

SURGERY FOR PHEOCHROMOCYTOMA: A PROSPECTIVE CLINICOEPIDEMIOLOGICAL STUDY

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Pheochromocytomas are rare tumors of chromaffin cells arising from adrenal medulla or elsewhere within the sympathetic paraganglionic axis. An estimated 800 cases are diagnosed yearly in the United States.¹ The importance of recognition of this disease lies in the fact that over 90% of the patients properly diagnosed and treated are curable.² Very few studies have been reported from Saudi Arabia and the Middle East on the operative experience on pheochromocytoma.³⁻⁵ This prospective study presents 10 years of clinical experience on the surgical management of pheochromocytoma carried out at the Riyadh Medical Complex (RMC), one of the tertiary referral centers in the Central Region of Saudi Arabia. The objective was to analyze the clinical presentation, localization, surgical management, pathology and outcome of consecutive patients of pheochromocytoma observed over the 10-year period.

Patients and Methods

All patients who were diagnosed and managed for pheochromocytoma at the Department of Surgery at RMC from January 1991 to December 2000 were included in the study. They included patients of all ages and both sexes. Various parameters studied were demographic data, clinical presentation, past medical and family history, preoperative laboratory and imaging studies for tumor confirmation and localization, preoperative preparation, surgical procedures, tumor pathology, morbidity and mortality. The diagnosis of pheochromocytoma was based on typical clinical presentation confirmed subsequently by increased catecholamine. The adult normal values for 24 hours urinary VMA ranged between 1-11 mg/24 hours, whereas the upper normal value for that of 24 hours urinary metanephrines was taken as 100 mcg/24 hours. Tumor localization was made employing ultrasonography and CT scan. MIBG scan was used to diagnose or exclude extra

adrenal or metastatic tumor. MRI scan was performed only selectively, to further confirm the diagnosis and in localization of extra-adrenal tumors or in pregnant patients.

Preoperative management included alpha-blockade with phenoxybenzamine in a dose ranging from 20 to 400 mg daily in divided doses for at least two weeks prior to surgery. The blockade was considered adequate with signs including normalization of blood pressure, postural hypotension, weight gain, nasal stuffiness and a decreased hematocrit. Beta-blockers (propranolol) were selectively used in patients with significant supraventricular tachycardia or ventricular tachycardia. Chemoprophylaxis included intravenous administration of 1.5 g of cefuroxime sodium at induction. Midline transabdominal approach was employed for resection in all cases. The intraoperative control of blood pressure was further maintained with intravenous sodium nitroprusside. The resections were carried out according to the standard principles of surgery for such tumors. This included adequate preoperative preparation, anesthetic precautions, minimal handling, careful mobilization, dissection and securing the venous drainage prior to arterial supply. The operative findings were recorded and tumor histopathology was obtained. The final diagnosis of malignancy was strictly made on the evidence of gross tumor infiltration into surrounding structures or presence of metastases along with microscopic capsular or vascular invasion. Perioperative mortality was defined as death within 90 days of hospital admission.⁶ Follow-up was made through documented outpatient visits, phone and postal questionnaire contact by the physician. Statistical analysis was performed using SPSS-MAC employing Students *t*-test and Chi-square test. A probability value of <0.05 was the limit of statistical significance.

Results

A total of 17 patients with adrenal and extra-adrenal pheochromocytoma were managed during the 10-year period under review. One patient who refused surgery and two who were lost to follow up were excluded from the final analysis. Of the remaining 14 patients with complete medical records and follow-up data, five (35.7%) were male and 9 (64.3%) were female. The mean age at presentation was 38.7 years (range, 29-43 years). Nine

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TABLE 1. *Clinical presentation of pheochromocytoma cases (n=14).*

Symptoms	No. of patients	%
Hypertension	12	85.7
Headache	8	57.1
Palpitations	7	50.0
Sweating	5	35.7
Flushing/Pallor	5	35.7
Pain abdomen	3	21.4
Weight loss	2	14.3
Obstructive jaundice	1	7.1

TABLE 2. *Summary of operative complications (n=14)**

Complication	No. of patients	%
Intraoperative		
Hypertensive crisis	1	7.1
Splenectomy	1	7.1
Inferior vena cava tear	1	7.1
Postoperative**		
Chest infection	3	21.4
Wound infection	2	14.3
Arrhythmias	2	14.3
Hemorrhage needing transfusion	1	7.1
Urinary tract infection	1	7.1

