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ORIGINAL ARTICLE

Risk Factors for Perioperative Complications, Treatment Outcomes and Aggressive Behavior of the Tumor in Patients with Pheochromocytoma

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Abstract

Introduction. Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells of the adrenal gland. Surgery is the only curative treatment with a high biochemical cure rate, low mortality and high risk of perioperative complications.

Objectives. To study the demographic characteristics of patients with pheochromocytoma and to identify the risk factors for perioperative complications, treatment outcomes, and aggressive behavior of the tumor.

Methodology. We retrospectively studied the data of pheochromocytoma patients registered from 2012 to 2022.

Results. In our study, a total of 30 patients with pheochromocytoma were included. The mean age of presentation was 35 ± 12.8 years. Fifty-six percent were females, and the sex ratio was 1.3:1. Pheochromocytoma spells (60%) was the most common complaint, followed by abdominal pain (53%), orthostatic complaints (10%) and incidentalomas (6%). The baseline mean 24-hour urinary total metanephrines was 2963.7 ± 2658 mcg/24 hours, and the mean tumor size was 7.3 ± 0.53 cm. Forty-three percent of patients underwent laparoscopic adrenalectomy, while the rest underwent open surgery. The mean Pheochromocytoma of Adrenal gland Scaled Score(PASS) was 3.41 ± 0.28, and 23% had a high risk for malignancy. Among perioperative complications, hypertensive crisis (17%) was the most common, followed by postoperative hypotension (13%), hypoglycemia (3%) and right-sided pneumothorax (3%). These patients with complications had higher metanephrine levels (5490 vs. 1880 mcg/24 hours, p = 0.001). Blood pressure normalized in 50%, and this was associated with male sex, younger age (29.5 vs. 40 years, p = 0.03), higher metanephrines (4619 vs. 1855 mcg/24 hours, p = 0.001) and smaller tumors (5.91 vs. 8.61 cm, p = 0.046). PASS score greater than or equal to 4 was associated with higher metanephrine levels (5104 vs. 2312 mcg/24 hours, p = 0.021) and larger tumors (9.28 vs. 6.68 cm, p = 0.024). Biochemical cure rate was achieved in 76% of patients after surgery and was associated with older age (37.7 years vs. 27.7 years, p = 0.047) and absence of pheochromocytoma spells (100% vs. 61%, p = 0.014).

Conclusion. Young age, smaller tumor size and higher metanephrine concentrations were associated with normalization of blood pressure post-surgery. On the other hand, older patients and those without pheochromocytoma spells had better biochemical cure rates. Patients with higher baseline metanephrine levels had increased perioperative complications. More aggressive tumor behavior was associated with higher metanephrine levels and larger tumors. Sex, baseline blood pressure and mode of surgery did not have any influence on treatment outcomes.

Key words: Pheochromocytoma spells, metanephrines, perioperative complications, PASS score

INTRODUCTION

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells of the adrenal gland. These are rare tumors seen in 0.1% to 0.6% of patients being evaluated for secondary hypertension.[1] Eighty to eighty-five percent are catecholamine-secreting tumors while the rest are paragangliomas arising from the sympathetic and parasympathetic ganglia.[2] These tumors can be subdivided into adrenergic, noradrenergic and dopaminergic phenotypes based on the predominant catecholamine produced and excreted.[2,3] The incidence of these tumors peaks in the fourth and fifth decades, with equal distribution among males and females. These patients typically present with pheochromocytoma spells- a triad of episodic palpitations, headache, and diaphoresis, with or without hypertension. Only 40% of patients have classic spells, 40% are incidentally detected, and 7 to 18% present with pheochromocytoma crisis, a serious condition characterized by uncontrolled hypertension associated

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with end-organ damage.[4] However, these tumors can present with a plethora of symptoms, as they vary widely in size, catecholamine production and urinary metabolite excretion.[5]

It is essential to suspect, localize, treat and resect these tumors to cure hypertension, reduce cardiovascular morbidity and prevent lethal paroxysms. Surgery is the only curative treatment, but it carries a high risk of massive catecholamine release, causing severe hypertensive crises. Hypotension can occur after tumor resection because of the sudden withdrawal of the pressor action of tumor metabolites.[6] Perioperative complications can occur despite adequate precautions like α-blockade and intravascular fluid replacement and will necessitate prompt medical management. The objectives of this study were to study the demographic characteristics of patients with pheochromocytoma and to identify the risk factors for perioperative complications, treatment outcomes and tumor aggressiveness.

