to have preoperative documentation of any unrelated abnormalities\(^{(28)}\).

**1.1.6. Therapy of TC\(^{(29,30,31)}\)**

The guidelines for the initial therapy of TC have been extensively reviewed in the papers mentioned below.

Treatment protocols for thyroid cancer are provided below, including a general treatment approach and treatment recommendations for differentiated, anaplastic (undifferentiated), and medullary thyroid cancer\(^{(29)}\).

**General treatment approach for thyroid cancer**

- Thyroid cancer is divided into 3 categories, which include differentiated (Hürthle cell, papillary, and follicular), anaplastic (undifferentiated), and medullary cancers
- The treatment of choice for patients diagnosed with thyroid cancer is surgery, when possible
- Usually, surgery is followed by treatment with radioiodine and thyroxine therapy
- Generally, radiation therapy and chemotherapy do not have a prominent role in the treatment of thyroid cancer

**General treatment recommendations for thyroid cancer**

*Radioactive iodine ablation:*

Postoperative whole-body scintigraphy scan may identify previously unrecognized disease and influence staging. If residual disease is found, radioactive iodine (RAI) may be considered adjuvant therapy. Ablation of residual normal thyroid tissue facilitates early detection of recurrence.
based on serum thyroglobulin measurement and/or RAI whole-body scan.

- RAI ablation is indicated for large (>4 cm) tumors, known distant metastasis, and/or gross extrathyroid extension.

- RAI ablation may be considered for moderate-size (1-4 cm) tumors that are node positive; grossly multifocal; aggressive, based on histology; and high risk, based on patient factors (age >45y, history of head and neck radiation, family history of thyroid cancer).

- RAI ablation is not recommended for small (< 1 cm), solitary tumors or multifocal tumors when all foci are < 1 cm.

- Early data seems to indicate that RAI is equally effective when used with thyroid hormone withdrawal or with recombinant human thyroid-stimulating hormone (rh-TSH) stimulation.\(^{(32)}\)

**Thyroid-stimulating hormone (TSH) suppression therapy (levothyroxine):**

- TSH suppression to < 0.1 mU/L is indicated in intermediate and high-risk disease

- TSH maintenance at or slightly below the lower-normal limit (0.3-2 mU/L) may be considered for low-risk disease

**Therapy for unresectable gross residual or recurrent disease or metastases:**

- Unresectable gross residual/recurrent disease/metastases may be treated with external beam radiation therapy (EBRT)

- Consider systemic treatment in the context of a clinical trial for persistent metastatic disease despite radioiodine, TSH suppression, and radiotherapy

- Consider tyrosine kinase inhibitors such as sorafenib 400 mg PO BID\(^{(33)}\) or sunitinib 50 mg PO daily for 4wk of a 6-wk cycle for patients who cannot participate in a clinical trial, as well as for those who are not likely to tolerate systemic therapy; since these
drugs are usually tumorostatic rather than tumoricidal, they are considered second-line therapy compared with systemic treatments in clinical trials

- Randomized phase III clinical trials supporting a tyrosine kinase inhibitor benefit in thyroid cancer is currently unavailable; thus, there are no specific regimens
- Doxorubicin 60 mg/m² as monotherapy or in combination with cisplatin 40 mg/m² may be considered for patients who cannot tolerate tyrosine kinase inhibitors or in whom tyrosine kinase inhibitors have failed; however, the efficacy of these, and other cytotoxic drugs, is very limited

**Treatment recommendations for differentiated thyroid cancer**

*Follicular neoplasm (indeterminate cytology):*

- Consider scintigraphy if not already done, especially in the setting of thyroid-stimulating hormone (TSH) in the low-normal range
- Hyperfunctioning nodules may be observed; however, if a concordant hyperfunctioning nodule is not identified, lobectomy or total thyroidectomy should be considered

*Papillary and follicular thyroid cancer stages I-IV (confirmed by cytology)*:

- Surgery is ultimately based on patient factors and surgeon expertise
- Total thyroidectomy is recommended for tumors > 1cm
- Hemithyroidectomy may be considered for small (< 1cm), low risk, unifocal, intrathyroid tumors in the absence of prior head and neck radiation and cervical nodal metastasis
- Therapeutic central neck dissection when cervical lymph nodes are involved
When lateral cervical lymph nodes have biopsy-proven disease, therapeutic central and lateral compartment neck dissection should be performed.

Prophylactic unilateral or bilateral central neck dissection may be considered in clinically N0 disease, especially for advanced primary tumors (T3 or T4).

**Treatment recommendations for anaplastic (undifferentiated) thyroid cancer**

* Surgery:
  - Because most patients have advanced disease at the time of diagnosis, surgery is often not indicated; however, if the tumor appears to be localized to the thyroid, lobectomy with wide margins of ipsilateral soft tissues is recommended, often in conjunction with postoperative adjuvant radiotherapy or combined-modality therapy.
  - As long as the tumor is small and entirely confined to the thyroid, total thyroidectomy does not appear to improve survival, as compared with lobectomy, and is associated with a higher risk for complications.
  - Surgical debulking may provide symptomatic relief for patients with very large tumors and significant airway compression.

* Combined-modality therapy:
  - Consider primary combined radiotherapy and chemotherapy for locally advanced, unresectable disease.
  - Since there are no randomized, controlled trials available to definitively prove the therapeutic efficacy of combined-modality therapy, most management strategies are based on single-
institution phase II trials and retrospective reviews; thus, there are no standard regimens

- Most studies use a doxorubicin-based regimen, such as doxorubicin 20 mg once weekly given prior to the first radiotherapy session
- Chemotherapy is followed by hyperfractionated radiation and often by an additional round of chemotherapy after radiotherapy completion
- Doxorubicin has also been given concurrently with radiation therapy as a radiosensitizer
- Consider surgical resection for patients who have a good response to treatment

_Palliative care:_

- Even with aggressive treatment, anaplastic thyroid cancer is almost always fatal, and there is no effective therapy for metastatic disease
- End-of-life issues, comfort, and care options are essential considerations during initial treatment planning