*Overall morbidity 28.6%; **some patients had more than one complications.

patients were Saudis, while five (35.7%) were non-Saudis. Family history of hypertension was available in five (35.7%) cases. One (7.14%) female patient presented with multiple endocrine neoplasia (MEN) type II A syndrome. Episodic or sustained hypertension was the most common clinical presentation which was observed in 12 (85.7%) patients, followed by headache (57.1%) and palpitations (50%) (Table 1). Mean time interval between initial symptoms and diagnosis was 2.3 years. All patients had raised vanillylmandelic acid (VMA) in 24-hour urine collection (100%), while raised catecholamine levels were detected in 12 (85.7%) cases. Ultrasound was able to detect all adrenal tumors (100%) and 1 of 3 extra-adrenal tumors (33.3%). MIBG scan (employed in 10 cases) localized the adrenal as well extra-adrenal tumors in all cases (100%). CT scan, performed in 13 patients, localized the tumors in 100% of both adrenal and extra-adrenal sites. MR scan, performed in 6 patients (including one pregnant patient), was diagnostic and localized the tumor in 5 (83.3%) cases (3 adrenal, 2 extra-adrenal), and missed one extra-adrenal tumor (16.7%). Nine (64.3%) patients had right-sided adrenal tumors, while 3 (21.4%) had left-sided tumors. Twelve (85.7%) patients had adrenal tumors and 2 (14.3%) had extra-adrenal tumors. One of them presented with hypertension and obstructive jaundice, and had tumor located in the region of porta hepatis (Figure 1). The second patient, a pregnant Syrian lady, was initially being managed as eclampsia of pregnancy, and was later found to have two extra-adrenal tumors located in right pararenal and subaortic regions (Figure 2). One patient (7.14%) developed hypertensive crisis during mobilization of the extra-adrenal tumor. This was managed successfully with intravenous nitroprusside infusion. One patient (7.14%)

with left adrenal tumor had gross invasion of the adjacent structures signifying malignancy, and needed additional splenectomy.

Histopathology was suggestive of benign pheochromocytoma in 11 (78.6%) cases, high microscopic risk of malignancy in 2 (14.3%) cases and invasive malignant pheochromocytoma in 1 (7.14%) case. Overall, morbidity was 28.6%. Chest infection was the most common postoperative complication observed in 3 (21.4%) patients. Table 2 summarizes various intraoperative and postoperative complications. There was no hospital mortality. Follow-up was available on all patients (mean 6.1 years). Surgery caused remission of hypertension in 8 (57.1%) patients, improvement in 4 (28.6%), and no change in 2 (14.3%) patients. In the last group, the interval between initial symptoms and diagnosis was significantly longer (5.7 years). No patient presented with recurrent tumor.

Discussion

Pheochromocytomas are infrequent tumors of the sympathetic paraganglionic axis. The exact incidence of these tumors is unknown, but it is estimated that pheochromocytoma occurs in 0.1%-0.2% of hypertensive patients in the United States.⁶ It is often stated that 10% of paraganglion tumors are extra-adrenal and 10% are malignant. The knowledge of and awareness about these rare tumors is important, as surgical excision offers a high rate of cure for hypertension.

The optimal management of adrenal and extra-adrenal pheochromocytomas has perplexed surgeons since 1926, when both Charles Mayo and Cesar Roux reported the resection of such tumors.⁷ The surgery on adrenal and extra-adrenal neoplasms is an infrequently performed procedure in general surgery. An open surgical approach, through posterior, anterior transabdominal or thoracoabdominal route, was considered as "gold standard" for adrenal surgery until the 1990s. With increasing worldwide experience, laparoscopic adrenalectomy has now been regarded as the new "gold standard" for nearly 60% of patients requiring adrenalectomy.⁸ When retrospectively compared to open surgery, laparoscopic resection, employing the transperitoneal or retroperitoneal approach, is superior in terms of postoperative pain, hospital stay, return to normal activity and morbidity. The results are safe, reproducible and effective with comparable morbidity and mortality.⁹ However, larger tumors greater than 8-10 cm diameter, adrenocortical carcinomas and ganglioneuromas of the adrenal still favor an open approach.¹⁰ In experienced hands, the laparoscopic technique has also been regarded as the procedure of choice for even pheochromocytoma.¹¹

There are few reports of adrenalectomy from the Gulf region. Bissada et al.³ (12 cases) and Al-Awami et al.⁵ (13 cases) have presented their experience on pheochromocytoma and adrenal surgery from Saudi Arabia

FIGURE 1. CT abdomen shows mass in portahepatis region (paraganglioma - marked as black square).

