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REVIEW

The indeterminate adrenal lesion

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Abstract

With the increasing use of abdominal cross-sectional imaging, incidental adrenal masses are being detected more often. The important clinical question is whether these lesions are benign adenomas or malignant primary or secondary masses. Benign adrenal masses such as lipid-rich adenomas, myelolipomas, adrenal cysts and adrenal haemorrhage have pathognomonic cross-sectional imaging appearances. However, there remains a significant overlap between imaging features of some lipid-poor adenomas and malignant lesions. 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) alone. Positron emission tomography (PET) is also increasingly used in clinical practice in characterizing incidentally detected lesions. We review the performance of the established and new techniques in CT, MRI and PET that can be used to distinguish benign adenomas and malignant lesions of the adrenal gland.

Keywords: *Adenomas; metastases; magnetic resonance imaging (MRI); computed tomography (CT); positron emission tomography (PET).*

Introduction

Incidentally detected adrenal masses in patients with no known malignancy occur in 5% of all abdominal computed tomography (CT) examinations[1–3]. The indications for the CT are variable, with abdominal pain and non-specific symptoms as the most frequent indications[3]. Adrenal masses are also frequently discovered during imaging performed for staging of patients with cancer. The incidence of adrenal masses increases to 9–13% in patients with a known underlying malignancy[1,2]. Adrenal adenomas are more common in some inherited diseases, including multiple endocrine neoplasia type I, Beckwith–Weidman 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 are benign non-functioning adenomas. The adrenal gland is a relatively frequent site for metastatic disease but even in patients with a known carcinoma, only 26–36% of adrenal masses 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 including positron emission tomography (PET) and occasionally fine-needle aspiration (FNA). Cross-sectional imaging readily characterizes benign adrenal masses, such as lipid-rich adenomas, myelolipomas, adrenal cysts, and adrenal haemorrhage as they have characteristic diagnostic imaging features such as the presence of lipid, intra-lesional fat, water or blood (Figs. 1–3). Chronic granulomas when completely calcified in chronic states may be characterized but in the acute phase of infections such as tuberculosis and histoplasmosis, the masses cannot be distinguished from other

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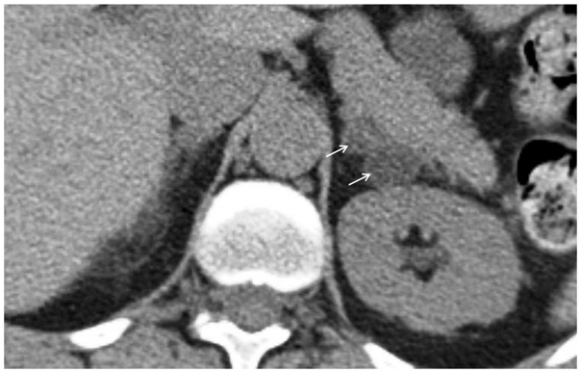

Figure 1 **Non-contrast-enhanced CT. There are 2 left adrenal masses (arrows) with attenuation values of 0 HU and −6 HU in keeping with benign adrenal adenomas. The patient has remained under CT surveillance and the adenomas remain unchanged after 2 years.**

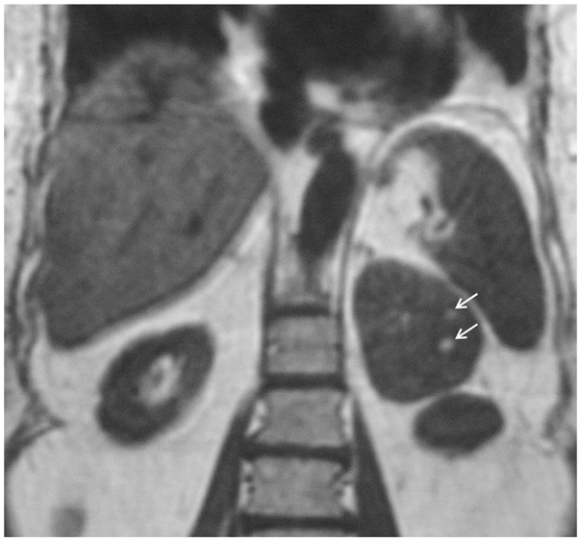

Figure 2 **Coronal T1-weighted image demonstrating a large left adrenal mass. There are small pockets of high T1 signal intensity in the mass in keeping with fat (arrows). The adrenal mass was resected and the pathological specimen confirmed a myelolipoma with scant amounts of macroscopic fat.**

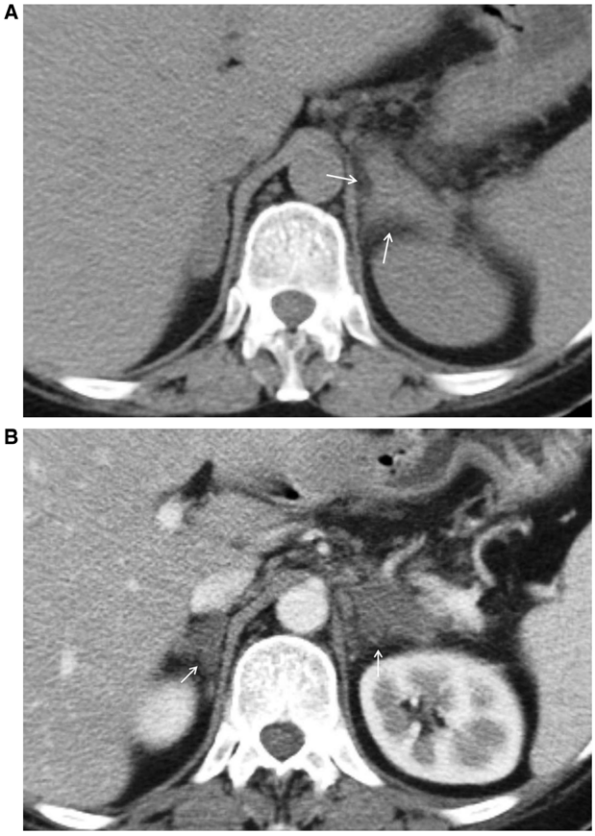

Figure 3 **(A) Non-contrast-enhanced CT in a 35-year-old woman who developed unexplained hypotension following minor abdominal surgery. The CT scan shows bilateral adrenal enlargement with surrounding peri-adrenal diffuse soft tissue (arrows). The pre-procedural CT (not illustrated) showed normal adrenal glands. (B) Contrast-enhanced CT obtained 60 s following administration of intravenous contrast. Both adrenal glands show no focal mass or enhancement and the appearances in the clinical context are consistent with bilateral adrenal haemorrhage.**

malignant lesions. 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 phaeochromocytomas (Figs. 4–6). It is clearly important to make the distinction between these lesions, even in patients undergoing staging for a known carcinoma, as the presence of metastases contraindicates radical curative surgery or radiotherapy. CT and magnetic resonance imaging (MRI) techniques are optimized to maximize specificity for benign adrenal adenomas whilst still maintaining an acceptable sensitivity. Conversely, PET/CT techniques are optimized for the detection of malignant disease. A variety of combinations of imaging techniques have been proposed in the literature for the characterization of adrenal masses and these are discussed in the following review.