_Treatment recommendations for medullary thyroid cancer_

_Surgery_\(^{(35)}\):

- Total thyroidectomy with prophylactic or therapeutic central neck dissection (level VI) is considered the standard of care for all patients with medullary thyroid cancer
- Assessment for metastatic disease by preoperative imaging of the neck, chest, and liver is recommended for patients with nodal metastasis and for those with serum calcitonin > 400 pg/mL
- Therapeutic compartmental lateral neck dissection should be attempted for patients with minimal or no distant metastasis
• In the presence of distant metastasis or advanced local disease, less aggressive neck surgery that preserves speech and swallowing function may be appropriate

• Palliative debulking surgery may be considered to relieve tracheal compression and local pain

• Preoperative exclusion or treatment of a concomitant pheochromocytoma is critical, given its high risk of surgery and anesthesia complications

• A second surgery, possibly with remedial central neck dissection, may be considered for patients with evidence of recurrent or persistent disease, rising serum calcitonin levels in the setting of an inadequate initial operation, or threatening tracheal invasion or compression; however, reoperation carries a higher risk of complications, including thoracic duct leak, recurrent laryngeal nerve injury, and hypoparathyroidism

*Thyroxine replacement therapy:*

• Thyroid replacement therapy (standard dosing with thyroxine replacement) should be initiated postoperatively with the goal of maintaining euthyroidism

• In contrast to epithelial cell–derived thyroid cancers, TSH suppression to lower-than-normal levels is not indicated, since C-cells are not TSH responsive (similarly, radioactive iodine [RAI] is not indicated in medullary thyroid cancer, because C-cells do not concentrate iodine)

*Therapy for unresectable or recurrent disease or for metastases:*

• Radiotherapy may be considered for patients with gross residual disease after surgery and for those with distant metastasis
The role of external beam radiation therapy (EBRT) in M0 or minimal M1 disease is controversial

Consider systemic therapy in the context of a clinical trial for patients with progressive metastatic disease who cannot be treated with surgery or radiotherapy

The low incidence of medullary thyroid cancer has limited widespread clinical consensus, as well as the ability to conduct large, definitive, randomized, controlled trials; thus, there are no standard regimens

The tyrosine kinase inhibitors (TKIs), vandetanib and cabozantinib, have been approved by the FDA for progressive, metastatic medullary thyroid cancer
  - Vandetanib: 300 mg PO daily
  - Cabozantinib: 140 mg PO daily
  - Dosage adjustment for these TKIs may be required depending on toxicity and coadministered dru

In all patients with TC (7th edition TNM \(^6\)), there is still some controversy about the extent of thyroid surgery, there are strong arguments in favor of total or near-total thyroidectomy (leaving only as limited thyroid tissue as is necessary to keep vital structures intact) in all patients \(^{36}\).

1.1.7. Follow-up of patients with DTC

The purpose of follow-up protocols in TC is to detect and prevent persistent or recurrent DTC. Recurrences are usually detected during the early years of followup but may be detected later, even after more than 15 years after initial treatment.
Most patients during follow up have been cured definitely, and, as a consequence, have a low pre-test probability for recurrent disease. Therefore, the sensitivity of the diagnostic test must be adequate to detect the few patients with evident thyroid carcinoma, whereas specificity must also be high to avoid unnecessary treatments in patients without recurrent disease. In addition, the burden of diagnostic tests for the patient should be kept at a minimum. The most important tools in follow up protocols are serum measurements of Tg, diagnostic whole body Ral scintigraphies and neck-ultrasound. Numerous studies have been performed on the diagnostic value of Tg measurements. The consensus is that the TSH stimulated Tg measurements have superior diagnostic value in TC (37). The interpretation of many studies and consequently of the guidelines on Tg performed so far is difficult because the analytical aspects of Tg measurements are complicated.
1.2 Literature review

The thyroid gland has been described throughout history but was first so named by the Romans for being a "shield-shaped" gland. Not only were thyroid masses mentioned in the literature throughout the 12th and 13th century, but in 1170 Robert Frugardi described the extirpation of a goiter.

French term goitre is the origin of the word goiter both originating from Latin word gutter increasing throat. Close anatomical association of these glands with the larynx led to the name of thyroid (shaped like a shield) after the designation given by Galen to the thyroid cartilage.

Thyroid carcinoma was known in 18th century only. Butlin in 1887 did a study with 50 patients. In 1950, papillary carcinoma were removed by lobectomy and excision of involved lymphnodes.\(^{(38)}\)

FNAC of thyroid was first described in 1930's by Martin and Ellis. In 1950 the technique was popularised in Scandinavia. It is Zajccek the first pathologist to embrace FNACA in collaboration with Franzen at the Karoliska Hospital defined the precise diagnostic criteria and determined the diagnostic accuracy.

There are certain pitfalls in FNAC diagnosis of thyroid. A safe and reliable differential diagnosis between thyroid and parathyroid neoplasms on morphological ground alone is difficult in cytological smears due to absence of well established criteria due to overlapping of cytological features of these lesions.

Thyroid surgery was undertaken well before thyroid gland physiology was understood. The procedures were often fraught with complications,
including massive hemorrhage, infection, and injury to surrounding structures, all of which were associated with morbidity and mortality rates of nearly 40%.

Even in the 19th century, thyroid surgery was considered barbaric, described by Samuel Gross as "horrid butchery," and banned by the French medical society due to its high mortality. As technology improved and with the advent of aseptic technique, mortalities associated with these surgeries decreased. During the 1850s, operations on the thyroid gland were undertaken via longitudinal, oblique, or vertical neck incisions. Jules Boeckel of Strasbourg introduced the collar incision to thyroid surgery in 1880, and this approach was popularized by Theodore Kocher. Theodor Kocher, whose own reported mortality rate for thyroidectomy dropped to 1%, was awarded the Nobel Prize in 1909 for his advancement of thyroid surgery in the late 19th century.

