College of Health Sciences, Department of Internal Medicine, Nuclear Medicine Unit

Patterns of Presentation and Management of Differentiated Thyroid Cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

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ABBREVIATIONS

ATA	American thyroid association
DTC	Differentiated Thyroid carcinoma
ESMO	European society of medical oncology
FNAC	Fine needle aspiration cytology
FTC	Follicular thyroid carcinoma
PTC	Papillary thyroid carcinoma
RAI	Radioactive Iodine
TASH	Tikur Anbessa Specialized Hospital
TNM	Tumor, Node, Metastasis
US	Ultrasound
Tg	Thyroglobulin
TgAb	thyroglobulin antibody

Abstract

Background: Thyroid cancer is one of the most commonly diagnosed endocrine malignancies around the world with the incidence still increasing. In spite of the increasing number of diagnosed cases, the mortality rate has stabilized or even decreased in some countries. This is achieved through the early diagnosis and implementation of effective modes of treatments.

Objective: To assess the patterns of presentation and the management of differentiated thyroid carcinoma patients at Tikur Anbessa specialized hospital from December 2017 to December 2022.

Methods: A Hospital based retrospective secondary data was used where 84 patients with the diagnosis of Differentiated thyroid cancer who attended endocrine surgical Unit of Tikur Anbessa Specialized Hospital from December 2017-December 2022 were included..

Results: 84 participants were enrolled in our study where their age ranges from 14 to maximum of 84 years, mean age was 44.5 ±14.8 years with a female predominance; male-to-female ratio of 1:1.9. Anterior neck swelling was the commonest presentation 58(69%) and risk factor 41(48.8%) for DTC . TNM stages 1&2 were the commonest presentation stages 59.9% with distant metastasis detected in 24(28.5%). Papillary thyroid cancer was detected in 63(75%) and follicular variant in 21(25%) of the cases. Total thyroidectomy was the commonest surgical procedure undertaken with 46.3%. Recurrence was detected in 26(30%). RAI therapy was indicated in 54(64%) cases.

Conclusion: Most of the participants were females and anterior neck swelling was the commonest presentation pattern. Papillary thyroid cancer was the most prevalent cellular type and total thyroidectomy was the procedure of choice in most cases. Radioiodine therapy was indicated in the majority of cases. The detected rate of recurrence was not negligible.

Key words: *differentiated thyroid carcinoma, thyroidectomy, radioactive Iodine therapy, thyroid cancer, Management*

1 Introduction

1.1 Background

Thyroid cancer is a malignant neoplastic disorder that arises from the cells that comprise the thyroid gland, a butterfly shaped endocrine organ located in the anterior neck region just below the thyroid cartilage. The thyroid gland mainly comprises follicular cells & C-cells along with the supporting parenchyma (1).

The papillary and follicular thyroid cancers, together termed differentiated thyroid cancers (DTC), comprise the majority of thyroid carcinomas (85%) and have an optimal prognosis. In fact, their five-year survival rates (>90–95% percent) are among the highest of any type of cancer. The remaining 15% includes the Anaplastic (undifferentiated) thyroid carcinoma, medullary carcinoma, which originates from the c cells of the thyroid gland and rarely, a lymphoma can arise from the thyroid gland (1, 2).

Thyroid cancer can occur at any age, but has a bimodal distribution peaking in the 3rd and 6th decades. Women are affected more than men (3:1)**;** history of DTC in a first-degree relative, exposure to radiation during childhood and rare genetic syndromes are among the known causes and risk factors that are strongly associated with DTC (3, 4).

Painless thyroid nodule is the most common presentation of DTC patients, but patients could present to the primary care physician with all sorts of symptoms ranging from hoarseness of voice to other compressive symptoms like neck fullness, dysphagia, odynophagia, choking, and dyspnea depending on the extent of the disease and the involvement of nearby structures (5).

Diagnostic neck ultrasound (US) should be performed in all patients with a suspicion of a thyroid nodule and is required to describe the characteristics of the thyroid nodule and to assess the cervical lymph node status. Fine needle aspiration (FNA) with cytological examination is the single most important diagnostic tool to detect or exclude DTC and the selection of patients who undergo FNA should be based on the clinical features and the US nodules characteristics.(4) The American thyroid association (ATA) & European society of medical oncology (ESMO) guidelines recommend restricting FNAs to patients with nodules >1 cm, unless there is a high clinical or US suspicion of malignancy. Consequently, performing FNA in nodules <1 cm should strongly consider the clinical context of the patient and critically balance the potential risks and

benefits of subsequent procedures. Therefore, active surveillance is the usually recommended option (6).

In DTC, different staging systems can be used. The tumor, node, metastasis (TNM) classification system is optimized to predict mortality from DTC. Furthermore, the risk stratification proposed by the ATA and ESMO guidelines predicts recurrence, which is a relevant outcome measure in DTC. These staging systems can be used as guidance for initial treatment strategies (4, 6, 7).

Despite recent developments that have questioned some of the traditional treatment strategies, particularly with respect to low-risk DTC, internationally accepted guidelines on the treatment of DTC patients recommend the mainstay treatment strategy for DTC to be a combination of surgery, radio-active iodine (RAI) administration and thyrotropin (TSH) suppression therapy. While extent of the treatment modalities depends on initial and ongoing risk stratification (4,6).

In spite of the increasing incidence of thyroid cancer in the recent decades, it is noteworthy that the mortality rate is stable or declining. The reason for these results is due to better diagnostic accuracy and more efficient treatment of thyroid cancer (8). This is achieved through deploying a multi-disciplinary team (MDT) that comprises different sets of specialty departments that play a crucial role in every step of the management, which extends from the diagnosis to follow-up after treatment of the patient.

1.2. Statement of the problem

In the developed world, mainly in the United States of America, the incidence rate of Thyroid carcinoma has more recently stabilized, although the estimated incidence previously was increasing by an average of approximately 5% annually between 2004 and 2013. The stabilization is likely due to more conservative indications for thyroid biopsy in the recent years. For the United States population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%. It is estimated that approximately 43,800 new cases of thyroid carcinoma will be diagnosed and approximately 2,230 cancer deaths will occur from thyroid carcinoma in the United States in 2022 (2).

In Africa Thyroid cancers are among the fairly well studied endocrine malignancies in the continent and results from review of biopsy specimens indicate that FTCs are sometimes the commonly encountered thyroid neoplasms in some geographical locations where there is an endemic goiter related to the iodine deficiency. And the recent documented prevalence rates of thyroid cancer are (papillary: 6.7–72.1%, follicular: 4.9–68%, anaplastic: 5–21.4%, and medullary: 2.6%–13.8%). For the DTC, there is a changing trend toward the more frequent occurrence of papillary CA compared to follicular CA which might be attributable to widespread iodization programs (9).

