ELSEVIER SAUNDERS

RADIOLOGIC CLINICS OF NORTH AMERICA

Radiol Clin N Am 46 (2008) 65–78

Imaging Techniques for Adrenal Lesion Characterization

Michael A. Blake, MRCPI, FFR(RCSI), FRCR[a,b,*], Nagaraj-Setty Holalkere, MD[a,b], Giles W. Boland, MD[a,b]

Radiology plays a critical role in the characterization of adrenal lesions. This review discusses the major adrenal imaging techniques currently available, including newly developed promising techniques, and outlines their underlying anatomic and physiologic imaging principles. It focuses primarily on the incidental adrenal lesion (IALs), or incidentalomas, which are adrenal nodules or masses discovered during imaging performed for indications other than adrenal disease [1]. With the burgeoning use of imaging, IALs are encountered more frequently, seen in approximately 4% to 6% of the imaged population [2–4]. The majority of IALs prove benign in patients who do not have a known history of cancer [4–9]. Alternatively, once patients have a known diagnosis of an extra-adrenal malignancy, the chance that an incidentally detected adrenal mass is malignant increases significantly [1]. Characterization of an adrenal lesion in these patients is essential to predict the prognosis of the primary disease and assess staging and direct therapy. The review finishes by discussing the role of adrenal biopsy briefly, indicated less frequently because of the noninvasive imaging advances designed to characterize adrenal lesions.

Prevalence and causes of adrenal lesions

IALs are detected in approximately 0.2% of CT scans performed on patients ages 20 to 29 years and increases to 7% to 10% of scans in older patients [1,3,6,7]. Adrenal masses are common in the general population, with a mean prevalence determined from several large autopsy studies of 2.3% [8]. Categories of adrenal lesions include functioning or nonfunctioning masses, primary or metastatic, and benign or malignant. The large majority of IALs are nonfunctioning cortical adenomas and 6% are functioning autonomous cortisol-secreting (5%) and sex-hormone– or aldosterone-producing tumors (1%) [1–3]. Other benign lesions making up approximately 1% to 2%

[a] Harvard Medical School, Boston, MA, USA
[b] Department of Radiology, Division of Abdominal Imaging and Intervention, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA
* Corresponding author. Department of Radiology, Division of Abdominal Imaging and Intervention, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114.
E-mail address: mblake2@partners.org (M.A. Blake).

0033-8389/08/$ – see front matter doi:10.1016/j.rcl.2008.01.003
radiologic.theclinics.com

combined of all adrenal lesions include myelolipoma (reported up to 9% of detected lesions), adrenal cysts, hemorrhage, hemangioma, ganglioneuroma, neuroblastoma, and granulomatous disease [1–4].

Malignant IALs account for approximately 2% to 3% of all detected lesions, increasing in number and proportion with patient age [1]. Investigators who are oncology based state this figure as much higher, however, up to 30% [3]. In most clinical practices, adrenal carcinomas and pheochromocytomas are uncommon tumors, probably accounting for less than 5% combined of all detected IALs [10]. Other rare adrenal malignancies include primary lymphoma of the adrenal, hemangiosarcoma, and neuroblastoma [11].

Nonetheless, the chance of an IAL being malignant depends greatly on whether or not patients have an underlying extra adrenal malignancy. Up to 27% of oncologic patients are reported to have microscopic adrenal metastases and approximately 50% of incidentally detected adrenal lesions in such patients represent metastatic disease [1,3,8,12]. Given this propensity for and the clinical importance of adrenal metastatic involvement, accurate diagnosis of adrenal masses is of critical importance in oncologic patients, in particular. Fortunately, as discussed later, noninvasive adrenal imaging techniques usually determine if a mass is benign or likely malignant.

Principles of adrenal imaging

The characterization of a detected IAL depends on if it is functioning or nonfunctioning and then benign or malignant. Functioning cortical adenomas and pheochromocytomas are characterized best by clinical assessment and appropriate biochemical analyses.

For a nonhyperfunctioning mass, the imaging and clinical challenge is to determine if the mass detected is benign or malignant. Accurate adrenal lesion characterization is critical for appropriate patient management and adrenal-imaging tests must be as specific as possible [13]. An adrenal characterization test, to be clinically useful, also should be reasonably sensitive, but it is far more sensible to accept that some lesions are indeterminate rather than risk missing a malignancy.

Morphologic features alone, although sometimes helpful, often are limited by poor test specificity. Other imaging techniques, however, have been developed that do satisfy the test requirements. These tests, using CT, MR imaging, and positron emission tomography (PET) and PET/CT, take advantage of three key physiologic principles: the intracellular lipid concentration of a mass, intravenous (IV) contrast washout behavior of a mass, and the metabolic activity of a mass. Each of these major adrenal imaging methods is examined in this review and useful adrenal morphologic features and new adrenal imaging developments are highlighted.

Morphologic imaging—CT and MR imaging

An important but sometimes overlooked principle is that IAL characterization often is made by comparison with any relevant prior imaging tests (Fig. 1). In general, long-term stability is consistent with a benign lesion but any adrenal lesion that increases significantly in size on interval imaging, usually 6 months, can be considered malignant. Some benign lesions (adenomas and myelolipomas), however, rarely increase in size very slightly over time and adrenal hemorrhage will cause abrupt adrenal enlargement [14]. In general, however, a significant increase in size during 6 months

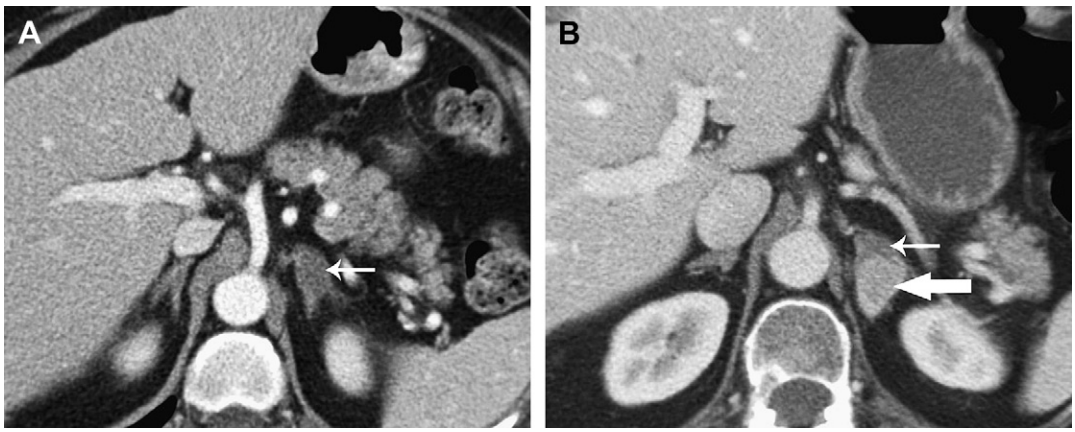

Fig. 1. Value of comparing with prior examinations. (*A*) CT scan demonstrating a low-density benign adenoma (*arrow*). (*B*) CT scan 6 months later shows development of a new enhancing mass (*large arrow*) displacing the former adenoma (*small arrow*) (collision tumor).

Fig. 2. Adrenal myelolipoma. Contrast-enhanced CT scan showing fat-containing mass (*arrow*) in right adrenal consistent with a myelolipoma.

is considered indicative of malignancy until proved otherwise.

