13
Current Status of Imaging for Adrenal Malignant Involvement

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Key Points

- CT, MRI, PET and PET/CT are useful in differentiating benign from malignant adrenal involvement.
- Image-guided adrenal biopsy should be considered if needed for treatment planning, and for the now relatively uncommon lesions that remain indeterminate by imaging.

1 Introduction

Adrenal masses are relatively common in the general population, with a mean prevalence determined from several large autopsy studies of 2.3 percent [1]. Given the propensity for and the clinical importance of adrenal metastatic involvement, accurate diagnosis of adrenal masses is of particular important in oncologic patients. Fortunately non-invasive radiology can usually determine whether a mass is benign or likely malignant (indeterminate lesion), based on recent research into the imaging characteristics of adrenal masses.

2 Role of CT

CT examinations, using specialized adrenal protocols, have been shown to characterize solid adrenal masses as benign or indeterminate (likely malignant) with a high degree of accuracy [2, 3, 4], thus providing the means to diagnose the vast majority of non-functional adrenal lesions in a single step, usually without the need for invasive procedures.

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Adrenal CT protocols exploit two significant differences between benign and malignant adrenal masses: their fat content and their vascular properties. Adenomas and myeloplipomas have relatively high fat content, compared to malignancies, and generally appear to be of low density in CT images (Fig.13.1). This difference was first taken advantage of in 1991, when Lee, et al. [5] demonstrated that the attenuation of adenomas on non-contrast CT images differed significantly from malignancies and, indeed, was superior to size measurements in this regard. Several studies have shown that malignant adrenal lesions with attenuations less than 10 Hounsfield units (HU) are extremely rare [5-9]. Consequently, a threshold value of 10 HU is now generally accepted as a practical cut-off value to distinguish an adenoma from a possible malignancy (indeterminate lesion) [9, 10] (Fig. 13.2).

There is considerable overlap in the enhanced attenuation values of malignant and benign adrenal masses following intravenous contrast administration. However, it has been shown that the contrast agent washes out from adenomas significantly more rapidly than that from metastatic masses ($p < .001$) [11]. Studies have since demonstrated that the washout of contrast from adenomas is rapid and reaches a plateau within 10 to 15 minutes, whereas much of the enhancement remains in non-adenomas after 45 minutes [12], including metastases, most pheochromocytomas [13] and adrenocortical carcinomas [3] (Fig. 13.3). Furthermore, adrenocortical carcinomas have a propensity to involve the adrenal veins and IVC.

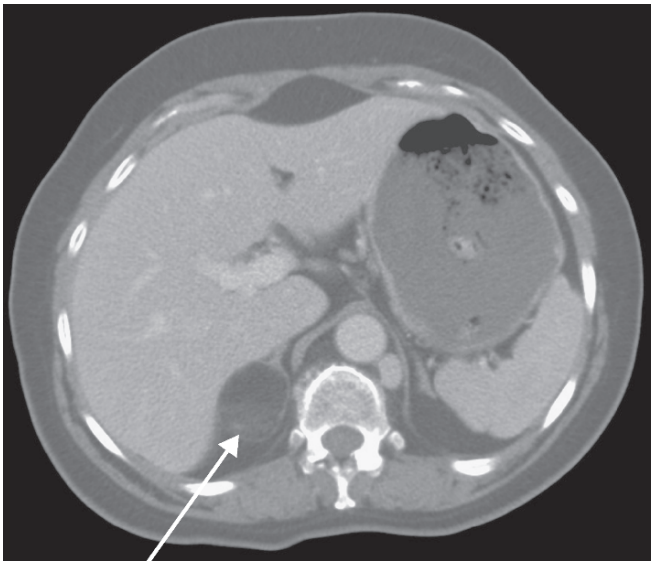

Fig. 13.1 Adrenal myelolipoma. Contrast-enhanced CT scan showing fat containing mass in right adrenal (arrow) consistent with a myelolipoma

