Adrenal Masses: CT Characterization with Histogram Analysis Method

PURPOSE: To evaluate a histogram analysis method for differentiating adrenal adenoma from metastasis at computed tomography (CT).

MATERIALS AND METHODS: In a retrospective review of 2 years of clinical CT records, 223 adrenal adenomas in 193 patients (115 with contrast material–enhanced CT, 43 with unenhanced and enhanced CT, and 35 with unenhanced CT) and 31 metastases (25 patients with enhanced CT) were found. In 158 patients with adenomas at enhanced CT, diagnosis was based on stable mass size for more than 1 year (n = 135) and characteristic signal intensity decrease at chemical shift magnetic resonance imaging (n = 23). In 35 patients with adenomas at unenhanced CT, mean attenuation was 10 HU or less. Diagnosis of all metastases was based on rapid growth of a mass or new mass in less than 6 months in patients with cancer. Adrenal metastases with extensive necrosis were excluded. Histogram analysis was performed in a circular region of interest (ROI) for mean attenuation, number of pixels, and range of pixel attenuation for all pixels and for the subset of pixels with less than 0 HU (“negative” pixels). Correlation between mean attenuation and percentage negative pixels was calculated.

RESULTS: Negative pixels were present in all 74 unenhanced adenomas with mean attenuation of 10 HU or less and in 14 of 16 unenhanced adenomas with mean attenuation above 10 HU. Of 184 enhanced adenomas, only 20 had mean attenuation of 10 HU or less, but 97 contained negative pixels (77 of these 97 masses had mean attenuation above 10 HU). Increase in percentage negative pixels was highly correlated with decrease in mean attenuation of both unenhanced and enhanced adenomas. None of the adrenal metastases had mean attenuation of 10 HU or less or contained negative pixels.

CONCLUSION: The histogram method is far more sensitive than the 10-HU threshold method for diagnosis of adrenal adenomas at enhanced CT, with specificity maintained at 100%.

Incidental discovery of adrenal masses is common at abdominal computed tomography (CT), occurring in up to 5% of patients (1). Most adrenal masses are adenomas. However, in a patient with a known extraadrenal neoplasm, particularly lung cancer, the finding of an adrenal mass is problematic. Detection of an adrenal mass requires the diagnosis or exclusion of an adrenal metastasis to determine appropriate therapy for the primary tumor.

Findings in many studies confirm the usefulness of CT attenuation measurements at both unenhanced (2–5) and delayed contrast material–enhanced (6–12) CT to differentiate benign from malignant lesions. Unlike metastases, adrenal adenomas often contain intracytoplasmic lipid in the adrenal cortex and thus demonstrate low attenuation at unenhanced CT. Korobkin et al (13) reported a high correlation between adrenal lipid content and low attenuation at CT. Boland et al (5) performed a meta-analysis of 10 CT studies and concluded that a threshold of 10 HU or less corresponded to a sensitivity of 71% and specificity of 98% in the diagnosis of adrenal adenomas. In addition, the delayed contrast-enhanced CT attenuation method has been used successfully to differentiate

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adrenomas from metastases. This delayed enhancement method relies on physiologic differences in perfusion between adrenal adenomas and metastases. Adenomas demonstrate rapid washout after administration of intravenous contrast medium. With this method, the diagnosis of adrenal adenomas has been highly accurate, with a percentage enhancement washout value of 60% or higher (10,12) or a relative percentage washout higher than 40% (10) or 50% (9) at delayed contrast-enhanced CT.

In clinical practice, the majority of adrenal masses are detected incidentally at contrast-enhanced CT. Diagnosis of adrenal adenomas on the basis of the attenuation measurement methods at unenhanced or delayed contrast-enhanced CT is often not feasible. Unenhanced CT scans are not obtained routinely, and patients frequently leave the department before the contrast-enhanced CT scans are reviewed. Mean CT attenuation of adrenal masses at contrast-enhanced CT has limited usefulness because there is too much overlap between the two groups to allow accurate differentiation between adrenal adenomas and nonadenomas (2,3). This overlap is in part due to the heterogeneous tissue composition in adrenal adenomas. With contrast enhancement, the attenuation of vascular tissue in an adrenal adenoma increases. As a result, the overall mean attenuation is elevated even though lipid tissue is present. Because of this tissue heterogeneity, particularly at contrast-enhanced CT, we postulated that for differentiating adrenal adenomas from nonadenomas (94 men, 99 women; age range, 34–97 years; mean age, 65 years) with 223 adrenal adenomas and 25 patients (19 men, six women; age range, 31–96 years; mean age, 62 years) with 31 metastases. Institutional review board approval was obtained for review of the image data, but informed consent was not required for a retrospective study that involves review of only previously obtained image data. Patient confidentiality was protected.

