Presentation, Imaging, Surgical Management and Outcome of Pheochromocytoma: NCI experience

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Abstract: Objective: To review the clinical presentation and outcome of the surgically managed pheochromocytomas in a tertiary cancer care center in Egypt. **Patients and methods:** A retrospective analysis of all patients (36 patients) diagnosed with pheochromocytomas and underwent surgery in NCI in Cairo University during the period from 2010 to 2015. **Results:** The most common presentation was abdominal pain in 20cases (55.6%), surgical resections of 35 pheochromocytomas were done through a classic laparotomy approach in 33 (91.7%) and 2 (5.6%) through laparoscopic resection. Intraoperative transient hypertensive crisis occurred in 33 (91.7%) cases despite the use of preoperative medical treatment for hypertensive cases. Cure was achieved in 33 cases (91.7%) with overall survival of 100% and recurrence in 2 cases (5.6%). **Conclusion:** The safe surgical management of pheochromocytomas requires close intraoperative monitoring of hemodynamic functions as well as tight intraoperative blood pressure control. Limiting manipulations of the tumor prior to ligation of adrenal veins which should be done early prevents life threatening hypertensive crisis especially when dealing with asymptomatic adrenal masses. Adequate exposure avoids other organ injury and helps complete tumor resection.
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1. Introduction

Pheochromocytomas (PC) are rare catecholamine secreting tumors arising mostly from the adrenal medulla or from extra adrenal sites (paragangliomas) in 10% of cases, with an incidence of 1-6 per million, and a prevalence of 0.1-0.6% in patients with hypertension. (1) referred to be the "10% tumor" because 10% are extra adrenal, 10% are malignant, 10% bilateral, 10% in children, and finally 10% are hereditary. The extra adrenal tumors are more likely to be multiple and malignant. They synthesize the catecholamines; norepinephrine, epinephrine and more rarely dopamine. There is no consistent correlation between circulating levels of the catecholamines and the presence of symptoms and/or hypertension (2) Headache, palpitations and sweating are described as the most common symptoms (3). The rarity and variability render these tumours very difficult to diagnose. The laboratory diagnosis of these tumours is based on the identification of excessive secretion of catecholamines and/or of their derivates (4,5). CT scanning and MRI have higher sensitivity in detecting pheochromocytomas than do nuclear medicine scanning with 131 metaiodobenzylguanidine (MIBG), although MIBG uptake is more specific. Some authors prefer to use (MIBG) uptake scanning as the initial screening modality because it enables whole-body imaging, making it useful for the detection of extra-adrenal tumors and metastatic deposits (6&7). Unfortunately, the cost and lack of availability of MIBG studies restrict its use (8). In addition, imaging with 131I-MIBG can be time-consuming, and the technique has limited ability to provide sufficiently accurate information for surgery. In case of positive scans, it may indicate patients that are potential candidates for [131I]-MIBG therapy (9).

Despite advances in medical treatment to palliate the debilitating symptoms of these tumors, Surgical excision remains the main line of treatment for benign and malignant pheochromocytomas (10).

In this retrospective study, we reviewed the presentation and the management and the outcome of the pheochromocytoma cases that presented to the National Cancer Institute, Cairo during a five years' period.

2. Patients and methods:

This is a retrospective chart review analysis of 36 patients diagnosed with PC and who underwent surgery. The study period was from 2010 to 2015in the National Cancer Institute in Cairo university. Data were retrieved from the files of the patients mainly the clinical presentation, pathologicaldata, imaging data, the perioperative management, surgery type, approach, intra and post-operative management including drugs, complications, Intensive care unit admission and MIBG therapy in one case with metastatic lesions. The outcome was assessed in the form of overall survival and disease free survival.

3. Results:

PC were diagnosed in 36 patients ranging in age from 11 to 65 years, median age is 37 years. Males represented 47.2% (17cases) and females 52.8% (19 cases). Malignant cases were 9(25%), benign cases (16.7 cases) and (58.3%) 21 cases are of borderline biologic behavior. The tumor site was mostly adrenal in 33 cases (91.7%) with 22 cases on the right side (61.7%), 10 cases on the left side (27.8%), 1 bilateralcase (2. 8%). Extra adrenal sites in 3cases (8.3%). No family history of endocrine malignancies in 34 cases (94.4%) and 2 cases (5.6%)had unknown family history.

