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The indeterminate adrenal mass in patients with cancer

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Abstract

With the increasing use of abdominal cross-sectional imaging, incidental adrenal masses are frequently detected. The commonest clinical question is whether these are benign adenomas or malignant primary or secondary masses. The nature of incidentally detected adrenal masses can be determined with a high degree of accuracy using computed tomography (CT) and magnetic resonance imaging (MRI) as benign adrenal masses such as myelolipomas, lipid-rich adenomas, adrenal cysts and adrenal haemorrhage which have pathognomonic imaging findings. However, there remains a significant overlap between the imaging features of some lipid-poor adenomas and malignant lesions. We review the recent advances in CT, MRI and positron emission tomography (PET) which can be used to distinguish between benign adenomas and malignant lesions of the adrenal gland.

Keywords: *Adenomas; metastases; MRI; CT; PET.*

Introduction

Incidentally detected adrenal masses occur in 2–5% of all abdominal computerized tomography (CT) scans[1,2]. The indications for the CT scans are variable and abdominal pain, non-specific symptoms and hypertension are the most frequent indications[3]. Adrenal masses are also frequently discovered during staging of patients with cancer. Adrenal adenomas are more common in some inherited diseases, including multiple endocrine neoplasia type I, Beckwith–Wiedemann syndrome and the Carney complex. The likelihood of developing an adenoma increases with age. Based on pathological studies, about 6% of patients over 60 years of age harbour an adrenal adenoma[4]. Of these, 80% of incidentally detected adenomas are benign non-functioning adenomas.

The adrenal gland is a relatively frequent site for metastatic disease but even in patients with a known carcinoma of any histology, only 26–36% are metastatic[5]. This incidence of metastatic adrenal lesions increases to 71% if the adrenal mass is larger than 4 cm and demonstrates an increase in size on follow-up imaging within 1 year[6]. The distinction between benign and malignant adrenal masses is usually based on cross-sectional imaging features, scintigraphy and occasionally fine needle aspiration (FNA). Cross-sectional imaging readily characterises benign adrenal masses, such as lipid-rich adenomas, myelolipomas, adrenal cysts, granulomas and adrenal haemorrhage as they have characteristic diagnostic imaging findings such as intra-lesional fat, water or blood. A small minority of adrenal masses elude characterization on cross-sectional imaging and remain indeterminate. These include lipid-poor adenomas, adrenal metastases, adrenal carcinomas and pheochromocytomas. For this group of adrenal masses, the commonest clinical setting is to differentiate between a benign adrenal adenoma and a malignant lesion, particularly a metastasis. This becomes essential in patients undergoing staging for a known carcinoma, as the presence of metastases may contraindicate curative surgery or radiotherapy. Cross-sectional CT and magnetic resonance imaging (MRI) techniques

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are optimised to maximise specificity for adrenal adenomas whilst still maintaining an acceptable sensitivity.

Computed Tomography

Lipid content

Adrenal adenomas are present in 4–6% of the general population[4]. The majority of adenomas have a high intracellular lipid content which lowers their density and attenuation value. If an adrenal mass measures 0 HU or less (threshold attenuation value of 0 HU), the specificity of the mass being an adenoma is 100% but the sensitivity is only an unacceptable 47%. Boland *et al.*[7] performed a meta-analysis of 10 studies demonstrating that if a threshold attenuation value of 10 HU was adopted, the specificity was 98% but the sensitivity increased to 71%. In clinical practice, therefore, 10 HU is the most widely used threshold attenuation value for the diagnosis of an adrenal adenoma.

Lesion size and contour

On non-enhanced CT, other imaging findings that have a higher likelihood of being malignant include lesion size, contour and change in size. Lesions greater than 4 cm in diameter have a higher likelihood to be either metastases or primary adrenal carcinomas[8,9]. However, size alone is a poor discriminator between adenomas and non-adenomas. In a study by Lee *et al.*, using 3.0 cm as the size cut-off, the specificity for adenomas was only 79% and the sensitivity 84%[8].

Although it has been suggested that adenomas have a smooth contour, whilst malignant lesions have an irregular shape, there is a very large overlap between the two groups and shape is therefore not a helpful differentiating feature. Rapid change in size suggests malignancy as adenomas are slow growing lesions.

Contrast washout characteristics

Contrast enhanced CT is acquired after the administration of intravenous contrast medium. CT contrast media contain iodine with a very high density and hence high attenuation value. The contrast medium is usually administered into an antecubital vein and injected at variable rates. The CT images are acquired at changeable time intervals after the administration of contrast and uptake of the contrast media into tissues is termed 'contrast enhancement'. Contrast enhancement is directly proportional to the vascularity of enhancing tissues. The increase in attenuation values of adrenal masses after contrast administration is a direct measurement of their contrast enhancement properties.

On non-contrast enhanced CT, up to 30% of benign adenomas have an attenuation value of greater than 10 HU and are considered 'lipid-poor'[9–11]. Malignant lesions are also lipid poor. Characterisation of adrenal masses using contrast enhanced CT utilises the different physiological perfusion patterns of adenomas and metastases. Adenomas enhance rapidly after contrast administration and also demonstrate a rapid loss of contrast medium – a phenomenon termed contrast washout. Metastases enhance rapidly but demonstrate a slower washout of contrast medium. In a standard abdominal CT obtained for staging patients with cancer, the CT images are acquired 60 s after contrast administration. Attenuation values of adrenal masses obtained 60 s after contrast medium injection show too much overlap between adenomas and malignant lesions to be of clinical value[12]. Adrenal masses with a CT attenuation value measuring less than 30 HU, on delayed images obtained 10–15 min after contrast enhancement, are almost always adenomas[11]. However, the percentage of contrast washout between initial enhancement (at 60 s) and delayed enhancement (at 15 min) can be used to differentiate adenomas from malignant lesions. Measurement of the attenuation value of the mass prior to injection of contrast medium, at 60 s following injection of contrast medium and then again at 10–15 min are made using an electronic cursor. These absolute contrast medium enhancement washout values are only applicable to relatively homogeneous masses without large areas of necrosis or haemorrhage. It has been demonstrated that washout of contrast from adenomas occurs much faster than from metastases[13]. Both lipid-rich and lipid-poor adenomas behave similarly, as this property of adenomas is independent of their lipid content.

The percentage of absolute enhancement washout can be calculated thus:

$$\%\ \text{absolute washout} = \frac{\left(\begin{array}{c}\text{enhanced attenuation value}\\ -\ \text{delayed attenuation value}\end{array}\right)}{\left(\begin{array}{c}\text{enhanced attenuation value}\\ -\ \text{non-enhanced attenuation value}\end{array}\right)} \times 100$$

The enhanced attenuation value is the attenuation value of the mass, measured in Hounsfield units, 60 s after contrast administration. The delayed attenuation value is the attenuation value of the mass, measured in Hounsfield units 15 min after contrast administration.