The group with adrenal adenomas consisted of 115 patients with contrast-enhanced CT scans, 43 patients with both unenhanced and contrast-enhanced CT scans, and 35 patients with unenhanced CT scans. Thirty adrenal adenomas were bilateral. In 158 patients with 184 adrenal adenomas at contrast-enhanced CT, the diagnosis of adenoma was established on the basis of stable size of the mass for more than 1 year (135 patients) and characteristic signal intensity decrease at chemical shift magnetic resonance (MR) imaging (23 patients). In the 35 patients (39 masses) with unenhanced CT scans only, all adrenal masses had a mean attenuation of 10 HU or less. The precise threshold attenuation at unenhanced CT that should be used to distinguish adenomas from nonadenomas has varied in reported series, but analysis of the results from published articles indicates that a threshold value of 10 HU has been well accepted (7,12). The adrenal adenomas in 37 of 43 patients with both contrast-enhanced and unenhanced CT scans had a mean attenuation of 10 HU or less on the unenhanced CT scans.

All metastases were imaged with contrast-enhanced CT. The diagnosis of metastasis was based on rapid growth of a mass or identification of a new mass in less than 6 months in a patient with cancer. In one case of metastases, histologic proof was available, and six masses were bilateral. The primary malignancies were in the lung (n = 18), colon (n = 4), kidney (n = 2), and esophagus (n = 1).

Spiral CT

Spiral CT images were acquired with either a single-detector row CT scanner (Somatom Plus 4; Siemens Medical Systems, Erlangen, Germany) or a multi-detector row CT scanner (Plus 4 Volume Zoom; Siemens Medical Systems). Standard parameters for spiral CT of the chest with a single-detector row CT scanner were 120 KVP, 120 mAs, 8-mm collimation, and 8-mm section thickness, whereas those with a multi-detector row CT scanner were 120 KVP, 120 mAs (effective), 4.0 × 2.5-mm detector configuration, and 5-mm reconstructed section thickness. Standard parameters for spiral CT of the abdomen with a single-detector row CT scanner were 120 KVP, 180 mAs, 5-mm collimation, and 8-mm section thickness, whereas those with a multi-detector row CT scanner were 120 KVP, 200 mAs (effective). Contrast-enhanced CT scans were obtained after intravenous injection of 120–150 mL of contrast material (optiray, loverson [320 or 350 mg of iodine per milliliter]; Tyco Health/Mallinckrodt, St Louis, Mo) by using a power injector at a rate of 2.0–4.0 mL/sec. The injection volume and rate of contrast medium delivery varied depending on the patient’s weight, vascular access, and the purpose of the study.

Data Measurement

CT images were retrieved from the institutional picture archiving and communication system, or PACS, to a clinical workstation (Siemens Medical Systems, Iselin, NJ). For each study, the CT image that contained the maximal cross-sectional area of the adrenal mass was selected. The maximal diameter was recorded in two orthogonal dimensions for each mass (P.F. or S.R.P.), and their geometric mean was computed to represent a mean diameter. A circular region of interest (ROI) was placed carefully over the adrenal mass (P.F. or S.R.P.). For the adrenal masses present on both unenhanced and contrast-enhanced CT images, the ROI was placed at approximately the same level in each phase of the study. The ROI covered approximately two-thirds of the mass, and the pixels in the peripheral zones and edges of the mass were avoided meticulously to prevent potential partial volume artifacts.