The Ethiopian context is also comparable with the rest of the world when it comes to the type of the most prevalent thyroid cancer subtype. According to a research done in 2005 at TASH by (Ersumo. et.al.), the frequency of thyroid malignancy was 7.5% and papillary thyroid carcinoma was the most common histologic type (72%) (10). Another study done at university of Gondar in 2014 (Melak et.al.) also revealed a comparable result with a prevalence of malignancy of 7.3% among a total of 846 thyroid enlarged patients; And papillary thyroid carcinoma was the leading histologic subtype, (45.2%), followed by follicular thyroid carcinoma, (29%), and the least type of thyroid malignancies were medullary thyroid carcinoma and hurtle cell carcinoma, each accounts (1.6%) (11).

Differentiated thyroid carcinomas, the most common forms of thyroid cancer (85%), arise from the follicular cells and usually have an excellent prognosis, with 10-year survival rates exceeding 90%–95% (2). But treating these DTCs can be a challenging task, because until recently, few prospective randomized trials of treatment have been done. There are many controversies

relating to the management of DTC ranging from types and extent of surgery to the use & dose of radioactive iodine and mode of follow-up but despite these controversies, there are a number of prognostic factors associated with thyroid cancer that determine the outcome and these can be further divided into patient, tumour and management factors. Nonetheless, most patients can be cured of this disease when properly treated by experienced physicians and surgeons (2, 8, 12).

According to the ATA 2015 guideline, management of DTC should be individualized based on the risk groups. But generally, the international community has accepted the treatment of choice as surgery, the extent depending on the tumor type, size and involvement, followed by radioactive iodine (RAI) ablation (iodine-131) in selected patients, likewise the dose being individualized based on the indication for the RAI therapy, and thyroxine therapy in most patients (2, 12).

According to the NCCN guideline published in 2022, the decision on the extent of surgery for patients with biopsy proven PTC, whether to choose lobectomy or total thyroidectomy should be made in consultation with the patient beforehand. There are circumstances in which lobectomy should be considered and those include T3 or T4 tumor, N1b disease, M1 disease, and poorly differentiated subtypes. Other factors such as family history, exposure history, and coexistent bilateral thyroid disease may also be considered when making decisions about the extent of surgery. Lobectomy is often a procedure of choice since most studies have found that the extent of surgery is not associated with overall survival for unifocal, cN0, cM0 tumors up to 4 cm in size. However, there are also situations where total thyroidectomy is recommended, that are, T3 or larger, clinical N1 disease, M1, aggressive cellular subtype, significant radiation exposure, significant family history, or coexistent thyroid disease. Of all of these features, tumor size remains to be the most debated upon and is the feature in which there is not uniform agreement (2).

In addition to the surgical approach the wide use of RAI therapy has reduced in the setting of low-risk DTC, but its use and efficacy in reducing recurrence in high risk and selected moderate risk DTC cases is an established fact (4, 6, 7, 12).

Our hospital, TASH, also has long standing record of treating DTC with experienced surgeons and endocrinologists, but due to lack of the RAI therapy the treatment of patients with DTC has never been fully complete. And we believe that DTC can be managed better in our hospital,

TASH, with a well-organized setup and this study will assess the importance of an MDT approach in the management of DTC patients, evaluate the management of DTC patents, and assess the gaps in practice in relation to the internationally accepted guidelines and peer-reviewed journals and their recommendations.

1.3. Significance of the study

DTC, even though rare, is the commonest endocrine malignancy and it has an excellent prognosis if managed well and modern management of differentiated thyroid cancer requires individualized care plans which tailor the intensity of therapy and follow-up to the estimated risks of recurrence and disease-specific mortality. This study will explain how patients with the diagnosis of DTC are being managed at TASH, Addis Ababa, Ethiopia. At the same time the study will assess the overall gaps in the management of DTC at TASH.

In addition, with the ongoing process of restarting the nuclear medicine activity at TASH, we find it necessary to have a new baseline study for evaluating the prevalence and types of DTC. Based on the results from this study, we will be able to demonstrate the magnitude of the positive impact that our unit is going to have in the management of those patients in the form of RAI therapy for the appropriately risk stratified patients.

Furthermore the results from this study will be used as baseline for future studies and utilized as a source of secondary data for other studies related to the topic of interest.

2 LITRATURE REVIEW

2.1 Management of well differentiated thyroid cancer

A 4-year retrospective study was done at Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain on 55 patients who were operated at the ENT department of the hospital with the diagnosis of DTC between 2007 and 2011. In addition, the main objective of the study was to present their experience in the management of DTC. Data was collected from medical records of patients with the diagnosis of DTC after they reviewed the surgical registry of their ENT department. Moreover, patients with the diagnosis of medullary or anaplastic thyroid carcinoma were excluded. The information collected included epidemiological data, comorbidities, forms of presentation, background relating to disease, time passing between diagnosis and surgery, results from fine needle aspiration prior to surgery in accordance with the Bethesda system, type of surgery performed, histological subtype, tumour stage, postsurgical complications, adjuvant treatment with radioactive iodine or radiotherapy, disease-free period and patient survival. The results were; the mean age at time of diagnosis was 49 years, and females predominated (78% of cases). Seventy eight percent of the patients were in stages II and I. The definitive histopathological diagnosis was papillary carcinoma in 84% and follicular carcinoma in the remaining 16%. All of the patients, with the exception of 2 (4%), underwent total thyroidectomy, with lymphadenectomy in 58% of cases. 9% of the patients had permanent hypoparathyroidism and although 18% suffered transitory unilateral recurrent laryngeal nerve paralysis, 40% of these female patients had completely recovered after 6 months. 89% of the patients were given radioiodine postoperatively. There was a recurrence rate of 40% most of which was at cervical level (29% of the patients). Survival at 5 years was 87%, 95% of the papillary subtype, falling to 56% of the follicular subtype (P=.001). And they concluded that the prognosis for differentiated thyroid carcinomas is excellent after appropriate surgical treatment, thorough preoperative assessment, and strict postoperative follow-up due to the significant recurrence rates (14)

Differentiated thyroid cancer (DTC) is the most commonly diagnosed cancer before the age of 30 among women in China. For postoperative DTC patients, metastatic disease is the most frequent cause of death. And radioactive iodine RAI remains a mainstay of therapy for these patients and can be used for thyroid remnant ablation and treatment of expected or proven metastases. For low-risk patients, 131-I with a specific activity between 30 and 100 mCi is often

administered. For high-risk patients, there are three possible approaches to determine the acceptable dose of RAI: a dose based on fixed empirical activity, on the calculation of a maximum tolerated activity, or on quantitative tumor lesional dosimetry. But most physicians in china tend to give a dose with fixed empirical activity. Furthermore, considering that a majority of patients receive inpatient care and will not be discharged from hospitals until residual activity in the body is less than 400 MBq, concerns about public radiation exposure seem to be greatly reduced. Post-therapy 131-I scanning performed approximately 3–5 days after the RAI administration. Following treatment, thyrotropin suppression therapy using levothyroxine is generally recommended while the dose can be individualized (13).

