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Quantitative CT Evaluation of Adrenal Gland Masses: A Step Forward in the Differentiation between Adenomas and Nonadenomas?[1]

PURPOSE: **To assess the attenuation of the adrenal gland with computed tomography (CT) before and after multiple phases of contrast enhancement in both control subjects and patients with adenomas and nonadenomas.**

MATERIALS AND METHODS: **Seventy-two patients with 78 adrenal masses (41 adenomas, 37 nonadenomas) underwent helical CT. Forty subjects served as controls. Unenhanced CT was performed followed by enhanced CT at 30, 60, 90, and 180 seconds and 30 minutes.**

RESULTS: **At unenhanced CT, mean attenuation was 4 HU ± 16 for adenomas compared with 37 HU ± 12 for the nonadenomas ($P < .001$) and 24 HU ± 3 for normal glands. Although the mean attenuation of nonademonas was significantly greater than that of adenomas on 60- and 90-second scans ($P < .001$), there was greater overlap in attenuation of the adenomas and nonadenomas than on unenhanced images. At 180 seconds, nonadenomas had higher attenuation than adenomas (73 HU ± 17 vs 41 HU ± 18; $P < .001$). At 30 minutes, all adenomas had attenuation less than 37 HU, whereas all nonadenomas had attenuation greater than 41 HU.**

CONCLUSION: **Delayed-enhanced CT scans obtained 30 minutes after administration of contrast material can enable differentiation of adenomas and nonadenomas.**

ADRENAL gland masses are often found incidentally during cross-sectional imaging of the abdomen (1). Even when discovered in an oncologic setting, many adrenal masses are benign (2,3). Since the introduction of noninvasive cross-sectional imaging modalities, invasive techniques such as adrenal biopsy and sampling of blood from the adrenal vein can be abandoned in certain instances. While some investigators have emphasized the usefulness of conventional computed tomography (CT) to characterize adrenal masses (4–7), others have used different magnetic resonance (MR) imaging techniques for differentiation of adrenal masses (8–13). With the CT criteria of size and attenuation, several studies have demonstrated relatively high predictive values to discriminate benign from malignant adrenal masses on unenhanced CT scans (4–7,14). Recently, Korobkin et al (14) have shown that a threshold value of 18 HU on unenhanced CT scans enabled diagnosis of adenoma with a specificity of 100% and a sensitivity of 85%. They found little value in the enhanced CT attenuation measurements because of great overlap in the ranges of the two groups, particularly for the smaller lesions.

Helical CT offers several advantages for the evaluation of adrenal pathologic processes that include minimizing respiratory misregistration and hence solving the problem of overlooking small lesions due to variations in the patient's depth of respiration on successive breath holds. Another advantage of helical CT is that the shortened time to complete the examination of an area of interest allows a more effective, focused use of contrast material. Such use allows finer control of the phase of intravascular contrast enhancement that is being studied, and thus different vascular and parenchymal information is obtained depending on the mode of administration of contrast material and the scanning delay time. Finally, the acquisition of volumetric data during a single breath hold allows comparison of identical measurements from scans obtained before and at multiple phases of contrast enhancement.

To our knowledge, no data are available to document the possible advantages of contrast material–enhanced helical CT for characterization of adrenal masses. Accordingly, the purpose of our study was to assess the attenuation of the adrenal gland before and after multiple phases of contrast enhancement in both control subjects and patients with adenomas and nonadenomas. Several time windows were used to determine whether early-enhanced and/or delayed-enhanced CT scans of the adrenal gland may play a role in characterization of adrenal masses.

