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Disease Characteristics and Management Outcome of Patients with Pheochromocytoma In Tikur Anbessa Specialized Hospital Follow-Up Clinics: A 10-Year Retrospective Review

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ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE

Disease Characteristics and management outcome of patients with Pheochromocytoma in TASH Follow-up clinics

A 10-year Retrospective Review

A thesis submitted to Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University for the partial fulfillment of the requirements for the Specialty certificate in internal Medicine

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Disease Characteristics and management outcome of patients with Pheochromocytoma in Tikur Anbessa Specialized Hospital: Endocrine and Surgical referral clinics: A 10-year Retrospective Review

Addis Ababa University

School of Graduate Studies

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Acronyms

AAU: Addis Ababa University

AOR: Adjusted odds ration

ANOVA: Analysis of variance

COMT: catechol-o-methyltransferase

COR: Crude odds ratio

CT: Computed Tomography

DOPA: dihydroxyphenylalanine

HMIS: Health Management Information System

HVA: dopamine to homovanillic acid

ICU: Intensive Care Unit

L: Liter

MAO: monoamine oxidase

Mcg: Microgram

MEN2: multiple endocrine neoplasia type 2

MIBG: metaiodobenzylguanidine

MRI: Magnetic Resonance Imaging

NF1: neurofibromatosis type 1

Nmol: nanomole

PHEO: Pheochromocytoma

RET: REarranged during Transfection

SDHB: Succinate Dehydrogenase Complex Iron Sulfur Subunit B

SDHC: Succinate Dehydrogenase Complex Subunit C

SDHD: succinate dehydrogenase complex subunit D

TASH: Tikur Anbessa Specialized Hospital

USA: United states of America

VHL: Von Hippel Lindau

VMA: Vanillylmandelic acid

Abstract

Background: Pheochromocytomas are catecholamine-secreting tumors, the majority of which arise from the adrenal medulla. Untreated, they are potentially lethal; early diagnosis and treatment offer a good chance of cure. It accounts for 0.2% of patients with Hypertension in western world. Limited data exists regarding pheochromocytoma in developing world. Knowing disease characteristics and presentation in this unstudied population helps to diagnose pheochromocytoma early.

Objectives: The objective of this study was to review the disease characteristics and management outcome of patients with pheochromocytoma among patients who were evaluated in Tikur Anbessa Specialized hospital, Addis Ababa Ethiopia over a 10-year period.

Methodology: Institution based retrospective cross sectional study design was used and all patients with pheochromocytoma evaluated from 2010 to 2020 medical records were reviewed, pertinent data was collected and analyzed using SPSS 26. Frequency tabulation, Chi square test, bivariate and multivariate logistic regression and Pearson correlation were used to study the relationship among different variables.

Results: Twenty-eight patients were included in the study, of which 43% were male and 57% female. The mean age was37 years (range 16–67). Incident of diagnosis was after the patients were symptomatic in 75% of patients and after incidental discovery of adrenal mass in 25% of patients. The median tumor size was 6 cm, and mean of 5.8±1.6cm, 30% were larger than 6 cm. 75% were located in the adrenal gland (n=21, 71% unilateral, 3.6% bilateral), and 21.4%(n=6) were extra-adrenal. The most common extra adrenal site was intra-abdominal paraganglioma (n=4, 14.3%). There were 3 patients (10.7%) with malignant pheochromocytoma as suggested by imaging features and recurrence. Clinical diagnosis of pheochromocytoma associated genetic syndrome was made in 3(10.7%) patients, MEN 2a in two patients and vHL in one patient. Surgical cure rate among symptomatic pheochromocytoma patients was 93.5% (n= 15). Although No significant predictor of risk of malignancy or risk of recurrence was found in this study, the trend was towards higher risk of recurrence for patients who are male and symptomatic at the time of diagnosis with extra adrenal location of the tumor. On the other hand, being not operated was associated with

increased risk having persistent symptoms (AOR: 58 P value: 0.006) and being older age at diagnosis (AOR: 0.7 P value: 0.04) was associated with decreased risk.

Conclusion and recommendation: Majority of patients with pheochromocytoma are symptomatic with classic symptoms, targeted screening with goal of early detection and surgical management is recommended. Large scale study with prospective follow up is necessary to known the burden of this rarely reported potentially malignant neoplasm.

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1. Introduction

A Pheochromocytoma is a tumor arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines: epinephrine, norepinephrine, and dopamine[1].

Dopamine, norepinephrine, and epinephrine are physiologically active molecules known as catecholamines. Catecholamines act both as neurotransmitters and hormones vital to the maintenance of homeostasis through the autonomic nervous system. Physiologic principles of catecholamines have numerous applications within pharmacology. Pheochromocytoma is a catecholamine-producing neoplasm relevant to clinical medicine[2].

Catecholamine synthesis within the adrenal medulla is controlled by serum concentration of the amino acid tyrosine. Tyrosine undergoes hydroxylation via tyrosine hydroxylase to form DOPA, which then undergoes decarboxylation to dopamine. Dopamine may be secreted into the bloodstream or undergo further hydroxylation to norepinephrine (noradrenaline). Norepinephrine can be secreted into the bloodstream or further modified by a methyltransferase to epinephrine (adrenaline) and then secreted. Glucocorticoids notably upregulate methyltransferase activity to increase epinephrine production. Degradation of catecholamines to their metabolites occurs either by monoamine oxidase (MAO) located in the outer mitochondrial membrane of the cell and/or by catechol-o-methyltransferase (COMT) found within the cytosol of the cell. MAO and COMT catabolize norepinephrine and epinephrine to vanillylmandelic acid (VMA), and dopamine to homovanillic acid (HVA). VMA and HVA are excreted in urine[2].

The “fight or flight” response of the sympathetic nervous system is a direct result of the multisystem action of catecholamines. Secretion from the adrenal medulla proceeding the activation of the sympathetic nervous system functions to regulate blood pressure by contracting the smooth muscle in the vasculature (via alpha-1 receptors). The adrenergic receptors linked to blood vessels have an especially high affinity for norepinephrine relative to the other amines. Further musculoskeletal actions of catecholamines include enhanced contractility of cardiac muscle (via beta-1 receptors), contraction of the pupillary dilator (via alpha-1 receptors), piloerection (via alpha-1 receptors), and relaxation of smooth muscle in the gastrointestinal tract, urinary tract, and bronchioles (via beta-2 receptors). Both epinephrine and norepinephrine modulate metabolism to increase blood glucose levels by stimulating glycogenolysis in the liver

(via beta-2 receptors), increased glucagon secretion (via beta-2 receptors) and decreased insulin secretion (via alpha-2 receptors) from the pancreas, and lipolysis in adipose tissue (via beta-3 receptors). Epinephrine also inhibits release of mediators from mast cells and basophils in type I hypersensitivity reactions[2].

After an external stimulus triggers the body's stress response, the pituitary-adrenal axis and sympathetic division of the autonomic nervous system is activated. Glucocorticoids production increases in the adrenal cortex, and acetylcholine (Ach) is released from sympathetic splanchnic nerves. Ach binds to nicotinic receptors located on the membrane of chromaffin cells in the adrenal medulla. These receptors promote exocytosis of catecholamine-filled vesicles for transport in the bloodstream. In the blood, catecholamines target alpha and beta-adrenergic receptors, a family of g protein coupled receptors (GPCRs). These alpha and beta receptors can be further subdivided and subtyped with alphanumeric designation based on their cellular localization. The adrenergic receptors utilize either cyclic adenosine monophosphate (cAMP) or phosphoinositol second messenger systems to activate ion channels that ultimately mediate the body's sympathetic response[2].

Of the several types of neoplasms arising from the adrenal gland, pheochromocytomas are tumors of the adrenal medulla responsible for unregulated secretion of catecholamines. Pheochromocytomas are particularly dangerous due to overactivation of adrenergic receptors which cause episodes of hypertensive urgency. Patients with pheochromocytomas also may experience episodes of other uncomfortable sympathomimetic symptoms including palpitations, sweating, headaches, or anxiety[3].

Rarely, these tumors are biochemically silent. A paraganglioma is a tumor derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. Paragangliomas also arise from parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull. About 80 to 85% of chromaffin-cell tumors are pheochromocytomas, whereas 15 to 20% are paragangliomas[4].

Statement of the Problem

The burden of pheochromocytoma is not well studied in low- and middle-income countries. In limited studies available, the disease characteristics are somehow different from what is reported from western countries.