If the percentage absolute enhancement washout is 60% or higher, this has a sensitivity of 89% and a specificity of 95% for the diagnosis of an adenoma[10] (Fig. 1). However, the measurement of this absolute contrast medium enhancement washout requires an unenhanced image. Frequently, in clinical practice only post contrast images are available. In these patients the percentage 'relative' enhancement washout can be calculated thus:

$$\%\ \text{relative washout} = \frac{\left(\begin{array}{c}\text{enhanced attenuation value}\\ -\ \text{delayed attenuation value}\end{array}\right)}{\text{enhanced attenuation value}} \times 100$$

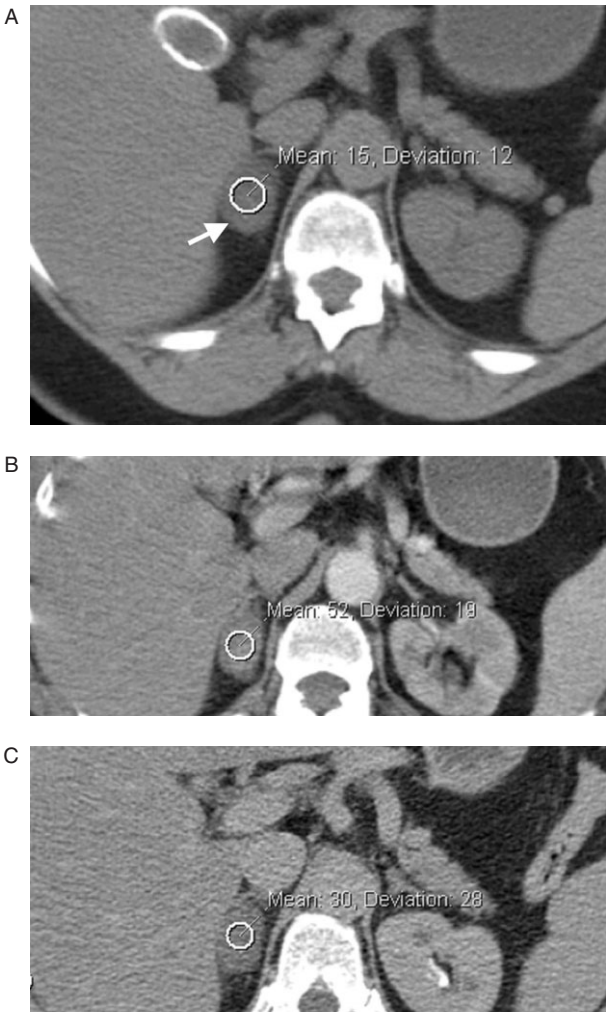

Figure 1 **(a) Non-contrast CT image showing a right adrenal mass with an attenuation value of 15 HU (arrow). The mass is not a typical lipid rich adenoma. (b) Contrast enhanced CT image at 60 s showing the mass with an attenuation value of 52 HU. (c) Delayed CT image 15 min following contrast administration showing the mass has an attenuation value of 30 HU. These contrast enhanced characteristics give an absolute contrast percentage washout of 63% and a relative percentage contrast washout of 42% confirming an adenoma. This mass remained unchanged over 3 years.**

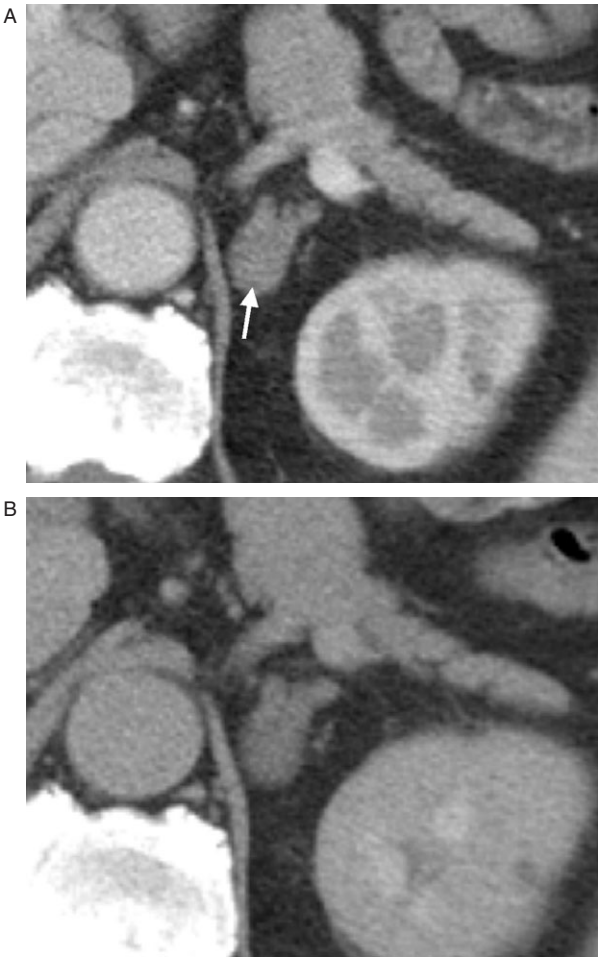

Figure 2 **(a) Contrast enhanced CT 60 s after contrast enhancement showing a left adrenal mass with a attenuation value of 52 HU (arrow). (b) After 15 min the delayed CT attenuation of the mass is 21 HU. This provides a relative percentage contrast washout of 60% in keeping with a benign adrenal adenoma.**

The enhanced and delayed attenuation values are measured as described previously.

At 15 min, if a relative enhancement washout of 40% or higher is achieved, this has a sensitivity of 83% and a specificity of 93% for the diagnosis of an adenoma[10] (Fig. 2). Blake *et al.*[14] proposed the use of enhanced images after 75 s and 10 min following intravenous contrast administration. Using these parameters, an absolute percentage contrast washout of 52% or greater has a sensitivity, specificity, PPV and NPV of 100%, 95%, 89% and 100% respectively for adenomas. A relative percentage contrast washout of 38% or greater has a sensitivity, specificity, PPV and NPV of 100%, 95%, 77% and 100% for the exclusion of malignant lesions. They also emphasised that a non-contrast CT attenuation value of 0 HU or lower is specific for adenomas and supersedes the contrast washout characteristics. Similarly, non-calcified, non-haemorrhagic lesions with a non-contrast attenuation value 43 HU or more should be considered malignant irrespective of their contrast washout characteristics[14].