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A Population-based study of all patients who had a therapeutic surgical procedure for thyroid cancer with the objective of describing the variations in practice prior to diagnosis and for the first year after diagnosis, including the investigations, the extent of surgery and the use of RAI 131, for all patients with thyroid cancer treated from Jan 1 2000 to Dec 2008 across Ontario Canada. Data was collected from holdings of the Institute of Clinical Investigative Sciences (ICES) linking the Ontario Cancer Registry to the Ontario Health Insurance Plan and to the Canadian Institutes of Health Information with a study population of 12,957 patients. And the analysis includes comparisons between health care utilization, geographic regions and between treating specialties. Findings showed that, there was a 112% increase in case detection over 9 years. In 37.6% of patients, the initial (index) surgery was less-than-total thyroidectomy (LTT). And 63.4% of the patients who had total thyroidectomy (TT) as an index surgery went on to adjuvant RAI, however there was wide variation in all aspects of patient care across the province, between Local Health Networks and between surgical specialties. The authors concluded that, there was wide variation for most aspects of the management of TC and, as the incidence of TC is increasing at least 7% per year in females, the study provide a foundation for future discussions, the provision of health care services and research (15).

A four year retrospective descriptive hospital-based research done at the National Cancer Institute in Wad Medani, Gezira State-Sudan from September 2016 to September 2020.The main objective of the study was study to investigate the pattern of presentation and management of differentiated thyroid cancer at the center. This research included all patients with differentiated

thyroid carcinoma who presented to the National Cancer Institute Wad Medani. The data collected using a standard structured data collection sheet, was evaluated with SPSS version 24. The results showed that a male-to-female ratio of 1:3.2, and18 of them (24.3%) were in the 41-50 year age category. Sixty-nine (93.2%) of patients presented with anterior neck swelling, whereas 15 (20.3%) reported shortness of breath. Sixty-six (89.2%) of patients had euthyroid status, and forty-nine (66.2%) had multi-nodular findings on ultrasonography, while the lateral compartment of lymph nodes was implicated in 8 (10.8 %) patients, the lateral and central compartments were engaged in 6 (8.1 %) patients, and the rest of the patients had no affected lymph nodes, 60 (81.1 %) had cold nodules on radioisotope scan, and 63 (85.1%) had cold nodules. 20 of the research subjects reported long term goiter, which was found out to be the most prevalent risk factor (27 %). PTC is the most common histological form, accounting for 38.4% of all cases. 41(55%) had a TNM stage-I. The scalp is the first site of metastases 6 (8.1%) in eighteen (24.3%) cases. The 38.4% of the patients had a total thyroidectomy was performed for 38.4% of the patients and it was followed by radioactive iodine therapy in 47.4% of the cases. The authors concluded that early thyroid cancer identification is critical for effective management of differentiated thyroid carcinoma (16).

A retrospective study was done in TASH with plan to present the experience on thyroid cancer of a main central referral hospital during the period 1993-2002. 137 cases of thyroid neoplasms were operated on in TASH, Addis Ababa. But only 114 patient records were retrieved and retrospectively reviewed. Neoplastic disease of the thyroid was found to be more common in younger age groups (mean age, 37 years) and in females (F: M ratio, 1.7: 1.0). Features of advanced malignant disease were not rare (21 cases). Among those patients a thyroid neoplastic disorder, 75 were cases of thyroid cancer; and papillary carcinoma was the most common histologic type (72%). The extent of surgical treatment included partial, subtotal, near total and total thyroidectomy. In 15 cases, the lesions were found to be unrespectable. Due to short follow up, it was difficult to evaluate the long-term outcome of the treatment (10).

2.2 Treatment outcomes of DTC

A 10 year retrospective cohort study was done at Louisiana state university, USA comparing the survival outcomes Following Postsurgical Radioactive Iodine (RAI) Versus External Beam Radiation (EBRT) in Stage IV Differentiated Thyroid Carcinoma. The main objective of the

study was to examine survival in patients with stage IV papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) who received radioactive iodine (RAI), external beam radiation therapy (EBRT), or neither following surgery. Data was collected from the National Cancer Data Base (NCDB) resulting 11,832 patients with stage IV DTC who underwent primary surgical treatment between 2002 and 2012. Patients were stratified by histology and sub-stage. Fully parametric, multilevel survival-time models were used to evaluate survival outcomes in three adjuvant treatment groups: RAI, EBRT, or no adjuvant radiation. Hazard ratios (HR) and time ratios (TR) were calculated against patients who did not receive radiation. All models were adjusted for demographic and clinical factors. The results showed that mean age of all patients was 61.6 years ($SD = 11.6$), and 57.5% were female. Patients who received EBRT had significantly higher 5- and 10-year hazards of death in several PTC sub-stages. For stage IV-B PTC requiring EBRT, lifespan after diagnosis was shortened by a factor of 3 when compared to patients who did not receive radiation. In contrast, RAI was significantly associated with improved 5- and 10-year survival in both PTC and FTC patients regardless of pathological sub-stage. Large reductions in mortality were observed in patients with FTC who were treated with RAI. When patients with stage IV-C FTC were treated with RAI, life-span after diagnosis doubled. The authors concluded that RAI was associated with improved survival for stage IV DTC. Despite treatment benefits conferred by adjuvant EBRT, indications to treat with EBRT were associated with poorer survival outcomes in patients with advanced-stage DTC, particularly PTC (17).

A decade long review of the literature on Differentiated thyroid cancer patients potentially benefitting from postoperative I-131 therapy was undertaken by varburg et al. from August 2007 to December 6, 2017. The main objective of the paper was to report the results of an updated structured review of the literature pertaining to the prognostic benefits of postoperative RIT in DTC in terms of recurrence-free and disease-specific survival. A systematic search of the literature was performed using the Medline and Cochrane Library database. Search terms used included “differentiated thyroid cancer” and “radioiodine therapy” amended by specific terms for recurrence/disease-free survival or overall and/or cancer-specific survival. Included in the search were systematic reviews, randomized clinical trials, or cohort studies consisting of both patients who underwent postoperative RIT and patients treated by surgery alone. Eleven retrospective cohort studies met the defined inclusion criteria and were included in the present review. Results

of the studies were mixed, with some showing a benefit of RIT even in microcarcinoma whereas others showed no benefit at all. And the authors concluded that Literature published in the last decade offers data that support adjuvant postoperative RIT in DTC patients with a tumor diameter exceeding 1 cm. Therefore, at least until randomized prospective studies prove otherwise, the prescription of adjuvant I-131 treatment to all DTC patients with a primary tumor diameter exceeding 1 cm remains a reasonable option (18).

