Pheochromocytoma – update on disease management

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Abstract: Pheochromocytomas are rare endocrine tumors that can present insidiously and remain undiagnosed until death or onset of clear manifestations of catecholamine excess. They are often referred to as one of the 'great mimics' in medicine. These tumors can no longer be regarded as a uniform disease entity, but rather as a highly heterogeneous group of chromaffin cell neoplasms with different ages of onset, secretory profiles, locations, and potential for malignancy according to underlying genetic mutations. These aspects all have to be considered when the tumor is encountered, thereby enabling optimal management for the patient. Referral to a center of specialized expertise for the disease should be considered wherever possible. This is not only important for surgical management of patients, but also for post-surgical follow up and screening of disease in patients with a hereditary predisposition to the tumor. While preoperative management has changed little over the last 20 years, surgical procedures have evolved so that laparoscopic resection is the standard of care and partial adrenalectomy should be considered in all patients with a hereditary condition. Follow-up testing is essential and should be recommended and ensured on a yearly basis. Managing such patients must now also take into account possible underlying mutations and the appropriate selection of genes for testing according to disease presentation. Patients and family members with identified mutations then require an individualized approach to management. This includes consideration of distinct patterns of biochemical test results during screening and the appropriate choice of imaging studies for tumor localization according to the mutation and associated differences in predisposition to adrenal, extra-adrenal and metastatic disease.

Keywords: pheochromocytoma, paraganglioma, management, clinical presentation, diagnosis, treatment, follow up, genetic testing

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Introduction – general aspects

Clinical presentation

Pheochromocytomas are rare tumors usually characterized by secretion of catecholamines and associated signs and symptoms of catecholamine excess. This secretion can arise in a sudden burst leading to paroxysmal symptoms. The classical symptom triad consists of palpitations, headaches and sweating lasting from only minutes to hours and occurring periodically on different occasions [Manger *et al.*, 1996]. Other symptoms, especially in an acute attack, include pallor, nausea and panic attacks, which may last for several minutes and resolve completely.

Apart from the above classic presentation, pheochromocytoma can also present with nonspecific symptoms such as flushing, nausea, tiredness or weight loss. Abdominal pain and constipation or chest pain mimicking myocardial infarction as in the case of inverted takotsubo cardiomyopathy can be caused by sudden catecholamine release [Prejbisz *et al.*, 2011]. A subtle sign may be new onset of diabetes, particularly in the young non-obese patient [La Batide-Alanore *et al.*, 2003].

Due to the diverse clinical manifestations, pheochromocytoma is therefore often referred as one of the great mimics in medicine. The first step in management of pheochromocytoma is to think of this rare disease and to then make the diagnosis [Manger, 2006].

Hypertension and incidentaloma

Pheochromocytoma is a rare cause of hypertension, but important because it is a usually curable cause of high blood pressure. The prevalence of the tumor among 4429 patients investigated for possible secondary hypertension has been reported at 0.3% [Anderson *et al.*, 1994]. This is still higher than revealed in large autopsy studies, where the prevalence ranged from 0.05 to 0.09% in 44,680 and 15,984 deceased individuals respectively [Minno *et al.*, 1954] [Schlegel, 1960] [McNeil *et al.*, 2000]. Thus, pheochromocytoma should be considered in patients with hypertension, but generally only when secondary causes of high blood pressure are being considered or when there are other symptoms or signs of catecholamine excess that can alert the physician to the tumor. Prevalence of pheochromocytoma is much higher, at 4.2 to 6.5%, in patients screened for the tumor due to an incidentally discovered adrenal mass [Mantero *et al.*, 2000] [Mansmann *et al.*, 2004]. All patients with adrenal masses should therefore be screened for pheochromocytoma, irrespective of the presence of hypertension and symptoms of catecholamine excess.

Diagnosis and localization

Diagnosis

As now widely recommended [Pacak *et al.*, 2007c], initial screening of pheochromocytoma should always include either or both measurements of urinary or plasma metanephrines, these metabolites comprising normetanephrine and metanephrine, the respective degradation products of the catecholamines, noradrenaline (NA) and adrenaline (A). Measurements of plasma free metanephrines have been shown by numerous independent studies to provide diagnostic sensitivity exceeding 96% with specificity between 85 to 100% [Pacak *et al.*, 2007c]. To minimize false-positive results blood samples should be drawn under stress free conditions in the supine position. Urinary fractionated metanephrines provide an alternative approach with similar diagnostic sensitivity [Brain *et al.*, 2006]. Diagnostic specificity at cut-offs for optimal sensitivity have, however, been reported as low as 45% for patients tested because of signs and symptoms [Lenders *et al.*, 2002], this representing a limitation of urinary measurements. Urinary fractionated metanephrines are also commonly measured after a deconjugation step and therefore reflect different metabolites from the free metanephrines in plasma. Nevertheless the urinary tests are commonly available and their high diagnostic sensitivity provides justification for use during initial screening, albeit with likelihood to rule out subsequent false-positive results.

Metanephrines in plasma or urine can be measured by three different methods. Measurement by liquid chromatography with electrochemical detection (LC-EC), although a well established method with high accuracy and precision, is a technically demanding procedure. Immunoassays, which are easily established and commonly used in European laboratories for hormone measurements, have disadvantages of calibration, accuracy and precision problems [Singh *et al.*, 2007] [Pillai *et al.*, 2010] [Mullins *et al.*, 2011]. In US and many other laboratories, liquid chromatography with tandem mass spectrometry (LC-MS/MS) has fast become the preferred method for determination of plasma and urinary metanephrines. This high-throughput method provides a precise, rapid, and specific method for biogenic amine measurements, but does require a large capital outlay and significant technical expertise [Lagerstedt *et al.*, 2004].

Localization of pheochromocytoma

Once a pheochromocytoma is confirmed biochemically, the next step is to locate the tumor [Figure 1]. If a pheochromocytoma is located extra-adrenally it is defined as a paraganglioma. Localization is usually achieved by either computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, with a sensitivity of 90-100% and a specificity of 70-80% [Maurea *et al.*, 1993] [Francis *et al.*, 1996] [Maurea *et al.*, 1996] [Lenders *et al.*, 2005]. However, specificity of MRI or CT imaging has been reported by some investigators as low as 50% [Ilias *et al.*, 2004]. Unsatisfactory results, for example, may also be obtained in patients with *SDHB* and *SDHD* mutations in whom paragangliomas can be located at extra-abdominal locations. For this reason, algorithms that include whole body MRI as part of the combination of conventional and

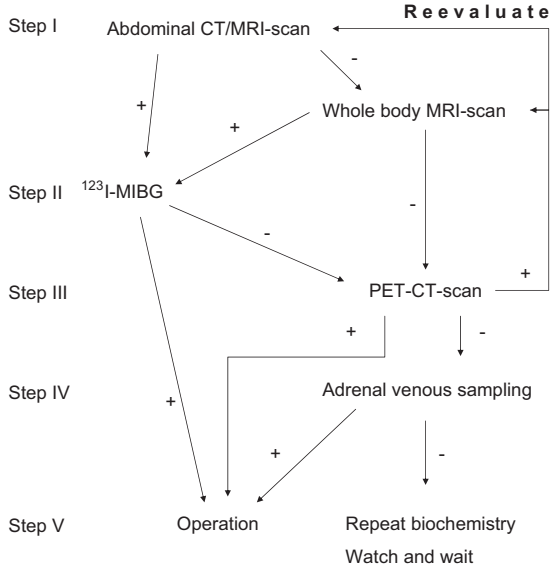

Figure 1. Algorithm for localization and confirmation of pheochromocytoma and paraganglioma

functional imaging have been proposed for disease localization and confirmation.

Imaging by ^{123}I-MIBG (metaiodobenzylguanidine) scintigraphy provides a widely used secondary imaging modality [Shapiro *et al.*, 1985] [Pacak *et al.*, 2001a]. This test has a high specificity and therefore should be considered in all patients with findings of adrenal tumors by conventional imaging. If the mass shows up on MIBG, the diagnosis is confirmed justifying surgical resection [Bravo, 1994] [Shapiro *et al.*, 1995] [Sisson *et al.*, 1999b] [Miskulin *et al.*, 2003]. MIBG can also point to additional lesions not indicated by conventional imaging in patients with metastatic disease or multifocal disease associated with mutations of disease-susceptibility genes. However, MIBG has lower sensitivity for detection of extra-adrenal tumors than adrenal tumors [Bhaita *et al.*, 2008]. MIBG is also nevertheless not as sensitive for detection of metastases compared to some other functional techniques [Timmers *et al.*, 2009].

If available, positron emission tomography, ideally combined with CT (PET/CT), and utilizing a range of labelled ligands provides an alternative functional imaging approach with improved resolution over scintigraphic methods. Such methods are particularly useful when MIBG scintigraphy, CT or MRI fail to locate the tumor. Radiotracers which have proven useful include ^{18}F-fluorodopamine [Pacak *et al.*, 2001b], especially in the diagnosis of metastatic disease [Ilias *et al.*, 2003], ^{18}F-fluorodopa [Hoegerle *et al.*, 2002], ^{11}C-hydroxyephedrine [Trampal *et al.*, 2004] [Pacak *et al.*, 2004], and ^{68}Ga-DOTATOC (tetraazacyclododecane-tetraaceticacid-tyr3-octreotide) [Kroiss *et al.*, 2011]. Accumulating evidence suggests that ^{18}F-fluorodeoxyglucose (FDG) is particularly valuable for detecting metastases in malignant pheochromocytoma and paraganglioma [Timmers *et al.*, 2007b] [Timmers *et al.*, 2009]. Adrenal venous sampling can be useful for localization of the tumor in selected cases when imaging results remain equivocal [Darr *et al.*, 2011].