MATERIALS AND METHODS

Study Population

The study protocol was approved by and in accordance with the recommenda-

Index terms: Adrenal gland, CT, 86.12114, 86.12115 • Adrenal gland, neoplasms, 86.30 • Computed tomography (CT), contrast enhancement, 86.12114 • Computed tomography (CT), helical, 86.12115

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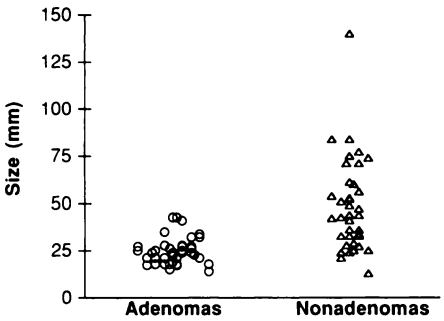

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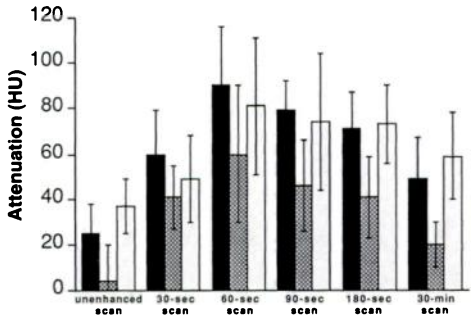

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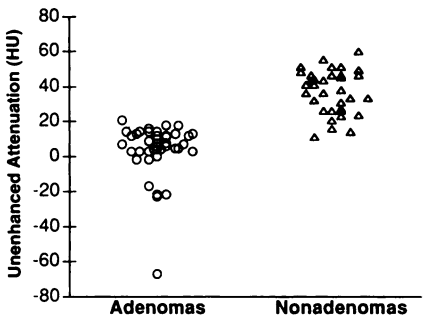

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Figures 1–3. **(1)** Scattergram of sizes of adrenal masses. ○ = adenomas, △ = nonadenomas. **(2)** Graph shows comparison of mean attenuation of normal adrenal glands (black bars), adrenal adenomas (gray bars), and nonadenomas (white bars) on unenhanced and enhanced scans. Note the substantial difference in attenuation of adenomas and nonadenomas on unenhanced and enhanced CT images except at 30 seconds after administration of contrast material. Error bars indicate standard deviation. **(3)** Scattergram of attenuation values on unenhanced CT images of adrenal adenomas and nonadenomas. All masses with attenuation less than 11 HU were adenomas. ○ = adenomas, △ = nonadenomas.

tions of the Human Research Committee at our institution. All patients gave written informed consent.

One hundred six patients with 112 adrenal masses were consecutively examined with helical CT and considered for entry into the protocol. The study group comprised 68 male and 38 female patients who ranged in age from 12 to 83 years (mean, 61 years). Proof of individual masses was based on biopsy results (n = 28), surgical findings (n = 11), or both imaging (observation with repeated CT studies) and clinical follow-up (n = 33). Stability documented at imaging follow-up for at least 12 months (mean, 13 months; range, 12–19 months) was also accepted as proof of a diagnosis of benign adenoma. Patients in whom neither imaging follow-up nor cytologic or histologic analysis was possible (n = 32) and patients with adrenal cysts (n = 2) were excluded from the study.

The remaining 72 patients (43 male and 29 female patients who ranged in age from 12 to 83 years [mean, 60 years]) fulfilled the criteria for inclusion into the study protocol. At diagnostic investigation, 36 patients (with 42 masses) had known malignant disease (three with small cell lung carcinomas, 15 with squamous cell lung carcinomas, four with breast carcinomas, four with renal cell carcinomas, three with colorectal carcinomas, two with non-Hodgkin lymphomas, one with pancreatic carcinoma, one with esophageal carcinoma, one with endometrial carcinoma, one with uterine sarcoma, and one with undifferentiated carcinoma); 29 masses (in 29 patients) were found incidentally (during CT performed for other reasons), and only seven patients (with seven masses) were examined because of abnormal results at chemical analysis of blood and urine (three patients with pheochromocytomas, three with Cushing syndrome, and one with primary hyperaldosteronism). In all, there were 78 masses in 72 patients: 41 adenomas (37 nonhyperfunctioning adenomas, three cortisol-secreting adenomas, one aldosterone-secreting adenoma) and 37 nonadenomas (30 metastases, three pheochromocytomas, three adrenocortical carcinomas, one neuroblastoma).

