

## REVIEW

# Distinguishing benign from malignant adrenal masses

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### Abstract

The approach to the radiological and clinical evaluation of adrenal masses in the oncologic and non-oncologic patient is discussed. In addition, the value of unenhanced and enhanced CT densitometry with emphasis on the washout features to distinguish between lipid-rich and lipid-poor adenomas and malignant lesions is detailed. The roles of magnetic resonance imaging and positron emission tomography in distinguishing benign from malignant adrenal masses will also be discussed.

**Keywords:** Adrenal gland; CT; MR; neoplasms; PET.

### Silent or incidental adrenal tumors

When evaluating the 'silent' or 'incidental' adrenal mass, some clinical information is helpful in narrowing down the differential considerations:

- a known underlying malignancy
- clinically overt or biochemical evidence for adrenal dysfunction.

### Non-oncological patient

In patients with no known malignancy, the most important differentiation is between an adrenal carcinoma and an incidental non-functioning adrenal adenoma. Most adrenal cancers do 'function', and can be diagnosed by elevated biochemical markers and therefore distinguished from incidental adenomas.

Most surgeons will surgically remove all masses larger than 5 cm in size, irrespective of their imaging appearances (except for classical adrenal cysts and adrenal myelolipomas), as the incidence of adrenal carcinoma tends to be higher in masses of this size. Masses ranging in size between 3 and 5 cm are in the

'grey zone'. They require additional imaging such as unenhanced/chemical-shift MRI to determine whether or not the lesion is a lipid-rich adenoma, in addition to biochemical evaluation to exclude a functioning lesion/mass. Smaller lesions (1–3 cm) with a non-specific appearance are usually presumed, in the absence of adrenal dysfunction, to represent adenomas, although a confirmatory imaging exam will usually be used to prove their benign nature.

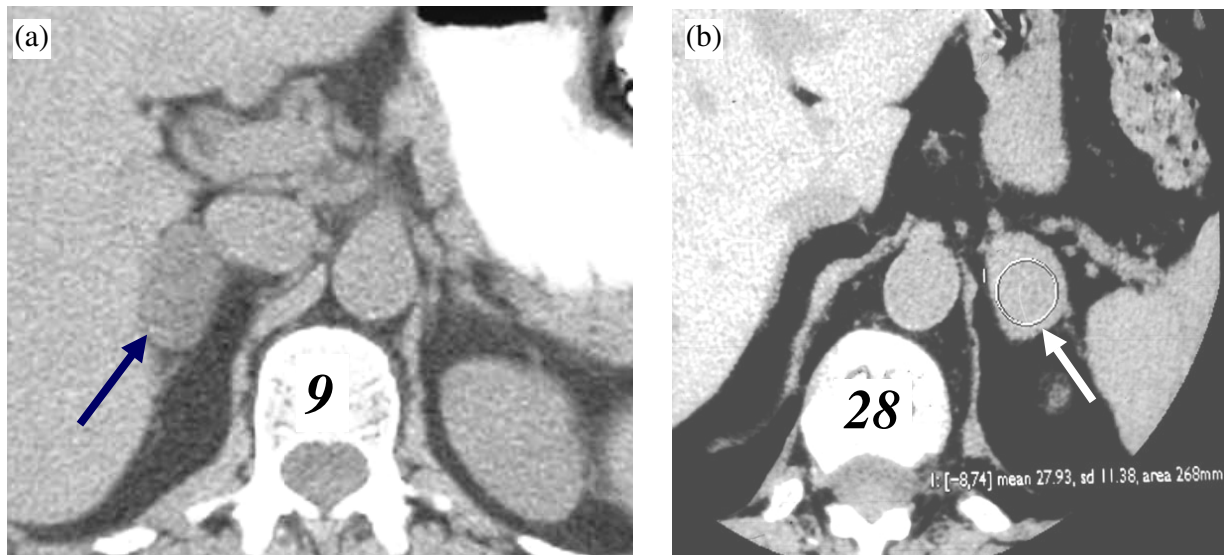
Metastatic disease to the adrenal glands without the detection of a primary neoplasm is very rare.