METHODOLOGY

After getting approval from the Institutional Ethics Committee (Certificate No. MC/190/2007/Pt-II/April 2023), we conducted an observational cross-sectional study in our department. We collected the data of patients with pheochromocytoma registered from 2012 to 2022. Patients with incomplete workups, paragangliomas and adrenal tumors secreting other hormones were excluded from the study. The authors confirm the availability of and access to all original data reported in this study.

Study procedure

Any patient with an adrenal tumor and significant elevation in plasma or urinary catecholamines or their metabolites was diagnosed with pheochromocytoma. Patient history, physical examination, biochemical and imaging data were obtained from case records and documented in a structured proforma. The initial biochemical screening test was a 24-hour urinary total metanephrine (metanephrine and normetanephrine) determination by high-performance liquid chromatography – electrochemical detection method. Cases with values over twice the upper limit were considered significant and subjected to anatomical imaging to localize the tumor.

Preoperative stabilization was achieved with α-blockers followed by ß-blockers, adequate hydration and liberal salt intake. Surgical details, histopathology reports and perioperative complications such as hypertension crisis, hypotension, hypoglycemia and other surgical complications were recorded. A repeat 24-hour urinary total metanephrines was done 1 to 2 weeks after surgery. Biochemical cure was defined as the normalization of urinary metanephrines after surgery.

Treatment outcomes like biochemical cure and normalization of blood pressure were assessed in all patients. The risk of malignancy or tumor aggressiveness was graded histopathologically in all patients using the Pheochromocytoma of Adrenal gland Scaled Score (PASS).

Statistical analysis was done using SPSS version 22. Descriptive statistics were used to extract the mean and standard deviation of continuous data. The normality of the data distribution was checked for all variables by using the Shapiro-Wilk test. An independent t-test was used to compare the means of continuous normally distributed data; otherwise, the Mann-Whitney U test was used for non-normal data distributions. The Chi-Square test was used to compare two categorical variables. In Table 1, patient baseline data is divided and compared between male and female groups using the appropriate statistical tests. Perioperative complications, biochemical cure, normalization of blood pressure post-surgery and PASS score were labeled as outcome or dependent variables. Patient baseline characteristics were considered independent variables. In Tables 2 and 3 we used the Chi-Square test and independent t-test to check for any association between independent and outcome variables. A p-value less than 0.05 is considered statistically significant.

RESULTS

Our study included 30 patients with pheochromocytoma after detailed records screening. The mean age of presentation was 35 ± 12.8 years (13 to 56 years). Most of them (70%) were diagnosed in the third, fourth and fifth decade; 20% (n=6) were younger than 18 years and 10% (n = 3) were older than 50 years. Of the 30 patients, 56% were females, with a female-to-male ratio of 1.3:1. The age of presentation was similar between both sexes. Pheochromo-cytoma spells were the most common presenting complaint (60%), followed by abdominal pain (53%), orthostatic complaints(10%) and incidental detection (6%) by imaging. Pheochromocytoma spells and abdominal pain were more common in females than males. Orthostatic symptoms and incidentalomas were predominantly seen in females and males, respectively. Patients with pheochromocytoma spells were younger (31.94 vs 40.27 years, p = 0.04) than those without the classic spell. On examination, 33% of patients were normotensive, 17% had paroxysmal hypertension, and 50% had sustained elevated blood pressure(Table 1). Blood pressure, body mass index(BMI) and glycemic status were similar between males and females. Syndromic associations were found in four subjects(13.33%). Two had features of MEN2B; one patient had neurofibromatosis, and the other was diagnosed with Von Hippel-Lindau syndrome.

