The diagnosis and management of malignant phaeochromocytoma and paraganglioma

Alexandra Chrisoulidou¹, Gregory Kaltsas^{2,4}, Ioannis Ilias³ and Ashley B Grossman⁴

¹Department of Endocrinology and Endocrine Oncology, Theagenion Hospital, Thessaloniki, Greece

²Department of Pathophysiology, National University of Athens, Athens, Greece

³Department of Endocrinology, Elena Hospital, Athens, Greece

⁴Department of Endocrinology, Barts and the London School of Medicine, St Bartholomew's Hospital, Queen Mary University of London, EC1A 7BE London, UK

(Correspondence should be addressed to A B Grossman; Email: a.b.grossman@qmul.ac.uk)

Abstract

Malignant phaeochromocytomas are rare tumours accounting for ~10% of all phaeochromocytomas; the prevalence of malignancy among paragangliomas is higher, especially those associated with succinate dehydrogenase subunit B gene mutations. Although a subset of these tumours has metastatic disease at initial presentation, a significant number develops metastases during follow-up after excision of an apparently benign tumour. Clinical, biochemical and histological features cannot reliably distinguish malignant from benign tumours. Although a number of recently introduced molecular markers have been explored, their clinical significance remains to be elucidated from further studies. Several imaging modalities have been utilised for the diagnosis and staging of these tumours. Functional imaging using radiolabelled metaiodobenzylguanidine (MIBG) and more recently, ¹⁸F-fluorodopamine and ¹⁸F-fluorodopa positron emission tomography offer substantial sensitivity and specificity to correctly detect metastatic phaeochromocytoma and paraganglioma and helps identify patients suitable for treatment with radiopharmaceuticals. The 5-year mortality rate of patients with malignant phaeochromocytomas and paragangliomas greater than 50% indicates that there is considerable room for the improvement of currently available therapies. The main therapeutic target is tumour reduction and control of symptoms of excessive catecholamine secretion. Currently, the best adjunctive therapy to surgery is treatment with radiopharmaceuticals using ¹³¹I-MIBG; however, this is very rarely curative. Chemotherapy has been used for metastatic disease with only a partial and mainly palliative effect. The role of other forms of radionuclide treatment either alone or in combination with chemotherapy is currently evolving. Ongoing microarray studies may provide novel intracellular pathways of importance for proliferation/cell cycle control, and lead to the development of novel pharmacological agents.

Endocrine-Related Cancer (2007) 14 569–585

Introduction

Phaeochromocytomas are tumours arising from chromaffin tissue of the adrenal medulla, whereas paragangliomas are chromaffin-cell tumours located at extra-adrenal sites along the sympathetic and/or the parasympathetic chain (Grossman & Kaltsas 2002, Neumann *et al.* 2002a). Although phaeochromocytomas are relatively rare tumours found in about 4% of adrenal incidentalomas (Kasperlik-Zalucka *et al.*

2006), autopsy series have revealed a much higher prevalence (McNeil *et al.* 2000). Phaeochromocytomas and paragangliomas can synthesise, store and secrete catecholamines causing a variety of clinical symptoms (functioning tumours); a number of them, particularly parasympathetic paragangliomas, may be non-functioning (Kaltsas *et al.* 2003). Most of these tumours are sporadic but can also occur as part of a familial syndrome such as von Hippel–Lindau disease

(VHL), multiple endocrine neoplasia (MEN) type 2 (MEN II), neurofibromatosis type 1 (NF-1; [Korper-shoek et al. 2006](#), [Mannelli et al. 2007](#)) and Carney's syndrome ([Young et al. 2002](#)). The probability of developing bilateral or multifocal tumours is higher in patients with syndromic forms ([Goldstein et al. 1999](#), [Gullu et al. 2005](#)). The majority of pheochromocytomas and abdominal paragangliomas are benign; malignant pheochromocytomas have been regarded as nearly 10% of all pheochromocytomas and 15–35% of abdominal paragangliomas or even higher if related to succinate dehydrogenase B (*SDHB*) gene mutations ([O'Riordain et al. 1996](#), [Amar et al. 2005](#), [Elder et al. 2005](#), [Brouwers et al. 2006a](#)). As there are no clinical, biochemical and histopathological differences between pheochromocytomas and paragangliomas, these tumours will be regarded as the same entity in the context of this review and designated as chromaffin-cell tumours ([Kaltsas et al. 2004b](#)). Clinical, biochemical and radiological features are inadequate to either predict malignancy or distinguish benign from malignant lesions ([Bravo & Tagle 2003](#), [Kaltsas et al. 2004b](#), [Ahlman 2006](#)). Clinically, malignancy is established in the presence of distant metastases mainly to the liver, lymph nodes, lung and/or bone either at diagnosis or during follow-up ([Goldstein et al. 1999](#)). Local invasion and various histopathological features can be suggestive; however, these features are not widely accepted and there is a need for the development of more sensitive and specific diagnostic means ([Eisenhofer et al. 2004a,b](#)). Therefore, the lack of firm predictors of malignancy, coupled with the variable course of this rare disease, make life-long follow-up of patients with chromaffin-cell tumours mandatory.

Clinical features of malignant chromaffin-cell tumours

Functioning malignant chromaffin-cell tumours have a clinical presentation similar to benign tumours: paroxysms of hypertension, palpitations, headaches and sweating mostly occur, but patients may present with variable symptoms and signs, such as dyspnoea, nausea, weakness, weight loss, visual disturbances, arrhythmias and mental problems ([Goldstein et al. 1999](#)). In non-functioning tumours, symptoms may not be present; occasionally symptoms may develop as a result of the metastatic growth of the tumour ([Loh et al. 1997](#)). The most common metastatic sites for chromaffin-cell tumours are local lymph nodes, bone (50%), liver (50%) and lung (30%; [Bravo 1994](#), [Loh et al. 1997](#)). Persisting post-operative symptoms in

patients with chromaffin-cell tumours in the absence of radiologically evident residual tumour may suggest the presence of occult metastases ([John et al. 1999](#)). Pheochromocytomas are uncommon in patients younger than 20 years of age (when extra-adrenal tumours mostly occur) and their incidence peaks in the fourth decade of life ([Bravo & Tagle 2003](#)). Malignant pheochromocytoma is rare in childhood and most published reports refer to isolated case reports ([Quissel et al. 1979](#)). The incidence of extra-adrenal disease is higher in children, reaching 50% of cases to one extensive review ([Coutant et al. 1999](#)). Overall, there appears to be little difference between the paediatric and adult disease regarding clinical presentation ([Sigmund et al. 1994](#)).

Biochemical diagnosis of malignant chromaffin-cell tumours

The best screening tests for initial assessment of functioning chromaffin-cell tumours is the measurement of plasma free and urinary fractionated metanephrines ([Lenders et al. 2002](#), [Ilias & Pacak 2005](#)). Chromaffin-cell tumours contain catechol-*O*-methyltransferase (the enzyme that metabolises adrenaline and noradrenaline to metanephrine and normetanephrine respectively); however, measurement of metanephrines may fail to identify tumours that secrete small amounts of catecholamines and those that exclusively produce dopamine ([Eisenhofer et al. 2003](#)). In dopamine-secreting tumours, measurement of plasma dopamine or its *O*-methylated metabolite, methoxytyramine, provides higher diagnostic accuracy than urinary dopamine ([Eisenhofer et al. 2005](#)). Overall, the measurement of plasma or urinary metanephrines is superior to urinary catecholamines as they show a sensitivity of 99 and 97% when compared with 86 and 84% of plasma and urinary catecholamines respectively ([Lenders et al. 2002](#)). Measurement of urinary vanillylmandelic acid (VMA) has a false negative rate of 41% in documenting catecholamine excess ([Bravo & Tagle 2003](#)). To minimise false positive results, medications known to interfere with catecholamine metabolism (tricyclic anti-depressants, phenoxybenzamine and labetalol) should be avoided if possible ([Eisenhofer et al. 2004b](#); [Table 1](#)).

Chromaffin-cell tumours may exhibit a different biochemical phenotype as extra-adrenal tumours secrete predominantly noradrenaline, whereas adrenal tumours mainly secrete adrenaline ([van der Harst et al. 2002](#)). This also applies in malignant pheochromocytomas and pheochromocytomas associated with VHL-disease, which produce mostly noradrenaline;

Table 1 Histological, immunohistochemical and molecular markers used for prediction of malignancy in chromaffin-cell tumours

Marker	Benign chromaffin-cell tumours	Malignant chromaffin-cell tumours
Tumour size	Usually < 5 cm	> 5 cm
Tumour weight	Usually small	Usually > 80 g
Mitotic activity	Low	Usually high
Vascular/capsular invasion	Usually absent	Usually present
DNA ploidy	DNA diploidy	DNA aneuploidy, tetraploidy
Ki-67	< 6%	> 6%
P53 positivity		High or low
Inhibin/activin β -subunit		Very low expression
hTERT mRNA	Low expression	High expression
HSP90		High
NPY mRNA		Very low expression
Cyclo-oxygenase		High expression
N-cadherin		High expression
VEGF		High expression
Endothelin receptor type A + B		High expression
EM66		Low expression

Ki-67, proliferative index; P53, protein 53; hTERT, human telomerase reverse transcriptase protein subunit; HSP90, heat shock protein 90; NPY, neuropeptide Y; VEGF, vascular endothelial growth factor; EM66, peptide derived from secretogranin II.

chromaffin-cell tumours associated with MEN 2 syndrome usually produce both adrenaline and nor-adrenaline (Rao *et al.* 2000, Eisenhofer *et al.* 2001, van der Harst *et al.* 2002). Occasionally, malignant tumours can secrete preferentially dopamine (Proye *et al.* 1986, Brouwers *et al.* 2006a) due to alterations of catecholamine synthesis in malignant phaeochromocytoma cells (John *et al.* 1999). It has been suggested that elevated plasma dopamine and urinary dihydroxy-phenylalanine levels and the presence of large, predominantly noradrenaline-secreting tumours can be used to predict malignancy (van der Harst *et al.* 2002, Grossman *et al.* 2006). In a recent series of 308 chromaffin-cell tumours, 57 were found to be malignant; in patients with malignant tumours, the log urinary total metanephrine excretion correlated with the time elapsed from surgical confirmation of the disease and could also be used as a surrogate indicator of tumour burden (Amar *et al.* 2006).

