Metastasis or adenoma? Computed tomographic evaluation of the adrenal mass

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■ **BACKGROUND** Determining the nature of an adrenal mass is often a clinical challenge.

■ **OBJECTIVE** To determine if unenhanced computed tomographic (CT) scanning can differentiate benign adenomas from metastases.

■ **METHODS** Twenty-four pathologically proven adrenal masses were retrospectively correlated with their appearance on unenhanced CT scanning.

■ **RESULTS** Metastases were significantly larger than adenomas and had higher attenuation coefficients. A sensitivity-to-specificity ratio of 33:100 was achieved at a threshold of 0 Hounsfield units (HU), while a threshold of 10 HU produced a ratio of 58:92. A threshold size of 2.5 cm produced a ratio of 58:100. Attenuation and size were the only useful criteria for differentiating adenomas from metastases.

■ **CONCLUSION** Measuring the size and attenuation of adrenal masses can help identify benign adenomas. Lesions exceeding specific thresholds may still be benign and may require biopsy. We advocate documenting lesion stability for longer than is usually done, as one metastatic lesion remained without significant change in appearance for 18 months.

■ INDEX TERMS: TOMOGRAPHY, X-RAY COMPUTED; ADRENAL GLAND NEOPLASMS; ADENOMA; NEOPLASM METASTASIS; DIAGNOSIS, DIFFERENTIAL
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SPECIFIC characterization of adrenal masses using various imaging modalities remains a radiologic challenge. This characterization is particularly important in patients with cancer, for whom the presence of a metastatic lesion in the adrenal gland could affect the choice of therapy.

Adrenal lesions are not uncommon. Incidental adrenal masses have been reported in 0.6% of all computed tomographic (CT) scans of the abdomen,[1] and 2% to 9% of adults have grossly visible nonhyperfunctioning adenomas at autopsy.[1,2] Moreover, microscopic evaluation of adrenal glands at autopsy reveals nonuniformity of the adrenal cortices with multiple small nodules in up to 50% of patients.[1] Even in patients with non-small cell carcinoma of the lung, two thirds of adrenal masses are benign.[3]

Multiple studies have evaluated the ability of CT scanning, magnetic resonance imaging (MRI), and scintigraphy to differentiate benign from malignant adrenal masses. In a recent report of a large series of patients, Lee et al[4] advocated measuring the attenuation value of adrenal masses on unen-

hanced CT scans to help in this differentiation. However, pathologic proof was available in only 5 of the 66 cases in their series. Therefore, we retrospectively evaluated a series of pathologically proven adrenal masses to verify this conclusion and to determine if any other characteristics would further aid in this important distinction.

MATERIALS AND METHODS

Using the computerized surgical-pathology records of our institution, we identified 21 patients with 25 adrenal lesions (four patients had bilateral lesions), all of whom had also undergone unenhanced CT scanning of the adrenal glands between January 1, 1988, and October 31, 1991. Two of these lesions, both in the same patient, were excluded because they had the characteristic CT appearance of adrenal cysts; clear fluid had been percutaneously aspirated from one mass, and the lesion eventually recurred. Both glands were subsequently resected because of a clinical suspicion of pheochromocytoma, and pathological study revealed benign adrenal cysts.

Additionally, two surgically proven adrenal lesions were excluded because no corresponding masses were seen on the preoperative CT scans. One of these lesions was in a patient with bilateral metastases in whom only one adrenal gland was enlarged. Five surgically proven adrenal lesions could not be characterized because the corresponding CT tape could not be found for retrospective analysis.

Five pheochromocytomas in four patients were identified. Three of these patients, including one with bilateral pheochromocytomas, had poorly controlled hypertension with elevated serum catecholamine levels and had been suspected of having a pheochromocytoma on clinical grounds. One patient with renal cell carcinoma and an adrenal mass suggesting metastatic disease was found to have an asymptomatic pheochromocytoma and was subsequently found to have Von Hippel-Lindau disease. These five lesions were excluded from our study because these adrenal masses identified by computed tomography in the appropriate clinical setting are usually not a diagnostic dilemma. Moreover, the small number of lesions precluded a meaningful analysis. This left 11 surgically proven adrenal lesions in 10 patients in whom corresponding unenhanced CT scans of the adrenal mass could be analyzed.