A retrospective study was done in Sestre milosrdnice University Hospital Centre, Zagreb, Croatia with the aim of evaluating Long-Term outcome of Differentiated Thyroid Cancer Patients. The study comprised 1382 patients with DTC and all of the patients were initially treated between the period of 1962 to 2012 and they were followed until April 2020 for a total of 50 years. The study assessed prognostic features of 1167 papillary (PTC) and 215 follicular (FTC) thyroid cancer patients. Age, gender, tumor size, presence of local and distant metastases at presentation, extrathyroidal extension, disease recurrence, and cancer-specific survival were evaluated as possible factors affecting the prognostic outcome of the disease. Findings showed that in a multivariate analysis, factors affecting the worse outcome were age ($p = 0.005$), tumor size ($p = 0.006$), and distant metastases ($p = 0.001$) in PTC, while extrathyroidal extension ($p < 0.001$), neck recurrence ($p = 0.002$), and distant metastases ($p < 0.001$) in FTC patients. Loco-regional recurrence rate was 6% for PTC and 4.7% for FTC patients, while distant metastases were detected in 4.2% PTC and 14.4% of FTC patients. The 10-year cancer-specific survival rates for PTC and FTC were 98.6% and 89.8%, respectively ($p < 0.001$). And they concluded that, negative prognostic factors, besides distant metastases, were older age and greater tumor size in PTC, and extrathyroidal extension and neck recurrence in FTC patients. The recurrence and mortality rates were very low (19).

2.3 Updates on the management of DTC

In October 2016, the American Joint Committee on Cancer published the eighth edition of the AJCC/TNM cancer staging system, replacing the seventh edition, which has been in use since 2009. A review of the major changes in the eighth edition for differentiated and anaplastic thyroid carcinoma was undertaken by Perrier et al. in January 2018. And the major changes as compared to the last edition are as follows; all patients younger than 55 years have stage I disease unless they have distant metastases, in which case their disease is stage II. In patients

aged 55 years or older, the presence of distant metastases confers stage IVB, while cases without distant metastases are further categorized based on the presence/absence of gross extrathyroidal extension, tumor size and lymph node status. Patients aged 55 years or older whose tumor is ≤4 cm (T1-2) and confined to the thyroid (N0, NX) have stage I disease and those whose tumor is >4 cm and confined to the thyroid (T3a) have stage II disease regardless of lymph node status. Patients aged 55 years or older whose tumor is confined to the thyroid and ≤4 cm (T1-2) with any lymph node metastases present (N1a or N1b) have stage II disease; those who demonstrate gross extrathyroidal extension, the disease is considered stage II if only the strap muscles are grossly invaded (T3b); stage III if there is gross invasion of the subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a); or stage IVA if there is gross invasion of the prevertebral fascia or tumor encasing the carotid artery or internal jugular vein (T4b). The same T definitions will be used for both differentiated and anaplastic thyroid cancer but the basic premise of the anatomic stage groups will remain the same (20).

A paper published in Romania with the main objective of assessing the diagnostic value of PET/CT in patients with differentiated thyroid carcinoma (DTC). They enrolled 173 PET/CT scans of DTC cases with elevated thyroglobulin (Tg) levels, negative Tg-antibody, negative Iodine-131 whole-body scanning (I-131 WBS) and with no signs of tumor recurrence or metastases. They reported that 38% of the participants had a positive PET/CT. The sensitivity, specificity, positive predictive values and the accuracy of PET/CT imaging were 88.09%, 98.6%, 93.1% and 96.53% respectively. The investigators concluded that with increased Tg levels and negative I-131 WBS, 18F-FDG PET/CT is a useful imaging tool that can identify cases with thyroid recurrence or metastases. In 89.2% of the positive PET/CT scan cases, the treatment plan was altered, demonstrating the need for 18F-FDG PET/CT imaging in follow-up plans for DTC patients (27).

2.4 Conceptual framework

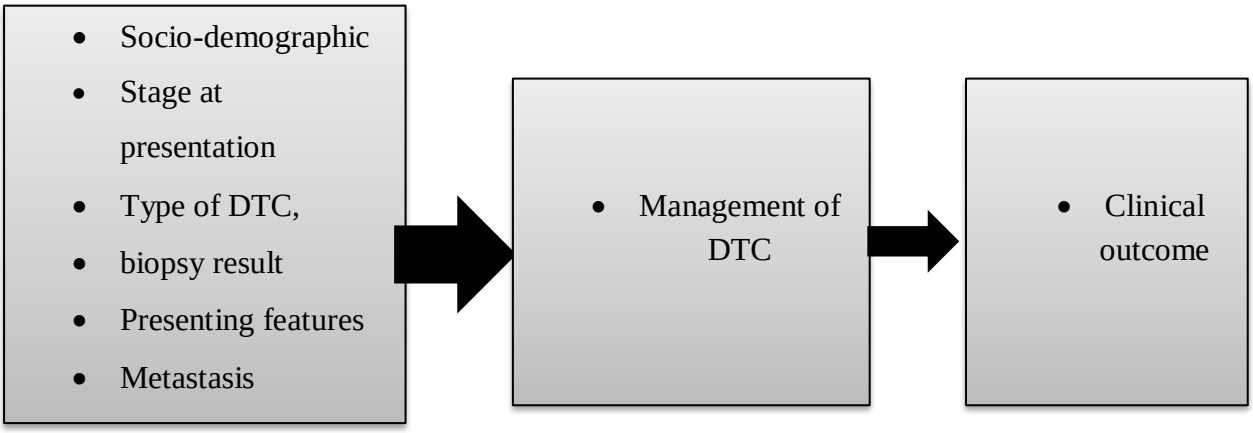

Figure: 1 Conceptual framework for patterns of presentation and management/outcome of differentiated thyroid carcinoma based on review of literatures.

3. OBJECTIVES

3.1. General objectives

To assess the patterns of presentation and the management of differentiated thyroid carcinoma patients at TASH.

3.2. Specific objectives

- To determine the management of differentiated thyroid carcinoma patients at TASH.
- To determine the patterns of presentation of differentiated thyroid carcinoma at TASH.
- To determine the prevalence and types of differentiated thyroid carcinoma cases at TASH.

4. METHODOLOGY

4.1. Study area

The study was conducted in Tikur Anbessa Specialized Hospital (TASH), which is found in Addis Ababa, Ethiopia. Tikur Anbessa specialized Hospital is one of the oldest health institutions in Ethiopia. It is believed to be established in 1972 and became the first site for training Medical Doctors. In 1998, the TASH, the largest referral hospital in the country, with 700 beds, was transferred to the School by the MoH, and it has since become a university teaching hospital. The Tikur Anbessa Specialized Hospital is now the main teaching hospital for both clinical and preclinical training of most disciplines. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation.

The TASH has 200 doctors, 379 nurses and 115 other health professionals dedicated to providing health care services. The various departments, faculties and residents under specialty training in the School of Medicine provide patient care in the hospital. The hospital also has 950 permanent and contract administrative staff to support the hospital activities. In addition, almost all regional and federal hospitals in Addis Ababa are affiliated to the School of Medicine as clinical services and training sites.

4.2. Study period

The study was conducted from August 2022 to February 2023

4.3. Study Design

Hospital based retrospective study design was employed.

4.4. Population

4.4.1. Source population

The source population for this study was all patients referred to the endocrine surgery clinic, at Tikur Anbessa Specialized Hospital from November 2017 – December 2022.

4.4.2. Study Population

The study population of this study was all patients diagnosed and treated for Differentiated thyroid carcinoma (Papillary & follicular thyroid carcinoma) from November 2017 – December 2022.

