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Research Article



# Pheochromocytoma in a Hinterland: A Descriptive Study

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## Abstract

**Objective:** This study aims to evaluate patients diagnosed with pheochromocytoma in a hinterland.

**Methods:** This descriptive study includes data from a tertiary endocrine center from January 1, 2010, to December 31, 2023. Patients with pheochromocytoma had demographic, laboratory, operation, and pathology data recorded.

**Results:** The study included 43 patients, 24 of whom were male (55.8%). The mean age was 51.4±12.4 (24-81) years. The median tumor size was 6,3 cm (1.6-24cm). Tumor localization (right/left/bilateral: 24/15/4) was most common on the right at 55,8%. Four patients had bilateral tumors. Five patients had MEN 2A syndrome, one patient had neurofibromatosis, and one patient had MEN 2B syndrome. Thirty-six patients were sporadic (%80). Average follow-up time was 51.8 (7-125) months. The median urinary metanephrine level was 666 (18-23115) (52-341 micrograms/day), and the median urinary normetanephrine level was 3342 (187-18900) (88-444 micrograms/day). It elevated urinary normetanephrine in 92% of patients. I mostly used phenoxybenzamine in preoperative preparation; phentolamine was most commonly administered for intraoperative hypertensive attacks. Patients using it were 78,9% and 88,9%, respectively. The recurrence and distant metastasis rates were 4,6% and 2,3%, respectively.

**Conclusion:** We observed pheochromocytoma equally in all genders. They localized it to the right adrenal gland. It often secretes norepinephrine. Epinephrine/norepinephrine is often increased in bilateral diseases. The most commonly used drugs are phenoxybenzamine and phentolamine. Doxasozin, amlodipine and sodium nitroprusside can be used for the operation. It requires long-term follow-up because of the high risk of recurrence.

**Keywords:** Pheochromocytoma, Adrenal gland, Neoplasms

**Main points:**

a) Pheochromocytoma occurs equally in both genders. It is mostly sporadic.

b) In most cases, it is located in the right adrenal gland. Bilateral disease refers to a MEN syndrome.

c) Blood pressure normalization was formerly achieved with Phenoxybenzamine/phentolamine; Nowadays, it can be provided with doxazosin/amlodipine/sodium nitroprusside.

d) An effective control of blood pressure virtually eliminates operative mortality.

e) It requires long-term follow-up because of the high risk of recurrence.

## Introduction

Pheochromocytoma is a tumour originating from catecholamine-producing chromaffin cells in the adrenal medulla. Paraganglioma is a tumour arising from non-adrenal chromaffin cells. They are rare; however, they may be fatal and curable causes of secondary hypertension [1]. The number of Pheochromocytoma/Paraganglioma (PPGL) cases has tripled in recent years due to better imaging and awareness. However, it only affects five people per million each year. Only 25% of patients have classic pheochromocytoma symptoms: headaches, sweating, and palpitations [2,3]. The first diagnostic method is usually urine catecholamines and abdominal CT imaging [4]. Limited data exist on PPGL, a rare disease, regarding patient and tumor characteristics, preoperative preparation, and long-term follow-up.

This study evaluated patients with PPGL.

## Methods

This study is a retrospective descriptive study.

The study included PPGL patients who were followed up at the tertiary endocrine center (Hinterland with a population of 6-7 million) between January 1, 2010, and December 31, 2022. They got patient data from the hospital data system. We excluded patients with missing data from the study. Patients' demographic data such as age, gender, family history of Multipl Endocrine-Neoplasia (MEN)/pheochromocytoma. Recording of metanephrine/normetanephrine levels in 24-hour urine and serum calcitonin levels was performed. We reviewed adrenal tomography and pathology reports. Tumor localization was recorded. Tumor size was the largest dimension. This research was approved by the Institutional Review Board at Dicle University Hospital, and all procedures followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects. Our study displayed categorical variables as numbers and percentages, and continuous variables as a median range.

## Results

A total of 43 patients (24 patients (55,8%) were male) were included in the study. Mean age was 51.4±12.4 (24-81) years. Median tumor size was 6.3cm, with an IQR of 3.8 cm (1.6-24cm). Tumor localization (right/left/bilateral: 24/15/4) was most common on the right at 55,8%. Four patients had bilateral tumors. Five patients (three from the same family) had MEN 2A syndrome, one patient had neurofibromatosis, and one patient had MEN 2B syndrome. One patient had pheochromocytoma, medullary thyroid cancer, and parathyroid adenoma. Thirty-six patients were sporadic. Urine metanephrine median level was: 666(18-23115), IQR: 3290 (52-341 micrograms/day), Urine normetanephrine median level was: 3342(187-18900) IQR: 3898(88-444 micrograms/day) Average follow-up time was 51.8 (7-125) months. In 92% of patients, urine normetanephrine levels were elevated. 65% of patients had elevated urine metanephrine levels. We found urine normetanephrine and metanephrine to be elevated at the same time in 80% of those with bilateral masses. I mostly used phenoxybenzamine in preoperative preparation; phentolamine was most commonly administered in intraoperative hypertensive attacks. Patients using it were 78.9% and 88.9%, respectively. The recurrence and distant metastasis rates were 4.6% and 2.3%, respectively (Table 1). Operation-related mortality was 0%.