The baseline mean 24-hour urinary total metanephrine level was 2963.7 ± 2658 mcg/24 hours (174 to 8838 mcg/24 hrs). Four patients had a noradrenergic phenotype, and the rest were adrenergic. Females had statistically significantly higher baseline values (3709.6 ± 3103 mcg/24 hours) than males (1879 ± 1560 mcg/24 hours). On imaging, the left

adrenal (60%) was more commonly involved than the right (35%), while one patient had bilateral adrenal involvement. The mean size of the tumor was 7.3 ± 0.53 cm (3-13 cm). Females had larger tumors than males, but this was not statistically significant (7.37 vs 7.1 cm, $p = 0.08$). In our study, 13 patients (43%) underwent laparoscopic adrenalectomy, and the rest underwent open surgery. Postoperative mean urinary metanephrines were 522 ± 166 mcg/24 hours and similar in both sexes. The mean PASS score was 3.41 ± 0.28, significantly higher in females than males. Overall, 23% had a high risk of malignancy based on PASS score and was similar in both sexes (Table 1).

Perioperative complications were documented in 33% of our patients. Hypertensive crisis was the most common (17%), followed by post-operative hypotension (13%), hypoglycemia and right-sided pneumothorax. Surgical wound site complications were seen in 3 patients. Complication occurrence was similar between males and females. Patients with perioperative complications had higher baseline metanephrine levels (5490 vs 1880 mcg/24 hours, $p = 0.001$). Other factors like age, sex, pheochromocytoma spells, tumor size and mode of surgery did not show significant association with complications (Table 2).

Treatment outcomes (Table 3)

Normalization of blood pressure – Blood pressure was normalized in 50% of 20 hypertensive patients after surgery. These patients were predominantly male, younger (29.5 vs. 40 yrs, $p = 0.03$), had higher metanephrine levels (4619 vs. 1855 mcg/24 hours, $p = 0.001$) and smaller tumor size (5.91 vs 8.61 cm, $p = 0.046$).

A biochemical cure rate was achieved in 76% (n = 23) of patients at 1 to 2 weeks post-surgery. Most patients who achieved biochemical cure were older (37.7 years vs. 27.7 years, $p = 0.047$) and without pheochromocytoma spells (100% vs. 61%, $p = 0.014$). Our study found no other significant associations between other baseline factors and biochemical cure rate.

Table 1. Demographic and perioperative characteristics of study subjects

Patient factors		Total N = 30 (%)	Male n = 13 (43.3%)	Female n = 17 (56.67%)	*p*-value
Age (years)		35 ± 12.8	34.15 ± 14	35.5 ± 12	0.39
Clinical features					
1. Pheo spells		18 (60%)	5 (28%)	13 (72%)	0.035
2. Pain abdomen		16 (53%)	6 (38%)	10 (62%)	0.491
3. Orthostatic symptoms		3 (10%)	0	3 (100%)	0.110
4. Incidentaloma		2 (6%)	2 (100%)	0	0.094
Patients with blood pressure	1. Sustained hypertension	15 (50%)	6 (40%)	9 (60%)	0.873
	2. Paroxysmal hypertension	5 (17%)	2 (40%)	3 (60%)	
	3. Normal blood	10 (33%)	5 (50%)	5 (50%)	
BMI (km/m²)		19.2	20.5	18	0.93
Patients with diabetes mellitus		9 (30%)	3 (33.33%)	6 (66.66%)	0.07
HBA1c (%)		8.2 ± 1.2%	8.2 ± 1%	8.6 ± 0.7%	0.87
24-hour urinary total metanephrines (mcg/24 hrs)	Pre-op	2963.7 ± 2658	1879 ± 1560	3709.6 ± 3103	0.022
	Post-op at 2 weeks	522 ± 911	290 ± 176	699 ± 1185	0.08
Size of tumor (cm)		7.3 ± 0.53	7.1 ± 0.68	7.37± 0.68	0.43
PASS score	Total mean score	3.41 ± 0.28	2.84 ± 0.4	3.82 ± 0.37	0.04
	Low risk <4 (n)	23 (77%)	11 (48%)	12 (52%)	0.368
	High risk ≥4 (n)	7 (23%)	2 (28.5%)	5 (71.5)	
Biochemical cure achieved		23 (76%)	8 (35%)	15 (65%)	0.087
Patients with perioperative complications	Total patients	10 (33.33%)	5 (50%)	5 (50%)	0.12
	HTN Crisis	5 (17%)	3 (60%)	2 (40%)	0.45
	Hypotension	4 (13%)	2 (50%)	2 (50%)	-
	Hypoglycemia	1 (3%)	0	1	-
	Surgical complications	3 (10%)	2 (66.66%)	1 (33.33%)	-

