

Medical management of pheochromocytoma: Role of the endocrinologist

M. K. Garg, Sandeep Kharb, K. S. Brar, Abhay Gundgurthi, Rakesh Mittal¹

Department of Endocrinology, Army Hospital (Research and Referral), Delhi Cantt, ¹Department of Pedodontics, NIMS Dental College, Jaipur, Rajasthan, India

ABSTRACT

Pheochromocytoma is a rare tumor arising from chromaffin cells in adrenal medulla or other paraganglia in the body, which may be associated with many genetic syndromes and mutation. The role of endocrinologist is in biochemical diagnosis of suspected cases; its anatomic and functional localization with the help of imaging like CT, MRI, and nuclear scanning; preoperative control of hypertension; and postoperative follow-up of cases that have undergone surgical resection. Familial and genetic screening of cases and their family is important to detect occult cases. Endocrinologist will also play a role in cases with malignant pheochromocytoma in assessment of metastasis, control, chemoradiotherapy, and follow-up.

Key words: Adrenal, hypertension, secondary hypertension, adrenal tumour

INTRODUCTION

Pheochromocytoma is a rare tumor arising from chromaffin cells in adrenal medulla or other paraganglia in the body.^[1] Pheochromocytomas cause increased catecholamine production leading to its clinical manifestations. Pheochromocytoma derives its name from phaios (dusky), chroma (color), cytoma (tumor). The term pheochromocytoma was coined by Pick in 1912.^[2] Eighty-five percent of pheochromocytomas are adrenal and remaining 15% are extra-adrenal. Extra-adrenal pheochromocytomas are usually called paragangliomas. Pheochromocytoma as an entity is known since 1886 and its first successful surgical removal was reported in 1926 by Roux.^[3] Most of pheochromocytomas are sporadic and earlier only 10% were believed to be familial but in recent series up to 24% are reported to be familial where they

may be associated with multiple endocrine neoplasia (2A and 2B), neurofibromatosis, Von-Hippel-Lindau syndrome, and human paragangliomas syndromes, cerebellar hemangio-blastoma, Sturge-Weber syndrome, and tuberous sclerosis.^[4] Extra-adrenal pheochromocytomas can be located along cranial nerves or vagus (parasympathetic), or they can be associated with sympathetic ganglia in pelvis, mediastinum, or neck. The most common extra-adrenal site in abdomen is at the origin of the inferior mesenteric artery called the area of Zuckerkandl.^[1]

ROLE IN DIAGNOSIS

Pheochromocytoma is present in about 0.01-0.1% of hypertensive population.^[5] A patient of hypertension should be investigated for the secondary cause of hypertension including pheochromocytoma if he/she has classical symptoms of pheochromocytoma; or presents with severe hypertension or hypertensive crisis; or presents at age <20 years or >50 years of age; or has resistant hypertension; family history of pheochromocytoma-associated hereditary syndromes; or detected incidental adrenal mass on imaging.^[6] Pheochromocytoma classically presents with triad of episodic headache, sweating, and hypertension. However, it is an enigmatic disease in which

Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/2230-8210.86976

Corresponding Author: Col. M. K. Garg, Department of Endocrinology, Army Hospital (Research and Referral), Delhi Cantt, New Delhi- 10, India.
E-mail: mkgargs@gmail.com

13% of patients are normotensive; 50% are persistently hypertensive; and 50% intermittently hypertensive. Patients with pheochromocytomas may present with sustained hypertension that is resistant to conventional treatment. Patients presenting with normal blood pressure usually have a small or large tumor (due to intratumoural metabolism); or pheochromocytoma that has been incidentally detected during familial screening, pure epinephrine secreting pheochromocytoma as in MEN-associated tumors, associated volume depletion, receptor down regulation due to persistently high levels of catecholamines, catecholamine induced dilated cardiomyopathy, or release of adrenomedullin by the tumor which is a vasodilatory peptide.^[7] Pheochromocytoma may also present with hypotension, particularly with postural hypotension, or with alternating episodes of high and low blood pressure if they are on high dose of antihypertensive medications or pure epinephrine secreting tumors.^[8] A patient can present with anxiety or fear attacks, stroke in young, or congestive heart failure. Less commonly, severe hypertensive reactions may occur during incidental surgery, following trauma, exercise, drug intake, or micturition (in the setting of bladder pheochromocytoma) when the diagnosis is unsuspected [Table 1]. An unrecognized pheochromocytoma may lead to death as a result of a hypertensive crisis, arrhythmia, myocardial infarction, or multisystem crisis.^[9]