Large size of an adrenal lesion, in general, is a suspicious feature for malignancy [1]. An IAL greater than 4 cm is reported to have an increased chance of malignancy of approximately 70% (and 85% if larger than 6 cm) [1,3]. Some investigators dispute these high figures, but it is unusual in clinical practice to see benign lesions greater than 4 cm other than these exceptions: (1) benign myelolipomas, but these usually are recognized confidently by the presence of macroscopic fat (Fig. 2) [1,4,14] and (2) benign pheochromocytomas, but they often are diagnosed biochemically and, furthermore, are removed given their malignant systemic circulation effects [15]. If patients have no other history of malignancy and a unilateral lesion larger than 4 to 5 cm, adrenal adenocarcinoma should be strongly suspected [16]. Adrenocortical carcinomas also have a propensity to involve the adrenal veins and inferior vena cava (IVC), and the tumor thrombus can be well displayed by contrast-enhanced CT or MR imaging (Fig. 3).

Lesion characterization usually depends on imaging principles other than morphologic features, although some such features can be helpful if used with care and in an informed manner. Most lesions, however, regardless of type, are small (<3 cm) when discovered and smooth and uniform in shape. Adrenal lesions, benign and, especially, malignant, may appear heterogeneous, particularly after the administration of IV contrast media. The finding of large necrotic areas within a mass usually represents malignancy. Metastases, however, when first detected, often are homogeneous and appear similar to adenomas, especially when small. Most adrenal cysts, because of their lack of enhancement and uniform nature, can be characterized morphologically (Fig. 4), although some are complex and difficult to distinguish from necrotic adrenal carcinomas [4,8,17].

The shape or margins of an adrenal lesion sometimes can assist in characterization, as large lesions with irregular borders usually are malignant (see Fig. 3). Adenomas sometimes demonstrate irregular margins, however, and even in patients who have a known extra-adrenal malignancy, multinodularity of the adrenals with preservation of adreniform shape usually is associated with benignity [18]. Adrenal shape and borders also can be assessed with multiplanar reformations and volume renderings, which readily are available with multidetector CT (see Fig. 4).

Lipid-sensitive imaging techniques—CT and MR imaging

CT and MR imaging lipid techniques can take advantage of up to 70% of adrenal adenomas

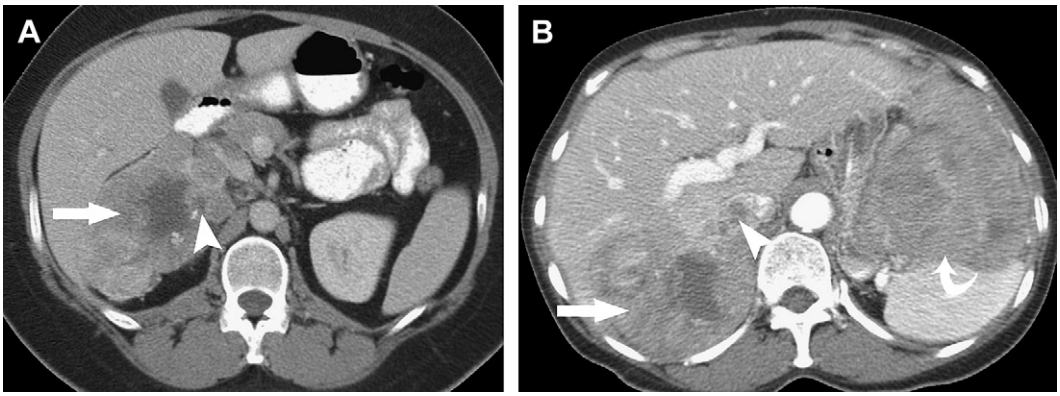

Fig. 3. Adrenal carcinoma. (*A*) Large irregularly enhancing adrenal mass (*arrow*) on contrast-enhanced CT with evidence of invasion of the IVC (*arrowhead*) and demonstrated delayed retention of contrast consistent with an adrenal carcinoma. (*B*) Large irregularly enhancing adrenal mass (*arrow*) on contrast-enhanced CT with evidence of invasion of the IVC (*arrowhead*) and left upper-quadrant, large soft tissue mass (*curved arrow*) representing metastatic disease.

Fig. 4. Left adrenal cyst. CT showing nonenhancing 2.5-cm left adrenal lesion (*arrow*) displacing normal adrenal parenchyma consistent with a cyst.

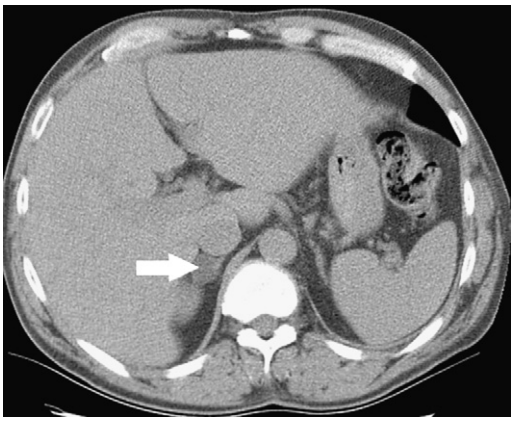

Fig. 5. Low-density adenoma. Right adrenal mass (*arrow*) measuring 6 HU on noncontrast CT representing a pathologically proved adenoma.

containing abundant intracellular fat, in contrast to almost all malignant lesions [19–24]. The presence of substantial amounts of intracellular fat is critical in making the specific diagnosis of adenoma with unenhanced CT or MR imaging.

CT techniques

Lee and colleagues were the first to report, in a seminal paper in 1991, that unenhanced CT attenuation could differentiate effectively many adrenal adenomas from nonadenomatous disease [22]. In their study, they demonstrated that the mean attenuation of adrenal adenomas (−2.2 Hounsfield units [HU]) was significantly lower than that of nonadenomas (28.9 HU). By choosing an attenuation threshold of 0 HU, these lesions could be differentiated with a sensitivity/specificity of 47%/100%. Korobkin and colleagues [19] then demonstrated an inverse linear relationship between fat concentration and the unenhanced CT attenuation value (Fig. 5). In contrast, almost all nonadenomatous lesions have a paucity of intracellular fat, and thus, higher CT attenuation values.

The attenuation measuring technique involves placing a region of interest (ROI) over the adrenal gland, avoiding hemorrhagic, necrotic, or calcified areas [4,19,23]. The ROI should be placed over one half to two thirds of the lesion area to decrease noise artifact and to avoid partial voluming effects from neighboring fat [4,19,23,24].

Boland and colleagues [13], using a meta-analysis study, demonstrated that if the CT attenuation threshold was 10 HU, then the test sensitivity increased (71%) while preserving high specificity (98%). The 10-HU threshold now is the standard by which radiologists differentiate lipid-rich adenomas from most other adrenal lesions on unenhanced CT. Up to 30% of adenomas, however, do not have abundant intracellular fat and, thus, show attenuation values greater than 10 HU on unenhanced CT, as do almost all malignant lesions [4,8,22–28]. Lesions above 10 HU on an unenhanced CT are considered indeterminate and other tests generally are required to characterize them. Furthermore, most CT scans that include the adrenals are performed after administration of IV contrast media so unenhanced attenuation measurements cannot be made. In addition, there is too much overlap between the attenuation values of adenomas and nonadenomas on dynamic enhanced CT to enable these entities to be distinguished [23–29].