**Table1:** Patient Characteristics.

| Patient Characteristics | |
|---|---|
| **Number of Patients:** | 43 |
| Male | 24 (55,8%) |
| Female | 19 (44,2%) |
| **Average age (years):** | 51,4±12,4 (24-81) |
| **Tumor Size:** | |
| Median (largest diameter, cm) | 6,3 (1,6-24) |
| **Localization:** | |
| Right | 24 (55,8%) |
| Left | 15 (34,9%) |
| Bilateral | 4 (9,3%) |
| **Urine Catecholamines (Median/Day):** | |
| Metanephrine (normal value: 52-341 mcg/day) | 666 (17-23115) |
| Normetanephrine (normal value: 88-444 mcg/day) | 2675 (187-18900) |
| Follow-up time (months): | 51.8±36.3 (7-125) |
| **Subcategory(n:43):** | |
| MEN2A | 5 |
| MEN2B | 1 |
| Neurofibromatosis | 1 |
| Sporadic | 36 |
| **Pre-op Medication(per-oral):** | |
| Phenoxybenzamine | 78.90% |
| Prazosin | 15.80% |
| Prazosin+amlodipine | 5.30% |
| **Intra-op Medication (Intravenous):** | |
| Phentolamine | 88.90% |
| Sodium nitroprusside | 11.10% |
| **Post-Operative Recurrence:** | 4.60% |
| **Distant metastasis:** | 2.30% |

## Discussion

In this 12-year descriptive study, PPGL was most frequently observed in the right adrenal. PPGL was almost equally common in all sexes and patients were in the fifth decade of life. We observed bilateral adrenal mass in MEN patients. Both urinary metanephrine and normetanephrine levels were high in bilateral disease. Bilateral and multiple pheochromocytomas are common in MEN with 2A/2B syndrome. MEN 2B syndrome is characterized by medullary thyroid cancer, PPGL, megacolon, marfanoid features, and special facial structures (pronounced upper lip, neuromas on the tongue, eyelid eversion). Moreover, patients with MEN 2B have bilateral pheochromocytoma [5,6]. In our study, one in seven patients had MEN 2 syndrome. We should investigate other comorbidities in patients presenting with any of the MEN 2 components. With the frequent use of genetic testing in recent years, we have revealed that approximately 40% of PPGL patients are hereditary [7]. There are predisposed individuals who experience a different presentation and course of the disease. This tumor is multiple, bilateral, more aggressive, recurrent, metastasizing, has a high incidence of paraganglioma, and exhibits accompanying phenotypic features. Considering this, we should perform advanced genetic analysis on all patients with PPGL to develop a treatment plan and follow-up schedule [8]. Since our study was retrospective, we performed genetic analysis on a few patients. Most of them were patients with five-year follow-up. As our knowledge of PPGL increases, genetics becomes more important.

Clinical suspicion tests for catecholamine levels in plasma or urine are performed for diagnosis. The patient must have a proper diet and not use certain medications for three days before the test. Stimulant drinks (coffee/tea), citrus fruits, chocolate, bananas, wafers, drugs that increase sympathetic activity, and paracetamol, a commonly used analgesic, should be avoided during the diet. They should measure catecholamines in plasma/urine on the fourth day. Images should be performed if catecholamine levels are four times greater than normal. Repeat the procedure if catecholamine levels are lower than expected [9,10]. Only urinary catecholamines were examined in all patients in the present study. Urine catecholamine levels were high in almost all patients. There were some patients whose urinary catecholamine levels were between two and four times higher. In addition, the number of patients with elevated urinary normetanephrine levels was higher.

Too much catecholamine in PPGL causes hypertension, decreased intravascular volume, and arrhythmias. Catecholamine discharge during surgery can be lethal. Preoperative alpha blockade and adequate fluid resuscitation should be performed for 7-10 days; if needed, beta blockade should be administered afterwards. The patient were operated with a normal pulse and blood pressure. Intraoperative hypertensive attacks are treated with phentolamine, sodium nitroprusside, and nitroglycerin [11]. Phenoxybenzamine was the most commonly used as a preoperative alpha blocker in our study. For intraoperative hypertensive attacks, we frequently used phentolamine. We achieved positive outcomes with oral extended-release doxazosin and intravenous sodium nitroprusside due to drug supply difficulties.

Because of its high recurrence risk, PPGL requires long-term follow-up. Genetic syndromes require lifelong follow-up. Large tumor size, dopamine release, non-adrenal localization, and Succinate Dehydrogenase (SDH) mutations are critical for recurrence [12]. There were two cases of recurrence in our study. They performed a second surgery on two patients because of local recurrence. However, extensive metastasis was detected in one patient with Ga68 DOTATATE imaging. It gave the patient three cycles of lutetium-based PPRT therapy. We planned systemic chemotherapy when no results were obtained.

The retrospective nature of the study led to limitations. Our limitations include incomplete patient data, not testing all patients' genes, being a single center experience, and having a small patient population.

In conclusion, Pheochromocytoma occurs equally in all sexes. They mostly localize it to the right adrenal gland. It usually secretes norepinephrine. Epinephrine/norepinephrine is often increased in bilateral diseases. MEN syndrome is common in bilateral diseases. The most commonly used drugs are phenoxybenzamine and phentolamine.

## Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

## Acknowledgments

None.

## Data Availability Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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