The most common presenting symptom was abdominal pain in 20 cases (55.6%) and those patients had normal blood pressure, only 13 patients had hypertension (36.1%) at diagnosis. Three patients had abdominal distension (8.3%) and hematuria in 2 cases (5. 6%) (table 1). Preoperative diagnosis was based on clinical symptoms, estimation of the 24 hours' urine sample of vanylmandelic acid(VMA), plasma epinephrine and norepinephrine which were normal in 21 cases (58.3%)and high in 11 cases (30.6%) before surgery. CT was positive for a suprarenal mass in 34 cases (94.4%) with a mean tumor size on CT of (8.1cm). Metaiodobenzylguanidine (MIBG) scan was used in only in 16 cases (44.4%) due to limited availability and the cost of the MIBG, nine of them (25%) were positive and the rest were negative (19.4%)for localization of the tumor as the lesion was not avid. Preoperative medical treatment in the form of alpha and beta blockers (minipress, amlodipineor capoten) were given in 12 cases (33.3%)with hypertension or high catecholamine levels 2 weeks before surgery to normalize the Blood pressure. Infusion of crystalloids was done before surgery to expand the circulating blood volume.

Surgical Treatment:

35 cases (97.2%) were excised through a laparoscopy in 2patients (5.6%) and laparotomyin 33 (91.7%) patients using subcostal incision in 27 cases (75%), midline incision in 5 cases (13.9%), suprapubic incision in 1 case (2.8%) and 1metastatic case to the lung and skin was biopsied only (2.8%) through laparoscopy. Positive lymph nodes both grossly and pathologically were present in 5 cases (13.8%) and negative in 30 cases (83.3%).

Intraoperative transient hypertensive crisis occurred in 31cases (86.1%) during manipulation of the gland which were controlled with sodium nitroprusside.

ICU admission was required for most of the patients 31 cases (86.1%) for monitoring of any haemodynamic instability following surgery. Postoperative hypertensive crisis occurred in 2 cases (5.6%).

Pathological marker chromogranin A was positive in 34 cases (94.4%) and not done in 2 cases (5.6%).

Metastatic Disease occurred in 2 patients (5.6%) in the form of lung metastasis30 months after surgery and the tumor was categorized as malignant by pathologist, lung and liver metastasis occurred in another patient 33 months after surgery with original tumor size 10x7cm and 11x10cm respectively. One of the two metastatic patients was referred to MIBG therapy and received 100mCi, the patient is partially controlled.

Overall survival was 100% with 33 cases free of symptoms with normal blood pressure after a mean follow up duration of 32 months.

Table (1): Clinical Presentation.

Clinical presentation	**Hypertension**	***13(36.1%)***
	Hematuria and dark urine	***2(5.6%)***
	Abdominal pain	***20(55.6%)***
	Abdominal distension	***3(8.3%)***

4. Discussion:

In this study the clinical presentation of PC. was variable and different from the classic well known triad of episodic headache, sweating, and palpitation (11). Abdominal pain was the most common symptom in 55.6% and hypertension was only present in 36.1%. Normotension in patients with PC was reported to have an incidence of 62.5% in previously published series on incidental PC in Italian patients (12). The incidence of PC is less than 0.5% in patients with hypertension; however, it has been demonstrated to account for as much as 4% in patients who present with an adrenal incidentaloma. In our series, hypertension was the presenting symptom in one patient as the clinical presentation of PC primarily depends on the type and pattern of catecholamine released from the tumor. PC may be asymptomatic and unsuspected(13). One explanation may be that tumour dependent hormone production may remain silent for long period of time, because active catecholamines can be converted into biologically inactive metanephrines by catechol-O-methyltransferase within the tumour (14, 15, 16).

In our study, there was a difference between the occurrence in the right (61%) and left (27%) adrenal which agree with other PC series reported a significantly more frequent occurrence in the right adrenal (17,18), but could not provide a sound explanation for their finding.

The urinary VMA has fallen out of favor as a routine test for PC, in our patients VMA was high only in 30.6% and so It is limited in literatures by its poor sensitivity of 76 percent. But elevated urinary

VMA should have changed management of this patient, as it has been shown to have a specificity of 96 % for the presence of a pheochromocytoma (19).

Computed tomography was the base for the diagnosis since it recognized an adrenal mass in all our cases. A value of greater than 10 HU is associated with malignancy, PC, and less commonly adenoma (roughly 30 percent of adenomas do not have a large lipid content). whereas carcinomas or PCs are associated with delayed (< 50 percent at 10 minutes) contrast material washout (20). But Computed tomography has a little role in cases of extra-adrenal location in comparison with MRI which is the most sensitive modality for identification of PCs and is particularly useful in cases of extra-adrenal location. The overall sensitivity is said to be 98% (21). The MIBG add great value in case of metastatic disease as reported by many studies. Unfortunately, in our study not all the patients underwent I^{131}-MIBG scan due to its limited availability and its cost yet one of the two metastatic patients underwent I^{131}- MIBG scanned was avid then referred for MIBG therapy and the patient was in partial remission.

