The optimal imaging of adrenal tumours: a comparison of different methods

Ioannis Ilias, Anju Sahdev¹, Rodney H Reznek¹, Ashley B Grossman² and Karel Pacak³

Department of Endocrinology, Elena Venizelou Hospital, Athens GR-11521, Greece
Departments of ¹Radiology and ²Endocrinology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK
³Section on Medical Neuroendocrinology, Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, 1 East, Room 1-3140, 10 Center Drive, MSC-1109, Bethesda, Maryland 20892-1109, USA

(Correspondence should be addressed to K Pacak; Email: karel@mail.nih.gov)

Abstract

Computed tomography (CT; unenhanced, followed by contrast-enhanced examinations) is the cornerstone of imaging of adrenal tumours. Attenuation values of <10 Hounsfield units on an unenhanced CT are practically diagnostic for adenomas. When lesions cannot be characterised adequately with CT, magnetic resonance imaging (MRI) evaluation (with T1- and T2-weighted sequences and chemical shift and fat-suppression refinements) is sought. Functional nuclear medicine imaging is useful for adrenal lesions that are not adequately characterised with CT and MRI. Scintigraphy with [¹³¹I]-6-iodomethyl norcholesterol (a labelled cholesterol analogue) can differentiate adrenal cortical adenomas from carcinomas. Phaeochromocytomas appear as areas of abnormal and/or increased uptake of [¹²³I]- and [¹³¹I]-meta-iodobenzylguanidine (a labelled noradrenaline analogue). The specific and useful roles of adrenal imaging include the characterisation of tumours, assessment of true tumour size, differentiation of adenomas from carcinomas and metastases, and differentiation of hyperfunctioning from non-functioning lesions. Adrenal imaging complements and assists the clinical and hormonal evaluation of adrenal tumours.

Endocrine-Related Cancer (2007) 14 587–599

Introduction

The endocrine oncologist frequently has to assess adrenal tumours, and many problems may arise in defining whether lesions are primary to the adrenal or represent other tissue, they are benign or malignant and they are functioning or not. Improvements in imaging modalities and their interpretation have increased dramatically over the past few years, and can now offer a considerable amount of material to help inform clinical decision making. The purpose of this review is to summarise the use of various imaging modalities in the assessment of adrenal tumours in order to allow the clinician to make a precise diagnosis and customise treatment accordingly.

The normal adrenals have an inverted Y-shape, are located supero-medial to the kidneys and each weigh 4–5 g (Mayo-Smith et al. 2001). On computed tomography (CT), the maximum width of the right adrenal limb is 0.28 cm and the left adrenal limb is 0.33 cm (Vincent et al. 1994). In neonates and young children, the glands are proportionately much larger than in the adult. By conventional cross-sectional imaging, the adrenal cortex and medulla cannot be distinguished. There are three cortical zones, glomerular, fascicular and reticular, producing aldosterone, cortisol and androgens respectively. The glands’ medulla produces adrenaline and noradrenaline. Tumours in the adrenals are common in humans, being present in 3% of autopsies performed in persons older than 50 years (Grumbach et al. 2003). Primary tumours in the adrenals can be hyperfunctioning (producing excess hormones from the cortex or the medulla and accompanied by clinical symptoms) or non-functioning (Ilias et al. 2004). Often adrenal tumours are incidentally detected with abdominal ultrasound (sensitivity is reported at 96 and 100% for tumours smaller and larger than 2 cm respectively; Trojan et al. 2002). Thorough imaging of such tumours is performed by anatomical imaging modalities (such as CT or magnetic resonance imaging (MRI) and functional imaging modalities (i.e. nuclear scintigraphy).
Computed tomography

The cornerstone of adrenal imaging is CT, performed before and after i.v. injection of contrast medium and acquired as 3–5 mm scans through the adrenal glands. The advent of multi-detector CT (MDCT) has allowed post-processing of the acquired data to narrow slice intervals and provides detailed reformatted images in any plane. On CT scanning the normal adrenals appear homogeneous and symmetric, with a density approximately equal to that of the kidney (Lockhart et al. 2002). Unenhanced CT is important to provide density measurements of lesions; it is usually followed by a, preferably delayed, contrast-enhanced study that can quantify the percentage of absolute or relative contrast enhancement washout and shows the vessels in the region of the adrenal glands (Lockhart et al. 2002, Slattery et al. 2006, Heinz-Peer et al. 2007). Visual assessment of the vascularity of a lesion and the homogeneity of its enhancement can also be helpful in characterising a lesion. The combination of unenhanced CT and contrast washout values of adrenal masses can assist in characterisation and distinguishing adenomas from other adrenal tumours with 98% sensitivity and 92% specificity (Korobkin et al. 1998, Caoili et al. 2002, Sahdev & Reznek 2004).