4.5. Inclusion and Exclusion criteria

4.5.1. Inclusion Criteria

All patients with the diagnosis DTC from the endocrine surgery clinic with full records during the study period were included in the study.

4.5.2. Exclusion Criteria

Patients with other types of thyroid cancer, those with insufficient data were excluded from the study.

4.6. Sample Size determination and sampling technique

4.6.1. Sample size determination

The formula used to determine sample size was as follows:

$$n= \frac{Z2(P)(1-P)}{C2}$$

Where:

n is the required sample size,

P is the percentage occurrence of a state or condition,

C is the percentage maximum error required and
Z is the value corresponding to level of confidence required.

Therefore,

$$n= \frac{(1.96)^2(0.5)(1-0.5)}{(0.05)^2}$$

n= 385

Total population of the study was expected to be less than 10,000; the minimum sample size (n')

Will be obtained by: n'=n/ (1+n/N), Where;

- n’ = Corrected (minimum) sample size
- n= determined sample size
- N= Total number of patients who had been diagnosed and treated for DTC from December 2017 to December 2022.

Total number of patients with DTC from November, 1, 2017 to December, 31 2022 = 152

4.6.2. Sampling Techniques

All the 152 cases of DTC seen at the endocrine surgery clinic from December 2017 – December 2022 were included in this study.

Therefore, by taking the corrected sample size calculated above and there were 68 missed and incomplete records, the final sample size allocated for this quantitative study was 152-68 = 84.

4.7. Data Collection Instruments and Techniques

Data was collected using semi-structured questionnaire. Data source was Patients’ medical records documented on patients’ cards and medical registry. Pretesting of the data collection format was carried out on 5% of the total expected number of patients to be included in the study.

4.8. Variables

4.8.1. Dependent Variables

- Type of surgery
- Indication for RAI therapy

4.8.2. Independent Variables

- Socio-demographic variables
- Stage of the disease at presentation
- Type of DTC
- Degree of cellular differentiation from biopsy result
- Presenting features
- Metastasis
- Risk factors
- Examinations

4.9. Operational Definitions

Diagnosed: Recognized as a disease or condition based on signs and symptom, or other investigation modalities.

Indication: a valid reason to use a certain test, medication, procedure, or surgery.

Risk factor: something that increases the risk or susceptibility of a certain disease or a condition.

Goiter: any swelling in the neck resulting from an enlarged thyroid gland.

Hypothyroidism: low level of the Thyroid hormone (T3, T4) in the bloodstream.

RAI therapy: treatment using radiation emanating from radioactive iodine.

Bethesda score: a standardized, category-based reporting system for thyroid fine-needle aspiration (FNA) specimens.

Total thyroidectomy: removal of the entire thyroid gland.

Near total thyroidectomy: an operation that involves the surgical removal of both thyroid lobes except for a small amount of thyroid tissue.

Subtotal thyroidectomy: a surgical procedure, in which a small thyroid remnant is left in-situ to preserve thyroid function, thereby preventing lifelong thyroid hormone supplementation therapy.

Lobectomy: a surgical procedure by which one lobe of the thyroid gland is removed; sparing the isthmus and the unaffected contralateral lobe.

Isthmusectomy: when the isthmus of the thyroid gland is removed

4.10. Data Quality

Before starting data collection, data collecting format (semi-structured questionnaire) will be cross matched with available information on records; then the study questions will be rearranged if necessary. Daily completeness of the data will be cross checked, if found incomplete, the card

will be reassessed again. Still if it is incomplete after revision, it will be discarded. Data will be collected by principal investigator and junior residents.

4.11. Data Analysis

The extracted data was entered, checked and analyzed using SPSS version 26. The distribution of variables was examined, and the presences of missing data, impossible and extreme values for all variables were evaluated for each objective. Frequencies, proportions and descriptive statistics were used to explain the study population with the relevant variables. All continuous variables were expressed as mean ± SD and categorical variables were expressed as numbers and percentages. The Pearson's chi-square test will be used to determine the associations between categorical variables. P value of less than 0.05 was considered to be statistically significant.

4.12. Ethical Consideration

Ethical clearance was obtained from the Addis Ababa University College of Health Sciences Ethical Clearance Committee and official letter was written to Tikur Anbessa Specialized Hospital to secure permission and the objective of study was explained. Therefore, informed consent for the study wasn't taken from the study subjects. The investigator made sure that the confidentiality of the information was assured in such a way that no disclosure of any name of the patient, the health care provider in relation to the finding was made.

4.13. Dissemination Plan

After the study is completed, the results with their respective discussions, interpretations and recommendations will be prepared into three copies and disseminated to TASH, School of Medicine and the Internal Medicine Department, Nuclear Medicine Unit. Finally, there will be a plan to publish on national or international journals.

5. RESULTS

5.1. Socio demographic characteristics

In our study, 84 patients with differentiated thyroid cancer were enrolled; the majority of them fell into the 31–40 age range, with the minimum and maximum age being 14 and 86 respectively. The mean age was 44.5 (SD ± 14.8). Among the study subjects, the majority were female 55 (65.5%) and 29 (34.5%) male patients. With M:F ratio of 1:1.9 (fig.1). Most of the study participants were from urban area with 69 % (n=58) and the rest 26(31%) were from rural areas. (Table1).

Table1. Socio-demographic characteristics

Characteristics	**No (%)**
Age group (in years)	
10-20	4 (4.8)
21-30	13 (15.4)
31-40	23 (27.4)
41-50	17 (20.3)
51-60	17 (20.3)
61-70	5 (5.9)
>70	5 (5.9)
Sex	
Female	55 (65.5)
Male	29 (35.5)
Residential area	
Urban	58 (69.0)
Rural	**26 31.0)**

5.2. Initial presentation and risk factors for differentiated thyroid carcinoma

In 58 (69 %) of the patients, anterior neck swelling was the most common presentation. Dyspnea was observed in 11(13.1%) of the patients, and Pain with anterior neck swelling was reported in 7 (7.1 %) of the patients. Dysphagia/odynophagia and hoarseness of voice were found to be the 4th and 5th commonest presentation features with 5 (6%) and 4 (4.8 %) patients (Table 2).The primary risk variables encountered were long-standing goiter (n=41; 48.8%), previous history of thyroid cancer (n=13; 15.5%), and family history of thyroid cancer (n=1; 1.2%), while the remaining 29 patients (34.5%) did not have any risk factors that could be identified (Table 2).

Table2. Initial presentation and risk factors for differentiated thyroid cancer

chief complaint		
	Frequency	Percentage %
Anterior neck swelling	58	69.0
Dyspnea	11	13.1
Dysphagia/odynophagia	5	6.0
Hoarseness of voice	4	4.8
Pain with swelling	6	7.1
Total	**84**	**100.0%**
Risk factors		
	Frequency	Percent
Goiter	41	48.8
Prev. hx	13	15.5
Family history	1	1.2
No risk found	29	34.5
Total	84	100.0

5.3. Investigations, cellular type and staging of differentiated thyroid cancer patients

All patients who were referred to the endocrine surgical unit were investigated well; with all 84 of the study subjects underwent ultrasound risk stratification and an FNAC cellular confirmation

of the neoplastic growth; but the Bethesda score was not found in any of the pathology reports. Thyroid scan was not performed for any of the patients in the study**.**

The commonest cellular sub-type of differentiated thyroid cancer among the participants was papillary thyroid carcinoma, comprising 63(75%) of all the patients under the study and follicular thyroid cancer was detected in 21(25%) (figure2).