Significance of the study

This study would add knowledge to the lacking evidence about the disease characteristics and management outcome of pheochromocytoma in Ethiopia specifically and in low- and middle-income countries at large.

2. Literature Review

Epidemiology and clinical presentation

Multiple studies were conducted in different parts of the world to evaluate the epidemiology, clinical and imaging characteristics and management outcome of patients with Pheochromocytoma and paraganglioma.

The prevalence of pheochromocytoma in patients with hypertension in general outpatient clinics is less than 0.2%.[5] The estimated incidence of pheochromocytoma and paraganglioma is about 0.6 cases per 100,000 person-years[6]. Nearly 5% of patients with incidentally discovered adrenal masses on anatomical imaging prove to have a pheochromocytoma[7].

Although pheochromocytomas may occur at any age, they are most common in the fourth to fifth decade and are equally common in men and women[8].

Symptoms are present in approximately 50 percent of patients with pheochromocytoma, and when present, they are typically paroxysmal. The classic triad of symptoms in patients with a pheochromocytoma consists of episodic headache, sweating, and tachycardia. Approximately one-half have paroxysmal hypertension; most of the rest have either primary hypertension or normal blood pressure. Most patients with pheochromocytoma do not have the three classic symptoms, and patients with primary hypertension may have paroxysmal symptoms[9].

In a study done to assess the magnitude of Pheochromocytoma among hypertensive patients in Brooklyn university hospital, New York, USA; Among 4,180 patients with essential hypertension encountered during a 42-month interval, 8 had pheochromocytoma. The most common clinical findings were diaphoresis, chest or abdominal pain, palpitations, headaches, and nausea. Clinical features were remarkable only for the significant correlation between urinary excretion of vanillylmandelic acid and tumor volume. Only one patient, with a history of medullary thyroid carcinoma, had multiple endocrine neoplasia[10].

On rare occasions, patients present with a condition termed pheochromocytoma crisis, or pheochromocytoma multisystem crisis. These individuals may have either hypertension or hypotension, hyperthermia, mental status changes, and other organ dysfunction[11].

Less common symptoms and signs include orthostatic hypotension, visual blurring, papilledema, weight loss, polyuria, polydipsia, constipation, increased erythrocyte sedimentation rate, insulin resistance, hyperglycemia, leukocytosis, psychiatric disorders, and, rarely, secondary erythrocytosis due to overproduction of erythropoietin. Rarely, pheochromocytoma is associated with cardiomyopathy attributed to catecholamine excess that is similar to stress-induced (takotsubo) cardiomyopathy[12].

At least one-third of all patients with pheochromocytoma have disease-causing germline mutations. The prevalence of pheochromocytoma in individuals carrying a germline mutation in pheochromocytoma susceptibility genes may be around 50%.Patients with hereditary pheochromocytoma typically present with multifocal disease and at a younger age than those with sporadic neoplasms[13].

In a study evaluating the need for genetic screening for patients presenting with sporadic pheochromocytoma in France, among one hundred patients with a pheochromocytoma-only phenotype and no family history, a germline mutation in one of the five susceptibility genes (VHL, RET, SDHD, SDHC, SDHB) was identified in eight patients (8%) with an age of onset between 13 and 57 years. Among them, six had a bilateral pheochromocytoma and only two had a unilateral tumor. According to this study, If the guidelines for genetic screening were age of onset less than 50 or bilateral pheochromocytoma, no patients with a hereditary tumor would be missed and a 24% cost reduction would be achieved. It also showed that a genetic predisposition test for hereditary pheochromocytoma seems not recommended in patients with a unilateral adrenal tumor diagnosed after 50 in the absence of familial, clinical, biological or imaging features for a familial disease[14].

Sporadic pheochromocytoma is usually diagnosed on the basis of symptoms or an incidental discovery on computed imaging, whereas syndromic pheochromocytoma is frequently diagnosed earlier in the course of disease because of biochemical surveillance or genetic testing. There are several familial disorders associated with adrenal pheochromocytoma, all of which have autosomal dominant inheritance: von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2), and less commonly, neurofibromatosis type 1 (NF1). The approximate frequency of pheochromocytoma in these disorders is 10 to 20 percent in VHL syndrome, 50 percent in MEN2,

and 0.1 to 5.7 percent with NF1.[6]Approximately 10 percent of all catecholamine-secreting tumors are malignant[6].

In a study done in Christian Medical Hospital, India, over a period of 10 years from 1988 to 1998, a total of 30 patients were diagnosed to have phaeochromocytoma. Extra-adrenal phaeochromocytoma accounted for 26.6% of cases. Ten per cent of cases were bilateral, 6.6% were malignant and one patient had a familial tumor (multiple endocrine neoplasia IIB). The tumors were localized pre-operatively in all patients. Multicentric extra-adrenal tumors were not found in this series. All patients except one were explored by the anterior transperitoneal approach. Persistent hypertension was noted in 30% of patients[15].

Data is scare in developing world. Only few reports were published in the last decades in sub-Saharan Africa.

In a study done to evaluate the characteristics and management outcome of patients with pheochromocytoma in black south Africans over a 30-year period, between 1980 and 2009, Fifty-four (41 female, 13 males; age range 8 - 57 years) patients were identified. Five (9%) had familial syndromes; 49 (91%) were deemed sporadic. All tumors were intra-abdominal: 34 (61%) were adrenal and 22 (39%) extra-adrenals in origin. The most common symptoms were headache (77%), palpitations (77%), and sweating (74%). In this study, all were hypertensive, almost equally divided between paroxysmal and sustained hypertension. Six (11%) presented in congestive cardiac failure including 2 with catecholamine-induced myocarditis. There were 4 deaths: 1 from postoperative hemorrhage, 1 from multisystem crisis, 1 from metastatic medullary thyroid carcinoma, and 1 from catecholamine-induced myocarditis[16].

In another study done from South Africa reviewing Sixty patients, 33% were male and 67% female. The mean age was 47 years. The median tumor size was 6 cm, with 45% larger than 6 cm. 92% were located in the adrenal gland (87% unilateral, 5% bilateral), and 8% were extra-adrenal. The conversion rate for laparoscopic cases was 20%, with 55% of cases overall completed laparoscopically. Eleven patients with tumors >6 cm were initially attempted laparoscopically, of which 3 were converted to open, without any associated increased morbidity. A major adverse event was recorded for 5 cases (8%), including 1 mortality. Overall morbidity, blood loss,

operating time and hospital stay were all significantly reduced in the laparoscopic group. There were 5 patients with malignant disease (8%)[17].

There were 12 case series reported from Tikur Anbessa Hospital, Addis Ababa, Ethiopia over a 10-year period. In this study done the patients' ages ranged between 21 and 60 years. There were 5 males and 7 females. The majority of patients presented with clinical features related to episodic elevation of catecholamines. Vanillylmandelic acid (VMA) in 24-hour urine was elevated in 10 patients. Localization of the tumors was made by ultrasonography or on exploration. The phaeochromocytomas were unilateral in 10 cases, seven of them on the left side. One patient had bilateral turnouts and one other patient had an ectopic tumor. The tumors were operated through transabdominal or lower transthoracic approach[18].

Diagnosis and management

The diagnosis of pheochromocytoma is made based upon biochemical confirmation of catecholamine hypersecretion, followed by identifying the tumor with imaging studies. 2014 Endocrine society guideline on pheochromocytoma recommend initial biochemical testing for pheochromocytoma to be measurements of plasma free metanephrines or urinary fractionated metanephrines.[19]

A positive test for a catecholamine-secreting tumor includes one or more of the following findings according to the Endocrine Society guideline from 24Hr urine fractionated catecholamine levels[20].

- Normetanephrine >900 mcg/24 hours or metanephrine >400 mcg/24 hours
- Norepinephrine >170 mcg/24 hours
- Epinephrine >35 mcg/24 hours
- Dopamine >700 mcg/24 hours

The normal ranges for plasma metanephrines and normetanephrine depend upon the method used to obtain the blood sample[21], with diagnostic cutoffs to exclude pheochromocytoma <0.3 nmol/L and <0.66 nmol/L for metanephrine and normetanephrine values respectively for a blood taken from an indwelling cannula. For venipuncture the diagnostic cutoffs is slightly higher, metanephrine <0.5 nmol/L and/or normetanephrine <0.9 nmol/L.