Considerations for management of hereditary syndromes

Advances in genetics

Classically, three syndromes are associated with pheochromocytoma, namely von Hippel Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2) and neurofibromatosis type 1 (NF1) [Neumann *et al.*, 1993] [Bryant *et al.*, 2003]. After germline mutations of succinate dehydrogenase (SDH) subunit genes were identified as responsible for familial paraganglioma, it became apparent that up to 30% of all pheochromocytomas were due to genetic mutations [Neumann *et al.*, 2002] [Burnichon *et al.*, 2011].

Mutations of all four SDH subunits are now identified as causes of hereditary paragangliomas: These include *SDHA* [Burnichon *et al.*, 2010] [Korpershoek *et al.*, 2011], *SDHB* [Astuti *et al.*, 2001], *SDHC* [Niemann *et al.*, 2000] and *SDHD* [Baysal *et al.*, 2000]. Together with other mutations such as of the succinate dehydrogenase assembly factor 2 (*SDHAF2*) [Kunst *et al.*, 2011] [Korpershoek *et al.*, 2011], the transmembrane protein 127 (*TMEM127*) [Qin *et al.*, 2010] and the *MAX*-gene [Comino-Mendez *et al.*, 2011], there are now 10 known genes in which mutations predispose to pheochromocytoma and paraganglioma.

Screening for pheochromocytoma in mutation carriers. With the exception of mutations associated with low disease penetrance (e.g., NF1), all patients identified with a genetic mutation require periodic screening for pheochromocytoma and must be tracked and traced lifelong on a usually recommended yearly basis. Surveillance for pheochromocytoma and paraganglioma should be individualized according to

the underlying genetic mutation. In particular, biochemical screening should account for the distinct mutation-dependent profiles of catecholamine production, best assessed by differences in plasma normetanephrine, metanephrine and methoxytyramine [Eisenhofer *et al.*, 2011b].

Pheochromocytomas in VHL tumors are characterized by a solely noradrenergic biochemical phenotype so that, screening should be directed to measurements of normetanephrine. Adrenal tumors are common and the tumor is bilateral in 40% of the cases [Neumann *et al.*, 2002], but extra-adrenal occurrence is possible and should always be considered in VHL syndrome. In contrast tumors in patients with MEN2 and NF1 also produce epinephrine, so that management of these patients should be directed to identification of increases in both metanephrine and normetanephrine. Since tumors are invariably intra-adrenal [Lairmore *et al.*, 1993] imaging studies should focus mainly on the adrenals, with MIBG-scanning a particularly useful functional imaging modality due to highly active uptake of the agent by these tumors.

Tumors due to *SDHB* and *SDHD* mutations are somewhat similar to those due to VHL mutations in that they lack significant epinephrine production, so are not characterized by increases in metanephrine [Timmers *et al.*, 2007a] [Eisenhofer *et al.*, 2010]. However, these tumors often produce dopamine (D). Thus, in addition to measurement of normetanephrine, management of these patients can be improved by extending biochemical testing with measurements of dopamine and its metabolite methoxytyramine.

Extraadrenal tumors predominate in patients with *SDHB* or *SDHD* mutations, so imaging studies should be extensive, best achieved by whole body MRI. Head and neck paragangliomas, which are particularly common in *SDHD* mutation carriers, should always be considered and are best screened for using magnetic resonance angiography [Neumann *et al.*, 2002] [Neumann *et al.*, 2004]. Periodic screening with whole body MRI has been advocated in patients with *SDHB* mutations since tumors are particularly primitive and abdominal paragangliomas have been reported that do not produce any significant increases in normetanephrine or methoxytyramine [Timmers *et al.*, 2008]. Tumors in *SDHB* mutation carriers also have a high potential for malignancy, demanding particular close and careful management of these patients [Amar *et al.*, 2005b] [Brouwers *et al.*, 2006]. Where malignancy is suspected, PET scanning with ^{18}F-FDG is the preferred technique [Zelinka *et al.*, 2008].

Screening for genetic mutations. Due to the high prevalence of germline mutations in pheochromocytoma and paragangliomas it is generally recommended that possible mutations be considered in all patients with the tumors. The extent of testing remains highly debatable, but it is now clear that management of this testing should always take into account clinical features that can point to a particular mutation [Grossman *et al.*, 2006] [Pacak *et al.*, 2007b].

Of primary importance for individualized genetic testing is to first check for any clinical stigmata suggestive of a particular syndrome or whether there may be any relatives with a history of or suggestive of the tumors or a particular syndrome. Testing then should be directed to those particular genes. In the absence of a family history or characteristic clinical signs, a younger age at presentation carries a higher likelihood of underlying genetic defect [Neumann *et al.*, 2002] [Amar *et al.*, 2005b]. Generally, *VHL*, *SDHB* and *SDHD* mutations present at a younger age compared with tumors in patients with NF1 and MEN2 [Eisenhofer *et al.*, 2011a]. Bilateral adrenal tumors or multifocal extra-adrenal tumors carry a particularly high risk of germ line mutations that should always be explored.

Apart from the above factors, other considerations that can be used to point to mutations in the management of patients include locations of the tumor, catecholamine biochemical profiles and presence of metastatic disease [Table 1]. Mutations of *RET, TMEM127* and *MAX* genes are rarely associated with extra-adrenal primary tumors [Yao *et al.*, 2010] [Comino-Mendez *et al.*, 2011], the presence of which dictates emphasis of genetic testing on mutations involving genes for succinate dehydrogenase subunits, which more often give rise to extra-adrenal than adrenal tumors. Patients with *SDHB* and *SDHD* mutations in particular often have tumors that produce methoxytyramine, usually with elevations of normetanephrine, but no or relatively insignificant elevations of metanephrine. Thus, in patients with these catecholamine biochemical profiles mutations of *SDHB* and *SDHD* genes should be considered. These mutations need not be considered for patients with tumors that produce

Table 1. Main features of hereditary mutations associated with pheochromocytoma, paraganglioma, and sporadic disease

		Onset	Adrenal	Bilateral	Extra-adrenal	Malignancy	Type
Sporadic	70%	40-50	90%	10%	10%	10%	
Hereditary	30%						
Gene	Chromosome						
SDHB	1p36.13	30	28%	multifocal	59% abdominal thoracic	60%	NA/D
SDHD	11q23	30	53%	multifocal	79% head&neck	17%	NA/D
VHL	3p25-26	30	88%	40%	12%	4%	NA
NF1	17q11.2	40	84%	10%	6%	11%	NA/A
RET	10q11.2	40	100%	38%	rare	4%	NA/A
SDHA	5p15	n.a.	n.a.	n.a.	n.a.	n.a.	Unknown
SDHAF2	11q12.2	30	n.a.	n.a.	extraadrenal	n.a.	Unknown
SDHC	1q23.3	n.a.	rare	rare	rare	rare	Unknown
TMEM127	2q11.2	n.a.	adrenal	bilateral	n.a.	5%	Unknown
MAX-gene	14q23	n.a.	n.a.	n.a.	n.a.	n.a.	Unknown

metanephrine. Similarly, *VHL* mutations do not lead to tumors that produce epinephrine or metanephrine, so that this gene need not be considered in patients with tumors associated with increases in metanephrine. In contrast, pheochromocytomas in MEN 2 always produce increases in metanephrine, so that *RET* mutations should be considered in patients with these tumors.

Immunohistochemical staining for SDHB in resected tumor samples can also provide useful information to guide genetic testing, which for *SDHB* or *SDHD* mutations is only indicated in SDHB negative tumors [Van Nederveen *et al.*, 2009]. *SDHB* gene mutations should also be strongly suspected in patients with metastatic disease, but not those where disease is associated with large increases in metanephrine.

Complications and potential pitfalls in the treatment of the discovered pheochromocytoma

Preoperative considerations

Once a pheochromocytoma has been diagnosed and localized the next step is preparation for surgery. This ideally should be an interdisciplinary task involving endocrinologists, radiologists, nuclear medicine physicians, anaesthesiologists and surgeons but may also involve oncologists, cardiologists and clinical chemists. The presence of potential metastatic disease should always be considered and ruled out, since any indication of this is likely to impact treatment options beyond surgery. Patient management related to extent and choice of functional imaging to check for additional tumors or metastases should take into account stratification of risk for malignancy. Patients with large or extra-adrenal tumors, tumors associated with elevated plasma concentrations of methoxytyramine or due to *SDHB* mutations all have increased likelihood of metastatic disease [Tischler, 2008] [Eisenhofer, 2011c]. Risk increases when these factors associate in any combination and can be used to justify more extensive functional imaging to rule out metastases than might otherwise be considered. With no evidence of malignant disease, surgery is justified.

Due to the effects of circulating catecholamines on the cardiovascular system and possible preexisting cardiomyopathy in a patient with pheochromocytoma [Schurmeyer *et al.*, 1997], cardiovascular function should be evaluated prior to surgery. This may include an electrocardiogram, ambulatory blood pressure monitoring to assess blood pressure variations, supine and standing blood pressure measurements to evaluate for postural hypotension, and echocardiography to determine heart dimensions and function.

Cardiac arrhythmias due to sudden catecholamine release during surgery and cardiac ischemia may occur [Quezado *et al.*, 1992], and preexisting coronary artery disease may be aggravated by sudden vasospasms due to catecholamine release [Mannelli, 2006]. Coronary vasospasms may mimick cardiac ischemia [Liao *et al.*, 2000], and direct catecholamine action may lead to pulmonary oedema [Tauzin-Fin *et al.*, 1999]. Also, cerebrovascular accidents are a severe complication of hypertensive crisis in patients with pheochromocytoma.

Although some have suggested otherwise [Lentschener *et al.*, 2011], it remains widely recommended that appropriate medications should always be employed prior to surgery to block the effects of circulating catecholamine in all patients with catecholamine-producing tumors [Russell *et al.*, 1998] [Kinney *et al.*, 2000]. There are no official guidelines on the types of blocking drugs, with both alpha-adrenergic blockers and calcium channel blockers representing the main medications chosen for the purpose [Tokioka *et al.*, 1988] [Boutros *et al.*, 1990] [Young, 1997] [Ulchaker *et al.*, 1999] [Van Der Horst-Schrivers *et al.*, 2006] [Pacak, 2007d].