Bae and colleagues [30], however, have reported a CT histogram analysis method that is more sensitive than the 10-HU threshold method for the diagnosis of adrenal adenoma on unenhanced and enhanced CT. The technique presumes that most adenomas (either lipid rich or lipid poor) contain sufficient intracytoplasmic fat for lesion characterization. The histogram analysis technique again involves placing an ROI (as previously discussed) and then processing with a histogram analysis tool, available on most current CT viewing workstations [30]. This gives the number and range of pixel attenuation measurements, which then can be visualized graphically (Fig. 6). The histogram is a graphic plot of pixel attenuation (CT numbers) along the X axis versus the frequency of pixels at each attenuation value along the Y axis. It allows estimation, therefore, of tissue attenuation distribution in a lesion rather than calculation of an overall mean attenuation in a ROI as with conventional CT densitometry. The technique also allows the measurement of mean attenuation, number of pixels, and range of pixel attenuation for all pixels in the ROI. The

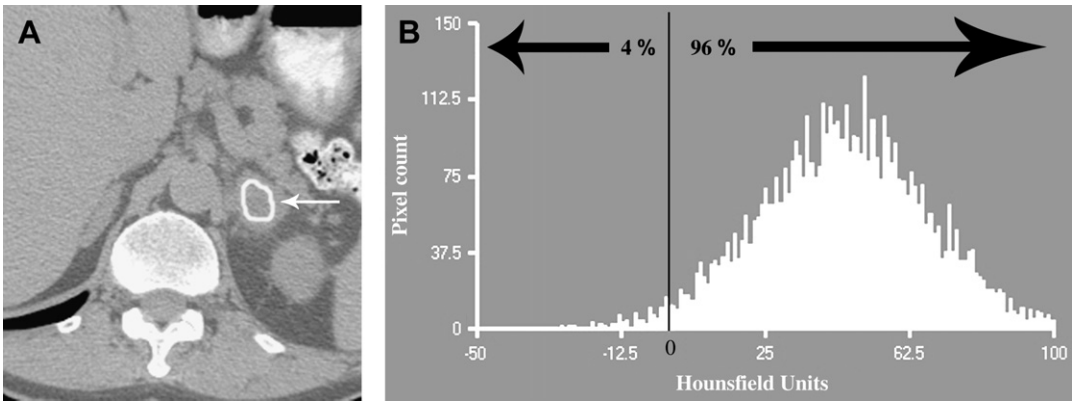

Fig. 6. Histogram analysis of adrenal mass. (*A*) CT scan showing left adrenal lesion with ROI placed within it. (*B*) Graphic display of distribution of HU values in the mass.

investigators proposed that lesions should be considered benign only if the negative pixel count is greater than 10%, as some nonadenomatous lesions sometimes contain negative pixels. Other investigators, however, have found the test sensitivity too low (71% and 12% for unenhanced and contrast-enhanced CT, respectively) for use in standard clinical practice [31,32]. Although volumetric analysis may improve its performance, the practical value of the histogram analysis method remains uncertain [32].

Dual-energy CT is a well-established technique for determining bone mineral density, is used for differentiating fatty liver from low-density masses in the liver, and can be applied to detecting fat in adrenal lesions [33,34]. The technique is based on the principle that differences in X-ray attenuation diminish with increasing energy of X rays used. This phenomenon can be exploited to quantify fat in the adrenal glands by measuring the difference in CT attenuation acquired at 140- and 80-kg voltage peaks (kV[p]). If the difference of attenuation between the two kV(p) images is greater than 6 HU, then it is suggestive of fat-containing lesions [33,34]. This technique could be applied in the adrenal to identify lesions, such as adenomas or myelolipomas. There are as yet no published papers discussing this technique for adrenal lesion characterization; however, a recent abstract presented by Li and colleagues [35] contains promising results. The technique is simple and can be performed on any scanner using routine software available on picture archiving and communication systems for analysis. The main weaknesses of this technique are the minimal increase in radiation dose and increased noise that results from the additional 80-kV(p) images. Further studies are necessary to understand its role in characterization of adrenal, particularly lipid poor, adenomas in comparison to the other well-established imaging techniques.

MR imaging techniques

Chemical-shift MR imaging (CSI) also characterizes adenomas by detecting their intracellular fat content but by exploiting the different resonant frequencies of fat and water protons rather than by attenuation differences as with CT [4,8,33–36]. Water protons precess at a higher frequency than fat protons so that the MR signals of water and lipid protons within a voxel can cancel each other out during out-of-phase (OOP) gradient-echo imaging [33–37]. This leads to signal loss relative to the in-phase (IP) images when, in contrast, the signals combine. Similar to his CT findings, Korobkin demonstrated there was an inverse linear relationship up to equal voxel concentrations of fat and water protons between the percentage of lipid-rich cells and the relative change in magnetic resonance (MR) signal intensity on CSI [19]. There needs to be a balance of fat and water protons (as seen with many lipid-rich adenomas) for signal loss on OOP CSI to occur (Fig. 7). Pure fat voxels (as seen in myelolipomas) show little or no signal loss on OOP imaging, as there are few, if any, water protons to cancel out the fat signal [8,38].

This CSI signal loss can be measured quantitatively, as the adrenal-to-spleen chemical-shift ratio, by dividing the lesion-to-spleen signal intensity ratios on the IP images by the OOP images. A CSI ratio of less than 0.71 indicates a lipid-rich adenoma [37]. The alternative adrenal signal intensity index is calculated as [(IP signal intensity−OOP signal intensity)/(IP signal intensity)] × 100%; using this formula, a measurement of greater than 16.5% is consistent with a lipid-rich adenoma [39]. In clinical practice, however, most radiologists evaluate chemical-shift change visually or qualitatively using muscle or spleen as the internal reference organ, which is more convenient and as effective as

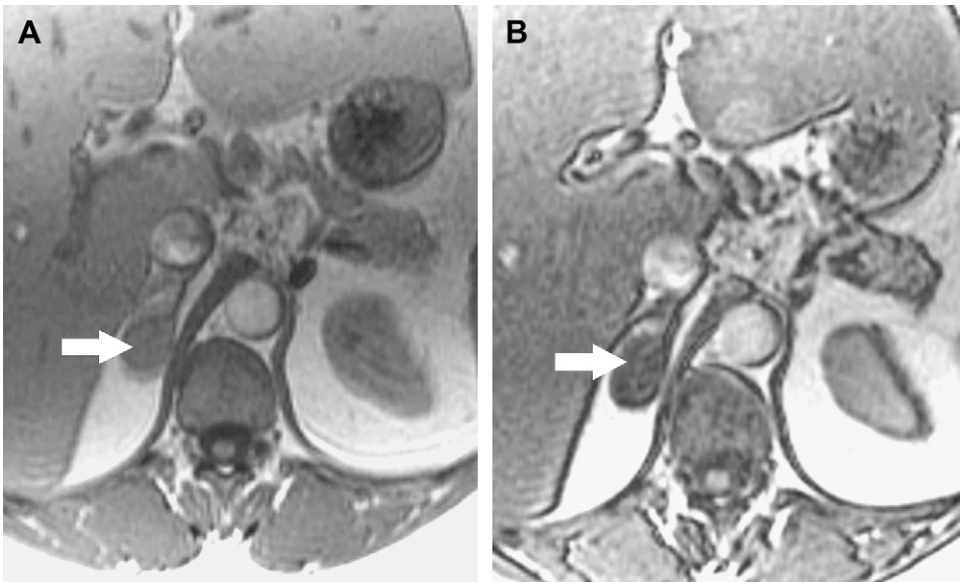

Fig. 7. CSI adenoma. MR image showing left adrenal masses (*arrows*) showing signal intensity drop between IP (*A*) and OOP (*B*) images consistent with adenoma. Notice how the liver also drops in signal on OOP imaging due to fatty liver, a behavior that makes it unsuitable as an internal standard reference organ.

quantitative methods [40,41]. The liver should not be used as the internal reference organ, as it also can show loss of OOP signal with fatty liver (see Fig. 7) [8,40].