### Oncological patient

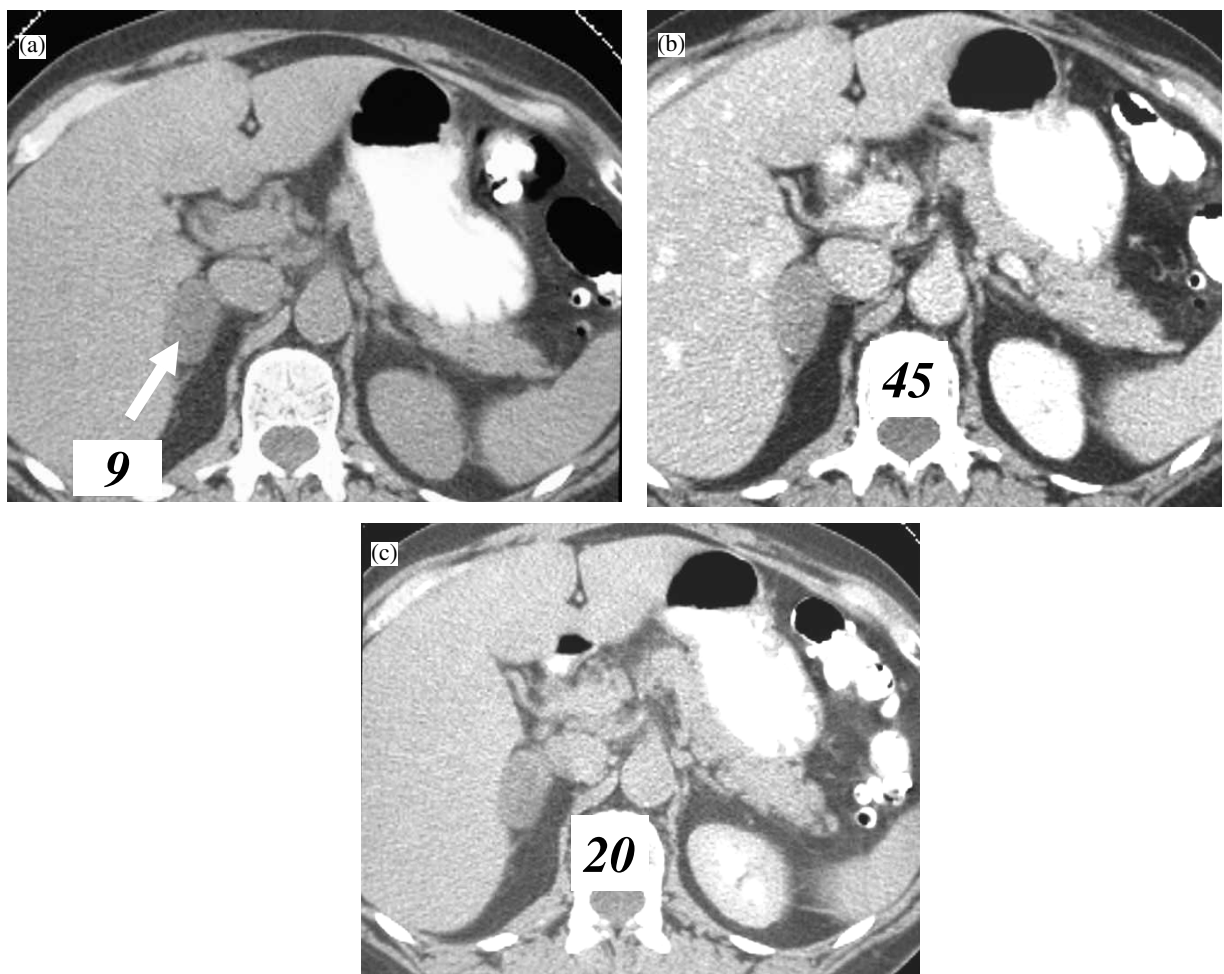
In oncological patients, differentiation between adenoma and metastases is important, as it affects treatment strategy. The tools available for making this distinction are:

- unenhanced CT
- enhanced CT and washout calculations
- chemical-shift MRI
- PET imaging
- adrenal biopsy.

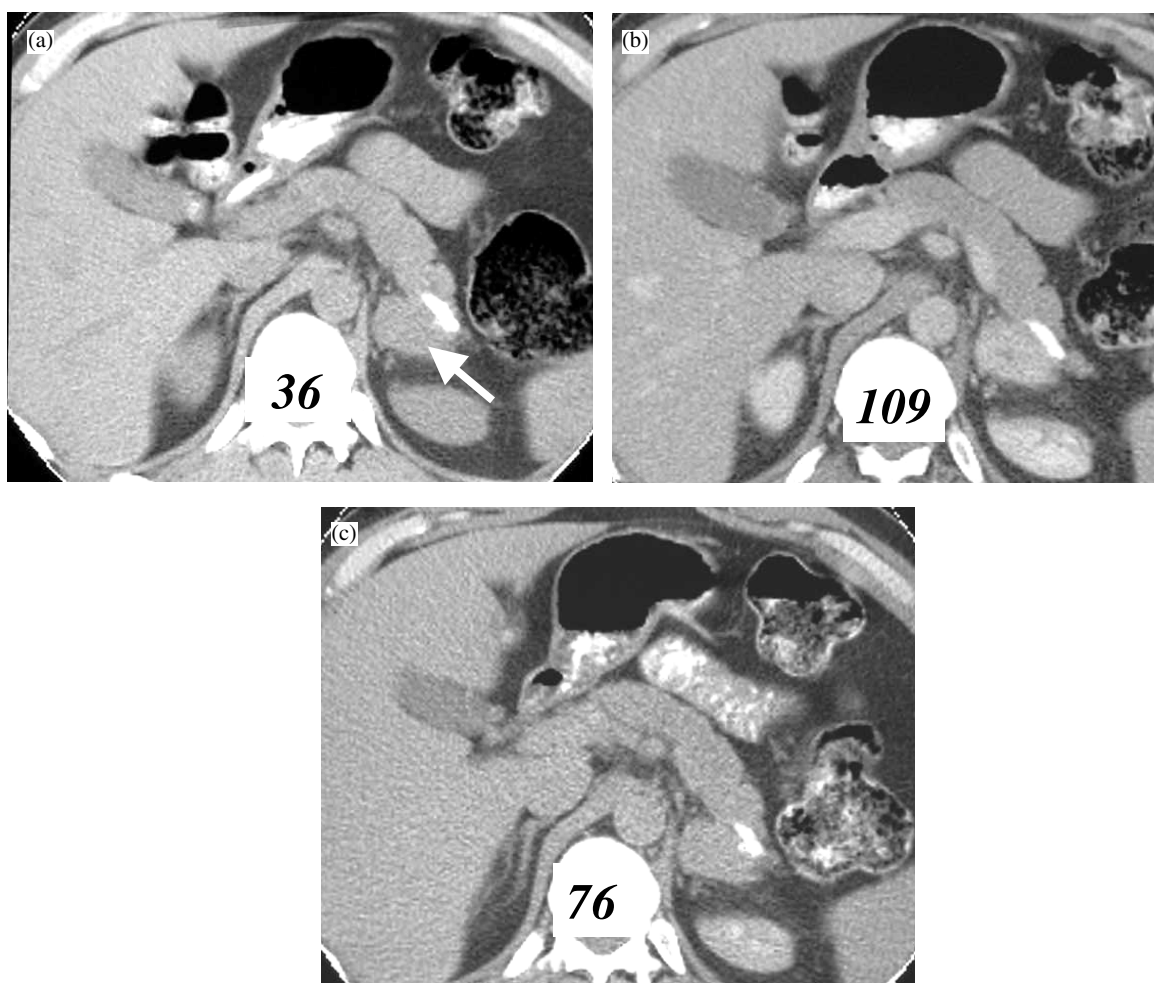
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**Figure 1** (a) Unenhanced images show a right adrenal mass (arrow) with a density measurement of 9 HU. This is typical for a lipid-rich adenoma. (b) Unenhanced images show a left adrenal mass (arrow) which measures 28 HU. This was a proven metastasis on subsequent biopsy.