Table 2. Association between patient characteristics and perioperative complications

Patient factors		Perioperative complications		*p*-value
		Yes (n=10)	No (n=20)	
Age (years)		29.44	37.23	0.078
Sex	Male (n=13)	5 (38%)	8 (62%)	0.314
	Female (n=17)	5 (30%)	12 (70%)	
Pheo spells (n=18)		5 (28%)	13 (72%)	0.538
Size (cm)		6.33	7.7	0.09
Urinary metanephrines (mcg/24 hrs)		5490	1880	0.001
PASS score		3.11	3.52	0.22
Type of Adrenalectomy	Open (n=17)	5 (30%)	12 (70%)	0.49
	Laparoscopy (n=13)	4 (31%)	9 (69%)	

Table 3. Association between patient characteristics and outcome variables

Patient factors		Normalisation of blood pressure in hypertensive patients (n=20)			Risk of malignancy			Biochemical cure achieved		
		Yes (n=10)	No (n=10)	*p*-value	High (n=7)	Low (n=23)	*p*-value	Yes (n=23)	No (n=7)	*p*-value
Age (years)		29.5	40.1	0.03	38.58	33.79	0.84	37.7	27.7	0.047
Sex	Male (n=13)	6 (75%)	2 (25%)	0.068	2 (15%)	11 (85%)	0.173	8 (61%)	5 (39%)	0.374
	Female (n=17)	4 (33%)	8 (67%)		5 (29%)	12 (71%)		15 (88%)	2 (12%)	
Pheo spells	Yes (n=18)	6 (43%)	8 (57%)	0.329	5 (28%)	13 (72%)	0.481	11 (61%)	7 (39%)	0.014
	No (n=12)	4 (66%)	2 (44%)		2 (17%)	10 (83%)		12 (100%)	0	
Urinarymetanephrines (mcg/24 hrs)		4619	1855	0.001	5104	2312	0.021	2875	3254	0.374
Size of tumor (cms)		5.91	8.61	0.046	9.28	6.68	0.024	7.29	7.27	0.493

Risk of malignancy by PASS score – In our study, 23% of patients had a high risk of malignancy (PASS score greater than or equal to 4). This was associated with higher metanephrine levels (5104 vs 2312 mcg/24 hours, $p = 0.021$) and larger tumor sizes (9.28 vs 6.68 cm, $p = 0.024$).

DISCUSSION

In our study, 86% of all tumors were sporadic, and four patients(14%) had features of genetic syndromes [i.e., MEN-2B(2), Neurofibromatosis (1), and VHL (1)]. According to previous studies, 80 to 85% of chromaffin-cell tumors are pheochromocytomas, and 15 to 20% are paragangliomas. One-third of these tumors had syndromic associations.[1] Similar to previous studies, most of our patients were diagnosed in their third to fifth decade, with equal occurrence among males and females.[2] Pheochromocytoma spells were common in females, younger patients, and higher metanephrine levels. Baseline characteristics and outcomes did not differ significantly between normotensive and hypertensive patients. Normotensive patients are either in the presymptomatic stage of the disease or have nonsecreting tumors.[8]

Surgery and complications

Minimally invasive surgery is the treatment of choice for small, solitary intra-adrenal pheochromocytomas without any malignant radiologic features. Otherwise, open surgery is preferred. A review by Araujo et al., on preoperative and anesthetic management recommends strict blood pressure and heart rate control, and blood volume optimization to reduce the risk of perioperative complications.[6] All our patients achieved target blood pressure, heart rate and adequate hydration before surgery. In the latest review of 40,363 post-adrenalectomy patients, surgical outcomes like complications, pulmonary compromise and length of hospital stay were better with laparoscopic adrenalectomy as compared to open surgery.[9] We did not find significant differences in complications based on the type of surgery. The key to success depends on the surgeon's expertise in handling the tumors and appropriate management of complications by the medical team to reduce morbidity.