Computed tomography

Lesion size and contour

On non-enhanced CT, imaging findings that suggest a higher likelihood of malignancy include a large lesion size, irregular contour, heterogeneous appearance and a temporal increase in size. Lesions greater than 4 cm in diameter have a higher likelihood to be either metastases or primary adrenal carcinomas[7]. New guidelines published by the American College of Radiology

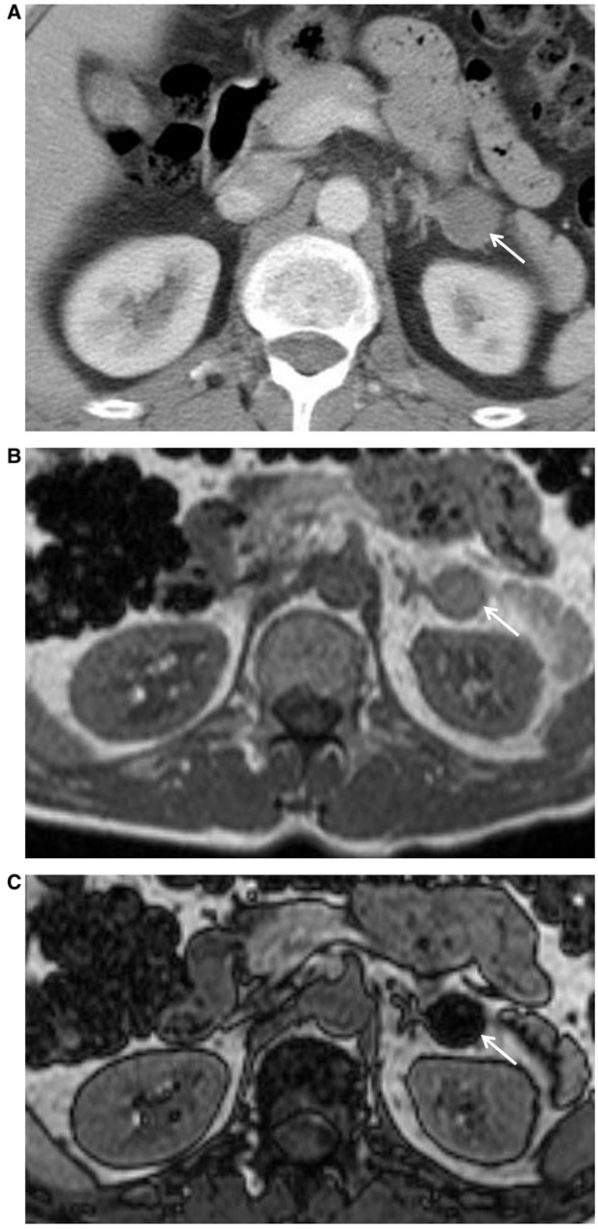

Figure 4 **(A) Non-contrast-enhanced CT demonstrating a left adrenal mass (arrow) with an attenuation value of 15 HU. (B) Axial in-phase image obtained as part of chemical shift imaging demonstrating the left adrenal mass with intermediate signal intensity (arrow). (C) Axial out-of-phase image obtained as part of chemical shift imaging shows marked loss of signal intensity, making the adrenal mass a benign adrenal adenoma.**

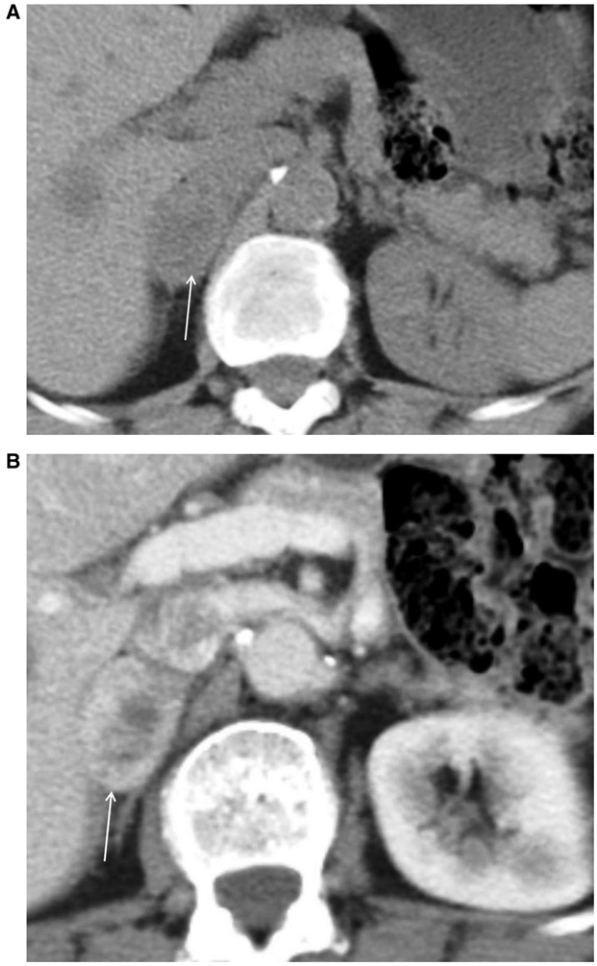

Figure 5 **(A) Non-contrast-enhanced CT in a 45-year-old man with refractile hypertension. The CT shows a large heterogeneous right adrenal mass with an attenuation value of 15 HU. (B) Contrast-enhanced CT obtained 60 s following administration of intravenous contrast. The right adrenal mass demonstrates heterogeneous enhancement with central necrosis and histological confirmation of a phaeochromocytoma was obtained.**

Incidentally Detected Abdominal and Pelvic Lesions Committee suggest that for lesions >4 cm in size that do not have typical imaging features such as those seen in myelolipomas, adenomas, cysts, etc., adrenal resection without any other additional imaging workup should be considered once a phaeochromocytoma has been biochemically excluded[8]. Although it has been suggested that adenomas have a smooth contour and malignant lesions have an irregular shape, there is a very large overlap between the 2 groups and shape is therefore not a helpful differentiating feature. Rapid change in size does raise the suspicion of malignancy as adenomas are slow-growing lesions. Small size, the absence of an irregular contour and a homogeneous appearance combined can occasionally be useful in terms of determining a follow-up protocol.