**Figure 2** (a) Unenhanced images show a right adrenal mass (arrow) which measures 9 HU. (b) This has an HU of 45 on the enhanced and (c) 20 on the delayed image. By enhancement washout calculations this mass has a washout of 70%, which is diagnostic of an adenoma. Subsequent follow-up imaging showed stability of the mass.



**Figure 3** (a) Unenhanced images show a left adrenal mass (arrow) which measures 36 HU. (b) This has an HU of 109 on the enhanced and (c) 76 on the delayed image. By enhancement washout calculations this mass has a washout of 45%, which is diagnostic of a non-adenoma. On subsequent surgical resection, this was a pheochromocytoma.

### Unenhanced CT

If an adrenal mass measures 0 HU (Hounsfield units) or less on unenhanced CT, the likelihood of it being a benign mass is almost 100%. In several recent studies, high specificity (greater than 90%) for adenoma diagnosis was achieved using a density cut-off of equal to or less than 10 HU on unenhanced CT (Fig. 1(a))<sup>[1-3]</sup>. While density measurements of greater than 10 HU can be seen in metastases, they can also be seen in lesions which are not lipid rich (Fig. 1(b)). This is because both lipid-poor and complicated (hemorrhagic) adenomas can have density measurements of greater than 10 HU on unenhanced CT.

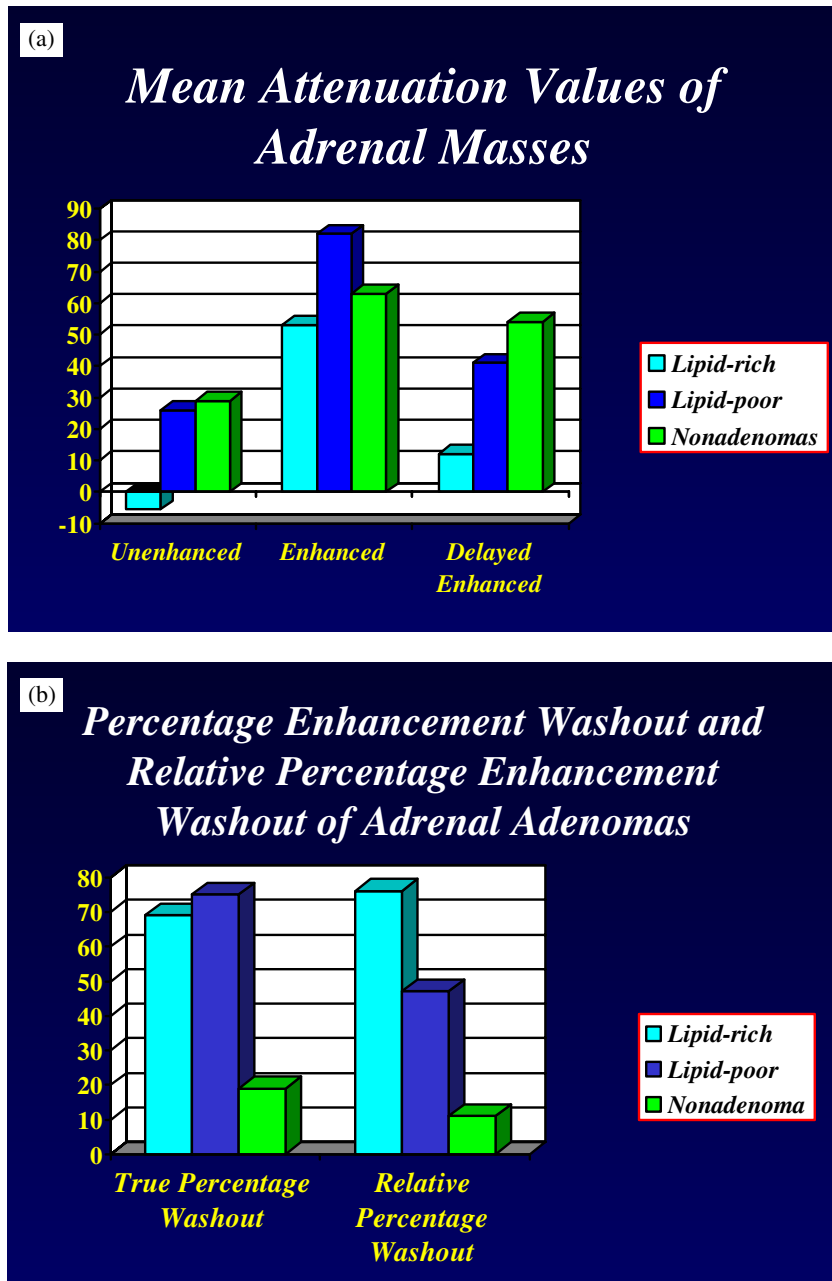
### Enhanced CT densitometry and washout features of adenomas and non-adenomas