In addition, 27 computed tomography-guided percutaneous biopsies were performed in 26 patients with adrenal masses (one patient underwent biopsy twice) between January 1, 1989, when computerized records began to be kept to retrospectively identify such patients, and October 31, 1991. Twelve patients, including the patient who underwent biopsy twice, were excluded because their tissue was unsatisfactory for cytologic analysis. Two other patients were excluded because their CT tapes could not be found. This left 13 diagnostic percutaneous biopsies in 13 patients.

In total, this series comprises 24 adrenal lesions in 23 patients in whom a surgical or cytologic diagnosis had been established and who had accompanying unenhanced CT scans of the adrenal glands. There were 7 men with 8 adrenal lesions and 16 women with 16 adrenal lesions. The men ranged in age from 54 to 75, with a mean age of 66; the women ranged in age from 34 to 72, with a mean age of 58. Eleven lesions were located within the right adrenal gland and the remaining 13 lesions were in the left adrenal gland.

Twelve patients had metastatic disease, which was proven by surgical excision in 3 and by percutaneous aspiration in 9. The primary tumors were renal cell carcinoma (4 patients), non-small cell carcinoma of the lung (2 patients), neoplasms of the liver, uterine endometrium, colon, stomach, and lung in 1 patient each, and squamous cell carcinoma of unknown origin in 1 patient.

Eleven patients had 12 adenomas; 6 of these patients had 7 nonhyperfunctioning adenomas, 3 proven by surgical excision and 4 proven by percutaneous aspiration. Five of these 6 patients had a known primary malignancy, and all 5 underwent biopsy to evaluate possible adrenal metastases. The 6th patient, who had large bilateral adrenal glands, underwent biopsy because of a clinical suspicion of adrenal insufficiency.

Five other patients had adenomas consistent with aldosteronoma, and all of these patients had a clinical history of hypertension, hypokalemia, hypernatremia, and elevated serum aldosterone. All of these tumors were surgically excised. There were no other functioning adenomas in this series, and there were no cases of primary adrenal carcinoma, adrenal inflammatory diseases, or other primary neoplasms metastatic to the adrenal glands.

We characterized the lesions with respect to size, CT appearance (homogeneous or heterogeneous,

TABLE
SIZE AND ATTENUATION COEFFICIENTS OF 24 ADRENAL MASSES

	Metastatic lesions (n = 12)	Adenomas (n = 12)	P
Mean size, cm*	3.80 ± 0.85	2.53 ± 0.89	.01
Attenuation coefficient, Hounsfield units	30.7 ± 8.2	8.58 ± 17.11	.001

*Values are means ± 1 standard deviation

with or without areas of calcification), margination (smooth, lobulated, or irregular), and attenuation coefficient in Hounsfield units (HU). The available tapes were reloaded, and each was analyzed in a blinded manner by one of two radiologists who had subspecialty training and experience in abdominal computed tomography. Size was measured on the axial scan using the distance cursors and recorded as the longest distance. The attenuation coefficients were determined using the method described by Lee et al.[4] In brief, a circular or ovoid region of interest was selected that contained approximately two thirds of the area of the lesion. The edge of the area of interest was at least 10 pixels from the margin of the lesion in order to reduce beam-hardening artifact.[5] Each lesion was analyzed at least three times, and both the mean attenuation coefficient and the standard deviation were calculated. The final recorded value was the average of these separate measurements.

A variety of CT scanners was used. A Picker 1200 130-kV, 95-mA scanner (Picker International, Cleveland, Ohio) was used in two lesions, a Technicare 2060 Quantum 120-kV, 100-mA scanner (Technicare Corporation, Solon, Ohio) was used in one lesion, and a Siemens Somatom Plus 120-kV, 290 mA scanner (Siemens Medical Systems, Iselin, New Jersey) was used in the remainder. Each scanner was calibrated daily using a water phantom and in accordance with the manufacturer's specifications. All scans were obtained without intravenous contrast. The slice thickness and collimation varied and included 5 × 5-mm contiguous axial slices (18 scans), 5 × 3-mm overlapping axial slices (2 scans), and 10 × 10-mm slices in the remaining 4 scans, in which the adrenal glands were included in abdominal studies performed without intravenous contrast. We did not feel that volume-averaging effects in these thicker slices were a problem, because these adrenal masses tended to be the largest in this series.