Imaging studies to locate pheochromocytoma should be initiated once there is clear biochemical evidence of pheochromocytoma. CT rather than MRI is recommended as the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis. MRI is recommended in patients with metastatic pheochromocytomas, for detection of skull base and neck paragangliomas, inpatients with surgical clips causing artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations, and those with recent excessive radiation exposure). The use of 123I-metaiodobenzylguanidine(MIBG) scintigraphy as a functional imaging modality is said to be limited in patients with metastatic pheochromocytoma detected by other imaging modalities when radiotherapyusing131I-MIBG is planned and occasionally in some patients with an increased risk for metastatic disease due to large size of the primary tumor or to extra-adrenal, multifocal (except skull base and neck paragangliomas), or recurrent disease[19].

Pheochromocytoma Characteristics and Behavior Differ Depending on Method of Discovery as observed by a study done in 2019 by Mayo clinic Minnesota, USA. In this particular study, two hundred seventy-one patients (52% women, median age 52.0 years) presented with 296 catecholamine secreting tumors. Discovery method was most often incidental finding on cross-section imaging (61%) rather than PHEO-related symptoms (27%) or mutation-based case detection testing (12%). Patients with incidentally discovered Pheochromocytoma were older than symptomatic and mutation-based case detection testing patients. Mutation-based case detection were smaller than those discovered due to symptoms (median size 29.0 vs 50.5 mm, P= 0.0027). Patients with PHEOs discovered due to symptoms had the highest median concentration of 24-hour urinary metanephrines and total plasma metanephrines (P= 0.0001). These patients required a higher cumulative phenoxybenzamine dose than patients with incidental or case detection PHEO (median 450 vs 375 vs 270 mg, P = 0.029)[22].

Regarding treatment, Surgical resection of pheochromocytoma or paraganglioma is the cornerstone of therapy. Most of these tumors are resected on the basis of biochemical and CT or MRI documentation. Combined α- and β-adrenergic blockade is standard treatment for patients with pheochromocytoma in order to control blood pressure and prevent intraoperative hypertensive

crises. Preoperative medical treatment for 7 to 14 days is recommended to allow adequate time to normalize blood pressure and heart rate. Treatment should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction preoperatively to prevent severe hypotension after tumor removal. Measuring plasma or urine levels of metanephrines on follow-up to diagnose persistent disease and lifelong annual biochemical testing to assess for recurrent or metastatic disease is also recommended[19].

Regarding surgical options, Minimally invasive adrenalectomy (eg,laparoscopic) for most adrenal pheochromocytomas is safe and effective and open resection should be reserved for large (e.g., >6 cm) or invasive pheochromocytomas to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence.[6] Open resection is the preferred choice of management for paragangliomas, but laparoscopic resection can be performed for small, noninvasive paragangliomas in surgically favorable locations[19].

In a study done to evaluate the success of laparoscopic adrenalectomy among 96 patients with pheochromocytoma in Rush University Medical Center, Chicago, USA; Mean age was 47 years. Tumors were found incidentally in 40% of patients. Of the 96 patients, 12 (13%) had familial syndromes. CT or MRI localized the adrenal lesion in all patients. Mean tumor size was 5.6 cm. Location was adrenal in 92 patients and extra adrenal in 9 patients. Laparoscopy was successful in 67 of 74 (91%) patients, with 20 of 67 (30%) having tumors of 6 cm or greater in size. Conversions to open procedures were performed in patients with 4 left, 2 right pheochromocytomas and 1 paraganglioma. Of the patients, 22 had an open procedure due to suspicion of malignancy or large tumors. Malignancy was observed in 4 of 92 (4.3%) pheochromocytomas and 4 of 9 (44%) paragangliomas. Average follow-up was 22 months. There were seven recurrences. Postoperative biochemical tests available in 64 patients were normal in 90%.

In another comparative study of open vs laparoscopic adrenalectomy among patients with unilateral pheochromocytoma in India, after Patient groups were well matched for age, gender, BMI, and clinical and pathological characteristics, mean tumor size was insignificantly larger in the open (7.6± 2.7 cm) than the laparoscopic group (6.6±2 cm, p=0.06). There were no significant differences in periop hemodynamic events. Mean blood loss, blood transfusion and analgesic requirements, and postop ICU and hospital stay were significantly lesser in laparoscopic than open and conversion groups ($p<0.05$). There was no periop mortality. Morbidity occurred more

frequently in the open (n=12) than in the laparoscopic group (n=3). At follow-up (mean, 44±33.7; range, 6–160 months), no patient had recurrent pheochromocytoma. Outcomes in terms of cure of pheochromocytoma and hypertension were not different between the three groups[24].

In a study done to evaluate prognostic markers of pheochromocytoma among 33 patients in University of Pittsburgh School of Medicine, USA, the study group included 33 patients, 19 men and 14 women, with a mean age of 45 years, including five cases of neurofibromatosis (NF), three familial, and one MEN IIb. Mean follow-up was 63.2 months. Ten patients were determined to have malignant pheochromocytomas by the presence of metastatic disease. Features found to be associated with malignancy included MIB-1 labeling index (5% vs 1%) (P = .0009), male gender (90% vs 43%) (P = 0.008), extra-adrenal location (40% vs 9%) (P = 0.03), tumor weight (481 gm vs 124 gm) (P = 0.05), and young age (38 years vs 49 years) (P = .05). None of the five cases with NF were malignant (P = 0.04)[25].

3. Research Question

This study aimed to answer the following questions

- What is the demographic and disease characteristics of pheochromocytoma among patients evaluated in Tikur Anbessa Specialized Hospital, endocrine clinic?
- What are the management outcome and factors affecting outcome of patients with Pheochromocytoma?

4. Objective of the study

4.1 General objective

The general objective of this study was to determine the disease characteristics and management outcome of patients with pheochromocytoma

4.2 Specific objectives

Specific objectives included were

- To Assess the demographic characteristics of pheochromocytoma
- To Assess the Disease characteristics of pheochromocytoma
- To evaluate management outcome and factors that affect outcome of patients with Pheochromocytoma among patients evaluated in endocrine clinic and surgical referral clinic in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

5. Materials and methods

5.1 Study area

The study was conducted at Tikur Anbessa Specialized Hospitals, Addis Ababa, Ethiopia. Addis Ababa is the capital and largest city of Ethiopia. It has 33 hospitals, of which 5 are managed under the health bureau of the city administration. Four are managed by the federal ministry of health (one of the hospitals, St Paul General Specialized Hospital is affiliated with a medical school), one university hospital (Tikur Anbessa Specialized Hospital is under AAU) and the rest are either privately owned or owned by non-governmental and other governmental organizations. Tikur Anbessa Specialized Hospital is a tertiary referral hospital and the largest of all public hospitals in Addis Ababa. The hospital has a total 800 beds.

One of the high Burdon follow-up clinics is the endocrine follow-up clinic and surgical referral clinics with over 10000 patients visiting the clinic per month. This study was conducted among patients visiting these clinics with the diagnosis of pheochromocytoma or pheochromocytoma.

5.2 Study design

Institutional based Retrospective Study design was used.

5.3 Study period

Study was conducted from among patients evaluated in endocrine and surgical referral clinics from September 2010 G.c. to September 2020G.c.

5.4 Source Population

All patients with Pheochromocytoma evaluated in the Tikur Anbessa Specialized Hospital, Endocrine clinic and surgical referral clinic over 10-year period, from 2010 up to 2020, were enrolled in the study.

5.5 Study Population

All patients with HMIS diagnosis of pheochromocytoma were evaluated in the specified period of time were assessed to study the disease characteristics and management outcome of patients with pheochromocytoma.

5.6 Sampling technique and sample size determination

Due to limited number of patients with the diagnosis of pheochromocytoma were evaluated in follow-up clinics, Convenient sampling method was used in which all patients who met the inclusion criteria and evaluated in the study period were included.

5.7. Eligibility Criteria

Inclusion Criteria:

- Patients with Pheochromocytoma evaluated in either endocrine follow-up clinic or surgical referral clinic TASH
- Diagnosis of Pheochromocytoma should be evidenced by either elevated 24Hr urinary catecholamine levels or histology diagnosis
    - Elevated 24hr catecholamine level was in reference to ES laboratory diagnostic criteria of pheochromocytoma.