Phaeochromocytomas may cause confusion as they may be of sufficiently low attenuation (1.8–42 HU) on non-contrast enhanced CT to be mistaken for adenomas and show contrast washout profiles similar to adenomas (absolute washout 40–89% and relative washout 16–83%) (Fig. 3). Phaeochromocytomas, although rare, may present as incidental masses and on CT mimic both adenomas and malignant masses[14,15]. Therefore, a combination of unenhanced CT and enhancement washout

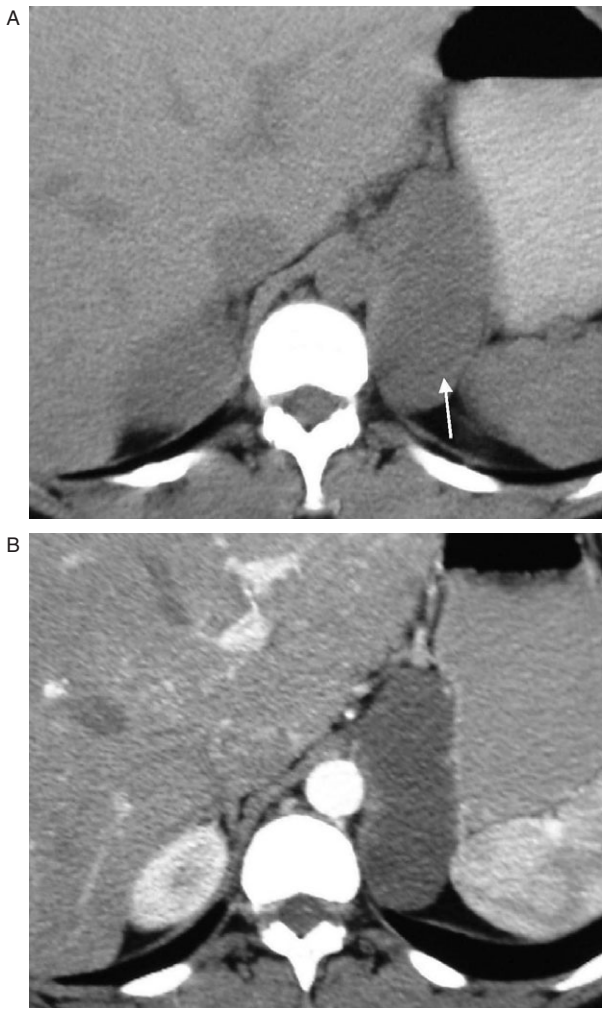

Figure 3 **(a) Non contrast CT image showing a large left adrenal mass (arrow) with low attenuation value of 12 HU. (b) Contrast enhanced CT image in the arterial phase no visual enhancement in the mass with the attenuation value of 30 HU. The patient had elevated urinary and plasma catecholamines and the mass was resected showing an atypical phaeochromocytoma with little post contrast enhancement and low attenuation similar to adenomas.**

characteristics correctly distinguishes between nearly all adrenal adenomas and metastases (Fig. 4).

Histogram analysis method

This technique is applied to non-contrast CT images[16–18]. A region of interest (ROI) cursor is drawn covering at least two-thirds of the adrenal mass. The individual attenuation values of all the pixels in the ROI are plotted against their frequency. This provides the range, mean and number or percentage of pixels within the ROI. The amount of lipid in the mass is proportional to the number of negative pixels (less than 0 HU) within it. The original studies demonstrated 97% of adenomas contain negative pixels. Eighty-five percent have more than 5% negative pixels and 83% have more

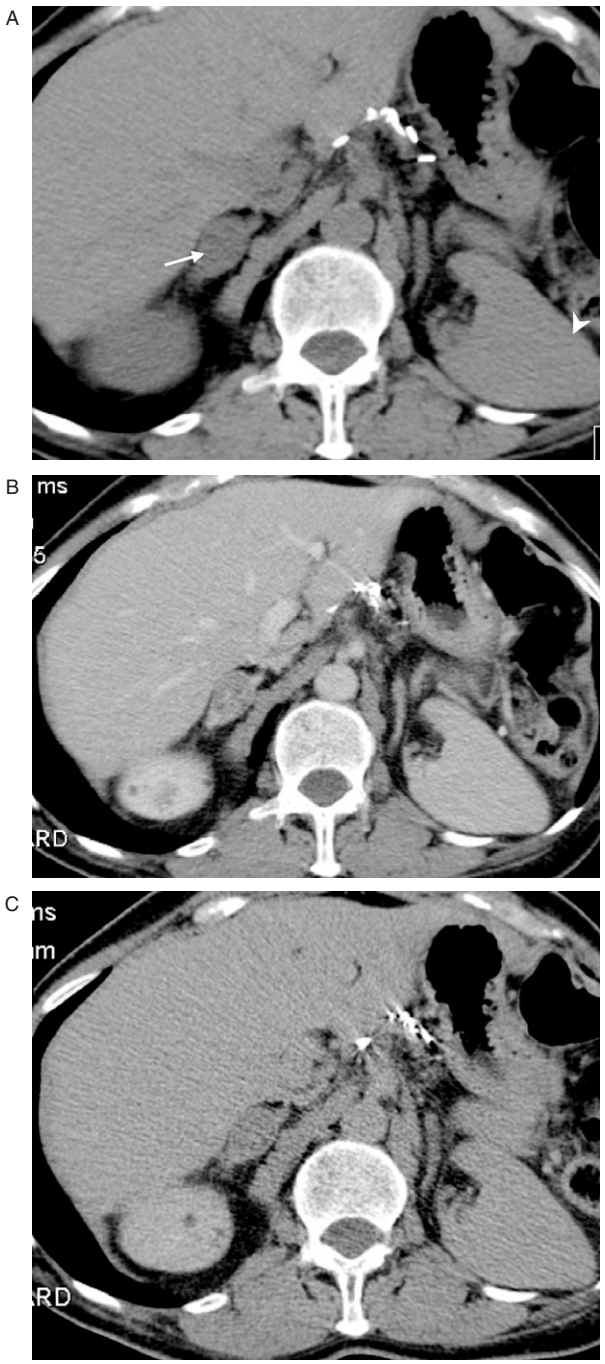

Figure 4 **(a) Non-contrast enhanced CT image demonstrating a right adrenal mass (arrow) and the left renal carcinoma (arrow head). The CT attenuation value of the adrenal mass is 27 HU. (b) 60 s post contrast enhanced CT image demonstrating enhancement of the adrenal mass and the renal carcinoma. The attenuation value of the adrenal mass is 64 HU. (c) 15 min delayed CT image demonstrates the adrenal mass has an attenuation value of 51 HU. This provides an absolute contrast washout percentage of 35%. The adrenal mass has therefore not been shown to be a typical adenoma and is likely to be a metastases in a patient with a contralateral renal carcinoma. This was confirmed at surgery.**

than 10% negative pixels. No metastases had negative pixels[16]. However, recent studies have demonstrated the presence of negative pixels in both adenomas and non-adenomas including metastases, pheochromocytomas, and carcinomas[17,18]. Using a threshold of more than 10% negative pixels within a lesion on non-enhanced CT images provides a diagnosis of an adenoma with a sensitivity between 46 and 71% and specificity between 88% and 100%. On enhanced CT, 10% negative pixel threshold diagnoses an adenoma with a sensitivity of 12% and specificity of 99%. Although specificity for the diagnosis of adenomas on enhanced CT scans with histogram analysis was high using a 10% negative pixel threshold, its low sensitivity precludes clinical usefulness[17]. Similarly, compared to MRI chemical shift imaging with a 20% signal intensity drop out, histogram analysis has a significantly lower sensitivity for adenomas (71% versus 46%)[18]. The poor sensitivity of histogram analysis currently limits its use in clinical practice.