The pixels in each ROI were processed with a histogram analysis that is a standard image measurement tool with our CT image viewing workstation. The histogram is a plot of pixel attenuation (CT numbers) along the x axis versus the frequency of pixels at each attenuation value along the y axis. Histogram analysis also allowed measurements of mean attenuation, number of pixels, and range of pixel attenuation for all pixels in the ROI. The upper and lower limits of pixel attenuation that were measurable with this histogram analysis were initially set.
These settings for the upper and lower limits allowed inclusion of all the pixels in the ROI. Subsequently, to include only the pixels with negative attenuation, the upper limit of pixel attenuation that was measurable with the histogram analysis was reset to $-1$ HU, and the histogram analysis was repeated for the same ROI. Throughout this article, we refer to the pixels with attenuation of less than 0 HU as “negative pixels.”
Data and Statistical Analysis

The percentage negative pixels was calculated from the total number of pixels and the number of negative pixels in each ROI. The percentage of adrenal masses with a mean attenuation of 10 HU or less was computed for the adrenal metastases at contrast-enhanced CT and for the adenomas at contrast-enhanced and unenhanced CT. The percentages of adrenal adenomas that contained any, more than 5%, and more than 10% of negative pixels were calculated for unenhanced and for contrast-enhanced CT groups. The effect of contrast enhancement on mean attenuation and percentage negative pixels was evaluated by comparing the measurements in 43 patients who had adenomas at both unenhanced and contrast-enhanced CT. Descriptive statistics were obtained. Correlation between mass diameter and mean attenuation was measured with the Pearson correlation coefficient in each group of adrenal metastases, unenhanced adenomas, and contrast-enhanced adenomas. Correlation analysis was also performed between mean attenuation and percentage negative pixels for the unenhanced and contrast-enhanced adenomas that contained negative pixels. A P value of less than .05 was considered to indicate a statistically significant difference.

RESULTS

The histogram analysis is shown in Figure 1. In this example, the upper and lower limits of pixel attenuation that were measurable with the histogram analysis were set to 100 and −100 HU, respectively, for the purpose of illustration. The x and y axes of the histogram represent the attenuation distribution of the pixels in the ROI and the frequency of pixels at each attenuation value, respectively. With contrast enhancement, attenuation of some pixels increased, which resulted in an increase in the mean attenuation of the mass and in changes in the histogram shape and attenuation distribution. The number of masses in various categories (diagnosis, range of mean attenuation, range of percentage negative pixels) and descriptive statistics for mean attenuation, size, and percentage negative pixels are summarized in the Table.

Adrenal Adenomas at Unenhanced CT

The mean attenuation of the 90 adrenal adenomas at unenhanced CT ranged from −20.0 to 37.4 HU (mean, 5.1 HU ± 10.1 [SD]). Eighty-seven of these 90 unenhanced adenomas contained negative pixels. The numbers of unenhanced adenomas with percentage negative pixels greater than 5% and greater than 10% were 85 and 83. Seventy-four unenhanced adenomas (82.2% [74 of 90]) had a mean attenuation of 10 HU or less, and all of them contained negative pixels. Fourteen of 16 adenomas with mean attenuation above 10 HU (87.5%) had negative pixels. Overall, the range of percentage negative pixels for unenhanced adenomas was 0%–97.7%, with a mean of 43.4% ± 20.3. Examples of unenhanced adrenal adenomas are shown in Figures 1 and 2. Little correlation (r = 0.05, P < .05) was noted between the mean attenuation and diameter of unenhanced adenomas. An increase in the percentage negative pixels was highly correlated with a decrease in mean attenuation (r = −0.79, P < .001) (Fig 3).

Adrenal Adenomas at Contrast-enhanced CT

At contrast-enhanced CT, the mean attenuation of the 184 adrenal adenomas ranged from −9 to 108 HU (mean, 49.5 HU ± 27.8). Only 10.9% (20 of 184) of these masses had mean attenuation of 10 HU or less, whereas 52.7% (97 of 184) of the masses contained negative pixels. The lowest percentage negative pixels in masses with mean attenuation of 10 HU or less was 9.8% (mean attenuation of this mass was 9 HU). The numbers of masses with more than 5% and more than 10% negative pixels were 66 and 51, respectively. The highest mean attenuation of an adenoma containing negative pixels (1.6%) was 79.6 HU. The range of percentage negative pixels was 0%–73.8%, with a mean of 15.5% ± 16.7.

