The diagnosis and management of malignant phaeochromocytoma and paraganglioma

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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.

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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-shock 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 (Kaltzas et al. 2004b). Clinical, biochemical and radiological features are inadequate to either predict malignancy or distinguish benign from malignant lesions (Bravo & Tagle 2003, Kaltzas 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 in 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, phenoxbenza-mine 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;
chromaffin-cell tumours associated with MEN 2 syndrome usually produce both adrenaline and noradrenaline (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. 2006) due to alterations of catecholamine synthesis in malignant phaeochromocytoma cells (John et al. 1999). It has been suggested that elevated plasma dopamine and urinary dihydroxyphenylalanine 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 (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

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

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.
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 phaeochromocytomas 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/resecretion pathway or non-specific ligands (Kaltas et al. 2005). Specific functional imaging, with [111]I- or preferentially [123]I-metaiodobenzylguanidine (MIBG) scintigraphy, has been extensively used for the diagnosis and staging of chromaffin-cell tumours (Kaltas 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). [123]I-MIBG is superior to [131]I-MIBG in terms of physical properties, quality of images and sensitivity (83–100 vs 77–90% respectively); scintigraphy with [123]I-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 [111]In-pentetreotide (Kaltas et al. 2004a). Although scintigraphy with [111]In-pentetreotide is of limited value for non-metastatic, solitary/adrenal phaeochromocytomas (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, Kaltas 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]-fluorodopa (18F)-DA) can detect metastatic phaeochromocytomas at rates higher than [131]I-MIBG (Ilias et al. 2003), whereas PET with 6-[18F]-fluoroDOPA ([18F]-DOPA) is superior in imaging extra-adrenal phaeochromocytomas and neck paragangliomas (Hoegerle et al. 2002). Partial intratumoral metabolism of glucose can be used for non-specific functional PET imaging. PET using 2-[18F]-fluoro-2-deoxy-D-glucose (FDG), [18F]FDG-PET, can identify glucose-avid metastatic lesions (Shulkin et al. 1999), particularly if they are [131]I-MIBG or [123]I-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 phaeochromocytomas 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, Kaltas 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, Kaltas 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 (HIF1α), 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 HIFα prolyl hydroxylase, stabilising the HIF1α 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, Salmekivii 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 (Salmekivii 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 (Salmekivii 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 phaeochromocytoma 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 phaeochromocytomas 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 123I-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 131I-MIBG**

The rationale for using radiolabelled MIBG for therapy of phaeochromocytomas and paragangliomas lies in its ability to enter the cell membrane and be stored in cytoplasmic granules via VMA transporters (VMAT 1 and 2; Kaltas et al. 2003, Ahlman 2006). 131I-MIBG was initially used for the treatment of malignant phaeochromocytoma in 1984, and since then several hundred patients have been treated with different therapeutic protocols using either single or cumulative doses of 131I-MIBG, with a variable total dosage (Sisson et al. 1984, Kaltas et al. 2003, Kaltas et al. 2005). Patients are selected on the demonstration of significant radioisotope uptake on diagnostic 123I-MIBG or 131I-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 131I-MIBG avid (Fitzgerald et al. 2006).
recently, quantitative determination of VMAT 1, 2 expression in surgical phaeochromocytoma specimens has been helpful in selecting patients suitable for 131I-MIBG treatment (Kolby et al. 2006; Table 2).

In a published comprehensive review of 116 patients who received 100–300 mCi of 131I-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 131I-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 131I-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 131I-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 131I-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 131I-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 131I-MIBG, as seen in 5 out of 119 children with neuroblastomas treated with 131I-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 131I-MIBG uptake study. Newer preparations of 131I-MIBG may also have higher specific activity, although whether this will translate into higher efficacy remains unclear.

Treatment with 131I-MIBG is not curative in most patients. The impact of treatment depends on the extent of disease at the time of therapy, and therefore 131I-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 131I-MIBG treatment, the integration of 131I-MIBG with other therapeutic modalities should be assessed (Shapiro et al. 1995, Kaltsas et al. 2001c). Pre-treatment with 131I-MIBG in patients receiving chemotherapy increased toxicity, although the tumour response was greater (Sisson et al. 1999). On the other hand, 123I-MIBG uptake may increase after a radiological response to chemotherapy, enabling successful 131I-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 111In-pentetreotide/111In-DOTA-octreotide, 90Y-DOTA-octreotide (Shapiro et al. 2001) and 177Lu-DOTA-octreotate, and 111In and 90Y-DOTA-lanreotide (Kaltsas et al. 2005). As in treatment with 131I-MIBG, only patients showing a high tumour uptake to scintigraphy (usually assessed with 111In-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 $^{131}$ metaiodobenzylguanidine ($^{131}$MIBG) treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of Patients</th>
<th>No of doses (mean)</th>
<th>Total dose (mCi)</th>
<th>Tumour response</th>
<th>Biochemical response</th>
<th>Toxicity</th>
</tr>
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<td>549</td>
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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-pentetretotide, 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-l-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 $\alpha$-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-demethoxy-geldanamycin 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
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. $^{131}$I exhibits very low absorbed values and is not suitable for small tumours. $\alpha$-emitters, $^{211}$At, bound to MIBG (MABG) may be more efficacious for the eradication of residual disease and/or micrometastases (Ahlman 2006). $^{177}$Lu-octreotate, which shows considerable activity at short distances, might complement $^{131}$I-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 $^{123}$I-MIBG and $^{111}$In-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). Cytoreductive 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**

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References


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