Magnetic resonance imaging

Conventional spin-echo imaging

Early reports were enthusiastic that MRI would allow differentiation of benign from malignant adrenal masses on the basis of signal intensity differences on T2-weighted spin-echo images. Metastases and carcinomas in general have higher fluid contents than adenomas and therefore are of higher signal intensity on T2-weighted images than the surrounding normal adrenal gland. Adenomas are homogeneously iso- or hypo-intense compared with the normal adrenal gland. However, considerable overlap exists between the signal intensities of adenomas and metastases and up to 31% of lesions remain indeterminate[18–21].

Gadolinium-enhanced magnetic resonance imaging

The accuracy of MRI in differentiating benign from malignant masses can be improved following intravenous gadolinium injection on gradient-echo sequences[22–24]. After gadolinium enhancement, 90% of adenomas demonstrate homogenous or ring enhancement while 60% of malignant masses have heterogenous enhancement[23]. On dynamic enhancement, Inan *et al.*[22] demonstrated that the time to reach peak enhancement was the strongest discriminator between adenomas and malignant adrenal masses. Adenomas achieved peak enhancement within 40 s whilst malignant masses achieved peak enhancement at around 65 s. Using 53 s, as the threshold time, the sensitivity and specificity for adenomas is 87.5 and 80% respectively. The value of peak enhancement has no statistical difference between adenomas and metastases[23]. Uniform early enhancement (capillary blush) at 18 s on post gadolinium images has been reported in up to 70% of adenomas, but is rare in other masses[25]. Adenomas also commonly demonstrate a thin rim of enhancement in the late phase of gadolinium and CT contrast enhancement. This 'rim enhancement' is thought to result from rapid contrast washout from the central adenoma with persistent enhancement in the periphery within the adrenal capsule and compressed normal adrenal tissue[26] (Fig. 5). However, as with signal characteristics alone, there is considerable overlap in the characteristics of benign and malignant masses, limiting its clinical applicability in distinguishing adenomatous from malignant masses.

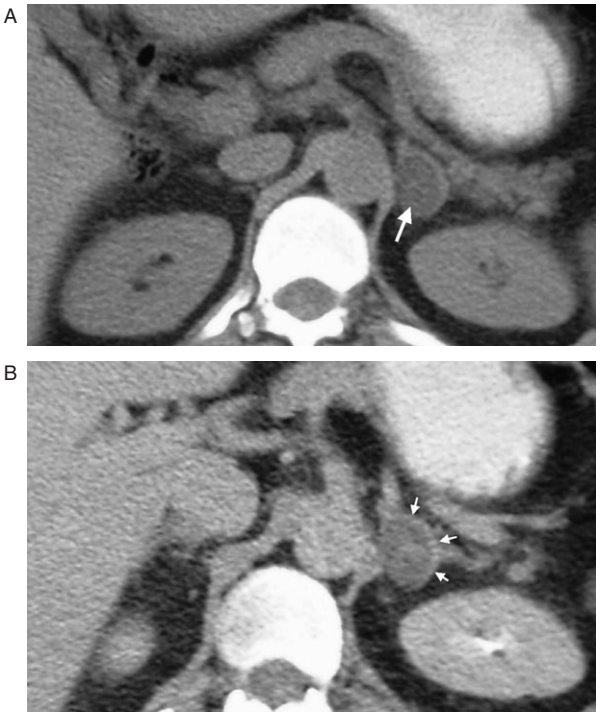

Figure 5 **(a) Non-contrast CT image showing a left sided adenoma (arrow) which has central low attenuation value of 5 HU. (b) Post contrast delayed CT image showing persistent enhancement in the periphery resulting in a 'rim' enhancing appearance (arrows) in the adenoma.**

Chemical-shift imaging

Chemical-shift imaging (CSI) relies on the fact that, within a magnetic field, protons in water molecules oscillate or precess at a slightly different frequency than the protons in lipid molecules. As a result, water and fat protons cycle in and out of phase with respect to one another. By selecting appropriate sequencing parameters, images can be acquired with the protons oscillating in and out of phase. The signal intensity of a pixel on in-phase images is derived from the signal of water plus fat protons if water and fat are present in the same pixel. On out-of-phase sequences, the signal intensity is derived from the difference of the signal intensities of water

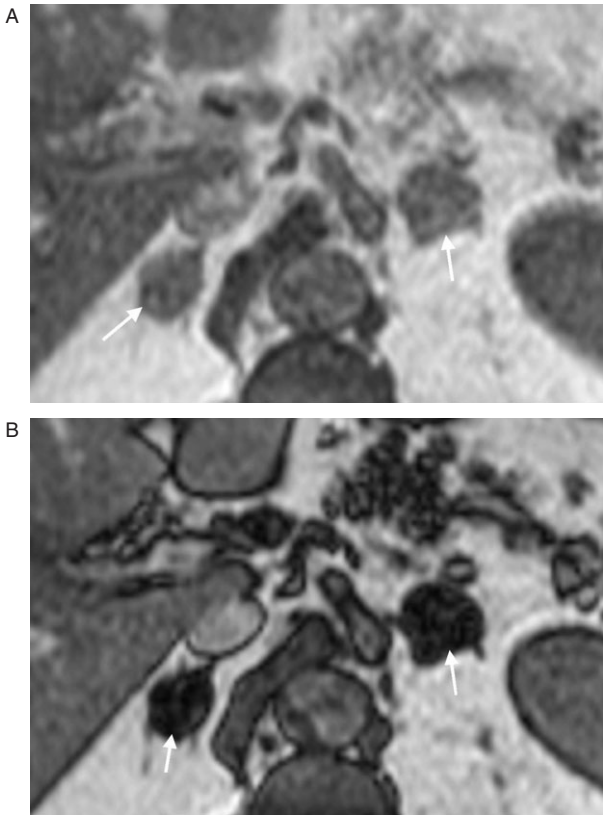

Figure 6 **(a) In-phase gradient echo axial T1-weighted MRI image obtained as part of chemical shift imaging demonstrating bilateral adrenal masses (arrows). (b) Out-of-phase gradient echo axial T1-weighted MRI image obtained as part of chemical shift imaging demonstrating marked visual loss of signal intensity in the bilateral adrenal masses in keeping with benign adrenal adenomas.**