Exclusion Criteria

- Patients with no documented elevated 24Hr urinary cathecolamine level or histology diagnosis of pheochromocytoma
- Patients with lost charts or with significant missed data

5.8. Data collection

Patient charts with pheochromocytoma evaluated from 2010 to 2020 were selected from HMIS log book from endocrine clinic and surgical referral clinic and charts and the recently working I care system were reviewed to assess the characteristics and management outcome of patients with pheochromocytoma. Relevant data from patient charts and I care system were collected and recorded in standardized data collection format. The data were collected by the assigned personnel and the investigator.

5.9. Variables

Dependent:

- Demographic and clinical Characteristics of pheochromocytoma among patients evaluated in TASH endocrine clinic in the specified period.
- Management outcome of patients with pheochromocytoma evaluated in TASH in the specified period.

Independent

- Demographic data

    - Patient age
    - Sex
    - Address
- Family History of Pheochromocytoma
- Clinical Presentation
- Tumor Location
- CT Characteristics of the tumor
- Histopathologic characteristics
- Comorbidities
- Complications

5.10. Operational definition

Pheochromocytoma: patient with biochemical evidence of elevated urinary or plasma metanephrine in appropriate clinical setting and/or patients with biopsy result documented to have pheochromocytoma or paraganglioma were labeled to be a patient with pheochromocytoma

5.11. Data Management, Processing and Analysis

Data were entered and checked for any errors using EPI INFO and were corrected. Different statistical analyses were used including frequencies of variables, descriptive statistics including mean and standard deviation and determination of statistical significance using chi-square test and one-way ANOVA. These were done using IBM SPSS for Window 26.0.

5.12. Ethical Consideration

The ethical approval and clearance letter of permission was obtained from Addis Ababa University, College of Health science ethical committee. After data collection, medical data were kept confidentially.

5.13. Dissemination of Findings

After the completion of this study, the findings will be submitted to Addis Ababa University, College of Health science, Department of internal medicine. The findings of this study would be published in peer reviewed national or international journal for the public.

6. Results

A total of 92 medical record numbers with HMIS diagnosis of Pheochromocytoma were Selected, of which 45 were from endocrine follow-up clinic and 47 were from surgical referral clinic. After reviewed for eligibility, 28 patient medical records were included in the study.

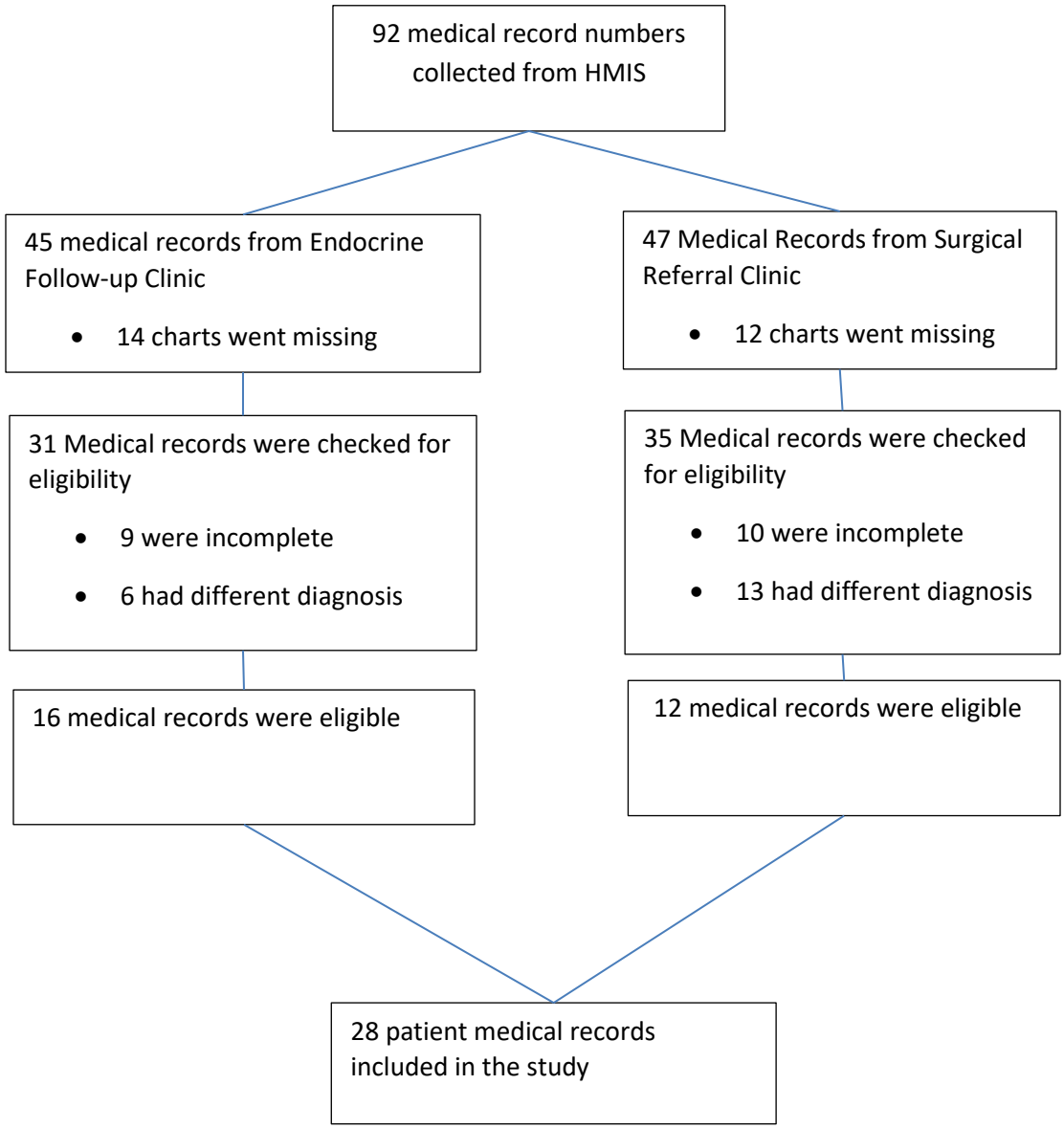

Figure1: Patient medical record selection and eligibility for the study

6.1 Sociodemographic Data

The mean age of patients with pheochromocytoma in this study was 37 years, with the minimum of 16 and maximum being 67 years of age. This study showed that 57.1% (n=16) of the patients with pheochromocytoma were female. Majority of patients with pheochromocytoma evaluated in Tikur Anbessa Specialized Hospital were from Addis Ababa, followed by Oromia region, making more than 89% of participants adding together.

Table 1: Sociodemographic Data

		Frequency	Percent
Age	15 - 30	8	28.6
	31 - 45	12	42.9
	46 - 60	6	21.4
	>61	2	7.1
Gender	Male	12	42.9
	Female	16	57.1
Address	AA	11	39.3
	Oromia	10	35.7
	Amhara	4	14.3
	SNNPE	1	3.6
	Other	2	7.1