Plasma chromogranin A (CgA), an acid-soluble protein stored and released along with catecholamines, has also been used for the diagnosis and prediction of malignant behaviour in chromaffin-cell tumours (O'Connor & Bernstein 1984). The CgA expression is present in both benign and malignant phaeochromocytomas, although different patterns of expression exist in malignant tumours (Portel-Gomes *et al.* 2001). The CgA is elevated in both functioning and non-functioning chromaffin-cell tumours (Guignat *et al.* 2001), whereas markedly increased levels may be indicative of a malignant tumour in a small series of patients (Rao *et al.* 2000). Besides its diagnostic significance, the CgA can also be used to monitor

response to treatment and/or indicate relapse of the disease (Grossrubatscher *et al.* 2006). The CgA levels also correlate well with plasma metanephrines and tumour mass (Giovanela *et al.* 2006). In addition to CgA, region-specific antibodies against epitopes to the C-terminal region of CgB and CgC (secretogranin II), that are co-secreted along with catecholamines from the synaptic vesicles, have also been used for the diagnosis of malignant chromaffin-cell tumours (Portela-Gomes *et al.* 2004). Secretogranin II and prohormone convertases 1 and 2 were found to be over-expressed in benign when compared with malignant tumours (Guillemot *et al.* 2006). Neuron-specific enolase has also been advocated as a screening marker since it can be significantly elevated in patients with malignant phaeochromocytomas (Oishi & Sato 1988). Of the several other peptides that can be produced from chromaffin-cell tumours, adrenocorticotrophin over-expression has been related to malignancy (Moreno *et al.* 1999).

Anatomical and functional imaging of malignant chromaffin-cell tumours

Malignant adrenal phaeochromocytomas are usually large and irregular in shape with some degree of necrosis and locoregional invasion (Zarnegar *et al.* 2006, Ilias *et al.* 2007). Metastatic disease may appear at sites in which chromaffin tissue is usually absent and can grow into the inferior vena cava, the kidney and the liver, or spread locally (Francis & Korobkin 1996). Paragangliomas can be found from the head and neck to the pelvis. Anatomical imaging modalities evaluate

lesions principally according to form, shape and tissue density, whereas functional (nuclear medicine) modalities assess tumour metabolism and receptor expression.

Anatomical imaging modalities widely used for the detection of chromaffin-cell tumours include computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US). CT can identify primary tumours and metastatic/extra-adrenal lesions above 1 cm in diameter with a 77–98% and 29–92% sensitivity and specificity respectively (Ilias & Pacak 2004); a density of 40–50 Hounsfield units is suggestive of a chromaffin-cell tumour in the relevant clinical and biochemical setting (Sahdev & Reznek 2004, Ilias et al. 2007). MRI has a higher sensitivity (90–100%) and specificity (50–100%) when compared with CT and is superior for the detection of extra-adrenal disease (Ilias & Pacak 2004). Increased signal intensity on T₂-weighted images is characteristic, but not diagnostic, for the presence of chromaffin-cell tumours. In large tumours, in particular, signal intensity at T₂-weighted images may be low due to haemorrhage and/or necrosis (Ilias & Pacak 2004). Imaging with US is of inherently limited diagnostic yield and should be reserved for pregnant women and children (Ilias & Pacak 2004). However, this technique can be useful for the evaluation of neck paragangliomas (Blake et al. 2004, Ilias & Pacak 2004).

In contrast to other types of tumours, most (chromaffin) cells of pheochromocytomas express the human norepinephrine transporter (hNET) that is responsible for catecholamine uptake into presynaptic sympathetic neurons (Shulkin et al. 2006). Radiolabelled ligands that are either catecholamines or their analogues are also transported into chromaffin cells via hNET (Shulkin et al. 2006). Functional imaging of chromaffin-cell tumours is performed either using ligands specific for the catecholamine uptake and synthesis/secretion pathway or non-specific ligands (Kaltsas et al. 2005). Specific functional imaging, with ¹³¹I- or preferentially ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy, has been extensively used for the diagnosis and staging of chromaffin-cell tumours (Kaltsas et al. 2001a,b,c, 2004a). Whole body studies can detect the extent of the disease not visible by CT and/or MRI and help identify multiple tumours and/or metastatic sites (Shulkin et al. 2006). ¹²³I-MIBG is superior to ¹³¹I-MIBG in terms of physical properties, quality of images and sensitivity (83–100 vs 77–90% respectively); scintigraphy with ¹²³I-MIBG should always include single photon emission computerised tomography (Shapiro 1991, Ilias & Pacak 2004). However, dopamine-secreting tumours do not usually enhance with MIBG and may benefit from specific positron emission tomography (PET) scanning

(Dubois & Gray 2005). Non-specific functional imaging with scintigraphy is performed targeting tumour expression of somatostatin receptors type-2 and type-5 with ¹¹¹In-pentetreotide (Kaltsas et al. 2004a). Although scintigraphy with ¹¹¹In-pentetreotide is of limited value for non-metastatic, solitary/adrenal pheochromocytomas (Shulkin et al. 2006), it can reveal extra-adrenal disease (de Herder et al. 2005) and metastases not avid to scintigraphy with MIBG (Tenenbaum et al. 1995, Kaltsas et al. 2001a).

PET imaging using the specific ligands [¹¹C]-hydroxyephedrine (Shulkin et al. 1992) and [¹¹C]-adrenaline (Shulkin et al. 1995) is hampered by the short half-lives of these radioisotopes (Shulkin et al. 2006). However, PET imaging using 6-[¹⁸F]-fluorodopamine ([¹⁸F]-DA) can detect metastatic pheochromocytomas at rates higher than ¹³¹I-MIBG (Ilias et al. 2003), whereas PET with 6-[¹⁸F]-fluorodopa ([¹⁸F]-DOPA) is superior in imaging extra-adrenal pheochromocytomas and neck paragangliomas (Hoegerle et al. 2002). Partial intratumoural metabolism of glucose can be used for non-specific functional PET imaging. PET using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG), ¹⁸FDG-PET, can identify glucose-avid metastatic lesions (Shulkin et al. 1999), particularly if they are ¹³¹I-MIBG or ¹²³I-MIBG negative (Mamede et al. 2006). Although not widely available, PET scanning is an efficient method to detect occult disease; in cases with high clinical suspicion, it can be supplemented with vena cava sampling for plasma metanephrines (Pacak et al. 2001b).

Overall, current imaging modalities exhibit a sensitivity of 90–100% for adrenal pheochromocytomas and ~90% for extra-adrenal disease, and/or detection of metastases or recurrences (Pacak et al. 2004). Imaging should begin with CT and/or MRI of the adrenals and the abdomen and, depending on the clinical presentation, of the thorax and neck (Pacak et al. 2004, Kaltsas et al. 2005). If extra adrenal/metastatic disease is suspected, and particularly if the anatomical imaging results are negative or equivocal, functional imaging should follow using specific ligands; if the specific functional imaging results are negative, non-specific functional imaging should be used to ascertain the extent of disease (Pacak et al. 2004, Kaltsas et al. 2005).

Histopathological and molecular markers of malignant chromaffin-cell tumours

There is considerable controversy as to whether the histopathological appearance of chromaffin cell tumours can predict malignancy in the absence of distant metastases (Schlumberger et al. 1992, Ahlman 2006). Classification of malignancy based on histology

has been of limited value; features such as cellular hyperchromatism, increased number of mitoses, vascular and capsular invasion cannot safely distinguish malignant from benign tumours (Scott & Halter 1984). In a number of 14 patients, who exhibited vascular and capsular invasion and were considered to be at 'high-risk' for malignancy, only one developed metastatic disease during a follow-up period of 11.5 years (Goldstein *et al.* 1999). Although histological findings do not permit definite diagnosis of malignancy in chromaffin-cell tumours, several possible correlates have been suggested: tumour weight > 80 g and high tumour concentration of dopamine (John *et al.* 1999), tumour size > 5 cm (75% prevalence of malignancy; Goldstein *et al.* 1999), the presence of confluent tumour necrosis (a common feature in larger tumours), extra-adrenal manifestations (50% prevalence of malignancy) and a younger age (Lehnert *et al.* 2004).

Succinate dehydrogenase (*SDH*) is a nuclear gene encoding a key mitochondrial enzyme. Specifically, *SDH* is a four-polypeptide complex (*SDH* A, B, C and D) located in the inner mitochondrial membrane that catalyses the oxidative dehydrogenation of succinate (Baysal 2006). Hypoxia physiologically induces hypoxia-inducible factor 1 subunit α (*HIF1 α*), a transcription factor that is involved in glycolysis and angiogenesis (which contribute to tumorigenesis; Stoppa-Lyonnet & Lenoir 2005). Inherited or somatic mutations in the *SDH* genes lead to accumulation of succinate in mitochondria, which in turn inhibits *HIF1 α* prolyl hydroxylase, stabilising the *HIF1 α* subunit even in normoxia (Dahia *et al.* 2005). The *NF-1* gene is a tumour suppressor gene located on chromosome 17q11.2; neurofibromin (the *NF-1* gene product) bears homology to the RAS/GTPase-activating protein (Koch *et al.* 2001). The mechanisms via which phaeochromocytoma appears in some patients with *NF-1* are not known: biallelic inactivation of *NF-1* and loss of neurofibromin expression have been suggested as tentative causes (Bausch *et al.* 2006).

A number of genomic mutations of the *VHL*, *RET*, *SDHD* and *SDHB* genes have been identified in sporadic phaeochromocytomas (Neumann *et al.* 2002b). The European Network for the Study of Adrenal Tumours (ENS@T) Phaeochromocytoma Working Group has recently shown that in about 25% of cases, chromaffin-cell tumours may be inherited (Gimenez-Roqueplo *et al.* 2006). Therefore, it has been advocated that germline mutation testing should be performed in every patient with a chromaffin-cell tumour as the expression of particular genes could identify patients at increased risk for malignant disease. Malignant chromaffin-cell tumours

are rare in patients with *VHL* syndrome but common in patients with *SDHB* mutations (Amar *et al.* 2005, Brouwers *et al.* 2006a). Patients with familial phaeochromocytomas in the context of MEN 2A, *VHL* and *NF-1* are found to have metastatic/locally invasive tumours in 4, 8 and 12% respectively (Fitzgerald *et al.* 2006). Malignant and/or extra-adrenal phaeochromocytomas (particularly in the abdomen) are strongly associated with *SDHB* mutations (Benn *et al.* 2006, Brouwers *et al.* 2006a, Gimenez-Roqueplo *et al.* 2006). In the case of malignant familial chromaffin-cell tumours, it has been suggested that *SDHB* gene mutation analysis should always be performed (Gimenez-Roqueplo *et al.* 2006).

