PAPER

J R Coll Physicians Edinb 2005; 35:206–213

An update on biochemical evaluation, imaging and treatment of phaeochromocytoma

KP Goh,[1] T Subramaniam[2]
[1]KP Goh, Registrar, Department of Medicine, Alexandra Hospital, Singapore [2]T Subramaniam, Consultant, Department of Medicine, Alexandra Hospital, Singapore

ABSTRACT The diagnosis of phaeochromocytoma requires both a biochemical demonstration of inappropriately increased catecholamine production as well as anatomical localisation of the tumour. The addition of plasma metanephrine and serum chromogranin A has increased the repertoire of biochemical tests available. Recent advances in functional imaging like MIBG and somatostatin receptor scintigraphy have improved the diagnostic yield in extra-adrenal, metastatic and recurrent tumours which may not be easily recognised on conventional imaging. Although excision of the tumour remains the mainstay of treatment, the importance of good peri-operative control of blood pressure and post-operative follow up care cannot be over-emphasised. This paper reviews the various tests currently available and their roles in the evaluation of phaeochromocytoma. It also highlights some of the peri-operative issues in the management of this condition.

KEYWORDS Biochemical, catecholamine, imaging, management, peri-operative, phaeochromocytoma

LIST OF ABBREVIATIONS [18F]-fluorodopamine ([18F]DA), computed tomography (CT), dihydroxyphenylalanine (DOPA), Hounsfield units (HU), magnetic resonance imaging (MRI), medullary thyroid carcinoma (MTC), metaiodobenzylguanidine (MIBG), multiple endocrine neoplasia (MEN), position emission tomography (PET), serum chromogranin A (CgA), single-photon emission CT (SPECT), vanillyl-mandelic acid (VMA)

DECLARATION OF INTERESTS No conflict of interests declared.

Correspondence to ***KP Goh, Department of Medicine, Alexandra Hospital, 378 Alexandra Road, 159964, Singapore***

tel. ***65-63793461***

fax. ***65-63793540***

e-mail
kian_peng_goh@alexhosp.com.sg

INTRODUCTION

The first case of an adrenal medullary tumour was described by Dr Felix Frankel in 1886.[1] The patient eventually died from circulatory failure. It was a pathologist, Dr Ludwig Pick who coined the term 'phaeochromocytoma' in 1912 to describe the chromaffin colour change in the tumour cells.[2] Cesar Rouks performed the first surgical excision in Lausanne, Switzerland in 1926[3] and CH Mayo in North America followed thereafter in the same year.[4]

Initial tests to diagnose the tumour included the use of histamine to precipitate hypertension and phentolamine to reduce the blood pressure.[1] We have come a long way since then and the current approach to diagnosis now includes biochemical determination of specific catecholamine and their metabolites as well as the use of radioisotope-labeled imaging and molecular markers.

PREVALENCE

The actual prevalence of this tumour is not known. It is one of the tumours which is frequently sought, but seldom found. Although it is rare, occurring in only less than 0·2% of hypertensive patients,[5] incident rates of up to 1·9% have been reported as well.[6] In some cases, the diagnosis was made incidentally in 10% to 14% of patients, either during autopsy or on imaging by CT or MRI.[7,8]

BIOCHEMICAL DIAGNOSIS

There are two aspects to the evaluation of a suspected phaeochromocytoma. Firstly, excess catecholamine production by the tumour, either in the urine or plasma, needs to be demonstrated to make a diagnosis of phaeochromocytoma. The Mayo group has recommended a 24-hour urinary catecholamines and metanephrines cut-off level of 2-fold above the upper limit of the normal population range to ensure a specificity of 97·7%.[9] Increased noradrenaline and normetanephrine levels are seen in extra-adrenal tumours, whereas a raised adrenaline level is suggestive of an adrenal phaeochromocytoma. An increased metanephrine level is usually associated with phaeochromocytoma in MEN 2 syndrome due to an increased metabolism of the catecholamines.[10]

Increased catecholamine metabolites and high adrenaline levels are associated more frequently with large and small

TABLE 1 Sensitivities and specificities of various biochemical tests.

Test	Sensitivity (%)		Specificity (%)	
	Familial	Sporadic	Familial	Sporadic
Urinary fractionated metanephrine	96	97	82	45
Urinary catecholamine	79	91	96	75
Urinary VMA	46	77	99	86
Plasma free metanephrine	97	99	96	82
Plasma catecholamine	69	92	89	72
Urinary dopamine	8		100	

TABLE 2 Causes of false positive biochemical tests.