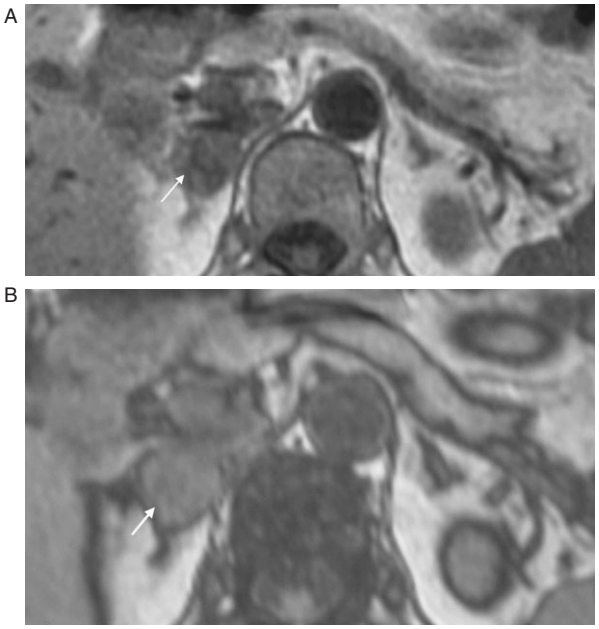

Figure 7 **(a) In-phase gradient echo axial T1-weighted MRI image obtained as part of chemical shift imaging in a patient with breast cancer demonstrating a right adrenal masses (arrows). (b) Out-of-phase gradient echo axial T1-weighted MRI image obtained as part of chemical shift imaging demonstrating no significant visual loss of signal intensity in the right adrenal mass in keeping with a adrenal metastases.**

and fat protons. Therefore, adenomas which contain intracellular lipid lose signal intensity on out-of-phase images compared with in-phase images, whereas malignant lesions and pheochromocytomas which lack intracellular lipid remain unchanged (Figs. 6 and 7).

There are several ways of assessing the degree of loss of signal intensity. Quantitative analysis can be made using the signal intensity index (SII) and the adrenal-splenic ratio (ASR). The ASR is a variety of ratios, essentially comparing the loss of signal in the adrenal mass with that of liver, paraspinal muscle or spleen on in-phase and out-of-phase images. MR signal intensity units are arbitrary therefore comparison of the signal intensity of the adrenal mass to an internal reference provides a more accurate analysis. This comparison is best made with the spleen. Fatty infiltration of the liver (particularly in oncology patients receiving chemotherapy) and iron overload make the liver an unreliable internal standard. Fatty infiltration may also affect skeletal muscle to a lesser extent[27].

To calculate the adrenal-lesion-to-spleen ratio (ASR), regions of interest (ROIs) are used to acquire the signal intensity (SI) within the adrenal mass and the spleen from in-phase and out-of-phase images. The ASR reflects the percentage signal drop-off within the adrenal lesion compared with the spleen and it can be calculated as follows:

$$\mathrm{ASR} = \frac{\left(\begin{array}{c}\text{SI lesion (out-cof-phase)/}\\ \text{SI spleen (out-of-phase)}\end{array}\right)}{\text{SI lesion (in-phase)/SI spleen (in-phase)}} \times 100$$

An ASR ratio of 70 or less has been shown to be 100% specific for adenomas but only 78% sensitive[27,28].

Signal intensity index is calculated as follows:

$$\mathrm{SII} = \frac{\text{SI lesion (inphase)} - \text{SI lesion (out-of-phase)}}{\text{SI lesion(inphase)}} \times 100$$

Adenomas characteristically have signal intensity indices greater than 5% whilst metastases have indices lower than 5%. Signal intensity indices have been shown to discriminate between adenomas and metastases with an accuracy of 100%[29] (Fig. 8). However subsequent studies have used thresholds of between 1 and 30% in identifying adenomas[28,30]. This variability can in part be explained by increasing T1 weighting, increasing TR and increasing flip angles which overestimate the lipid content[31].

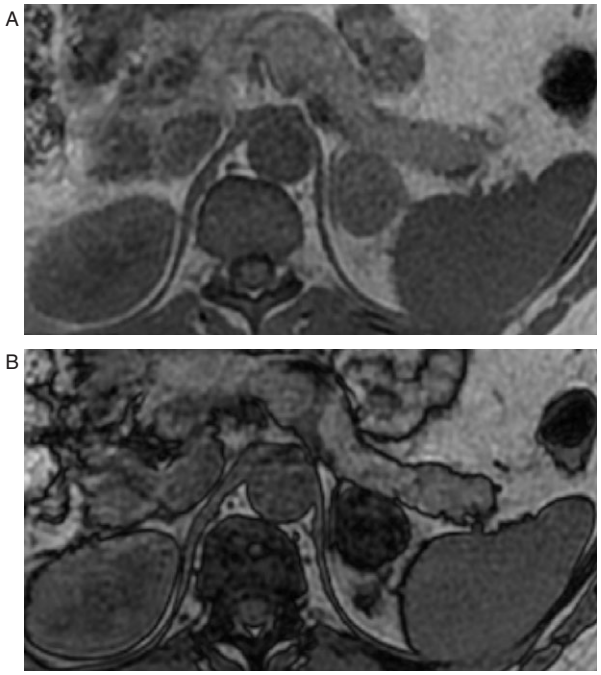

Figure 8 **(a) In-phase gradient echo axial T1-weighted MRI image with signal intensity values of a left adrenal mass (426) and the spleen (365). (b) Out-of-phase gradient echo axial T1-weighted MRI image with signal intensity values of a left adrenal mass (158) and the spleen (363). These values provide an ASR ratio of 36% and a signal intensity index of 63% indicating a benign adrenal adenoma.**

Simple visual assessment of relative signal intensity loss is just as accurate but quantitative methods may be useful in equivocal cases. A signal intensity loss within an adrenal mass on out-of-phase images of greater than 20% is diagnostic of adenomas[28]. The combination of spin-echo signal characteristics, gadolinium enhancement and chemical shift imaging is currently 85–90% accurate in distinguishing between adenomas and non-adenomas[28,29].

There are few direct comparisons between CT and MRI. Evidence from one histological study showed that because both non-contrast CT alone and chemical shift imaging rely upon the same property of adenomas, namely their lipid content, the techniques correlate[30]. Our own work and recent studies suggest that CSI may be more sensitive in the detection of intracellular lipid than CT[22,32,33]. Whereas on non-contrast enhanced CT, up to 30% of adenomas are lipid poor, only 8% demonstrate no loss of signal intensity on CSI[22]. In addition, more lipid poor adenomas can be distinguished from non-adenomas using signal intensity indices. When CSI is applied to lipid poor adenomas with non-contrast CT attenuation values between 10 and 30 HU, CSI detected adenomas with a sensitivity of 89%. Therefore in this group of adrenal masses, CSI detects more adenomas than non-contrast enhanced CT.

More recently, further modification of CSI has been proposed by using subtraction CSI[34]. In this technique the opposed phase images are subtracted from the in-phase images and the subtraction images are assessed quantitatively and qualitatively. Qualitative assessment of the subtraction images is based on assessing the visual signal intensity of the adrenal mass on subtraction images with adenomas demonstrating higher signal intensities than metastases on subtraction images. Quantitatively the mean signal intensities are significantly different with no overlap between adenomas and metastases (213 versus 18) on subtraction images. The reported accuracy in distinguishing adenomas from metastatic tumours is 100% if the cutoff value of the signal intensity selected was 36–106. For quantitative analysis, one advantage of subtraction MRI is the technique uses no calculation of ratios or formulas[34].