Magnetic resonance imaging

MRI of the adrenal glands should include T1- and T2-weighted images, plus chemical shift imaging (CSI) which consists of in-phase and out-of-phase imaging. T1-fat-suppressed imaging before and after i.v. gadolinium administration is optional. Multi-planar MRI allows precise localisation and separation of adrenal masses from the surrounding structures, particularly the liver, spleen, stomach, pancreas and kidneys. Normal adrenal glands have T1 and T2 signal intensity equal or slightly lower than that of the normal liver (Lockhart et al. 2002).

Adrenal adenomas

CT can detect adrenal masses >5 mm in diameter. Of these, non-functioning adrenocortical adenomas are the most common. They are usually homogeneous, round and small, have smooth borders and well-delineated margins that separate them from adjacent structures (Thompson & Young 2003). Larger adenomas may distort the body, medial or lateral limbs of the adrenal. Lipid-rich adenomas have an unenhanced CT attenuation <10 Hounsfield units (HU; Thompson & Young 2003; Fig. 1). However, some 25–30% of adenomas are lipid poor and have unenhanced CT attenuation values >10 HU (Fig. 2).

Figure 1 Lipid-rich adenoma. (A) Unenhanced CT of the abdomen showing a left adrenal mass with a HU measurement of −6 HU (arrow). (B) Contrast-enhanced CT acquired 60 s after administration of i.v. contrast shows enhancement of the adrenal mass to 50 HU. (C) On delayed CT, acquired 15 min after administration of i.v. contrast, the mass measures 15 HU. These measurements provide an absolute contrast enhancement washout of 63% and a relative contrast washout of 70% proving a lipid-rich adenoma.
Although adenomas may show the same density as normal adrenal tissue on unenhanced CT, they show greater enhancement on contrast-enhanced CT than the surrounding normal adrenal tissue (Dunnick & Korobkin 2002). Contrast-enhanced CT utilises the unique property of adenomas of early enhancement after contrast administration and early washout of the contrast from the adenoma. Non-adenomas have a slower contrast washout phase than adenomas. Two criteria exist for the calculation of washout thresholds, absolute and relative. Calculation of the absolute washout requires a Hounsfield value from unenhanced CT but relative washout does not (Table 1). An absolute contrast washout of >60% and a relative contrast washout of >40% characterise an adenoma with a sensitivity and specificity of 98 and 92% respectively (Dunnick & Korobkin 2002, Sahdev &

Reznek 2004, Szolar et al. 2005). This technique is very valuable in lipid-poor adenomas (Fig. 2).

On MRI, adenomas appear homogeneous on all sequences. Their contrast enhancement is mild; they have low or equal signal intensity to the liver on T2-weighted images and may appear of lower signal intensity than the rest of the adrenal gland (Thompson & Young 2003). As on CT, characterisation of adenomas is dependent on the presence of intracellular lipid. Therefore, on CSI adenomas lose at least 30% of their signal intensity on the out-of-phase images when compared with the in-phase images (Fig. 3). This loss of signal can be appreciated visually but can also be measured using the adreno-splenic ratio (ASR) and the signal intensity index (SII). An ASR ratio of <70% has been shown to be highly specific for adenomas and has a 78% sensitivity (Mayo-Smith et al. 2001). Using the SII, a minimum of 5% signal loss characterises an adrenal adenoma with an accuracy of 100% (Table 1).

Non-adenomatous benign adrenocortical tumours

Myelolipomas

Myelolipomas are heterogeneous and contain mature adipose tissue and haemopoietic tissue. They are characterised by detecting fat on CT and MRI. On CT, the presence of low attenuation fat in the lesion which has a density ≤30 HU is a specific and diagnostic finding (Dunnick & Korobkin 2002, Lockhart et al. 2002; Fig. 4). On MRI, the fat components in the lesion demonstrate high signal on T1- and T2-weighted images and lose signal on T1-fat-saturated images resembling intra-abdominal fat. It is important to appreciate that myelolipomatous tissue can coexist with other tumours, such as adenomas or carcinomas.

Haemangiomas

Haemangiomas in the adrenals are usually large and well-defined masses. On unenhanced CT, they show soft-tissue attenuation and calcification. On contrast-enhanced CT, they can be inhomogeneous, enhancing peripherally with central low attenuation (Dunnick & Korobkin 2002, Lockhart et al. 2002). Haemangiomas have a lower signal when compared with that of the liver, on T1-weighted images, although higher signals can be seen centrally, caused by haemorrhage and/or necrosis (Dunnick & Korobkin 2002, Lockhart et al. 2002). On T2-weighted views, their signal is typically moderate or high (Dunnick & Korobkin 2002, Lockhart et al. 2002). Foci of low signal on T1- and T2-weighted images are caused by calcification or haemorrhage.
Adrenocortical tumours