As the distinction between malignant and benign phaeochromocytomas is difficult, there is a growing need to identify markers that can reliably predict tumours with malignant behaviour or potential. DNA aneuploidy and tetraploidy have been considered to suggest aggressive behaviour in phaeochromocytoma (Nativ *et al.* 1992), but can also be found in benign tumours (Kopf *et al.* 2001). A >6% Ki-67 proliferative index is most commonly found in malignant tumours (Brown *et al.* 1999, Salmenkivi *et al.* 2003). Inhibin/activin β -subunit that is expressed in the normal adrenal medulla has been found to be high in benign phaeochromocytomas and near negative in malignant tumours (Salmenkivi *et al.* 2001a). Telomerase is a ribonucleoprotein complex including a catalytic subunit (hTERT). hTERT mRNA was expressed in both malignant and benign tumours, but its expression was high in malignant and low in benign tumours (Vezzosi *et al.* 2006). The heat shock protein (HSP) 90, a component of the telomerase complex, has also been found to be increased in malignant phaeochromocytomas (Boltze *et al.* 2003). Neuropeptide Y (NPY) mRNA was expressed in all benign tumours and in only 4 of 11 malignant phaeochromocytomas (Helman *et al.* 1989), suggesting that lack of NPY mRNA expression may have some prognostic significance. Cyclo-oxygenase (Salmenkivi *et al.* 2001b) and *N*-cadherin were also over-expressed in malignant phaeochromocytomas (Khorram-Manesh *et al.* 2002) as well as genes encoding the vascular endothelial growth factor (VEGF), the endothelin receptor type A and type B (Favier *et al.* 2002). However, these studies do not take into account that changes may appear in these indices during prolonged follow-up period. None of these markers is specific for the disease, and we will probably have to rely on a combination of immunohistochemical and molecular markers for a sound earlier diagnosis.

More recently, higher levels of EM66, produced from the intravesicular proteolysis of chromogranins, were found to be higher in benign when compared with malignant tissue, suggesting that this peptide could represent a marker for disease prognosis (Anouar *et al.* 2006). The genes that encode the cytoskeleton protein γ -tubulin, the granulocyte-macrophage colony-stimulating factor 2 and the interleukin 2 receptor γ -subunit were more aberrantly expressed in malignant when compared with benign tumours (Anouar *et al.* 2006). Using oligonucleotide microarray analysis, 70% of these genes were under-expressed in malignant when compared with benign tumours. Thus, malignant potential in chromaffin-cell tumours is apparently characterised by a less-differentiated pattern of gene expression (Brouwers *et al.* 2006b). However, these findings need to be validated in clinical practice.

Treatment of malignant chromaffin-cell tumours

The clinical course of disease in patients with malignant pheochromocytoma varies. Some tumours recur after a long period whereas others follow an aggressive course, developing early metastases (Mornex *et al.* 1992). The overall 5-year survival in patients with malignant pheochromocytomas ranges from 40 to 74% (John *et al.* 1999, Fitzgerald *et al.* 2006, Nguyen-Martin & Hammer 2006). At present there is no universally effective therapy for malignant chromaffin-cell tumours. Most treatments are palliative, although there is a great variability in patients' responses.

Established treatment

Surgery can potentially provide cure of malignant chromaffin-cell tumours. However, due to the type of tumour dissemination, curative resection can seldom be performed (Ahlman 2006). Nevertheless, surgery should always be considered even in the presence of metastatic disease, particularly when there is an associated secretory tumour, as it ameliorates symptoms by reducing tumour bulk and may also increase the efficacy of other therapeutic modalities. To obtain tumour reduction and palliation of symptoms, treatment can be initiated with surgical debulking, or ablative procedures, followed by radionuclide therapy and/or chemotherapy. However, there is no current evidence that this strategy offers an advantage in survival due to the absence of comparative studies.

Surgery of the primary tumour and cytoreductive techniques

Surgical treatment aims at the removal of primary tumour and the resection of local and distant metastatic sites. Although surgery alone is seldom curative, it may prolong survival by reducing abdominal tumour mass and hormonal activity, by debulking prior to other therapies (chemotherapy and radiotherapy) and by removing metastases at life-threatening anatomical sites (Eisenhofer *et al.* 2004a,b). The transabdominal approach is usually preferred in large tumours with a high risk of malignancy. In these cases, total adrenalectomy and resection of locoregional lymph nodes or complete excision of paragangliomas and removal of distant metastases are recommended (Brauckhoff *et al.* 2004). Pre-operative ^{123}I -MIBG scintigraphy with intraoperative γ -probe is a valuable tool prior to surgery in order to localise lesions that are not visualised by other imaging techniques (Buhl *et al.* 2002). In the presence of hepatic metastases, arterial embolisation or chemoembolisation of hepatic metastases has produced transient responses (Kebebew & Duh 1998). Similar results have been obtained with cryoablation and radiofrequency ablation (Pacak *et al.* 2001c). Multiple hepatic metastases, especially those not amenable to chemotherapy, may benefit from transcatheter arterial embolisation, which should be performed only in specialised centres (Takahashi *et al.* 1999).

Treatment of malignant chromaffin-cell tumours with radiopharmaceuticals

Treatment with ^{131}I -MIBG

The rationale for using radiolabelled MIBG for therapy of pheochromocytomas and paragangliomas lies in its ability to enter the cell membrane and be stored in cytoplasmic granules via VMA transporters (VMAT 1 and 2; Kaltsas *et al.* 2003, Ahlman 2006). ^{131}I -MIBG was initially used for the treatment of malignant pheochromocytoma in 1984, and since then several hundred patients have been treated with different therapeutic protocols using either single or cumulative doses of ^{131}I -MIBG, with a variable total dosage (Sisson *et al.* 1984, Kaltsas *et al.* 2003, Kaltsas *et al.* 2005). Patients are selected on the demonstration of significant radioisotope uptake on diagnostic ^{123}I -MIBG or ^{131}I -MIBG scans ($>1\%$ uptake of the injected dose) with the only limitation of this form of treatment being the total radiation dose to critical organs as the bone marrow (Bomanji *et al.* 1993, Ahlman 2006). Approximately 60% of metastatic sites are ^{131}I -MIBG avid (Fitzgerald *et al.* 2006). More

recently, quantitative determination of VMAT 1, 2 expression in surgical pheochromocytoma specimens has been helpful in selecting patients suitable for ^{131}I -MIBG treatment (Kolby *et al.* 2006; Table 2).

In a published comprehensive review of 116 patients who received 100–300 mCi of ^{131}I -MIBG per course, with a mean of 3.3 doses at 3–14 months intervals, an objective tumour response was seen in 30% of patients, disease stabilisation in 57% and disease progression in 13%; the hormonal response ranged between 15 and 45% (Loh *et al.* 1997). In general, patients with limited disease had an increased change of tumour response, while those with soft tissue metastases responded better than osseous metastases (Loh *et al.* 1997, Kaltsas *et al.* 2003). Hormonal and symptomatic responses were more frequently seen after ^{131}I -MIBG therapy irrespective of the tumour response (Troncone & Rufini 1997, Mukherjee *et al.* 2001). In those patients with a response or stable disease at 6 months after the last treatment, a prolonged progression-free survival was seen; however, in another series 72% of patients developed progression of the disease at 18 months after an initial response (Buscombe *et al.* 2005). Apart from the total administered dose and response to therapy, the initial ^{131}I -MIBG dose could be an important determinant of patient's response and survival, as patients who received high initial doses (>500 mCi) lived longer than those who received lower doses (Safford *et al.* 2003). More recently, higher single doses of ^{131}I -MIBG, ranging from 386 to 866 mCi, were administered in 12 patients (Rose *et al.* 2003). Although the number of patients was small, this therapeutic regime induced a complete response in patients with skeletal and soft tissue metastases. As expected, with higher doses the haematological toxicity was greater. In subsequent studies, single high dose of ^{131}I -MIBG was favoured, whereas recently repeated intermediate doses have been advocated (Lawrence *et al.* 2004, Lam *et al.* 2005). Despite the high cumulative dose, therapy with ^{131}I -MIBG is generally well tolerated. Side effects include mainly transient leucopenia and thrombocytopenia; severe myelosuppression, infections and hepatic failure (in patients with widespread hepatic metastases) are rarely seen (Mukherjee *et al.* 2001). The high-dose regimen induced high-grade bone marrow toxicity that required stem cell rescue (Ahlman 2006). The question of the development of second malignancies after therapy with ^{131}I -MIBG, as seen in 5 out of 119 children with neuroblastomas treated with ^{131}I -MIBG, is not fully answered (Garaventa *et al.* 2003). Currently, we are exploring the use of initial high doses in the region of 300–400 mCi, which can be customised to have

marrow limiting toxicity on the basis of a dose-finding ^{131}I -MIBG uptake study. Newer preparations of ^{131}I -MIBG may also have higher specific activity, although whether this will translate into higher efficacy remains unclear.

Treatment with ^{131}I -MIBG is not curative in most patients. The impact of treatment depends on the extent of disease at the time of therapy, and therefore ^{131}I -MIBG could be a useful tool to eradicate residual disease shortly after surgery in an adjuvant setting (Mukherjee *et al.* 2001, Kaltsas *et al.* 2005). In addition, possible synergistic effects with other forms of therapy need to be addressed (Scholz *et al.* 2007). In cases with progressive disease after surgery and/or ^{131}I -MIBG treatment, the integration of ^{131}I -MIBG with other therapeutic modalities should be assessed (Shapiro *et al.* 1995, Kaltsas *et al.* 2001c). Pre-treatment with ^{131}I -MIBG in patients receiving chemotherapy increased toxicity, although the tumour response was greater (Sisson *et al.* 1999). On the other hand, ^{123}I -MIBG uptake may increase after a radiological response to chemotherapy, enabling successful ^{131}I -MIBG therapy to follow (Hartley *et al.* 2001). However, no firm recommendations can be made on the basis of experience derived from present retrospective studies including few patients, different protocols, no dosimetric studies and different individual follow-up.