Both slow-release nifedipine, a dihydropyridine calcium-channel blockers and diltiazem, a non-dihydropyridine calcium-channel blocker [Tokioka *et al.*, 1988], have been described to control hypertension in pheochromocytoma. Immediate-release nifedipine, however, must be avoided because of potentially life-threatening cardiac accidents associated with this formulation. Otherwise calcium channel blockers can safely be used also in the cardiovascular patient, mitigating coronary vasospasms due to sudden noradrenaline release [Bravo *et al.*, 2003]. Nifedipine is given at a dose of 30-60 mg once daily, doses up to 120 mg per day have also been described [Proye *et al.*, 1989].

Most usually pre-operative blockade of catecholamine action employs the irreversible non-selective alpha-adenergic receptor, phenoxybenzamine. The drug is titrated according to patient needs. The starting dose is 10 mg twice a day, with stepwise increases of 10 to 20 mg every 2-3 days until the final dose of 1 mg/kg of body weight is reached. This dose is given in three divided doses over the day and is normally reached within 10-14 days, while the patient can be followed on an outpatient basis [Witteles *et al.*, 2000]. Blood pressure monitoring should be ensured two to three times a day, but even more important is measurement of standing blood pressure to gauge eventual orthostatic hypotension. Clinical signs of the optimal dose are a stuffy nose and slight dizziness due to postural hypotension.

Alternatively to phenoxybenzamine, the selective and reversible alpha$_1$-blocker doxazosin may be used [Bravo *et al.*, 2003]. Doxazosin is started at a dose of 1 mg and increased thereafter to 32 mg once a day. In contrast to phenoxybenzamine, strong catecholamine bursts can displace doxazosin from its receptor binding site and thus reduce efficacy. The advantage on the other hand is thought to be a reduced hypotensive response after surgery but this issue still remains unresolved [Kinney *et al.*, 2002] [Kocak *et al.*, 2002] [Prys-Roberts *et al.*, 2002]. In our outpatient setting, we normally use phenoxybenzamine for the preoperative treatment. Exceptions from this routine are the operation of head and neck paraganglioma especially if this tumor does not produce catecholamines or only dopamine [Mannelli, 2006].

In order to reduce tachycardic reflex responses, a low dose beta-blockade can be initiated in patients with evidence of tachycardia before surgery. Cardioselective beta$_1$-blockers such as metoprolol at 50 to 100 mg, bisoprolol at 5-10 mg or atenolol at 25-50 mg once daily [Prys-Roberts, 2000] are recommended. Intraoperative tachycardias may be controlled by esmolol [Gray, 1988]. Although labetalol has been used in the pharmacological treatment of pheochromocytoma [Van Stratum *et al.*, 1983] [Yabe *et al.*, 1987], its use is controversial [Reach *et al.*, 1980]. Briggs et al. reported about a hypotensive reaction in a patient in postural position and a reactive hypertensive crisis in supine position after labetalol, cautioning against the use of this drug in pheochromocytoma [Briggs *et al.*, 1978].

Alpha-methyl-para-tyrosine (metyrosine) has been used for additional preoperative treatment of pheochromocytoma [Perry *et al.*, 1990], but today is primarily relegated to patients in whom disease is extensive and accompanied by large increases in catecholamines. Metyrosine blocks catecholamine biosynthesis by inhibiting the conversion of tyrosine to L-dopa [Sjoerdsma *et al.*, 1965]. Usually metyrosine is started with an oral dose of 250 mg 3 to 4 times per day and gradually increased to a total dose of 1,5 to 4,0 g/d [Pacak *et al.*, 2007a].

Acute hypertensive attacks can be managed with the short acting alpha-blocker phentolamine as an infusion of e.g. 100 mg in 500 ml of 5% dextrose in water with 1mg/min [Pacak *et al.*, 2007a]. Other drugs in these emergency cases proven useful are vasodilating agents such as nitroprusside and nitroglycerin [Prys-Roberts, 2000] [Kinney *et al.*, 2002] [Prys-Roberts *et al.*, 2002] as well as urapidil in Europe [Tauzin-Fin *et al.*, 2004]. Interestingly good results in treating hypertension in patients with pheochromocytoma have been achieved with magnesium sulphate and therefore magnesium may be tried as a second line therapy for blood pressure control [James, 1989]. The action of magnesium is thought to be an inhibition of catecholamine release from the normal adrenal gland and from adrenergic nerve terminals [Douglas *et al.*, 1963] [Von Euler *et al.*, 1973].

Anaesthesia – aspects

Premedication with a benzodiazepine can be employed in patients with pheochromocytoma and no premedication has been shown to be superior to others [Kinney *et al.*, 2002]. For operation usually general anaesthesia is chosen. For induction, thiopental has been used with success [Desmonts *et al.*, 1984] and seems to decrease plasma catecholamine levels [Joyce *et al.*, 1983]. Also propofol and etomidate have been used with etomidate providing more cardiovascular stability [Hull, 1986]. Causing indirect catecholamine release, ketamine, morphine or meperidine, as well as droperidol [Sumikawa *et al.*, 1977] and ephedrine are not recommended [Kinney *et al.*, 2002].

For muscle relaxation, vecuronium [Gencarelli *et al.*, 1981], pancuronium [Desmonts *et al.*, 1984] and atracurium [Prys-Roberts, 2000] have been used, with atracurium possibly causing catecholamine release via histamine. As this also applies for tubocurarine and curare, and gallamine causing vagolytic effects, all those drugs should be avoided in patients with pheochromocytoma. Pancuronium has been used with success in the past but has been associated with severe hypertension [Jones *et al.*, 1981]. Because of its cardiac side effects, succinylcholine should be avoided [Stoner *et al.*, 1968]. Also, succinycholine may result in muscle fasciculation with ensuing mechanical stimulation of the tumor, and potentially life threatening catecholamine bursts [Desmonts *et al.*, 1984].

Regarding maintenance of anesthesia with volatile agents, sevoflurane [Kinney *et al.*, 2002], isoflurane [Kinney *et al.*, 2000] and enflurane [Janeczko *et al.*, 1977] can safely be used. Desflurane causes sympathetic activation but has also been administered [Lippmann *et al.*, 1994].

Operation - aspects

Today, pheochromocytomas of the abdomen normally can be operated on laparoscopically [Janetschek *et al.*, 1998] [Gill, 2001]. Single access retroperitoneoscopic adrenalectomy (SARA) may be an elegant alternative [Walz *et al.*, 2010]. The laparoscopic approach, together with adequate preoperative management, reduces perioperative mortality to 2.4% [Plouin *et al.*, 2001]. It also reduces morbidity, hospital stay and costs [Fernandez-Cruz *et al.*, 1996] [Sprung *et al.*, 2000], and is feasible and safe in solitary, bilateral, multiple, and recurrent pheochromocytoma [Walz *et al.*, 2002] [Jaroszewski *et al.*, 2003].

Partial adrenalectomy has been recommended in hereditary phechromocytoma to avoid adrenal insufficiency and lifelong hormone replacement therapy [Neumann *et al.*, 1999] [Walther *et al.*, 2000]. However partial adrenalectomy may predispose patients to an increased risk of recurrent disease. When performed in hereditary disease [Brauckhoff *et al.*, 2004], recurrence rate has been described in the range between 21% and 60% [Lee *et al.*, 1996] [Inabnet *et al.*, 2000]. Furthermore, partial adrenalectomy may not always ensure cortisol independency postoperatively [Yip *et al.*, 2004]. Therefore the benefits and risks of partial and total adrenalectomy must be discussed with the patient in each single case.

Open surgery may be indicated, when tumors are multiple or very large [Vargas *et al.*, 1997] but even tumors sized more than 9 cm may safely be removed laparascopically depending on the experience of the surgeon [Pacak *et al.*, 2007a]. Nevertheless, it is now becoming increasingly clear that risk of malignant disease increases with tumor size [Eisenhofer, 2011c]. Minimizing risk of spillage associated with laparoscopic surgery may therefore be important to consider with large tumors or for those associated with increased risk of malignancy due to other established risk factors (i.e., *SDHB* mutations, extra-adrenal locations). Difficult extra-adrenal operative sites include tumors located in the bladder, the chest or the head and neck [Manger, 2006].

Since head and neck paragangliomas rarely secrete catecholamines these tumors mostly do not require preoperative treatment. The main risks are related to operative difficulties. Complications include intraoperative nerve lesions, especially of the recurrent laryngeal nerve with subsequent hoarseness and difficulties of speaking and breathing. Other cranial nerves may be injured causing impairment of swallowing, hearing or facial muscle paralysis. In some cases, loss of blood pressure control due to baroreflex trauma may occur [Mannelli, 2006].

Postoperative considerations

Main challenges of the immediate postoperative period are blood pressure instability and heart rate control, as well as symptomatic hypoglycaemia, necessitating close patient monitoring for at least 24 h after operation [Mannelli, 2006]. Loss of peripheral vasoconstriction after operation may lead to hypovolemic hypotension, despite preoperative loading with normal saline. The amount of fluid required may be as large as 6-7 liters within the first two days after operation. Also, the effect of irreversible preoperative alpha-blockade may persist for more than 36 hours postoperatively [Bergman *et al.*, 1978]. Under these circumstances hypotension may be nor- and adrenaline resistant, and vasopressin may be needed for blood pressure control [Augoustides *et al.*, 2004].