The sensitivity and specificity of CSI for the differentiation of adrenal lesions are reported at 78% to 100% and 87% to 100%, respectively [35]. Studies suggest that there is no significant difference between the CT and CSI tests for characterizing lipid-rich adenomas but that CSI might be superior when evaluating lipid poor adenomas, up to an attenuation of 30 HU [42,43]. CT contrast washout tests, however (discussed later), have proved the most accurate diagnostic imaging tool with which to differentiate adrenal lesions [4,5,23,26,28,29,44,45].

An important MR advance that can be applied to adrenal imaging is parallel MR imaging, which, by taking advantage of an array of coils' inherent ability to encode multiple lines of MR data simultaneously, can be used to reduce scan time or increase spatial resolution. A MR advance that also may be applied to adrenal imaging is MR diffusion and MR spectroscopy (MRS), and initial preliminary reports are promising [46–48].

Diffusion-weighted imaging (DWI) can provide insight into water composition within a tumor [46]. Diffusion is thermally induced motion of water molecules in biologic tissues, called Brownian motion. Changes in tissue structure, such as cell membranes, vascular structures, and viscosity of the media, can limit or restrict the amount of diffusion. Benign tumors tend to have a balanced increase of cells and intercellular space whereas malignant tumors usually have a disproportionate increase of cells (mitotic activity) as compared with interstitial tissue. These properties of malignancies result in selective restriction of diffusion of water molecules that may provide strong evidence for malignancy in an adrenal lesion (Fig. 8).

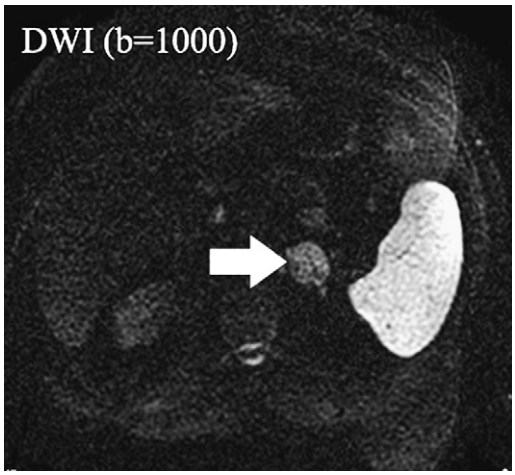

Fig. 8. Diffusion MR image of metastasis. MR image of a 52-year-old man who had a history of renal cell cancer that demonstrates a hyperintense adrenal lesion (*arrow*) on left side on a high b-value DWI consistent with restricted diffusion, which typically is seen in malignant lesions. The lesion proved to be a renal cell cancer metastasis on histopathology.

Alternatively, the lack of restricted diffusion may correlate with a benign lesion [46,47]. The diffusion data can be presented as signal intensity or as an image map of the apparent diffusion coefficient (ADC). Calculation of the ADC requires two or more acquisitions with different diffusion weightings. As yet, there are no published studies on the usefulness of DWI and ADC maps in characterization of adrenal lesions. Uhl and colleagues [47], however, have demonstrated restricted diffusion in 7 of 7 (100%) neuroblastomas, including two in adrenal glands. Based on this and the authors' early experience with this technique, the authors believe that the DWI and ADC maps may increase the accuracy of detection of malignancy in the adrenal gland. The lack of radiation and IV contrast requirements represent major advantages of DWI whereas the lack of experience with the technique and lack of published data remain the main current limitations.

MRS is useful in quantification of liver fat and is useful in identifying fat in benign adrenal lesions [48]. In vivo nuclear MRS is advancing because of the development of effective MR instrumentation and increasing availability of whole-body MR imaging systems. Absolute quantification of metabolite concentrations is useful, as a lipid peak at 1.3 ppm on the MR spectra in an adrenal lesion could characterize adrenal lesions confidently as benign. Quantification of choline-containing compounds at 3 to 3.3 ppm also is of great interest, as such compounds are increased in malignancy [48]. Researchers actively are investigating adrenal lesion characterization as a practical application of MRS. MRS has the potential to emerge as a promising tool in adrenal imaging with the continuing developments in MR scanners and postprocessing techniques.

Perfusion imaging is well established for brain tumors and has proved valuable in other abdominal tumors, such as hepatocellular carcinoma and rectal cancer [49]. Similar to these tumors, malignant adrenal tumors are likely to demonstrate higher permeability surface as a result of the presence of disorganized neovasculature and increased blood flow in contrast to benign adenomatous lesions, where the vascular organization is preserved [50]. Thus, CT or MR perfusion (dynamic or functional) imaging also may prove useful in the characterization of indeterminate adrenal lesions. Currently, CT and MR perfusion imaging are being evaluated for various organs in the body and their application in adrenal lesion evaluation not yet is evaluated fully. From the authors' experience with a few selected patients, however, perfusion imaging is another potential tool for adrenal lesion characterization but further study is needed.

CT washouts of the adrenals

After the successful noncontrast CT attenuation results for characterization of lipid-rich lesions, other investigators reported that the CT densitometry could characterize some adrenal lesions by performing attenuation measurements after different scan delays up to 1 hour [24,26,27]. They noticed that after administering IV contrast, adenomas tended to de-enhance faster than nonadenomatous lesions [5]. Malignancies have abnormal vasculature with a high microvascular density leading to slow blood flow and abnormally high vascular endothelial permeability [51]. Because of these vascular abnormalities, administered IV contrast agents more likely accumulate, and are retained for a longer period, in malignant tissues. These differences explain why contrast agent washout rates are significantly faster from benign adenomas compared with malignant masses [24,26,27].