In addition, the study population comprised 40 subjects (23 men and 17 women who ranged in age from 42 to 69 years [mean, 50 years]) with normal adrenal glands who underwent CT for another medically indicated reason. The absence of adrenal disease was established by means of normal helical CT findings and normal findings from blood and urine analysis.

Imaging Protocol

All studies were performed with a Somatom Plus 4 helical scanner (Siemens, Erlangen, Germany). All scans were obtained at 292 mA and 120 kV. The helical CT protocol consisted of a volumetric data acquisition through the adrenal glands (upper abdomen) with 5-mm collimation, 7.5 mm/sec table feed, and 4-mm increments before and after intravenous bolus injection of contrast material in all patients. The scanning time for one revolution of the x-ray tube was 0.75 second. All scans (acquisition time, 18–24 seconds per scan) were obtained with the patient at full inspiration to optimize the reproducibility of starting measurements. Initially, unenhanced scans were obtained through the adrenal glands. An 18- or 20-gauge intravenous catheter (Angiocath; Becton Dickinson, Franklin Lakes, NJ) was then placed in an antecubital vein and tested by rapidly infusing 10 mL of saline by hand. Subsequently, 120 mL of nonionic contrast material (iopromide 300, Ultravist; Schering Pharmaceuticals, Berlin, Germany) was infused at a rate of 2.5 mL/sec with a power injector (MCT Plus; Medrad, Pittsburgh, Pa).

For the second and third helical scans, both subjects (n = 20 per group) and patients were assigned to two different groups according to the following scan delays: (*a*) 30 seconds and 90 seconds (n = 31 patients; 18 adenomas, 13 nonadenomas) and (*b*) 60 seconds and 180 seconds (n = 41 patients; 23 adenomas, 24 nonadenomas) after the start of the infusion of contrast material, respectively. The third helical scan was preprogrammed for the same collimation, table feed, and duration used in the previous two scans.

In addition, a fourth helical CT scan was obtained in 20 subjects and the patients with adenomas (n = 24) and nonadenomas (n = 19) at 30 minutes (range, 24–36 minutes) after the start of the injection of contrast material. Images were obtained by using standard soft-tissue settings (window width, 400 HU; window level, 40 HU).

Image and Data Analysis

Image interpretation and size and attenuation measurements were performed with a commercially available Sparc 10 CT/MR workstation (Sienet MagicView 1100; Siemens) by two radiologists (D.H.S., F.K.) experienced in CT who did not have knowledge of clinical, histologic, or follow-up findings and who worked independently. The size was recorded with a distance cursor to measure the diameter in the axial plane. The attenuation was measured in subjects and patients by means of circular region-of-interest cursors placed over the normal and pathologic area, respectively. The region-of-interest circle was made as large as possible, while avoiding lesion edges to preclude partial volume effects. Cystic, necrotic, and hemorrhagic components of the adrenal mass were excluded whenever possible. The measurements obtained by the two radiologists were averaged.

Statistical analysis was performed by using commercially available software (StatView; Abacus Concepts, Berkeley, Calif). Primary statistical analysis for the pooled data was based on the paired t test for mean differences in objective region-of-interest measurements of attenuation values between the different helical series. A confirmatory analysis was performed by using repeated measures of analysis of variance (15). This method compares means for more than one group when measurements are obtained at more than one point, providing for control of differences among patients, differences among lesions within individual patients, and interactions between patients and helical scan sequences. The mean size, mean unenhanced CT attenuation value, and mean enhanced CT attenuation value were cal-

Sensitivity versus Specificity at Several Thresholds for Diagnosis of Adenomas with Unenhanced and Delayed-enhanced CT