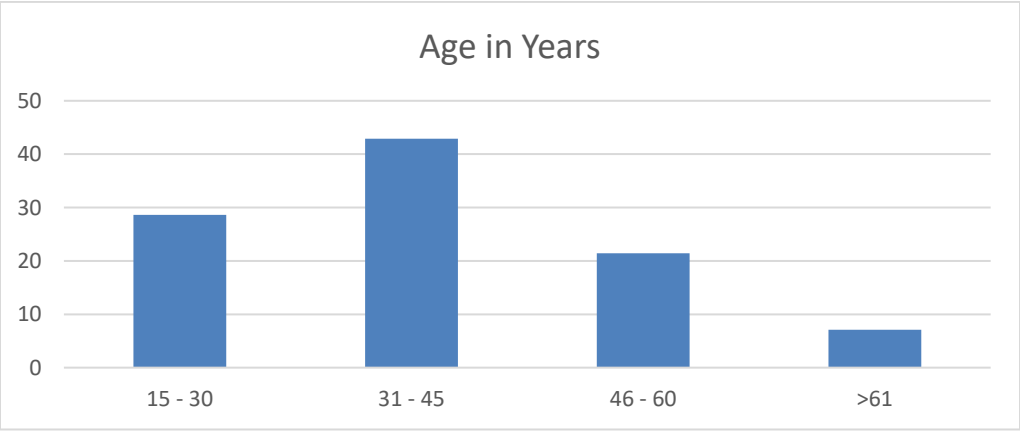

Fig. 2. Age distribution of patients with pheochromocytoma

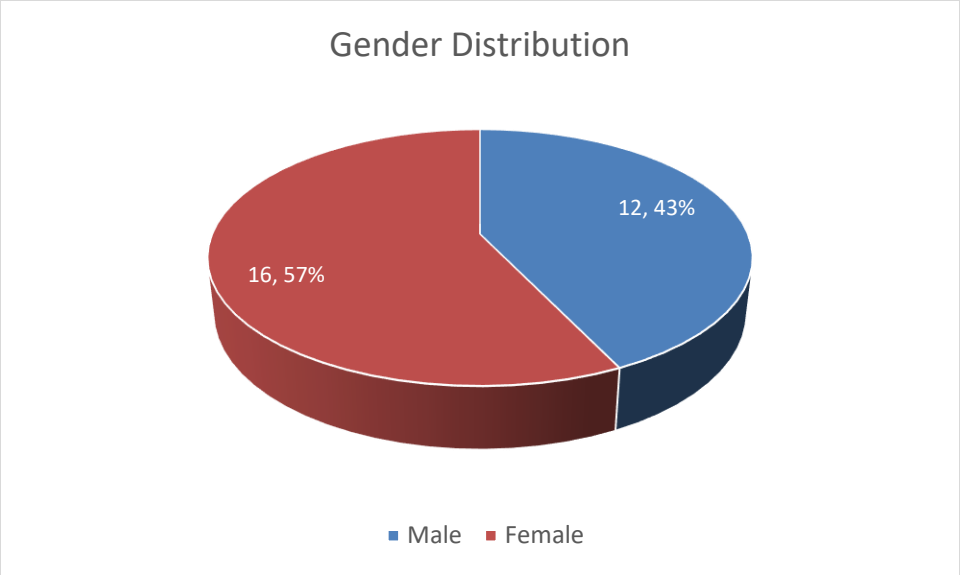

Fig 3. Pie chart showing Gender distribution of patients with pheochromocytoma

6.2. Clinical Characteristics and Mode of Diagnosis

Significant Number of patients (n=7, 25%) with Pheochromocytoma were diagnosed incidentally when worked up for unrelated condition. 75%(n=21) of patients had one or more classic symptoms of pheochromocytoma, meaning paroxysms of Palpitation, headache and/or excessive sweating.

Other symptoms like blurring of vision and poly symptoms were documented in 21% of participants each, and significant weight loss was documented in 10% of participants. 71.4%(n=20) of patients with pheochromocytoma were having hypertension at the time of diagnosis. Among Hypertensive patients at the time of diagnosis, the mean duration of Hypertension was 4.6years. 32%(n=9) of patients with pheochromocytoma had comorbidities other than Hypertension, among which T2 Diabetes Mellites was diagnosed in 5(17%) patients, 1 patient each had psychiatric illness and retroviral infection. Only 1 patient admitted to have family history of pheochromocytoma related symptoms

Table 2: Clinical manifestation and mode of diagnosis of patients with pheochromocytoma

Clinical Manifestation		Frequency	Percent
Headache	Yes	21	75.0
	No	7	25.0
Excessive Sweating	Yes	20	71.4
	No	8	28.6
Palpitation	Yes	21	75.0
	No	7	25.0
Visual Blurring	Yes	6	21.4
	No	22	78.6
Weight Loss	Yes	3	10.7
	No	25	89.3
Poly Symptoms	Yes	6	21.4
	No	22	78.6
Hypertension	Yes	20	71.4
	No	8	28.6
Mode of Diagnosis	Symptom	21	75
	Incidental	7	25

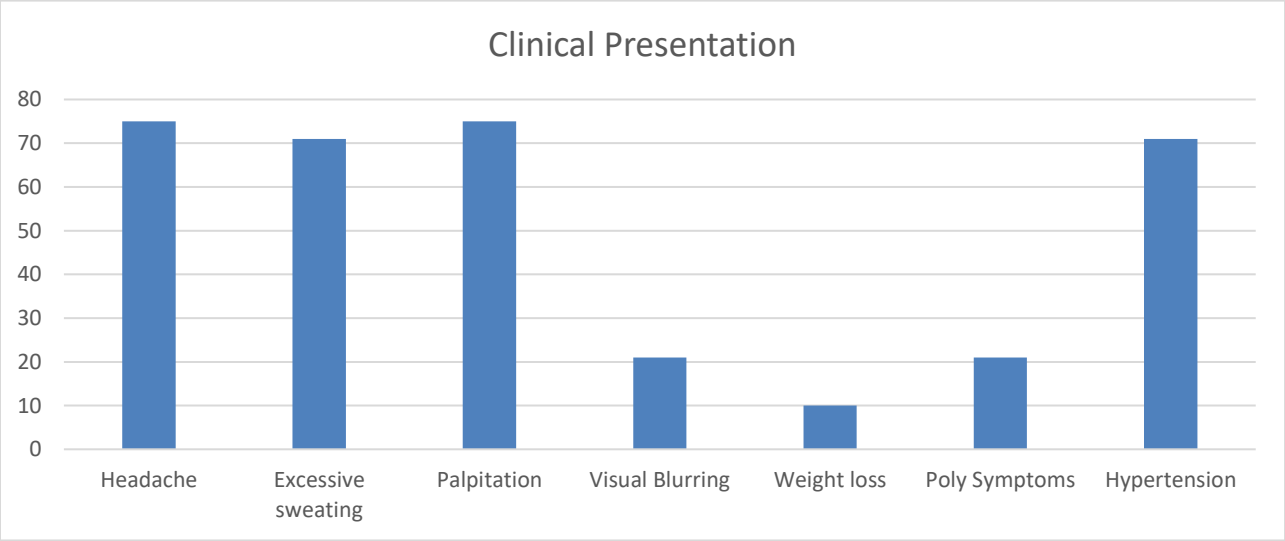

Fig 4. Bar graph showing Clinical Presentation of patients with pheochromocytoma

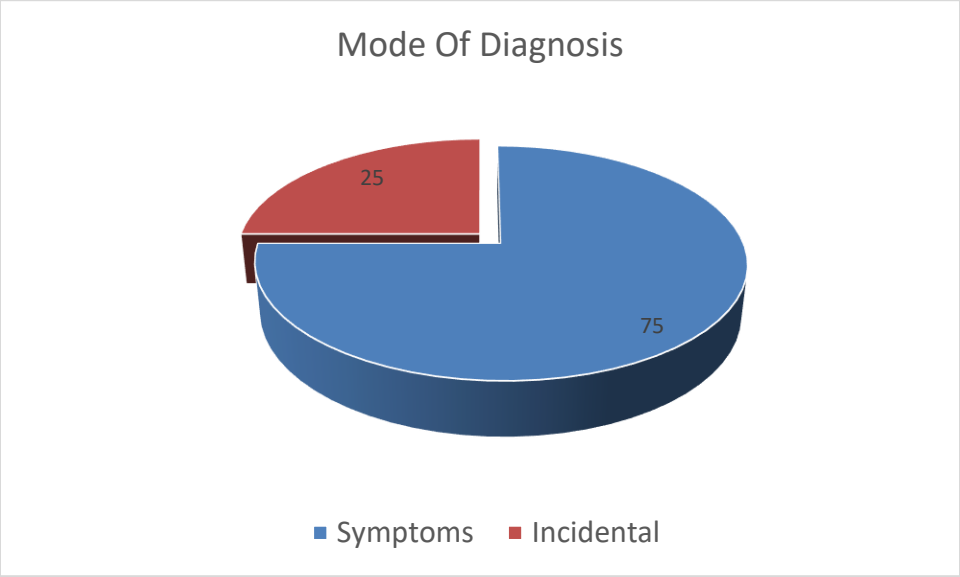

Fig 5. Pie chart showing mode or incident of diagnosis of pheochromocytoma

6.3. Laboratory and imaging characteristics

The mean White blood cell count of patients with pheochromocytoma was 7866±2748cells/micL and mean hemoglobin concentration of 14±1.4gm/dl. 14 and 17 patients had documented 24Hr urinary metamachine and normetanephrine value with the mean of 8556±7627 and 877±1985micg respectively.

The mean size of catecholamine secreting tumor as detected by abdominal CT scan was 5.8±1.6cm and minimum of 3cm and maximum being 10cm. Pearson correlation study demonstrated a positive relation of higher tumor size with higher urine metanephrine level, but the correlation was not statistically significant with P Value of 0.83. Among 12 patients who have documented both 24Hr urinary levels of metanephrine and normetanephrine, only one patient had isolated metanephrine elevation, others have predominant elevation of normetanephrine level.