Lipid content

The majority of adenomas have a high intracellular lipid content, which lowers their non-contrast CT density and attenuation value. If an adrenal mass measures 0 HU or less, the specificity of the mass being an adenoma is 100% but the sensitivity is only an unacceptable 47%. Boland *et al.*[9] performed a meta-analysis of 10 studies

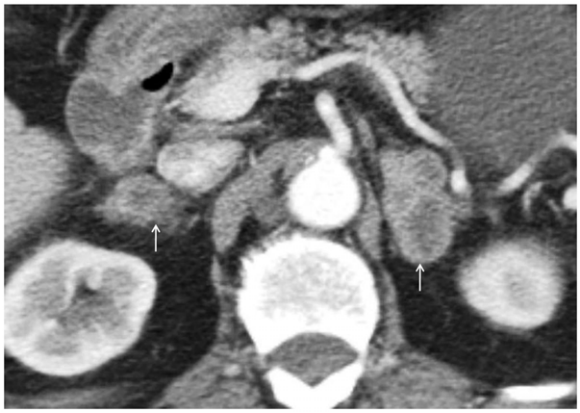

Figure 6 **Contrast-enhanced CT obtained 60 s following administration of intravenous contrast in a patient with small cell carcinoma of the lung. There are bilateral heterogeneous adrenal metastases (arrows) confirmed on PET-CT.**

demonstrating that if a threshold attenuation value of 10 HU was adopted, the specificity was 98% and the sensitivity increased to 71%. In clinical practice, therefore, 10 HU is the most widely used threshold attenuation value for the diagnosis of a lipid-rich adrenal adenoma. In a recent study by Song *et al.*[3] on 973 consecutive patients with 1049 incidental adrenal masses, adenomas accounted for 75% of incidental masses of which 78% were lipid-rich adenomas, with a non-contrast CT attenuation value of less than 10 HU. Therefore in patients with no known malignancy, 66% of adrenal lesions are lipid-rich adenomas. By using a threshold of 10 HU, the sensitivity and specificity for the detection of an adenoma at non-enhanced CT is reported as 89% and 100%, respectively[10]. Therefore these lesions can be fully characterized on non-contrast CT alone and require no further confirmatory imaging. Lesions with a non-contrast CT attenuation greater than 10 HU require further evaluation with either contrast washout CT, MRI or scintigraphy.

Contrast enhancement and contrast washout characteristics

On unenhanced CT, up to 12–30% of benign adenomas have an attenuation value of greater than 10 HU and are considered lipid poor[9–11]. Malignant lesions and phaeochromocytomas are usually lipid poor although clear cell renal cell carcinoma metastasis, adrenal carcinoma and some pheochromocytomas may be lipid rich[12]. Characterization of adrenal masses using contrast-enhanced CT utilizes the unique physiological perfusion patterns of adenomas. Adenomas enhance rapidly after contrast administration and demonstrate a rapid loss of contrast medium, a phenomenon termed contrast enhancement washout. Malignant lesions and phaeochromocytomas usually enhance rapidly but demonstrate a slower washout of contrast medium. Rare phaeochromocytomas have been described with washout characteristics mimicking adenomas[13].

Absolute 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[13]. However, if the delay is timed at 10 min after contrast enhancement, adrenal masses with a CT attenuation value of less than 30 HU have been shown to be adenomas with a sensitivity of 80% and a specificity of 100% respectively[10].

The combination of an unenhanced CT and measurement of the difference in contrast enhancement washout characteristics between adenomas and malignant lesions has been shown to be a more consistent and reliable technique[14–17]. Measurement of the attenuation values of the mass prior to injection of contrast medium, at 60 s following injection of contrast medium and then again at 15 min are made using an electronic cursor that encompasses at least 50% of the mass. These contrast medium enhancement washout values are only applicable to relatively homogeneous masses without large areas of necrosis or haemorrhage. Both lipid-rich and lipid-poor adenomas behave similarly, as this property of adenomas is independent of their lipid content. The percentage of absolute contrast enhancement washout (ACEW) can be calculated thus: % ACEW=[(contrast-enhanced CT attenuation at 60 s − delayed CT attenuation)/(CT attenuation at 60 s − non-contrast CT attenuation)] × 100. The contrast-enhanced CT value is the attenuation value of the mass, measured in Hounsfield units, 60 s after commencement of intravenous contrast administration. The delayed attenuation value is the attenuation value of the mass, measured in Hounsfield units 10 or15 min after commencement of contrast administration. Non-contrast CT attenuation is the attenuation value of the mass prior to administration of contrast media. If a 15 min delayed protocol is used, an ACEW of 60% or higher has a sensitivity of 86–88% and a specificity of 92–96% for the diagnosis of an adenoma[16,17]. If a 10 min delayed protocol is used, a sensitivity of 100% and a specificity of 98% is obtained for a threshold ACEW value of 52%[15].

However, the measurement of this absolute contrast medium enhancement washout requires an unenhanced image. Frequently, in clinical practice, only post contrast and delayed images are available. In these patients the percentage relative contrast enhancement washout (RCEW) can be calculated thus: % RCEW=[(contrast-enhanced CT attenuation at 60 s − delayed CT attenuation)/CT attenuation at 60 s)] × 100. The enhanced and delayed attenuation values are measured as described previously. If a 10 min delayed protocol is used, a relative enhancement washout of 50% or higher has sensitivity and specificity of 98% and 100% for the detection of adenoma[10]. After 15 min, if a relative enhancement washout of 40% or higher is achieved, this has a

sensitivity of 96% and a specificity of 100% for the diagnosis of an adenoma[17].