CT Study	Threshold (HU)	Sensitivity (%)	Specificity (%)
Unenhanced CT	11	61	100
	18	93	92
	21	100	89
Delayed-enhanced CT (180 sec)	64	91	100
	68	96	92
	70	100	83
Delayed-enhanced CT (30 min)	40	100	100

Note.—At unenhanced CT, 41 adenomas and 37 nonadenomas were evaluated. At delayed-enhanced CT, 23 adenomas and 24 nonadenomas were evaluated at 180 seconds, and 24 adenomas and 19 nonadenomas were evaluated at 30 minutes.

culated for the groups and were analyzed with the unpaired *t* test. A *P* value less than .01 was considered to indicate a statistically significant difference. Scattergrams were generated to assess the reliability of size and unenhanced and enhanced CT attenuation values of the adrenal mass to help distinguish adenomas from nonadenomas.

RESULTS

Size

Figure 1 shows the maximum transverse diameter of the adrenal mass in all 78 cases. The adrenal masses were 1.1–14.0 cm in diameter. The mean diameter of adenomas was 2.4 cm ± 0.9 (range, 1.1–3.5 cm) compared with 4.9 cm ± 2.4 (range, 1.3–14.0 cm) for nonadenomas ($P < .001$). The difference between the mean values for the two groups was statistically significant; however, this was due to the presence of nine nonadenomas larger than 6.0 cm in diameter. Given a threshold level of 2.5 cm, the sensitivity versus specificity values for the diagnosis of adrenal adenoma were 66% versus 84%.

Attenuation

Figure 2 shows the average attenuation (in Hounsfield units) and standard deviations of the normal adrenal gland, the adenomas, and the nonadenomas from both unenhanced and enhanced CT scans.

Unenhanced CT.—The mean attenuation of the normal adrenal gland on unenhanced CT scans was 24 HU ± 3. The 41 adenomas had a mean attenuation of 4 HU ± 16 compared with 37 HU ± 12 for the 37 nonadenomas ($P < .001$). Figure 3 shows the attenuation values on the unenhanced CT images. None of the 37 nonadenomas had an attenuation less than 11 HU, whereas 25 of the 41 (61%) adenomas did. The sensitivity versus specifity values, therefore, for the diagnosis of adrenal adenoma were 61% versus 100% at a threshold of 11 HU. The positive predictive value was 100%, and the negative predictive value was 70%.

With a threshold of 18 HU, as recently proposed by Korobkin et al (14), three (two metastases of small cell lung carcinoma, one metastasis of colorectal carcinoma) of the 37 (8%) nonadenomas and 38 of the 41 (93%) adenomas had an attenuation less than 18 HU. Three adenomas (two nonhyperfunctioning adenomas, one cortisol-secreting adenoma), however, had an attenuation above 18 HU. Thus, the sensitivity versus specificity values for the diagnosis of adrenal adenoma were 93% versus 92% at a threshold of 18 HU. The positive predictive value was 93%, and the negative predictive value was 92%. The Table provides the sensitivity versus specificity values at several thresholds for diagnosis of adenomas with unenhanced and delayed-enhanced CT.

Early-enhanced CT.—After administration of contrast material, the normal gland exhibited higher attenuation during the first 90 seconds than both adenomas and nonadenomas (Fig 2). Average attenuation between adenomas (41 HU ± 14) and nonadenomas (49 HU ± 19) at 30 seconds after injection of contrast material was slightly but not significantly different ($P = .024$). Peak attenuation values were observed in all groups at 60 seconds after injection of contrast material. The adrenal glands in the 20 subjects had a mean attenuation of 90 HU ± 26, whereas the 23 adenomas had a mean attenuation of 60 HU ± 30 and the 24 nonadenomas had a mean attenuation of 81 HU ± 30. Although average attenuation of the nonadenomas was significantly greater than that of the adenomas on the 60-second and 90-second scans (74 HU ± 30 vs 46 HU ± 20, respectively) ($P < .001$), there was much greater overlap in the attenuation values of the adenomas and nonadenomas on early-enhanced images than on the unenhanced images. Figure 4 shows the attenuation values on the early-enhanced CT images.