The detection and localization of pheochromocytoma have been facilitated by recent advances in biochemistry, radiology, and functional imaging in the form of ¹²³I-meta-iodo-benzyl-guanidine (MIBG), 18-fluoro-dihydroxyphenylalanine (¹⁸F-DOPA) positron emission tomography (PET-CT), 18-fluorodeoxyglucose (¹⁸F-FDG) PET-CT, and octreotide scan. But still clinical recognition of pheochromocytoma is missed many times;^[10] and missed diagnosis or improperly treated can prove fatal; thus its early detection and complete treatment is a must which usually involves surgical resection.^[11]

Classically pheochromocytomas are described as

Table 1: Conditions which can precipitate adrenergic crisis

1. Postural changes or increase in intra-abdominal pressure
2. Exertion, trauma
3. Foods and beverages: i.e. banana, cheese, caffeine
4. Emotional stress
5. Urination (Bladder pheochromocytoma)
6. Drugs: Corticosteroids, metoclopramide, phenothiazines, tricyclic antidepressants, sympathomimetics, morphine nasal decongestants, glucagon, chemotherapeutic agents
7. Intravenous urographic contrast
8. Induction of anesthesia
9. Manipulation of tumour

catecholamine secreting tumors but it is important to understand that though secretion of catecholamines is episodic but their metabolism is constantly going on inside pheochromocytomas,^[12] which has important implication in screening for pheochromocytomas as the best screening test for pheochromocytoma is assessment of metabolites of epinephrine and nor-epinephrine which are metanephrine and nor-metanephrine respectively.

Presently the best screening test to confirm pheochromocytoma is serum-free metanephrines and normetanephrines levels in view of its high (97-100%) sensitivity, but it has low specificity (82-85%) resulting in high false positive cases. Also plasma-free metanephrine assays are still not standardized world over.^[13,14] Secretion of catecholamines from pheochromocytoma is episodic; thus single estimation of urinary epinephrine and norepinephrine is likely to miss the diagnosis of pheochromocytoma in many cases, more so in familial cases where up to 29% cases may have false negative results.^[15] A plasma-free metanephrine and normetanephrine test can miss exclusively dopamine secreting tumors, or small pheochromocytomas (<1 cm size).^[12,14] Twenty-four-hour urinary-fractionated metanephrines and normetanephrines can be used with slightly less sensitivity (97%) but better specificity (98%). One advantage of urinary assays is that they are more standardized; however, 24-hour urine samples are difficult to collect in children and are quite cumbersome to the patient and many times urinary sampling is inaccurate so it is advised to measure urinary creatinine along with it to confirm adequacy of specimen.^[16]

Importantly due to lower prevalence of pheochromocytoma and high sensitivity of the plasma metanephrine test; false positive cases are likely to exceed true positive cases. Thus, one clinical dilemma in the case of positive biochemical test is to rule out false positive results. False positive results can be minimized by collecting plasma samples with patients lying supine for at least 20 minutes before sampling. To avoid any stress associated with the needle stick, samples should ideally be collected through a previously inserted intravenous line. Patients should have refrained from nicotine and alcohol for at least 12 hours, and to minimize analytical interference should have fasted overnight before blood sampling. There is also often a need for patients to avoid medications which affect assays or which interfere with catecholamine metabolism. Most common drugs causing false positive results are tricyclic antidepressants and antihypertensive medications.^[17] Other drugs can also interfere with plasma and urinary metanephrine estimations [Table 2].^[18] In such cases with false positive results, high plasma normetanephrine to norepinephrine

or metanephrine to epinephrine ratios have been found to be strongly predictive of pheochromocytoma. Lack of decrease (fall in normetanephrine by 40% or below upper reference limit) and elevated plasma levels of norepinephrine or normetanephrine after clonidine also confirm pheochromocytoma with high specificity (98-100%).^[17] A provocative test with glucagon is not used now days.

About one-fourth of pheochromocytomas are familial and are associated with various syndromes.^[4] Hence, genetic analysis and family screening are prudent on part of endocrinologist as per Figure 1.

Table 2: DO's and DON'T in pheochromocytoma

- A. For 24 hour urine collection: To avoid false-positive results for catecholamines and metanephrines, tell your patient to avoid these drugs for 3-5 days before the 24-hour urine collection: acetaminophen, benzodiazepines, buspirone, caffeine, cocaine, diuretics, dopamine, dopaminergic agents, labetalol, levodopa, MAO inhibitors, metoclopramide, methyl dopa, nicotine, sympathomimetics, tricyclic antidepressants, vasodilators.
- B. For pre-operative preparation and intra-operative management:
1. Avoid diuretics for control of hypertension
 2. Don't restrict salt
 3. Avoid alone beta-blockers
 4. Achieve adequate pre-operative heart rate and BP control
 5. Achieve volume replete state pre-operatively with iv fluid
 6. Stop phenoxybenzamine 48 hour before operation
 7. Keep phentolamine/sodium nitroprusside/labetalol ready
 8. Do vigorous fluid replacement on ligation of adrenal vein
 9. In extra-adrenal/bilateral pheochromocytoma rule out multiple pheochromocytoma by functional imaging before surgery