Table 1 Non-specific findings of anatomical imaging that may help in differentiating benign from malignant adrenal masses (modified in part from Ilias et al. 2004)

<table>
<thead>
<tr>
<th></th>
<th>Benign mass</th>
<th>Malignant tumour (primary adrenal carcinoma or metastasis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>&lt;4 cm</td>
<td>&gt;4 cm</td>
</tr>
<tr>
<td><strong>Shape/margins</strong></td>
<td>Round/smooth</td>
<td>Thick/irregular</td>
</tr>
<tr>
<td><strong>Homogeneity CT or MRI</strong></td>
<td>Homogeneous</td>
<td>Heterogenous</td>
</tr>
<tr>
<td><strong>Lipid content</strong></td>
<td>High (except lipid-poor adenomas)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Growth rate</strong></td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>CT density</strong></td>
<td>&lt;10 HU (lipid-rich adenomas)</td>
<td>&gt;10 HU</td>
</tr>
<tr>
<td><strong>CT enhancement after contrast administration</strong></td>
<td>Early enhancement and early washout</td>
<td>Variable enhancement with slow washout</td>
</tr>
<tr>
<td><strong>% Absolute enhancement washout (AEW)</strong></td>
<td>&gt;60%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td><strong>% Relative enhancement washout (REW)</strong></td>
<td>&gt;40%</td>
<td>&lt;40%</td>
</tr>
<tr>
<td><strong>MRI signal on T2-weighted sequences</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>CSI signal loss on out-of-phase</strong></td>
<td>&gt;30%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td><strong>Adreno-splenic ratio (ASR)</strong></td>
<td>&lt;70%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td><strong>Signal intensity index (SII) signal loss</strong></td>
<td>&gt;5%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

**a** AEW = 100 × enhanced attenuation value − delayed attenuation value/enhanced attenuation value − unenhanced attenuation value; (Sahdev & Reznek 2004).

**b** REW = 100 × enhanced attenuation value − delayed attenuation value/enhanced attenuation value. Enhanced attenuation value (HU) = attenuation value of the mass 60 s post-contrast administration. Delayed attenuation value (HU) = attenuation value of the mass, 15 min post-contrast administration (Sahdev & Reznek 2004).

**c** ASR = 100 × (S_A/S_S) / (S_P/S_S) in − phase. S_A = signal intensity of the adrenal mass. S_S = signal intensity of the spleen.

**d** SII = 100 × (S_OP adrenal − S_IP adrenal) / S_IP adrenal. S_OP adrenal = signal intensity of adrenal mass on in-phase images. S_IP adrenal = signal intensity of adrenal mass on out-of-phase images.

**Ganglioneuromas**

Adrenal ganglioneuromas are benign solid masses that may be of considerable size (range 4–22 cm). They have a soft-tissue density less than that of muscle on unenhanced CT. Contrast-enhanced views can show them to be homogeneous or mildly heterogeneous (Dunnick & Korobkin 2002). Ganglioneuromas are homogeneous and have a lower T1 signal intensity than liver (Dunnick & Korobkin 2002). On T2-weighted images, ganglioneuromas show non-specific heterogeneity, depending on their content of myxoid stroma; the more stroma there is the higher is the T2 signal, while cellular and fibrous components lower the T2 signal intensity (Rha et al. 2003).

**Malignant adrenocortical tumours**

**Adrenal carcinomas**

At the time of discovery, the majority of primary adrenal carcinomas tend to be larger than adenomas, usually 5–10 cm in diameter. Approximately 50% are hyper-functioning (Lockhart et al. 2002, Thompson & Young 2003). In many of these, the margins are irregular and the contents inhomogeneous with areas of necrosis, haemorrhage and calcification (Fig. 5). Nevertheless, smaller lesions may be homogeneous on unenhanced CT (Lockhart et al. 2002). For carcinomas, the attenuation on unenhanced studies is higher than 10 HU (Young 2007). On contrast-enhanced studies, carcinomas enhance avidly due to their vascularity. The pattern of enhancement can be homogeneous, unless there is central necrosis (Dunnick & Korobkin 2002, Lockhart et al. 2002, Young 2007). The relative percentage washout of carcinomas is <40% (Slattery et al. 2006). On MRI, adrenal carcinomas are noted for heterogeneity, with intermediate to high signal intensity, on T1-weighted images. Heterogeneity is also noted on T2-weighted images due to haemorrhage and/or necrosis. As with CT, contrast-enhanced studies enable the assessment of retroperitoneal lymph nodes, vascular extension and thrombosis, and encroachment of adrenal and renal veins or the inferior vena cava (Dunnick & Korobkin 2002).