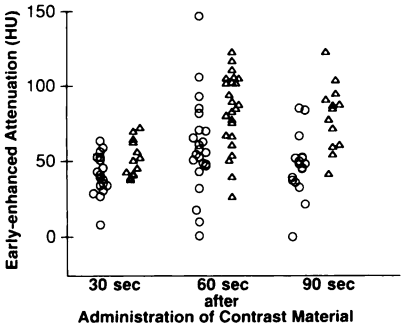
Delayed-enhanced CT.—At 180 seconds after injection of contrast material, normal adrenal glands and nonadenomas had similar attenuation (71 HU ± 16 and 73 HU ± 17, respectively), while adenomas had significantly less attenuation (41 HU ± 18) ($P < .001$). With a threshold of 64 HU at 180 seconds after administration of contrast material, 21 of the 23 (91%) adenomas had attenuation below the threshold, while all 24 (100%) nonadenomas had attenuation above the threshold (Fig 5). Thus, the sensitivity versus specificity values for the diagnosis of adrenal adenoma were 91% versus 100% at a threshold of 64 HU (Table). The positive predictive value was 100%, and the negative predictive value was 92%.

At 30 minutes after administration of contrast material, however, all adenomas ($n = 24$) exhibited attenuation less than 37 HU (mean, 20 HU ± 10), whereas all nonadenomas ($n = 19$) had attenuation above 41 HU (mean, 59 HU ± 19) (Fig 6). With a threshold level of 40 HU at 30 minutes after administration of contrast material, the sensitivity versus specificity values for the diagnosis of adrenal adenoma were 100% versus 100% (Table). The mean attenuation of the normal adrenal gland at 30 minutes after administration of contrast material was 49 HU ± 18.

DISCUSSION

Benign adrenal masses are relatively common, present on 1%–3% of CT scans. The importance of and approach to management of adrenal masses remains a diagnostic dilemma despite continuous refinements in CT and MR imaging technology and protocols, particularly in the presence of a primary extraadrenal cancer. To our knowledge, this is the first study to prospectively evaluate the CT attenuation of adrenal masses and the normal adrenal gland on identically collimated helical CT scans before and during several phases of adrenal enhancement.

Our results can be summarized as follows: The size, a commonly used criterion for characterization of an adrenal mass, is a poor predictor of benignity and is not useful in differenti-



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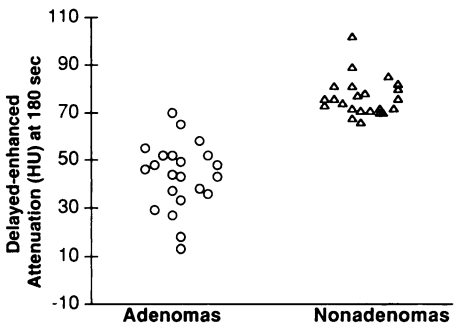

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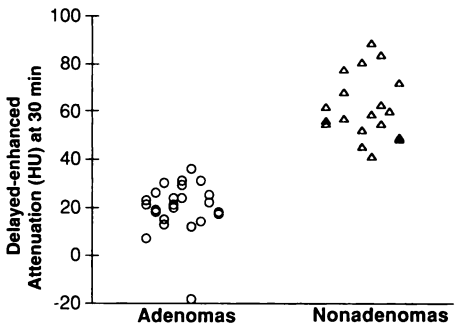

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Figures 4–6. ○ = adenomas, △ = nonadenomas. **(4)** Scattergram of attenuation values on early-enhanced CT images of adrenal adenomas and nonadenomas. Attenuations of adenomas and nonadenomas demonstrate substantial overlap. **(5)** Scattergram of attenuation values on delayed-enhanced CT images of adrenal adenomas and nonadenomas obtained at 180 seconds after administration of contrast material. Statistically significant differences are seen in attenuation between adenomas and nonadenomas. **(6)** Scattergram of attenuation values on delayed-enhanced CT images of adrenal adenomas and nonadenomas obtained at 30 minutes after administration of contrast material. All adenomas had attenuation below 37 HU, whereas all nonadenomas had attenuation above 41 HU.