**IN SUDAN:**

In Omran M, Ahmed ME. Study of thyroid carcinoma from Khartoum showed that one hundred and twelve patients with thyroid malignancy seen. The female to male ratio was 2.5:1.0 with a high incidence of the disease between the ages of 40 and 70 years. Follicular carcinoma was the commonest (42%) followed by papillary (22.3%) and anaplastic (21.4%). Goitre was the main presenting symptom (92.9%). Cervical lymphadenopathy was present almost equally in these three histological types, 26.6%, 32%, and 33% respectively. Anaplastic and squamous cell carcinoma showed a locally aggressive behaviour to nearby structures resulting in hoarseness of voice, dyspnoea and dysphagia indicating advanced disease. Most patients presented with advanced disease limiting the option of total thyroidectomy (40%).
In Bashier study in Khartoum showed Ninety four patients with solitary and significantly dominant thyroid nodules were studied. (13.5%) were malignant nodules (6 follicular, 5 papillary and one anaplastic). The incidence of malignancy in the clinically solitary nodules was 14% (compared to 10% for the dominant nodules which increased to 16% versus 10% respectively after ultrasonography and histopathological confirmation of the nature of the gland. There is a low positive predictive value for follicular neoplasm with fine needle aspiration cytology (FNAC) (44%).(40)

**IN AFRICA:**
Reports from tertiary centers in West Africa showed that 322 patients underwent thyroidectomy for cancer. Overall, 31.5% had papillary thyroid cancer (PTC), and 30.3% had FTC. From 1980 to 1989, 27.3% had PTC and 35.8% had FTC. From 1990 to 2004, 35.7% had PTC and 24.8% had FTC.(41)
In another study in Africa: Dakar were found the sex ratio for thyroid cancer in Ouagadougou is 1 : 2 (M : F), thus mainly women. It affects mainly women in their 30s. Thyroid cancer at Ibadan was found to be papillary carcinoma in 45.3% of cases; follicular forms were seen in 44.5% and this series includes 5% of medullary cancers, with a mean age of 34 years. Already other cases from Francophone sub-Saharan Africa have been noticed. Iodine deficiency is suggested to play a role because follicular cancer in southern Africa accounts for up to 55% of thyroid cancers. Thyroid cancers in Algeria are associated with low socioeconomic status and characterized by a high prevalence of cancers discovered at an advanced stage and of anaplastic carcinomas(42)
**IN UK:**

In Olaleye Study documenting changes in incidence, staging and morphologic types of TC. TC was commoner amongst females (73%) than males (27%) with a 2.7:1 F : M ratio. Mean age at diagnosis was 53 years (Range 5-99) years. An increasing incidence trend was observed in early stage disease, in young adults aged ≤ 49 years.\(^{(43)}\)

In national population-based study of thyroid carcinomas, 80% papillary; 14.5% follicular; 3.5% medullary and 6% anaplastic/undifferentiated TCs 2% were evaluated. The M/F-ratio was 1:3.2, the mean age 48.3 years (range: 13-92). The overall age-standardized (world population) incidence rates over the two 5-year periods increased from 7.4 per 100,000 to 10.1 per 100,000 in females, from 2.3 per 100,000 to 3.6 per 100,000 in males. The majority of the patients (50%) were between 45 and 69 years of age.\(^{(44)}\)

**Recent advances in thyroid surgery:**\(^{(45)}\)

The surgical treatment of thyroid carcinoma has evolved over the past two decades in many aspects. Large numbers of thyroid operations are now being performed at high-volume tertiary referral centers, resulting in the never-ending pursuit of improvements in patient care and outcomes. Two aspects that have advanced greatly are the introduction of same-day thyroidectomy and the use of endoscopic and robotic technology to perform thyroid surgery.

**Same day thyroid surgery**

As mentioned above, thyroidectomy is generally a safe procedure that has few complications. The most catastrophic complication is a compressive neck hematoma that obstructs the airway, which can develop even beyond 24 h after the procedure and requires correct
identification and rapid treatment. For this reason, patients typically remain hospitalized for several days after a thyroidectomy. Nevertheless, in the past two decades a short hospital stay after thyroidectomy has become the most common practice. This trend has been driven in part by efforts to reduce medical costs, and has been supported by the very low rate of complications requiring readmission after the procedure.

Same-day thyroidectomy was initially described in 1986. The rationale for performing same day thyroidectomy relies on a combination of factors: firstly, patients and health insurance providers usually prefer short hospital stays, which limit the cost of treatment. The use of improved antiemetic drugs helps to reduce both the discomfort associated with the procedure and the risk of postoperative hematoma. Patients generally feel well after thyroidectomy and experience only mild discomfort; in addition, the rate of complications that necessitate in-hospital treatment is very low.

Same-day thyroidectomy should be performed at high-volume centers by experienced surgeons and that careful selection of patients for the procedure is of the utmost importance. A support system that enables close follow-up and rapid problem solving is necessary to assure these patients' safety.

**Endoscopic and robotic surgery**

The open method of thyroid excision provides adequate access to the tumor, and leaves a scar that is often well-hidden in the skin crease, the possibility of scar hypertrophy and the search for improved cosmoses has resulted in the development of minimally invasive and video-assisted surgical techniques.

The first reported endoscopic thyroid surgery was described in 1997. Since then, several endoscopic approaches for thyroid surgery have been
described. The technique most commonly used in North America is termed minimally invasive video-assisted thyroidectomy (MIVAT). In this technique, thyroidectomy is performed via a small anterior neck incision, with comparable results to open thyroid surgery.

Robotic or endoscopic transaxillary thyroidectomy offers two advantages over conventional neck incisions: excellent cosmesis, as the operation scar is in the axilla, and absence of postoperative hypesthesia and fibrotic contracture in the anterior neck. However, extra-cervical approaches often lead to increased operative times, greater postoperative pain, and involve a greater amount of dissection versus cervical approaches.

The first single-incision, robot-assisted, transaxillary thyroidectomy was described in 2010 by Chung and colleagues. Compared with conventional endoscopy, robotic surgical systems offer superior visualization and improved maneuverability of the surgical instruments. Robotic thyroidectomy is associated with several limitations. First, the operative time is longer than that of open procedures. Secondly, a much larger dissection is needed to reach the thyroid gland via the axilla than via the cervical approach and the axillary route is associated with complications that have not been reported with open (cervical) surgery. Thirdly, the very high cost of robotic procedures and of the device itself is the main factor limiting the applicability of robotic thyroid surgery.