Drugs

- tricyclic anti-depressant
- benzodiazepine
- buspirone
- haloperidol
- levodopa
- bromocriptine
- phentolamine
- acetaminophen
- nicotine

Stresses

- acute withdrawal of illicit drugs, ethanol or clonidine
- surgery
- congestive cardiac failure (NYHA class 3 or 4)
- acute hypoglycaemia
- obstructive sleep apnoea (a form of nocturnal stress)
- advanced renal failure

tumours respectively. The association was thought to be due to the high turnover rate in smaller tumours releasing mainly unmetabolised catecholamines. Hence, a high catecholamine metabolites to free catecholamine ratio is seen in large (more than 50 g) cystic tumours, whereas a smaller tumour is associated with a lower ratio.[11]

Various other tests are also available for the biochemical diagnosis of phaeochromocytoma. The use of plasma free metanephrine has been suggested to be a good tool because of its excellent sensitivity even in syndromic cases. It is a good marker since plasma metanephrine are produced continuously and independent of episodic tumour catecholamine release. Moreover, some tumours do not secrete catecholamines, but metabolise catecholamines to free metanephrine. The sensitivities of plasma free metanephrine and urinary fractionated metanephrine are 99% and 97% respectively. These tests have a higher sensitivity but lower specificity for sporadic cases compared to familial cases. The low specificity of plasma free metanephrine gives rise to a relatively high false positive rate.[13] It is for this reason that it is not recommended for use as a first line screening tool and should only be used if there is high suspicion of the diagnosis or difficulty in collecting a 24-hour urine sample. Secondly, despite its high sensitivity, it can still give a false negative result in dopamine secreting tumours.

Urinary VMA, though having a low sensitivity, has a good specificity, especially in familial cases. Occasionally, patients may have a normal VMA excretion despite high urinary catecholamine levels.[12] (Table 1)[9,13]

It is important to ensure, while collecting the samples, that the patient is not on any drugs which may interfere with the biochemical testing as a number of agents can give a false positive result including various physical stresses (Table 2).[14] Fortunately, most anti-hypertensive agents do not interfere with the result, provided a high-pressure liquid chromatography assay is used, instead of the less specific fluorometric analyses.[15]

The risk of obtaining a false negative result may be reduced by ensuring that sampling is done during a paroxysm, or at the very least, when the patient is still hypertensive.

Serum chromogranin A level correlates with tumour size and is increased in 80% of patients. It has a sensitivity and specificity of 98% and 97% respectively when combined with an increased plasma metanephrine, but by itself has a poor specificity of 50%.[16]

Provocative tests like the glucagon stimulation test and the clonidine suppression tests are seldom used nowadays as they run the risks of severe hypertension and hypotension respectively. However, a diagnosis of phaeochromocytoma is considered highly unlikely if both tests are negative.[17] The glucagon stimulation test has a low sensitivity (81%) but high specificity (100%), whereas the clonidine suppression test has a high sensitivity (97%) but low specificity (67%).[18]

LOCALISATION

The next step after a biochemical diagnosis is localisation of the tumour. The aims of localisation studies are two-fold: Anatomical localisation to aid surgical planning, and exclusion of metastatic disease in cases at high risk of malignancy. There are two categories of imaging studies; Anatomical imaging studies and functional imaging studies.[19]

Anatomical imaging studies

Both CT and MRI are commonly used. Characteristically, the density measurement of the tumour is 10 HU or more on an unenhanced CT. There may also be peripheral contrast enhancement. In addition, larger tumours may be haemorrhagic, have a cystic interior or have areas of hypodensity seen after tumour necrosis. Speckled calcification can be found in 12% of patients.

Extra-adrenal tumours are often multifocal.[14] Common extra-adrenal locations, in order of decreasing frequency, are the superior and inferior pancreatic areas (75%), bladder (10%), thorax (10%) and the head, neck and pelvis (5%).[20] Computed tomography can localise adrenal tumours 0·5–1·0 cm or larger and extra-adrenal tumours 2 cm or larger. Although the sensitivity for detecting an adrenal phaeochromocytoma is high at 98%, it drops to 90% in cases of extra-adrenal, metastatic or recurrent tumours.