Seventy-seven of 184 adenomas with mean attenuation above 10 HU (41.8%) had negative pixels. Among these masses, 13 (of 14), 12 (of 14), and 19 (of 23)

<table>
<thead>
<tr>
<th>Category</th>
<th>Adrenal Adenoma</th>
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<td>Range</td>
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<td>Mean ± SD</td>
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<tr>
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masses with mean attenuation ranges of 10–20, 20–30, and 30–40 HU, respectively, contained negative pixels (Table). Adrenal adenomas at contrast-enhanced CT with varying mean attenuation and percentage negative pixels are shown in Figures 1 and 4. Little correlation ($r = 0.07, P < .001$) was noted between the mean attenuation and the diameter of contrast-enhanced adenomas. An increase in percentage negative pixels was highly correlated with a decrease in mean attenuation ($r = -0.75, P < .001$) (Fig 5).

Adrenal Adenomas on Paired Unenhanced and Contrast-enhanced CT Scans

All 51 adrenal adenomas on paired unenhanced and contrast-enhanced CT scans showed an increase in mean attenuation (mean increase, 45.6 HU ± 23.8) and a reduction in percentage negative pixels (mean decrease, 31.6% ± 18.0) after contrast medium administration. Fifty of 51 masses had mean attenuation above 10 HU at contrast-enhanced CT, while 25 of the 51 masses demonstrated persistent negative pixels on contrast-enhanced CT scans.

Adrenal Metastases at Contrast-enhanced CT

None of the 31 adrenal metastases had negative pixels. The mean attenuation of the adrenal metastases ranged from 22 to 199 HU (mean, 73.8 HU ± 31.9). Thus, the specificity for diagnosis of adrenal adenoma was 100% with the histogram analysis and with the mean attenuation measurement method. Examples of adrenal metastases are shown in Figure 6. A weak correlation ($r = 0.28, P < .001$) was noted between mean attenuation and diameter of metastases.

DISCUSSION

Our proposed histogram method is practical and useful for reducing the diagnostic uncertainty that is encountered frequently in the interpretation of adrenal masses at routine contrast-enhanced CT. The 10-HU threshold–based mean attenuation method is known to be useful for differentiating adenomas from metastases at unenhanced CT and has a sensitivity of 71% for diagnosis of adrenal adenoma (5). However, the latter method is not sensitive in the differentiation of adenomas from nonadenomas at contrast-enhanced CT because there is too much overlap in mean attenuation between the two groups (2,3). Unfortunately, the majority of clinical CT examinations in patients with cancer, in whom characterization of adrenal masses is important for oncology management and prognosis, are contrast enhanced. Without available unenhanced CT scans or previous comparison CT scans, patients may be required to return for unenhanced CT or MR imaging for further characterization of incidentally detected adrenal masses. An alternative method that can be used to characterize an adrenal mass is assessment of the enhancement washout pattern of the mass on 15-minute delayed contrast-enhanced CT scans (9,12). This approach is not practical because of the 15-minute window to review and interpret the CT findings and determine the need for repeat CT scanning while the patient is kept in the radiology CT department. An additional consideration is the cost and inefficiency involved in performing repeat CT.
Comparison of Histogram and Mean Attenuation Methods

Boland et al (5), in their meta-analysis of 10 reported studies in which unenhanced CT was used to characterize adrenal masses, showed that an increase in the mean attenuation threshold leads to more overlap between adrenal adenomas and metastases. As a result, sensitivity of diagnosis of adrenal adenomas increases, but specificity decreases. We observed the same trend in our study when we used mean attenuation to characterize adrenal adenomas at contrast-enhanced CT. For example, 34 of 184 adenomas and none of the metastases had a mean attenuation of less than 20 HU at contrast-enhanced CT. With a threshold of 30 HU, however, the number of adenomas increased to 48 and one metastasis was included.