Treatment with radioactive somatostatin analogues

Due to the expression of somatostatin receptor in chromaffin-cell tumours, radiopharmaceuticals based on the somatostatin analogues, octreotide and lanreotide, have been used. Several radiopharmaceuticals with different physical properties have been applied including ^{111}In -pentetreotide/ ^{111}In -DOTA-octreotide, ^{90}Y -DOTA-octreotide (Shapiro *et al.* 2001) and ^{177}Lu -DOTA-octreotate, and ^{111}In and ^{90}Y -DOTA-lanreotide (Kaltsas *et al.* 2005). As in treatment with ^{131}I -MIBG, only patients showing a high tumour uptake to scintigraphy (usually assessed with ^{111}In -pentetreotide) will benefit from this form of treatment. Hormone secretion and tumour growth have been reported to be stabilised in 25% of cases and even decrease in 20% of cases (Eriksson & Oberg 1999). Side effects include mainly leucopenia and thrombocytopenia. Treatment with non-labelled octreotide has not been generally very successful, and only a few patients have showed transient responses (Wiseman & Kvols 1995, Kaltsas *et al.* 2005). This is because these tumours express somatostatin receptor subtype 2 (SST2), the type of somatostatin receptor with the

Table 2 Cumulative results of treatment with ¹³¹I metaiodobenzylguanidine (¹³¹I MIBG) treatment

Reference	No of Patients	No of doses (mean)	Total dose (mCi)	Tumour response					Biochemical response					Toxicity
				CR	PR	SD	DP	NR	CR	PR	SD	DP	NR	
Vetter <i>et al.</i> (1983)	2	2.5	215	0	2	0	0	0	1	0	1	0	0	NR
Theilade <i>et al.</i> (1988)	1	7	680	0	1	0	0	0	0	1	0	0	0	0
Shapiro <i>et al.</i> (1991)	28	2.6	479	0	2	16	9	1	0	12	6	10	0	8GI, 3MS, 3HT
Lewington <i>et al.</i> (1991)	13	NR	632	0	2	11	0	0	0	8	0	0	5	2MS (1 death aplasia)
Lumbroso <i>et al.</i> (1991)	9	2.2	245	0	1	1	4	3	0	1	1	4	3	2MS
Krempf <i>et al.</i> (1991)	15	4.6	651	0	5	7	3	0	4	3	6	2	0	2GI, 1LFT, 2MS
Fisher (1991)	13	NR	652	0	2	7	4	0	0	0	0	0	13	7GI, 1HT
Bestagno <i>et al.</i> (1991)	6	3.3	599	0	2	3	1	0	0	4	1	1	0	NR
Troncone <i>et al.</i> (1991)	5	4	408	1	1	1	2	0	0	2	3	0	0	1MS
Colombo <i>et al.</i> (1991)	4	3.25	281	0	0	3	1	0	0	1	3	0	0	0
Schvartz <i>et al.</i> (1991)	3	3	445	0	1	0	2	0	0	3	0	0	0	NR
Hoefnagel <i>et al.</i> (1991)	4	3.5	700	0	1	3	0	0	0	3	0	0	1	NR
Mc Ewan (1991)	3	NR	NR	1	2	0	0	0	0	0	0	0	3	NR
Baulieu <i>et al.</i> (1991)	1	2	427	0	1	0	0	0	0	0	0	0	1	NR
Nakabeppu & Nakajo (1994)	3	3.3	295	0	1	1	1	0	0	2	0	1	0	0
Sakahara <i>et al.</i> (1994)	5	2	206	0	2	2	1	0	0	1	4	0	0	2INF
Sisson <i>et al.</i> (1994)	6	2.7	206	0	2	2	1	1	0	2	2	2	0	2MS
Pujol <i>et al.</i> (1995)	1	6	900	0	1	0	0	0	1	0	0	0	0	MS
Loh <i>et al.</i> (1997)	3	1.3	505	1	0	1	1	0	1	0	2	0	0	2GI, 2MS
Castellani <i>et al.</i> (2000)	12	6.6	378	1	4	6	1	0	1	6	2	0	3	2MS
Mukherjee <i>et al.</i> (2001)	15	3.4	638	0	6	3	5	1	2	6	1	0	6	1MS, 1LFT
Rose <i>et al.</i> (2003)	12	1.6	1141	2	2	5	2	1	2	3	0	1	6	MS
Lam <i>et al.</i> (2005)	2	8.5	1400	1	1	0	0	0	0	2	0	0	0	0
Total no. of patients/ percentage of response	166	3.7	549	4.2%	25.3%	43.4%	22.9%	4.2%	7.2%	36.1%	19.3%	12.7%	24.7%	

CR, complete response; PR, partial response; SD, stable disease; DP, disease progression; NR, not recorded; GI, gastrointestinal; MS, myelosuppression; LFT, abnormal liver function; HT, hypothyroidism; INF, side effects during infusion.

higher affinity to currently available somatostatin analogues, at lower levels than other neuroendocrine tumours, and therefore the ratio of tumour-to-blood activity is low (Ahlman 2006).

Treatment with combinations of radiopharmaceuticals

Since some patients have MIBG-positive and MIBG-negative lesions, whereas some negative lesions can demonstrate uptake to scintigraphy with ^{111}In -pentetreotide, it is possible that combined treatment using radiolabelled MIBG and a radiolabelled somatostatin analogue might have a synergistic effect (Ahlman 2006). The potentially divergent side effects (bone marrow toxicity for ^{131}I and mainly renal toxicity for ^{177}Lu) could allow the delivery of higher organ limiting doses (Ahlman 2006). Although the combination of ^{90}Y - and ^{177}Lu - has been shown to be more efficacious than either radionuclide alone (de Jong *et al.* 2002), the relatively low expression of SST2 limits their potential application. The combination of ^{131}I -MIBG and ^{177}Lu -octreotate might be more favourable and with fewer side effects than a single high dose of ^{131}I -MIBG with potential severe bone marrow toxicity (Forsell-Aronsson *et al.* 2006). It is also possible that the introduction of somatostatin analogues with a wider array of somatostatin receptor affinities, such as pasireotide (SOM230, Novartis), will increase the applicability of this type of therapy.

Chemotherapy

Chemotherapy can be considered when the tumour is inoperable and/or in the presence of extensive residual disease (Kaltsas *et al.* 2001b). In 1988, a combination of cyclophosphamide, vincristine and dacarbazine (CVD) was reported to be a successful scheme as it provided partial remission and transient symptomatic improvement in up to 50% of cases, although of short duration (Averbuch *et al.* 1988). CVD has been used for the treatment of malignant phaeochromocytoma with symptomatic and hormonal response rates of 50–100%, but with minimal tumoural responses (Kaltsas *et al.* 2004a). As CVD can induce hypertensive crises, combined treatment with α -methyl-*p*-tyrosine to inhibit catecholamine synthesis has been advocated (Wu *et al.* 1994, Tada *et al.* 1998). Apart from CVD, treatments with etoposide and cisplatin (Schlumberger *et al.* 1992), anthracycline plus CVD (Nakane *et al.* 2003) and cytokine arabinoside (Iwabuchi *et al.* 1999) have been used with some success. Although individualised chemotherapy has been proven to be useful for palliation and may improve the prognosis of the tumour,

more specific chemotherapeutic agents are needed. The over-expression of HSP 90 and hTERT in malignant phaeochromocytomas may be important signalling pathways for these tumours and specific inhibitors such as geldanamycin may prove to be helpful (Park *et al.* 2003, Sausville *et al.* 2003). Our own approach has been to use the combination of lomustine (CCNU; 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and 5-fluorouracil (or more recently its pro-drug capecitabine) for slowly progressive tumours, and etoposide and a platinum-based drug for those more rapidly progressive.

External radiotherapy

Radiotherapy is considered for control of inoperable tumours and palliation of painful osseous metastases. However, during radiation therapy the patient should be closely monitored to avoid acutely exacerbated hypertension and inflammatory signs caused by radiation-induced tumour destruction (Teno *et al.* 1996).

Novel and evolving therapies

Recently, novel anti-neoplastic therapies have been tried in patients with malignant phaeochromocytomas. A combination of temozolomide and thalidomide achieved a 40% biochemical and a 33% radiological response in patients with malignant chromaffin-cell tumours (Kulke *et al.* 2006). However, lymphopenia, accompanied by opportunistic infections, occurred in the majority of patients. Novel principles for targeted therapy interfering with signalling pathways may develop following microarray studies, including high expression of angiogenic factors, receptor antibodies and tyrosine kinase inhibitors with anti-VEGF activity (Strock *et al.* 2006). However, imatinib mesylate did not prove to be effective in a small number of cases (Gross *et al.* 2006). Following the over-expression of HSP90 in malignant phaeochromocytomas, the new inhibitor of this protein 17-allylamino, 17-demethoxygeldanamycin may be of additional value (Sausville *et al.* 2003). The mTOR (mammalian target of rapamycin) inhibitor everolimus (RAD001, Novartis) has been shown to have some efficacy in neuroendocrine tumours generally, although our experience with this drug in two patients with malignant paragangliomas was not very positive. Due to the complexity of the different pathways involved, it is more likely that a combination rather than a single form of treatment may be necessary to obtain adequate control.

Somatostatin-targeted chemotherapy in SST2 and SST5 positive tumours may prove useful and further studies are needed to establish its efficacy (Jenkins *et al.* 2001). Novel approaches including somatostatin

Figure 1 Suggested algorithm for the treatment of possibly malignant and metastatic chromaffin-cell tumours.

analogues combined with anti-angiogenic factors or gene therapy may also become important tools for the management of these tumours. In addition, the physical characteristics of a variety of radionuclides could affect the response to treatment with radiopharmaceuticals. ¹³¹I exhibits very low absorbed values and is not suitable for small tumours. α -emitters, ²¹¹At, bound to MIBG (MABG) may be more efficacious for the eradication of residual disease and/or micrometastases (Ahlman 2006). ¹⁷⁷Lu-octreotate, which shows considerable activity at short distances, might complement ¹³¹I-MIBG for small lesions/micrometastases, and has relatively few side effects due to the different limiting doses. An optimal dose-planning resulting in administration of activities up to tolerance levels for both bone marrow and kidney should allow administration of higher activities and/or more fractions (Ahlman 2006).