The indications for choosing MRI over CT are evaluation in children and pregnancy, allergy to contrast agents and a normal CT in a biochemically proven phaeochromocytoma. The signal intensity on T1 weighted images is similar to liver, kidney and muscle, whereas on T2 images, there is a very bright signal due to its hypervascularity, often described as a bulb glow. Even though MRI has a high sensitivity, most reports have shown a specificity of only 50%. False positive results can be due to haemorrhage, haematoma and carcinoma.

Ultrasound has both low sensitivity and specificity and is not routinely used as a first-line imaging modality. Although endosonography may detect tumours missed by routine imaging, it is not useful in differentiating benign from malignant lesions.[21]

Functional imaging studies[19]

The main indications for functional imaging are a negative anatomical imaging in a biochemically proven phaeochromocytoma and detection of metastatic lesions or multiple tumours when CT or MRI are normal. Its main drawbacks are a lower sensitivity compared with MRI and a decreased ability to localise tumours close to the kidneys, head of pancreas, and bladder as the radioisotopes are excreted in the urine.

Metaiodobenzylguanidine resembles noradrenaline and is taken up to accumulate in the adrenergic tissues. Radioactive labeling with ^{131}I or ^{123}I is performed and phaeochromocytomas appear as abnormal areas of increased MIBG uptake. The limited sensitivity and spatial resolution of MIBG scans are improved when ^{123}MIBG is combined with SPECT.[22] Metaiodobenzylguanidine scans allow for both anatomical and functional localisation. An added advantage of MIBG is that it allows whole body scanning and is useful in detecting recurrent or metastatic tumours, tumours in unusual locations or in areas with distorted anatomy and in the presence of fibrosis. False positive cases can result from carcinoid tumours, medullary thyroid carcinoma and small cell lung carcinoma.[23]

[18F]-fluorodopamine PET has several advantages compared to a MIBG scan.[24, 25] It has a low radiation exposure, superior spatial resolution and does not require thyroid blocking with radioiodine which may have adverse thyroid effects. It is usually performed immediately after [18F]DA administration which means there is no one to two day delay (as in MIBG) for background radiation to disappear. It is a better substrate for the norepinephrine transporter than other amines, including norepinephrine. However, its use is probably limited to detecting metastatic disease that is MIBG-negative and it is also not widely available. The other disadvantage is its limited scanning area (from neck to pelvis) compared to the whole body in MIBG.

The other recent development in the functional imaging of phaeochromocytoma is somatostatin receptor scintigraphy. It involves the intravenous administration of octreotide followed by scintigraphic views at 4, 24, and 48 hours. It is usually performed together with a SPECT scan and has a higher detection rate for malignant and metastatic tumours over MIBG scan. (87% vs 57% of tumours.)[26]

The sensitivities and specificities of some of the modalities discussed are listed in Table 3.[19] In general, the sensitivity of CT and MRI decreases if it is an extra-adrenal, metastatic or recurrent tumour post-operatively. It is in these cases that functional imaging like MIBG may have an advantage over anatomical imaging. MIBG also has better specificity than CT and MRI in detecting both adrenal and extra-adrenal tumours.[27]

MALIGNANCY

The presence of an extra-adrenal phaeochromocytoma increases the risk of the tumour being malignant. As benign and malignant tumours are histologically and biochemically indistinguishable from each other, the only clues to malignancy are local invasion and the presence of distant metastases which may occur up to 15 years post-operatively. There are however several risk factors for

TABLE 3 Sensitivities and specificities of imaging modalities.

Modality	Sensitivity	Specificity
CT	77–98	29–92
MRI	90–100	50–100
Ultrasound	83–89	60
^{131}MIBG	77–90	95–100
^{123}MIBG	83–100	95–100

malignancy:[14] 1) Extra-adrenal phaeochromocytomas (52% prevalence of malignancy); 2) tumour diameter 5 cm or larger (76% prevalence of malignancy); 3) confluent tumour necrosis (common in larger tumours); 4) elevated human telomerase reverse transcriptase activity;[28, 29] 5) presence of DNA aneuploidy or tetraploidy;[30] 6) abundant c-*myc* mRNA[31] and heat shock protein 90[32] levels.

PRE-OPERATIVE MANAGEMENT

Some pre-operative management issues to be considered include:[33] 1) Evaluation of patient's overall health; 2) assess the effectiveness of α adrenergic blockade; 3) assess presence of cardiac dysfunction; and 4) reassure patient.