In a total of 58 patients who were in the age group of < 55 years, Stage I, which represented 34 patients (or 58.6%), was the most common stage. 12 (20.7%) had distant metastasis (TNM stage 2) and the TNM staging of 12 patients (20.7%) couldn't be identified due to incomplete registry information in the patients' medical records. Whereas in those within the age group of > 55 years 26(30.9%), stage 4 (46.1%) was most common presentation. Which is followed by stage 3(34.6%) and both stage 1 and stage 2 accounting for 7.6% of the study subjects in this age category (Table 3).

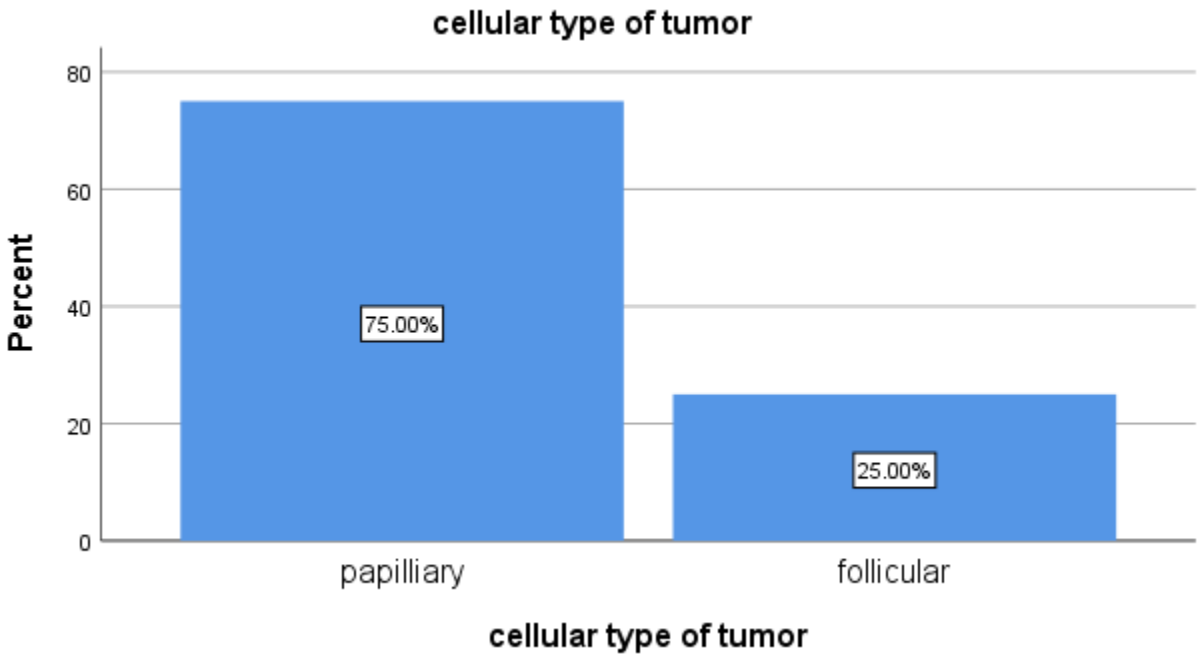

Figure2. Cellular sub-type of DTC

Table3. TNM staging of study subjects

TNM stage					
	TNM stage 1	**TNM stage 2**	**TNM stage 3**	**TNM stage 4**	**Stage unknown**
Age <55 years	34	12	NA	NA	12
Age >55 years	2	2	9	12	1
Total	36	14	9	12	13

NA: not applicable

5.4. Treatment and post-surgical complication

The time between the FNAC diagnosis of the differentiated thyroid neoplasm and the definitive management with surgery was not well documented in nearly 50% of the patients. In the well documented cases, the minimum time was 30 days and the maximum time lapse between the diagnosis and surgery was 485 days. The mean waiting time between diagnosis and surgery was 113.12 days.

The majority of patients (46.4%) underwent a total thyroidectomy, 15 (17.9%) underwent near-total thyroidectomy, 11 (13.1%) underwent a completion thyroidectomy, 2 (2.4%) underwent Lobectomy, and finally debulking surgery & sub-total thyroidectomy being the least performed surgical procedures accounting for only 1 patient each. In our study, 15 (17.9%) patients had un-resectable tumor for reasons of local invasiveness, an already metastatic disease or other co-morbidities that deemed the patient unfit for surgery.-(fig.3)

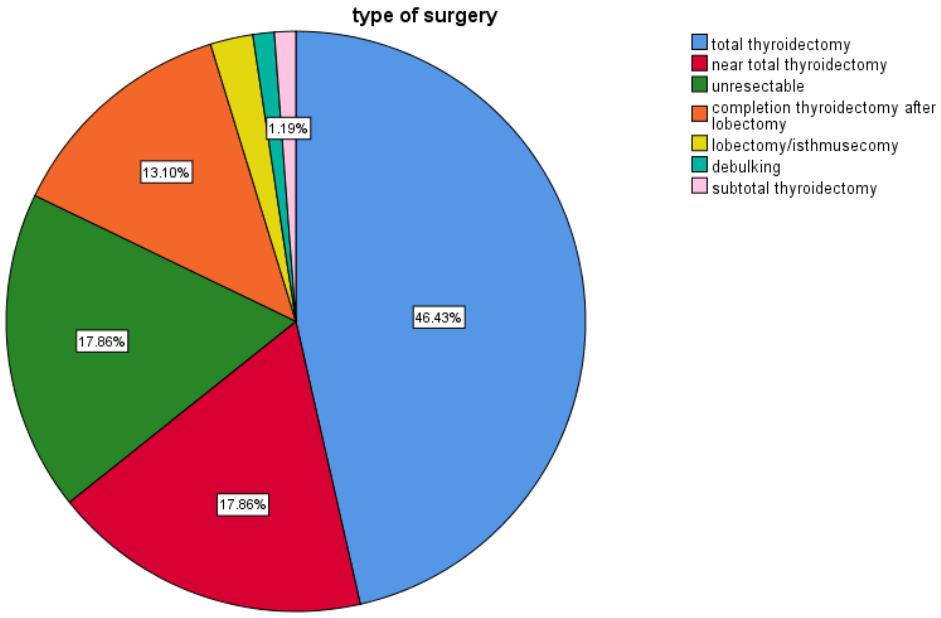

Figure3. Type of surgery

Among the post thyroidectomy complications, Hypothyroidism was found to be the commonest with a total of 31(36.9%) study subjects followed by vocal cord paralysis which was found in 21(25%) subjects. Hypoparathyroidism was detected in 12(14.3%) patients. The post-surgical hormonal status was unknown in 19 patients for thyroid hormone and in as much as 56 patients in case of parathyroid hormone profiles (Table 4).