Some controversy remains as to the use of minimally invasive endoscopic techniques for the management of thyroid cancers. Although most surgeons would agree that highly malignant or aggressive tumors are not suitable for such techniques. Consequently, some researchers propose that such procedures should only be offered to patients with tumors <3 cm in size and total ultrasonographically estimated thyroid volume of <20 ml. Contraindications include previous irradiation to
the neck, previous neck surgery, aggressive tumors, extracapsular or nodal spread of the tumor, and previous thyroiditis. Dissection might also be difficult in patients with obesity and those with long necks.

**Controversies**

The extent of surgery recommended for patients with TC is a hotly debated topic. Some of the arguments in support of total thyroidectomy are based on the fact that this procedure involves a minimal risk of postoperative complications and has an excellent outcome when performed by experienced surgeons. Furthermore, total thyroidectomy also removes any undiagnosed microscopic or macroscopic tumor in the contralateral lobe. Total thyroidectomy can also be combined with adjuvant therapy, such as radioactive iodine, and thyroglobulin levels can be evaluated as a marker for disease recurrence during follow-up. By contrast, a limited procedure that includes an ipsilateral thyroid lobectomy and isthmusectomy offers the clear advantage of avoiding any risk of injury to the nerves or the parathyroid glands on the contralateral side. Moreover, the presence of the remaining thyroid lobe might attenuate the need for thyroid hormone replacement therapy in some patients, whereas patients aged >45 years, or patients with nodular, cystic, or fibrotic lobe might require hormone replacement therapy. Consequently, risk-stratification models have been proposed to identify high-risk patients who should be offered a total thyroidectomy as the first line of treatment. Such models differ between institutions, however, and the risk groups include patients with various ages, tumor grades and sizes, as well as differing in whether extrathyroidal extension, completeness of resection, distant metastases.
Some evidence suggests that patients with low-risk DTC who are treated with lobectomy and isthmusectomy have similar long-term outcomes to those treated with total thyroidectomy, and that low-risk patients treated with total thyroidectomy do not benefit from the addition of radioactive iodine ablation. Despite attempts to improve these risk-stratification models, the current ATA recommendations suggest total or near-total thyroidectomy for all patients with DTCs >1 cm in size. As mentioned above, these recommendations are supported by data that demonstrate improved recurrence and survival for these patients. Obviously, an aggressive approach is warranted in patients with additional risk factors, such as the presence of contralateral thyroid nodules, or regional or distant metastases. Patients with a history of head and neck radiation, or a first-degree family history of DTC, should also be treated with total or near-total thyroidectomy. The final decision on the extent of surgery depends on the preferences of the patient, the endocrinologist, and the surgeon\textsuperscript{[45]}
1.3 Justifications & Objectives

1.3.1 Justifications

During my training period in Wad Medani Teaching Hospital I and my colleagues noticed significant number of patients presenting with Thyroid cancer, and significant number of them presenting with distant Mets. Most of them coming from rural areas, where the health facilities are poor, and usually they present late. I noticed, although few reports examining the distribution of thyroid carcinoma (TC) in Sudan, no study has previously reported on the characteristic clinicopathologic features of thyroid carcinoma in WMTH and NCI. According to the hospital Statistical records there were 21 patients with (TC) in 2010, there were 19 female and the rest were 2 male, 27 patients in 2011, there were 23 female and the rest were 4 male, While there were 11 female and 1 male, with a total of 12 patients in the year 2012.

1.3.2 Objectives:-

1.3.2.1 General objectives:
To assess pattern of thyroid cancer in WMTH and NCI.

1.3.2.2 Specific objectives:
To evaluate:

1. To determine age & sex distribution.

2. To determine the commonest symptoms of presentation.

3. To assess the fine needle aspiration cytology versus the histopathological diagnose.

4. To determine the stage of presentation.
2.1.1 Study design:

The design of the study was a prospective hospital based clinical study, which was conducted in 60 patients in Wad Medani Teaching Hospital (WMTH) & National Cancer Institute from January 2010 to December 2012. The descriptive data of thyroid cancer were provided by the national cancer institute registry, which is the population-based cancer registry at national level which collects data on about 95% of the precancerous and cancerous lesions verified by microscopic examinations.

These thyroid cancer cases had been exclusively diagnosed and "double-read" in the central division of pathology by senior pathologists.

2.1.2 Study area:

Wad Medani is capital of Gezira State. The area of Gezira State is 8901 square kilometer with population of 2,706,941 (1993 census).

Wad Medani is one of the most popular towns in Sudan; it is surrounded by small towns and villages. The health services are provided through centers which give only the outpatient consultation and refer all serious surgical cases.

2.1.2.1 Wad-medani Teaching Hospital:

This is a tertiary hospital that serves the whole Gezira state and nearby states. It is the main teaching hospital. It includes the following departments; Medicine, Surgery, ENT, Orthopaedics, radiology, Blood
Bank, ICU, CCU, 5 Referred clinics, Medical Emergency Department, Surgical Emergency Department, Laboratory, Pharmacy, 3 operative theatres. Department of Radiology contains facility of Ct-scan, MRI & U/S

2.1.2.2 National cancer institute:

Established in 1994 as the second center in Sudan for nuclear medicine and molecular biology. In 1999 Oncology department has been added to the institute.

NCI is the only cancer center outside the capital of Sudan, Khartoum. The catchment’s area covered from all over country.

All patients with surgical malignancies referred to NCI will go through a weekly combined clinic by surgeons and oncologists where detailed evaluation and design of treatment plan is made. The option of management available in NCI including radiotherapy, chemotherapy and hormonal therapy.