In our study, 33.3% of patients had tumor-related perioperative complications. We found that complications were associated with higher levels of metanephrines. In similar studies, established risk factors for hemodynamic instability were high plasma catecholamines, larger tumor size (larger than 4 cm), and blood pressure fall of >10 mm Hg after alpha blockade.[7] Perioperative hypertensive crisis is caused by a massive release of catecholamines while handling the tumor, by anesthetic agents, or stress-induced. Proposed mechanisms of post-operative hypotension are withdrawal of the pressor effect of the tumor, excess use of anti-hypertensives, contracted plasma volume, or surgical blood loss.[10] Among our patients, post-operative hypotension promptly recovered with adequate intravenous fluids and minimal dosage of vasopressors. Postsurgical hypoglycemia occurs due to a rebound increase in insulin secretion, as excess catecholamines suppress insulin secretion. This complication is usually seen in 10% of pheochromocytoma patients who undergo surgery.[11] In our patients with hypoglycemia, this occurred about 6 hours after surgery. The patient was managed with IV dextrose and recovered within 24 hours of surgery.

Treatment outcomes

Normalization of blood pressure after surgery was achieved in 50% of patients in our study. Predominantly, these patients were younger and had higher metanephrines and smaller tumor sizes. The increase in tumor size was associated with failure to normalize blood pressure. Other studies have documented normalization of blood pressure in 75% of patients who undergo surgery, comparable to our study.[1] According to previous studies, persistent elevation of blood pressure post-surgery is due to incomplete resection of the primary tumor, occult metastasis, or underlying essential hypertension. Other possible causes may include excessive intravenous fluids, return of autonomic reflexes, permanent changes in vessel walls and inadvertent ligation of the renal artery.[12] Possible explanations for the low normalization rate of hypertension in our study may be due to relatively older age among these patients and low biochemical cure rates.

Biochemical cure post-surgery: The appropriate timing for post-operative evaluation of metanephrines is still debated. Few guidelines suggest testing after 1 to 2 weeks, while others suggest 2 to 6 weeks after surgery.[2,3] It is reasonable to test before the patient's discharge from the hospital or at least one week after surgery. Failure to

normalize metanephrine levels after surgery may be due to residual tumor or occult metastasis.[13] These patients have to be followed up with anatomical imaging at least 3 to 6 months after surgery.[3] In our study, 76% of patients achieved a biochemical cure. We found that the biochemical cure rate was higher in older patients and those without pheochromocytoma spells.

Risk of malignancy: In previous studies, 10 to 15% of pheochromocytomas are malignant.[14] Currently, there are no definite prognostic markers to predict the malignant behaviour of pheochromocytoma. PASS is a histological algorithm with a structural scoring system to predict aggressive biological behavior. It incorporates 12 histological parameters overexpressed in metastatic cases, and a score greater than or equal to 4 predicts the risk of future aggressive behavior.[15] This score has a high negative predictive value, with a sensitivity of close to 100% and specificity of 75% to identify malignant potential.[16,17] In our study, 23% of patients had PASS greater than or equal to 4, associated with higher metanephrines and larger tumor size.

This study has certain limitations. It included a relatively small sample size and was conducted at a tertiary referral center. Hence, most patients were referred due to increased severity and end-stage disease.

CONCLUSION

Pheochromocytomas are rare large tumors with varied clinical presentation, high biochemical cure rates, and low mortality. Young age, smaller tumors and higher metanephrine concentrations were associated with the normalization of blood pressure post-surgery. In our study, older patients and those without pheochromocytoma spells had better biochemical cure rates. Patients with higher baseline metanephrines are predisposed to perioperative complications, whereas both higher metanephrines and large-size tumors were associated with aggressive behavior of the tumor. Sex, blood pressure and mode of surgery may not have any effect on treatment outcomes. Regular annual follow-up is recommended in all postoperative patients.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
GN: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization; **DS:** Methodology, Validation, Formal analysis, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **UKS:** Validation, Formal analysis, Investigation, Resources, Visualization, Supervision, Supervision; **AB:** Conceptualization, Methodology, Software, Validation, Resources, Data curation, Writing – review and editing, Supervision; **AKB:** Conceptualization, Methodology, Software, Formal analysis, Resources, Data curation, Writing – original draft preparation, Visualization, Supervision.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

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