Table 4. Post-thyroidectomy complications

Post-surgical complications			
	Frequency	Percent (out of 84 patients)	Status unknown
Hypothyroidism	31	36.9	19
Hypoparathyroidism	12	14.3	58
Vocal cord paralysis	21	25.0	0
No complication	8	9.5	-

5.5. Post-surgery follow up, rate of recurrence and indication of RAI therapy

Among the study subjects 59 (70.2%) are currently being followed whereas 25(29.8%) of the patients in our study are lost to follow-up. During the patient follow-up evaluation, Thyroglobulin measurement was only found once among our study subjects. Cancer recurrence was detected in 26(30.9%) of the patients under study and was confirmed with FNAC.

64.3% (n=54) patients in the study had a definite indication for Radioiodine therapy, whereas 22(26.2%) of the patients had no indication for RAI therapy. On the rest of the patients (8(8.5%)), the indication for RAI couldn't be well identified due to some incomplete registration of patient information. (Table5).

Table5. Follow-up, recurrence and RAI indication

Currently on follow-up		
	Frequency	Percent
Currently on follow-up	59	70.2
Not on follow-up	25	29.8
Total	84	100.0
Indication for RAI		
	Frequency	Percent
Yes	54	64.3
No	22	26.2
Couldn't be evaluated	8	9.5
Total	84	100.0
Cancer recurrence		
	Frequency	Percent
Recurrence detected	26	30.9
No recurrence	58	69.1
Total	84	100.0

6. DISCUSSION

In this study, the initial presentation patterns, risk factors, diagnostic procedures, the management procedures, and follow-up was assessed from medical records of DTC patients who visited the endocrinology surgical unit of TASH from December 2017-december 2022.

Among the 84 patients who participated in the study, it was found out that females were more likely to develop differentiated thyroid cancer than males with a male-to-female ratio of 1:1.9 which was consistent with other studies that have been undertaken previously in Ethiopia and also in other parts of the world. In 2005 Ersumo *et al.* published a comparable result of a M:F ratio of 1:1.7. According to a Sudanese study by Mahjoub *et al*, the male-to-female ratio was 1:3.2. Another study conducted by Fernandez et.al.in Spain showed that DTC predominantly occurred in females (78%). The reason for the increased risk of DTC predominance in females, Lupoli *et al* suggested that female cancer risk may be influenced by hormonal or reproductive variables such as frequency of pregnancy and estrogen therapy (8, 10, 14, and 16).

In our study majority of the participants 40 (47.6%) fall in the age group of 30-50. The mean age of our participants was 44.5 & with an age range of (15-86).This was comparable to a finding by Mahjoub *et al,* who reported a majority of patients (45%) between. the ages 40 to 60. Fernandez et al reported a similar result with an age range (15-89) and mean age of 49 years (14, 16).

In our study group, the most prevalent symptom was anterior neck swelling, which was reported by 69 % of the patients, followed by shortness of breath in 20.3% and pain with an anterior neck swelling being the third commonest presentation pattern with 7.1%.

A long standing goiter was found out to be the commonest risk factor associated with DTC in our participants. Family history of thyroid cancer was found in only 1 participant. 29(34.5%) had no risk factor for DTC. This was consistent with a finding by Mahjoub *et al*, who reported 27% of participants with long-term goiter as their primary risk factor. Goiter is a quite common endocrine disorder in our country and this could be the reason for the higher frequency of long standing goiter as a primary risk factor for DTC among our participants. This can also be evidenced by Apostolou K *et al.*, who reported a strong association between incidence of thyroid cancer and goiter (14, 16, and 26).

All our study participants were investigated with an anterior neck ultrasound with lateral neck compartment evaluation for lymph nodes along with a cytological characterization of the nodules with a following FNAC. This is consistent with the recommendations of most standard guidelines which suggest the scoring of the findings on both the imaging and cytological findings for risk stratification purposes, which is important in the management planning of patients with DTC. In our findings, cytological scoring (Bethesda scoring) was missing from the medical records of our participants (2, 6, 7, and 20).

Regarding the biopsy results of our study participants, PTC (75%) was by far the commonest type of DTC and FTC accounting for the remaining 25%, which matched a previous study conducted at TASH by Ersumo *et al* with 72% PTC and Melak *et al* that reported a PTC (45.2%) and FTC (29%). Another study consistent with our finding was a review by Ogebra *et al*, which reported that a changing trend of PTC predominance over the FTC (35.7% vs. 24.8%) in studies from western Africa. In contrast to our finding, Yisihak S. *et al* reported a finding of a predominantly follicular neoplasm of 54% and a PTC of 20%, study conducted at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia (9, 10, 11, and 22). Even though it is missing from our findings, cellular grading is an important factor that is used in the risk stratification, management planning and prognostication of patients with DTC according to accepted guidelines (6, 7, and 20).

The majority of our study participants were in early stages I-II (59.5%) and 24 (28.5%) participants in both age groups of less than and greater than 55 years showed distant metastasis. This result was comparable with findings by Mahjoub *et al*, which showed that the majority of cases (51%) falling under stages I and II. They reported 21% of their participants presented with distant metastasis, which was a bit lower than our finding. In our study, we used the latest TNM-AJCC approach, which takes into account factors such as the tumor size, the presence and degree of extra-thyroidal invasion, the number of nodal metastases, and presence of distant metastasis. We found it difficult to accurately stage 13 (15.5%) participants due to missing parameters that are essential for the chosen approach of staging (16).

Total thyroidectomy was the most frequent procedure done with 39 (46.4%) cases followed by near-total thyroidectomy and completion thyroidectomy with 17.9% &13.1% respectively. Our finding of total-thyroidectomy being the most commonly performed procedure among DTC

cases is in line with Bhansali *et al*. who reported an 84% of total thyroidectomy among their participants. Another study by Enewold *et al*. matched our result with total thyroidectomy performed in 86.1% low- risk & 89.7% high-risk differentiated thyroid cancer cases (5, 24).

Regarding the post-surgical complications, Hypothyroidism was detected in the majority of the participants 31(36.9%), followed by vocal cord paralysis in 21(25%) patients. Hypoparathyroidism, which was assessed in the form of serum hypocalcaemia, was detected in 12(14.3%) participants. An Ethiopian study by Suga *et al*. reported Transient hypocalcaemia (3.2%) and hoarseness of voice (1.8%) as the commonest post thyroidectomy complications. Fernandez et al. reported a 36% incidence of post thyroidectomy hypoparathyroidism and 18% incidence of unilateral recurrent laryngeal nerve injury, which was temporary. In our study, 58(69%) participants' parathyroid hormone panel was missing from their medical records; this was also the case in 19 patients, whose thyroid hormone panel was missing suggesting either the panels are not done or it was not compiled into the medical records (14, 22).