2.1.3 Criteria of the study:

Patients of all nationalities, races or ethnic origins living in Gazira State and treated for thyroid cancer were considered. Disease histology was limited to the four major histological types, including papillary, follicular differentiated, medullary and anaplastic undifferentiated carcinomas and their variants, diagnosed according to the WHO-classification. Tumours of the thyroid gland recorded as malignant carcinoid, lymphomas or mesenchymal malignant tumours were excluded from the current review.

This prospective study is based on 60 patients admitted in the Department of General Surgery, WMTH & NCI, for last three years with
neoplastic thyroid swellings. The evaluation was done as per the following criteria. Detailed history was taken more stress was given on clinical presentation and age & sex distribution. General physical examination was done. More stress was given on local examination allowed an interpretation in relation to tumour size, the local and regional spread, the lymph node. They were analysed with respect to the TNM-system (i.e.: T: extent of primary tumour; N: regional lymph node metastasis; M: distant metastasis), according to the International guidelines of TC (5,6). In our series the histological Beside the evaluation of the frequency of the TCs the changes in incidence of thyroid carcinomas in relation to four of patients grouped in youngest (<20 years of age), younger (20–39 years), middle aged (40–59 years) and elderly (60 years and above) patients were reviewed. The age-standardized (world population) incidence rates of TCs, diagnosed in NCI during the period 2010–2012, were compared with the data of other geographical African & European regions with similar population density and characteristics, published by the WHO.

Various investigations including thyroid function tests, indirect laryngoscopy, thyroid scan, FNAC, histopathology were performed. The patients were clinically assessed for any metastasis. Special investigations like bone scan were performed only if there was a high clinical suspicion. After surgery, all tissues were subjected to histopathological examination and benign tumours were excluded from the study. Some of the patients were subjected to surgery. After surgery and final histopathological diagnosis, all the malignant patients were referred to the Department of Nuclear Medicine and Radiotherapy for further management.
Patients were followed in the combined clinic.

An informed consent was sought from all the patients who were included in the study. The methodology of the study was explained to the patients individually in a language of their understanding. The patients were also informed that the data collected from this study would be used for medical research and the material could be published, and the authors would take responsibility to protect the privacy of the patients.

These data were analyzed using computer, statistical package for social science (SPSS) version 17, Microsoft excel and office 2007. The data was presented in percentage and table forms.
CHAPTER THREE

3.1 Result

Age group & Sex distribution: Table 3

The total number of patients studied was 60 patients. There were male and female with M : F ratio of 1 : 4.

The study showed that there were patients (25%) fall in the age group (20-39) year, patients (45%) fall in the age group (40-59) year and patients (30%) with an age more than 60 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 -39</td>
<td>2</td>
<td>13</td>
<td>15</td>
<td>25%</td>
</tr>
<tr>
<td>40 – 59</td>
<td>4</td>
<td>23</td>
<td>27</td>
<td>45%</td>
</tr>
<tr>
<td>60+</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>46</td>
<td>60</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3: The age group and sex distribution of 60 patients in the study of pattern of thyroid cancer in WMTH& NCI in central of Sudan. (2010-2012).

Residence of patients: Table 4

<table>
<thead>
<tr>
<th>Rural</th>
<th>%</th>
<th>Urban</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Patients</td>
<td>43</td>
<td>No of Patients</td>
<td>17</td>
</tr>
<tr>
<td>%</td>
<td>71.7%</td>
<td>%</td>
<td>28.3%</td>
</tr>
</tbody>
</table>

Table 4: Residence of 60 patients in the study of pattern of thyroid cancer in WMTH& NCI in central of Sudan. (2010-2012).
The symptoms at presentation:

There were 60 patients (100%) presented with anterior neck swelling, 19 patients (31.6%) presented with hoarseness of voice, 17 patients (28.3%) presented with throat or neck pain, 16 patients (26.6%) presented with difficulty in swallowing, 16 patients (26.6%) presented with difficulty in breathing and 7 patients (11.7%) presented with bone pain. The rest 4 patients were presented with cough (6.7%)

Figure 1: Types of symptoms in 60 patients with thyroid cancer in WMTH & NCI in central of Sudan. (2010-2012).
The clinical examination:

Figure 2: Size of thyroid swelling 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

Figure 3: Site of thyroid swelling 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
Figure 4: Consistency of thyroid swelling 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

Figure 5: Tenderness in thyroid swelling in 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
Figure 6: Mobility of thyroid swelling 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

Figure 7: Cervical lymph node in 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
Preoperative diagnostic procedures:

The diagnosis was achieved in 60 patients by clinical examination and other diagnostic tools

Thyroid scan shows in 39 patients (65%) solitary nodule, 20 patients (33.3%) multi nodular and one patients (1.7%) diffuse goiter.

Figure 8: Thyroid scan in 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

Fine needle aspiration cytology shows in 21 patients (35%) follicular neoplasm, 19 patients (31.7%) papillary carcinoma, 11 patients (18.3%) anaplastic carcinoma and medullary carcinoma in 4 patient (6.7%). The rest 5 patient (8.3%) it shows benign colloid nodule.
Figure 9: Fine needle aspiration cytology in 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

Types of surgical intervention:

- Thyroid surgery was done in 49 patients (81.7%). Total thyroidectomy was done for 29 patients (48.3%), lobectomy together with isthmectomy was done in 10 patients (16.7%). Near total thyroidectomy was done for 10 patient (16.7%). 11 patients (18.3%) were not operable.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Freq</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy</td>
<td>29</td>
<td>48.3%</td>
</tr>
<tr>
<td>Lobectomy + isthmectomy</td>
<td>10</td>
<td>16.7%</td>
</tr>
<tr>
<td>Near total thyroidectomy</td>
<td>10</td>
<td>16.7%</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>81.7%</td>
</tr>
</tbody>
</table>

Table 5: Type of thyroid surgery done for 49 patients in the study of pattern of thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
The histopathological examination:

There were 24 patients (40%) with follicular carcinoma, 21 patients (35%) with papillary carcinoma, 11 patients (18.3%) with anaplastic carcinoma and 4 patients (6.7%) with medullary carcinoma. Those who did not underwent thyroidectomy histopathology was obtained through incisional biopsy or Tru-cut biopsy.