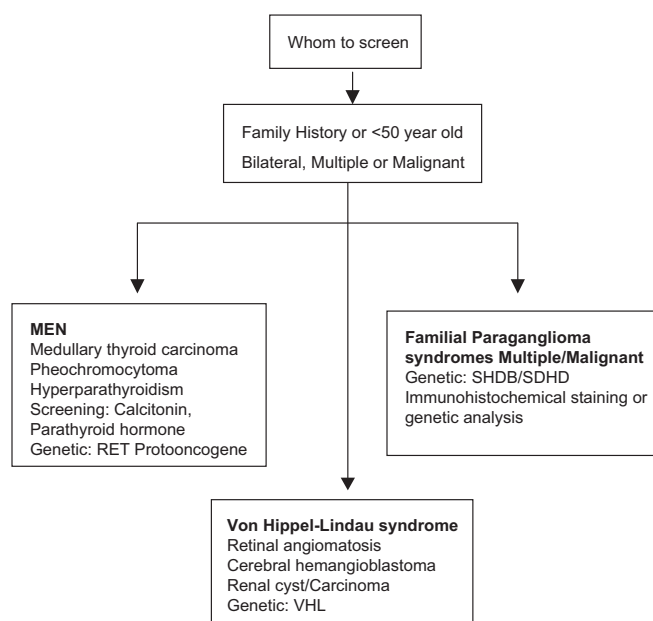


Figure 1: Genetic screening in patients with pheochromocytoma

Localization of pheochromocytomas

Localization of Pheochromocytomas is only done once biochemical diagnosis is confirmed. Magnetic resonance imaging (MRI) and computerized tomography (CT) scan have around 95% sensitivity and 70% specificity for adrenal pheochromocytomas [Table 3]. For extra-adrenal pheochromocytomas MRI is better than a CT scan as it has higher (90%) sensitivity in localizing extra-adrenal pheochromocytomas. On T1 imaging pheochromocytomas are isointense to liver, kidney, and muscle while highly intense signal is seen on T2 images and no signal loss on opposed phase images because of the absence of fat in pheochromocytomas.^[19,20]

After localization of pheochromocytomas before surgery functional imaging is also required to rule out extra-adrenal pheochromocytoma in view of about 24% of pheochromocytomas being hereditary and to rule out metastatic pheochromocytomas.^[21] Ninety-seven percent of the tumors are found in the abdomen, 2-3% are found in the thorax, and 1% are found in the neck. Currently, ¹²³I-MIBG scintigraphy is recommended only to evaluate for ¹³¹I-MIBG treatment or when other functional imaging modalities like, e.g., 18-fluorodopamine (¹⁸FDA) are not available.^[21] In some cases, no definite abnormality is seen on CT or MRI, and ¹²³I-MIBG scans are negative in around 15% of pheochromocytomas and in up to 50% of malignant tumors because of relatively lower affinity of ¹²³I-MIBG to the norepinephrine transporters in comparison to newer compounds, the lack of storage granules or the loss of transporters by tumor cell dedifferentiation. This can lead to a dilemma in patients with only borderline elevation of catecholamine levels, especially norepinephrine (or normetanephrine), in whom a negative ¹²³I-MIBG scan fails to bring closure to the search for a pheochromocytoma, causing anxiety in the patient and doctor.^[22] In some of these “¹²³I-MIBG-negative” patients, the pheochromocytoma

Table 3: Sensitivity and specificity of various tests

Test	Sensitivity (%)	Specificity (%)
Plasma		
Free metanephrines	97-99	82-96
Catecholamines	69-92	72-89
Urine		
Fractionated metanephrine	96-97	45-82
Catecholamines	79-91	75-96
Total metanephrines	60-88	89-97
Vanillylmandelic acid	46-77	86-99
Imaging		
USG abdomen	83-89	30-60
CT abdomen	85-94	29-50
MRI abdomen	93-100	50-100
123I-MIBG	83-100	95-100
18F-DOPA PET	100	100