FIGURE 2. CT abdomen shows left suprarenal tumor (marked as squares labeled 1 & 2) — malignant pheochromocytoma.

previously. At Riyadh Medical Complex, laparoscopic adrenal surgery is still in the learning curve. This study only presents the experience of open resectional surgery for pheochromocytoma. The slight female preponderance (1.8:1), though statistically insignificant, represents a higher predilection for the female sex. This is in accordance with the local and Western experience.^{5,6,12,13} The mean age of 38.7 years is also similar to other reports.^{5,12} Young patients presenting with hypertension need a careful search and thorough investigations for a treatable surgical pathology. One patient (7.14%) was found to have MEN type II A syndrome which is well within the 10.9% presented by Pommier et al.¹⁴ Extra adrenal tumors accounted for 14.3% and is in accordance with the 15% incidence reported in the review by Whalen et al.² Hypertension, sustained or episodic, was the most common clinical presentation observed in 85.7% cases. This is similar to regional and Western figures.^{3,5,8,12} CT scan localized the tumors in 100% cases and can be regarded as the localizing investigation of choice in tumors of the paraganglionic origin. CT has been reported to underestimate the real size of adrenal lesions that are larger than 3 cm by 18%.¹⁵ Surgeons and endocrinologists should interpret the preoperative size of adrenal lesions with caution before planning a resectional surgery. I¹³¹MIBG scan localized both adrenal and extra-adrenal tumors in all the cases (100%). For pheochromocytomas in general, it demonstrated sensitivity of 90% and specificity approaching 99%.¹⁶ It has the added advantages of imaging the entire body and being noninvasive. The disadvantages include limited availability, high cost, poor anatomical localization and the necessity to perform scanning 24, 48 and 72 hours after injection.

MRI scan (performed selectively in 6 patients) localized the tumor in 83.3% cases. It clearly demonstrated its superiority in localizing the multiple extra-adrenal lesions in one pregnant patient. MRI has been used with success in pregnant patients in whom ultrasound is usually ineffective and CT and MIBG scans are deferred to avoid exposure to ionizing radiation.¹⁷ Its additional advantages include noninvasiveness, lack of radiation exposure, good tissue characterization, and a clear demonstration of the relationships between lesion and surrounding structures. Its disadvantages, however, include limited anatomical coverage, high cost and long duration of examination.

All three imaging modalities have their own advantages and disadvantages but, if not specifically contraindicated, may be regarded as complementary to each other. Two (14.3%) patients developed preoperative complications; one had hypertensive crisis, and the second had to undergo

splenectomy due to extensive tumor infiltration. Intraoperative hypertensive crisis and splenectomy have been reported as known complications during adrenal surgery, and may be independent of tumor manipulation and location.^{13,18} However, careful preoperative blood pressure control along with vigilant intraoperative monitoring help in preventing the hypertensive crisis. The overall postoperative morbidity (28.6%) was slightly higher than the 23.6% reported by Plouin et al.,¹⁸ but may be explained by the small sample size, presentation with obstructive jaundice (wound infection and chest infection) and malignancy (wound infection). The development of arrhythmias in two patients may be explained by mobilization of tumors in multiple extra-adrenal tumors in one patient, and an element of pre-eclampsia in the second patient. Invasive malignant pheochromocytoma was found in one patient (7.31%), which was well within the 10% incidence of malignancy reported in the literature.^{6,7}

There are no histologic features that distinguish benign from malignant pheochromocytoma. Microscopic evidence for local invasion of tissue or blood vessels is suggested to be associated with malignancy.¹⁹ Criteria based on tumor size, mitotic index, and DNA ploidy have also been reported to be helpful in some series, although they are not always reliable predictors of biologic behaviour.²⁰⁻²²

Because the distinction between benign and malignant tumors cannot be made with certainty, careful surveillance is recommended for a prolonged period after the initial surgical resection. The remission of hypertension observed in 57.1% and improvement in another 28.6% is similar to the experience of Mannelli et al.¹² Alleviation of hypertension and no tumor recurrence during a mean follow up of 6.1 years well justifies the early resectional surgery for this potentially curable rare cause of hypertension in young patients. Reversal of hypertension by surgery, however, depends on an early diagnosis.⁸

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