ating adenomas from nonadenomas. A threshold of 18 HU on unenhanced CT scans for differentiation of adenomas from nonadenomas provides both acceptable sensitivity and specificity but is still associated with the risk of misdiagnosis of adrenal masses. Normal adrenal glands exhibit higher attenuation during the first 90 seconds after administration of contrast material than both adenomas and nonadenomas. During the early phase of contrast enhancement ($\leq$90 seconds), adrenal adenomas could not be distinguished from nonadenomas because of great overlap in attenuation, and hence, early-enhanced CT was not helpful for characterizing adrenal masses.

However, there were statistically significant differences in attenuation between adenomas and nonadenomas at delayed-enhanced CT. With a threshold of 64 HU at 180 seconds after administration of contrast material, 21 of the 23 adenomas had attenuation below this threshold, while all 24 nonadenomas had attenuation above the threshold. With the threshold value of 40 HU at 30 minutes after administration of contrast material, however, the sensitivity versus specificity values for the diagnosis of adrenal adenoma were 100% versus 100%.

To our knowledge, no data are available with regard to the value of helical CT performed before and during several phases of contrast enhancement to differentiate adrenal adenomas from nonadenomas. Previous reports have indicated variable success in differentiating benign from malignant adrenal masses with the use of conventional CT criteria (4–7). More recently, Korobkin et al (14) have shown that unenhanced CT attenuation values at a threshold of 18 HU can enable characterization of an adrenal mass as a benign adenoma with high specificity and acceptable sensitivity. Our findings provide similar information compared with that (14) and other published reports (4–7) on the attenuation of adrenal masses on unenhanced CT scans.

Although the accuracy of unenhanced CT in distinguishing adenomas from nonadenomas is high, some lesions will still be incorrectly classified. Therefore, the threshold should be further defined. As shown in Figure 3, there were three low-attenuation (threshold $<$18 HU) nonadenomas and three high-attenuation (threshold $>$18 HU) adenomas, which permitted a specific diagnosis of adrenal adenoma on the basis of the unenhanced CT attenuation value alone. With a threshold of 18 HU for our series, the sensitivity versus specificity values for the diagnosis of adenoma were 93% versus 92%. Korobkin et al (14) also found little value in the enhanced CT attenuation for discriminating adenomas and nonadenomas; this limited value has been attributed to differential enhancement in the two groups or to the variable interval between injection of contrast material and imaging of the adrenal glands.

To our surprise, none of the previously published series that evaluated CT attenuation values of adrenal masses presented data on enhanced CT values measured at a later phase of contrast enhancement. Our data are supported by those of Krestin et al (11), who used contrast-enhanced fast gradient-echo MR imaging to differentiate adrenal masses. They found a mild enhancement and quick washout of MR contrast medium in adenomas, while a strong enhancement and slower washout of gadopentetate dimeglumine were observed in nonadenomas. These differences in contrast material dynamics have been attributed to higher perfusion and increased capillary permeability in nonadenomas. This disturbed capillary permeability leads to an increased diffusion of contrast material into the interstitial space. In the cases of nonadenomas, the contrast material is retained in the extravascular space for a longer period, resulting in longer enhancement of nonadenomas probably because of expansion of the effective extracellular space due to tumor infiltration and loss of cellular membrane integrity.