may be located on whole-body CT or MR imaging. However, these are prone to false-positive or false-negative results. Selective venous sampling may also be used to locate the pheochromocytoma, but this is a specialized technique (requiring an expert interventional radiologist) which is easy to misinterpret and carries risks including the provocation of a hypertensive crisis and is therefore rarely used. In cases of “occult” pheochromocytoma, PET scanning may provide a firm diagnosis. Also normal adrenal can have some ^{123}I -MIBG uptake, FDA uptake leading to additional confusion which can be removed by using ^{18}F -DOPA PET which does not have any uptake in normal adrenal. Also SUV values on PET scan can be used for differentiating physiological uptake from pheochromocytoma as SUV > 10 confirm pheochromocytoma. PET radiotracers that have been successfully used in the investigation of pheochromocytoma include ^{18}F -DOPA, ^{18}F FDG, DOTA-Tyr3-octreotide (DOTATOC) and DOTA-Nal-octreotide (DOTANOC), and ^{18}F -FDG. Both ^{18}F -DOPA and ^{18}F FDG PET have been reported to be highly sensitive and specific for pheochromocytoma, while ^{18}F -FDG PET, although less sensitive and specific for benign pheochromocytoma, may be particularly useful in imaging malignant pheochromocytoma where tumor cells exhibit higher metabolic activity. ^{123}I -MIBG and ^{18}F -dopamine uptake is dependent on the expression of catecholamine uptake and storage mechanisms (including the norepinephrine transporter (SLC6A2 NET1) and the vesicular monoamine transporters (VMAT1 and VMAT2)) in tumor cells; ^{18}F -DOPA uptake is governed by the expression of neutral amine precursor uptake and decarboxylation mechanisms; and ^{18}F FDG uptake is related to glucose uptake by tumor cells. Thus, the more specific cellular uptake mechanisms are mainly confined to cells of neuroendocrine origin, while those for glucose uptake are more globally expressed. This explains the differences in sensitivity and specificity of the various radiotracers in pheochromocytoma tissue.^[22] Nuclear MR spectroscopy could compliment the findings of the other modalities such as CT, MR imaging, and PET.^[6] The algorithm for localization of pheochromocytoma is given in Figure 2.

ROLE IN PREOPERATIVE PREPARATION

Optimal therapy for pheochromocytoma is surgical resection of the tumor. However, it is associated with high rates of mortality if not properly prepared.^[11] Before discussing drugs which are used during treatment of pheochromocytoma, it is important to know about drugs which are not to be used during course of pheochromocytoma management as it may be associated with fatal results. Various drugs can precipitate adrenergic and hypertensive crisis in patients

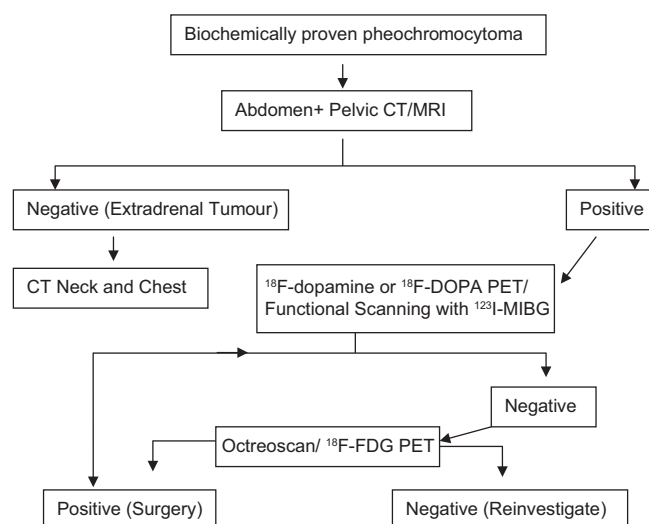


Figure 2: Algorithm for the localization of pheochromocytoma

with pheochromocytoma, hence are contraindicated [Table 1].^[18] Adequate blood pressure (BP) control is important to avoid hypertensive crisis during intraoperative handling of the tumor, minimizing adverse effects of anesthesia, and maintenance of stable BP during surgery.^[18,23]

An important aspect of BP control in pheochromocytoma is initial treatment with α -blockers and after achieving adequate α -blockade, the patient can be treated with β -blockers to achieve heart rate control. Phenoxybenzamine is a preferred α -blocker; however, prazosin, terazosin, doxazosin can also be used. Phenoxybenzamine is a nonselective blocker of α -receptors. It is started with initial dose of 10 mg twice daily and increased by 10–20 mg every third day. Factors favoring phenoxybenzamine use are its long duration of action leading to twice daily dosing and that it causes noncompetitive blockade of α -receptors; thus it prevents episodic surges of catecholamine releases during pre- and post-operative period.^[24] However, disadvantages of phenoxybenzamine include tachycardia, persistent postoperative hypotension in view of covalent, noncompetitive binding to the α -receptor, somnolence, stuffiness of nose, headache, and postural hypotension requiring intravenous fluid replacement.^[24] Prazosin is another option and is usually well tolerated with the exception of occasional first-dose hypotension and poor intraoperative BP control because of short duration of action. In the author’s experience short-acting prazosin has good results similar to phenoxybenzamine. Prazosin can be used in doses of 1 mg thrice daily initially and increased to maximal doses of up to total 12 mg daily dose. Doxazosin and terazosin are selective α_1 receptor blockers which can also be used. Doxazosin has a long half-life allowing once daily dosing while prazosin is short