Positron Emission Tomography

Whole body positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (^{18}F-FDG) allows the recognition of malignant adrenal lesions. The contribution of ^{18}F-FDG PET has been well evaluated in large studies in relation to lung cancer and is highly accurate in differentiating benign non-inflammatory lesions from malignant disease[35,36]. Using ^{18}F-FDG PET, these studies have shown a 100% sensitivity and specificity for the diagnosis of a malignant adrenal mass when CT or MRI identify enlarged adrenal glands or a focal mass[37]. PET-CT has been recently used to distinguish between adenomas and non-adenomas. Using qualitative visual assessment alone, FDG activity in benign adrenal adenomas is variable ranging from mild, moderate to high FDG uptake. Malignant masses have moderate to high uptake. When compared to the FDG uptake in the liver, adenomas have FDG uptake less than, equal to, or more than the liver in 51%, 38%, and 10% respectively. Non-adenomas were equal to, or more active than liver in 25%, and 75%, respectively. No non-adenomas had activity less than the liver. Adrenal mass activity, visibly less than liver, was more specific for adenoma, whereas adrenal mass activity visibly greater than liver was more specific for malignancy[38,39] (Figs. 9 and 10). However, adrenal masses with moderate FDG uptake remain problematic as they may be adenomas or malignant masses with equal frequency. Quantitative evaluation using standardized uptake values (SUVs) using a cutoff value of 2.68–3.0 separates malignant from benign adrenal masses with a sensitivity, specificity, positive predictive value, and negative predictive value of 98.5%, 92%, 89.3%, 98.9%, respectively. When combined FDG PET and CT data, including contrast

washout characteristics, are analysed, the sensitivity, specificity, positive predictive value, and negative predictive value for malignant adrenal masses improves to 100%, 98%, 97%, 100%, respectively[38–40]. Caoili *et al.*[38] also found SUV values alone unreliable with no significant difference and a considerable overlap between adenomas and non-adenomas[38].

False-positive findings are encountered at integrated PET-CT in approximately 5% of adrenal lesions identified as positive at PET, including adrenal adenomas,

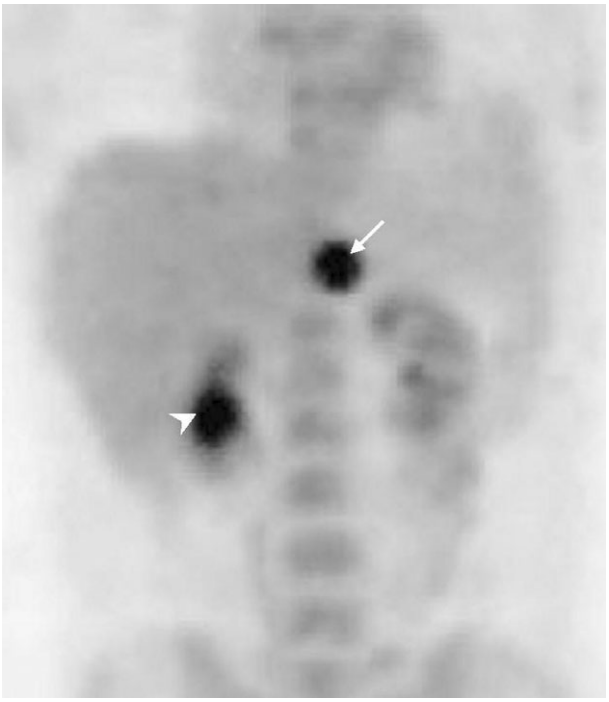

Figure 9 **Coronal static FDG-PET image demonstrating avid tracer uptake in the right kidney at the site of a known renal carcinoma (arrowhead) and in the left adrenal gland (arrow). The left adrenal mass was shown to be a metastases at surgery. The avid tracer uptake, greater than liver, is typical for malignant masses.**

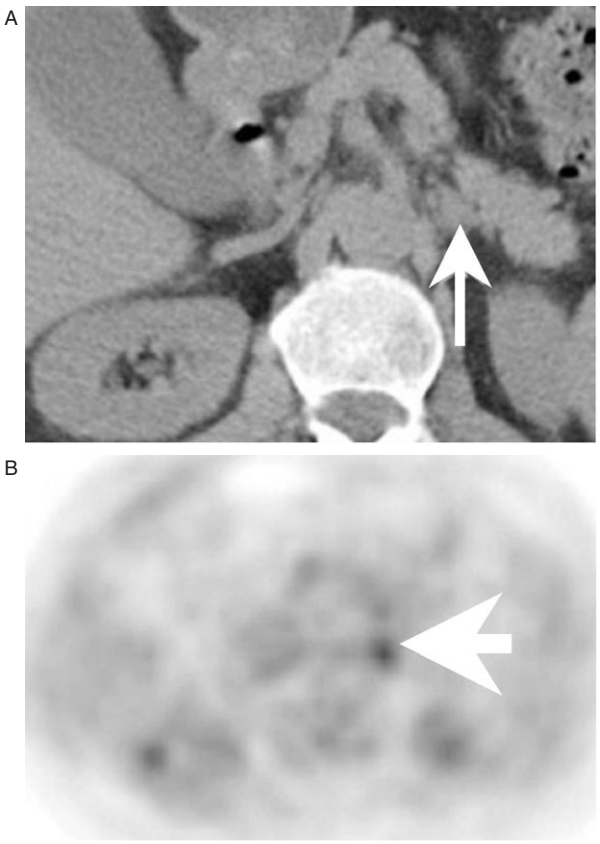

Figure 10 **(a) Non-contrast enhanced CT image of a left adrenal mass with an attenuation value of 18 HU (arrow). The patient was known to have a bronchogenic carcinoma and therefore underwent a pre-operative FDG-PET imaging. (b) Axial FDG-PET image corresponding to the axial CT image in Fig. 9(a) shows moderate tracer uptake in the left adrenal mass (arrow) which may be seen in malignant adrenal masses or benign adrenal adenomas. This mass was histologically proven to be a metastases from the patients bronchogenic carcinoma.**