Sensitivity of diagnosis of adrenal adenoma at contrast-enhanced CT was higher with the histogram method than with the mean attenuation method. Whereas only 10.9% (20 of 184) of adrenal adenomas had a mean attenuation of 10 HU or less, 52.7% (97 of 184) of them contained negative pixels. Although none of the metastases in our study demonstrated negative pixels, we are uncertain at this point that the presence of any pixel with a negative attenuation provides 100% specific evidence for the diagnosis of adrenal adenoma (excluding obvious necrotic or fatty masses). If more conservative criteria are used—for example, diagnosis of adenomas as masses with more than 5% or more than 10% negative pixels sensitivity decreases to 35.9% (66 of 184) or 27.7% (51 of 184). Even these more stringent criteria for the histogram method provide higher sensitivities than the 10.9% sensitivity with the 10-HU mean attenuation threshold. However, a further increase in the threshold for percentage negative pixels would reduce the test sensitivity too much for it to be a clinically useful adjunct to the mean attenuation method. On the basis of our current data, it appears that a threshold of at least 10% negative pixels may be an appropriate criterion for diagnosis of an adenoma because the lowest percentage negative pixels in masses with mean attenuation of 10 HU or less was 9.8%.

Adrenal adenomas may have low attenuation at CT because of abundant intracytoplasmic lipid in the adrenal cortex. In contrast, metastases have little intracytoplasmic lipid and thus do not have low attenuation at unenhanced CT. Korobkin et al (13) demonstrated a high correlation between adrenal lipid content and both low attenuation at CT and signal intensity decrease at chemical shift MR imaging. In our study, we found an inverse correlation between the percentage negative pixels and the mean attenuation of both unenhanced and contrast-enhanced adenomas. The correlation was slightly stronger for unenhanced adeno-
mas than that for contrast-enhanced adenomas. Correlation between the size and mean attenuation was weak for both adenomas and metastases.

All adrenal adenomas with a mean attenuation of 10 HU or less demonstrated the presence of negative pixels. To have a mean attenuation this low, a substantial portion of the mass contains lipid (the lowest percentage negative pixels was 9.8% in an adenoma with a mean attenuation of 9 HU at contrast-enhanced CT). Mean attenuation of an adrenal adenoma, however, is affected considerably by the relative proportion of lipid and higher attenuation nonlipid tissues. With a high contribution of nonlipid tissue, the mean attenuation of a mass increases, especially when nonlipid tissue enhances after contrast medium administration.

All adenomas imaged with both unenhanced and contrast-enhanced CT demonstrated an increase in mean attenuation and a decrease in percentage negative pixels on contrast-enhanced images. If we assume that lipid tissue does not enhance, the percentage negative pixels of an adrenal mass should remain constant despite an increase in the mean attenuation of the mass. The decrease in percentage negative pixels of adenomas at contrast-enhanced CT may be explained by the effect of pseudoenhancement (14–16), which was introduced to explain artifactual enhancement of simple renal cysts at contrast-enhanced CT. Pseudoenhancement is thought to result from inadequate algorithmic correction for CT x-ray beam hardening. This phenomenon may cause a decrease in percentage negative pixels in contrast-enhanced adenomas as a result of artifactual enhancement of lipid tissue related to enhancing adjacent nonlipid tissue.

**Technical Considerations in Histogram Analysis Method**

Histogram analysis has been used successfully as a method for CT densitometry in other clinical applications to characterize the tissue composition of organs that are composed of heterogeneous distributed tissues (17–19). To our knowledge, histogram analysis has not been applied to the characterization of adrenal masses. Despite their usefulness, quantitative CT techniques have been used infrequently for routine interpretation of clinical CT images because such measurements are not readily available when hard copy CT images are interpreted. Histogram measurement is a standard tool available on most CT image reading workstations. Our method is fast (<1 minute) and easy to perform, but the user interface of histogram programs can be modified further for more convenient calculation and display of percentage negative pixels.