Blake *et al.*[14] 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 of 43 HU or more should be considered malignant irrespective of their contrast washout characteristics[14]. Phaeochromocytomas, although rare, may present as incidental masses and on CT mimic both adenomas and malignant masses[12,17]. However, a combination of unenhanced CT, absolute enhanced values and contrast enhancement washout characteristics correctly distinguishes nearly all adrenal adenomas from malignant masses.

Histogram analysis method

Although contrast enhancement washout criteria have a high sensitivity and specificity for adenomas, the technique is somewhat cumbersome requiring contrast administration and delayed images up to 15 min after contrast enhancement. Non-contrast CT alone, when using a threshold of 10 HU or less has 100% specificity but a low sensitivity of between 66% and 75% for adenomas. CT histogram analysis is a technique that has been applied to both unenhanced and contrast-enhanced images[18–22]. A region of interest (ROI) cursor is drawn covering at least two-thirds of the adrenal mass, excluding areas of necrosis. The individual attenuation values of all the pixels in the ROI are plotted against their frequency. This provides the mean, range and number or percentage of pixel values within the ROI (Fig. 7). 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 than 10% negative pixels. No metastases had negative pixels[18].

However, subsequent studies have shown some variability in the performance of histogram analysis, reporting negative pixels in both adenomas and non-adenomas including metastases, pheochromocytomas and carcinomas[19,20]. Earlier studies using a 10% or more negative pixel threshold in non-contrast-enhanced CT images maintained good specificity, close to 100%, for the diagnosis of an adenoma but reported very poor sensitivities of between 70 and 83%[19,20]. More recent studies using the same criteria, report improved sensitivities of 85–91% whilst maintaining 100% specificity for adenomas[21,22]. CT histogram analysis on non-contrast-enhanced images can therefore be used as an adjunct to the CT attenuation values, as the combination of CT attenuation value <10 HU or $>10\%$ negative pixel content would correctly identify 91% of adenomas compared with 66% using CT attenuation values alone[11,21,22].

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[20]. Similarly, compared with MRI chemical shift imaging with a 20% signal intensity drop out, histogram analysis has a significantly lower sensitivity for adenomas (71% versus 46%)[20].

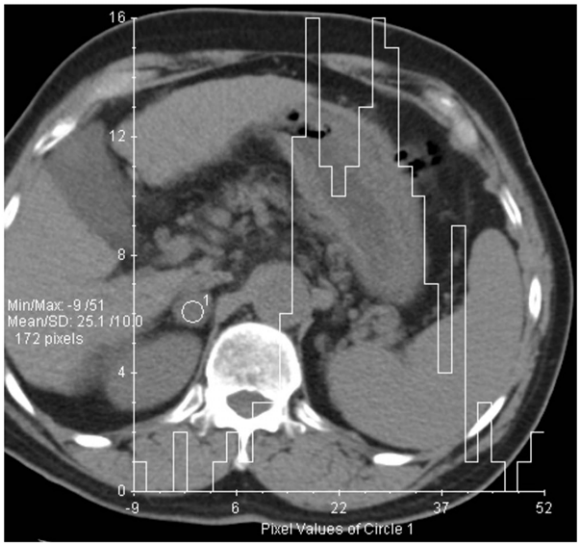

Figure 7 **Non-contrast-enhanced CT of a lipid-poor adenoma with a mean CT attenuation value of 25 HU. The overlaid histogram shows the adenoma with the range of pixels within the mass ranging from −9 to 51 HU. Five percent of pixels have a negative pixel value in keeping with an adenoma.**

On current assessment of the literature, the best clinical application of histogram analysis is as an adjunct to non-contrast CT where it can improve the sensitivity to almost 90% whilst maintaining a high specificity for adenomas. Nevertheless, this methodology is very dependent on the scanner and scanning technique and is not widely used in daily clinical practice.

Magnetic resonance imaging

Conventional spin-echo imaging

Early reports were enthusiastic that MRI would allow differentiation of benign and malignant adrenal masses on the basis of signal intensity differences on T2-weighted spin-echo images. Metastases and carcinomas in general have higher fluid content 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[23–25].

Gadolinium-enhanced magnetic resonance imaging

The accuracy of MRI in differentiating benign from malignant masses can be improved by using intravenous gadolinium injection and T1-weighted gradient-echo sequences[26–28]. After gadolinium enhancement, 90% of adenomas demonstrate homogenous or ring enhancement while 60% of malignant masses have heterogeneous enhancement[27]. On MRI, adenomas again show the early peak enhancement seen on CT. On dynamic enhancement, Inan *et al.*[26] showed that 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[26]. 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[29–30]. However, as with signal characteristics alone, there is considerable overlap in the enhancement characteristics of benign and malignant masses, limiting its clinical applicability in distinguishing adenomas from malignant masses.

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, separate 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 where 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 and fat protons. Therefore, adenomas that contain intracellular lipid lose signal intensity on out-of-phase images compared with in-phase images, whereas malignant lesions and pheochromocytomas that lack intracellular lipid remain unchanged. Simple visual assessment of relative signal intensity loss is accurate in most cases but quantitative methods may be useful in equivocal cases.

There are several ways of assessing the degree of loss of signal intensity. Quantitative analysis can be made using the adrenal/splenic ratio (ASR) and signal intensity index (SII). MR signal intensity units are arbitrary units and therefore comparison of signal intensity of the adrenal mass to an internal reference provides a more accurate analysis than evaluation of 2 values from the same organ. A variety of ratios comparing the loss of signal intensity in the adrenal mass with that of the liver, paraspinal muscle or spleen on in-phase and out-of-phase images have been used. 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[31]. To calculate the ASR, 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: $ASR = [(SI\ adrenal\ lesion\ out\ of\ phase/SI\ spleen\ out\ of\ phase)/(SI\ adrenal\ lesion\ in\ phase/SI\ spleen\ in\ phase)] \times 100$. An ASR ratio of 70 or less has been shown to be 100% specific for adenomas but only 78% sensitive[31,32].