Hypoglycaemia may occur because of rebound hyperinsulinemia [Isles *et al.*, 1983] [Ostenson *et al.*, 1989], and may be aggravated by prolonged postoperative alpha-blockade. Also, overt hypoglycaemic reactions may be masked due to impaired gluconeogenesis and glucogenolysis after beta$_2$-receptor blockade [Kinney *et al.*, 2002]. Therefore, close monitoring of blood glucose levels is mandatory, and prompt dextrose-infusions should be initiated when necessary [Meeke *et al.*, 1985]. If both hypotension and hypoglycaemia occur in a patient after bilateral partial or complete adrenalectomy [Costello *et al.*, 1988], suspicions about hypocortisolism and its most severe form, Addisonian crises should be raised, and plasma and urinary cortisol and plasma adrenocorticotropic hormone (ACTH) levels measured. If confirmed immediate steroid replacement should be started [Pacak *et al.*, 2007a].

Incomplete tumor removal, coexisting essential hypertension, volume overload, autonomic instability, postoperative pain or accidental ligation of the renal artery may result in postoperative hypertension [Engelman, 1977] [Young, 1997] [Pacak *et al.*, 2007a]. If hypertension persists the underlying cause should be determined and therapy instituted accordingly.

Follow-up

To ascertain that resection was complete and successful, biochemical testing should be undertaken dependent on the patient´s recovery within 2-6 weeks after surgery. As recurrence rates of up to 14% have been reported in pheochromocytoma and of up to 30% in extra-adrenal disease [Amar *et al.*, 2005a], lifelong follow up is recommended in all patients [Scott *et al.*, 1984] [Jaroszewski *et al.*, 2003]. Also, tumors may recur beginning from one year for up to 16 years after initial diagnosis and operation [Plouin *et al.*, 1997]. Therefore all patients with histologically proven pheochromocytoma or paraganglioma should be referred to and followed in specialized centers to ensure appropriate follow-up measurements [Mannelli, 2006]. Yearly follow up is also indicated in patients who are not willing to be or cannot be operated on for reasons such as previous adrenalectomy, putting them at increased risk for lifelong hormone replacement therapy, or because of an unacceptably high patient morbidity. In patients with sporadic pheochromocytoma follow up should be 10 years at least. Patients with either extra-adrenal disease or familial pheochromocytoma should be screened indefinitely in an individualized manner on a yearly basis [Lenders *et al.*, 2005]. Follow up visits every 6 months are indicated in patients with metastatic pheochromocytoma.

The patient with malignant pheochromocytoma and paraganglioma

Although attempts have been made to identify malignant pheochromocytoma by histomorphologic features [Thompson, 2002], proof of malignant disease to date relies on pathological confirmation of tumor metastases at sites where chromaffin tissue normally is absent, including bones, lungs, liver and lymph nodes. There are, however, several factors that can be used to predict future development of malignant disease. The presence of an *SDHB* mutation represents the single most important predictor for increased risk of malignancy [Gimenez-Roqueplo *et al.*, 2003]. As shown by Eisenhofer [Eisenhofer,

2011c], the high risk of malignancy assocociated with *SDHB* tumors entirely reflects both the predominant extra-adrenal locations and large size reached by tumors in patients with these mutations. Both extra-adrenal location and large tumor size are independent factors that contribute to increased risk of malignancy. Additionally, elevations of methoxytyramine, the O-methylated metabolite of dopamine, indicate an increased likelihood of metastases [Eisenhofer, 2011c].

Treatment options of malignant disease are limited. Disappointing results with only temporary remissions lasting for up to two years [Eisenhofer *et al.*, 2004] have been obtained with i.v. cyclophosphamide, vincristine and dacarbazine combination chemotherapy [Averbuch *et al.*, 1988]. Future therapy options may include LB1, a small molecule inhibitor of serine/threonine protein phosphatase 2A (PP2A), combined with temzolamide [Martiniova *et al.*, 2011] or sunitinib [Joshua *et al.*, 2009]. Symptomatic medical therapy is directed towards control of blood pressure and largely follows preoperative disease management rules. In addition alpha-methyl-para-tyrosine has been shown effective in case of high levels of plasma catecholamines [Decoulx *et al.*, 1987].

^{131}MIBG-radiotherapy either alone or in combination with chemotherapy has been reported to result in partial tumor remission [Sisson *et al.*, 1999a]. However, progressive disease has also been reported using this treatment modality [Schlumberger *et al.*, 1992]. It is presently unclear, whether higher doses of radiation might improve patient survival [Rose *et al.*, 2003]. The low remission rate observed may at least in part be due to the fact that malignant pheochromocytoma do not readily accumulate ^{131}MIBG [Ilias *et al.*, 2003].

Surgery is restricted to debulking strategies as there is no curative approach [Eisenhofer *et al.*, 2004]. Surgery can reduce the total amount of the catecholamine producing mass and the deleterious results of elevated catecholamines on the heart [Mishra *et al.*, 2000]. Furthermore, surgery can remove lesions that are life threatening due to their location [Nonaka *et al.*, 2000]. Finally, surgery can serve as an adjuvant measure prior to radiotherapy or chemotherapy. Nevertheless, prognosis of malignant disease is poor. In a postoperative survival study, 5 year survival rate has been estimated to be 20%, while no patient was alive ten years after surgery [John *et al.*, 1999]. In one single report a patient was alive more than 25 years after initial diagnosis [Yoshida *et al.*, 2001].

Pheochromocytoma in pregnancy - special considerations

With a prevalence of 1 in 50,000, pheochromocytoma is only rarely seen in pregnancy, where it shares two main symptoms with pre-eclampsia, namely spells of hypertension [Mannelli *et al.*, 2002] and headaches. Suspicions of pheochromocytoma should be raised in any pregnant woman with new onset hypertension [Manger, 2009], especially in the first half of pregnancy [Lenders, 2011]. Hypertensive crisis may compromise placental circulation while placental enzymes protect the fetus from direct catecholamine actions [Brunt, 2001] [Pacak *et al.*, 2007a].

Phenoxybenzamine in the pretreatment period before surgery seems to be safe for the fetus [Ahlawat *et al.*, 1999]. In hypertensive crisis, phentolamine can be used with 1 mg/min, as well as sodium nitroprusside as a final backup but only at a low dose and not over a prolonged time period to avoid fetal cyanide poisoning [Molitch, 1992]. Also, control of hypertension may be achieved with magnesium sulphate provided adequate magnesium levels are reached [James *et al.*, 1988]. Care should be taken to avoid hypotension since similar to hypertension, this can compromise placental circulation [Griffen *et al.*, 1969].

Special regards are necessary concerning diagnosis and tumor localization. The clonidine test cannot be performed in pregnant women, but measurement of urinary metanephrines after overnight sampling may be a useful alternative [Sullivan *et al.*, 1975] [Peaston *et al.*, 1996]. Abdominal ultrasound has a low diagnostic sensitivity especially for small tumors. Magnetic resonance tomography with gadolinium enhancement is the imaging procedure of first choice. However confirmation of a mass as pheochromocytoma or paraganglioma by scintigraphy is not feasible, leaving physicians and the mother in doubt of its origin.

Due to its infrequent occurrence, management of pheochromocytoma in pregnancy remains a medical challenge. If unrecognized, the risk of miscarriage, and of both maternal and fetal mortality is high, with reported mean ranges of 40 through 48% and 44 through 56%, respectively

[Griffen *et al.*, 1969] [Schenker *et al.*, 1982] [Pacak *et al.*, 2007a], while rapid diagnosis reduces these rates approximately by half [Grodski *et al.*, 2006]. However, despite unquestionable progress in recent years still antenatal diagnosis is made in only 30% to 50% of patients. These are sobering results considering that with antenatal diagnosis maternal mortality rate decreases nearly to zero and mortality of the unborn child to 15-18%, respectively [Harper *et al.*, 1989] [Oishi *et al.*, 1994].

There is general agreement that the tumor should be resected before the third trimenon and also that the method of choice should be laparascopy [Demeure *et al.*, 1998]. The risk of spontaneous abortion is greatest in the first trimenon [Yumi, 2008]. In the third trimenon, cesarean section should be performed prior to tumor removal [Manger *et al.*, 1996]. The issue of whether both operations should be carried out simultaneously is unsettled, unless in case of uncontrolled hypertension, hemorrhage or other emergency situations [Pacak *et al.*, 2007a].

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The Authors declare that there is no conflict of interest.

References

Ahlawat, S.K., Jain, S., Kumari, S., Varma, S., and Sharma, B.K. (1999) Pheochromocytoma Associated with Pregnancy: Case Report and Review of the Literature. *Obstet Gynecol Surv* 54: 728–737.

Amar, L., Servais, A., Gimenez-Roqueplo, A.P., Zinzindohoue, F., Chatellier, G., and Plouin, P.F. (2005a) Year of Diagnosis, Features at Presentation, and Risk of Recurrence in Patients with Pheochromocytoma or Secreting Paraganglioma. *J Clin Endocrinol Metab* 90: 2110–2116.

Amar, L., Bertherat, J., Baudin, E., Ajzenberg, C., Bressac-De Paillerets, B., Chabre, O. *et al.* (2005b) Genetic Testing in Pheochromocytoma or Functional Paraganglioma. *J Clin Oncol* 23: 8812–8818.

Anderson, G.H., Jr., Blakeman, N., and Streeten, D.H. (1994) The Effect of Age on Prevalence of Secondary Forms of Hypertension in 4429 Consecutively Referred Patients. *J Hypertens* 12: 609–615.

Astuti, D., Latif, F., Dallol, A., Dahia, P.L., Douglas, F., George, E. *et al.* (2001) Gene Mutations in the Succinate Dehydrogenase Subunit Sdhb Cause Susceptibility to Familial Pheochromocytoma and to Familial Paraganglioma. *Am J Hum Genet* 69: 49–54.

Augoustides, J.G., Abrams, M., Berkowitz, D., and Fraker, D. (2004) Vasopressin for Hemodynamic Rescue in Catecholamine-Resistant Vasoplegic Shock after Resection of Massive Pheochromocytoma. *Anesthesiology* 101: 1022–1024.