An absolute attenuation measurement on a delayed scan has not been found practical as it depends on the type, total dose, and injection rate of IV contrast material and patient cardiac output [4,5,23,28]. The ratio of the washout-delayed attenuation, however, when compared with the dynamic enhanced attenuation, can help characterize adrenal lesions with great accuracy [5,27]. This phenomenon first was noticed by MR imaging investigators but considered too variable for use in routine MR clinical practice [50]. Korobkin and colleagues described a corresponding CT washout value with sensitivities and specificities for the diagnosis of adrenal adenoma. The percentage washout represents the percentage of the dynamic enhancement that is washed out at delayed scanning [4,5,26]. If the unenhanced attenuation value is available, an absolute percentage washout (APW) can be calculated. If no unenhanced scan is available, it is as useful to calculate the relative percentage washout (RPW). Many reports have corroborated the accuracy of using APW or RPW, and these measures now are used commonly in standard clinical practice. The RPW and APW are calculated as follows:

$$\text{RPW} = \frac{100 \times (\text{enhanced HU} - \text{delayed HU})}{\text{enhanced HU}}$$

$$\text{APW} = \frac{100 \times (\text{enhanced HU} - \text{delayed HU})}{\text{enhanced HU} - \text{noncontrast HU}}$$

The only difference between the respective formulae is that RPW gives a 0 value to the

noncontrast HU field, whereas APW incorporates the true noncontrast attenuation value. Many investigators use a 40% threshold on a 15-minute delayed scan for RPW (or 60% for APW). Any adrenal lesion that demonstrates greater than 40% RPW (or >60% APW) at 15 minutes indicates an adenoma, with almost perfect sensitivity/specificity. Lesions that demonstrate RPW washouts less than 40% (or <60% APW) on a 15-minute delayed scan almost always are malignant (Fig. 9) [23,28,29,44,46]. Some investigators choose a 10-minute delay scan as more time efficient for CT scheduling and find the RPW 40% threshold (38% in the authors' series) as effective on a 10-minute delayed study [46,48]. There are some caveats to this technique: a noncontrast attenuation less than 0 H supercedes the washout profile in the evaluation of an adrenal mass; all noncalcified and nonhemorrhagic adrenal lesions measuring over 43 HU precontrast should be considered malignant, whatever the washout values. These data-driven caveats are intuitive as few malignant lesions are expected to measure less than HU and few adenomas expected to measure greater than 43 HU. Furthermore, the inconsistent behavior by pheochromocytomas in terms of fat content and contrast washout also should be remembered when assessing an adrenal mass, especially in the correct clinical setting [15,45]. While bearing in mind these caveats, the APW value should be calculated when available, as it is a truer measure of de-enhancement. For 10-minute delay scans, the optimal APW threshold was 52% compared with 60% on the 15-minute delay scans. The lower threshold values on 10-minute delay postcontrast scans compared with 15 minutes delayed scans are to be expected, as the 10-minute delay gives 5 minutes less time for lesions to de-enhance. Importantly, most lipid poor adenomas also can be characterized using this technique leading to a much higher sensitivity for differentiating adrenal lesions using RPW than using unenhanced CT alone (Fig. 10) [23,28,29,44,45].

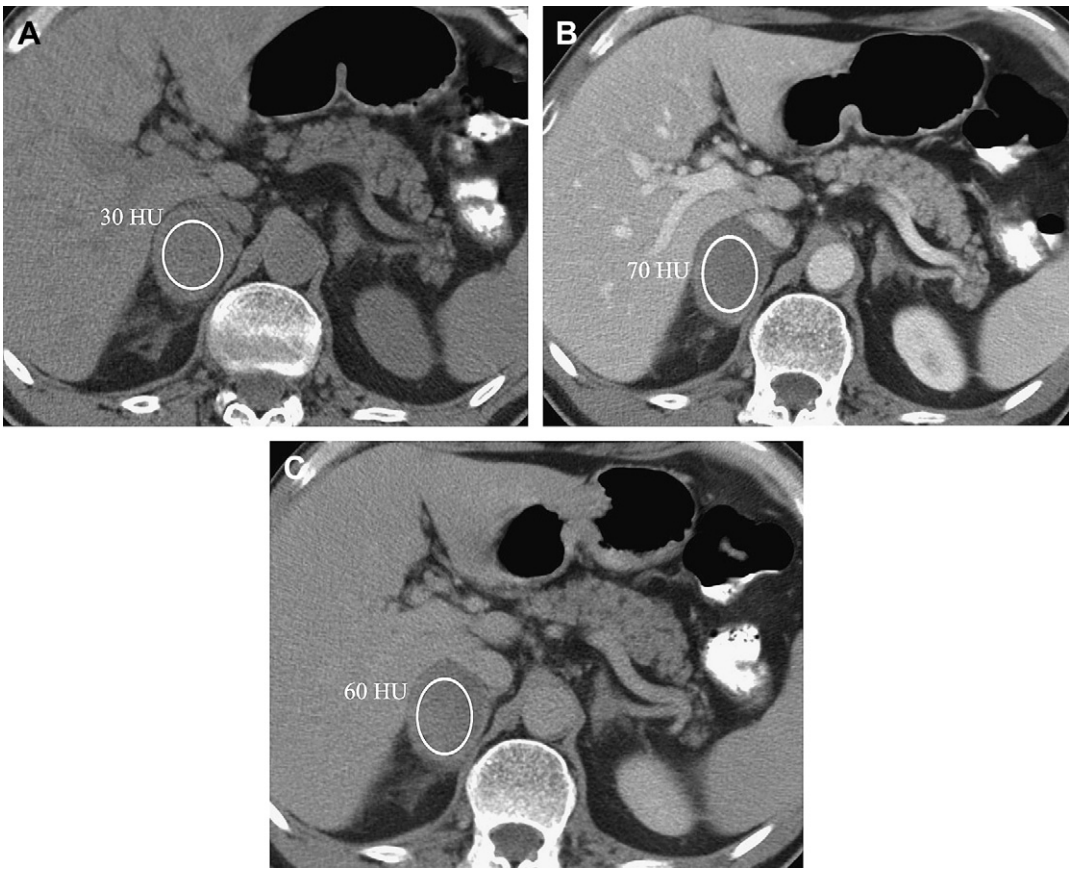

Fig. 9. Adrenal metastasis from lung cancer on washout analysis. Right adrenal mass giving ROI measurements of 30 HU precontrast (*A*), 70 HU on dynamic imaging (*B*), and 60 HU on delayed 10-minute images (*C*). The lesion is indeterminate by noncontrast criteria greater than 10 HU but as the RPW = 50% and APW = 66.6%, it is consistent with an indeterminate lesion (suspicious for malignancy).

Fig. 10. Lipid-poor adrenal adenoma on washout analysis. Right adrenal mass giving ROI measurements of 20 HU precontrast (*A*), 80 HU on dynamic imaging (*B*), and 40 HU on delayed 10-minute images (*C*). The lesion is indeterminate by noncontrast criteria greater than 10 HU, but as the RPW = 50% and APW = 66.6%, it is consistent with a lipid-poor adenoma.

Positron emission tomography and positron emission tomography/CT

Several radioisotopes are used to help characterize adrenal lesions, including NP-59 iodomethylnorcholesterol, metaiodobenzylguanidine (MIBG), and 18F-fluorodeoxyglucose PET (FDG-PET) [51–69]. Although NP-59 iodomethylnorcholesterol has a high positive predictive value for the detection of adenoma, it is not used effectively in clinical practice. MIBG may be helpful in the evaluation of some pheochromocytomas, particularly if ectopic or metastatic [54,62,64]. Most pheochromocytomas show increased FDG uptake but more impressive results are reported with fluorodopamine PET and 11C-hydroxyephedrine PET, both of which having greater specificity for characterizing pheochromocytoma [69–72].