Alpha-adrenergic blockers

Certain criteria have been suggested by Roizen *et al.* to determine if a patient has adequate α adrenergic blockade.[34]

Phenoxybenzamine, a non-selective α adrenoceptor antagonist of the haloalkylamine class, is commonly used for pre-operative control of blood pressure. It forms covalent bonds with the receptor resulting in an irreversible competitive inhibition of the adrenergic activity. The result is orthostatic hypotension and a fall in arterial blood as the effect of the α adrenergic mediated vasoconstriction is removed. This allows for the spontaneous restoration of plasma volume with gradual re-expansion of intravascular volume and the initial haemodilution usually corrects itself over two weeks.[35] Central venous pressure monitoring and correction with intravenous fluids few days prior to surgery will further optimise the haemodynamic status.

The use of α adrenergic blockade is not universally practiced. Boutro *et al.* reported no adverse outcome in 29 patients who did not receive any α adrenergic blockade prior to surgery over a ten year period and concluded that phaeochromocytoma patients can undergo successful surgery without pre-operative profound and long-lasting alpha adrenergic blockade. This was attributed to improved monitoring capability and the availability of fast-acting agents to correct sudden haemodynamic changes during surgery.[36] Another group reported no adverse outcomes with the exclusive use of nicardipine on ten patients.[37] Calcium channel blockers have the added advantage of not producing orthostatic hypotension or overshoot hypotension seen with α blockers and hence, may be safely used in normotensive patients with occasional episodes of paroxysmal hypertension. In addition, they prevent catecholamine-induced coronary vasospasm and myocarditis.[14]

Beta-adrenergic blockers

Propranolol is a commonly used agent for β adrenergic blockade. It is used to control the tachycardia from the circulating catecholamines and from the α adrenergic blockade. However, its use is contraindicated in the absence of α adrenergic blockade as the unopposed α adrenergic-mediated vasoconstriction may lead to a hypertensive crisis with acute pulmonary oedema.[38, 39] In order to limit the effect of β2 blockade, the use of selective β1 adrenergic blockers is preferred over non-selective β blockers.

Other medical options

There are other alternative options which should also be mentioned.

Labetolol has been used in the pre-operative management of phaeochromocytoma with good results, including the rapid preparation of a patient for surgery.[40] It is a combined α and β adrenergic blocker with a greater β blocking effect. Therefore, it may still cause hypertension if used exclusively without pre-existing α blockade.[41]

Tyrosine hydroxylase inhibition

The conversion of tyrosine to DOPA is the rate limiting step during catecholamine synthesis, mediated by the enzyme, tyrosine hydroxylase. Alpha-methyl-para-tyrosine is a competitive inhibitor of this reaction and can decrease the synthesis of catecholamines by up to 80%.[42] A retrospective analysis showed that combination metyrosine and α adrenergic blockade resulted in better blood pressure control during surgery compared to the use of phenoxybenzamine alone. However, there was no comparison with combined α and β blockade.[43] In another study, metyrosine-prepared patients also appeared to have less blood loss and required less volume replacement during surgery compared to their non-metyrosine-prepared counterparts.[44] However, the use of metyrosine is probably limited by its high incidence of side effects which include sedation, depression, diarrhea, anxiety, nightmares, crystalluria.

INTRA-OPERATIVE MANAGEMENT

Anaesthetic considerations[35]

Fentanyl, benzodiazepines and buprenorphine are suitable premedication anxiolytics, which unlike other opioids, do not cause histamine release or trigger catecholamine release. Atropine should also be avoided as it can increase the heart rate and blood pressure. The choice of general over regional anaesthesia does not affect the surgical outcome.

Induction agents commonly used include propofol, thiopentone and etomidate. Both vecuronium and rocuronium are good paralysing agents to use as they do not induce histamine release or stimulate the sympathetic system, unlike atracurium and suxamethonium respectively.[45]

Inhalational agents like halothane and enflurane are contraindicated as they are arrhythmogenic in nature. Isoflurane is the agent of choice. Alternatives include sevoflurane and nitric oxide.

Blood pressure control[35]

Hypertension during surgery can arise from noxious stimuli like tracheal intubation and tumour manipulation.[33] The ideal agent to counter peri-operative catecholamine release must have sufficient potency, have a rapid onset and a short duration of action. Sodium nitroprusside, a potent arterio-venodilator, is generally preferred over nitroglycerin which is less potent as it is only a venodilator.