Averbuch, S.D., Steakley, C.S., Young, R.C., Gelmann, E.P., Goldstein, D.S., Stull, R. *et al.* (1988) Malignant Pheochromocytoma: Effective Treatment with a Combination of Cyclophosphamide, Vincristine, and Dacarbazine. *Ann Intern Med* 109: 267–273.

Baysal, B.E., Ferrell, R.E., Willett-Brozick, J.E., Lawrence, E.C., Myssiorek, D., Bosch, A. *et al.* (2000) Mutations in Sdhd, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma. *Science* 287: 848–851.

Bergman, S.M., Sears, H.F., Javadpour, N., and Keiser, H.R. (1978) Postoperative Management of Patients with Pheochromocytoma. *J Urol* 120: 109–112.

Bhatia, K.S., Ismail, M.M., Sahdev, A., Rockall, A.G., Hogarth, K., Canizales, A. *et al.* (2008) 123i-Metaiodobenzylguanidine (Mibg) Scintigraphy for the Detection of Adrenal and Extra-Adrenal Phaeochromocytomas: Ct and Mri Correlation. *Clin Endocrinol (Oxf)* 69: 181–188.

Boutros, A.R., Bravo, E.L., Zanettin, G., and Straffon, R.A. (1990) Perioperative Management of 63 Patients with Pheochromocytoma. *Cleve Clin J Med* 57: 613–617.

Brain, K.L., Kay, J., and Shine, B. (2006) Measurement of Urinary Metanephrines to Screen for Pheochromocytoma in an Unselected Hospital Referral Population. *Clin Chem* 52: 2060–2064.

Brauckhoff, M., Gimm, O., Brauckhoff, K., and Dralle, H. (2004) Repeat Adrenocortical-Sparing Adrenalectomy for Recurrent Hereditary Pheochromocytoma. *Surg Today* 34: 251–255.

Bravo, E.L. (1994) Evolving Concepts in the Pathophysiology, Diagnosis, and Treatment of Pheochromocytoma. *Endocr Rev* 15: 356–368.

Bravo, E.L. and Tagle, R. (2003) Pheochromocytoma: State-of-the-Art and Future Prospects. *Endocr Rev* 24: 539–553.

Briggs, R.S., Birtwell, A.J., and Pohl, J.E. (1978) Hypertensive Response to Labetalol in Phaeochromocytoma. *Lancet* 1: 1045–1046.

Brouwers, F.M., Eisenhofer, G., Tao, J.J., Kant, J.A., Adams, K.T., Linehan, W.M. *et al.* (2006)

High Frequency of Sdhb Germline Mutations in Patients with Malignant Catecholamine-Producing Paragangliomas: Implications for Genetic Testing. *J Clin Endocrinol Metab* 91: 4505–4509.

Brunt, L.M. (2001) Phaeochromocytoma in Pregnancy. *Br J Surg* 88: 481–483.

Bryant, J., Farmer, J., Kessler, L.J., Townsend, R.R., and Nathanson, K.L. (2003) Pheochromocytoma: The Expanding Genetic Differential Diagnosis. *J Natl Cancer Inst* 95: 1196–1204.

Burnichon, N., Briere, J.J., Libe, R., Vescovo, L., Riviere, J., Tissier, F. *et al.* (2010) Sdha Is a Tumor Suppressor Gene Causing Paraganglioma. *Hum Mol Genet* 19: 3011–3020.

Burnichon, N., Vescovo, L., Amar, L., Libe, R., De Reynies, A., Venisse, A. *et al.* (2011) Integrative Genomic Analysis Reveals Somatic Mutations in Pheochromocytoma and Paraganglioma. *Hum Mol Genet* 20: 3974–3985.

Comino-Mendez, I., Gracia-Aznarez, F.J., Schiavi, F., Landa, I., Leandro-Garcia, L.J., Leton, R. *et al.* (2011) Exome Sequencing Identifies Max Mutations as a Cause of Hereditary Pheochromocytoma. *Nat Genet* 43: 663–667.

Costello, G.T., Moorthy, S.S., Vane, D.W., and Dierdorf, S.F. (1988) Hypoglycemia Following Bilateral Adrenalectomy for Pheochromocytoma. *Crit Care Med* 16: 562–563.

Darr, R., Eisenhofer, G., Kotzerke, J., Zophel, K., Stroszczynski, C., Deinum, J. *et al.* (2011) Is There Still a Place for Adrenal Venous Sampling in the Diagnostic Localization of Pheochromocytoma? *Endocrine* 40: 75–79.

Decoulx, M., Wemeau, J.L., Racadot-Leroy, N., Grimbert, I., Proye, C., and Plane, C. (1987) [Alpha-Methyl-Paratyrosine in the Treatment of Malignant Pheochromocytoma]. *Rev Med Interne* 8: 383–388.

Demeure, M.J., Carlsen, B., Traul, D., Budney, C., Lalande, B., Lipinski, A. *et al.* (1998) Laparoscopic Removal of a Right Adrenal Pheochromocytoma in a Pregnant Woman. *J Laparoendosc Adv Surg Tech A* 8: 315–319.

Desmonts, J.M. and Marty, J. (1984) Anaesthetic Management of Patients with Phaeochromocytoma. *Br J Anaesth* 56: 781–789.

Douglas, W.W. and Rubin, R.P. (1963) The Mechanism of Catecholamine Release from the Adrenal Medulla and the Role of Calcium in Stimulus-Secretion Coupling. *J Physiol* 167: 288–310.

Eisenhofer, G., Bornstein, S.R., Brouwers, F.M., Cheung, N.K., Dahia, P.L., De Krijger, R.R. *et al.* (2004) Malignant Pheochromocytoma: Current Status and Initiatives for Future Progress. *Endocr Relat Cancer* 11: 423–436.

Eisenhofer, G., Pacak, K., Huynh, T.T., Qin, N., Bratslavsky, G., Linehan, W.M. *et al.* (2010) Catecholamine Metabolomic and Secretory Phenotypes in Phaeochromocytoma. *Endocr Relat Cancer* 18: 97–111.

Eisenhofer, G., Timmers, H.J., Lenders, J.W., Bornstein, S.R., Tiebel, O., Mannelli, M. *et al.* (2011a) Age at Diagnosis of Pheochromocytoma Differs According to Catecholamine Phenotype and Tumor Location. *J Clin Endocrinol Metab* 96: 375–384.

Eisenhofer, G., Lenders, J.W., Timmers, H., Mannelli, M., Grebe, S.K., Hofbauer, L.C. *et al.* (2011b) Measurements of Plasma Methoxytyramine, Normetanephrine, and Metanephrine as Discriminators of Different Hereditary Forms of Pheochromocytoma. *Clin Chem* 57: 411–420.

Eisenhofer, G., Lenders, J.W., Siegert, G., Bornstein, S., Friberg, P., Milosevic, D., Mannelli, M., Linehan, W.M., Adams, K., Timmers, H., Pacak, K. (2011c) Plasma Methoxytyramine: A Novel Biomarker of Metastatic Pheochromocytoma and Paraganglioma in Relation to Established Risk Factors of Tumor Size, Location and Sdhb Mutation Status. *Eur J Cancer*: in press.

Engelman, K. (1977) Phaeochromocytoma. *Clin Endocrinol Metab* 6: 769–797.

Fernandez-Cruz, L., Taura, P., Saenz, A., Benarroch, G., and Sabater, L. (1996) Laparoscopic Approach to Pheochromocytoma: Hemodynamic Changes and Catecholamine Secretion. *World J Surg* 20: 762-768; discussion 768.

Francis, I.R. and Korobkin, M. (1996) Pheochromocytoma. *Radiol Clin North Am* 34: 1101–1112.

Gencarelli, P.J., Roizen, M.F., Miller, R.D., Joyce, J., Hunt, T.K., and Tyrrell, J.B. (1981) Org Nc45 (Norcuron) and Pheochromocytoma: A Report of Three Cases. *Anesthesiology* 55: 690–693.

Gill, I.S. (2001) The Case for Laparoscopic Adrenalectomy. *J Urol* 166: 429–436.

Gimenez-Roqueplo, A.P., Favier, J., Rustin, P., Rieubland, C., Crespin, M., Nau, V. *et al.* (2003) Mutations in the Sdhb Gene Are Associated with Extra-Adrenal and/or Malignant Phaeochromocytomas. *Cancer Res* 63: 5615–5621.

Gray, R.J. (1988) Managing Critically Ill Patients with Esmolol. An Ultra Short-Acting Beta-Adrenergic Blocker. *Chest* 93: 398–403.

Griffen, W.O., Jr., Dilts, P.V., Jr., and Roddick, J.W., Jr. (1969) Non-Obstetric Surgery During Pregnancy. *Curr Probl Surg*: 1–56.

Grodski, S., Jung, C., Kertes, P., Davies, M., and Banting, S. (2006) Phaeochromocytoma in Pregnancy. *Intern Med J* 36: 604–606.

Grossman, A., Pacak, K., Sawka, A., Lenders, J.W., Harlander, D., Peaston, R.T. *et al.* (2006) Biochemical Diagnosis and Localization of Pheochromocytoma: Can We Reach a Consensus? *Ann N Y Acad Sci* 1073: 332–347.

Harper, M.A., Murnaghan, G.A., Kennedy, L., Hadden, D.R., and Atkinson, A.B. (1989) Phaeochromocytoma in Pregnancy. Five Cases and a Review of the Literature. *Br J Obstet Gynaecol* 96: 594–606.

Hoegerle, S., Nitzsche, E., Altehoefer, C., Ghanem, N., Manz, T., Brink, I. *et al.* (2002) Pheochromocytomas: Detection with 18f Dopa Whole Body Pet--Initial Results. *Radiology* 222: 507–512.

Hull, C.J. (1986) Phaeochromocytoma. Diagnosis, Preoperative Preparation and Anaesthetic Management. *Br J Anaesth* 58: 1453–1468.