In practice, an increasing number of adrenal lesions are detected and characterized with FDG-PET or, in particular, FDG-PET/CT. In general, malignant masses usually show increased FDG uptake

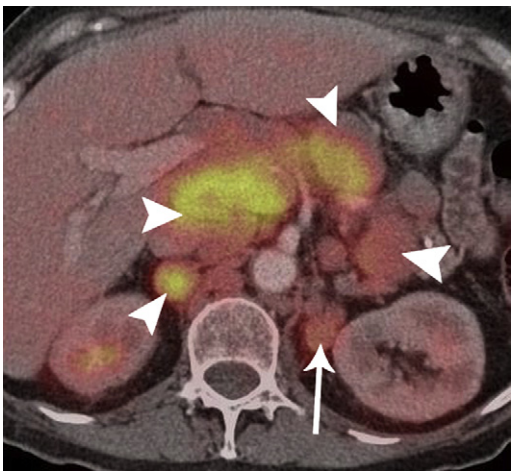

Fig. 11. PET CT of lymphoma. Overlaid PET/CT image demonstrating a left adrenal mass (*arrow*) and multiple upper-abdominal lymph nodes (*arrowheads*), all showing increased FDG activity resulting from involvement with lymphoma.

Fig. 12. Adrenal metastases from lung cancer on PET/CT. Axial and coronal PET/CT images demonstrating intense FDG uptake in the primary left upper lobe lung carcinoma (*curved arrow*) and in the adrenal metastases (*arrows*).

due to increased glucose metabolism (Figs. 11 and 12), whereas benign noninflammatory masses, in general, do not show significantly increased uptake [51,54]. Many studies have demonstrated that FDG-PET imaging can help differentiate benign from malignant adrenal disease [45,51–53,55–61,63,64,67,68]. Early metastatic disease sometimes can be detected using this technique.

Sensitivity/specificity results reported for PET or PET/CT imaging range from 93%/80%, respectively, to 100%/100% [45,67,68], although most investigators believe that specificity is closer to 95% [57,67]. Some adrenal adenomas (5%) and inflammatory and infectious lesions demonstrate slight increased radiotracer uptake compared with the liver (the internal reference organ for normal uptake). Occasionally necrotic or hemorrhagic malignant adrenal lesions may cause false-negative findings showing poor FDG uptake [67]. PET imaging is not reliable for lesions less than 1 cm in size, as metastatic lesions of this size may demonstrate less radiotracer uptake than normal liver [67].

The use of PET/CT offers clear advantages over PET alone, as lesion morphology on CT can be coregistered with the metabolic activity from PET, allowing for accurate anatomic localization of any FDG abnormalities (Fig. 13). Furthermore, CT densitometry and washout measurements (if a contrast-enhanced CT and delays also are performed) can be incorporated into the analysis. Thus, three of the most effective tests used to characterize adrenal lesions may be combined in one scan. Under these circumstances, it has been demonstrated that sensitivity/specificity lesion characterization in a report with 41 masses was 100%/100%, although further studies with larger patient numbers are required to corroborate these findings [44]. Results in practice likely are less perfect as there is some clustering of benign and malignant lesions around the adrenal/liver threshold ratio on PET and the washout

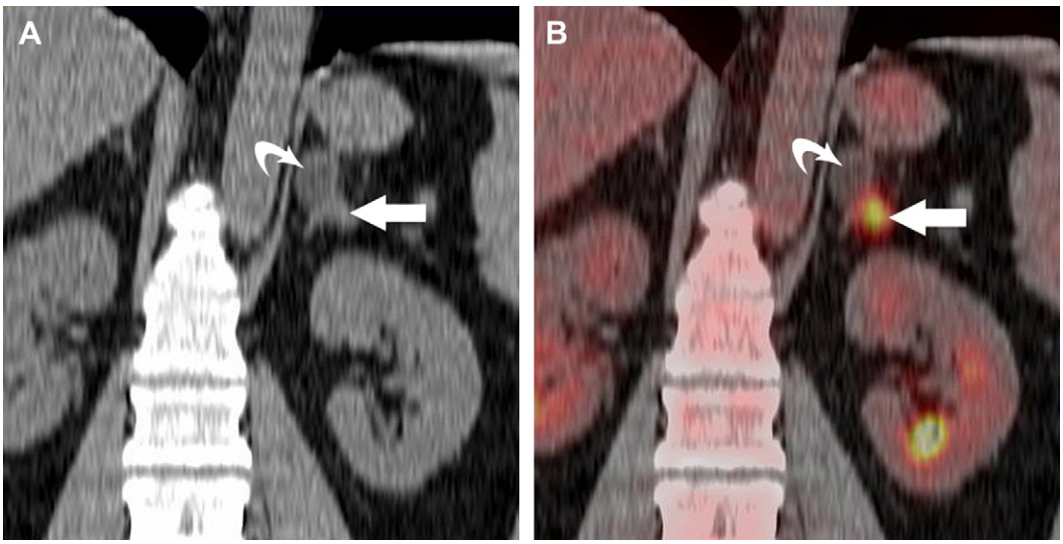

Fig. 13. Collision tumors. Coronal reconstruction of contrast-enhanced CT scan (*A*) shows low-density left adrenal lesion (*curved arrow*) stable compared with previous scans consistent with an adenoma in a patient who had breast cancer. CT scan, however, also shows a new enhancing mass (*arrow*) in left adrenal. Overlaid PET/CT image (*B*) demonstrating that the new lesion shows increased FDG uptake, consistent with breast cancer metastasis, displacing the low-density, non–FDG-avid adenoma (collision tumors).

thresholds on CT [45]. Most patients who have known adrenal lesions likely are referred for characterization with PET or PET/CT only if CT densitometry or washout analyses are inconclusive on a separate CT study. PET/CT is becoming the oncology imaging test of choice for many tumors, so greater numbers of adrenal lesions will be encountered and diagnosed on PET/CT in the future.

Adrenal biopsy

The number of requested adrenal biopsies has been reduced significantly by the improved accuracy of current adrenal imaging techniques [73]. Biopsy still is required in some cases, however, particularly if patients have an underlying extra-adrenal malignancy. Sometimes imaging findings with conventional adrenal imaging tests are indeterminate, there is suspicion that the lesion still could be malignant, or there are discordant imaging results. The frequency and necessity for adrenal biopsy depend to a certain extent on a department's familiarity with adrenal imaging and biopsy techniques.

CT-guided percutaneous needle aspiration biopsy (PNAB) is a well-established technique and the method of choice for sampling adrenal lesions. The procedure usually is performed with patients in the decubitus position, with the adrenal mass ipsilateral side down to reduce the risk for pneumothorax (Fig. 14). Rarely, it may be necessary to use a transhepatic approach. Adrenal biopsy procedures have a good safety record with a low complication rate (most commonly adrenal hemorrhage or pneumothorax) and good accuracy rates (83%–96% diagnostic accuracy) [74,75]. It should be remembered, however, that sampling error sometimes leads to false-negative PNAB results. Collision tumors affecting the adrenal gland (see Fig. 13) (when two different tumors coexist in the adrenal) occasionally occur and PET/CT helps identify and direct appropriate biopsy in such circumstances [76]. Biopsy generally is not indicated for patients who have suspected pheochromocytoma because of the risk for precipitating a hypertensive crisis, although these tumors sometimes are biopsied inadvertently without untoward clinical complications [74,75]. If biopsy absolutely is required in a suspected case of pheochromocytoma, then appropriate prophylaxis blockade with endocrine and anesthesiology consultation should be sought.