**Angiosarcomas and leiomyosarcomas**

Adrenal angiosarcomas and leiomyosarcomas are very rare tumours. On CT, they have irregular margins and are inhomogeneous, and calcification may also be prominent (Pasqual et al. 2002). Leiomyosarcomas and their imaging characteristics are indistinguishable from those of adrenal cortical carcinomas or metastatic cancers (Lee et al. 2006). Leiomyosarcomas show low intensity on T1-weighted images, high intensity on
T2-weighted images and marginal enhancement after i.v. gadolinium administration (Lee et al. 2006).

**Adrenal lymphomas**

Secondary adrenal lymphomatous involvement occurs in up to 25% of patients with lymphoma at some stage of their disease (Lerttumnongtum et al. 2004) and may present as bilateral adrenal masses (Ogilvie et al. 2006). Primary lymphoma of the adrenal glands is rare, and <100 cases have been reported in the world literature. It most commonly affects elderly men, is bilateral, and 50% present with symptoms of adrenal insufficiency, fever and weight loss (Kumar et al. 2005). On CT, they are usually large solid masses with variable necrosis and enhancement after contrast administration. On MRI, they have intermediate soft-tissue signal intensity and a high T2 signal intensity. On CSI, no loss of signal intensity is demonstrated on the out-of-phase imaging. Their appearance is therefore indistinguishable from that of other malignant adrenal tumours and biopsy of the mass is required to establish the diagnosis (Li et al. 2006).

**Adrenal medullary tumours**

**Phaeochromocytomas**

Most sporadic adrenal phaeochromocytomas are at least 2–3 cm in diameter and can be readily visualised with CT. Smaller (1–2 cm in diameter) phaeochromocytomas are usually homogeneous in appearance, with a density of 40–50 HU on unenhanced CT (Sohaib et al. 2001). Larger phaeochromocytomas, however, can be inhomogeneous with areas of haemorrhage, and low attenuation necrosis may be present (Mayo-Smith et al. 2001). Adrenal phaeochromocytomas have signal intensity on MRI T1 sequences equal to or higher than that of the liver, kidney and muscle (Mayo-Smith et al. 2001;
Phaeochromocytomas have a higher signal intensity than that of fat on T2-weighted sequences. This characteristic finding is due to the hypervascularity of the tumours. On CSI, there is no signal loss on opposed-phase images (Mayo-Smith et al. 2001; Fig. 4). After contrast administration, phaeochromocytomas enhance avidly and have a prolonged contrast washout phase. In heterogeneous tumours, the viable areas of the tumour enhance whilst necrotic areas do not.

Neuroblastomas

Two-thirds of neuroblastomas arise from the adrenals and occur in infants and children. Most are of irregular shape, lobulated and are usually unencapsulated with variable amounts of amorphous or mottled calcification (Rha et al. 2003). Extension to the liver, adjacent lymph nodes and vessels is not uncommon. Necrosis and/or haemorrhage within the tumour leads to an inhomogeneous appearance on CT. Neuroblastomas in the adrenals give a heterogeneous low-intensity signal on T1-weighted sequences and high signal on T2-weighted views (cystic changes may also be observed; Elsayes et al. 2004). MRI is the modality of choice for imaging neuroblastomas as intra-spinous extension and hepatic metastases are better demonstrated using MRI when compared with CT.

Adrenal metastases

The adrenal gland can be the site of metastatic disease from carcinoma of the lung, breast, lymphoma or melanoma (Rajaratnam & Waugh 2005). Adrenal metastases can have irregular margins and are often bilateral (Thompson & Young 2003). On unenhanced CT, adrenal metastases usually have attenuation values >10 HU (Young 2007). In patients with metastases from melanoma, attenuation values may be lower (Rajaratnam & Waugh 2005). Contrast-enhanced examinations can be variable: larger metastatic lesions may be inhomogeneous if necrosis is present, whereas smaller lesions may be homogeneous (Dunnick & Korobkin 2002; Fig. 7). Metastases have <60% absolute and <40% relative contrast washout after contrast-enhanced CT. On MRI, metastases are homogeneous with T1-weighted signal intensity equal to that of the liver. Adrenal metastases usually have a higher signal on T2-weighted images (Thompson & Young 2003). Larger lesions can be inhomogeneous due to the presence of areas of necrosis and haemorrhage, with high signal intensity on both T1- and T2-weighted sequences (Lack 1995, Dunnick & Korobkin 2002).

Figure 6 Adrenal phaeochromocytoma on MR chemical shift imaging. (A) Axial T1-weighted in-phase image of a left heterogeneous adrenal mass (arrow). (B) Axial T1-weighted out-of-phase image demonstrating no loss of signal intensity within or in the periphery of the mass. The adrenal mass is hence an indeterminate mass (non-adenoma) on MR chemical shift imaging. This is an example of a surgically confirmed phaeochromocytoma.