Although the main advantage of quantitative analysis is objectivity, certain technical and CT scanner variability issues must be considered to standardize the application of our method. It is likely that the histogram analysis method is sensitive to changes in CT image quality and noise profile. CT image quality is affected by a number of patient and technical factors, including patient body habitus, breathing motion artifact, size and location of ROI, kilovolt peak and milliampere second values, collimation, section thickness, reconstruction kernel, intravenous contrast medium injection, and CT scan delay. In our retrospective study, many of these technical parameters were not standardized. Furthermore, we did not attempt to standardize the volume or rate of administration of contrast medium. Some CT scans were obtained during the arterial phase and others during the venous phase of contrast enhancement. However, the timing of imaging after contrast medium administration may not be a critical factor with the histogram analysis method for characterizing adrenal masses as it is with the perfusion washout method.

The CT images evaluated in our study were reconstructed with a smooth soft-tissue kernel that is the standard for abdominal CT or for mediastinal chest CT. CT images reconstructed with a sharp lung or bone kernel are noisier and result in mean attenuations with larger SDs than those for images reconstructed with a soft-tissue kernel. The percentage negative pixels, which represents the group of pixels distributed in the lower attenuation end of the two tails of the histogram, increased with increasing SD, although the mean attenuation remained more or less constant. Noisy pixels may simulate false-positive percentage negative pixels. One strategy to handle this potential problem may be to measure the SD of attenuation in background air or a reference body part and use it to determine the applicability of the histogram analysis method or to normalize the estimated number of negative pixels. A phantom study will be necessary to investigate the effect of various image reconstruction kernels and the resulting SD of attenuation on the percentage negative pixels calculation. At this point, we recommend that the CT images be acquired with the standard milliamper second and kilovolt peak values used for the abdomen and be reconstructed with the standard soft-tissue kernel prior to application of histogram analysis.

Another technical factor to be considered is the potential difference in attenuation calibration among CT scanners of different manufacturers. This difference likely affects both the mean attenuation and histogram analysis methods. However, we speculate that the reference attenuation of the histogram analysis method (ie, 0 HU) would be determined accurately with minimal fluctuation with CT scanners of different vendors because
daily calibration of CT scanners with a water phantom is standard practice. There are several other limitations in our study. First, there is a potential subject-selection bias because the patients included in the study were a selected population of only those whose CT reports contained the words “adrenal adenomas” or “adrenal metastasis.” This type of subject-selection bias is a common limitation in a retrospective study. Second, the diagnosis of adenoma at contrast-enhanced CT was based on the stability of an adrenal mass during follow-up of more than 1 year or on findings at chemical shift MR imaging without histologic verification. The diagnosis of adenoma at unenhanced CT only was established solely on the basis of attenuation of 10 HU or less. This criterion has been accepted in a number of prior studies. Third, without a tissue diagnosis, a few of the lesions in our study that contained mostly negative pixels could have been lipomas or myelolipomas. Nevertheless, we regarded these lesions as adenomas because they are benign and subject to the same clinical management as are adrenal adenomas. Fourth, the diagnosis of metastasis was based on rapid growth of a mass or identification of a new mass in less than 6 months in a patient with cancer. Only one lesion had histologic proof at biopsy. Fifth, overtly necrotic metastases were not included in our study because their diagnosis is straightforward on the basis of morphologic features even though the attenuation of the necrotic portion may be near that of water and close to 0 HU. As a result of intrinsic measurement fluctuations, some pixels in the necrotic area could have negative Hounsfield unit values at histogram analysis, especially at unenhanced CT, which result in apparent negative pixels. Such a mass should not be interpreted as an adenoma.

Sixth, histogram and attenuation measurements were obtained only in homogeneous portions of an adrenal mass. The possibility of a heterogeneous metastasis or another mass coexisting with an adenoma (20) was not addressed in our study. Finally, in our series of 31 adrenal metastases, only two masses had mean attenuation of less than 40 HU. Our sample size may be too small to critically test the specificity of our histogram analysis method. A larger study is necessary to collect a large series of low-attenuation contrast-enhanced metastases.

In conclusion, the sensitivity of diagnosis of adrenal adenoma at contrast-enhanced CT is increased substantially with histogram analysis compared with that for the 10-HU threshold-based mean attenuation method, with specificity maintained at 100%. Histogram analysis enables diagnosis of many adenomas with mean attenuation above 10 HU at contrast-enhanced CT and is more sensitive than the 10-HU threshold-based mean attenuation method for diagnosis of adrenal adenoma at unenhanced CT.

References