Recommendations and conclusions

Malignant chromaffin-cell tumours are rare and their management requires a multidisciplinary approach. Although surgery is almost universally applied, it is rarely curative. Patients with chromaffin-cell tumours with local and/or distant metastases should have scintigraphy with both ¹²³I-MIBG and ¹¹¹In-pentetreotide to evaluate the possibility of radionuclide therapy which is currently evolving. Tumour biopsies can be used to provide expression of VMAT1-2 and SST1-5, and decide

individual dose planning in patients in whom beneficial therapeutic effects are anticipated. Radionuclide therapy can achieve substantial objective tumour responses and eradication of micrometastases. Chemotherapy should be considered for patients without avidity to radionuclide treatment when there is progression of the disease (and/or in combination with other modalities). Cytreductive techniques are used to alleviate symptoms aiming at reducing tumour load. As there is no currently specific therapy and due to the unfavourable prognosis of the disease, the quality of life of these patients must be an important issue. Experience in dealing with such patients is important and collaboration between physicians in specialised centres will help to determine the optimum therapeutic protocols and to ameliorate the current management. As various investigatory methods and therapeutic options emerge, a consensus on the best strategy should be agreed based upon the evidence from the published series and the experience gained so far (Pacak et al. 2007). We include a suggested algorithm for treatment but would emphasise that these are merely guidelines and there are no fixed rules for investigation and therapy in this difficult area (Fig 1).

Acknowledgement

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

References

- Ahlman H 2006 Malignant pheochromocytoma. State of the field with future projections. *Annals of New York Academy of Sciences* **1073** 449–464.
- Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, Chabre O, Chamontin B, Delemer B, Giraud S, Murat A *et al.* 2005 Genetic testing in pheochromocytoma or functional paraganglioma. *Journal of Clinical Oncology* **23** 8812–8818.
- Amar L, Peyrard S, Rossignol P, Zinzindohoue F, Gimenez-Roqueplo AP & Plouin PF 2006 Changes in urinary total metanephrine excretion in recurrent and malignant pheochromocytomas and secreting paragangliomas. *Annals of New York Academy of Sciences* **1073** 383–391.
- Anouar Y, Yon L, Guillemot J, Thouennon E, Barbier L, Gimenez-Roqueplo AP, Bertherat J, Lefebvre H, Klein M, Muresan M *et al.* 2006 Development of novel tools for the diagnosis and prognosis of pheochromocytoma using peptide marker immunoassay and gene expression profiling approaches. *Annals of New York Academy of Sciences* **1073** 533–540.
- Averbuch SD, Steakley CS, Young RC, Gelmann EP, Goldstein DS, Stull R & Keiser HR 1988 Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine and dacarbazine. *Annals of Internal Medicine* **109** 267–273.
- Baulieu JL, Guilloteau D, Calais G, Lefloch O & Besnard JC 1991 [¹³¹I]metaiodobenzylguanidine treatment of a malignant pheochromocytoma. *Journal of Nuclear Biology and Medicine* **35** 313–314.
- Bausch B, Koschker AC, Fassnacht M, Stoevesandt J, Hoffmann MM, Eng C, Allolio B & Neumann HP 2006 Comprehensive mutation scanning of NF1 in apparently sporadic cases of pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **91** 3478–3481.
- Baysal BE 2006 A phenotypic perspective on mammalian oxygen sensor candidates. *Annals of New York Academy of Sciences* **1073** 221–233.
- Benn DE, Richardson AL, Marsh DJ & Robinson BG 2006 Genetic testing in pheochromocytoma and paraganglioma-associated syndromes. *Annals of New York Academy of Sciences* **1073** 104–111.
- Bestagno M, Pizzocaro C, Maira G, Terzi A, Panarotto MB & Guerra P 1991 Results of [¹³¹I]metaiodobenzylguanidine treatment in malignant pheochromocytoma. *Journal of Nuclear Biology and Medicine* **35** 277–279.
- Blake MA, Kalra MK, Maher MM, Sahani DV, Sweeny AT, Mueller PR, Hann PF & Boland G 2004 Pheochromocytoma: an imaging chameleon. *Radiographics* **24** S87–S99.
- Boltze C, Mundschenk J, Unger N, Schneider-Stock R, Peters B, Mawrin C, Hoang-Vu C, Roessner A & Lehnert H 2003 Expression profile of the telomeric complex discriminates between benign and malignant pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **88** 4280–4286.
- Bomanji J, Britton KE, Ur E, Hawkins L, Grossman AB & Besser GM 1993 Treatment of malignant pheochromocytoma, paraganglioma and carcinoid tumours with [¹³¹I]-metaiodobenzylguanidine. *Nuclear Medicine Communications* **14** 856–861.
- Brauckhoff M, Gimm O & Dralle H 2004 Preoperative and surgical therapy in sporadic and familial pheochromocytoma. Lehnert H (eds): Pheochromocytoma, Pathophysiology and clinical management. *Frontiers of Hormone Research* **31** 121–144.
- Bravo EL 1994 Evolving concepts in the pathophysiology, diagnosis and treatment of pheochromocytoma. *Endocrine Reviews* **15** 356–368.
- Bravo EL & Tagle R 2003 Pheochromocytoma: state of the art and future prospects. *Endocrine Reviews* **24** 539–553.
- Brouwers FM, Eisenhofer G, Tao JJ, Kant JA, Adams KT, Linehan WM & Pacak K 2006a High frequency of SDHB germline mutations in patients with malignant catecholamine-producing paragangliomas: implications for genetic testing. *Journal of Clinical Endocrinology and Metabolism* **91** 4505–4509.
- Brouwers FM, Elkahoul AG, Munson PJ, Eisenhofer G, Barb J, Lineham WM, Lenders JW, De Krijger R, Manelli M, Udelsman R *et al.* 2006b Gene Expression Profiling of Benign and Malignant Pheochromocytoma. *Annals of New York Academy of Sciences* **1073** 541–556.
- Brown HM, Komorowski RA, Wilson SD, Demeure MJ & Zhu Y 1999 Predicting metastasis of pheochromocytomas using DNA flow cytometry and immunohistochemical markers of cell proliferation. *Cancer* **86** 1583–1589.
- Buhl T, Mortensen J & Kjaer A 2002 I-123 MIBG imaging and intraoperative localization of metastatic pheochromocytoma: a case report. *Clinical Nuclear Medicine* **27** 183–185.
- Buscombe JR, Cwikla JB, Caplin ME & Hilson AJ 2005 Long-term efficacy of low activity meta-[¹³¹I]iodobenzylguanidine therapy in patients with disseminated neuroendocrine tumors depends on initial response. *Nuclear Medicine Communications* **26** 969–976.
- Campbell L, Mouratidis B & Sullivan P 1996 Improved detection of disseminated pheochromocytoma using post therapy [¹³¹I]-MIBG scanning. *Clinical Nuclear Medicine* **21** 960–963.
- Castellani MR, Chiti A, Seregni E & Bombardieri E 2000 Role of [¹³¹I]-metaiodobenzylguanidine (MIBG) in the treatment of neuroendocrine tumors. Experience of the National Cancer institute of Milan. *Quarterly Journal of Nuclear Medicine* **44** 77–87.
- Colombo L, Lomuscio G, Vignati A & Dottorini ME 1991 Preliminary results of [¹³¹I]metaiodobenzylguanidine therapy administered in metastatic malignant pheochromocytoma. *Journal of Nuclear Biology and Medicine* **35** 300–304.
- Coutant R, Pein F, Adamsbaum C, Oberlin O, Dubouset J, Guinebreiere JM, Teinturier C & Bougneres PF 1999 Prognosis of children with malignant pheochromocytoma. *Hormone Research* **52** 145–149.