Figure 7 Adrenal metastases. Contrast-enhanced CT of the abdomen demonstrating a large right-sided adrenal metastasis (arrowhead) and multiple liver metastases (arrows) in a patient with disseminated breast cancer.
Functional imaging

Patients that harbour adrenal masses, which are not adequately characterised with CT or MRI, can be further evaluated with functional nuclear medicine modalities. These modalities are based on physiological and pathophysiological processes (cellular metabolism, tissue perfusion and local synthesis, uptake and storage of hormones and their receptors) and assist the preoperative staging of tumours. Furthermore, they can be of use in the evaluation of suspicious lesions and the identification of metastatic or recurrent tumours.

Nuclear medicine modalities that are available for the study of adrenal disease include conventional planar or single photon emission computed tomographic (SPECT) scintigraphy with various radionuclide tracers, and positron emission tomographic (PET) scintigraphy with various short-lived radionuclides. With PET, higher doses of radionuclides can be administered for a similar radiation exposure to SPECT. Imaging with PET has higher spatial resolution than conventional SPECT.

Hyperfunctioning adrenal tumours

Functional imaging modalities specific for cortical tumours

Cholesterol is the basic molecule for steroid biosynthesis. $[^{131}I]$-6-iodomethyl norcholesterol (NP-59) is a radiopharmaceutical that resembles cholesterol, binds specifically to low-density lipoproteins, and after receptor-mediated uptake is stored in the adrenocortical intracellular lipid droplets. Conventional NP-59 examinations are planar, although recently SPECT with NP-59 has been assessed (Imperiale et al. 2005). Normal adrenals are visualised at $\geq 5$ days after injection of NP-59 (Mayo-Smith et al. 2001). Unilateral adrenal uptake seen before day 5 suggests a functioning steroid-synthesising adenoma (Mayo-Smith et al. 2001), including aldosteronomas (Thompson & Young 2003). The minimum size of the adrenal mass to be evaluated with NP-59 is $> 2$ cm. Its practical use is further hampered by limited availability (Ruffini et al. 1992). $[^{11}C]$-metomidate is a PET ligand with inhibitor properties for the synthesis of adrenocortical steroids. It has been assessed in small series of adrenal masses, showing indiscriminately high uptake in adenomas and carcinomas (the latter with irregular uptake; Eriksson et al. 2005).

Functional imaging modalities specific for medullary tumours

Most phaeochromocytomas express the noradrenaline transport system (NET; Schulz et al. 2004). This system is responsible for the uptake of noradrenaline and adrenaline from the synaptic cleft into sympathetic presynaptic neurons, terminating neural transmission. This uptake process also enables specific functional imaging with various radioligands that depend upon NET for transport into phaeochromocytoma cells.

The alkylguanidine meta-iodobenzylguanidine (MIBG) is a noradrenaline analogue that is taken up by phaeochromocytoma cells. Initially, MIBG was labelled with $[^{131}I]$ but $[^{123}I]$-MIBG has become more common because it permits better quality SPECT imaging with low radiation exposure. The half-life of $[^{125}I]$ is much shorter, though, compared with that of $[^{131}I]$ (13.2 h vs 8 days). Phaeochromocytomas appear as areas of abnormal increased $[^{131}I]$- or $[^{123}I]$-MIBG uptake (Fujita et al. 2000). For phaeochromocytomas, scintigraphy with $[^{131}I]$-MIBG has 77–90% sensitivity and 95–100% specificity (Bravo & Tagle 2003), while with $[^{123}I]$-MIBG it has 83–100% sensitivity and 95–100% specificity (van der Harst et al. 2001). False-negative MIBG examinations may be caused by non-compliance not only with instructions to stop medications that interfere with MIBG uptake but also occurs with phaeochromocytomas that have undergone necrosis or dedifferentiation (Figs 8 and 9).

$[^{11}C]$-metahydroxyephedrine is a positron-emitter-labelled PET ligand that resembles noradrenaline but is not susceptible to intracellular degradation by monoamine oxidase (MAO). Excellent PET imaging studies of phaeochromocytomas (better than with $[^{123}I]$-MIBG) have been obtained with it (Mann et al. 2006); however, the 20-min half-life of $[^{11}C]$ precludes widespread application. $[^{11}C]$-labelled adrenaline is a PET radioligand that is a substrate for the catecholamine catabolic enzymes catechol-O-methyltransferase and MAO. PET with $[^{11}C]$-adrenaline localises fewer phaeochromocytomas than MIBG scintigraphy and the very short half-life of $[^{11}C]$ is again a deterrent to widespread use (Shulkin et al. 1995). Dopamine (DA) labelled with $[^{18}F]$ is substrate specific for the NET and is an excellent PET agent (better than $[^{131}I]$-MIBG) to localise adrenal and extra-adrenal phaeochromocytomas (Pacak et al. 2001, Ilias et al. 2003). Dihydroxyphenylalanine (an amino acid that is converted by aromatic amino acid decarboxylase to DA) labelled with $[^{18}F]$ has also been evaluated with success in imaging mainly adrenal phaeochromocytomas (Hoegerle et al. 2002).