<table>
<thead>
<tr>
<th>Histopathological type</th>
<th>Freq</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular carcinoma</td>
<td>24</td>
<td>40%</td>
</tr>
<tr>
<td>papillary carcinoma</td>
<td>21</td>
<td>35%</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>11</td>
<td>18.3%</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>4</td>
<td>6.7%</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 6: The histopathological type for 60 patients in the study of pattern of thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

<table>
<thead>
<tr>
<th>Types of Thyroid</th>
<th>Types &amp; Sex Distribution</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>46</td>
</tr>
</tbody>
</table>

Table 7: The age & sex distribution for histopathological type for 60 patients in the study of pattern of thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
<table>
<thead>
<tr>
<th>Histopathology</th>
<th>FNAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular carcinoma*</td>
<td>24</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>21</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>11</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>4</td>
</tr>
</tbody>
</table>

* FNAC showed follicular neoplasm

Table 8: Comparison of fine needle aspiration cytology Diagnosis with histopathology diagnosis for 60 patients in the study of pattern of thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

7-post operative whole body scan:

Post operative whole body scan was performed for most of cases
It showed no activity in 7 patient (11.7%), bone metastasis in 11 patients (18.3%) and metastastic deposit in the lung 6 patients (10%). The rest 36 patient (60%) showed lymph node deposit

<table>
<thead>
<tr>
<th>Post operative whole body scan</th>
<th>Freq</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>no activity</td>
<td>7</td>
<td>11.7%</td>
</tr>
<tr>
<td>bone metastasis</td>
<td>11</td>
<td>18.3%</td>
</tr>
<tr>
<td>lung metastasis</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>lymph node metastasis</td>
<td>36</td>
<td>60%</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 9: Post operative whole body scan done for 60 thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
7-Stage of presentation:

Stage 1 there were 7 patients (11.7%), 14 patients (23.3%) present at stage 2, 10 patients (16.7%) present at stage 3 and 29 patients (48.3%) present at stage 4.

![Stage of presentation](image)

Figure 10: Stage of presentation for 60 patients with thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).

7-Adjuvant therapy:

There were 38 patients (63.4%) received external radiotherapy, 14 patients (23.3%) received radioactive iodine and 6 patients (10%) received chemotherapy. The rest two patients (3.3%) received radiotherapy in combination with radioactive iodine.

<table>
<thead>
<tr>
<th>The type of adjuvant therapy</th>
<th>Freq</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>38</td>
<td>63.4%</td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td>14</td>
<td>23.3%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>Radiotherapy + radioactive iodine</td>
<td>2</td>
<td>3.3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>60</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Table 10: The type of adjuvant therapy done for 60 thyroid cancer in WMTH&NCI in central of Sudan. (2010-2012).
3.2 Discussion

Thyroid cancer is the most common endocrine neoplasm, and it is estimated that 44,670 new diagnoses of thyroid cancer (10,740 men and 33,930 women) were made in the USA in 2010. This represents nearly a 2.5-fold increase since the early 1970s. The reasons for the increased incidence are unclear, with potential explanations including increased screening, more widespread diagnostic testing of asymptomatic thyroid nodules, changing demographics, and changing environmental risk factors.

Age group & Sex distribution

The hospital based incidence of thyroid malignancy was found to be 0.12% out total number of malignancy. Highest number of patients belong to rural areas (71.7%)(table 4). In our series highest patients were females (76.7%) with overall female to male ration of 3.3:1. In papillary carcinoma female to male ration was 3.2 : 1, follicular carcinoma female to male ration was 2.8:1, anaplastic carcinoma female to male ration was 4.5:1 and in medullery carcinoma female to male ration was 3:1(table 3&7). Lowered incidence of thyroid carcinoma has been reported by WHO in their study reported in anaplastic carcinoma female to male ratio 1.5:1 and in medullery carcinoma occurring female to male ratio 1.2:1. However, the incidence of thyroid cancer is significantly higher in women compared with men. The 2002 GLOBCAN database reports 103,589 female thyroid cancer cases worldwide compared with only 37,424 male thyroid cancer cases, representing a female to male (F:M) ratio of greater than 2:1. This overall increased incidence of thyroid cancer in females is observed across different geographic populations.
with a F:M ratio ranging from 1.44 in Northern Territory, Australia to 7.40 in Granada, Spain, as well as across ethnicities, ranging within the USA from 2.88 in Caucasians to 3.57 in Hispanics. However, this incidence pattern is not observed across all thyroid cancer types. When categorized by histology, the incidence of differentiated thyroid cancer (DTC; papillary thyroid carcinoma [PTC] or follicular thyroid carcinoma [FTC]) is three-times higher in women than in men, while that of anaplastic thyroid carcinoma (ATC) is twice as common in women than men. There is no significant difference in the incidence of medullary carcinomas (MTC) between men and women.\(^{47}\)

Majority of our patients with thyroid carcinoma presented in 4th decade (table 3&7). In our series the overall mean age of presentation (49.9) which is in accordance with the age of presentation of patients described by many other authors.\(^{40,43}\)

In case of follicular carcinoma mean age of presentation in our study is 42.2 years. All cases of anaplastic carcinoma presented after 50 years of age with a mean age of presentation 56.75 years. Mean age of presentation of medullary carcinoma was 60.2 years. WHO reported mean age of presentation of 35 years for papillary carcinoma, 50 year for follicular carcinoma, 45 years for medullary carcinoma and 70 years for anaplastic carcinoma.\(^{2}\)

The increased F:M ratio in thyroid cancer incidence does not remain static with age. Steady decrease in F:M ratio with age continues, and the peak male rate does not occur until between 65 and 69 years of age, compared with the earlier peak female rate between 45 and 49 years of age, just before the mean age of menopause at 50 years.
In reference to historical trends, thyroid cancer incidence has steadily increased overall. Over the period 1973–2002, there was a 2.4-fold increase in age-adjusted rate of incidence of thyroid cancer. However, the F:M ratio has remained fairly constant during this time period, and the rate of increase in incidence in females has been similar, if not slightly higher, than in males.\(^{(47)}\)

In our study follicular carcinoma was the commonest found in 40% followed papillary carcinoma in 35%, anaplastic carcinoma in 18.3% and medullary carcinoma in 6.7%\(^{(table\ 6)}\). Omran reported follicular carcinoma in 42%, papillary carcinoma in 23.3% and anaplastic carcinoma in 21.4\%.\(^{(39)}\) There is a higher incidence of follicular carcinoma than papillary carcinoma in our series which is against the literature, this higher level may indicate environmental or genetic susceptibility.