Among patients with documented Mass attenuation and delayed contrast washout on abdominal CT scan, 66% had homogeneous and 34% had heterogenous enhancement with more than 50% delayed contrast washout.

In this study, 20(71.4%) patients with catecholamine secreting tumor had their tumor localized in the unilateral adrenal gland most commonly on the right-side (n=17, 85% of adrenal PHEOs), only 1(3.6%) patient had bilateral catecholamine secreting adrenal adenoma. The most common extra adrenal site was intra-abdominal catecholamine secreting tumor (n=4, 14.3%).

3(10.7%) patients had imaging features of malignant pheochromocytoma like adjacent tissue invasion on abdominopelvic CT scan.

Table 4: Imaging characteristics of patients with pheochromocytoma

Imaging Characteristics		Frequency	Percent
Location	Adrenal Unilateral	20	71.4
	Adrenal, Bilateral	1	3.6
	Extra-adrenal, Abdominal	4	14.3
	Extra-Adrenal, Other	2	7.1
	Unknown Primary	1	3.6
Unilateral adrenal mass	Right	17	85.0
	Left	3	15.0
Mass attenuation	Homogenous	6	66.7
	Heterogenous	3	33.4
Delayed contrast washout	<50%	0	0
	>50%	2	100
Imaging feature of Malignant pheochromocytoma	Yes	3	10.7
	No	25	89.3
Tumor Size	Mean	5.8	1.6(SD)

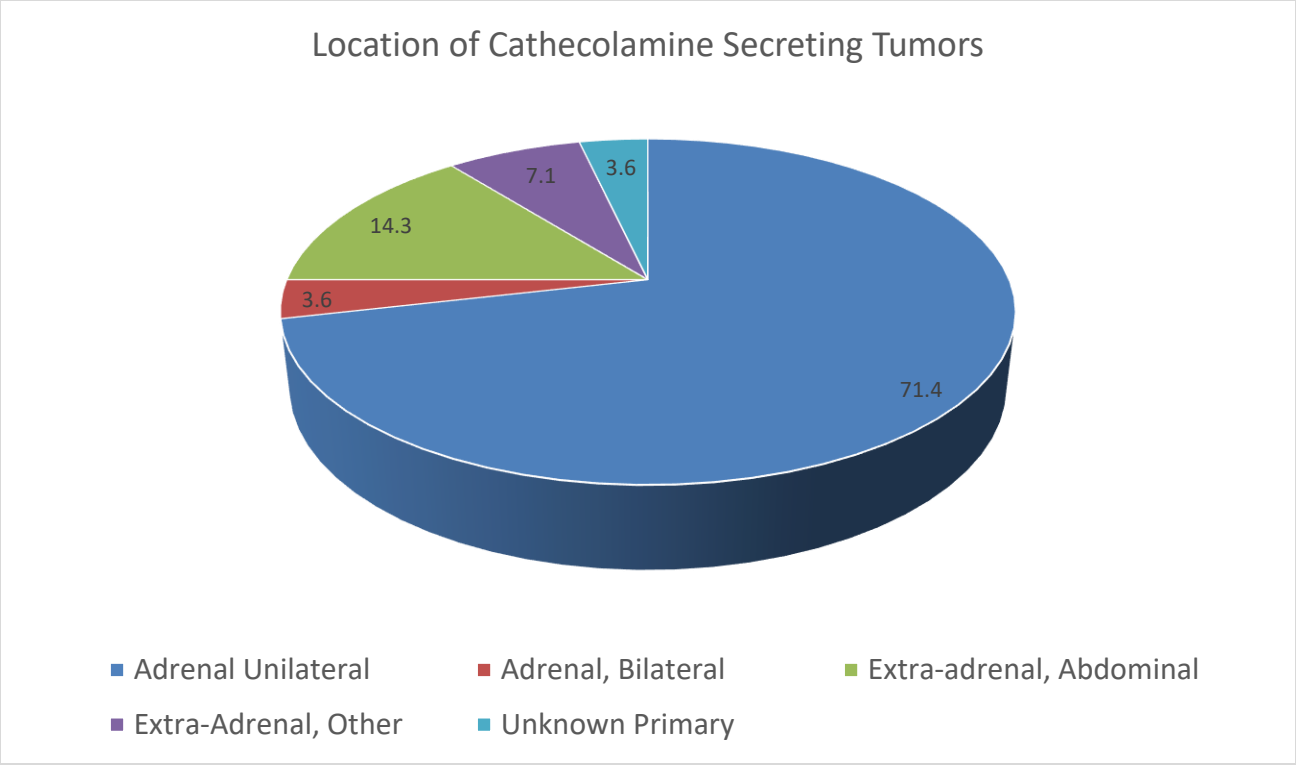

Fig 6. Pie chart showing location of catecholamine secreting tumor

Table 5: Laboratory characteristics of patients with pheochromocytoma

Laboratory Characteristics	Mean	Standard Deviation	Minimum	Maximum
WBC(Cells/micL)x10^3	7.8	2.7	4.0	1.2
HgB(mg/dl)	14.6	1.46	13.0	17.0
24Hr Urinary Met(mig)	877.0	1985.5	13.00	8222.00
24Hr Urinary Normet(mig)	8556.7	7627.6	250.0	22526.0

6.4. Genetic syndrome

Genetic syndrome was suspected and diagnosed based on clinical bases on 3(10.7%) patients. Among the genetic syndromes diagnosed clinically, MEN 2a was diagnosed in 2(7.1%) and vHL in only 1(3.6%) patient. No documented genetic testing was done.

Table 6: Clinical diagnosis of genetic syndrome among patients with pheochromocytoma

Genetic syndrome		Frequency	Percent
Clinical features of genetic syndrome present	Yes	3	10.7
	No	25	89.3
Clinical or genetic diagnosis of Genetic syndrome	MEN2a	2	66.7
	vHL	1	33.3
	NF1	0	0

6.5. Management

In this study Most (85%) of patients with catecholamine secreting tumor were operated with perioperative medical management given. Only 4(14.3%) patients were managed with medical management alone due to reasons given for patient refusal(n=2) and medical frailty(n=1) for 3 patients and unlocalized tumor for 1 patient. Among operated patients, open surgical adrenalectomy was done for 19(79%) patients and paraganglioma excision was done for 5(21%) patients.

More than 75% of patients were operated before 5 years or less with the mean being 3.4 years with standard deviation of 3.38. The shortest time for being 1st operated was 4 months before the study was started and longest being 10 years back. 3 patients were reoperated, 2 were reoperated once, and one patient was operated 4 times, the most common reason for reoperation being tumor recurrence for two patients and malignancy for 1 patient. Most patients with documented perioperative antihypertensive agent, majority were treated with an agent other than phenoxybenzamine, including calcium channel blockers, alfuzosin, and other alpha blockers like prazocin and Blood pressure control was adequate with this agent. Only 2(7.1%) patients had perioperative hypotension as documented surgical complications, other surgeries were uneventful.

Table 7: Management of patients with pheochromocytoma

Management		Frequency	Percent
Primary mode of management	Surgical	24	85.7
	Medical only	4	14.3
Surgical procedure	Open adrenalectomy	19	79.2
	Paraganglioma excision	5	20.8
Reoperation	Yes	3	12.5
	No	21	87.5
Perioperative complication	Yes	2	8.3
	No	22	91.6

6.6. Management Outcome

The current status of patients with pheochromocytoma till the end of the study period was known in 26(92%) patients. 12(42%) patients were cured of their manifestation, including one patient was cured of T2DM. 5 patients had Hypertension persisted after medical or surgical intervention, of which 2 patients were managed surgically and 1 patient had stroke.

In this study, after surgical or medical management of pheochromocytoma, Classic Pheochromocytoma symptoms like paroxysms of headache, palpitation and excessive sweating were present in 4(15.4%) patients. Only 1 patient with surgical management had persistent classic pheochromocytoma symptoms, the rest 4 patient with persistent symptoms had only medical management.