Non-specific functional imaging modalities

$[^{18}F]$-fluorodeoxyglucose (FDG) is a PET glucose analogue. It shows the metabolic activity of glucose in tumours. $[^{18}F]$-FDG PET studies have not shown
Figure 8 Phaeochromocytoma. (A) Whole-body single-photon emission computed tomography with $^{[123]}$I-meta-iodobenzylguanidine ($^{[123]}$I-MIBG) (anterior and posterior views). No abnormal radionuclide uptake is seen. (B) Reprojected image obtained with $^{[18]}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) of the same patient (anterior view). High heterogeneous uptake is seen in a large tumour in the right adrenal (arrow).

Figure 9 Phaeochromocytoma. (A) Whole-body single-photon emission computed tomography with $^{[123]}$I-meta-iodobenzylguanidine ($^{[123]}$I-MIBG) (anterior and posterior views). Radionuclide uptake is seen in the right adrenal (arrow). (B) Reprojected image obtained with $^{[18]}$F-fluorodopamine (FDA) positron emission tomography (PET) of the same patient (anterior view). High homogeneous uptake is seen in a large tumour in the right adrenal (arrow).
uptake in adrenal adenomas (Tenenbaum et al. 2004) but they have shown uptake in adrenal metastases (Dunnick & Korobkin 2002). Phaeochromocytomas have been imaged with $[^{18}F]$-FDG PET (Shulkin et al. 1999). $[^{18}F]$-FDG PET is useful for the localisation of phaeochromocytomas that do not accumulate MIBG or other specific radionuclides (mainly dedifferentiated and/or rapidly growing phaeochromocytomas; Mamede et al. 2006; Fig. 6).

Phaeochromocytomas may express somatostatin receptors (in decreasing rate of occurrence SST-2A, -3, -4, -5 and -1; Ueberberg et al. 2005). Octreotide is a synthetic octapeptidic analogue of somatostatin that is chelated with diethylenetriaminepentaacetate (DTPA) and is usually labelled with $^{111}$Indium ($^{[111}\text{In}]$) for diagnostic imaging. Studies with $^{[111}\text{In}]-\text{DTPA-octreotide}$ did not show it to be of use in the evaluation of neuroendocrine tumours that were limited to the adrenals. In particular, most patients (66–75%) with benign phaeochromocytoma had negative $^{[111}\text{In}]-\text{DTPA-octreotide}$ scans (despite positive $^{[123}\text{I}]$-MIBG or $^{[131}\text{I}]$-MIBG imaging results; van der Harst et al. 2001). Furthermore, normal intense uptake is noted in the liver, spleen and kidneys, and excretion into the gastrointestinal tract. However, $^{[111}\text{In}]-\text{DTPA-octreotide}$ studies have been positive in patients with malignant/metastatic phaeochromocytomas and paragangliomas, where their sensitivity was $\sim 90\%$ (Tenenbaum et al. 1995, van der Harst et al. 2001, Ilias et al. 2004).

**Functional imaging modalities for non-hyperfunctioning tumours**

Usually, no NP-59 uptake is seen with carcinomas (Thompson & Young 2003). Rarely, false-positive $^{[131}\text{I}]$-MIBG examinations have been reported with adrenal carcinomas (Maurea et al. 2002). Adrenal adenomas have shown false-positive $^{[123}\text{I}]$-MIBG uptake as well as false-positive $^{[18}\text{F}]$-FDG PET uptake (Al-Hawary et al. 2005).

**Important points in imaging the adrenal glands**

**Characterising adrenal tumours**

MDCT is the single most useful modality for identification and characterisation of adrenal tumours. Unenhanced thin section images of the adrenal glands are essential. If an adrenal mass is demonstrated, the attenuation value should be measured using a region of interest cursor that includes most of the mass. Small, solid homogeneous masses that have an attenuation value of $< 10\text{ HU}$ can be considered to be benign lipid-rich adenomas (Hamrahian et al. 2005); no further imaging is necessary. In the presence of bilateral disease, heterogeneous masses or a mass of $> 10\text{ HU}$, a contrast-enhanced CT should be performed. Thin section CT is performed at 60 s and 15 min after i.v. contrast administration (delayed views are more informative). The absolute contrast washout can then be calculated to distinguish between adenomas ($> 60\%$ contrast washout) and non-adenomas ($< 60\%$ contrast washout). If the mass is detected only on post-contrast scans, then the *relative* contrast washout criteria can be calculated. Non-adenomas include metastases, phaeochromocytomas and carcinomas (Mayo-Smith et al. 2001, Dunnick & Korobkin 2002).