acting.^[25] Labetalol can also be used but it has a fixed α : β antagonistic ratio (1:7; if used orally) thus causing inadequate α -blockade with more effect on the heart rate and may cause paradoxical hypertension.^[26] Adequate α -blockade is indicated clinically by postural hypotension and then the patient is advised liberal salt and fluid intake for reexpansion of plasma volume. Diuretics should not be used. Target BP is less than 120/80 mm of Hg in sitting position and systolic BP not less than 90 mm of Hg on standing. Once adequate α -blockade is achieved β -blockers are started to control tachycardia to achieve pulse rate of 60--80 per minute. β -blockers are to be used only after adequate α -blockade as otherwise initial use of β -blockers will lead to unopposed α -stimulant action of catecholamines leading to hypertensive crisis.^[27] Usually 10 mg QID of propranolol is used for β -blockade and later converted to daily long-acting dose.

Another option is calcium channel blockers (CCBs) alone in place of α - and β -blockers, which can be used in low-risk patients with added benefit that it does not interfere with plasma normetanephrine assays. CCBs are used mainly to supplement α -blockers in patients with inadequate blood pressure control, to obviate the need to increase the dosage of α -blockers, to replace α -blockers in patients with severe side effects, and to prevent α -blocker-induced sustained hypotension in patients with only intermittent hypertension. Calcium channel blockers do not cause hypotension or orthostatic hypotension during the normotensive period.^[18,28]

Metyrosine is a very effective drug for BP control; it acts by inhibiting tyrosine hydroxylase, thus causing depletion of adrenal stores of catecholamines. It is started with doses of 250 mg thrice daily and then doses are increased gradually up to a total dose of 1.5-4 g/day. It is usually used as short-course treatment because of its side effect profile (sedation, depression, anxiety, galactorrhoea, rarely extrapyramidal side effects).^[29] Metyrosine and α -blockers when used together result in less labile blood pressure during anesthesia and surgery, reduced intraoperative blood loss, and reduced volume replacement during surgery compared with the use of α -blockers alone.^[18,29] It is currently not available in India. Though there are thoughts that preoperative BP control do not alter outcome of surgery and intraoperative complications,^[30] we believe in adequate BP control prior to surgery should be achieved like in any other elective surgery and vigilant cardiovascular status assessment during surgery.

Thus, during the preoperative period combined α - and β -blockers are used most commonly while in cases with low-risk pheochromocytomas CCBs can be used. If

metyrosine is available it can be used along with α - and β -blockers in the preoperative period for short duration. On the preoperative day the patient is started on intravenous normal saline to increase intravascular volume usually at a rate of 100 ml/h in adults.

Also preoperatively the patient should be assessed thoroughly as any other major surgery with particular stress on cardiac evaluation. Volume status of the patient should be assessed and if the patient has large left-sided pheochromocytoma and it is likely to require splenectomy; then preoperative vaccination for H. influenzae, pneumococcus, and meningococcus should be done.^[18]

During the intraoperative period patients are prone to accelerated hypertension, hypotension, arrhythmias, and cardiovascular instability due to release of catecholamines during intraoperative handling of the tumor and effects of anesthetic agents. Thus patients require a trained anesthetist team during surgery. Currently laproscopic surgery is most commonly performed for pheochromocytomas. In experienced hands, the operative mortality is less than 2-3% and the end result of complete surgical resection of benign pheochromocytoma is a normal life expectancy.^[5]

ROLE IN POSTOPERATIVE MANAGEMENT AND FOLLOW-UP

In an immediate postoperative period hypotension is a common problem which is managed with intravenous fluids because vascular bed is effectively paralyzed by preoperative medications. Volume replacement is quite large during initial 12-36 hours. Another important issue is persistent hypertension which in the immediate postoperative period can be because of the residual tumor, autonomic instability, pain, volume overload; however, coexisting essential hypertension is still most likely diagnosis if it persists longer. Twenty-five percent patients may remain hypertensive after pheochromocytoma removal.^[31] There is general agreement that biochemical testing should be repeated approximately 14 days following surgery to check for remaining disease. Importantly, normal postoperative biochemical test results do not exclude remaining microscopic disease, so patients should not be misinformed that they are cured and no further follow-up is necessary. Repeat evaluations are done annually thereafter or recurrence of symptoms whichever is early.^[32] Long-term survival after complete resection is equal to the age- and sex-matched population.^[33] Patients undergoing removal of bilateral pheochromocytoma will develop adrenal insufficiency and will require steroid replacement therapy. However, we have observed that these patients develop hypertrophy of adrenal rest tissue

and steroid replacement can be tapered after documenting appropriate response to the ACTH stimulation test.