- Dahia PL, Aguiar RC, Tsanaclis AM, Bendit I, Bydlowski SP, Abelin NM & Toledo SP 1995 Molecular and immunohistochemical analysis of p53 in pheochromocytoma. *British Journal of Cancer* **72** 1211–1213.
- Dahia PLM, Ross KN, Wright ME, Hayashida CY, Santagata S, Barontini M, Kung AL, Sanso G, Powers JF, Tischler AS *et al.* 2005 A HIF1a regulatory loop links hypoxia and mitochondrial signals in pheochromocytomas. *PLoS Genetics* **1** 72–80.
- D' Herbomez M, Gouze V, Huglo D, Nocaudie M, Pattou F, Proye C, Wemeau JL & Marchandise X 2001 Chromogranin A assay and ¹³¹I-MIBG scintigraphy for diagnosis and follow-up of pheochromocytoma. *Journal of Nuclear Medicine* **42** 993–997.
- Dubois LA & Gray DK 2005 Dopamine-secreting pheochromocytomas: in search of a syndrome. *World Journal of Surgery* **29** 909–913.
- Eisenhofer G, Walther MM, Huynh TT, Li ST, Bornstein SR, Vortmeyer A, Manelli M, Goldstein DS, Linehan WM, Lenders JW *et al.* 2001 Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. *Journal of Clinical Endocrinology and Metabolism* **86** 1999–2008.
- Eisenhofer G, Goldstein DS, Kopin IJ & Crout JR 2003 Pheochromocytoma: rediscovery as a catecholamine-metabolizing tumor. *Endocrine Pathology* **14** 193–211.
- Eisenhofer G, Bornstein S, Brouwers F, Cheung NV, Dahia PL, de Krijger RR, Giordano TJ, Greene LA, Goldstein DS, Lehnert H *et al.* 2004a Malignant pheochromocytoma: current status and initiatives for future progress. *Endocrine-Related Cancer* **11** 423–436.
- Eisenhofer G, Lenders JWM & Pacak K 2004b Biochemical diagnosis of pheochromocytoma. Lehnert H (eds): Pheochromocytoma, Pathophysiology and clinical management. *Frontiers of Hormone Research* **31** 76–106.
- Eisenhofer G, Goldstein DS, Sullivan P, Csako G, Browers FM, Lai EW, Adams KT & Pacak K 2005 Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. *Journal of Clinical Endocrinology and Metabolism* **90** 2068–2075.
- Elder EE, Elder G & Larsson C 2005 Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. *Journal of Surgical Oncology* **89** 193–201.
- Eriksson B & Oberg K 1999 Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: a future outlook. *Annals of Oncology* **10** S31–S38.
- Mc Ewan AJB 1991 Treatment of patients with malignant pheochromocytoma with [¹³¹I]-metaiodobenzylguanidine. Abstract book of the International Workshop 'The role of [¹³¹I]-metaiodobenzylguanidine in the treatment of neural crest tumors', Rome. Abstract 42.
- Favier J, Plouin PF, Corvol P & Gasc JM 2002 Angiogenesis and vascular architecture in pheochromocytomas: distinctive traits in malignant tumors. *American Journal of Pathology* **161** 1235–1246.
- Fernandez-Cruz L, Saenz A, Taura P, Sabater L, Astudillo E & Fontanals J 1998 Helium and carbon dioxide pneumoperitoneum in patients with pheochromocytoma undergoing laparoscopic adrenalectomy. *World Journal of Surgery* **22** 1250–1255.
- Fisher M 1991 Therapy of pheochromocytoma with [¹³¹I]-metaiodobenzylguanidine. *Journal of Nuclear Biology and Medicine* **35** 292–294.
- Fitzgerald PA, Goldsby RE, Huberty JP, Price DC, Hawkins RA, Veatch JJ, Dela Cruz F, Jahan TM, Linker CA, Damon L *et al.* 2006 Malignant pheochromocytomas and paragangliomas: a phase II study of therapy with high-dose ¹³¹I-metaiodobenzylguanidine (¹³¹I-MIBG). *Annals of New York Academy of Sciences* **1073** 465–490.
- Forsell-Aronsson E, Bernhardt P, Wangberg B, Kolby L, Nilsson O & Ahlmann H 2006 Aspects on radionuclide therapy in malignant pheochromocytomas. *Annals of New York Academy of Sciences* **1073** 498–504.
- Francis IR & Korobkin M 1996 Pheochromocytoma. *Radiologic Clinics of North America* **34** 1101–1112.
- Garaventa A, Gambini C, Villavecchia G, Di Cataldo A, Berolazzi L, Pizzitola MR, De Bernardi B & Haupt R 2003 Second malignancies in children with neuroblastoma after combined treatment with ¹³¹I-metaiodobenzylguanidine. *Cancer* **97** 1332–1338.
- Gimenez-Roqueplo AP, Lehnert H, Manelli M, Neumann H, Opocher G, Maher ER, Plouin PF & On behalf of the European Network for the Study of Adrenal Tumours (ENS@T) Pheochromocytoma Working Group 2006 Pheochromocytoma, new genes and screening strategies. *Clinical Endocrinology* **65** 699–705.
- Giovanella L, Squin N, Ghelfo A & Ceriani L 2006 Chromogranin A immunoradiometric assay in diagnosis of pheochromocytoma: comparison with plasma metanephrines and ¹²³I-MIBG scan. *Quarterly Journal of Nuclear Medicine and Molecular Imaging* **50** 344–347.
- Goldstein RE, O'Neill JA, Holcomb GW, Morgan WM, Neblett WW, Oates JA, Brown N, Nadeau J, Smith B, Page DL *et al.* 1999 Clinical experience over 48 years with pheochromocytoma. *Annals of Surgery* **229** 755–766.
- Gross DJ, Munter G, Bitan M, Siegal T, Gabizon A, Weitzen R, Merimsky O, Ackerstein A, Salmon A, Sella A *et al.* 2006 The Israel Glivec in Solid Tumors Study Group, The role of imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R. *Endocrine-Related Cancer* **13** 535–540.
- Grossman AB & Kaltsas GA 2002 Adrenal medulla and pathology. In *Comprehensive Clinical Endocrinology*, edn 3, pp 223–237. Eds M Besser & MO Thorner. Philadelphia: Elsevier Science.
- Grossman A, Pacak K, Sawka A, Lenders JW, Harlander D, Peaston RT, Reznick R, Sisson J & Eisenhofer G 2006 Biochemical diagnosis and localization of pheochromocytoma. Can we reach a consensus? *Annals of New York Academy of Sciences* **1073** 332–347.

- Grossrubatscher E, Dalino P, Vignati F, Gambacorta M, Pugliese R, Boniardi M, Rossetti O, Marocchi A, Bertuzzi M & Loli P 2006 The role of chromogranin A in the management of patients with pheochromocytoma. *Clinical Endocrinology* **65** 287–293.
- Guignat L, Bidart JM, Nocera M, Comoy E, Schlumberger M & Baudin E 2001 Chromogranin A and the alpha-subunit of glucoprotein hormones in medullary thyroid carcinoma and pheochromocytoma. *British Journal of Cancer* **84** 808–812.
- Guillemot J, Barbier L, Thouennon E, Vallet-Erdtmann V, Montero-Hadjadje M, Lefebvre H, Klein M, Muresan M, Plouin PF, Seidah N *et al.* 2006 Expression and processing of the neuroendocrine protein secretogranin II in benign and malignant pheochromocytomas. *Annals of New York Academy of Sciences* **1073** 527–532.
- Gullu S, Gursoy A, Erdogan MF, Dizbaysak S, Erdogan G & Kamel N 2005 Multiple endocrine neoplasia type 2A/localized cutaneous lichen amyloidosis associated with malignant pheochromocytoma and ganglioneuroma. *Journal of Endocrinological Investigation* **28** 734–737.
- Van der Harst E, de Herder WW, de Krijger RR, Bruining HA, Bonjer HJ, Lamberts SW, van den Meiracker AH, Stijnen TH & Boomsma F 2002 The value of plasma markers for the clinical behavior of pheochromocytomas. European. *Journal of Endocrinology* **147** 85–94.
- Hartley A, Spooner D & Brunt AM 2001 Management of malignant pheochromocytoma: a retrospective review of the use of MIBG and chemotherapy in the West Midlands. *Clinical Oncology* **13** 361–366.
- Helman LJ, Cohen PS, Avenbuch SD, Cooper MJ, Keiser HR & Israel MA 1989 Neuropeptide Y expression distinguishes malignant from benign pheochromocytomas. *Journal of Clinical Oncology* **7** 1720–1725.
- De Herder WW, Kwekkeboom DJ, Valkema R, Feelders RA, van Aken MO, Lamberts SW, van der Lely AJ & Krenning EP 2005 Neuroendocrine tumors and somatostatin: imaging techniques. *Journal of Endocrinological Investigation* **28** 132–136.
- Hoefnagel CA, Schornagel J & Valdes Olmos RA 1991 [¹³¹I]-metaiodobenzylguanidine therapy of malignant pheochromocytoma: interference of medication. *Journal of Nuclear Biology and Medicine* **35** 305–307.
- Hoegerle S, Nitzsche E, Althoefer C, Ghanem N, Manz T, Brink I, Reincke M, Moser E & Neumann HP 2002 Pheochromocytomas: detection with ¹⁸F DOPA whole-body PET-initial results. *Radiology* **222** 507–512.
- Ilias I & Pacak K 2005 Diagnosis and management of tumors of the adrenal medulla. *Hormone and Metabolic Research* **37** 717–721.
- Ilias I & Pacak K 2004 Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **89** 479–491.
- Ilias I, Yu J, Carrasquillo JA, Chen CC, Eisenhofer G, Whately M, McElroy B & Pacak K 2003 Superiority of 6-[¹⁸F]-Fluorodopamine positron emission tomography versus [¹³¹I]-Metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **88** 4083–4087.
- Ilias I, Sahdev A, Reznick RH, Grossman AB & Pacak K 2007 The optimal imaging of adrenal tumours: a comparison of different methods. *Endocrine-Related Cancer* **14** 587–599.
- Iwabuchi M, Oki Y & Nakamura H 1999 Palliative chemotherapy for malignant pheochromocytoma: symptomatic palliation of two cases. *Internal Medicine* **38** 433–435.
- Jenkins SA, Kynaston HG, Davies ND, Baxter JN & Nott DM 2001 Somatostatin analogues in oncology: a look to the future. *Chemotherapy* **47** 162–196.
- John H, Ziegler WH, Hauri D & Jaeger P 1999 Pheochromocytomas: can malignant potential be predicted? *Urology* **53** 679–683.
- de Jong M, Valkema R, Jamar F, Kvols LK, Kwekkeboom DJ, Breeman WA, Bakker WH, Smith C, Pauwels S & Krenning EP 2002 Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings. *Seminars in Nuclear Medicine* **32** 133–140.
- Kaltsas G, Korbonits M, Heintz E, Mukherjee JJ, Jenkins PJ, Chew SL, Reznick R, Monson JP, Besser GM, Foley R *et al.* 2001a Comparison of somatostatin analog and metaiodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. *Journal of Endocrinology and Metabolism* **86** 895–902.
- Kaltsas G, Mukherjee JJ, Plowman PN & Grossman AB 2001b The role of chemotherapy in the nonsurgical management of malignant neuroendocrine tumors. *Clinical Endocrinology* **55** 575–587.
- Kaltsas G, Mukherjee JJ & Grossman AB 2001c The value of radiolabeled MIBG and octreotide in the diagnosis and treatment of neuroendocrine tumors. *Annals of Oncology* **12** S47–S50.
- Kaltsas GA, Mukherjee JJ, Foley R, Britton KE & Grossmann AB 2003 Treatment of metastatic pheochromocytoma and paraganglioma with ¹³¹I-Meta-Iodobenzylguanidine (MIBG). *Endocrinologist* **13** 1–13.
- Kaltsas GA, Besser GM & Grossman AM 2004a The diagnosis and management of advanced neuroendocrine tumors. *Endocrine Reviews* **25** 458–511.
- Kaltsas GA, Papadogias D & Grossman A 2004b In Pheochromocytoma. *Pathophysiology and Clinical Management, Frontiers of Hormone Research*, vol 31, pp 61–75. Ed H Lehnert, Basel: Karger.
- Kaltsas GA, Papadogias D, Makras P & Grossman AB 2005 Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues. *Endocrine-Related Cancer* **12** 683–699.
- Kasperlik-Zalucka AA, Roslonowska E, Slowinska-Szednicka J, Otto M, Cichocki A, Cwikla J, Slapa R & Eisenhofer G 2006 1111 patients with adrenal incidentalomas observed at a single endocrinological center: incidence of chromaffin tumors. *Annals of New York Academy of Sciences* **1073** 38–46.