If a lesion cannot be characterised as an adenoma with CT, then further assessment can be done with MRI (particularly using chemical shift sequences). CSI will identify an additional small group of adenomas in which the intracellular lipid content is minimal (therefore $> 10\text{ HU}$ on unenhanced CT) but sufficient to be detected on CSI (Korobkin et al. 1996). Mostly lipid-poor masses that are characterised as non-adenomas on imaging and are biochemically not phaeochromocytomas may require biopsy (provided the mass does not give the impression of being a carcinoma; in such a case, biopsy is contraindicated) or surgical resection (Grumbach et al. 2005). Nuclear medicine modalities can add information on adrenal lesions and assist anatomical imaging with functional information (Mayo-Smith et al. 2001). Nuclear medicine studies may assist in the characterisation of phaeochromocytomas and may also provide information on coexistent metastases or multiple tumours elsewhere. This is particularly relevant for adrenal tumours larger than 5–6 cm and extra-adrenal phaeochromocytomas or in patients with familial phaeochromocytomas (since all these tumours have a higher potential for metastases or multiple tumours). It is also important in case of distorted, post-operative anatomy. Thus, as outlined above, for most of biochemically proven phaeochromocytomas CT or MRI examinations should be followed by specific functional modalities ($^{[123}\text{I}]$-MIBG SPECT and $^{[18}\text{F}]$-DA PET) and then by non-specific functional imaging modalities ($^{[111}\text{In}]$-DTPA-octreotide SPECT and $^{[18}\text{F}]$-FDG PET) in case specific functional imaging studies are negative. However, the precise place of such nuclear medicine scintigraphy with a well-imaged and biochemically proven tumour remains unclear.

**Differentiating adenomas from metastases**

In a patient with cancer, it is often critical to distinguish between an adenoma and metastases. Adenomas are typically smaller than metastases on unenhanced CT.
imaging (Table 1). Metastases are more heterogeneous than adenomas and their margins are not well defined. However, small metastases may be homogeneous and with well-defined margins. Approximately 70% of adenomas can be identified using CT with no contrast enhancement (Mayo-Smith et al. 2001). The remaining 30% of adenomas are lipid poor and cannot be reliably differentiated from metastases with this technique (Mayo-Smith et al. 2001). Most adenomas have attenuation values lower than metastases on unenhanced CT examinations (Dunnick & Korobkin 2002). With a cut-off attenuation value of 10 HU, sensitivity has been reported to be 71% with a specificity of 98% (Dunnick & Korobkin 2002, Lockhart et al. 2002). On contrast-enhanced CT images, lesions with attenuation values <30–40 HU (taken with a 15-min delay) are almost always adenomas, whereas metastases may show a thick enhancing peripheral rim (Dunnick & Korobkin 2002, Lockhart et al. 2002). Adenomas can be differentiated from metastases with a specificity of 97% using percentage of enhancement washout (Dunnick & Korobkin 2002). More rapid washout of contrast medium is seen in adrenal adenomas when compared with adrenal metastases (Dunnick & Korobkin 2002).

The signal intensity of an adenoma on MRI T2-weighted sequences is usually low, but this finding is not very useful for differentiating adenomas from metastases because there is a 20–30% overlap in the range of signal intensity between them (Dunnick & Korobkin 2002). Chemical shift MRI can differentiate adrenal adenomas from metastases (Dunnick & Korobkin 2002). The signal intensity loss on opposed-phase images compared with in-phase images shows mixed lipid and non-lipid tissue in adenomas, which is absent in metastases (Dunnick & Korobkin 2002). Chemical shift MRI enables the calculation of the adreno-splenic ratio (ASR)=lesion intensity relative to spleen on in-phase images/signal ratio of lesion to spleen on opposed-phase images. An ASR <70% indicates an adenoma with 78% sensitivity and 100% specificity (Lockhart et al. 2002).

FDG PET scanning has been used in several studies to distinguish benign from malignant adrenocortical lesions and >95% accuracy has reported (Becherer et al. 2001), along with excellent sensitivity and specificity (both approaching 100%) for primary and secondary adrenal cortical tumours.