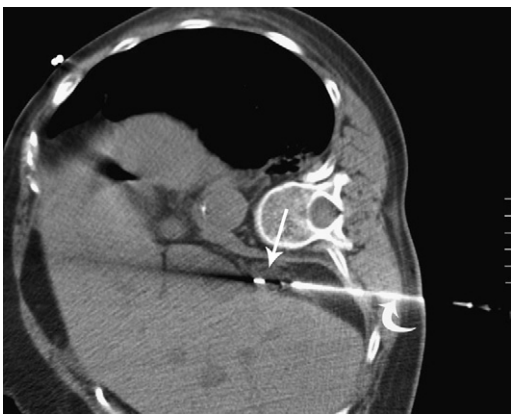

Fig. 14. Adrenal biopsy. CT image from CT guided biopsy of an indeterminate right adrenal lesion (*arrow*) with the needle in place. The patient has been placed in a right side down decubitus to reduce the risk for a biopsy-induced pneumothorax by decreasing the amount of visualized lung on this side at the percutaneous access level.

Summary

Adrenal imaging techniques have undergone significant advances in recent years, allowing characterization of most adrenal lesions discovered at imaging. CT, MR imaging, PET, and PET/CT all are clinically useful in differentiating benign from malignant adrenal lesions although all use fundamentally different principles to make their adrenal diagnoses. Recently developed applications of dual-energy CT and histogram analysis may offer additional information. The new functional imaging techniques, such as perfusion, DWI, and MRS, may play a role in lesion characterization in the near future. Image-guided adrenal biopsy occasionally should be considered for treatment planning or for the uncommon lesions that remain indeterminate by imaging. The overall goal of adrenal imaging is to detect and achieve accurate characterization of most adrenal lesions and to direct patient management correctly.

References

[1] Young WF Jr. The incidentally discovered adrenal mass. N Engl J Med 2007;356:601–10.
[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] Mansmann G, Lau J, Blak E, et al. The clinically inapparent adrenal mass. Update in diagnosis and treatment. Endocr Rev 2004;25(2):309–40.
[4] Dunnick NR, Korobkin M. Imaging of adrenal incidentalmomas. AJR Am J Roentgenol 2002; 179:559–68.
[5] Korobkin M. CT characterization of adrenal masses: the time has come. Radiology 2000; 217:629–32.
[6] Kloos RT, Gross MD, Francis IR, et al. Incidentally discovered adrenal masses. Endocr Rev 1995;16:460–84.

[7] Young WF Jr. Management approaches to adrenal incidentalomas: a view from Rochester, Minnesota. Endocrinol Metab Clin North Am 2000; 29:159–85.
[8] Barzon L, Sonino N, Fallo F, et al. Prevalence and natural history of adrenal incidentalomas. Eur J Endocrinol 2003;149:273–85.
[9] Song JH, Chaudhry FS, Mayo-Smith WW. The incidental indeterminate adrenal mass on CT (>10HU) in patients without cancer. Is further imaging necessary? Follow-up of 321 consecutive indeterminate adrenal masses. AJR Am J Roentgenol 2007;189:1119–23.
[10] Slattery JM, Blake MA, Kalra MK, et al. Adrenocortical carcinoma: contrast washout characteristics on CT. AJR Am J Roentgenol 2006;187: W21–4.
[11] Angeli A, Osella G, Ali A, et al. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. Horm Res 1997;47:279–83.
[12] Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma: analysis of 1000 autopsied cases. Cancer 1950;3:74–85.
[13] Boland GW, Lee MJ, Gazelle GS, et al. Characterization of adrenal masses using unenhanced CT: an analysis of the CT literature. AJR Am J Roentgenol 1998;171:201–4.
[14] Russell C, Goodacre BW, vanSonnenberg E, et al. Spontaneous rupture of adrenal myelolipoma: spiral CT appearance. Abdom Imaging 2000;25: 431–4.
[15] Blake MA, Kalra MK, Maher MM, et al. Pheochromocytoma: an imaging chameleon. Radiographics 2004;24:S87–9.
[16] Szolar DH, Melvyn Korobkin M, Reittner P, et al. Adrenocortical carcinomas and adrenal pheochromocytomas: mass and enhancement loss evaluation at delayed contrast-enhanced CT. Radiology 2005;234:479–85.
[17] Rozenblit A, Morehouse HT, Amis SE Jr. Cystic adrenal lesions: CT features. Radiology 1996; 201:541–8.
[18] Benitah N, Yeh BM, Qayyum A. Minor morphologic abnormalities of adrenal glands at CT: prognostic importance in patients with lung cancer. Radiology 2005;235:517–22.
[19] Korobkin M, Giordano TJ, Brodeur FJ, et al. Adrenal adenomas: relationship between histologic lipid and CT and MR findings. Radiology 1996; 200:743–7.
[20] Anderson JB, Gray GF. Adrenal pathology. In: Vaughan ED, Carey RM, editors. Adrenal disorders. New York: Thieme Medical; 1989. p. 18–9.
[21] Carney JA. Adrenal gland. In: Sternberg SS, editor. Histology for pathologists. New York: Raven; 1992. p. 150–4.
[22] Lee MJ, Hahn PF, Papanicolau N, et al. Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. Radiology 1991;179:415–8.
[23] Caoili EM, Korobkin M, Francis IR, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 2002;222:629–33.
[24] Boland GW, Hahn PF, Pena C, et al. Adrenal masses: characterization with delayed contrast-enhanced CT. Radiology 1997;202:693–6.
[25] Korobkin M, Brodeur FJ, Yutzy GG, et al. Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. AJR Am J Roentgenol 1996;166:531–6.
[26] Korobkin M, Brodeur FJ, Francis IR, et al. CT time-attenuation washout curves of adrenal adenomas and nonadenomas. AJR Am J Roentgenol 1998;170:747–52.
[27] Szolar DH, Kammerhuber FH. Adrenal adenomas and nonadenomas: assessment of washout at delayed contrast-enhanced CT. Radiology 1998;207:369–75.
[28] Pena CS, Boland GW, Hahn PF, et al. Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. Radiology 2000;217: 798–802.
[29] Caoili EM, Korobkin M, Francis IR, et al. Delayed enhanced CT of lipid-poor adrenal adenomas. AJR Am J Roentgenol 2000;175:1411–5.
[30] Bae KT, Fuangtharnthip P, Prasad SR, et al. Adrenal masses: CT characterization with histogram analysis method. Radiology 2003;228:735–42.
[31] Jhaveri KS, Wong F, Ghai S, et al. Comparison of CT histogram analysis and chemical shift MRI in the characterization of indeterminate adrenal nodules. Am J Roentgenol 2006;187:1303–8.
[32] Remer EM, Motta-Ramirez GA, Shepardson LB, et al. CT histogram analysis in pathologically proven adrenal masses. Am J Roentgenol 2006; 187:191–6.
[33] Wang B, Gao Z, Zou Q, et al. Quantitative diagnosis of fatty liver with dual-energy CT. An experimental study in rabbits. Acta Radiol 2003; 44(1):92–7.
[34] Raptopoulos V, Karellas A, Bernstein J, et al. Value of dual-energy CT in differentiating focal fatty infiltration of the liver from low-density masses. AJR Am J Roentgenol 1991;157(4): 721–5.
[35] Li J, Kalra MK, Small WC. Adrenal mass: differentiation by attenuation characteristics using dual-energy MDCT. Am J Roentgenol 2007;188(Suppl 5):A59–62.
[36] Korobkin M, Lombardi TJ, Aisen AM, et al. Characterization of adrenal masses with chemical shift and gadolinium-enhanced MR imaging. Radiology 1995;197:411–8.
[37] Outwater EK, Siegelman ES, Huang AB, et al. Adrenal masses: correlation between CT attenuation value and chemical shift ratio at MR imaging with in-phase and opposed-phase sequences. Radiology 1996;200:749–52.
[38] Fujiyoshi F, Nakajo M, Kukukura Y, et al. Characterization of adrenal tumors by chemical shift