The SII uses the same characteristics of the adrenal mass on both in- and out-of-phase imaging and can be calculated as follows: $SII = [(lesion\ SI\ in\text{-}phase\ imaging - lesion\ SI\ out\text{-}of\text{-}phase\ imaging)/lesion\ SI\ in\text{-}phase\ imaging] \times 100$. SIIs have been shown to discriminate between adenomas and metastases with an accuracy of 100%[33]. Adenomas characteristically have signal intensity indices greater than 5% whilst metastases have indices lower than 5%. However, subsequent studies have used thresholds of between 1% and 30% in identifying adenomas[32,34]. This variability can be partly explained by the difference in imaging parameters including T1 weighting, repetition time, and flip angles that can affect the quantification of lipid content[35]. Individual centres need to determine which threshold to use depending on the imaging parameters employed.

There is growing evidence that the SII is more reliable than the ASR in distinguishing adenomas from non-adenomas. The combination of spin-echo signal characteristics, gadolinium enhancement and CSI is currently 85–90% accurate in distinguishing between adenomas and non-adenomas[32,33]. There are few direct comparisons between CT and MRI. Evidence from one histological study showed that because both non-contrast CT alone and CSI rely upon the same property of adenomas, namely their lipid content, the techniques correlate[34]. Recent studies suggest that CSI may be more sensitive in the detection of intracellular lipid than CT[35–37]. Whereas on non-contrast-enhanced CT, up to 30% of adenomas are lipid poor, only 8% demonstrate no loss of signal intensity on CSI[36]. In addition, more lipid-poor adenomas can be distinguished from non-adenomas using signal intensity indices without the use of intravenous contrast media. 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[38]. In this technique the out-of-phase images are subtracted from the in-phase images and the subtracted images are assessed either quantitatively or qualitatively. Qualitative assessment of the subtracted images is based on assessing the visual signal intensity of the adrenal mass with adenomas demonstrating higher signal intensities than metastases on subtracted images. Quantitatively the mean signal intensity from an ROI in the subtracted image is obtained. In a study of 35 patients with 42 adrenal masses, no overlap between adenomas and metastases was identified. The reported accuracy was 100% if the cut-off values of the subtracted signal intensities selected were above 106 for adenomas and below 36 for metastases. One advantage of subtraction MRI is that the technique uses no calculation of ratios or formulas[38]. This technique can be used in equivocal cases to further improve diagnostic accuracy in distinguishing adenomas from non-adenomas.

Positron emission tomography

Whole-body PET with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) improves 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 adrenal benign non-inflammatory lesions from malignant disease[39,40]. Using [^{18}F]FDG-PET, these earlier studies showed a 100% sensitivity and specificity for the diagnosis of a malignant adrenal mass in patients with an adrenal mass detected on CT or MRI[41]. Larger more recent studies confirm the high sensitivity of PET/CT in detecting malignant lesions but the specificity is lower, ranging between 87 and 97%. This loss of specificity is attributable to a small number of adenomas and other benign lesions that mimic malignant lesions[42–43].

To distinguish between adenomas and non-adenomas, qualitative visual assessment alone of FDG activity in benign adrenal adenomas is variable ranging from mild, moderate to high FDG uptake. Malignant masses have moderate to high uptake (Fig. 8). When compared with FDG uptake in the liver, adenomas have been shown to have FDG uptake less than, equal to, or more than the liver in 51%, 38%, and 10%, respectively (Figs. 9 and 10). Non-adenomas have FDG uptake equal to or more than the liver in 25% and 75%, respectively. No non-adenomas

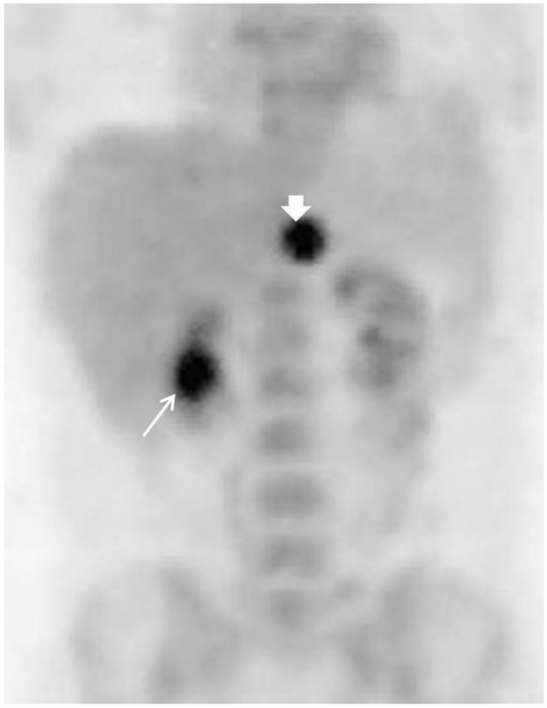

Figure 8 **Coronal PET-scintigraphy MIP image in a patient with a right renal cell carcinoma (arrow) and a left adrenal metastasis (block arrow).**

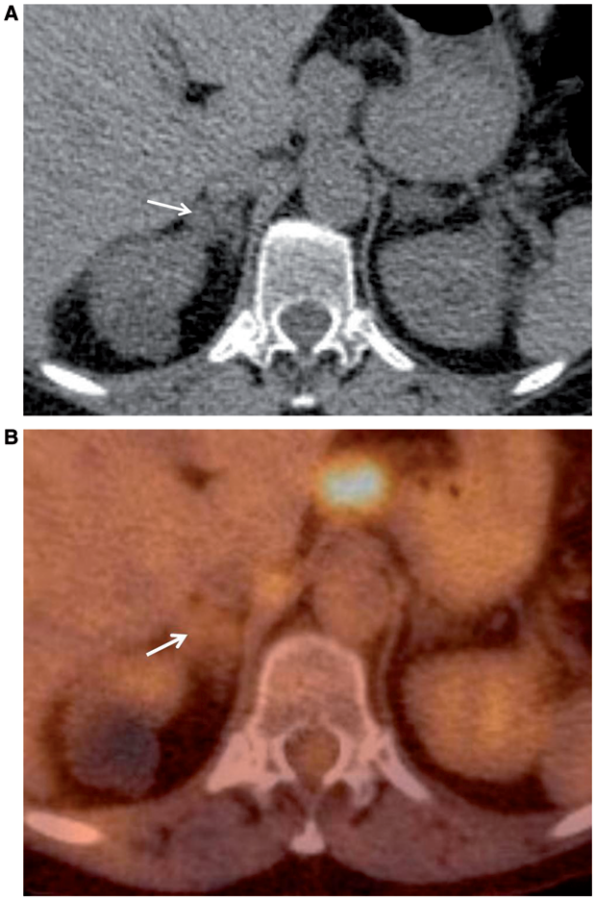

Figure 9 **(A) Non-contrast-enhanced CT in a patient undergoing a restaging CT for follicular lymphoma. A right adrenal mass is seen (arrow) with an attenuation value of in keeping with a lipid-rich adenoma. (B) Fused axial PET-CT image demonstrating [^{18}F]FDG uptake in the adrenal adenoma equivalent to some portions of the liver (arrow).**