**Clinical Presentation**

Commonest presenting symptom of thyroid malignancy was swelling in front of neck alone (100%) or associated with other symptoms like hoarseness of voice (31.6%), throat or neck pain (28.3%), dysphagia (26.6%), dyspnoea (26.6%), bone pain (11.7%) and cough (6.7%)\(^{(Figure\ 1)}\). The duration of symptoms in our study ranged from 2 month to 8 years. Anaplastic carcinoma was found rapidly growing tumour and duration of symptoms was only 1-4 months.

Omran showed goitre was the commonest presenting symptom (92.9%). Anaplastic showed a locally aggressive behavior to nearby structures resulting in hoarseness of voice, dyspnoea and dysphagia. Most patients presented with advanced disease limiting the option of total thyroidectomy (40%).\(^{(39)}\)
The site was found bilateral in 40%, Rt. lobe in 30%, Lt. lobe and isthmus in 13.3%, Lt. lobe in 11.7% and Rt. lobe and isthmus in 5% cases (Figure 3). 68% of patients presented with size of the tumor more than 4 cm and 32% between 2 to 4 cm (Figure 2). 60% of patients presented with hard swelling, however, the consistency was firm in 38.15% of patients and cystic in 1.85% (Figure 4). Swelling was found free in 75.93% cases and in 24.07% cases swelling was found fixed (Figure 6). Tenderness was found in 23.3% cases and in 76.6% cases there was no tenderness (Figure 5). Palpable cervical lymph node was found in 36.7% cases and in 63.3% cases there was no palpable lymph node (Figure 7). Which conclude that enlargement of thyroid gland is the commonest mode of presentation; thyroid cancer swelling is usually hard, noduler surface, free and not tender. Clinical examination does not always provide a clue.

Investigations

The international guideline recommend for thyroid nodule evaluation begins by an US exam and TSH+FT4 measurement. With a low serum TSH additional tests are done to rule out hyperthyroidism. When TSH is normal and US shows a suspicious/indeterminate nodule >1.0cm, the next step is US-guided FNA. Most nodules yield benign aspirates and are followed. When cytology is either suspicious or malignant, surgery is recommended.\(^{29}\)

In our series majority of patients were having hemoglobin levels within normal limits. Only three patients were found diabetic and were controlled on oral hypoglycemic drugs. T3, T4, TSH levels were normal in all patients explaining the statement that most of thyroid cancers occur in euthyroid individual. In our study thyroid scan showed solitary nodule 65%, multi nodular 33.3 and diffuse goiter 1.7(Figure 8). Which indicate
that TC is common among solitary nodules and that multi noduler and diffuse goiter has a malignant susceptibility change. None of the patient underwent neck ultra sound, although it is sensitive available diagnostic tool.\(^{(28)}\) In our study FNAC shows follicular neoplasm 35\%, papillary carcinoma 31.7\%, anaplastic carcinoma 18.3\%, medullery carcinoma 6.7\% and benign colloid nodule in 8.3\% (Figure 9); comparable to histopathology; those who did not underwent surgery histopathology was obtained through incisional biopsy or Tru-cut biopsy; which shows (40\%) with follicular carcinoma, (35\%) with papillary carcinoma, (18.3\%) with anaplastic carcinoma and (6.7\%) with medullary carcinoma (table 8). Sensitivity of FNAC in our study was 91.67\% and specificity was 88.95\% which compares well with the published data \(^{(26,27)}\). The problem is that the distinction of benign and malignant follicular neoplasms is difficult to make by FNA, as the crucial criterion for FTC versus (FA) is capsular invasion, which cannot be determined by cytology. In addition, the distinction between FA and Follicular carcinoma (FC) is also difficult, because the crucial criterion here is the aspect of the nuclei.

**Types of surgical intervention**

Surgical therapy for thyroid neoplasms is based on tumor histology and comprises stage-adapted procedures with a high degree of inter-individual variability. This can range from waiting and monitoring, to extensive multivisceral surgery. Grouping together histologically different types of malignancies leads to false assumptions when gauging the radicality of surgery necessary in each particular case. Surgical therapy requires not only an understanding of the biological behavior of the tumour and the risk that it or the therapy poses to the patient, but
also knowledge of a wide surgical spectrum of limited and complex resection procedures in the neck and thorax region.(45)

In management of these patients, (81.7%) patients underwent thyroid surgery. Total thyroidectomy was done in 48.3% patient, lobectomy together with ismthectomy was done in 16.7% patients (table 5). These figures go with the international guide lines. Although in our series all of the patient present with a size of tumour more than 2 cm their were16.7% patient underwent near total thyroidectomy which is not recommended in the international guide lines, for patients with thyroid cancer less than 1cm, the initial surgical procedure should be a near-total or total thyroidectomy unless there are contraindications to this surgery, Thyroid lobectomy alone may be sufficient treatment for small (less than 1cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastasis (29). In our series there were no any patient underwent therapeutic or prophylactic lymph node dissection.

Post operative whole body scan was performed for most of cases in 11.7% patient it showed no activity, bone metastasis in (18.3% patient and metastastic deposit in the lung in 10% patient. The rest 60% patient showed lymph node deposit(table 9).