fast-low angle shot MR imaging: comparison of four methods of quantitative evaluation. Am J Roentgenol 2003;180:1649–57.
[39] Mayo-Smith WW, Lee M, McNicholas MM, et al. Characterization of adrenal masses (<5 cm) by use of chemical shift MR imaging: observer performance versus quantitative measures. Am J Roentgenol 1995;165:91–5.
[40] McNicholas MM, Lee MJ, Mayo-Smith WW, et al. An imaging algorithm for the differential diagnosis of adrenal adenomas and metastases. Am J Roentgenol 1995;165:1453–9.
[41] Israel GM, Korobkin M, Wang C, et al. Comparison of unenhanced CT and chemical shift MRI in evaluating lipid-rich adrenal adenomas. AJR Am J Roentgenol 2004;183:215–9.
[42] Haider MA, Ghai S, Jhaveri K, et al. Chemical shift MR imaging of hyperattenuating (>10 HU) adrenal masses: does it still have a role? Radiology 2004;231:711–6.
[43] Park BK, Kim CK, Kim B, et al. Comparison of delayed enhanced CT and chemical shift MR for evaluating hyperattenuating incidental adrenal masses. Radiology 2007;243: 760–5.
[44] 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.
[45] Blake MA, Kalra MK, Sweeney AT, et al. Distinguishing benign from malignant adrenal masses: multi–detector row CT protocol with 10-minute delay. Radiology 2005;238:578–85.
[46] Luypaert R, Boujraf S, Sourbron S, et al. Diffusion and perfusion MRI: basic physics. Eur J Radiol 2001;38(1):19–27.
[47] Uhl M, Altehoefer C, Kontny U, et al. MRI-diffusion imaging of neuroblastomas: first results and correlation to histology. Eur Radiol 2002;12(9): 2335–8.
[48] Faria JF, Goldman SM, Szejnfeld J, et al. Adrenal masses: characterization with in vivo proton MR spectroscopy—initial experience. Radiology 2007;245:788–97.
[49] Sahani DV, Holalkere NS, Mueller PR, et al. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue—initial experience. Radiology 2007;243(3):736–43.
[50] Jain RK, Munn LL, Fukumura D. Dissecting tumour pathophysiology using intravital microscopy. Nat Rev Cancer 2002;2:266–76.
[51] 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.
[52] Murea S, Mainolfi C, Bazzicalupo I, et al. Imaging of adrenal tumors using FDG-PET: comparison of benign and malignant lesions. AJR Am J Roentgenol 1999;173:25–9.
[53] Boland GW, Goldberg MA, Lee MJ, et al. Indeterminate adrenal mass in patients with cancer: evaluation at PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995;194:131–4.
[54] Erasmus JJ, Patz EF Jr, McAdams HP, et al. Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. AJR Am J Roentgenol 1997;168:1357–60.
[55] Maurea S, Klain M, Mainolfi C, et al. The diagnostic role of radionuclide imaging in evaluation of patients with nonhypersecreting adrenal masses. J Nucl Med 2001;42:884–92.
[56] Gupta NC, Graeber GM, Tamim WJ, et al. Clinical utility of PET-FDG imaging in differentiation of benign from malignant adrenal masses in lung cancer. Clin Lung Cancer 2001;3: 59–64.
[57] Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. Radiology 2004;231:305–32.
[58] Elaini AB, Shetty SK, Chapman VM, et al. Improved detection and characterization of adrenal disease with PET-CT. Radiographics 2007;27: 755–67.
[59] Metser U, Miller E, Lerman H, et al. 18F-FDG PET/CT in the evaluation of adrenal masses. J Nucl Med 2006;47:32–7.
[60] Rao SK, Caride VJ, Ponn R, et al. F-18 fluorodeoxyglucose positron emission tomography-positive benign adrenal cortical adenoma: imaging features and pathologic correlation. Clin Nucl Med 2004;29:300–2.
[61] Bagheri B, Maurer AH, Cone L, et al. Characterization of the normal adrenal gland with 18F-FDG PET/CT. J Nucl Med 2004;45:1340–3.
[62] Francis IR, Smid A, Gross MD, et al. Adrenal masses in oncologic patients: functional and morphologic evaluation. Radiology 1988;166: 353–6.
[63] Francis IR, Glazer GM, Shapiro B, et al. Complementary roles of CT and 131I-MIBG scintigraphy in diagnosing pheochromocytoma. AJR Am J Roentgenol 1983;141:719–25.
[64] Shulkin BL, Koeppe RA, Francis IR, et al. Pheochromocytomas that do not accumulate metaiodobenzylguanidine: localization with PET and administration of FDG. Radiology 1993;186: 711–5.
[65] Shapiro B, Copp JE, Sisson JC, et al. Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma: experience in 400 cases. J Nucl Med 1985;26:576–85.
[66] Maurea S, Cuocolo A, Reynolds JC, et al. Iodine-131-metaiodobenzylguanidine scintigraphy in preoperative and postoperative evaluation of paragangliomas: comparison with CT and MRI. J Nucl Med 1993;34:173–9.
[67] Freitas JE. Adrenal cortical and medullary imaging. Semin Nucl Med 1995;25:235–50.
[68] Chong S, Lee KS, Kim AH. Intergrated PET-CT for the characterization of adrenal lesions in cancer patients: diagnostic efficacy and interpretation pitfalls. Radiographics 2006;26:1811–26.

[69] Yun M, Kim W, Alnafisi N, et al. 18F-FDG PET in characterizing adrenal lesions detected on CT or MRI. J Nucl Med 2001;42:1795–9.
[70] Shulkin Bl, Thompson NW, Shapiro B, et al. Pheochromocytomas: imaging with 2-[fluorine -18]fluoro-2-deoxy-D-glucose PET. Radiology 1999;212:35–41.
[71] Ilias I, Yu J, Carrasquillo JA, et al. Superiority of 6-[18F]-fluorodopamine positron emission tomography versus [131I] metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. J Clin Endocrinol Metab 2003;88:4083–7.
[72] Trampal C, Engler H, Juhlin C, et al. Pheochromocytomas: detection with 11C hydroxyephedrine PET. Radiology 2004;230:423–8.
[73] Paulsen SD, Nghiem HV, Korobkin M, et al. Changing role of imaging-guided percutaneous biopsy of adrenal masses: evaluation of 50 adrenal biopsies. AJR Am J Roentgenol 2004;182: 1033–103.
[74] Welch TJ, Sheedy PF II, Stephens DH, et al. Percutaneous adrenal biopsy: review of a 10-year experience. Radiology 1994;193: 341–4.
[75] Silverman SG, Mueller PR, Pinkney LP, et al. Predictive value of image-guided adrenal biopsy: analysis of results of 101 biopsies. Radiology 1993;187:715–8.
[76] Blake MA, Sweeney AT, Kalra MK, et al. Collision adrenal tumors on PET/CT. Am J Roentgenol 2004;183(3):864–5.