**Differentiating adenomas from carcinomas**

On axial imaging alone, large adrenal masses may be difficult to differentiate from exophytic renal tumours arising from the upper pole (Lockhart et al. 2002). MDCT with accurate multi-planar reformations has effectively solved this problem. Analysis with receiver operated characteristics of >1000 adrenal incidentalomas has pointed to a lesion diameter of 4 cm as a reasonable cut-off to differentiate benign from malignant lesions. Using 4 cm, the sensitivity, specificity and negative predictive value of detecting a malignant lesion is 93, 42, and 98%, specifically. If larger size criteria are used to diagnose malignant masses, the sensitivity falls to 81% for 5 cm and 74% for 6 cm lesions (Mantero et al. 2000). Hence, in order to maintain a good sensitivity for malignant masses, the 4 cm size cut-off has been advocated to select patients for surgery (Bertherat et al. 2002). With increasing size, the probability of malignancy becomes higher (Table 1). For lesions >6 cm, the ratio of benign to malignant tumours is 1:8 (Bertherat et al. 2002). Because size is important in the assessment and management of adrenal lesions, it is important to point out that CT is known to underestimate the size of adrenal tumours (Fajardo et al. 2004). To improve the performance of CT against histological size, a formula has been proposed by Linos (2000). The finding of a unilateral adrenal mass either on CT or MRI with a diameter >4 cm is suggestive of adrenal cortical carcinoma, especially in those patients without signs and symptoms of catecholamine, cortisol or aldosterone excess (Dunnick & Korobkin 2002; Table 1). The presence of necrosis, haemorrhage or calcification leans more to the diagnosis of carcinoma (Rockall et al. 2004). On MRI examination, if the entire lesion loses signal on the out-of-phase images the mass is an adenoma. Adrenal carcinomas have no or only partial loss of signal intensity on out-of-phase images. Nevertheless, the data on adrenal cortical carcinoma and CT or chemical shift MRI are limited, and at present no firm conclusions can be formulated (Dunnick & Korobkin 2002). Some reports indicate that FDG PET has 100% sensitivity and 80–100% specificity for differentiating malignant from benign adrenal masses (Mayo-Smith et al. 2001, Dunnick & Korobkin 2002).

**Differentiating hyperfunctioning from non-functioning lesions**

Anatomical cross-sectional imaging concentrates on differentiating solid adrenal masses into benign adenomas and non-adenomas. It cannot reliably differentiate between functioning and non-functioning adenomas and relies on the biochemical profile (Israel & Krinsky 2003). In ACTH-independent Cushing’s syndrome, adrenal adenomas and carcinomas account
for 92% of the cases. Other rare causes included collision tumours with adenomas and primary pigmented nodular adrenal dysplasia (PPNAD). In PPNAD, uni- or bilateral small (2–5 mm) adrenal nodules have been reported (Rockall et al. 2004). There have also been reports of normal CT scans and a report of myeloid metaplasia of the nodules (with very high lipid content; Courcoutsakis et al. 2004). Older subjects with PPNAD may have macronodules >1 cm. In 70% of patients with ACTH-dependent Cushing’s disease, the adrenal glands are enlarged bilaterally. The adrenal glands are larger in patients with ectopic ACTH source when compared with pituitary-dependent disease (Sohaib et al. 1999). Cortical hyperplasia can be distinguished from focal tumours with sensitivity >95% using CT. In a study of 34 patients with primary hyperaldosteronism (17 due to bilateral adrenal hyperplasia and 17 due to adenomas), CT was shown to detect aldosteronomas with a sensitivity and specificity of 87 and 93% respectively (Lingam et al. 2004). In patients with aldosteronomas, the adrenal glands may be normal, show minimal unilateral adrenal thickening, uni- or bilateral solitary or multiple adenomas (ranging in size from <1 to >1 cm; Young 2003). Nevertheless, most aldosteronomas are unilateral and small (with a median size <2 cm). Usually, they are encapsulated and the remaining adrenal cortex does not show any atrophy. However, some have recommended that, regardless of CT/MRI findings, when localisation of a putative aldosteronoma is attempted all patients should undergo selective adrenal venous sampling (pre- and post-corticotrophin infusion) to precisely locate the tumour (Rossi 2007).

Non-hyperfunctioning adenomas of the adrenal cortex synthesise and secrete hormones like normal adrenal cortical tissue. These lesions show uptake of NP-59, but so does the surrounding normal adrenal tissue (Dunnick & Korobkin 2002). NP-59 scintigraphy can complement biochemical and radiological imaging results to identify abnormal adrenal function in an adenoma (Maurea et al. 2004). It has a high specificity (100%) and reasonable sensitivity (about 70% for tumours >2 cm in diameter) for distinguishing benign functioning adrenal adenomas from other space-occupying adrenal lesions (Maurea et al. 2004). The positive predictive value of NP-59 is 100% for lesions ≥2 cm in diameter. Nevertheless, well-differentiated adrenal cancer may show NP-59 uptake (Gross et al. 2007). Moreover, the scarcity of NP-59, its limited spatial resolution and the prolonged necessary examination time, in light of the results obtained with other modalities, may lead to its eventual abandonment. Because 40–50% of primary adrenal carcinomas are hyperfunctioning and 50–60% are not, it is apparent that further biochemical diagnostic work-up is necessary in cases of doubtful diagnosis (Lockhart et al. 2002).

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

References
Ilias et al.: Imaging of adrenal tumours