More recently, two separate studies by Szolar and Korobkin have shown that adrenal adenomas have unique

washout features, very different from those of non-adenomas on contrast-enhanced CT. In both studies, adenomas had high washout rates of contrast material, beginning at about 5 min and reaching a maximum of about 50–60% at 15 min, following the intravenous administration of iodinated contrast medium (Fig. 2)<sup>[4-9]</sup>. In contrast, non-adenomas tended to retain contrast material and have significantly less washout (15–25%) at 15 min (Fig. 3). Specificities of more than 90% were achieved for the separation of adenomas from malignant lesions in these two studies, using a threshold washout percentage of greater than 50%<sup>[7,8]</sup>.

#### *Washout features of lipid-poor adenomas*

Although lipid-poor adenomas account for between 5 and 15% of all adenomas, they pose a diagnostic problem, as they cannot be reliably distinguished from metastases on both unenhanced and enhanced CT using



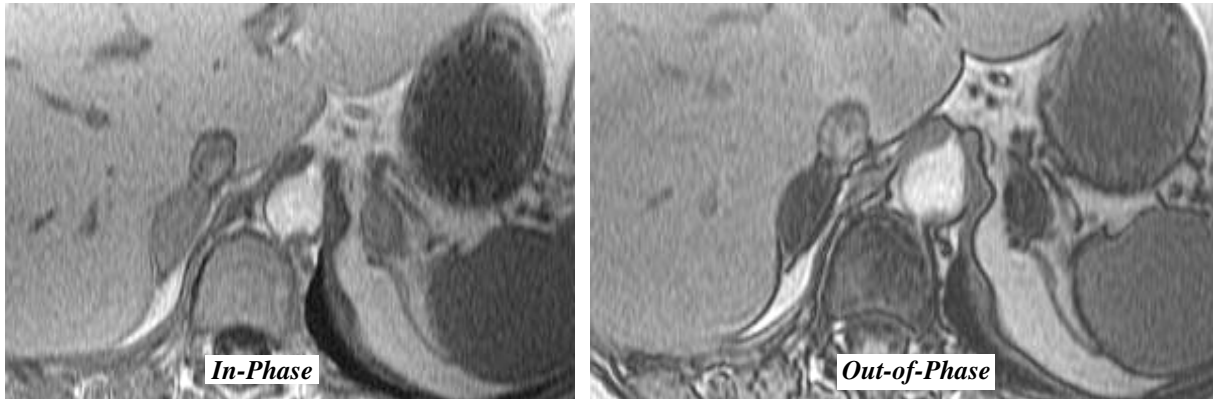
**Figure 4** (a) Mean density measurements of lipid-rich, lipid-poor adenomas and non-adenomas on unenhanced, enhanced and delayed CT images showing that differentiation between lipid-poor adenomas and non-adenomas is not possible. (b) Mean percentage and relative percentage washout of lipid-rich, lipid-poor adenomas and non-adenomas on unenhanced, enhanced and delayed CT images showing that lipid-poor adenomas can be distinguished from non-adenomas.

density measurements alone (Fig. 4(a)). We recently investigated the washout features of adenomas and malignant lesions, and found that both lipid-rich and lipid-poor adenomas do indeed share similar washout characteristics and can therefore be distinguished from malignant lesions. In a study of 18 lipid-poor adenomas, we found that the relative washout percentage of lipid-poor adenomas was 74% (similar to that of lipid-rich adenomas), compared with 19% for non-adenomas