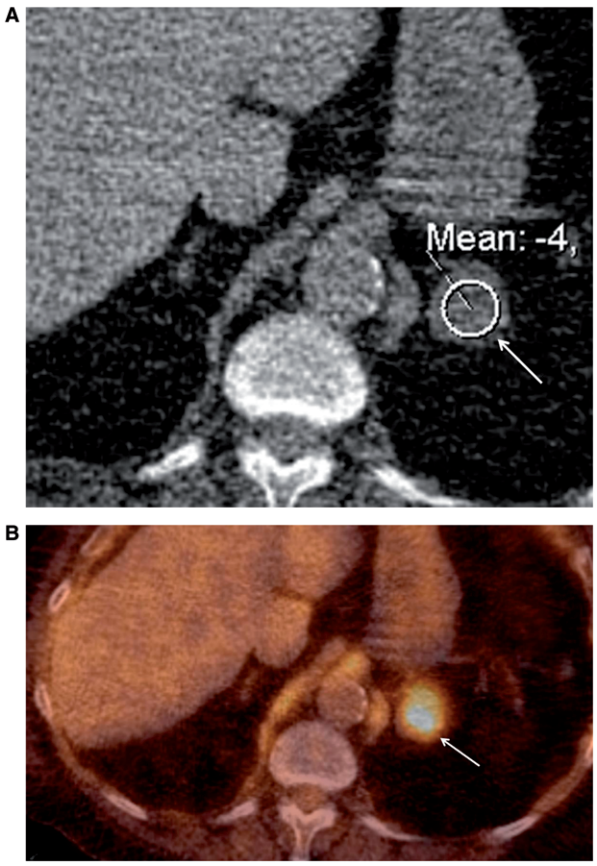

Figure 10 **(A) Non-contrast-enhanced CT acquired as part of an [^{18}F]FDG-PET/CT study in a patient undergoing staging for non-Hodgkin lymphoma. A left adrenal mass is present with an attenuation value of −4 HU in keeping with a benign lipid-rich adrenal adenoma (arrow). (B) Fused axial PET/CT image demonstrating significantly higher [^{18}F]FDG uptake in the adrenal adenoma compared with the liver (arrow). The absolute SUV of the adrenal adenoma was 6.**

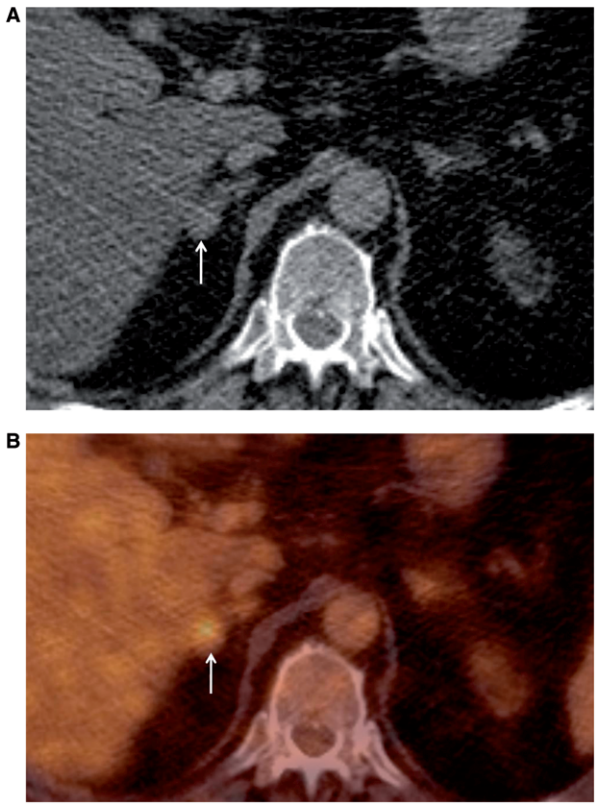

Figure 11 **(A) Non-contrast-enhanced CT acquired as part of an [^{18}F]FDG-PET/CT study in a patient undergoing staging for colorectal carcinoma. A small right adrenal mass is seen with an attenuation value of 7 HU in keeping with a lipid-rich adrenal adenoma (arrow). (B) Fused axial PET/CT image demonstrating significantly higher [^{18}F]FDG uptake in the right adrenal adenoma compared with the liver (arrow). The absolute SUV of the adrenal adenoma was 8.**

had activity less than the liver[44,45]. 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 cut-off value of 2.68–3.0 separates malignant from benign adrenal masses with sensitivity, specificity, positive predictive value, and negative predictive values 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 improve to 100%, 98%, 97%, 100%, respectively[44–46]. False-positive lesions for malignancy encountered at integrated PET/CT in approximately 3–13% of adrenal lesions include adrenal adenomas, phaeochromocytomas, adrenal endothelial cysts, inflammatory and infectious lesions[42–44]. False-negatives for malignancy have been reported in adrenal metastases with haemorrhage or necrosis, small (5–10 mm) metastatic nodules, and metastases from pulmonary bronchioloalveolar carcinoma or carcinoid tumours[46,47].