Ilias, I., Yu, J., Carrasquillo, J.A., Chen, C.C., Eisenhofer, G., Whatley, M. *et al.* (2003) Superiority of 6-[18f]-Fluorodopamine Positron Emission Tomography Versus [131i]-Metaiodobenzylguanidine Scintigraphy in the Localization of Metastatic Pheochromocytoma. *J Clin Endocrinol Metab* 88: 4083–4087.

Ilias, I. and Pacak, K. (2004) Current Approaches and Recommended Algorithm for the Diagnostic Localization of Pheochromocytoma. *J Clin Endocrinol Metab* 89: 479–491.

Inabnet, W.B., Caragliano, P., and Pertsemlidis, D. (2000) Pheochromocytoma: Inherited Associations, Bilaterality, and Cortex Preservation. *Surgery* 128: 1007-1011;discussion 1011–1002.

Isles, C.G. and Johnson, J.K. (1983) Phaeochromocytoma and Diabetes Mellitus: Further Evidence That Alpha 2 Receptors Inhibit Insulin Release in Man. *Clin Endocrinol (Oxf)* 18: 37–41.

James, M.F., Huddle, K.R., Owen, A.D., and Van Der Veen, B.W. (1988) Use of Magnesium Sulphate in the Anaesthetic Management of Phaeochromocytoma in Pregnancy. *Can J Anaesth* 35: 178–182.

James, M.F. (1989) Use of Magnesium Sulphate in the Anaesthetic Management of Phaeochromocytoma: A Review of 17 Anaesthetics. *Br J Anaesth* 62: 616–623.

Janeczko, G.F., Ivankovich, A.D., Glisson, S.N., Heyman, H.J., El-Etr, A.A., and Albrecht, R.F. (1977) Enflurane Anesthesia for Surgical Removal of Pheochromocytoma. *Anesth Analg* 56: 62–67.

Janetschek, G., Finkenstedt, G., Gasser, R., Waibel, U.G., Peschel, R., Bartsch, G. *et al.* (1998) Laparoscopic Surgery for Pheochromocytoma: Adrenalectomy, Partial Resection, Excision of Paragangliomas. *J Urol* 160: 330–334.

Jaroszewski, D.E., Tessier, D.J., Schlinkert, R.T., Grant, C.S., Thompson, G.B., Van Heerden, J.A. *et al.* (2003) Laparoscopic Adrenalectomy for Pheochromocytoma. *Mayo Clin Proc* 78: 1501–1504.

John, H., Ziegler, W.H., Hauri, D., and Jaeger, P. (1999) Pheochromocytomas: Can Malignant Potential Be Predicted? *Urology* 53: 679–683.

Jones, R.M. and Hill, A.B. (1981) Severe Hypertension Associated with Pancuronium in a Patient with a Phaeochromocytoma. *Can Anaesth Soc J* 28: 394–396.

Joshua, A.M., Ezzat, S., Asa, S.L., Evans, A., Broom, R., Freeman, M. *et al.* (2009) Rationale and Evidence for Sunitinib in the Treatment of Malignant Paraganglioma/Pheochromocytoma. *J Clin Endocrinol Metab* 94: 5–9.

Joyce, J.T., Roizen, M.F., and Eger, E.I., 2nd. (1983) Effect of Thiopental Induction on Sympathetic Activity. *Anesthesiology* 59: 19–22.

Kinney, M.A., Warner, M.E., Vanheerden, J.A., Horlocker, T.T., Young, W.F., Jr., Schroeder, D.R. *et al.* (2000) Perianesthetic Risks and Outcomes of Pheochromocytoma and Paraganglioma Resection. *Anesth Analg* 91: 1118–1123.

Kinney, M.A., Narr, B.J., and Warner, M.A. (2002) Perioperative Management of Pheochromocytoma. *J Cardiothorac Vasc Anesth* 16: 359–369.

Kocak, S., Aydintug, S., and Canakci, N. (2002) Alpha Blockade in Preoperative Preparation of Patients with Pheochromocytomas. *Int Surg* 87: 191–194.

Korpershoek, E., Favier, J., Gaal, J., Burnichon, N., Van Gessel, B., Oudijk, L. *et al.* (2011) Sdha Immunohistochemistry Detects Germline Sdha Gene Mutations in Apparently Sporadic Paragangliomas and Pheochromocytomas. *J Clin Endocrinol Metab* 96: E1472–1476.

Kroiss, A., Putzer, D., Uprimny, C., Decristoforo, C., Gabriel, M., Santner, W. *et al.* (2011) Functional Imaging in Phaeochromocytoma and Neuroblastoma with 68ga-Dota-Tyr 3-Octreotide Positron Emission Tomography and 123i-Metaiodobenzylguanidine. *Eur J Nucl Med Mol Imaging* 38: 865–873.

Kunst, H.P., Rutten, M.H., De Monnink, J.P., Hoefsloot, L.H., Timmers, H.J., Marres, H.A. *et al.* (2011) Sdhaf2 (Pgl2-Sdh5) and Hereditary Head and Neck Paraganglioma. *Clin Cancer Res* 17: 247–254.

La Batide-Alanore, A., Chatellier, G., and Plouin, P.F. (2003) Diabetes as a Marker of

Pheochromocytoma in Hypertensive Patients. *J Hypertens* 21: 1703–1707.

Lagerstedt, S.A., O'kane, D.J., and Singh, R.J. (2004) Measurement of Plasma Free Metanephrine and Normetanephrine by Liquid Chromatography-Tandem Mass Spectrometry for Diagnosis of Pheochromocytoma. *Clin Chem* 50: 603–611.

Lairmore, T.C., Ball, D.W., Baylin, S.B., and Wells, S.A., Jr. (1993) Management of Pheochromocytomas in Patients with Multiple Endocrine Neoplasia Type 2 Syndromes. *Ann Surg* 217: 595-601; discussion 601–593.

Lee, J.E., Curley, S.A., Gagel, R.F., Evans, D.B., and Hickey, R.C. (1996) Cortical-Sparing Adrenalectomy for Patients with Bilateral Pheochromocytoma. *Surgery* 120: 1064-1070; discussion 1070–1061.

Lenders, J.W., Pacak, K., Walther, M.M., Linehan, W.M., Mannelli, M., Friberg, P. *et al.* (2002) Biochemical Diagnosis of Pheochromocytoma: Which Test Is Best? *Jama* 287: 1427–1434.

Lenders, J.W., Eisenhofer, G., Mannelli, M., and Pacak, K. (2005) Phaeochromocytoma. *Lancet* 366: 665–675.

Lenders, J. (2011) Review Topic: Endocrine Disorders in Pregnancy Phaeochromocytoma and Pregnancy:A Deceptive Connection. *Eur J Endocrinol*: in press.

Lentschener, C., Gaujoux, S., Tesniere, A., and Dousset, B. (2011) Point of Controversy: Perioperative Care of Patients Undergoing Pheochromocytoma Removal-Time for a Reappraisal? *Eur J Endocrinol* 165: 365–373.

Liao, W.B., Liu, C.F., Chiang, C.W., Kung, C.T., and Lee, C.W. (2000) Cardiovascular Manifestations of Pheochromocytoma. *Am J Emerg Med* 18: 622–625.

Lippmann, M., Ford, M., Lee, C., Ginsburg, R., Foran, W., Raum, W. *et al.* (1994) Use of Desflurane During Resection of Phaeochromocytoma. *Br J Anaesth* 72: 707–709.

Manger, W.M. and Gifford, R.W. (1996) Clinical and Experimental Pheochromocytoma. Blackwell Science.

Manger, W.M. (2006) An Overview of Pheochromocytoma: History, Current Concepts, Vagaries, and Diagnostic Challenges. *Ann N Y Acad Sci* 1073: 1–20.

Manger, W.M. (2009) The Protean Manifestations of Pheochromocytoma. *Horm Metab Res* 41: 658–663.

Mannelli, M. and Bemporad, D. (2002) Diagnosis and Management of Pheochromocytoma During Pregnancy. *J Endocrinol Invest* 25: 567–571.

Mannelli, M. (2006) Management and Treatment of Pheochromocytomas and Paragangliomas. *Ann N Y Acad Sci* 1073: 405–416.

Mansmann, G., Lau, J., Balk, E., Rothberg, M., Miyachi, Y., and Bornstein, S.R. (2004) The Clinically Inapparent Adrenal Mass: Update in Diagnosis and Management. *Endocr Rev* 25: 309–340.

Mantero, F., Terzolo, M., Arnaldi, G., Osella, G., Masini, A.M., Ali, A. *et al.* (2000) A Survey on Adrenal Incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab* 85: 637–644.

Martiniova, L., Lu, J., Chiang, J., Bernardo, M., Lonser, R., Zhuang, Z. *et al.* (2011) Pharmacologic Modulation of Serine/Threonine Phosphorylation Highly Sensitizes Pheo in a Mpc Cell and Mouse Model to Conventional Chemotherapy. *PLoS One* 6: e14678.

Maurea, S., Cuocolo, A., Reynolds, J.C., Tumeh, S.S., Begley, M.G., Linehan, W.M. *et al.* (1993) Iodine-131-Metaiodobenzylguanidine Scintigraphy in Preoperative and Postoperative Evaluation of Paragangliomas: Comparison with Ct and Mri. *J Nucl Med* 34: 173–179.

Maurea, S., Cuocolo, A., Reynolds, J.C., Neumann, R.D., and Salvatore, M. (1996) Diagnostic Imaging in Patients with Paragangliomas. Computed Tomography, Magnetic Resonance and Mibg Scintigraphy Comparison. *Q J Nucl Med* 40: 365–371.

Mcneil, A.R., Blok, B.H., Koelmeyer, T.D., Burke, M.P., and Hilton, J.M. (2000) Phaeochromocytomas Discovered During Coronial Autopsies in Sydney, Melbourne and Auckland. *Aust N Z J Med* 30: 648–652.