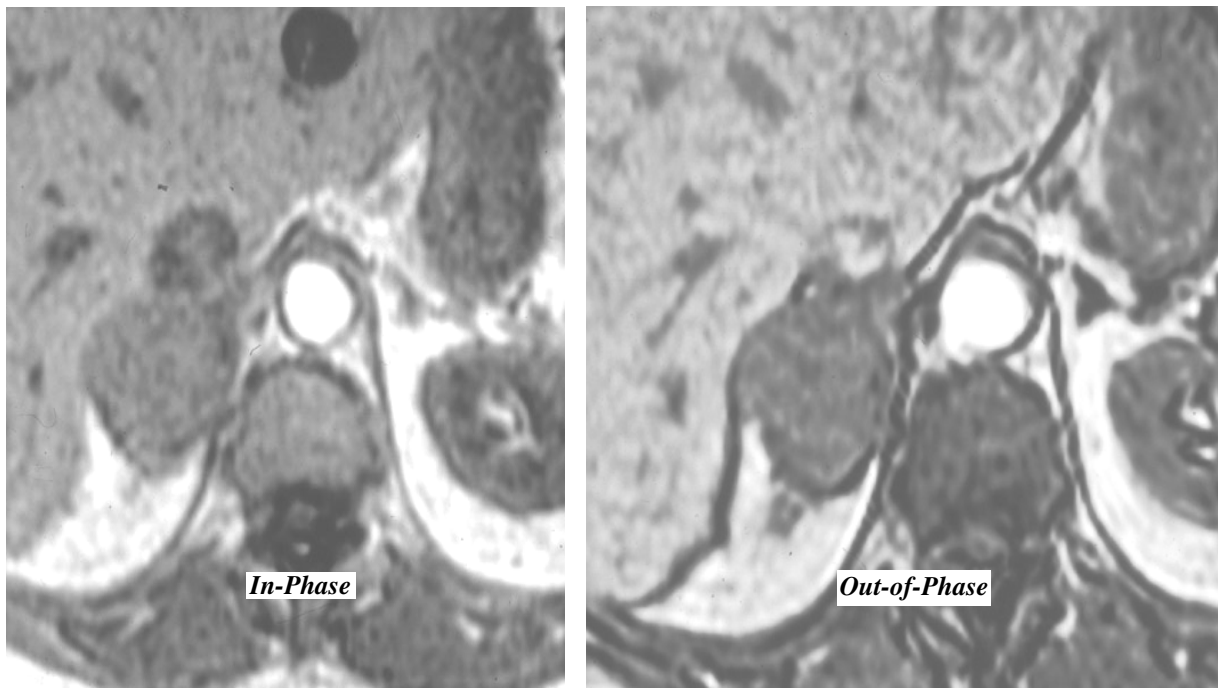
(optimal threshold washout percentage value greater than or equal to 60%) (Fig. 4(b))<sup>[9,10]</sup>. Therefore even lipid-poor adenomas can be distinguished from metastases using washout calculations.

### Magnetic resonance imaging

Chemical-shift MRI is now the most commonly used imaging technique to distinguish between adenomas and

**LIPID-RICH ADENOMAS**

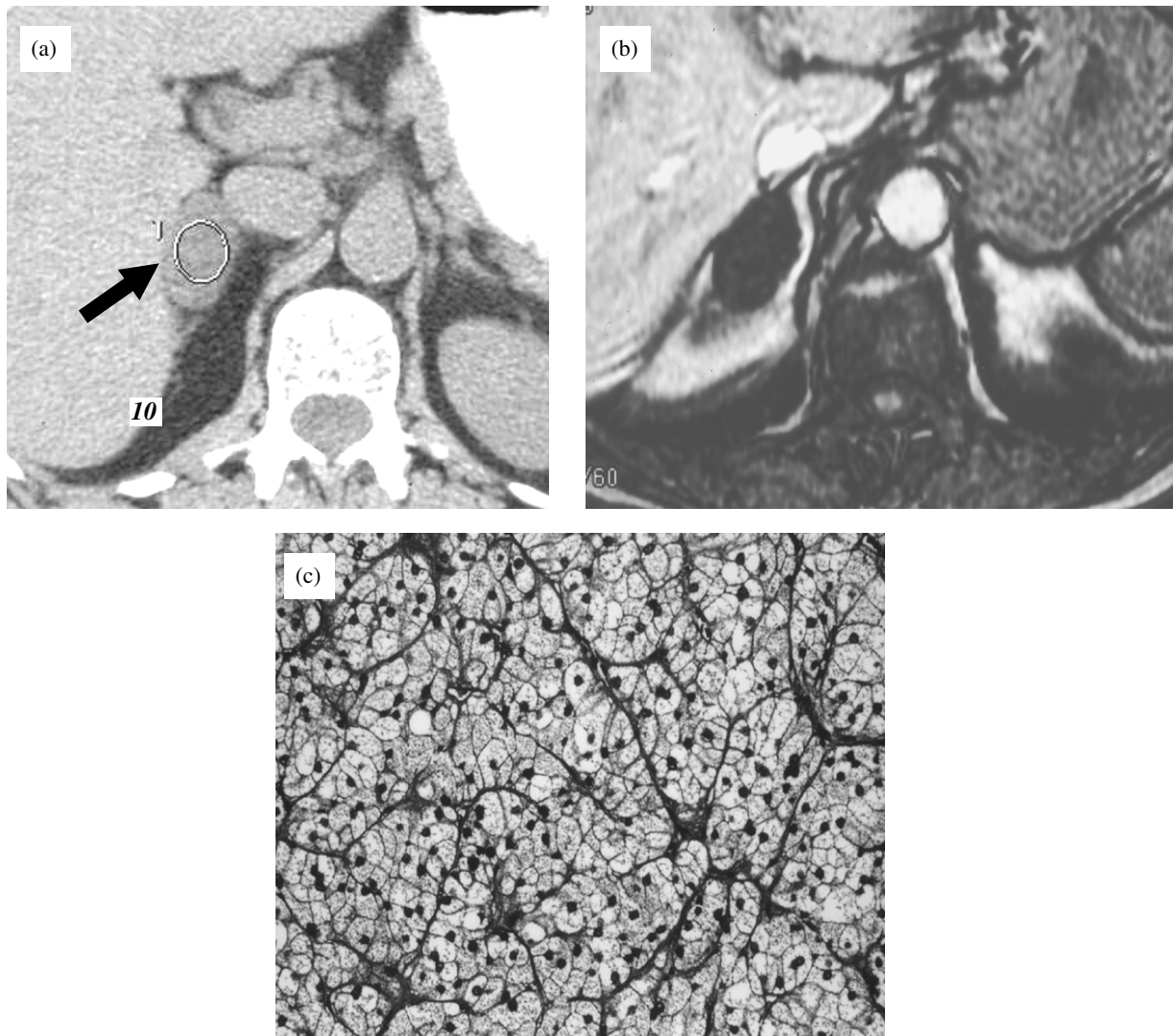
**Figure 5** On the out-of-phase images, bilateral adrenal masses show pronounced loss of SI when compared to the in-phase images using the spleen as a reference, proving that the masses contain lipid and are lipid-rich adenomas.