Table 8: Management outcome of patients with pheochromocytoma

Management Outcome and Complications			Frequency	Percent
Management Outcome		Alive, cured of Manifestation	12	42.9
		Alive, With Manifestations	4	14.3
		Alive, With Complication, HTN, Stroke	5	17.9
		Status Not Known	2	7.1
		Alive, not symptomatic initially	5	17.9
Classic Pheochromocytoma symptoms persisted		Yes	4	79.2
		No	22	20.8
BP controlled atter intervention	Medical	Yes	1	25
		No	3	75
	Surgical	Yes	20	90.9
		No	2	9.1

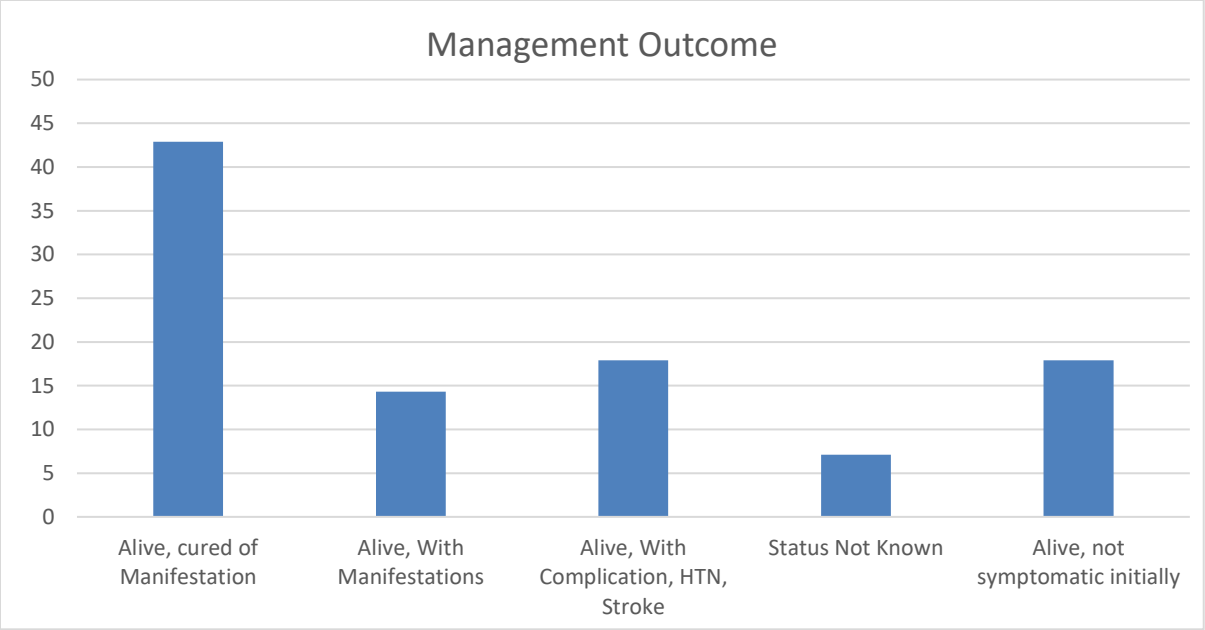

Fig 7. Bar graph showing management outcome of patients with pheochromocytoma.

6.7. Factors affecting Disease characteristics and management outcome

Gender doesn't seem to affect the mode of diagnosis at presentation, either being symptomatic or incidental or the having malignant feature or not. The mean 24Hr urinary metanephrine value was higher for patients who were diagnosed after being symptomatic than those who were diagnosed incidentally, but the difference was not statistically significant. Adrenal Location of catecholamine secreting tumors tends to be more symptomatic at the time of diagnosis than extra adrenal location (OR: 1.12 95% CI: 0.2-11) but the difference was not statistically significant.

Among 4 patients with persistent pheochromocytoma symptoms after medical or surgical intervention, the primary mode of management was medical for 3(75%) patients and surgical for 1(25%) patient. The difference was statistically significant (p value=0.006, OR: 63, 95% CI 3 - 1296). Surprisingly, the mean size of catecholamine secreting tumor was higher among patients diagnosed incidentally than those who had classic pheochromocytoma symptom at the time of diagnosis (P value= 0.059, OR:2.4, 95%CI0.9-6.3)

In this study, among 3 patients with imaging feature of malignant pheochromocytoma, 2(66.7%) were symptomatic at the time of diagnosis, whereas 1(33.4%) patient was diagnosed incidentally,

but the difference was not statistically significant. Patients with malignant pheochromocytoma were relatively younger than patient with no features of malignant pheochromocytoma with the mean age of 34.6 and 37.3 years respectively. Although still not statistically significant, having clinical diagnosis of associated genetic syndrome seem to increase the probability of having malignant pheochromocytoma (OR= 5.7 95% CI 0.3 – 94). Among 3 patients with clinical diagnosis of pheochromocytoma associated genetic syndromes, 1(33.3%) patient had features of malignant pheochromocytoma on imaging studies and Among 25 patients with no such suggestive features of genetic syndrome, only 2(8%) had malignant pheochromocytoma.

Patients with imaging features of malignant pheochromocytoma had higher mean tumor size compared to patients with no such suggestive features with mean of 6.6±1.5cm and 5.6±1.7cm respectively, but the difference was not statistically significant.

Table 9: Factors Affecting the probability of mode of diagnosis as predicted by bivariate logistic regression

Factors affecting mode of diagnosis		**Mode of diagnosis**		COR (95% CI)	P Value
		Symptomatic	Incidental		
		Frequency (%)	Frequency (%)		
Gender	Male	9(75%)	3(25%)	1.00(0.17 – 5.63)	0.66
	Female	12(75%)	4(25%)		
Age	Mean (SD)	37(13)	36(±13)	0.99(0.92-1.06)	0.87
24 Hr urinary normetanephrine	Mean	7534(±7728)	12306(±7255)	1(1)	0.35
24 Hr Urinary Metanephrine	Mean	1041(±2262)	341(±221)	1(0.99 – 1.01)	0.55
Location of the tumor	Adrenal	16(76.2%)	5(23.8%)	1.60(0.22-11.4)	0.50
	Extra Adrenal	4(66.7%)	2(33.3%)		
Size of the tumor	Mean (SD)	5.3(±1.3)	7.2(±1.9)	2.47(0.95- 6.34)	0.059

Table 10: Factors Affecting the probability of persistently symptomatic after medical or surgical management of pheochromocytoma as predicted by Bivariate Binary logistic regression

Factors affecting probability of persistently being symptomatic		Persistent Pheochromocytoma symptoms		COR (95% CI)	P Value
		Yes	No		
		Frequency (%)	Frequency (%)		
Primary Mode of management	Medical	3(75)	1(25)	63(3.06-1296)	0.006
	Surgical	1(4.5)	21(95.5)		
Age	Mean	51(±4.9)	35(±12)	0.90(0.81-0.99)	0.04
Gender	Male	1(9.1)	10(90.9)	0.40(0.03-4.47)	0.42
	Female	3(20)	12(80)		

Table 11: Factors Affecting the probability of mode of diagnosis as predicted by multivariate logistic regression

Factors affecting mode of diagnosis		**Mode of diagnosis**		AOR (95% CI)	P Value
		Symptomatic	Incidental		
		Frequency (%)	Frequency (%)		
Size of the tumor	Mean (SD)	5.3(±1.3)	7.2(±1.9)	3.50(0.91-13.4)	0.06

Table 12: Factors Affecting the probability of persistently symptomatic after medical or surgical management of pheochromocytoma as predicted by multivariate Binary logistic regression

Factors affecting probability of persistently being symptomatic		Persistent Pheochromocytoma symptoms		AOR (95% CI)	P Value
		Yes	No		
		Frequency (%)	Frequency (%)		
Primary Mode of management	Medical	3(75)	1(25)	58(2.8-2000)	0.01
	Surgical	1(4.5)	21(95.5)		
Age	Mean	51(±4.9)	35(±12)	0.7(0.5-0.9)	0.04

Table 13: Factors predicting the probability of a catecholamine secreting tumor being malignant: as Predicted by Bivariate Binary Logistic regression

Factors affecting Probability of malignant pheochromocytoma		**Malignant Pheochromocytoma**		COR (95% CI)	P Value
		Yes	No		
		Frequency (%)	Frequency(%)		
Incident of diagnosis	Symptomatic	2(9.5)	19(90.5)	0.63(0.04-8.25)	0.5
	Incidental	1(14.3)	6(85.7)		
Age	Mean	34.6(±2)	37.3(±13)	1.01(0.92-1.12)	0.74
Gender	Male	1(8.3)	11(91.7)	0.63(0.05-7.96)	0.61
	Female	2(12.5)	14(87.5)		
Clinical diagnosis of PHEO related genetic syndrome	Yes	1(33.3)	2(66.7)	5.75(0.34-94.7)	0.29
	No	2(8)	23(92)		
Tumor size	Mean	6.6±1.5	5.6±1.7	0.71(0.33-1.45)	0.34
Tumor Location	Adrenal	1(4.8)	20	0.10(0.07-1.32)	0.11
	Extra adrenal	2(33.3)	4		
Persistent Classic PHEO symptoms post Management	Yes	0	4(100)	1.15(0.98-1.36)	0.59
	No	3(13.6)	19		

7. Discussion

Although well described in developed nations, there is a paucity of data on the presentation and surgical management of Pheochromocytoma in developing world contexts, particularly in Sub-Saharan Africa.