The positive chromogranin A is essential to diagnose the tumor pathologically and it was done for all the patients in this study. Matched with Von Dobschuetz *et al.,* found chromogranin A and synaptophysin to be highly positive in PCs and paragangliomas (22).

In our study the MIBG scan for 16 patients, 9 of them were true positive and the rest were false negative with sensitivity 56 % and specificity 100 % with agreement regarding specificity yet not matched in case of sensitivity with Sisson. JC, *et al.,* that reported that the gold standard functional imaging method for PHEOs/PGLs was scintigraphy with [131I]-MIBG, with reported sensitivity of 77%–90% and specificity of 95%–100% (23).

Although debatable the preoperative medical management was essential especially that almost all cases (hypertensive and normotensive) had an intraoperative hypertensive crisis that could have been worse without the preoperative medical measures(24).

There are published data advocating the elimination of the preoperative medical treatment in PCs as administration of preoperative fluids and hypotensive drugs as this management is not supported by any evidence based study(25).

The intraoperative hypertensive crisis are mainly due to tumor manipulation, so careful surgical handling of tumor tissue, early ligation of renal veins, limited intraabdominal pressure (in laparoscopy), adequate depth of anesthesia and muscular relaxation, and the use of fast-acting vasoactive agents are the only proven means for limiting intraoperative hypertension and so, administration of fluid and/or vasopressor agents intraoperatively, whenever necessary, is as effective as preoperative fluid infusion in controlling post tumor removal hypotension(26).

Intraoperative communication between the anesthesiologist and the surgical team is very vital. Intraoperative hypertensive crisis occurred transiently in 86.1 % of our cases during manipulation of the adrenal tumor prior to vascular control of the venous drainage. Usually, cessation of manipulation is sufficient to improve hemodynamic function. To avoid hypertensive crises from catecholamine release, it is important to ligate the adrenal vein early. However, vascular control of the adrenal vein can also cause hemodynamic instability as a sharp decrease in catecholamine release to the peripheral blood stream can cause a drop-in blood pressure.

In This study, with the exception of the 2 cases resected laparoscopically which were 4x4 cm in size, the rest of the cases were resected through a laparotomy approach mainly because of the large size of the tumor on CT that was proved pathologically. To our knowledge there is no randomized clinical trial comparing the laparoscopic approach and the open technique because of rarity of PC. Laparoscopic adrenalectomy is now used for resection of small adrenal tumors(27). Several series showed that laparoscopic adrenalectomy is associated with less pain, less blood loss, less hospital stay, and less surgical morbidity than open adrenalectomy (12). Other series recommended open resection for tumors larger than 6 cm in size to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence and in paragangliomas which are more likely to be malignant and are frequently found in areas difficult for laparoscopic resection (12).

All patients were admitted to intensive care unit as PC patients may require invasive cardiovascular monitoring. As large amounts of alpha antagonists are used intraoperatively, postoperative hypotension may be observed. These patients may require extensive fluid resuscitation and vasoconstrictive agents to maintain blood pressure (28). Also, blood glucose level must be monitored as increased insulin secretion as a result of decreased levels of catecholamines due to removal of the tumor may cause life-threatening hypoglycemia (29).

Metastatic disease occurred only in 2 patients with a tumor size more than 10cm, in agreement with several studies that showed large tumors (>5 cm) have a higher incidence of recurrence and metastasis and therefore should be followed vigilantly. Routine imaging and testing of plasma or urinary metanephrines for prompt diagnosis of recurrence should be done (30).

5. Conclusion:

Surgical excision remains the main line of treatment of pheochromocytomas. Intraoperative communication between the anesthesiologist and the surgical team is very vital, Limited manipulations, tight intraoperative blood pressure control, Adequate exposure to avoid other organ injury, early ligation of adrenal veins and complete tumor resection, all will lead to safe surgical management of pheochromocytomas, MIBG therapy add role in metastatic functioning lesions with fair control if the lesions are avid in diagnostic scan.

Abbreviations:

Pheochromocytomas (PC)
Metaiodobenzylguanidine (MIBG)
Vanylmandelic acid (VMA)

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Conflict of interests: The authors report no conflict of interest.

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