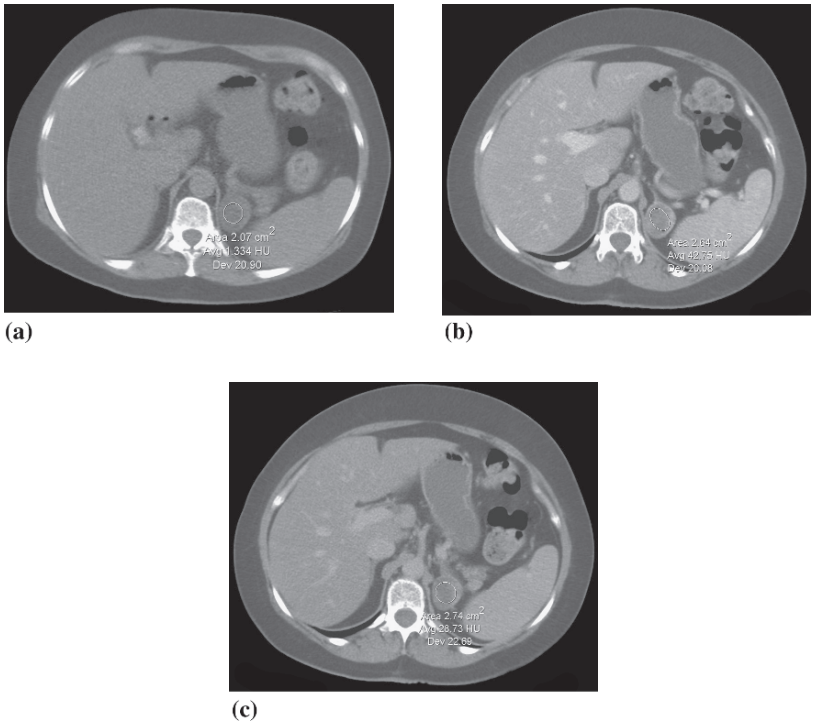

Fig. 13.2 Adrenal adenoma on CT. Large left adrenal mass measuring 1 HU pre-contrast (**a**), 43 HU on dynamic imaging (**b**) and 29 HU on 10-minute delayed imaging (**c**). The low pre-contrast attenuation of the lesion <10 HU is consistent with a lipid rich adenoma although the washout values are not very high

Malignancies have abnormal vasculature with high microvascular density, accompanied by slow flow and abnormally high vascular endothelial permeability [14]. Due to these vascular abnormalities, more contrast agent is likely to accumulate in and to be retained for a longer period in malignant tissue. These differences explain why the contrast agent washout rate from benign adenomas is significantly faster, compared to malignant masses.

Dedicated adrenal CT protocols, which combine non-contrast, early and delayed enhancement, avail of both the physiological differences described above and have been shown to be both highly sensitive and specific [2, 4]. The attenuation (HU) of the adrenal mass is measured on all three scans and the washout rate is calculated from pre-contrast attenuation (P), contrast-enhanced attenuation (E) measured during the portal venous phase and delayed contrast enhancement (D) attenuation measured 10 to 15 minutes later (Fig. 13.4.). The absolute percentage washout

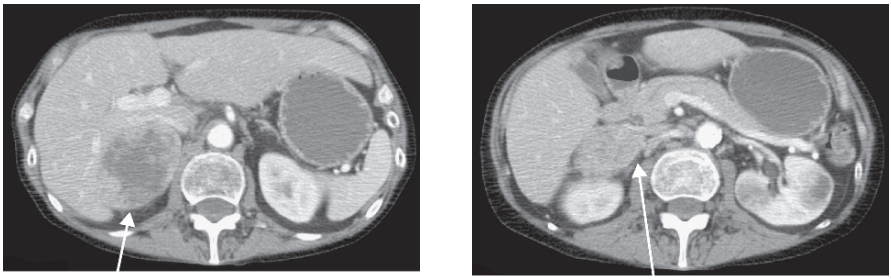

Fig. 13.3 Adrenal carcinoma. Large irregularly enhancing adrenal mass (**a**) on contrast-enhanced CT with evidence of invasion of the IVC (arrow) (**b**) and demonstrated delayed retention of contrast consistent with an adrenal carcinoma