Meeke, R.I., O'keeffe, J.D., and Gaffney, J.D. (1985) Phaeochromocytoma Removal and Postoperative Hypoglycaemia. *Anaesthesia* 40: 1093–1096.

Minno, A.M., Bennett, W.A., and Kvale, W.F. (1954) Pheochromocytoma; a Study of 15 Cases Diagnosed at Autopsy. *N Engl J Med* 251: 959–965.

Mishra, A.K., Agarwal, G., Kapoor, A., Agarwal, A., Bhatia, E., and Mishra, S.K. (2000) Catecholamine Cardiomyopathy in Bilateral Malignant Pheochromocytoma: Successful Reversal after Surgery. *Int J Cardiol* 76: 89–90.

Miskulin, J., Shulkin, B.L., Doherty, G.M., Sisson, J.C., Burney, R.E., and Gauger, P.G. (2003) Is Preoperative Iodine 123 Meta-Iodobenzylguanidine Scintigraphy Routinely Necessary before Initial Adrenalectomy for Pheochromocytoma? *Surgery* 134: 918-922; discussion 922–913.

Molitch, M.E. (1992) Endocrine Emergencies in Pregnancy. *Baillieres Clin Endocrinol Metab* 6: 167–191.

Mullins, F., O'shea, P., Fitzgerald, R., and Tormey, W. (2011) Enzyme-Linked Immunoassay for Plasma-Free Metanephrines in the Biochemical Diagnosis of Phaeochromocytoma in Adults Is Not Ideal. *Clin Chem Lab Med*: in press.

Neumann, H.P., Berger, D.P., Sigmund, G., Blum, U., Schmidt, D., Parmer, R.J. *et al.* (1993) Pheochromocytomas, Multiple Endocrine Neoplasia Type 2, and Von Hippel-Lindau Disease. *N Engl J Med* 329: 1531–1538.

Neumann, H.P., Reincke, M., Bender, B.U., Elsner, R., and Janetschek, G. (1999) Preserved Adrenocortical Function after Laparoscopic Bilateral Adrenal Sparing Surgery for Hereditary Pheochromocytoma. *J Clin Endocrinol Metab* 84: 2608–2610.

Neumann, H.P., Bausch, B., Mcwhinney, S.R., Bender, B.U., Gimm, O., Franke, G. *et al.* (2002) Germ-Line Mutations in Nonsyndromic Pheochromocytoma. *N Engl J Med* 346: 1459–1466.

Neumann, H.P., Pawlu, C., Peczkowska, M., Bausch, B., Mcwhinney, S.R., Muresan, M. *et al.* (2004) Distinct Clinical Features of Paraganglioma Syndromes Associated with Sdhb and Sdhd Gene Mutations. *Jama* 292: 943–951.

Niemann, S. and Muller, U. (2000) Mutations in Sdhc Cause Autosomal Dominant Paraganglioma, Type 3. *Nat Genet* 26: 268–270.

Nonaka, K., Makuuchi, H., Naruse, Y., Kobayashi, T., and Goto, M. (2000) Surgical Excision of Malignant Pheochromocytoma in the Left Atrium. *Jpn J Thorac Cardiovasc Surg* 48: 126–128.

Oishi, S. and Sato, T. (1994) Pheochromocytoma in Pregnancy: A Review of the Japanese Literature. *Endocr J* 41: 219–225.

Ostenson, C.G., Cattaneo, A.G., Doxey, J.C., and Efendic, S. (1989) Alpha-Adrenoceptors and Insulin Release from Pancreatic Islets of Normal and Diabetic Rats. *Am J Physiol* 257: E439–443.

Pacak, K., Linehan, W.M., Eisenhofer, G., Walther, M.M., and Goldstein, D.S. (2001a) Recent Advances in Genetics, Diagnosis, Localization, and Treatment of Pheochromocytoma. *Ann Intern Med* 134: 315–329.

Pacak, K., Eisenhofer, G., Carrasquillo, J.A., Chen, C.C., Li, S.T., and Goldstein, D.S. (2001b) 6-[18f] Fluorodopamine Positron Emission Tomographic (Pet) Scanning for Diagnostic Localization of Pheochromocytoma. *Hypertension* 38: 6–8.

Pacak, K., Eisenhofer, G., and Goldstein, D.S. (2004) Functional Imaging of Endocrine Tumors: Role of Positron Emission Tomography. *Endocr Rev* 25: 568–580.

Pacak, K., Eisenhofer, G., and Lenders, J.W.M. (2007a) Pheochromocytoma: Diagnosis, Localization, and Treatment. Blackwell Pub.

Pacak, K., Eisenhofer, G., Ahlman, H., Bornstein, S.R., Gimenez-Roqueplo, A.P., Grossman, A.B. *et al.* (2007b) Pheochromocytoma: Recommendations for Clinical Practice from the First International Symposium. October 2005. *Nat Clin Pract Endocrinol Metab* 3: 92–102.

Pacak, K. and Eisenhofer, G. (2007c) An Assessment of Biochemical Tests for the Diagnosis of Pheochromocytoma. *Nat Clin Pract Endocrinol Metab* 3: 744–745.

Pacak, K. (2007d) Preoperative Management of the Pheochromocytoma Patient. *J Clin Endocrinol Metab* 92: 4069–4079.

Peaston, R.T., Lennard, T.W., and Lai, L.C. (1996) Overnight Excretion of Urinary Catecholamines and Metabolites in the Detection of Pheochromocytoma. *J Clin Endocrinol Metab* 81: 1378–1384.

Perry, R.R., Keiser, H.R., Norton, J.A., Wall, R.T., Robertson, C.N., Travis, W. *et al.* (1990) Surgical Management of Pheochromocytoma with the Use of Metyrosine. *Ann Surg* 212: 621–628.

Pillai, D. and Callen, S. (2010) Pilot Quality Assurance Programme for Plasma Metanephrines. *Ann Clin Biochem* 47: 137–142.

Plouin, P.F., Chatellier, G., Fofol, I., and Corvol, P. (1997) Tumor Recurrence and Hypertension Persistence after Successful Pheochromocytoma Operation. *Hypertension* 29: 1133–1139.

Plouin, P.F., Duclos, J.M., Soppelsa, F., Boublil, G., and Chatellier, G. (2001) Factors Associated with Perioperative Morbidity and Mortality in Patients with Pheochromocytoma: Analysis of 165 Operations at a Single Center. *J Clin Endocrinol Metab* 86: 1480–1486.

Prejbisz, A., Lenders, J.W., Eisenhofer, G., and Januszewicz, A. (2011) Cardiovascular Manifestations of Phaeochromocytoma. *J Hypertens* 29: 2049–2060.

Proye, C., Thevenin, D., Cecat, P., Petillot, P., Carnaille, B., Verin, P. *et al.* (1989) Exclusive Use of Calcium Channel Blockers in Preoperative and Intraoperative Control of Pheochromocytomas: Hemodynamics and Free Catecholamine Assays in Ten Consecutive Patients. *Surgery* 106: 1149–1154.

Prys-Roberts, C. (2000) Phaeochromocytoma–Recent Progress in Its Management. *Br J Anaesth* 85: 44–57.

Prys-Roberts, C. and Farndon, J.R. (2002) Efficacy and Safety of Doxazosin for Perioperative Management of Patients with Pheochromocytoma. *World J Surg* 26: 1037–1042.

Qin, Y., Yao, L., King, E.E., Buddavarapu, K., Lenci, R.E., Chocron, E.S. *et al.* (2010) Germline Mutations in Tmem127 Confer Susceptibility to Pheochromocytoma. *Nat Genet* 42: 229–233.

Quezado, Z.N., Keiser, H.R., and Parker, M.M. (1992) Reversible Myocardial Depression after Massive Catecholamine Release from a Pheochromocytoma. *Crit Care Med* 20: 549–551.

Reach, G., Thibonnier, M., Chevillard, C., Corvol, P., and Milliez, P. (1980) Effect of Labetalol on Blood Pressure and Plasma Catecholamine Concentrations in Patients with Phaeochromocytoma. *Br Med J* 280: 1300–1301.

Rose, B., Matthay, K.K., Price, D., Huberty, J., Klencke, B., Norton, J.A. *et al.* (2003) High-Dose 131i-Metaiodobenzylguanidine Therapy for 12 Patients with Malignant Pheochromocytoma. *Cancer* 98: 239–248.

Russell, W.J., Metcalfe, I.R., Tonkin, A.L., and Frewin, D.B. (1998) The Preoperative Management of Phaeochromocytoma. *Anaesth Intensive Care* 26: 196–200.

Schenker, J.G. and Granat, M. (1982) Phaeochromocytoma and Pregnancy–an Updated Appraisal. *Aust N Z J Obstet Gynaecol* 22: 1–10.

Schlegel, G.C. (1960) [Recklinghausen's Neurofibromatosis and Pheochromocytoma]. *Schweiz Med Wochenschr* 90: 31–39.

Schlumberger, M., Gicquel, C., Lumbroso, J., Tenenbaum, F., Comoy, E., Bosq, J. *et al.* (1992) Malignant Pheochromocytoma: Clinical, Biological, Histologic and Therapeutic Data in a Series of 20 Patients with Distant Metastases. *J Endocrinol Invest* 15: 631–642.

Schurmeyer, T.H., Engeroff, B., Dralle, H., and Von Zur Muhlen, A. (1997) Cardiological Effects of Catecholamine-Secreting Tumours. *Eur J Clin Invest* 27: 189–195.

Scott, H.W., Jr. and Halter, S.A. (1984) Oncologic Aspects of Pheochromocytoma: The Importance of Follow-Up. *Surgery* 96: 1061–1066.

Shapiro, B., Copp, J.E., Sisson, J.C., Eyre, P.L., Wallis, J., and Beierwaltes, W.H. (1985) Iodine-131 Metaiodobenzylguanidine for the Locating of Suspected Pheochromocytoma: Experience in 400 Cases. *J Nucl Med* 26: 576–585.