SPECIAL SITUATIONS

Pheochromocytoma in children

Pheochromocytomas are rare tumors in the general population and even more uncommon in the pediatric population. However, important points about pheochromocytomas in childhood are that they are more commonly familial as well as incidence of malignant pheochromocytomas/paragangliomas is high (47%), particularly in those with apparently sporadic disease, paraganglioma, and tumor diameters of >6 cm. Clinical presentation and management is quite similar to adult pheochromocytomas. Surgical resection remains the treatment of choice for pheochromocytoma and paraganglioma. The 10-year disease-specific survival rates are reported to be 81% for all patients and < 30% for patients with malignant tumors. Familial screening and the patient's genetic analysis are must in pediatric pheochromocytoma cases.^[34]

Pheochromocytoma in pregnancy

Pregnancy is a hyperdynamic state and normal pregnancy has many symptoms similar to pregnancy and detection of pheochromocytomas during pregnancy require high index of suspicion. Failure to diagnose pheochromocytomas during pregnancy can lead to adverse fetal and maternal outcomes varying from hypertension to fetal and maternal death.^[35] Pheochromocytoma may become overt during pregnancy because of increases in intraabdominal pressure, fetal movements, uterine contractions, process of delivery, an abdominal surgical intervention, and even general anesthesia.^[36] The 24-hour urinary catecholamines estimation is recommended for diagnosis in pregnant patients.^[37] For localization MRI is preferred modality as it is radiation free and locates adrenal or extra-adrenal tissue with good sensitivity. During medical management main stress is to prevent hypertensive crisis which can be lethal for both mother and fetus. Long-acting α -blockers are commonly used (phenoxybenzamine) and if required later a β -blocker may be added for tachycardia after adequate α -blockade has been achieved.^[38] Definitive treatment is surgical resection. If gestation is <24 weeks, pheochromocytoma is resected laparoscopically (size < 7 cm) or by open laparotomy.^[39] If gestation is >24 weeks, then pheochromocytoma is resected at the time of caesarean section. Vaginal delivery is contraindicated in such patients because of increased mortality associated with vaginal delivery (31%) compared with caesarean section (19%).^[40] Good anesthetic care is must during surgery. Follow-up is the same as in nonpregnant patients.

Malignant pheochromocytoma

Malignant pheochromocytoma is a very rare tumor in the general population, and 3-13% of pheochromocytomas are malignant, with extra-adrenal pheochromocytomas being more commonly malignant.^[41] Sites of metastatic disease most commonly observed include lymph nodes, bones, liver, and lungs. Long-term survival in malignant pheochromocytoma has been reported to be variable between 34% and 60% and patients with bone metastasis survive the longest, and those with lung and liver metastasis have shorter life expectancy.^[42] Clinically it presents with features similar to benign pheochromocytoma. Management of hypertension is similar to benign pheochromocytoma. There are no definite molecular and cellular markers to differentiate benign from malignant pheochromocytoma; it is only diagnosed on detection of metastasis. Biochemical confirmation of recurrence and localization of metastatic lesions with ¹²³I-MIBG scans can confirm the presence of metastasis. The large tumor size (5.5 cm) and minimally elevated 24-hour urinary vanillylmandelic acid (≤ 2.1 mg/day/cm²) are significantly associated with a higher probability of a malignant pheochromocytoma portending a lower metastasis-free survival and mandates more rigorous follow-up after surgery.^[43]

Complete surgical resection, if possible, is the treatment of choice with adjunct-targeted radiation therapy using ¹³¹I MIBG (if residual disease); however, recurrence rates are high. ¹³¹I MIBG therapy by itself is rarely curative but is most useful when the tumor is not resectable or a residual tumor is there. In a group of 28 patients shown to have sufficient uptake of ¹³¹I MIBG, objective partial responses were observed in 29% of the patients, and biochemical improvement was noted in 43% of the patients.^[44] No evidence exists that partial surgical debulking of the tumor results in improved survival or reduction in symptoms. Radiation therapy or combination chemotherapy may be palliative for symptoms or morbidity resulting from local invasion by the tumor. Second line of management is chemotherapy in which combination of cyclophosphamide, vincristine, and dacarbazine (CVD) therapy is most commonly used. CVD has shown positive response in 55% of the tumors by decreased size criteria and 72% of the tumors had biochemical response. The median duration of the response is 20 months.^[45] Thus, it does not offer survival benefit. Since hypertensive episodes have been reported following chemotherapy, patients need to be prepared with adrenergic blockers prior to treatment. Somatostatin analogs have not been found to be efficacious in treatment. Targeted therapies with DOTATOC and DOTANOC in receptor-positive patients are other modalities; however, limited data are available