**ADRENAL CORTICAL CARCINOMA**

**Figure 6** A large right adrenal mass shows no loss of SI on the out-of-phase images when compared to in-phase images using the spleen as a reference. This shows that the lesion is not a typical lipid-rich adenoma. This was proved to be an adrenal cortical carcinoma on subsequent surgical resection.

metastases. The premise with this technique is that most adenomas contain lipid and more than 80% are of the lipid-rich variety<sup>[11]</sup>. In general, malignant adrenal lesions do not contain lipid. In using lipid-sensitive sequences, this technique is able to distinguish between lipid-rich adenomas and most malignant lesions. For accurate interpretation of these images, the in-phase and out-of-phase images (where fat and water are in and out-of-phase with each other) should be compared, and the signal intensity (SI) of the adrenal mass should

be compared with that of a reference organ such as the spleen. It is essential that the technical parameters (except the echo time) be kept identical to ensure that the observation is valid. Lipid-rich adenomas lose signal on the chemical-shift or out-of-phase (opposed-phase) images, while lipid-poor lesions will not lose signal. Thus if a lesion loses SI, it is a lipid-rich adenoma (Fig. 5). If it does not lose SI, all one can state is that the lesion does not contain lipid and is therefore not a lipid-rich adenoma. It may either be a malignant lesion or a lipid-

**LIPID-RICH ADENOMA**

**Figure 7** Lipid-rich adenoma. (a) A low-density right adrenal mass (arrow) measuring 10 HU on unenhanced CT. (b) Loss of SI on the out-of-phase MR image. (c) Abundant lipid is seen on histology.

poor adenoma (Fig. 6). These patients therefore need further evaluation<sup>[11,12]</sup>.

#### *Comparison of unenhanced CT densitometry and chemical-shift MRI*

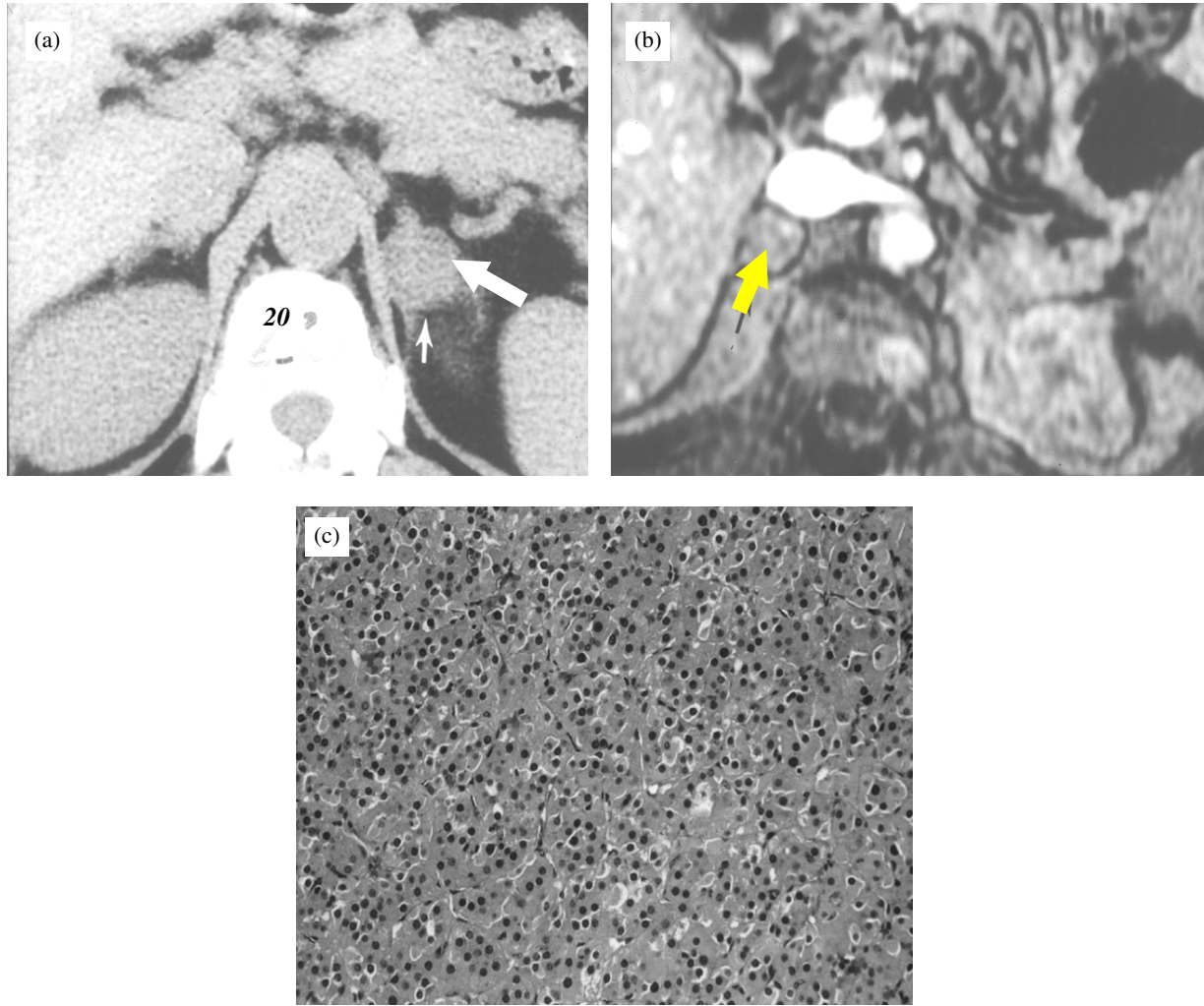
In two studies, these two techniques were used to evaluate the same group of patients with adrenal adenomas. It was shown that there was linear correlation between unenhanced CT numbers of the adrenal masses, and relative loss of SI on chemical-shift MRI<sup>[13,14]</sup>. This suggests that both techniques evaluate the same tissue composition of the adenoma, i.e. its lipid component. In instances where unenhanced CT numbers were indeterminate, chemical-shift MRI was not helpful and vice versa. So whilst one of the two tests could be used