In another study, Semelka et al (16) prospectively compared contrast-enhanced fast low-angle shot and fat-suppressed spin-echo MR imaging with unenhanced and contrast-enhanced CT in 30 patients with adrenal masses. Their assessment of helical CT scans, obtained at 45 seconds after initiation of contrast material administration, entailed only qualitative analysis such as the pattern of enhancement. Contrary to the findings of Krestin et al (11), they found only the difference in signal intensity between the periphery and the center of adrenal masses to be a useful adjunct to morphologic findings. The degree of contrast enhancement was not considered helpful in distinguishing between adenomas and nonadenomas. This controversial outcome (16) has been related to an earlier timing of image acquisition (at 20 seconds) after contrast material injection, which would correspond to a capillary phase, whereas Krestin et al acquired images at approximately 1 minute, which would correspond to an interstitial phase of contrast enhancement. The percentage of enhancement on

images obtained at 10 minutes or later was not determined.

In this respect, our data also compare favorably with those of Semelka et al (16), since we did not find helical CT during the early phase of contrast enhancement (within the first 90 seconds after injection of contrast material) useful in differentiating adenomas from nonadenomas.

Korobkin et al (17) recently demonstrated that CT attenuation on delayed scans obtained 1 hour after contrast enhancement enables differentiation of adenomas from metastatic lesions in a manner similar to that with unenhanced CT. At a threshold of 30 HU, they found a specificity and positive predictive value for the diagnosis of an adrenal adenoma of 100% with a sensitivity of 95%. Their study was limited, however, by a relatively small number of patients ($n = 10$) with metastases to the adrenal gland and by the fact that diagnosis of many of the adenomas was based primarily on a delayed-enhanced attenuation less than 18 HU rather than long-term follow-up, unenhanced CT (ie, attenuation less than 12 HU), or histologic confirmation. The results of Korobkin et al (17), however, are in strong agreement with those obtained in our series with a larger number ($n = 24$) and variety of adrenal nonadenomas (metastases, adrenocortical carcinomas, and pheochromocytomas). In addition, both the findings of the study by Korobkin et al (17) and of our study are supported by unenhanced CT attenuation measurements and long-term follow-up with repeated CT measurements of all masses in our series.

Our results may have substantial clinical and economic implications. CT is an important tool in staging many malignancies, particularly bronchogenic carcinoma. Resection of the primary lesion in patients with adrenal metastasis offers no hope of cure and is associated with surgical mortality rates. Hence, such patients can be spared unnecessary thoracotomy. Of greater importance, however, is denying potentially curative surgery on the basis of false-positive CT findings. Therefore, our findings may be extremely helpful in characterizing an adrenal mass in a patient with extra-adrenal cancer when the adrenal lesion is the only site of possible metastasis.

Since most adrenal masses are initially depicted on contrast-enhanced CT scans, the differentiation of adenomas from nonadenomas with delayed-enhanced CT scans may obviate repeating an unenhanced CT scan on a subsequent day and decrease both the morbidity and expense of more aggressive procedures in patients with cancer. In addition, serial CT or MR imaging of incidentally detected adrenal masses can be avoided, thereby reducing the cost of medical care for many patients. Our suggestion to repeat imaging at 30 minutes after intravenous administration of contrast material allows a practical approach. The patient could be removed from the CT scanner and wait while the next patient is examined. The first patient could then be returned for a few repeat images through the adrenal mass. This approach makes delayed scanning a cost-effective technique and would result in only minimal delay to the patient and no substantial disruption to the CT schedule. Delayed-enhanced CT scans, however, are not expected to help differentiate different nonadenomas, such as pheochromocytomas and metastases. Clinical history will usually differ in these two patient populations.

In conclusion, our clinical series provides strong support for an important role of delayed-enhanced CT scans, particularly those obtained at 30 minutes after administration of contrast material, in accurate differentiation of adenomas and nonadenomas. However, as the history of adrenal CT and MR imaging has shown us, a greater amount of clinical experience is needed to see if delayed-enhanced CT scans will be sufficiently reliable for discrimination of both entities and thus obviate biopsy of an adrenal mass in patients with cancer. Further study is needed to more precisely define the optimal (and most cost-effective) temporal window in patients with adrenal masses. ■

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