regarding their efficiency and these are associated with bone marrow suppression and impaired renal function.^[46] Experimental modalities of therapies still in research stages include heat shock protein 90 (HSP 90) inhibitors, mTOR inhibitors, hypoxia inducible factor (HIF) inhibitors, prolyl hydroxylase activators, and ERBB 2 inhibitors.^[47] Sunitinib (tyrosine kinase inhibitor) has shown good response in phase II studies.^[47]

REFERENCES

- Manger WM, Gifford RW. Pheochromocytoma. *J Clin Hypertens* 2002;4:62-72.
- PPick L. Das Ganglioma embryonale sympathicum (sympthoma embryonale). *Berl Klin Wochenschr* 1912;49:16-22.
- Welbourn RB. Early surgical history of pheochromocytoma. *Br J Surg* 1987;74:594-6.
- Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, *et al.* Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346:1459-66.
- Young WF Jr. Endocrine hypertension: Then and now. *Endocr Pract* 2010;16:888-902.
- Faria JF, Goldman SM, Szejnfeld J, Melo H, Kater C, Kenney P, *et al.* Adrenal masses: Characterization with *in vivo* proton MR spectroscopy--Initial experience. *Radiology* 2007;245:788-97.
- Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RW Jr. Clonidine-suppression test: A useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981;305:623-6.
- Bravo EL, Gifford RW Jr. Pheochromocytoma. *Endocrinol Metab Clin North Am* 1993;22:329-41.
- Gundgurthi A, Gupta S, Garg MK, Ganguly P, Bhardwaj R. Unsuspected pheochromocytoma multisystem crisis: A fatal outcome in a young male patient. *J Assoc Physicians India [In Press]*.
- Gundgurthi A, Dutta MK, Pakhetra R, Garg MK. Missed diagnosis of MEN – 2B. *MJAFI* 2010;60:295-7.
- Brouwers FM, Lenders JW, Eisenhofer G, Pacak K. Pheochromocytoma as an endocrine emergency. *Rev Endocr Metab Disord* 2003;4:121-8.
- Eisenhofer G, Goldstein DS, Kopin JJ, Crout JR. Pheochromocytoma: Rediscovery as a catecholamine-metabolizing tumor. *Endocr Pathol* 2003;14:193-212.
- Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, *et al.* Biochemical diagnosis of pheochromocytoma: Which test is best? *JAMA* 2002;287:1427-34.
- Raber W, Raffesberg W, Bischof M, Scheuba C, Niederle B, Gasic S, *et al.* Diagnostic efficacy of unconjugated plasma metanephrines for the detection of pheochromocytoma. *Arch Intern Med* 2000;160:2957-63.
- Eisenhofer G, Lenders JW, Linehan WM, Walther MM, Goldstein DS, Keiser HR. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. *N Engl J Med* 1999;340:1872-9.
- Sawka AM, Jaeschke R, Singh RJ, Young WF. A comparison of biochemical tests for pheochromocytoma: Measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 2003;88:553-8.
- Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, *et al.* Biochemical diagnosis of pheochromocytoma: How to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* 2003;88:2656-66.
- Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab* 2007;92:4069-79.
- Maurea S, Cuocolo A, Reynolds JC, Neumann RD, Salvatore M. Diagnostic imaging in patients with paragangliomas. Computed tomography, magnetic resonance and MIBG scintigraphy comparison. *Q J Nucl Med* 1996;40:365-71.
- Schmedtje JF Jr, Sax S, Pool JL, Goldfarb RA, Nelson EB. Localization of ectopic pheochromocytomas by magnetic resonance imaging. *Am J Med* 1987;83:770-2.
- Havekes B, King K, Lai EW, Romijn JA, Corssmit EP, Pacak K. New imaging approaches to pheochromocytomas and paragangliomas. *Clin Endocrinol* 2010;72:137-45.
- Mackenzie IS, Gurnell M, Balan KK, Simpson H, Chatterjee K, Brown MJ. The use of 18-fluoro-dihydroxyphenylalanine and 18-fluorodeoxyglucose positron emission tomography scanning in the assessment of metaiodobenzylguanidine-negative pheochromocytoma. *Eur J Endocrinol* 2007;157:533-7.
- Mannelli M. Management and treatment of pheochromocytomas and paragangliomas. *Ann N Y Acad Sci* 2006;1073:405-16.
- Hull CJ. Pheochromocytoma: Diagnosis, pre-operative preparation, and anesthetic management. *Br J Anaesth* 1986;58:1453-68.
- Cubeddu LX. New alpha 1-adrenergic receptor antagonists for the treatment of hypertension: Role of vascular alpha receptors in control of peripheral resistance. *Am Heart J* 1988;116:133-62.
- Kanto PJ. Current status of labetalol and other agents that block both α and β -blocking agents. *Int J Clin Pharmacol Ther Toxicol* 1985;23:617-28.
- Sloand EM, Thompson BT. Propranolol-induced pulmonary edema and shock in a patient with pheochromocytoma. *Arch Intern Med* 1984;144:173-4.
- Bravo EL. Pheochromocytoma. *Cardiol Rev* 2001;10:44-50.
- Steinsapir J, Carr AA, Prisant LM, Bransome ED Jr. Metyrosine and pheochromocytoma. *Arch Intern Med* 1997;157:901-6.
- Lentschener C, Gaujoux S, Tesniere A, Dousset B. Point of controversy: Perioperative care of patients undergoing pheochromocytoma removal--time for a reappraisal? *Eur J Endocrinol* 2011;165:365-73.
- Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *J Clin Endocrinol Metab* 2005;90:2110-6.
- Pacak K, Timmers H, Eisenhofer G. Pheochromocytoma. In: Jameson JL, De Groot LJ, editors. *Endocrinology Adult and Pediatrics*. 6th ed. Philadelphia: Elsevier Saunders; 2010. p. 1990-2018.
- Stenstrom G, Ernest I, Tisell LE. Long-term results in 64 patients operated upon for pheochromocytoma. *Acta Med Scand* 1988;223:345-52.
- Pham TH, Moir C, Thompson GB, Zarroug AE, Hamner CE, Farley D, *et al.* Pheochromocytoma and paraganglioma in children: A review of medical and surgical management at a tertiary care center. *Pediatrics* 2006;118:1109-17.
- Desai AS, Chutkow WA, Edelman E, Economy KE, Dec GW. Clinical problem solving: A crisis in late pregnancy. *N Engl J Med* 2009;361:2271-7.
- Ahlatwat SK, Jain S, Kumari S, Varma S, Sharma BK. Pheochromocytoma associated with pregnancy: Case report and review of the literature. *Obstet Gynecol Surv* 1999;54:728-37.
- Manger WM, Eisenhofer G. Pheochromocytoma: Diagnosis and management update. *Curr Hypertens Rep* 2004;6:477-84.
- Oliva R, Angelos P, Kaplan E, Bakris G. Pheochromocytoma in Pregnancy. A Case Series and Review. *Hypertension* 2010;55:600-6.
- Kalra JK, Jain V, Bagga R, Gopalan S, Bhansali AK, Behera A, *et al.*