Another option is phentolamine which is a competitive α1 and weak α2 adrenergic receptor antagonist. However, there is a concern regarding possible incomplete α1 blockade resulting in hypertension and tachycardia, although it does not seem to be a problem in patients who are adequately β blocked.[46]

Intra-operative tachycardia or arrhythmias are best controlled by esmolol[47] or lignocaine, both of which have a rapid onset and short duration of action.[33]

Hypotension can occur during the clamping of the feeding vessel or resection of the tumour. Fluid replacement and discontinuation of antihypertensive agent is usually the initial management before the use of pressor agents as inotropic agents are generally ineffective in the presence of persistent hypovolaemia.[48]

Use of magnesium sulphate

The increasing acceptance to use magnesium sulphate during phaeochromocytoma surgery started after James reported its successful use in a series of 17 patients.[49] Good results have also been reported in other cases[40, 50, 51] including a report on three cases using magnesium as the sole agent in controlling blood pressure during surgery.[52] The mechanism of action of magnesium includes:[53, 54, 55] 1) inhibition of catecholamine release from the adrenal medulla and adrenergic nerve endings; 2) direct adrenoceptor blockade; 3) direct predominantly arteriolar vasodilatory effect on vessel walls; 4) anti-arrhythmic properties; and 5) myocardial protection. Its actions are believed to be mediated by its calcium antagonising property which disrupts the coupling of catecholamine release from the adrenal medulla and adrenergic nerve terminals. Catecholamine concentration was also shown to be decreased after magnesium infusion.[49] The result is a decreased peripheral vascular resistance with a reduction of systolic arterial blood pressure and increased coronary blood flow. These properties make it an attractive agent for use in phaeochromocytoma surgery.

Surgical approaches[56]

Over the years, surgery for phaeochromocytoma has evolved from the classical midline open approach to the retroperitoneal approach to laparoscopic surgery and even partial adrenalectomy. The obvious benefit of the open approach is better access permitting exploration for other tumours in cases of extra-adrenal tumours and metastases.

Mortality is usually low in most cases. In a large surgical series, peri-operative mortality and morbidity rates for phaeochromocytomas were 2·4% and 24% respectively.[57] The incidence of splenic complications was particularly high at 8%. Independent risk factors for complications are high pre-operative systolic blood pressure, high urinary metanephrine excretion and number of re-operations.

Immediate post-operative period

Post-operative monitoring for hypoglycemia is important. High levels of circulating catecholamines increase glycogenolysis and gluconeogenesis via its α1 and β2 adrenergic effects and lipolysis via its β3 effect. This leads to pre-operative hyperglycaemia in 60% patients.[33] However, removal of the tumour results in a decrease in catecholamine levels and may cause hypoglycaemia from rebound hyperinsulinaemia. The use of β blockers may further worsen the situation by blocking the adrenergic symptoms of hypoglycaemia.

Approximately 50% patients remain hypertensive post-operatively due to elevated catecholamine stores in adrenergic nerve endings. Most instances of hypertension usually resolve within a week.[48] Persistence of immediate post-operative hypertension can be due to pain from insufficient analgesia, the presence of a residual tumour from inadequate resection and drugs which include anti-emetics like droperidol, which block α2 receptors and metoclopropamide, a dopamine and 5-hydroxytryptamine receptor antagonist.

The other post-operative complication is hypotension, which can be due to intravascular volume depletion from inadequate fluid replacement, hypovolaemia from intra-abdominal bleeding, residual effects of pre-operative adrenergic blockade and alteration of vascular compliance.[33, 58]

OTHER TREATMENT OPTIONS

Surgical

There exist alternative surgical modalities to adrenalectomies. Firstly, partial adrenalectomy is an option in familial cases to preserve adrenal function and avoid lifelong steroid replacement.[59] Secondly, the issue of repeated surgical debulking versus conservative

management in patients with multiple tumours or recurrences remains a contentious one.[56]

Non-surgical

The use of metyrosine, which has been alluded to earlier, can be extended to include patients in whom surgery is no longer a viable option. Another non-surgical option in malignant cases is combination chemotherapy with the use of cyclophosphamide, vincristine and dacarbazine, which has been shown to produce a clinical and radiological response in 57% of patients and a urinary biochemical response in 79% of patients.[60]

Other palliative options include high dose ^{131}MIBG in inoperable malignant tumours which have shown variable response, external beam radiotherapy for painful metastases[61] and radioiodine-labeled octreotide.[62]

RECURRENCE AND PROGNOSIS

There is a need for continued monitoring of the blood pressure despite a seemingly successful resection of the tumour as residual non-paroxysmal hypertension can be found in 27% to 38% of patients.[17] This persistence of hypertension can be due to a variety of reasons:[63] 1) fluid overload; 2) return of autonomic reflexes; 3) residual tumour; 4) accidental ligation of renal artery; and 5) essential hypertension.