We reviewed each of the 23 patients' charts to obtain the clinical history.

We grouped the lesions into the categories of metastasis or adenoma, combining the aldosteronomas with the nonhyperfunctioning adenomas into a single group. The rationale for this is twofold. First, on pathologic study, these types of adenomas cannot be differentiated from one another. This distinction, instead, requires an appropriate clinical history and supportive biochemical data. Secondly, even in patients with hyperaldosteronism, an adrenal mass identified on computed tomography may be due to a cause other than an aldosteronoma.[6]

We calculated the mean size and the mean attenuation coefficient of the metastatic lesions and the adenomas, and we analyzed the differences between the groups using the Wilcoxon rank-sum test. In addition, we performed receiver operating characteristic (ROC) analysis to compare the diagnostic accuracy of lesion size and attenuation coefficient. One lesion from the patient with bilateral masses was randomly omitted from all statistical comparisons.

Other CT features such as margination, heterogeneity, and presence or absence of calcifications were tabulated but not statistically analyzed due to the relative uniformity in appearance of all lesions regardless of cause.

RESULTS

The metastatic lesions were significantly larger ($P = .01$) and had significantly higher attenuation coefficients ($P = .001$) than the benign adenomas (*Table*).

Figure 1 displays the ROC curves for lesion size and attenuation coefficient. Sensitivity was defined as the probability that a truly benign lesion would be categorized as benign, and specificity referred to the probability of accurately classifying a truly malignant lesion. The nonparametric estimate of the area under each curve is significantly greater than 0.5 (0.78 ± 0.09 for size and 0.83 ± 0.10 for attenuation), indicating that both parameters are useful in distinguishing benign from malignant lesions. The difference between the two areas, however, is not statistically significant[7] ($P = .64$), suggesting that both parameters are equally useful.

The partial area under the curve, defined as the area under the curve for a select false-positive fraction, was also analyzed to determine if either parameter was more valuable in the high-specificity

range. For the false-positive fraction range of interest, 0.00 to 0.05, the partial areas of the curves were 0.032 ± 0.008 for size and 0.036 ± 0.008 for attenuation, which were not significantly different.[8]

We also analyzed the observed sensitivity and specificity for each parameter at the same cutoff points used by Lee et al.[4] An attenuation coefficient threshold of 0 HU resulted in a sensitivity-to-specificity ratio of 33:100; at 10 HU the ratio was 58:92. A threshold size of 2.5 cm resulted in a sensitivity-to-specificity ratio of 58:100.

Other CT features were not helpful. The most common appearance, regardless of cause, was a round, smooth, homogeneous lesion. Only 5 of the 24 lesions in this study were heterogenous, including 1 metastatic lesion, 2 aldosteronomas, and 2 nonhyperfunctioning adenomas. Only 2 lesions contained areas of calcification, and both lesions were nonhyperfunctioning adenomas.

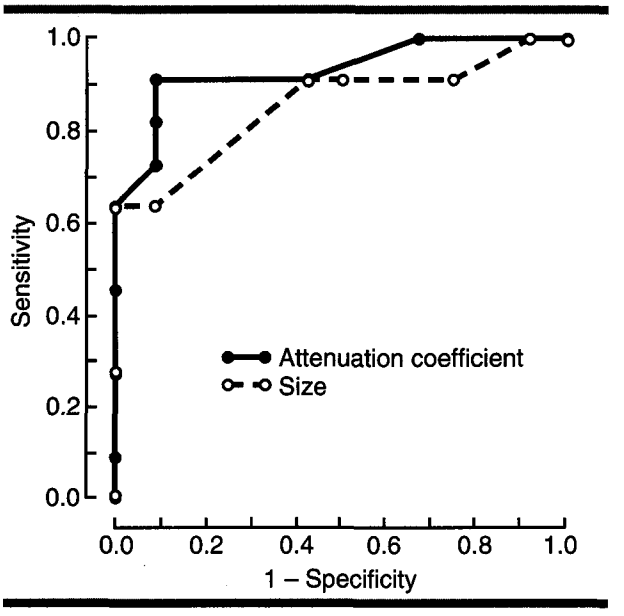

FIGURE 1. Receiver operating characteristic curves for computed tomographic attenuation coefficient and lesion size for distinguishing metastatic tumors in the adrenal glands from benign adrenal adenomas.