In this study 57% of patients with pheochromocytoma were females, which was similar to similar review done in Tikur Anbessa Hospital, which was 58%[18]. It was slightly lower than the reported 64% from California. The difference can be due to difference in methodology.[8]

Due to the increasing use and availability of high-resolution imaging techniques, the rate of incidental diagnosis of Pheochromocytoma in asymptomatic patients has steadily increased worldwide[22]. The rate of incidental diagnosis in this study was 25% and is comparable to the 11–50% found in published series elsewhere[23]. It is also comparable to a study done in South Africa which was 23% among 60 confirmed cases of pheochromocytoma[17]. But it was lower to a study done in Mayo clinic[22], in which the rate of incidental diagnosis was 61%, this difference may be explained by the shift in the modern era in the developed world due to increased use of cross-sectional imaging techniques for other purposes.

In this study, it was found that 71% of patients with pheochromocytoma have classic triads of episodic headache, palpitation and excessive sweating. This was in contrast to a study done in France[9], among 41 patients with Pheochromocytoma, only 23% had classic triads, this difference can be explained by the subjective nature of clinical symptoms, delayed presentation in developing nations, and early health seeking behavior in developed world. 71.4% of patients with pheochromocytoma in this study had documented high Blood pressure, this was comparable to a study done in France[9].

In this study, 21.4% of patients with catecholamine secreting tumor had extra adrenal tumor, which is comparable to a study done in Christian Medical Hospital, India[15], where the rate of extra adrenal tumor was 26.6%, and lower than a study done in South Africa[17], which was

39%, and higher than similar study done in Tikur Anbessa Hospital[18] (8.3%) and another study from south Africa[16] (8%)

The mean size of catecholamine secreting tumor in this study was 5.8±1.6cm which is slightly higher than reported cases from developed countries which was in the range of 3.6 to 5.6cm[23], this may be explained by delayed presentation and referral and different genetic background. But it was lower than a study done in south Africa[17] with the mean tumor size of 6.8cm and to a study done in Northern India, which was 7.1cm.[24]. This may be explained in difference in mode of diagnosis, methodology and genetic back ground.

Historically, genetic factors were believed to be implicated in only 10% of phaeochromocytoma, but recent data suggest that germline mutations may be detected in approximately 25% of unselected cases.[6] In this study, only 10.7% (3) of patients were diagnosed clinically with Pheochromocytoma associated genetic syndrome, 2 patients with MEN2a and 1 patient with vHL. This may be explained by lack of access to genetic testing for our patients. The result was comparable to a study done in South Africa[16] which showed 5(9%) out of 54 patients with pheochromocytoma had associated familial syndrome.

The malignancy rate in this study was 10.7%. This was comparable to a study done in South Africa[17]. A number of factors, including extra-adrenal location, familial syndrome and larger size, have been reported to be associated with malignant pheochromocytoma[25]. Consistent with this, In this study, although not statistically significant, there was a positive relation with increased risk of malignancy with clinical diagnosis of genetic syndrome, larger tumor size and extra adrenal location of the tumor.

In this study, given the lack of laparoscopic surgery, the surgical method used to manage patients with catecholamine secreting tumor was open surgical intervention. Perioperative Mortality was not documented, comparable with reports elsewhere with reported perioperative mortality of 0–6%.[17],[23]

8. Conclusion

Majority of Patients with catecholamine secreting tumor in our setup are female in the young age group and are diagnosed after being symptomatic. The classic triads of pheochromocytoma are present in more than 70% of patients with Pheochromocytoma in this study. Interestingly polysymptoms like polyuria and polydipsia were found in more than 20% of our patients. Significant number of our patients had their pheochromocytoma located outside of the adrenal gland. Only one patient has unlocalized catecholamine secreting tumor until the end of this study. Syndromic genetic diseases were likely on 10% of patients with pheochromocytoma in this study. Majority of patients were managed surgically with >50% cure rate among symptomatic patients including one of the five patients with Diabetes mellitus. The surgical procedures were all open adrenalectomy or paraganglioma excision based on the site of the tumor. The risk of recurrence of tumor and/or persistent classic pheochromocytoma symptoms and perioperative complications after surgical intervention was very low in this study (<5%). No significant associated factor was found after adjusting for confounders other than being not operated to increase the risk of having persistent symptoms despite different medical therapies.

9. Recommendations

- Large scale long term study is required to better characterize the disease chracteristics and management outcome in developing world
- In this study, as majority of patients with pheochromocytoma are symptomatic, it seems screening for pheochromocytoma with 24Hr urinary catecholamine level should focus among symptomatic patients with classic triads of pheochromocytoma.
- Surgical management is the only curative management option for catecholamine secreting tumors with medical therapy only reserved for temporary symptom and BP control until surgery is done.
- As evidence is lacking on the perioperative challenge of managing patients with pheochromocytoma in developing world, further studies on this area are recommended.

10. Limitations

The number of patients were small to take recommendation from this study to the general population. The fact that the study was retrospective, institution based and of limited participants and some incomplete investigations were the challenges faced and caution should be taken to generalize recommendation. Imaging investigations and documentations were not protocol based and made the possible comparison of results with other per protocol procedures from literatures. None of the patients in this study had documented genetic testing done and the diagnosis of pheochromocytoma associated genetic syndrome was solely based on clinical diagnosis of constellation of signs and symptoms. This may question the reliability of genetic syndrome diagnosis on clinical bases alone.

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12. Annexes

Data collection Form

This is a data collection form designed to study the characteristics and management outcome of pheochromocytoma among patients evaluated in Tikur Anbessa Hospital, Addis Ababa, Ethiopia.

1. Patient
   ID……
2. Age……..
3. Sex…….....
4. Ethnicity……..
5. Address……..
6. Clinical Presentation
   - Headache
   - Palpitation
   - Excessive Sweating
   - Abdominal/flank pain
   - Hypertension
   - Other
     (mention)……...
7. Comorbidity
   - Cardiac disease
   - DM
   - Psychiatric illness
   - Other
     (mention)……
8. 24Hr urinary cathecolamine level
   - 24 Hr Urinary Normetanephrine level…….
   - 24 Hr Urinary Metanephrine Level
   - 24 Hr Urinary Dopamine Level……
   - 24 Hr Urinary VMA level…….
9. CT/MRI characteristics

- Size…….
- Location:
    - Adrenal: Unilateral…….Bilateral…….....
    - Extra-Adrenal (mention, if known)……
- Attenuation……
- Contrast washout…….
- Features of malignant pheochromocytoma present?
    - Yes
    - No

10. Basic investigations
    - WBC
    - HgB
    - FBS
11. Clinical or Genetic diagnosis of associated Genetic syndrome
    - MEN2a
    - vHL
    - NF1
    - Other(Mention)…….
12. Primary Management
    - Surgical
      (mention)…….
    - Medical
      (mention)……..
13. Duration since last operated for pheochromocytoma……
14. Reoperated?
    - Yes
    - No
15. If yes how many times were you operated?.....
16. Reason for reoperation
    - Pheochromocytoma recurrence
    - Other reason(Mentioned)…….

17. When was the last time you were operated?.....
18. Any Perioperative complications?
    - Yes
    - No
19. If yes Mention……
20. Management Outcome
    - Alive, Cured of manifestains
    - Alive with complication
    - Status not known……
    - Died…….
    - Alive with manifestations……..
    - Alive, Not symptomatic initially……
21. Are the classic manifestations of pheochromocytoma like headache, palpitation and excessive sweating present after medical or surgical intervention?
    - Yes
    - No
22. Is the patient on any medication now?
    - Yes
    - No
23. If yes Mention…….