- Kebebew E & Duh Q-Y 1998 Benign and malignant pheochromocytoma. *Surgical Oncology Clinics of North America* **7** 765–789.
- Khorram-Manesh A, Ahlman H, Jansson S & Nilsson O 2002 N-cadherin expression in adrenal tumors: upregulation in malignant pheochromocytoma and downregulation in adrenocortical carcinoma. *Endocrine Pathology* **13** 99–110.
- Koch CA, Vortmeyer AO, Huang SC, Alesci S, Zhuang Z & Pacak K 2001 Genetic aspects of pheochromocytoma. *Endocrine Regulations* **35** 43–52.
- Kolby L, Bernhardt P, Johanson V, Wangberg B, Muth A, Jansson S, Forsell-Aronson E & Nilsson O 2006 Ahlman, can quantification of VMAT and SSTR expression be helpful for planning radionuclide therapy of malignant pheochromocytomas? *Annals of New York Academy of Sciences* **1073** 491–497.
- Kopf D, Goretzki P & Lehnert H 2001 Clinical management of malignant adrenal tumors. *Journal of Cancer Research and Clinical Oncology* **127** 143–155.
- Korpershoek E, Van Nederveen FH, Dannenberg H, Petri BJ, Komminoth P, Perren A, Lenders JW, Verhofstad AA, De Herder WW, De Krijger RR *et al.* 2006 Genetic analyses of apparently sporadic pheochromocytomas. The Rotterdam experience. *Annals of New York Academy of Sciences* **1073** 138–148.
- Krempf M, Lumbroso J, Mornex R, Brendel AJ, Wemeau JL, Delisle MJ, Aubert B, Carpentier P, Fleury-Goyon MC, Gibold C *et al.* 1991 Treatment of malignant pheochromocytoma with [¹³¹I]metaiodobenzylguanidine: a French multicentric study. *Journal of Nuclear Biology and Medicine* **35** 284–287.
- Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, Vincitore M, Michelini A & Fuchs CS 2006 Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *Journal of Clinical Oncology* **24** 401–406.
- Lam MGEH, Lips CJM, Jager PL, Dullaart RPF, Lentjes EGWM, van Rijk PP & de Klerk JMH 2005 Repeated [¹³¹I]metaiodobenzylguanidine therapy in two patients with malignant pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **90** 5888–5895.
- Lawrence JK, Maher ER, Sheaves R & Grossman AB 2004 Familial paraganglioma: a novel presentation of a case and response to therapy with radiolabeled MIBG. *Hormones* **3** 127–131.
- Lehnert H, Mundschenk J & Hann K 2004 Malignant pheochromocytoma In Lehnert H (eds) Pheochromocytoma. Pathophysiology and clinical management. *Frontiers of Hormone Research* 155–162.
- Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, Keiser HR, Goldstein DS & Eisenhofer G 2002 Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* **287** 1427–1434.
- Lewington VJ, Zivanovic MA, Tristram M, Mc Ewan AJ & Ackery DM 1991 Radiolabelled metaiodobenzylguanidine targeted radiotherapy for malignant pheochromocytoma. *Journal of Nuclear Biology and Medicine* **35** 280–283.
- Loh KC, Fitzgerald PA, Matthay KK, Yeo PPB & Price DC 1997 The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (¹³¹I-MIBG): A comprehensive review of 116 reported patients. *Journal of Endocrinological Investigation* **20** 648–658.
- Lumbroso J, Schlumberger M, Tenenbaum F, Aubert B, Travagli JP & Parmentier C 1991 [¹³¹I]metaiodobenzylguanidine therapy in 20 patients with malignant pheochromocytoma. *Journal of Nuclear Biology and Medicine* **35** 288–291.
- Mamede M, Carrasquillo JA, Chen CC, Del Corral P, Whitley M, Ilias I, Ayala A & Pacak A 2006 Discordant localization of 2-[¹⁸F]-fluoro-2 deoxy-D-glucose in 6-[¹⁸F]-fluorodopamine- and [(123)I]-metaiodobenzylguanidine-negative metastatic pheochromocytoma sites. *Nuclear Medicine Communications* **27** 31–36.
- Mannelli M, Simi L, Gagliano MS, Opocher G, Ercolino T, Becherini L & Parenti G 2007 Genetics and biology of pheochromocytoma. *Experimental and Clinical Endocrinology and Diabetes* **115** 160–165.
- Maurea S, Cuocolo A, Reynolds JC, Neumann RD & Salvatore M 1996 Diagnostic imaging in patients with paragangliomas, computed tomography, magnetic resonance and MIBG scintigraphy comparison. *Quarterly Journal of Nuclear Medicine* **40** 365–371.
- McNeil AR, Blok BH, Koelmeyer TD, Burke MP & Hilton JM 2000 Pheochromocytomas discovered during coronal autopsies in Sydney, Melbourne and Auckland. *Australian and New Zealand Journal of Medicine* **30** 648–652.
- Moreno AM, Castilla-Guerra L, Martinez-Torres MC, Torres-Olivera F, Fernandez E & Galera-Davidson H 1999 Expression of neuropeptides and other neuroendocrine markers in human pheochromocytomas. *Neuropeptides* **33** 159–163.
- Mornex R, Badet C & Peyrin L 1992 Malignant pheochromocytoma: a series of 14 cases observed between 1966 and 1990. *Journal of Endocrinological Investigation* **15** 643–649.
- Mukherjee JJ, Kaltsas GA, Islam N, Plowman PN, Foley R, Hikmat J, Britton KE, Jenkins PJ, Chew SL, Monson JP *et al.* 2001 Treatment of metastatic carcinoid tumours, pheochromocytoma, paraganglioma and medullary carcinoma of the thyroid with [¹³¹I]-meta-iodobenzylguanidine (¹³¹I-MIBG). *Clinical Endocrinology* **55** 47–60.
- Nakabeppu Y & Nakajo M 1994 Radionuclide therapy of malignant pheochromocytoma with [¹³¹I]-MIBG. *Annals of Nuclear Medicine* **8** 259–268.
- Nakane M, Takahashi S, Sekine I, Fukui I, Koizumi M, Kage K, Ito Y, Aiba K, Horikoshi N, Hatake K *et al.* 2003 Successful treatment of malignant pheochromocytoma with combination chemotherapy containing anthracycline. *Annals of Oncology* **14** 1449–1451.
- Nativ O, Grant CS, Sheps SG, O’Fallon JR, Farrow GM, van Heerden JA & Lieber MM 1992 The clinical significance of nuclear DNA ploidy pattern in 184 patients with pheochromocytoma. *Cancer* **69** 2683–2687.

- Neumann HPH, Hoegerle S, Manz T, Brenner K & Iliopoulos O 2002a How many pathways to pheochromocytomas. *Seminars in Nephrology* **22** 88–99.
- Neumann HPH, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Althoefer C, Zeres K *et al.* 2002b Germ-line mutations in nonsyndromic pheochromocytoma. *New England Journal of Medicine* **19** 1459–1465.
- Nguyen-Martin MA & Hammer GD 2006 Pheochromocytoma: an update on Risk Groups, Diagnosis, and Management. *Hospital Physician* **42** 17–24.
- O'Connor DT & Bernstein KN 1984 Radioimmunoassay of chromogranin A in plasma as a measure of exocytotic sympathoadrenal activity in normal subjects and patients with pheochromocytoma. *New England Journal of Medicine* **311** 764–770.
- Oishi S & Sato T 1988 Elevated neuron specific enolase in patients with malignant pheochromocytoma. *Cancer* **61** 1167–1170.
- O'Riordain DS, Young WF Jr, Grant CS, Carney JA & van Heerden JA 1996 Clinical spectrum and outcome of functional extraadrenal paraganglioma. *World Journal of Surgery* **20** 916–922.
- Pacak K, Ghrousos GP, Koch CA, Lendes JW & Eisenhofer G, 2001a Pheochromocytoma: Progress in diagnosis, therapy and genetics. In *Adrenal Disorders*, pp 479–523. Eds A Margioris & GP Ghrousos Totowa: Humana Press.
- Pacak K, Goldstein DS, Doppman JL, Shulkin BL, Udelsman R & Eisenhofer G 2001b A 'phea' lurks: novel approaches for locating occult pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **86** 3641–3646.
- Pacak K, Linehan WM, Eisenhofer G, Walther MM & Goldstein DS 2001c Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Annals of Internal Medicine* **134** 315–329.
- Pacak K, Eisenhofer G & Ilias I 2004 Diagnostic imaging of pheochromocytoma. *Frontiers of Hormone Research* Basel Karger, **31** 107–120.
- Pacak K, Eisenhofer G, Ahlman H, Bornstein S, Gimenez-Roqueplo A-P, Grossman AB, Kimura N, Mannelli M, McNicol A-M & Tischler AS 2007 Pheochromocytoma: recommendations for clinical practice from the First International Symposium. *Nature Clinical Practice. Endocrinology and Metabolism* **3** 92–102.
- Park JW, Yeh MW, Wong MG, Lobo M, Hyun WC, Duh QY & Clark OH 2003 The heat shock protein 90-binding geldanamycin inhibits cancer cell proliferation, down-regulates oncoproteins, and inhibits epidermal growth factor-induced invasion in thyroid cancer cell lines. *Journal of Clinical Endocrinology and Metabolism* **88** 3346–3353.
- Portela-Gomes GM, Stridsberg M, Grimelius L, Falkmer UG & Falkmer S 2004 Expression of chromogranins A, B and C (secretogranin II) in human adrenal medulla and in benign and malignant pheochromocytomas. An immunohistochemical study with region-specific antibodies. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica* **112** 663–673.
- Portel-Gomes GM, Grimelius L, Johansson H, Wilander E & Stridsberg M 2001 Chromogranin A in human neuroendocrine tumors: an immunohistochemical study with region-specific antibodies. *American Journal of Pathology* **25** 1261–1267.
- Proye C, Fossati P, Fontaine P, Lefebvre J, Decoulx M, Wemeau JL, Dewailly D, Rwamasirabo E & Cecat P 1986 Dopamine secreting pheochromocytoma: An unrecognized entity?, Classification of pheochromocytoma according to their type of secretion *Surgery* **100** 1154–1161.
- Pujol P, Bringer J, Faurous P & Jaffiol C 1995 Metastatic pheochromocytoma with a long-term response after iodine-131 metaiodobenzylguanidine therapy. *European Journal of Nuclear Medicine* **22** 382–384.
- Quissel B, Mohammad A, Bauer JH & Hakami N 1979 Malignant pheochromocytoma in childhood: report of a case with familial neurofibromatosis. *Medical and Pediatric Oncology* **7** 327–333.
- Rao F, Keiser HR & O'Connor DT 2000 Malignant pheochromocytoma, Chromaffin granule transmitters and response to treatment. *Hypertension* **36** 1045–1052.
- Rose B, Matthey KK, Price D, Huberty J, Klencke B, Norton JA & Fitzgerald PA 2003 High dose ¹³¹I-metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. *Cancer* **98** 239–248.
- Safford SD, Coleman RE, Gockerman JP, Moore J, Feldman JM, Leight GS Jr, Tyler DG & Olson JA 2003 Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. *Surgery* **134** 956–963.
- Sahdev A & Reznick RH 2004 Imaging evaluation of the non-functioning indeterminate adrenal mass. *Trends in Endocrinology and Metabolism* **15** 271–276.
- Sakahara H, Endo K, Saga T, Hosono M, Kobayashi H & Konishi J 1994 ¹³¹I-metaiodobenzylguanidine for malignant pheochromocytoma. *Annals of Nuclear Medicine* **8** 133–137.
- Salmenkivi K, Arola J, Voutilainen R, Ilvesmaki V, Haglund C, Kahri AI, Heikkila P & Liu J 2001a Inhibin/activin β B-subunit expression in pheochromocytomas favors benign diagnosis. *Journal of Clinical Endocrinology and Metabolism* **86** 2231–2235.
- Salmenkivi K, Haglund C, Ristimäki A, Arola J & Heikkila P 2001b Increased expression of cyclooxygenase-2 in malignant pheochromocytomas. *Journal of Clinical Endocrinology and Metabolism* **86** 5615–5619.
- Salmenkivi K, Heikkila P, Haglund C, Louhimo J & Arola J 2003 Lack of histologically suspicious features, proliferative activity and p53 expression suggests benign diagnosis in pheochromocytomas. *Histopathology* **43** 62–71.
- Sausville EA, Tomaszewski JE & Ivy P 2003 Clinical development of 17-allylamino, 17-demethoxygeldanamycin. *Current Cancer Drug Targets* **3** 377–383.