DISCUSSION

Specific characterization of adrenal lesions is crucial, especially in patients with a known primary neoplasm in another organ who are being considered for surgical resection or in whom the presence of an adrenal metastasis might alter their management. At our institution, we will perform a biopsy of an adrenal mass if there are clinical clues that suggest metastatic disease, but we advocate a more conservative approach if there are strong indicators that the lesion is benign.

We were able to obtain pathologic proof of 24 masses for which unenhanced CT scans of the adrenal glands were available, along with the respective data tapes, and we were able to record a variety of parameters for each lesion. The only parameters that were useful for characterization were size and attenuation coefficient. They were equally valuable and statistically significant in the differentiation of benign adenomas from metastatic adrenal masses.

Lee et al[4] reported a similar study of the value of measuring the size and the attenuation coefficient of adrenal masses on unenhanced CT scanning. Their estimated diagnostic accuracy for size (0.84) and attenuation coefficient (0.91) exceeded ours (0.78 and 0.83), although not significantly. Moreover, they identified the attenuation value as a significantly better discriminator than lesion size. There were, however, several design differences between these two studies.

First, the patient samples differed in the two studies. Lee et al[4] excluded functioning adenomas. We included them because the clinical distinction between functioning and nonhyperfunctioning adenomas is not always clear. Although this distinction is usually clinically evident, if the proper biochemical data are not obtained, the correct subclassification is precluded, as these lesions cannot be separated from one another by pathologic study. Moreover, hyperaldosteronism, even in patients with adrenal nodules identified on CT scanning, may be due to a cause other than a functioning adenoma.[6]

Second, our study is affected by a verification bias. That is, we could not obtain pathologic proof in a series of sequentially identified adrenal masses. Instead, pathologic proof was obtained only for those clinically or radiologically suspicious lesions that were amenable to percutaneous biopsy. This selection bias could lead to overestimation of the specificity and underestimation of the sensitivity. For example, the results may be influenced by a minimal size criterion below which biopsy was deemed not practical. This minimal size criterion would tend to decrease the discriminating ability of lesion size. Indeed, two metastatic lesions were detected histologically at surgical resection where no

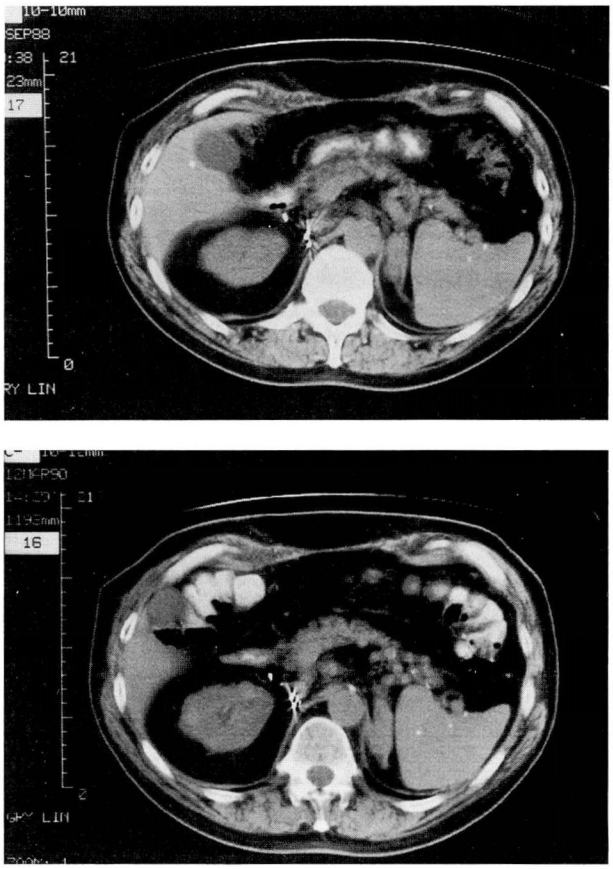

FIGURE 2. Stable appearance on computed tomography of a metastatic adrenal lesion in a 68-year-old man who had previously undergone a left nephrectomy for renal cell carcinoma. A scan of the abdomen in September 1988 (top) shows a 4 × 2-cm lobulated left adrenal mass. A follow-up scan in March 1990 (bottom), obtained with a different field-of-view diameter, shows no significant change in lesion size.

adrenal mass was seen on CT scanning. Measurement of attenuation may be less affected by this selection bias; therefore, preferential use of the attenuation coefficient to help differentiate benign adenomas from malignant metastases may be reasonable, although size and attenuation were equally powerful in our study.