Table 1 Characteristic features of adrenal masses on imaging

	Lipid rich adenoma	Lipid poor adenoma	Non-adenomas/metastases
Non-contrast CT	Low density, low attenuation value less than 10 HU	Soft tissue density, attenuation value more than 10 HU	Homogenous/heterogeneous masses attenuation values more than 10 HU
Contrast enhanced CT	Early rapid enhancement and rapid washout of contrast media (delay 15 min)		Slower enhancement and slower washout than adenomas
	Greater than 60% absolute washout of contrast		Less than 60% absolute washout of contrast
	Greater than 40% relative washout of contrast		Less than 40% washout of contrast
MRI	Variable T2-weighted signal intensity equal or lower than the surrounding normal adrenal gland		T2-weighted signal intensity greater than surrounding normal adrenal gland
	Commonly have thin rim enhancement		Frequently have heterogeneous contrast enhancement
Chemical shift imaging	Signal loss of more than 20% on the out-of-phase imaging		Signal loss of less than 20% on out-of-phase imaging
	ASR ratio of less than 70%		ASR ratio of more than 70%
^{18}F-FDG PET	No/mild/moderate uptake of FDG PET tracer		Moderate/marked uptake of tracer (PET positive)

phaeochromocytomas, adrenal endothelial cysts, inflammatory and infectious lesions. False-negative findings are seen in adrenal metastases with haemorrhage or necrosis, small (<10 mm) metastatic nodules, and metastases from pulmonary bronchioloalveolar carcinoma or carcinoid tumours[40,41]. The specificity of PET can be improved with [^{11}C]metomidate (MTO), a marker of 11-beta-hydroxylase, as a tracer for adrenocortical tissue. With this tracer, pheochromocytomas, metastases to the adrenal gland, and non-adrenal masses are all MTO uptake negative. However, the tracer has an increased uptake in both adenomas and adreno-cortical carcinomas hence there is an overlap in their appearances[42]. ^{18}F-FDG PET also has the advantage of simultaneously detecting metastases at other sites. It is a useful tool for evaluating masses that are indeterminate on both CT and MRI, substituting for percutaneous biopsy and as a non-invasive investigation, it is safer for the patient (Table 1).

Percutaneous adrenal biopsy

With improved imaging and recent techniques, such as contrast medium washout measurement on CT and CSI in MRI, only a small percentage of adrenal masses, cannot be accurately characterized and require percutaneous biopsy for diagnosis. However, prior to percutaneous biopsy the possibility of a pheochromocytoma must be excluded due to the risk of an adrenal crisis induced by the biopsy. In a study by Harisinghani *et al.*[44] the NPV of adrenal biopsies has been shown to be between 98 and 100%. They evaluated 225 CT guided biopsies where no malignant lesion was missed on the first biopsy. They concluded that a single negative biopsy for malignancy can be regarded as a true negative with no necessity to repeat the biopsy. Percutaneous CT guided adrenal biopsy is a relatively safe procedure in patients with a known extra-adrenal malignancy. Minor complications of adrenal biopsy include abdominal pain, haematuria, nausea and small pneumothoraces. Major complications, generally regarded as those requiring treatment, occur in 2.8–3.6% of cases and include pneumothoraces requiring intervention, and haemorrhage, with isolated reports of adrenal abscesses, pancreatitis and seeding of metastases along the needle track[45,46].

Non-metastatic adrenal enlargement

Diffuse adrenal enlargement without metastatic adrenal involvement and without ectopic adrenocorticotrophic hormone (ACTH) has been demonstrated in patients with malignant disease, including lymphoma. The glands enlarge uniformly, with preservation of the normal shape of the adrenal gland without CT evidence of focal or multifocal masses. It is thought to be caused by adrenal hyperplasia and is not related either to the site of primary disease or the stage of disease[47]. These patients can be shown not to suppress serum cortisol levels on a low dose dexamethasone suppression test, indicating that they have biochemical evidence of Cushing's syndrome. Nevertheless, the ACTH levels are low, indicating that this phenomenon is not a result of ectopic ACTH but is mediated through some other factor[48]. Minor adrenal morphological abnormalities have been observed in patients with lung cancer. Smooth adrenal enlargement and minor nodularity at baseline staging CT is not associated with increased risk of subsequently developing adrenal metastases[49].

Conclusion

Non-hyperfunctioning adrenal masses are common in patients with cancer. Most are lipid-rich adenomas and these can be confirmed on a single unenhanced CT with an attenuation value of less than 10 HU. These adenomas do not require further imaging or follow-up. Lipid-poor lesions include malignant adrenal lesions and lipid-poor adenomas. Most lipid-poor adenomas can be separated from this group by recent advances in CT and MRI as discussed above. As CT is available in most hospitals, lipid-poor adrenal masses should first be evaluated by studying contrast medium washout characteristics. If available MRI, particularly CSI, can replace contrast enhanced CT. The small number of masses that remain indeterminate following these investigations, require percutaneous biopsy or PET/PET-CT imaging. Both these procedures have a very high specificity for malignant disease. However, the limited availability of PET/PET-CT presently limits its clinical use.

References

[1] Glazer HS, Weyman PJ, Sagel SS, Levitt RG, McClennan BL. Non-functioning adrenal masses: incidental discovery on computed tomography. AJR 1982; 139: 81–5.

[2] Bovio S, Cataldi A, Reimondo G, *et al.* Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. J Endocrinol Invest 2006; 29: 298–302.

[3] Arnold DT, Reed JB, Burt K. Evaluation and management of the incidental adrenal mass. Proc (Bayl Univ Med Cent) 2003; 16: 7–12.

[4] Libe R, Bertherat J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. Eur J Endocrinol 2005; 153: 477–87.

[5] Oliver Jr TW, Bernardino ME, Miller JI, Mansour K, Greene D, Davis WA. Isolated adrenal masses in non small-cell bronchogenic carcinoma. Radiology 1984; 153: 217–8.

[6] Frilling A, Tecklenborg K, Weber F, *et al.* Importance of adrenal incidentaloma in patients with a history of malignancy. Surgery 2004; 136: 1289–96.

[7] Boland GW, Lee MJ, Gazelle GS, *et al.* Characterization of adrenal masses using unenhanced CT: an analysis of the CT literature. AJR 1998; 171: 201–4.

[8] Lee MJ, Hahn PF, Papanicolaou N, *et al.* Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. Radiology 1991; 179: 415–8.

[9] Francis IR, Gross MD, Shapiro B, Korobkin M, Quint LE. Integrated imaging of adrenal disease. Radiology 1992; 184: 1–13 (Erratum in: Radiology 1992; 185: 286).