- Schlumberger M, Gicquel C, Lumbroso J, Tenenbaum F, Comoy E, Bosq J, Fonseca E, Ghillani PP, Aubert B & Travagli JP 1992 Malignant pheochromocytoma: clinical, biological, histologic and therapeutic data in a series of 20 patients with distant metastases. *Journal of Endocrinological Investigation* **15** 631–642.
- Scholz T, Eisenhofer G, Pacak K, Dralle H & Lehnert H 2007 Current treatment of malignant pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **92** 1217–1225.
- Schwartz C, Gibold C, Vuillemin B & Delisle MJ 1991 Results of [¹³¹I] metaiodobenzylguanidine therapy administered to three patients with malignant pheochromocytoma. *Journal of Nuclear Biology and Medicine* **35** 305–307.
- Scott HW Jr & Halter SA 1984 Oncologic aspects of pheochromocytoma: the importance of follow-up. *Surgery* **96** 1061–1066.
- Shapiro B 1991 Summary, conclusions and future directions of [¹³¹I] metaiodobenzylguanidine in the treatment of neural crest tumors. *Journal of Nuclear Biology and Medicine* **35** 357–363.
- Shapiro B, Sisson JC, Wieland DM, Mangner TJ, Zempel SM, Mudgett E, Gross MD, Carey JE, Zasadny KR & Beierwaltes WH 1991 Radiopharmaceutical therapy of malignant pheochromocytoma: results from ten years of experience. *Journal of Nuclear Biology and Medicine* **35** 269–276.
- Shapiro B, Sisson JC, Shulkin BL, Gross MD & Zempel S 1995 The current status of radioiodinated metaiodobenzylguanidine therapy of neuro-endocrine tumors. *Quarterly Journal of Nuclear Medicine* **39** 55–57.
- Shapiro B, Gross MD & Shulkin B 2001 Radioisotope diagnosis and therapy of malignant pheochromocytoma. *Trends in Endocrinology and Metabolism* **12** 469–475.
- Shulkin BL, Wieland DM, Schwaiger M, Thompson NW, Francis IR, Haka MS, Rosenspire KC, Shapiro B & Kuhl DE 1992 PET scanning with hydroxyephedrine: an approach to the localization of pheochromocytoma. *Journal of Nuclear Medicine* **33** 1125–1131.
- Shulkin BL, Wieland DM, Shapiro B & Sisson JC 1995 PET adrenaline studies in pheochromocytoma. *Journal of Nuclear Medicine* **36** 229P.
- Shulkin BL, Thompson NW, Shapiro B, Francis IR & Sisson JC 1999 Pheochromocytomas: Imaging with 2-deoxy-D-glucose PET. *Radiology* **212** 35–41.
- Shulkin B, Ilias I, Sisson J & Pacak K 2006 Current trends in functional imaging of pheochromocytomas and paragangliomas. *Annals of New York Academy of Sciences* **1073** 374–382.
- Sigmund HE, Weitzman S, Thorner P, Seagram CG & Filler RM 1994 Pediatric malignant pheochromocytoma. *Journal of Pediatric Surgery* **29** 1197–1201.
- Sisson J, Shapiro B, Beierwaltes W, Glowinski JV, Nakajo M, Mangner TJ, Carey JE, Swanson DP, Copp JE, Satterlee WG et al. 1984 Radiopharmaceutical treatment of malignant pheochromocytoma. *Journal of Nuclear Medicine* **24** 197–206.
- Sisson JC, Shapiro B, Hutchinson RJ, Carey JE, Zasadny KR, Zemple SA & Normolle DP 1994 Predictor of toxicity in treating patients with neuroblastoma by radiolabeled metaiodobenzylguanidine. *European Journal of Nuclear Medicine* **21** 46–52.
- Sisson JC, Shapiro B, Shulkin BL, Urba S, Zempel S & Spalding S 1999 Treatment of malignant pheochromocytomas with [¹³¹I]-metaiodobenzylguanidine and chemotherapy. *American Journal of Clinical Oncology* **22** 356–370.
- Stoppa-Lyonnet D & Lenoir G 2005 Prédispositions génétiques aux cancers: actualités et perspectives en 2005. *Medical Science* **21** 962–968.
- Strock CJ, Park JI, Rosen DM, Ruggeri B, Denmeade SR, Ball DW & Nelkin BD 2006 Activity of irinotecan and the tyrosine kinase inhibitor CEP-751 in medullary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **91** 79–84.
- Tada K, Okuda Y & Yamashita K 1998 Three cases of malignant pheochromocytoma treated with cyclophosphamide, vincristine, and dacarbazine combination chemotherapy and alphamethyl-p-tyrosine to control hypercatecholaminemia. *Hormone Research* **49** 295–297.
- Takahashi K, Ashizawa N, Minami T, Suzuki S, Sakamoto I, Hayashi K, Tomiyasu S, Sumikawa K, Kitamura K, Eto T et al. 1999 Malignant pheochromocytoma with multiple hepatic metastases treated by chemotherapy and transcatheter arterial embolization. *Internal Medicine* **38** 349–354.
- Tenenbaum F, Lumbroso J, Schlumberger M, Mure A, Plouin PF, Caillou B & Parmentier C 1995 Comparison of radiolabeled octreotide and meta-iodobenzylguanidine (MIBG) scintigraphy in malignant pheochromocytoma. *Journal of Nuclear Medicine* **36** 1–6.
- Teno S, Tanabe A, Nomura K & Demura H 1996 Acutely exacerbated hypertension and increased inflammatory signs due to radiation treatment for metastatic pheochromocytoma. *Endocrine Journal* **43** 511–516.
- Theilade K, Bak M, Olsen K, Nielsen SL & Christensen NJ 1988 A case of malignant pheochromocytoma treated by [¹³¹I]-metaiodobenzylguanidine. *Acta Oncologica* **27** 296–297.
- Tonkin AL, Frewin DB, Russell WJ & Jonsson JR 1994 Pheochromocytoma: intraoperative changes in blood pressure and plasma catecholamines. *Clinical Autonomic Research* **4** 167–173.
- Troncone L, Rufini V, Daidone MS, De Santis M & Luzi S 1991 [¹³¹I]-metaiodobenzylguanidine treatment of malignant pheochromocytoma: experience of the Rome group. *Journal of Nuclear Biology and Medicine* **35** 295–299.
- Troncone L & Rufini V 1997 [¹³¹I]-MIBG therapy of neural crest tumours. *Anticancer Research* **17** 1823–1832.
- Vetter H, Fischer M, Muller-Rensing R, Vetter W & Winterberg B 1983 [¹³¹I]-metaiodobenzylguanidine in treatment of malignant pheochromocytomas. *Lancet* **2** 107.

- Vezzosi D, Bouisson M, Escourrou G, Laurell H, Selves J, Seguin P, Pradayol L, Caron P & Buscail L 2006 Clinical utility of telomerase for the diagnosis of malignant well-differentiated endocrine tumours. *Clinical Endocrinology* **64** 63–67.
- Wiseman GA & Kvols LK 1995 Therapy of neuroendocrine tumors with radiolabelled MIBG and somatostatin analogues. *Seminars in Nuclear Medicine* **115** 272–278.
- Wu LT, Diczpinigaitis P, Bruckner H, Manger W & Averbuch S 1994 Hypertensive crises induced by treatment of malignant pheochromocytoma with a combination of cyclophosphamide, vincristine, and dacarbazine. *Medical and Pediatric Oncology* **22** 389–392.
- Young AL, Baysal BE, Deb A & Young W Jr 2002 Familial malignant catecholamine-secreting paraganglioma with prolonged survival associated with mutation of the succinate dehydrogenase B gene. *Journal of Endocrinology and Metabolism* **87** 4101–4105.
- Zarnegar R, Kebebew E, Duh QY & Clark OH 2006 Malignant pheochromocytoma. *Surgical Oncology Clinics of North America* **15** 55–571.