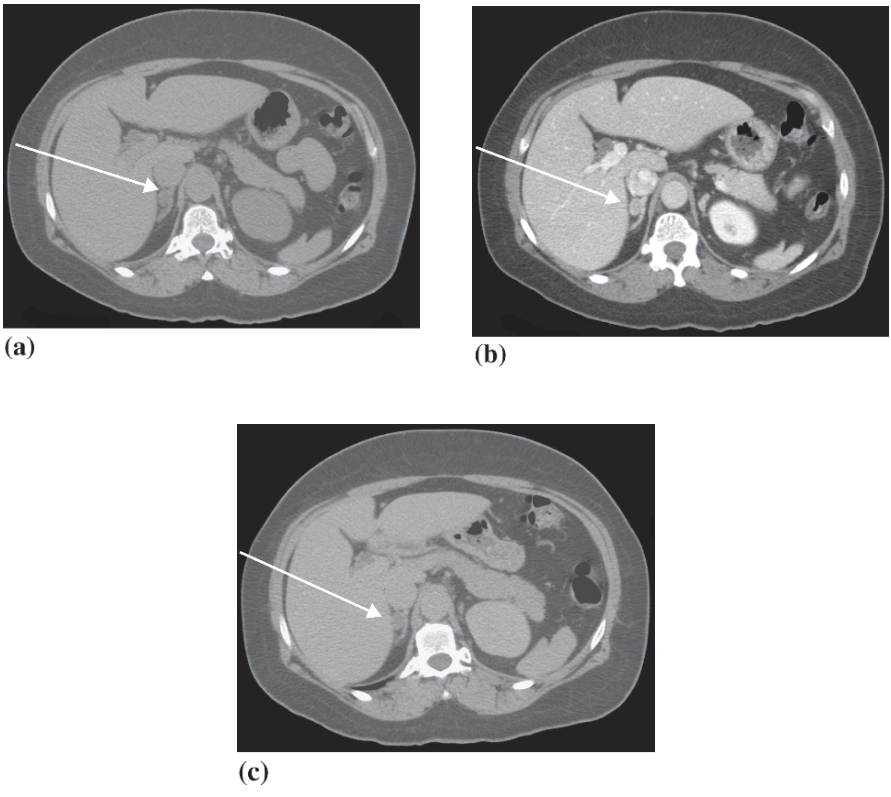

Fig. 13.4 Lipid-poor adrenal adenoma on washout analysis. Right adrenal mass (arrows) measuring 20 HU pre-contrast (**a**) 80 HU on dynamic imaging (**b**) and 40 HU on delayed 10-minute images. The lesion is indeterminate by non-contrast criteria > 10 HU, but as the RPW = 50 percent and APW = 66.6 percent it is consistent with a lipid-poor adenoma

(APW) and the relative percentage washout (RPW) are calculated from the following formulae:

$$APW = 100\,x\,([E-D]/[E-P]$$

$$RPW = 100\,x\,[E-D]/E$$

We have demonstrated that the combination of pre-contrast attenuation (threshold: <0 HU for adenomas, > 43 HU for malignancies), 10-minute relative percentage washout (threshold: > 37.5 percent) and 10-minute absolute percentage washout (threshold: > 52.0 percent) gives a sensitivity of 100 percent and a specificity of 98 percent for differentiating between benign and malignant lesions [2]. As expected, these cut-off values are somewhat lower than those reported (40 percent and 60 percent, respectively) in an earlier study from the University of Michigan in which the final CT was at a 15 minute, rather than a 10 minute delay after the contrast injection [4]. Other researchers have reported the sensitivity and specificity for detection of adenomas by using the percentage washout of contrast after 10 or 15 minutes to be 83 percent to 98 percent and 93 percent to 100 percent, respectively [15-17]. Using these protocols, the vast majority of adrenal masses can thus be diagnosed as indeterminate (suspicious for malignancy) or benign and, if the latter, require no further diagnostic workup, reducing the number of patients who require invasive biopsy evaluation or surgery. However, if no conclusive categorization of an incidentally adrenal mass has been obtained, follow-up CT imaging has been advised at six, 12 and 24 months after the initial discovery of the adrenal lesion, although there are no data from long-term studies to provide supportive evidence [18].

Recent initial reports of CT histogram analysis of individual pixel attenuations have not yet reached a clinical consensus, but suggest it may also give clinically useful adrenal diagnostic information [19, 20].

The imaging characteristics of pheochromocytomas are variable, but they usually contain little fat and, therefore, usually have attenuations >10 HU. Pheochromocytomas typically enhance avidly with contrast, but can be heterogeneous or show no enhancement due to cystic changes. In addition, washout rates are inconsistent, and it is possible to misclassify pheochromocytomas as adenomas or metastases on imaging [13, 21] (Fig. 13.5). Pheochromocytomas can also demonstrate hemorrhage and any hemorrhagic adrenal lesion needs to be carefully studied with follow-up imaging to exclude an underlying tumor that has bled (Fig. 13.6) Extra-adrenal pheochromocytomas are called paragangliomas and can occur anywhere along the sympathetic chain (Fig. 13.7).