Although the maximum SUV uptake values for adenomas are lower than metastases, considerable overlap remains. More sophisticated quantification methods have been proposed looking at the ratio of SUV of the adrenal mass and the liver. This avoids contamination from background tracer uptake which results in an apparent increase within the adrenal lesion. Groussin *et al.*[43] showed that using a threshold ratio of 1.45, malignant adrenal lesions can be distinguished from adenomas with a sensitivity of 100% and a specificity of 88%. Boland *et al.*[42] applied an absolute SUV of 2.3 to obtain 100% sensitivity for the detection of adrenal malignant lesions. However, this provides a specificity of only 94% as several adenomas show SUV >2.31. Similarly they showed all malignant lesions had an SUV greater than

Table 1 Adapted from the ACR recommendations for the management of incidentally detected adrenal masses

Clinical status	Recommendations	Comments
No history of malignancy; mass 1–4 cm in diameter. Initial evaluation	1. CT abdomen without contrast	1. Presumes that a non-contrast CT has not already been performed
	2. Dedicated adrenal CT with contrast	2. Indicated if non-contrast CT is indeterminate (density >10 HU) or adrenal mass is discovered on early contrast-enhanced CT
	3. MRI abdomen without contrast	3. May be helpful when non-enhanced CT is equivocal
Follow-up evaluation in 12 months	1. CT abdomen without contrast 2. MRI abdomen without contrast	
No history of malignancy; mass >4 cm in diameter (if not typical for adenoma, myelolipoma, haemorrhage or simple cyst, consider resection)	1. CT abdomen with contrast	1. As part of pre-operative staging
	2. MRI abdomen with contrast	2. As part of pre-operative staging
	3. FDG-PET	3. As part of pre-operative staging but the evidence is poor. Should be performed if CT and MRI are inconclusive. Some malignancies (including renal cancer) may not be PET avid
History of malignancy. Mass <4 cm. Initial evaluation	1. CT abdomen without contrast	1. Presumes that a non-contrast CT has not already been performed
	2. MRI without contrast	2. If there is no chemical shift MRI and if CT washout is not diagnostic of an adenoma
	3. Adrenal contrast CT	3. If non-contrast CT density of lesion is >10 HU or if no loss of signal is seen on chemical shift imaging
	4. Adrenal biopsy	4. To confirm metastases and in cases where imaging is inconclusive. Phaeochromocytoma should be excluded
	5. FDG-PET whole body	5. If CT and MRI not diagnostic of a benign lesion and there is no prior imaging. Documented indications are for lung cancer, colon cancer, lymphoma, and neuroendocrine tumours; however, it is likely that adrenal metastases from other primary tumours may be detectable by FDG-PET
History of malignancy; mass >4 cm in diameter	1. FDG-PET	
	2. Adrenal biopsy	

the liver but also that a small minority of adenomas had an SUV greater than the liver yielding a specificity of 97%[42].

Therefore lesions that demonstrate visual uptake and SUV less than the liver have now been confirmed on several studies to be benign lesions with a specificity of 100%. A negative PET may predict a benign tumour that would potentially prevent the need for biopsy or surgery in lesions with inconclusive CT or MR imaging. However, lesions with visual and SUV uptake equal to or greater than the liver still remain problematic as the specificity for malignant disease is between 88% and 94%[42–44] (Figs. 10 and 11).

The specificity of PET can be improved with the use of [^{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 adrenocortical carcinomas hence there is an overlap in their appearances[48].

Percutaneous adrenal biopsy

The indications for adrenal biopsy have evolved with the availability of new imaging techniques that can characterize adrenal adenomas with high specificity. With improved imaging including PET/CT, only a small percentage of adrenal masses cannot be accurately characterized. Masses with imaging features suggestive of malignancy, mainly metastasis to the adrenal gland in patients with an extra-adrenal primary malignancies, prior to deeming them unresectable have a clinical indication for 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.*[49] the negative predictive value 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[50,51].

Non-metastatic adrenal enlargement

Diffuse adrenal enlargement in lesions without metastatic adrenal involvement and without evidence of ectopic adrenocorticotrophic hormone (ACTH) has been demonstrated in patients with malignant disease, including lymphoma. The glands enlarge uniformly, with preservation of the normal shape without CT evidence of focal or multifocal masses. Adrenal enlargement is thought to be caused by adrenal hyperplasia not related to the site of primary disease or the stage of disease[52]. These patients have biochemical evidence of Cushing syndrome as they do not show suppressed serum cortisol levels on a low-dose dexamethasone suppression test. Nevertheless, ACTH levels are low, indicating that this phenomenon is not a result of ectopic ACTH but is mediated through some other factor[53]. Minor adrenal morphological abnormalities have also been observed in patients with lung cancer. This smooth adrenal enlargement and minor nodularity at staging CT is not associated with increased risk of subsequently developing adrenal metastases[54].

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 using CT and MRI including contrast washout characteristics and CSI. As CT is available in most hospitals, lipid-poor adrenal masses are usually first evaluated by studying contrast medium washout characteristics. If available, MRI with CSI can replace contrast-enhanced CT or be used in cases that remain equivocal. The remaining indeterminate masses may benefit from PET/CT imaging. Masses with no or low tracer uptake can be considered benign. Although lesions with moderate and high uptake are likely to be malignant, some adenomas can show significant tracer uptake. For this very small number of lesions, where CT/MRI indicates an adenoma and PET/CT demonstrates high tracer uptake, percutaneous biopsy may be required to exclude malignancy.

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] Song JH, Chaudhry FS, Mayo-Smith WW. The incidental adrenal mass on CT: prevalence of adrenal disease in 1,049 consecutive adrenal masses in patients with no known malignancy. AJR 2008; 190: 1163–8. doi:10.2214/AJR.07.2799. PMid:18430826.

[4] Libe R, Bertherat J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. Eur J Endocrinol 2005; 153: 477–87. doi:10.1530/eje.1.02004. PMid:16189167.

[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. doi:10.1016/j.surg.2004.06.060. PMid: 15657589.

[7] 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.

[8] Francis IR, Casalino DD, Arellano RS, *et al.* ACR appropriateness criteria. Incidentally discovered adrenal mass. http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonUrologicImaging/IncidentallyDiscoveredAdrenalMassDoc7.aspx (accessed 1 December 2009).

[9] 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.

[10] 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.

[11] Korobkin M, Brodeur FJ, Yutzy GG, *et al.* Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. AJR 1996; 166: 531–6.

[12] Blake MA, Krishnamoorthy SK, Boland GW, Sweeney AT, Pitman MB, Harisinghani M, *et al.* Low-density pheochromocytoma on CT: a mimicker of adrenal adenoma. AJR Am J Roentgenol 2003; 181: 1663–8.

[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. doi:10.1148/radiol.2382041514. PMid:16371582.

[15] Caoili EM, Korobkin M, Francis IR, Cohan RH, Platt JF, Dunnick NR, *et al.* Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 2002; 222: 629–33. doi:10.1148/radiol.2223010766. PMid:11867777.