[10] Caoili EM, Korobkin M, Francis IR, Cohan RH, Dunnick NR. Delayed enhanced CT of lipid-poor adrenal adenomas. AJR 2000; 175: 1411–5.
[11] Pena CS, Boland GW, Hahn PF, Lee MJ, Mueller PR. Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. Radiology 2000; 217: 798–802.
[12] Korobkin M, Brodeur FJ, Yutzy GG, *et al.* Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. AJR 1996; 166: 531–6.
[13] Szolar DH, Kammerhuber FH. Adrenal adenomas and nonadenomas: assessment of washout at delayed contrast-enhanced CT. Radiology 1998; 207: 369–75.
[14] Blake MA, Kalra MK, Sweeney AT, *et al.* Distinguishing benign from malignant adrenal masses: multi-detector row CT protocol with 10-minute delay. Radiology 2006; 238: 578–85.
[15] Dunnick NR, Korobkin M. Imaging of adrenal incidentalomas: current status. AJR 2002; 179: 559–68.
[16] Bae KT, Fuangtharnthip P, Prasad SR, Joe BN, Heiken JP. Adrenal masses: CT characterization with histogram analysis method. Radiology 2003; 228: 735–42.
[17] Remer EM, Motta-Ramirez GA, Shepardson LB, Hamrahian AH, Herts BR. CT histogram analysis in pathologically proven adrenal masses. AJR 2006; 187: 191–6.
[18] Jhaveri KS, Wong F, Ghai S, Haider MA. Comparison of CT histogram analysis and chemical shift MRI in the characterization of indeterminate adrenal nodules. AJR 2006; 187: 1303–8.
[19] Reinig JW, Doppman JL, Dwyer AJ, Johnson AR, Knop RH. Adrenal masses differentiated by MR. Radiology 1986; 158: 81–4.
[20] Chang A, Glazer HS, Lee JK, Ling D, Heiken JP. Adrenal gland: MR imaging. Radiology 1987; 163: 123–8.
[21] Glazer GM, Woolsey EJ, Borrello J, *et al.* Adrenal tissue characterization using MR imaging. Radiology 1986; 158: 73–9.
[22] Inan N, Arslan A, Akansel G, Anik Y, Balci NC, Demirci A. Dynamic contrast enhanced MRI in the differential diagnosis of adrenal adenomas and malignant adrenal masses. Eur J Radiol 2007(Apr 25; Epub ahead of print).
[23] Krestin GP, Steinbrich W, Friedmann G. Adrenal masses: evaluation with fast gradient-echo MR imaging and Gd-DTPA-enhanced dynamic studies. Radiology 1989; 171: 675–80.
[24] Semelka RC, Shoenut JP, Lawrence PH, *et al.* Evaluation of adrenal masses with gadolinium enhancement and fat-suppressed MR imaging. J Magn Reson Imaging 1993; 3: 337–43.
[25] Chung JJ, Semelka RC, Martin DR. Adrenal adenomas: characteristic postgadolinium capillary blush on dynamic MR imaging. J Magn Reson Imaging 2001; 13: 242–8.
[26] Ichikawa T, Ohtomo K, Uchiyama G, *et al.* Adrenal adenomas: characteristic hyperintense rim sign on fat-saturated spin-echo MR images. Radiology 1994; 193: 247–50.
[27] Mayo-Smith WW, Lee MJ, McNicholas MM, Hahn PF, Boland GW, Saini S. Characterization of adrenal masses (<5 cm) by use of chemical shift MR imaging: observer performance versus quantitative measures. AJR 1995; 165: 91–5.
[28] Dunnick NR, Korobkin M, Francis I. Adrenal radiology: distinguishing benign from malignant adrenal masses. AJR 1996; 167: 861–7.
[29] Tsushima Y, Ishizaka H, Matsumoto M. Adrenal masses: differentiation with chemical shift, fast low-angle shot MR imaging. Radiology 1993; 186: 705–9.
[30] Korobkin M, Giordano TJ, Brodeur FJ, *et al.* Adrenal adenomas: relationship between histologic lipid and CT and MR findings. Radiology 1996; 200: 743–7.
[31] Al-Hawary MM, Francis IR, Korobkin M. Non-invasive evaluation of the incidentally detected indeterminate adrenal mass. Best Pract Res Clin Endocrinol Metab 2005; 19: 277–92.
[32] Elias D, *et al.* Comparison of chemical shift imaging and non-contrast CT in the diagnosis of adrenal adenomas (abstract). Radiology 2001; 217: 416.
[33] Haider MA, Ghai S, Jhaveri K, Lockwood G. Chemical shift MR imaging of hyperattenuating (>10 HU) adrenal masses: does it still have a role? Radiology 2004; 231: 711–6.
[34] Savci G, Yazici Z, Sahin N, Akgoz S, Tuncel E. Value of chemical shift subtraction MRI in characterization of adrenal masses. AJR 2006; 186: 130–5.
[35] Lowe VJ, Naunheim KS. Current role of positron emission tomography in thoracic oncology. Thorax 1998; 53: 703–12.
[36] Erasmus JJ, McAdams HP, Patz Jr EF. Non-small cell lung cancer: FDG-PET imaging. J Thorac Imaging 1999; 14: 247–56.
[37] Yun M, Kim W, Alnafisi N, Lacorte L, Jang S, Alavi A. ^{18}F-FDG PET in characterizing adrenal lesions detected on CT or MRI. J Nucl Med 2001; 42: 1795–9.
[38] Caoili EM, Korobkin M, Brown RK, Mackie G, Shulkin BL. Differentiating adrenal adenomas from nonadenomas using (18)F-FDG PET/CT quantitative and qualitative evaluation. Acad Radiol 2007; 14: 468–75.
[39] Blake MA, Slattery JM, Kalra MK, *et al.* Adrenal lesions: characterization with fused PET/CT image in patients with proved or suspected malignancy-initial experience. Radiology 2006; 238: 970–7.
[40] Chong S, Lee KS, Kim HY, *et al.* Integrated PET-CT for the characterization of adrenal gland lesions in cancer patients: diagnostic efficacy and interpretation pitfalls. Radiographics 2006; 26: 1811–24.
[41] Maurea S, Mainolfi C, Bazzicalupo L, *et al.* Imaging of adrenal tumors using FDG PET: comparison of benign and malignant lesions. AJR 1999; 173: 25–9.
[42] Hennings J, Lindhe O, Bergstrom M, Langstrom B, Sundin A, Hellman P. [^{11}C]metomidate positron emission tomography of adrenocortical tumors in correlation with histopathological findings. J Clin Endocrinol Metab 2006; 91: 1410–4.
[43] Metser U, Miller E, Lerman H, Lievshitz G, Avital S, Even-Sapir E. ^{18}F-FDG PET/CT in the evaluation of adrenal masses. J Nucl Med 2006; 47: 32–7.
[44] Harisinghani MG, Maher MM, Hahn PF, *et al.* Predictive value of benign percutaneous adrenal biopsies in oncology patients. Clin Radiol 2002; 57: 898–901.
[45] Welch TJ, Sheedy 2nd PF, Stephens DH, Johnson CM, Swensen SJ. Percutaneous adrenal biopsy: review of a 10-year experience. Radiology 1994; 193: 341–4.
[46] Mody MK, Kazerooni EA, Korobkin M. Percutaneous CT-guided biopsy of adrenal masses: immediate and delayed complications. J Comput Assist Tomogr 1995; 19: 434–9.
[47] Vincent JM, Morrison ID, Armstrong P, Reznek RH. Computed tomography of diffuse, non-metastatic enlargement of the adrenal glands in patients with malignant disease. Clin Radiol 1994; 49: 456–60.
[48] Jenkins PJ, Sohaib SA, Trainer PJ, Lister TA, Besser GM, Reznek R. Adrenal enlargement and failure of suppression of circulating cortisol by dexamethasone in patients with malignancy. Br J Cancer 1999; 80: 1815–9.
[49] Benitah N, Yeh BM, Qayyum A, Williams G, Breiman RS, Coakley FV. Minor morphologic abnormalities of adrenal glands at CT: prognostic importance in patients with lung cancer. Radiology 2005; 235: 517–22.