to determine whether or not an adrenal mass is a lipid-rich adenoma, the two tests used in conjunction are not complementary.

#### *Histological correlation of unenhanced CT densitometry and chemical-shift changes on MR in adrenal adenomas*

A study by Korobkin and colleagues correlated and graded the low density of adrenal masses on unenhanced CT and loss of SI on chemical-shift MR with the amount of lipid in pathologically resected adenomas. In this study it was convincingly shown that the degree of low density seen on unenhanced CT and the loss of SI on the opposed or out-of-phase MR images were directly related to the amount of lipid seen histologically within these tumors (Figs 7 and 8)<sup>[15]</sup>.

**LIPID-POOR ADENOMA**



**Figure 8** Lipid-poor adenoma. (a) A left adrenal mass (arrow) measuring 20 HU on unenhanced CT. (b) A right adrenal mass (arrow) showing no loss of SI on the out-of-phase image. (c) Dense compact cells with no lipid are seen on histology.

*University of Michigan adrenal mass characterisation protocol using CT*

If an adrenal mass is seen on a contrast-enhanced staging CT, we bring the patient back for a dedicated adrenal CT. We initially perform unenhanced scans using 3–5 mm thick slices through the adrenal mass. Then an ROI (region of interest) is placed over the mass and if the mass measures less than 10 HU, the workup stops, as we have a diagnosis of a lipid-rich adenoma. If the lesion measures greater than 10 HU, then we administer 100–120 ml of non-ionic IV contrast (3 ml/s) and then re-scan the adrenal mass initially after a 60 s scan delay followed by images at 15 min. Care must be taken to use an imaging technique identical to that used for the unenhanced scans. Identical-sized ROIs are used to measure the density of the adrenal mass at the same location on the unenhanced, early-enhanced and delayed-enhanced images.

% enhancement washout

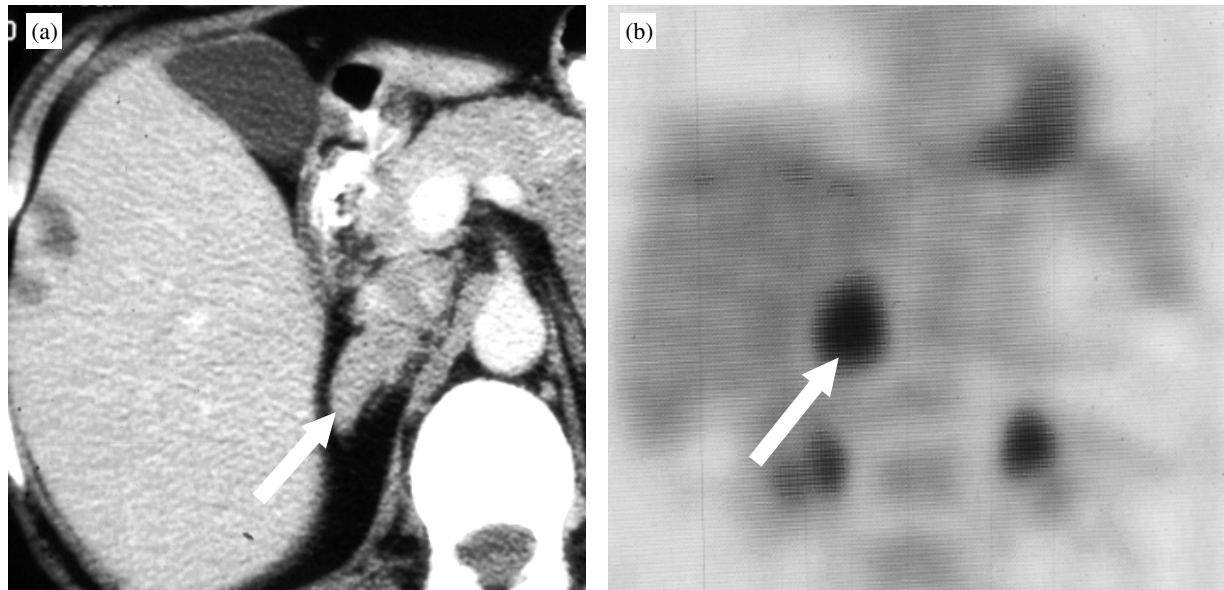
$$= \frac{\text{density on enhanced CT} - \text{density on delayed CT}}{\text{density on enhanced CT} - \text{density on unenhanced CT}}$$