[16] Korobkin M, Brodeur FJ, Francis IR, Quint LE, Dunnick NR, Londy F. CT time-attenuation washout curves of adrenal adenomas and nonadenomas. AJR Am J Roentgenol 1998; 170: 747–52.
[17] Dunnick NR, Korobkin M. Imaging of adrenal incidentalomas: current status. AJR 2002; 179: 559–68.
[18] Bae KT, Fuangtharnthip P, Prasad SR, Joe BN, Heiken JP. Adrenal masses: CT characterization with histogram analysis method. Radiology 2003; 228: 735–42. doi:10.1148/radiol.2283020878. PMid:12954893.
[19] Remer EM, Motta-Ramirez GA, Shepardson LB, Hamrahian AH, Herts BR. CT histogram analysis in pathologically proven adrenal masses. AJR 2006; 187: 191–6. doi:10.2214/AJR.05.0179. PMid:16794176.
[20] 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. doi:10.2214/AJR.05.1022. PMid:17056920.
[21] Halefoglu AM, Bas N, Yasar A, Basak M. Differentiation of adrenal adenomas from nonadenomas using CT histogram analysis method: a prospective study. Eur J Radiol 2009; doi:10.1016/j.ejrad.2008.12.010.
[22] Ho LM, Paulson EK, Brady MJ, Wong TZ, Schindera ST. Lipid-poor adenomas on unenhanced CT: does histogram analysis increase sensitivity compared with a mean attenuation threshold? AJR 2008; 191: 234–8. doi:10.2214/AJR.07.3150. PMid:18562751.
[23] Reinig JW, Doppman JL, Dwyer AJ, Johnson AR, Knop RH. Adrenal masses differentiated by MR. Radiology 1986; 158: 81–4.
[24] Chang A, Glazer HS, Lee JK, Ling D, Heiken JP. Adrenal gland: MR imaging. Radiology 1987; 163: 123–8.
[25] Glazer GM, Woolsey EJ, Borrello J, *et al.* Adrenal tissue characterization using MR imaging. Radiology 1986; 158: 73–9.
[26] 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 2008; 65: 154–62. doi:10.1016/j.ejrad.2007.03.012. PMid:17466481.
[27] Krestin GP, Steinbrich W, Friedmann G. Adrenal masses: evaluation with fast gradient-echo MR imaging and Gd-DTP–enhanced dynamic studies. Radiology 1989; 171: 675–80.
[28] 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. doi:10.1002/jmri.1880030208. PMid:8448395.
[29] Chung JJ, Semelka RC, Martin DR. Adrenal adenomas: characteristic postgadolinium capillary blush on dynamic MR imaging. J Magn Reson Imaging 2001; 13: 242–8. doi:10.1002/1522-2586(200102)13:2<242::AID-JMRI1035>3.3.CO;2-R.
[30] 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.
[31] Mayo-Smith WW, Lee MJ, McNicholas MM, Hahn PF, Boland GW, Saini S. Characterization of adrenal masses by use of chemical shift MR imaging: observer performance versus quantitative measures. AJR 1995; 165: 91–5.
[32] Dunnick NR, Korobkin M, Francis I. Adrenal radiology: distinguishing benign from malignant adrenal masses. AJR 1996; 167: 861–7.
[33] Tsushima Y, Ishizaka H, Matsumoto M. Adrenal masses: differentiation with chemical shift, fast low-angle shot MR imaging. Radiology 1993; 186: 705.
[34] Korobkin M, Giordano TJ, Brodeur FJ, *et al.* Adrenal adenomas: relationship between histologic lipid and CT and MR findings. Radiology 1996; 200: 743–7.
[35] 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. doi:10.1016/j.beem.2004.09.002. PMid:17889598164830081284983712849 83511464239332 0538.
[36] Israel GM, Korobkin M, Wang C, Hecht EN, Krinsky GA. Comparison of unenhanced CT and chemical shift MRI in evaluating lipid-rich adrenal adenomas. AJR 2004; 183: 215–9.
[37] Haider MA, Ghai S, Jhaveri K, Lockwood G. Chemical shift MR imaging of hyperattenuating (410 HU) adrenal masses: does it still have a role? Radiology 2004; 231: 711–6. doi:10.1148/radiol.2313030676. PMid:15118113.
[38] 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. doi:10.2214/AJR.04.1370. PMid:16357391.
[39] Lowe VJ, Naunheim KS. Current role of positron emission tomography in thoracic oncology. Thorax 1998; 53: 703–12. doi:10.1136/thx.53.8.703. PMid:9828860.
[40] Erasmus JJ, McAdams HP, Patz Jr EF. Non-small cell lung cancer: FDG-PET imaging. J Thorac Imaging 1999; 14: 247–56. doi:10.1097/00005382-199910000-00004. PMid:10524805.
[41] 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.
[42] Boland GW, Blake MA, Holalkere NS, Hahn PF. PET/CT for the characterization of adrenal masses in patients with cancer: qualitative versus quantitative accuracy in 150 consecutive patients. AJR 2009; 192: 956–62. doi:10.2214/AJR.08.1431. PMid:19304700.
[43] Groussin L, Bonardel G, Silvéra S, *et al.* ^{18}F-Fluorodeoxyglucose positron emission tomography for the diagnosis of adrenocortical tumors: a prospective study in 77 operated patients. J Clin Endocrinol Metab 2009; 94: 1713–22. doi:10.1210/jc.2008-2302.
[44] 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. doi:10.1016/j.acra.2007.01.009. PMid:17368217.
[45] 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: 9707.
[46] 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. doi:10.1148/rg.266065057. PMid:17102052.
[47] 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.
[48] 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. doi:10.1210/jc.2005-2273.
[49] Harisinghani MG, Maher MM, Hahn PF, *et al.* Predictive value of benign percutaneous adrenal biopsies in oncology patients. Clin Radiol 2002; 57: 898–901. doi:10.1053/crad.2002.1054. PMid:12413913.
[50] 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.
[51] 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.
[52] 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. doi:10.1016/S0009-9260(05)81740-4.

[53] 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. doi:10.1038/sj.bjc.6690603. PMid:10468302.

[54] 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. doi:10.1148/radiol.2352031708. PMid:15858092.