3 Applications of MRI

MRI is not considered quite as accurate as adrenal protocol CT, but may be useful if a CT examination is equivocal, especially if an unenhanced CT has been performed, and the use of CT contrast agent is contraindicated. Chemical shift MRI exploits the same physiological difference between adenomas and malignancies as

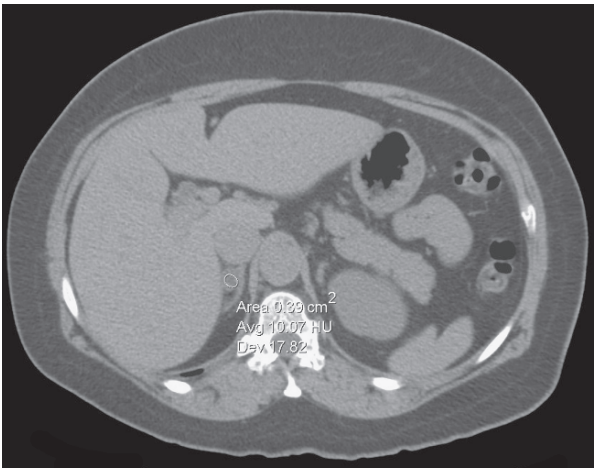

Fig. 13.5 Low density pheochromocytoma. Right adrenal mass representing pathologically proven pheochromocytoma which measured 10 HU on non-contrast CT (arrow)

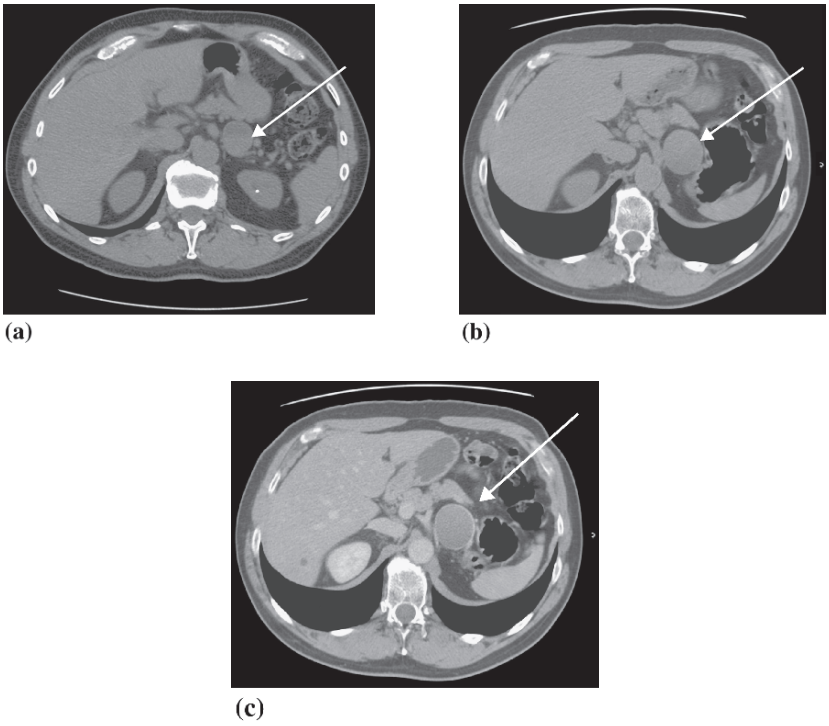

Fig. 13.6 Adrenal hemorrhagic cyst. Large left adrenal lesion (arrow) with hematocrit level and dense component in non-dependent component on non-contrast supine (**a**) and prone (**b**) CT scans, respectively. Contrast-enhanced CT scan (**c**) shows no underlying enhancing lesion (arrow) and further follow-up scans were also negative of underlying tumor