- Pheochromocytoma associated with pregnancy. *J Obstet Gynaecol Res* 2003;29:305-8.
40. Junglee N, Harries SE, Davies N, Scott-Coombes D, Scanlon MF, Rees DA. Pheochromocytoma in pregnancy: When is operative intervention indicated? *J Womens Health* 2007;16:1362-5.
41. De Lellis RA, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs. 3rd ed, Vol 8. Lyon, France: IARC Press; 2004.
42. Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB. Pheochromocytoma: Recommendations for clinical practice from the First International Symposium, October 2005. *Nat Clin Pract Endocrinol Metab* 2007;3:92-102.
43. Park J, Song C, Park M, Yoo S, Park SJ, Hong S. Predictive characteristics of malignant pheochromocytoma. *Korean J Urol* 2011;52:241-6.
44. Shapiro B, Sisson JC, Wieland DM, Mangner TJ, Zempel SM, Mudgett E. Radiopharmaceutical therapy of malignant pheochromocytoma with [¹³¹I] metaiodobenzylguanidine: Results from ten years of experience. *J Nucl Biol Med* 1991;35:269-76.
45. Huang H, Abraham J, Hung E, Averbuch S, Merino M, Steinberg SM, *et al.* Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: Recommendation from a 22-year follow-up of 18 patients. *Cancer* 2008;113:2020-8.
46. Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnert H. Clinical review: Current treatment of malignant pheochromocytoma. *J Clin Endocrinol Metab* 2007;92:1217-25.
47. Grogan RH, Mitmaker EJ, Duh QY. Changing paradigms in the treatment of malignant pheochromocytoma. *Cancer Control* 2011;18:104-12.

Cite this article as: Garg MK, Kharb S, Brar KS, Gundgurthi A, Mittal R. Medical management of pheochromocytoma: Role of the endocrinologist. *Indian J Endocr Metab* 2011;15:329-36.

Source of Support: Nil, **Conflict of Interest:** None declared.