The optimal threshold value for a percentage enhancement washout of greater than or equal to 60% has a specificity of 95% and sensitivity of 79–89% for adenoma diagnosis.

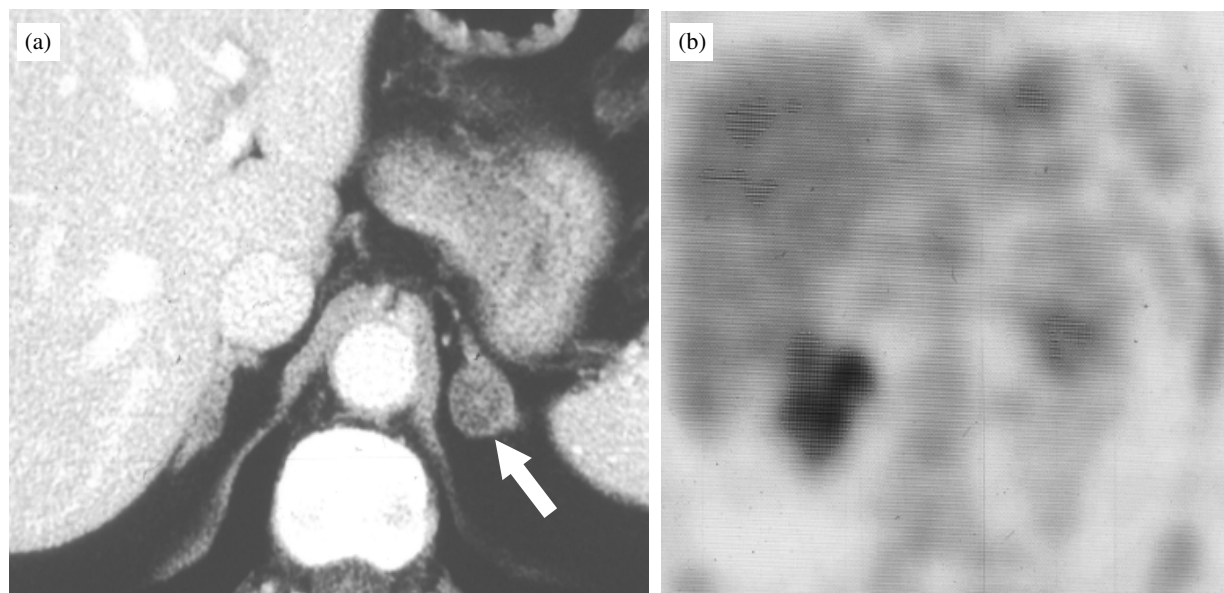
If the unenhanced scan's data are not available, then the relative percentage enhancement washout can be calculated as:

$$\text{relative \% enhancement washout} = \frac{\text{density on enhanced CT} - \text{density on delayed CT}}{\text{density on enhanced CT}}$$

For the diagnosis of an adenoma using relative percentage enhancement washout, the optimal threshold value is a value equal to 50% or greater than 50% [6–10].



**Figure 9** In a patient with colon cancer and rising CEA (carcino-embryonic antigen). (a) CT shows right adrenal mass (arrow), (b) which takes up FDG on PET scan. Biopsy confirmed metastatic disease.



**Figure 10** (a) In a patient with lung cancer, CT shows a left adrenal mass, (b) which demonstrates no FDG uptake. Follow-up imaging confirmed stability, suggesting that it is an adenoma.

### PET-FDG imaging

Initial studies have suggested very high accuracy and specificity for distinguishing adenoma from metastases, although infrequently benign lesions can show increased FDG uptake. Metastases in general have high FDG uptake (Fig. 9) while most adenomas are not FDG avid (Fig. 10)<sup>[16,17]</sup>. PET-FDG imaging is being used with increasing frequency in whole-body staging of various malignancies and will emerge as an excellent tool in the differentiation between benign and malignant adrenal lesions.

### Adrenal biopsy

Although adrenal biopsy is a very valuable tool in the differentiation between metastases and adrenal adenoma, it is less frequently used than in days prior to the use of unenhanced CT densitometry and chemical-shift MRI. CT and MR are now being used to triage which patients will require biopsy or operation. So at our institution, adrenal biopsies are performed only when imaging studies are equivocal and a malignant lesion is strongly suspected.



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