**Stage of Presentation**

In the stage of presentation we find late presentation is the commonest. Most of the patients had their thyroid swelling for several months or even years, before their presentation for consultation in the casualty. Stage 4 is the most common presentation (48.3%), (11.7%) patients presented with stage 1, (23.3%) patients presented with stage 2 and (16.7%) patients presented with stage 3( Figure 10 ). African present in
a more advanced stage than American and European countries. Hollenbeak showed African had poorer survival from thyroid cancer relative to White patients; this difference may be explained by differences in disease characteristics such as a relatively higher rate of anaplastic thyroid cancer, follicular cancer and larger tumors at presentation.\(^{48}\) This of course is an indication of the better health services in developed countries beside the good health awareness in these areas.\(^{29,48}\)

**Adjuvant therapy:**

NCCN Clinical Practice Guidelines in Oncology: Thyroid Cancer reported treatment depends on the type of thyroid cancer, surgery is most often done. The entire thyroid gland is usually removed. If the doctor suspects that the cancer has spread to lymph nodes in the neck, these will also be removed. Radiation therapy may be done with or without surgery. Patients who are treated for thyroid cancer must take thyroid hormone pills for the rest of their lives. The dose is usually a little higher than what your body needs. This can keep the cancer from coming back.

If the cancer does not respond to surgery or radiation and has spread to other parts of the body, chemotherapy may be used.\(^{29}\)

There were (63.4%) patient received external radiotherapy: for locally advanced tumours in which gross residual was left, grossly positive lymph nodes, and irresectable tumours, it was used also in cases where there were bone metastasis for palliation or to counteract for pain and (23.3%) patient received radioactive iodine: for residual activity detected by post operative whole body scan for ablation, therapy or both,
and (10%) patient received chemotherapy. The rest (3.3%) patient received radiotherapy in combination with radioactive iodine (table 10). Although thyroid cancer represents less than 1% of malignant tumours, its increased incidence detected in recent years and the appearance and development of new drugs targeting specific molecular targets has attracted the attention of the doctors involved in this pathology, especially surgical oncologists. For this reason it is important at this critical point, when treatment may be substantially changed, to establish and agree updated guidelines. These guidelines should incorporate the newly developed strategies that, although still preliminary in evidence level, will surely have an important role, especially in relapsed and refractory tumours, which are unsuitable for surgical or radio-iodine treatment. Particular histological and molecular features of these tumours must be taken into account in order to optimize therapeutic approaches.
CHAPTER FOUR

1.1. Conclusion and Recommendations

4.1.1 Conclusion:

The pattern of thyroid cancer was as follows:

1. The general features of the studied group are mainly elderly females with overall female to male ration of 3.3:1 from rural areas, where medical care is very low. The Overall mean age of presentation (49.9 ± 14), In case of follicular carcinoma mean age of presentation is 42.2 years, Papillary carcinoma mean age of presentation 40.6 years Anaplastic carcinoma mean age of presentation 56.75 years. Mean age of presentation of medullary carcinoma was 60.2 years.

2. Follicular carcinoma (40%) is the most common type of thyroid carcinoma, followed by papillary carcinoma (35%), anaplastic carcinoma (18.3%) and medullary carcinoma (6.7%).

3. Anterior neck swelling is the commonest presentation, followed by hoarseness of voice.

4. Fine needle aspiration cytology in the studied group found to be sensitive diagnostic tool with a sensitivity rate 91.67% and specificity 88.95%

5. Stage 4 is the commonest stage of presentation.
4.1.2 Recommendation

1. Screening for thyroid cancer every 2 years in a female aged 35-50 & with high-risk history; family history of TC and previous neck radiation, Should be encouraged at the level of family medicine.
2. Health professionals should be aware to suspect carcinoma in a solitary thyroid nodules and clinically hard glands so that they can be evaluated at an earlier stage of the disease.
3. The initial treatment of thyroid carcinoma should always be preceded by careful survey of the neck by ultrasound to assess the size of the nodule, the internal texture, the shape, the echogenicity, the margin, the presence of calcification, the presence of adjacent structures and guidance to perform an aspiration biopsy.
4. Fine needle aspiration cytology should be considered as gold standard investigation.
5. Therapeutic lymph node dissection should be performed for patients with biopsy proven metastatic cervical lymph adenopathy.
5.1 REFERENCES

1. Cooper DS, Doherty GM, Haugen BR et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16(2):109-142.


22. Royaux IE, Suzuki K, Mori A et al. Pendrin, the protein encoded by the Pendred syndrome gene (PDS), is an apical porter of iodide in the thyroid and is regulated by thyroglobulin in FRTL-5 cells. Endocrinology 2000; 141(2):839-845.


32. Tala H, Robbins R, Fagin JA, Larson SM, Tuttle RM. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. J Clin Endocrinol Metab. Jul 2011;96(7):2105-11.


APPENDICES

Data Sheet

(A) Personal data

1. Serial No .......................... 2. SEX ............................................. 3. Age ............................................. 4. occupation .................................

5. Residence ..............................

(B) Work up

History:

Ant. Neck swelling?  Y ( ) N ( )

Difficulty in swallowing?  Y ( ) N ( )

Throat or neck pain?  Y ( ) N ( )

Hoarseness of voice?  Y ( ) N ( )

Breathing difficulty?  Y ( ) N ( )

Cough?  Y ( ) N ( )

Bone pain?  Y ( ) N ( )

O/E:

Pallor  Y ( ) N ( ) Jaundice  Y ( ) N ( )

Side of the thyroid swelling  Lt( ) bilateral( ) ismth( ) Rt( )

Size ......................

Consistency  firm ( ) soft( ) hard( )

Tender  Y ( ) N ( )
Freely mobile ( )  Fixed ( )

Palpable cervical lymph node?  Y ( )  N ( )

**Investigation**

CBC : .................................................................

Thyroid function test: ...........................................................

Thyroid scan : .................................................................

Ultrasound : .................................................................

FNAC : .................................................................

Laryngoscope : .................................................................

Ch. XR : .................................................................

Bone scan : .................................................................

( C ) Histological type

| Follicular .......... | Papillary .......... | Medullery .......... | Anaplastic .......... |

(D) Stage

| I ................. | II ............. | III ............. | IV ............. |

(E) Treatment:

Type of Surgery: lobectomy + ismthactomy ( )  Total thy. ( )  Near total thy. ( )

Radiation therapy  ...

Chemotherapy  ...

Thyroid hormone therapy  ...

- 64 -