Shapiro, B., Sisson, J.C., Shulkin, B.L., Gross, M.D., and Zempel, S. (1995) The Current Status of Meta-Iodobenzylguanidine and Related Agents for the Diagnosis of Neuro-Endocrine Tumors. *Q J Nucl Med* 39: 3–8.

Singh, R.J. and Eisenhofer, G. (2007) High-Throughput, Automated, and Accurate Biochemical Screening for Pheochromocytoma: Are We There Yet? *Clin Chem* 53: 1565–1567.

Sisson, J.C., Shapiro, B., Shulkin, B.L., Urba, S., Zempel, S., and Spaulding, S. (1999a) Treatment of Malignant Pheochromocytomas with 131-I Metaiodobenzylguanidine and Chemotherapy. *Am J Clin Oncol* 22: 364–370.

Sisson, J.C. and Shulkin, B.L. (1999b) Nuclear Medicine Imaging of Pheochromocytoma and Neuroblastoma. *Q J Nucl Med* 43: 217–223.

Sjoerdsma, A., Engelman, K., Spector, S., and Udenfriend, S. (1965) Inhibition of Catecholamine Synthesis in Man with Alpha-Methyl-Tyrosine, an Inhibitor of Tyrosine Hydroxylase. *Lancet* 2: 1092–1094.

Sprung, J., O'hara, J.F., Jr., Gill, I.S., Abdelmalak, B., Sarnaik, A., and Bravo, E.L. (2000) Anesthetic Aspects of Laparoscopic and Open Adrenalectomy for Pheochromocytoma. *Urology* 55: 339–343.

Stoner, T.R., Jr. and Urbach, K.F. (1968) Cardiac Arrhythmias Associated with Succinylcholine in a Patient with Pheochromocytoma. *Anesthesiology* 29: 1228–1229.

Sullivan, J.M. and Solomon, H.S. (1975) The Diagnosis of Pheochromocytoma. Overnight Excretion of Catecholamine Metabolites. *Jama* 231: 618–619.

Sumikawa, K. and Amakata, Y. (1977) The Pressor Effect of Droperidol on a Patient with Pheochromocytoma. *Anesthesiology* 46: 359–361.

Tauzin-Fin, P., Hilbert, G., Krol-Houdek, M., Gosse, P., and Maurette, P. (1999) Mydriasis and Acute Pulmonary Oedema Complicating Laparoscopic Removal of Phaechromocytoma. *Anaesth Intensive Care* 27: 646–649.

Tauzin-Fin, P., Sesay, M., Gosse, P., and Ballanger, P. (2004) Effects of Perioperative Alpha1 Block on Haemodynamic Control During Laparoscopic Surgery for Phaeochromocytoma. *Br J Anaesth* 92: 512–517.

Thompson, L.D. (2002) Pheochromocytoma of the Adrenal Gland Scaled Score (Pass) to Separate Benign from Malignant Neoplasms: A Clinicopathologic and Immunophenotypic Study of 100 Cases. *Am J Surg Pathol* 26: 551–566.

Timmers, H.J., Kozupa, A., Eisenhofer, G., Raygada, M., Adams, K.T., Solis, D. *et al.* (2007a) Clinical Presentations, Biochemical Phenotypes, and Genotype-Phenotype Correlations in Patients with Succinate Dehydrogenase Subunit B-Associated Pheochromocytomas and Paragangliomas. *J Clin Endocrinol Metab* 92: 779–786.

Timmers, H.J., Kozupa, A., Chen, C.C., Carrasquillo, J.A., Ling, A., Eisenhofer, G. *et al.* (2007b) Superiority of Fluorodeoxyglucose Positron Emission Tomography to Other Functional Imaging

Techniques in the Evaluation of Metastatic Sdhb-Associated Pheochromocytoma and Paraganglioma. *J Clin Oncol* 25: 2262–2269.

Timmers, H.J., Pacak, K., Huynh, T.T., Abu-Asab, M., Tsokos, M., Merino, M.J. *et al.* (2008) Biochemically Silent Abdominal Paragangliomas in Patients with Mutations in the Succinate Dehydrogenase Subunit B Gene. *J Clin Endocrinol Metab* 93: 4826–4832.

Timmers, H.J., Chen, C.C., Carrasquillo, J.A., Whatley, M., Ling, A., Havekes, B. *et al.* (2009) Comparison of 18f-Fluoro-L-Dopa, 18f-Fluoro-Deoxyglucose, and 18f-Fluorodopamine Pet and 123i-Mibg Scintigraphy in the Localization of Pheochromocytoma and Paraganglioma. *J Clin Endocrinol Metab* 94: 4757–4767.

Tischler, A.S. (2008) Pheochromocytoma and Extra-Adrenal Paraganglioma: Updates. *Arch Pathol Lab Med* 132: 1272–1284.

Tokioka, H., Takahashi, T., Kosogabe, Y., Ohta, Y., and Kosaka, F. (1988) Use of Diltiazem to Control Circulatory Fluctuations During Resection of a Phaeochromocytoma. *Br J Anaesth* 60: 582–587.

Trampal, C., Engler, H., Juhlin, C., Bergstrom, M., and Langstrom, B. (2004) Pheochromocytomas: Detection with 11c Hydroxyephedrine Pet. *Radiology* 230: 423–428.

Ulchaker, J.C., Goldfarb, D.A., Bravo, E.L., and Novick, A.C. (1999) Successful Outcomes in Pheochromocytoma Surgery in the Modern Era. *J Urol* 161: 764–767.

Van Der Horst-Schrivers, A.N., Kerstens, M.N., and Wolffenbuttel, B.H. (2006) Preoperative Pharmacological Management of Phaeochromocytoma. *Neth J Med* 64: 290–295.

Van Nederveen, F.H., Gaal, J., Favier, J., Korpershoek, E., Oldenburg, R.A., De Bruyn, E.M. *et al.* (2009) An Immunohistochemical Procedure to Detect Patients with Paraganglioma and Phaeochromocytoma with Germline Sdhb, Sdhc, or Sdhd Gene Mutations: A Retrospective and Prospective Analysis. *Lancet Oncol* 10: 764–771.

Van Stratum, M., Levarlet, M., Lambilliotte, J.P., Lignian, H., and De Rood, M. (1983) Use of Labetalol During Anesthesia for Pheochromocytoma Removal. *Acta Anaesthesiol Belg* 34: 233–240.

Vargas, H.I., Kavoussi, L.R., Bartlett, D.L., Wagner, J.R., Venzon, D.J., Fraker, D.L. *et al.* (1997) Laparoscopic Adrenalectomy: A New Standard of Care. *Urology* 49: 673–678.

Von Euler, U.S. and Lishajko, F. (1973) Effects of Mg2+ and Ca2+ on Noradrenaline Release and Uptake in Adrenergic Nerve Granules in Differential Media. *Acta Physiol Scand* 89: 415–422.

Walther, M.M., Herring, J., Choyke, P.L., and Linehan, W.M. (2000) Laparoscopic Partial Adrenalectomy in Patients with Hereditary Forms of Pheochromocytoma. *J Urol* 164: 14–17.

Walz, M.K., Peitgen, K., Neumann, H.P., Janssen, O.E., Philipp, T., and Mann, K. (2002) Endoscopic Treatment of Solitary, Bilateral, Multiple, and Recurrent Pheochromocytomas and Paragangliomas. *World J Surg* 26: 1005–1012.

Walz, M.K., Groeben, H., and Alesina, P.F. (2010) Single-Access Retroperitoneoscopic Adrenalectomy (Sara) Versus Conventional Retroperitoneoscopic Adrenalectomy (Cora): A Case-Control Study. *World J Surg* 34: 1386–1390.

Witteles, R.M., Kaplan, E.L., and Roizen, M.F. (2000) Safe and Cost-Effective Preoperative Preparation of Patients with Pheochromocytoma. *Anesth Analg* 91: 302–304.

Yabe, R., Suenaga, K., Niimura, S., Itoh, N., Tani, M., Kunii, N. *et al.* (1987) Treatment of Pheochromocytoma with Dilevalol. *J Med* 18: 147–152.

Yao, L., Schiavi, F., Cascon, A., Qin, Y., Inglada-Perez, L., King, E.E. *et al.* (2010) Spectrum and Prevalence of Fp/Tmem127 Gene Mutations in Pheochromocytomas and Paragangliomas. *Jama* 304: 2611–2619.

Yip, L., Lee, J.E., Shapiro, S.E., Waguespack, S.G., Sherman, S.I., Hoff, A.O. *et al.* (2004) Surgical Management of Hereditary Pheochromocytoma. *J Am Coll Surg* 198: 525–534; discussion 534–525.

Yoshida, S., Hatori, M., Noshiro, T., Kimura, N., and Kokubun, S. (2001) Twenty-Six-Years' Survival with Multiple Bone Metastasis of Malignant Pheochromocytoma. *Arch Orthop Trauma Surg* 121: 598–600.

Young, W.F., Jr. (1997) Pheochromocytoma: Issues in Diagnosis & Treatment. *Compr Ther* 23: 319–326.

Yumi, H. (2008) Guidelines for Diagnosis, Treatment, and Use of Laparoscopy for Surgical Problems During Pregnancy: This Statement Was Reviewed and Approved by the Board of Governors of the Society of American Gastrointestinal and Endoscopic Surgeons (Sages), September 2007. It Was Prepared by the Sages Guidelines Committee. *Surg Endosc* 22: 849–861.

Zelinka, T., Timmers, H.J., Kozupa, A., Chen, C.C., Carrasquillo, J.A., Reynolds, J.C. *et al.* (2008) Role of Positron Emission Tomography and Bone Scintigraphy in the Evaluation of Bone Involvement in Metastatic Pheochromocytoma and Paraganglioma: Specific Implications for Succinate Dehydrogenase Enzyme Subunit B Gene Mutations. *Endocr Relat Cancer* 15: 311–323.