59(70%) of the study participants were on follow-up during the evaluation of the medical records and recurrence of cancer was detected in 26(30%) of the participants this was a lower when compared to a study by Fernandez *et al*. who reported a 40% recurrence. The main reason for the relatively lower recurrence rate could have been due to the loss of patients, after the surgical management, to other referral clinics for follow up and we only included those patients at the endocrine surgery unit. In our study, a multivariate analysis was done between recurrence and indication for RAI therapy, but no significant correlation was found. Thyroglobulin measurement was done for single participant it was 1.0 ng/dl. This was in contrast to publications regarding the use of serial Tg measurement as a follow-up tool for patients who had undergone a total or near total thyroidectomy. Johnson et al. concluded in their study that the currently used strategies in the follow-up of patients rely primarily on serial serum thyroglobulin measurements combined with cervical ultrasonography & FNA biopsy of suspicious lesions. Baudin *et al* suggested that a rise at two consecutive measurements of thyroglobulin should be interpreted as disease progression and a reduction being attributed to late effects of treatment. Lupoli *et al*. recommended RIA methods are more appropriate modalities in the presence of TgAbs that interfere in the measurement of Tg level. (8, 14, 23, and 25)

Patients' indication for RAI therapy was assessed in accordance with the widely accepted guidelines (AMES & MACIS CRITERIA) on the management and risk stratification of DTC and 54(64.3%) of our participants had clear indications for post-operative RAI therapy but it was impossible to evaluate the radioiodine uptake of the tumors since pre-op RAI uptake was not done for any of our participants (7, 12, 18, and 20).

7. Strength and Limitation of the Study

7.1. Strength of the study

One of the strengths of this study is that the data was collected from multiple sources (medical records and medical registries) gathering as much clean data as possible.

This research will be a baseline for future studies on the DTC and update data from the last study published from TASH back in 2005.

7.2. Limitations of the study

Since it is a retrospective study, much data was lost in the span of 5 years, making the interpretation of some of the variables difficult.

The sample size was small due to exclusion of possible participants from the study population due to incompleteness of data on their medical records.

8. Conclusion & Recommendations

8.1. Conclusions

In conclusion, differentiated thyroid carcinoma was more common in females than males and most patients were in their 3rd &4th decades of their lives. Anterior neck swelling was the commonest form of presentation pattern followed by shortness of breath. A long standing goiter was found to be the most frequent risk factor reported. Ultrasound and FNAC were used as initial investigative modalities.

Total thyroidectomy was the commonest procedure performed for our participants followed by near-total thyroidectomy and completion thyroidectomy. Papillary thyroid cancer was by far the commonest subtype of DTC. Hypothyroidism was the most frequent post-op complication encountered followed by vocal cord paralysis and hypoparathyroidism. Follow-up of patients was revealed a recurrence rate of 30%. RAI therapy was indicated in the majority of our study participants.

8.2. Recommendations

To surgical OPD staff and health professionals at TASH

- The socio-demographic characteristics, clinical information and results of imaging and invasive procedures of patients should be recorded completely based on the format.
- A detailed & proper documentation of the intra-op and immediate post-op findings should be practiced.
- We recommend the utilization of a less invasive procedure for appropriately risk stratified case, as it is associated with less post-op complications.
- We recommend the addition of serial thyroglobulin as a follow-up parameter for patients with total/near-total thyroidectomy.
- We recommend the use of Radioiodine as an adjuvant therapy modality for the properly risk stratified patients.
- Increase of nuclear medicine awareness among medical doctors, continuing medical education to practicing clinicians and development of national guidelines for the management of thyroid cancer in Ethiopia should be done.

- Finally we would like to recommend a multi-disciplinary team approach in the management of patients with DTC which includes the surgeon, an endocrinologist, a radiologist, a pathologist, a nuclear medicine physician & an oncologist.

To pathology department at TASH

- A complete report on the cellular differentiation, neurovascular involvement of tumor and proper scoring of specimens should be practiced routinely. As it is an essential part of risk stratification and management planning in patients with differentiated thyroid malignancy.

To nuclear medicine unit at TASH

- Thyroglobulin measurement using RIA techniques should be restarted along with the other nuclear medicine activities as soon as possible since it is the core part of managing patients with DTC.
- A research on clinician's awareness and knowledge on the management of DTC and the use of RAI in Ethiopia should be done

Federal Ministry of Health (FMoH)

- FMoH should give emphasis on the application of nuclear medicine in the management of DTC and create programs to increase clinician's knowledge about nuclear medicine services.

- FMoH should also work on expanding and strength of nuclear service in Ethiopia.

For future studies

- Future studies, a larger sample size and a longer follow-up time are needed to better understand the patterns of presentation and the management of differentiated thyroid carcinoma patients

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10. Annexes

10.1. Semi-structured data collecting format

1. Socio demographic characteristics of the patients
   - Age (years) _____
   - Sex -- M ☐ F ☐
   - Marital status……Single ☐ Married ☐
   - Location……..Urban ☐ Rural ☐
   - Level of education
2. Chief complaint at presentation
   - Anterior neck swelling ☐
   - Dyspnea ☐
   - Dysphagia/Odynophagia ☐
   - Hoarseness of voice ☐
   - Other ☐
3. Risk factors
   - Goiter…… yes ☐ no ☐
   - Family history ……..yes ☐ no ☐
   - Radiation history ……..yes ☐ no ☐
   - Smoking …….yes ☐ no ☐
4. Investigation results
   - Ultrasound – yes ☐ no ☐
   - Thyroid scan …..yes ☐ no ☐
   - FNAC …….yes ☐ no ☐
     - Bethesda score _____
5. Time between diagnosis (FNAC diagnosis) and surgery (days) _____
6. Type of surgery
   - Total thyroidectomy ☐
   - Near-total thyroidectomy ☐
   - Lobectomy/isthmusectomy ☐
7. Tumor type and TNM staging (biopsy result)

- Cellular type …….Follicular ☐ Papillary☐
- cellular differentiation
  - Low grade ☐
  - Intermediate grade ☐
  - High grade ☐
- TNM staging _____
- If possible ……..T_____, N_____, M_____

8. Post-surgical complications (long-term)
   - Hypothyroidism ……yes ☐ no ☐ status not known ☐
   - Vocal cord paralysis……. yes ☐ no ☐
   - Hypoparathyroidism (hypocalcemia or low parathyroid level)
     Yes ☐ no ☐ status not known ☐

9. Currently on follow up ……yes ☐ no ☐

10. Recurrence ……yes ☐ no ☐

    - Thyroglobulin level _____

11. Indication for RAI therapy yes ☐ no ☐

DECLARATION

I, the undersigned, declare that this thesis is my original work, has not been presented for a degree in Addis Ababa University or any other universities. I also declare that all sources of materials used for the thesis have been duly acknowledged.

Name of the candidate: Dr. Kirubel Tesfaye Teklu

Signature: _____

Place: Addis Ababa University, Addis Ababa, Ethiopia

Date of Submission: _____

The thesis has been submitted for examination with my approval as University Advisors.

	Name	signature	Date
1.	_____	_____	_____
2.	_____	_____	_____