In one study involving 129 patients,[64] the presence of risk factors for essential hypertension, like age and family history of hypertension, are found to be predictors of post-operative hypertension. The ten-year estimate of phaeochromocytoma-free survival in patients at risk of recurrence was 80%, and that of hypertension-free survival in those without recurrence, 45%. Recurrence, defined as the reappearance of disease after normalisation of biochemical tests, occurred in 16% of patients. Independent risk factors for recurrence include the presence of familial disease and a low ratio of adrenaline to adrenaline plus noradrenaline. Although recurrence was more frequent in larger and bilateral or extra-adrenal tumours, the associations were not significant in multivariate analysis if the above independent risk factors were considered.

Follow-up at six weeks post-operatively on the blood pressure and urinary catecholamines is reasonable as the urine levels usually take up to two weeks to normalise. Thereafter, it should be three monthly for the first year, followed by six monthly and yearly thereafter.

In malignant tumours, a repeat MIBG scan is done several months after the surgery to look for recurrence and metastases. A high or rising serum CgA level is also a sign of possible recurrence or metastases. Although MTC normally occurs eight years before the onset of phaeochromocytoma in MEN patients,[65] follow-up should still include screening for MTC even when it has not presented itself.

Although the five year survival rate in malignant tumours is less than 50%, the diagnosis of malignancy may only present itself up to 15 to 20 years later,[23,66] hence the need for life-long follow up especially in a patient with an extra-adrenal tumour.

CONCLUSION

Despite the advances in the diagnostic evaluation of phaeochromocytoma, the importance of the potential for cure with surgery especially in benign cases, cannot be over-emphasised. Future research should focus more on developing better diagnostic and prognostic tests and markers to distinguish benign from malignant and other forms of phaeochromocytoma[67] as well as conducting comparative trials between these tests. For the present time, a high index of suspicion, coupled with screening by urinary catecholamines and metanephrines offer good chance of confirming the diagnosis, while anatomical and functional localisation provide us with tools to better plan management strategies to achieve a favorable outcome.

REFERENCES

1 Welbourn RB. Early surgical history of phaeochromocytoma. *Br J Surg* 1987; **74(7):**594–6.
2 Elakovic D, Manojlovic D, Milovic N. Surgical treatment of pheochromocytoma-personal experience. *Srp Arh Celok Lek* 2002; **130(2):**31–7.
3 Saegesser F. Cesar Roux (1857–1934) et son époque. *Rev Med Suisse Romande* 1984; **104:**403–54.
4 Mayo CH. Paroxysmal hypertension with tumour of retroperitoneal nerve. *JAMA* 1927; **89:**1047–50.
5 Stein, PP, Black, HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. *Medicine (Baltimore)* 1991; **70:**46.
6 Smythe GA, Edwards G, Graham P, Lazarus L. Biochemical diagnosis of pheochromocytoma by simultaneous measurement of urinary excretion of epinephrine and norepinephrine. *Clin Chem* 1992; **38(4):**486–92.
7 Kudva YC, Young Jr Wf, Thompson GB *et al.* Adrenal incidentaloma: an important component of the clinical presentation spectrum of benign sporadic adrenal phaechromocytoma. *Endocrinologist* 1999; **(9):**77–80.
8 Stenstrom G, Svardsudd K. Pheochromocytoma in Sweden 1958–1981. An analysis of the National Cancer Registry Data. *Acta Med Scand* 1986; **220(3):**225–32.
9 Kudva YC, Sawka AM, Young WF Jr. Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab* 2003; **88(10):**4533–9.
10 Eisenhofer G, Walther MM, Huynh TT *et al.* Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. *J Clin Endocrinol Metab* 2001; **86(5):**1999–2008.
11 Crout JR, Sjoerdsma A. Turnover and metabolism of catecholamines in patients with pheochromocytoma. *J Clin Invest*