Lastly, the study of Lee et al[4] may be affected by a classification bias. They classified an adrenal lesion as benign if no change was identified over an interval ranging from 6 months to 3 years (mean 13 months, median 9 months). However, one metastatic lesion in our series (*Figure 2*) did not significantly change in size or CT appearance over approximately 18 months; it was resected because a follow-up MRI study was not considered classic in appearance for a benign adrenal adenoma. Misclassification of the lesions may lead to biases if pathologic proof is not available.

These design differences and biases make comparing the two studies difficult. However, both studies found size and attenuation values useful discriminators in differentiating benign from metastatic lesions. Other CT characteristics that we studied, including homogeneity, calcification, shape, and margination, were of no help in discriminating benign from malignant lesions.

In patients with an adrenal mass identified on an enhanced CT study, a follow-up noninvasive test (ie, an unenhanced CT scan) may enable a confident diagnosis of a benign adrenal enlargement, thereby making biopsy unnecessary.

Other imaging modalities, including scintigraphy and MRI, have been advocated to differentiate benign from metastatic adrenal lesions.

Scintigraphy with iodine-131-6-iodomethyl-19-norcholesterol (NP-59) has been shown to be of value in diagnosing benign adrenal lesions that are > 2 cm.[9] Smaller lesions, however, demonstrate variable uptake. In any event, this radionuclide is not readily available.

The use of MRI to characterize adrenal lesions has received much attention. The signal ratios of adrenal mass-to-liver and adrenal mass-to-fat have been reported to be useful in differentiating benign from malignant causes of adrenal enlargement at a variety of pulse sequences and magnet strengths.[10–15] Unfortunately, overlap occurs in each category resulting in the classification of many lesions as indeterminate and limits the utility of MRI examination of the adrenal glands in daily clinical practice. MRI is also less sensitive than CT scanning in detecting extrahepatic tumors in the examination of the abdomen for potential sites of metastatic disease. Moreover, CT scanning is more widely available and costs less; at our institution an MRI study of the adrenal glands costs nearly twice as much as an unenhanced CT scan. However, MRI is more specific for the diagnosis of pheochromocytomas[16] and, at our institution, MRI has nearly replaced CT scanning for initial adrenal imaging in patients with clinical and biochemical evidence of pheochromocytoma.

In conclusion, we recommend using unenhanced computed tomography to differentiate benign adrenal adenomas, either functioning or nonhyperfunc-

tioning, from metastases. In this series of pathologically proven adrenal lesions, threshold values for size and attenuation correctly classified all metastatic adrenal lesions while still maintaining a relatively high sensitivity. Masses exceeding these thresholds may still be benign and are therefore best evaluated by percutaneous biopsy if long-term stability cannot be documented and metastatic disease in the adrenal gland is of clinical concern.

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Commentary

Computed tomographic (CT) scanning was the first noninvasive test with sufficient resolution to locate small adrenocortical tumors with a high degree of diagnostic accuracy. However, its widespread use has created new diagnostic challenges for physicians. Currently, high-resolution abdominal CT scanning reveals incidental adrenal masses in 0.6% of patients. Although most asymptomatic and previously undetected adrenal masses are benign and nonfunctional, several diseases must be ruled out. These disorders include pheochromocytoma, subclinical functional adrenal adenomas, early adrenal carcinoma, and metastases.

In their study, Singer and coworkers assessed the clinical utility of unenhanced CT scanning to differentiate benign adrenocortical adenomas from metastatic adrenal lesions. They evaluated 12 pathologically proven metastatic lesions and 12 adenomas and found that metastatic lesions were significantly larger and had significantly higher attenuation coefficients than benign adenomas. They also performed receiver operating characteristic analysis and found that size and attenuation were equally useful in distinguishing benign from malignant lesions. These findings extend the observations of Lee and coworkers[1] and, if corroborated by larger prospective studies, will provide an alternative to biopsy and magnetic resonance imaging.

However, CT examination alone will not provide complete information for proper management. A complete history, a thorough physical examination, appropriate laboratory and hormonal assessment, and CT evaluation are all needed for conclusive diagnosis and therapy.

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