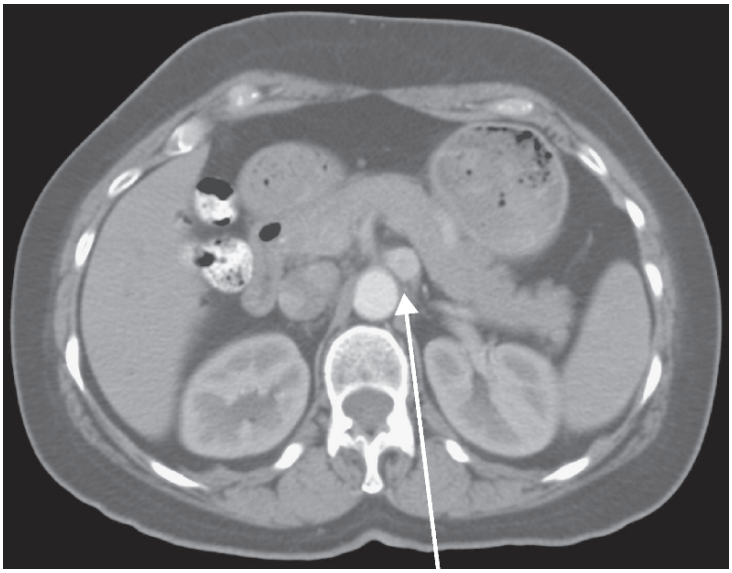

Fig. 13.7 Extra-adrenal pheochromocytoma/paraganglioma. CT scan showing 2.2 cm-enhancing mass (arrow) anterolateral to the aorta consistent with an extra-adrenal paraganglioma

non-contrast CT imaging, namely the high fat content of adenomas. In this method, T1-weighted images are acquired at echo times that are in-phase and out-of-phase to take advantage of the consequences of the different resonant frequency rates of protons in fats and protons. In adenomas, out-of-phase signal intensity is lower due to cancellation of the signals for fat and water protons than that on in-phase images where the signals combine. The reported sensitivity of chemical shift MRI ranges from 81-100 percent and the specificity from 94-100 percent [23,24]. Simple cysts can be distinguished from necrotic malignancy on MRI by their uniformly low signal on T1 weighted images, uniformly hyperintense on T2 weighted images and lack of enhancement on post contrast images (Figure 8).

3 PET and PET/CT

PET using the tracer 2-[18F]-fluoro-deoxyglucose (FDG) is a very good method for detecting metastatic cancer to the adrenals [25-29]. Studies report that sensitivities and specificities of FDG-PET for detecting adrenal malignancy are in the range of 93 percent to 100 percent and 78 percent to 100 percent, respectively. False negatives have been reported due to hemorrhage and necrosis [27], while in one case a renal cell carcinoma metastasis was not identified with FDG-PET [30]. Combined PET/CT scanning has been used to show that the combination of unenhanced CT

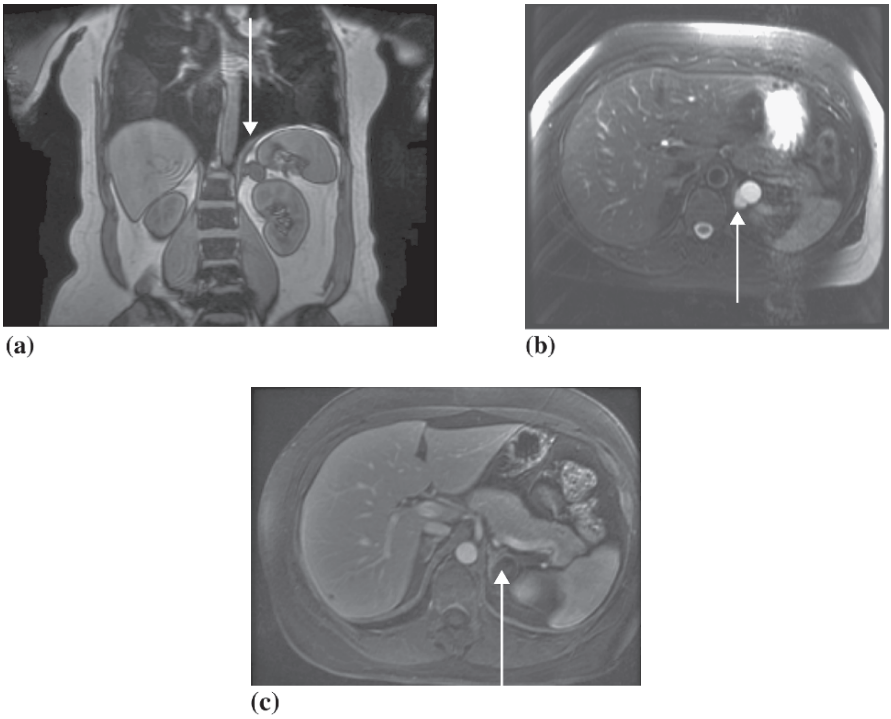

Fig. 13.8 Left adrenal cyst. Coronal T1-weighted **(a)**, axial T2-weighted **(b)** and gadolinium-enhanced **(c)** MR images demonstrating a T1 hypointense, T2 hyperintense non-enhancing 2.5 cm left adrenal lesion (arrows) consistent with a cyst

with PET is better than PET alone for diagnosing malignant adrenal masses [26, 28] (Fig. 13.9), while one study found that PET/CT when using an adrenal protocol CT scan was even better, with a sensitivity and specificity of 100 percent in that study population [26].