1964; **43:**94–102.
12 Crout Jr, Pisano JJ, Sjoerdsma A. Urinary excretion of catecholamines and their metabolites in pheochromocytoma. *Am Heart J* 1961; **61:**375–81.
13 Lenders JW, Pacak K, Walther MM *et al.* Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002; **287(11):**1427–34.
14 Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. *Endocr Rev* 2003; **24(4):**539–53.
15 Young WF Jr. Pheochromocytoma: issues in diagnosis & treatment. *Compr Ther* 1997; **23(5):**319–26.
16 Canale MP, Bravo EL. Diagnostic specificity of serum chromogranin-A for pheochromocytoma in patients with renal dysfunction. *J Clin Endocrinol Metab* 1994; **78(5):**1139–44.
17 Pacak K, Linehan WM, Eisenhofer G *et al.* Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med* 2001; **134(4):**315–29.
18 Grossman E, Goldstein DS, Hoffman A, Keiser HR. Glucagon and clonidine testing in the diagnosis of pheochromocytoma. *Hypertension* 1991; **17(6 Pt 1):**733–41.
19 Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab* 2004; **89(2):**479–91.
20 Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. J Urol 1992; **147(1):**1–10.
21 Kann PH, Wirkus B, Behr T *et al.* Endosonographic imaging of benign and malignant pheochromocytomas. *J Clin Endocrinol Metab* 2004; **89(4):**1694–7.
22 Furuta N, Kiyota H, Yoshigoe F *et al.* Diagnosis of pheochromocytoma using [123I]-compared with [131I]-metaiodobenzylguanidine scintigraphy. *Int J Urol* 1999; **6(3):**119–24.
23 Manger WM, Gifford RW Jr. Pheochromocytoma: current diagnosis and management. *Clev Clin J Med* 1993; **60:**365–78.
24 Manger WM. Editorial: In search of pheochromocytomas. *J Clin Endocrinol Metab* 2003; **88(9):**4080–2.
25 Ilias I, Yu J, Carrasquillo JA *et al.* Superiority of 6-[18F]-fluorodopamine positron emission tomography versus [131I]-metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. *J Clin Endocrinol Metab* 2003; **88(9):**4083–7.
26 van der Harst E, de Herder WW, Bruining HA *et al.* [(123)I]metaiodobenzylguanidine and [(111)In]octreotide uptake in begnign and malignant pheochromocytomas. *J Clin Endocrinol Metab* 2001; **86(2):**685–93.
27 Maurea S, Cuocolo A, Reynolds JC *et al.* Diagnostic imaging in patients with paragangliomas. Computed tomography, magnetic resonance and MIBG scintigraphy comparison. *Q J Nucl Med* 1996; **40(4):**365–71.
28 Kubota Y, Nakada T, Sasagawa I *et al.* Elevated levels of telomerase activity in malignant pheochromocytoma. *Cancer* 1998; **82(1):**176–9.
29 Boltze C, Mundschenk J, Unger N *et al.* Expression profile of the telomeric complex discriminates between benign and malignant pheochromocytoma. *J Clin Endocrinol Metab* 2003; **88(9):**4280–6.
30 Hosaka Y, Rainwater LM, Grant CS *et al.* Pheochromocytoma: nuclear deoxyribonucleic acid patterns studied by flow cytometry. *Surgery* 1986; **100(6):**1003–10.
31 Liu J, Voutilainen R, Kahri AI, Heikkila P. Expression patterns of the c-myc gene in adrenocortical tumors and pheochromocytomas. *J Endocrinol* 1997; **152(2):**175–81.
32 Elder EE, Xu D, Hoog A *et al.* KI-67 AND hTERT expression can aid in the distinction between malignant and benign pheochromocytoma and paraganglioma. *Mod Pathol* 2003; **16(3):**246–55.
33 Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothorac Vasc Anesth* 2002; **16(3):**359–69.
34 Roizen MF, Schreider BD, Hassan SZ. Anesthesia for patients with pheochromocytoma. *Anesthesiol Clin North Am* 1987; **5:**269–75.
35 Singh G, Kam P. An overview of anaesthetic issues in phaeochromocytoma. *Ann Acad Med Singapore* 1998; **27(6):**843–8.
36 Boutros AR, Bravo EL, Zanettin G, Straffon RA. Perioperative management of 63 patients with pheochromocytoma. *Cleve Clin J Med* 1990; **57(7):**613–7.
37 Proye C, Thevenin D, Cecat P *et al.* Exclusive use of calcium channel blockers in preoperative and intraoperative control of pheochromocytomas: hemodynamics and free catecholamine assays in ten consecutive patients. *Surgery* 1989; **106(6):**1149–54.
38 Hull CJ. Phaeochromocytoma. Diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58(12):**1453–68.
39 Sloand EM, Thompson BT. Propranolol-induced pulmonary edema and shock in a patient with pheochromocytoma. *Arch Intern Med* 1984; **144(1):**173–4.
40 Poopalalingam R, Chin EY. Rapid preparation of a patient with pheochromocytoma with labetolol and magnesium sulfate. *Can J Anaesth* 2001; **48(9):**876–80.
41 Briggs RS, Birtwell AJ, Pohl JE. Hypertensive response to labetalol in phaeochromocytoma. *Lancet* 1978; **1(8072):**1045–6.
42 Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. *Endocr Rev* 1994; **15(3):**356–68.
43 Steinsapir J, Carr AA, Prisant LM, Bransome ED Jr. Metyrosine and pheochromocytoma. *Arch Intern Med* 1997; **157(8):**901–6.
44 Perry RR, Keiser HR, Norton JA *et al.* Surgical management of pheochromocytoma with the use of metyrosine. *Ann Surg* 1990; **212(5):**621–8.
45 Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, el-Bakry AK. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth* 1995; **75(5):**588–92.
46 Prys-Roberts C. Pheochromocytoma-recent progress in its management. *Br J Anaesth* 2000; **85:**44–57.
47 Nicholas E, Deutschman CS, Allo M, Rock P. Use of esmolol in the intraoperative management of pheochromocytoma. *Anesth Analg* 1988; **67(11):**1114–7.
48 Desmonts JM, Marty J. Anaesthetic management of patients with phaechromocytoma. *Br J Anaesth* 1984; 56:781–9.
49 James MF. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics. *Br J Anaesth* 1989; **62(6):**616–23.
50 Lim KS, Low TC, Ng BK, Rajasoorya C. A case report of the use of magnesium sulphate during anaesthesia in a patient who had adrenalectomy for phaeochromocytoma. *Ann Acad Med Singapore* 2000; **29(4):**518–20.
51 James MF, Huddle KR, Owen AD, van der Veen BW. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. *Can J Anaesth* 1988; **35(2):**178–82.
52 James MF, Cronje L. Pheochromocytoma crisis: the use of magnesium sulfate. *Anesth Analg* 2004; **99(3):**680–6, table of contents.
53 Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; **83(2):**302–20.
54 Vigorito C, Giordano A, Ferraro P *et al.* Hemodynamic effects of magnesium sulfate on the normal human heart. *Am J Cardiol* 1991; **67(16):**1435–7.
55 Dube L, Granry JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. *Can J Anaesth* 2003; **50(7):**732–46.
56 Duh QY. Evolving surgical management for patients with pheochromocytoma. *J Clin Endocrinol Metab* 2001; **86(4):**1477–9.
57 Plouin PF, Duclos JM, Soppelsa F, Boublil G, Chatellier G. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. *J Clin Endocrinol Metab* 2001; **86(4):**1480–6.
58 Ram CVS. Phechromocytoma. *Cardiol Clin* 1988; **6:**517–35.
59 Walz MK, Peitgen K, Diesing D *et al.* Partial versus Total Adrenalectomy by the Posterior Retroperitoneoscopic Approach:

Early and Long-term Results of 325 Consecutive Procedures in Primary Adrenal Neoplasias. *World J Surg* 2004; **28(12):**1323–9.
60 Averbuch SD, Steakley CS, Young RC *et al.* Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. *Ann Intern Med* 1988; **109(4):**267–73.
61 Kaltsas G, Mukherjee JJ, Plowman PN, Grossman AB. The role of chemotherapy in the nonsurgical management of malignant neuroendocrine tumours. *Clin Endocrinol (Oxf)* 2001; **55(5):**575–87.
62 Wiseman GA, Kvols LK. Therapy of neuroendocrine tumors with radiolabeled MIBG and somatostatin analogues. *Semin Nucl Med* 1995; **25(3):**272–8.
63 Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothorac Vasc Anesth* 2002; **16(3):**359–69.
64 Plouin PF, Chatellier G, Fofol I, Corvol P. Tumor recurrence and hypertension persistence after successful pheochromocytoma operation. *Hypertension* 1997; **29(5):**1133–9.
65 Howe JR, Norton JA, Wells SA Jr. Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. *Surgery* 1993; **114(6):**1070–7.
66 Remine WH, Chong GC, van Heerden JA *et al.* Current management of pheochromocytoma. *Ann Surg* 1974; 179:740–8.
67 Eisenhofer G, Bornstein SR, Brouwers FM *et al.* Malignant pheochromocytoma: current status and initiatives for future progress. *Endocr Relat Cancer* 2004; **11(3):**423–36.