Pheochromocytomas are also metabolically active and can also be detected with FDG-PET. In addition, some new agents – ^{18}F-fluorodopamine and ^{11}C-hydro-xyephedrine – show promise as more specific and sensitive agents for pheochromocytomas [21].

4 Adrenal Biopsy

Adrenal biopsy should be considered if needed for treatment planning and for the relatively few cases in which CT, MRI or PET imaging do not provide a definitive diagnosis [23, 31-34]. CT-guided percutaneous needle aspiration biopsy (PNAB) is

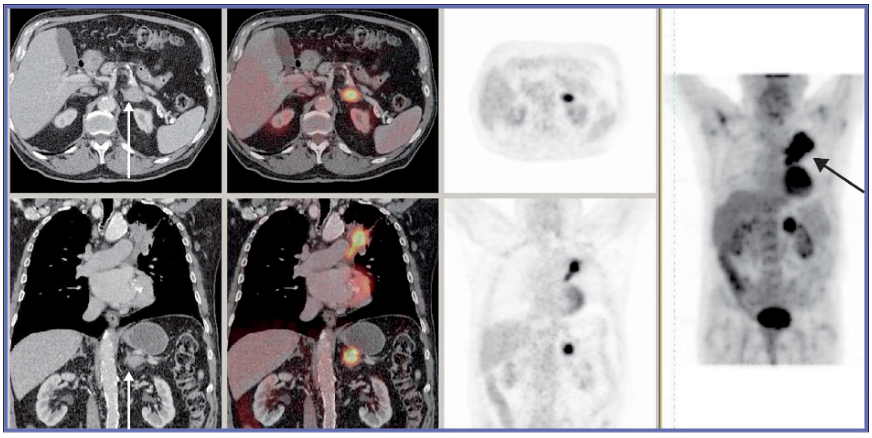

Fig. 13.9 Adrenal metastasis from lung cancer on PET/CT. Axial and coronal PET/CT images demonstrating intense FDG uptake in the primary left upper lobe lung carcinoma (black arrow) and in the left adrenal metastasis (white arrows)

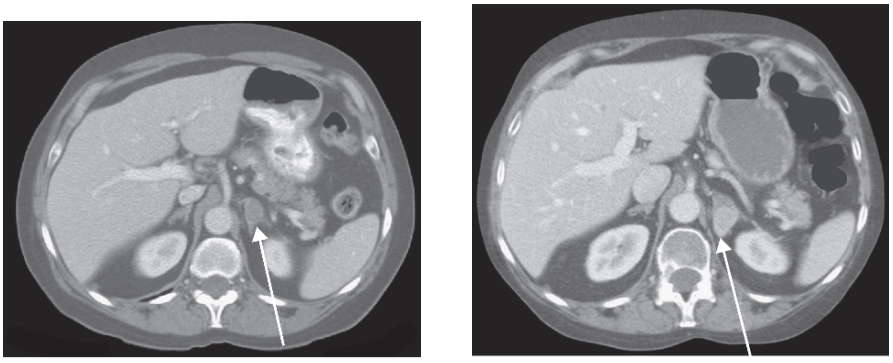

Fig. 13.10 Collision tumors. Contrast-enhanced CT scan **(a)** shows a low density left adrenal lesion stable, compared with previous scans consistent with an adenoma in a patient with breast cancer. CT scan **(b)** six months later shows new enhancing mass (arrow) in left adrenal consistent with breast cancer metastasis displacing the low density adenoma (collision tumors)

a well-established technique and the method of choice. However, pheochromocytoma must be recognized and, prophylaxized against if indicated, to avoid a hypertensive crisis provoked by the PNAB. Histological samples can be useful for the evaluation of metastasis in patients with no other signs of metastases and a heterogenous adrenal mass with a high attenuation value (> 20 HU). However, sampling error can sometimes lead to false negative PNAB results. Collision tumors affecting the adrenal gland (Fig. 13.10) when two different tumors co-exist in the adrenal can occasionally

occur and PET/CT has been shown to help identify and direct appropriate biopsy in such a circumstance [35].

Summary

CT, MRI, PET and PET/CT have all been shown to be clinically useful in differentiating benign from malignant adrenal involvement. Image-guided adrenal biopsy should be considered if needed for treatment planning and for the now relatively uncommon lesions that remain indeterminate by imaging.

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