Can Adrenal Adenomas Be Differentiated From Adrenal Metastases at Single-Phase Contrast-Enhanced CT?

**OBJECTIVE.** The purpose of this study is to evaluate whether adrenal metastases can be reliably differentiated from adenomas at single-phase contrast-enhanced CT.

**MATERIALS AND METHODS.** Sixty-one consecutive patients from a single-institution lung cancer registry (40 metastases and 36 adenomas) who underwent single-phase contrast-enhanced CT at baseline diagnosis were retrospectively studied by two radiologists (blinded to the diagnoses) who independently evaluated four features previously described in adenomas: smooth margin, rim enhancement, central vein sign (preserved adrenal vein), and homogeneity (using a 5-point Likert scale). A third radiologist measured size and attenuation and performed quantitative texture analysis. Comparisons were performed using chi-square, logistic regression, and ROC analysis.

**RESULTS.** Metastases were larger than adenomas (mean ± SD) 24 ± 11 mm [range, 11–66 mm] vs 19 ± 5 mm [range, 11–34 mm]; p = 0.012), with overlap between groups. Attenuation of metastases and adenomas did not differ significantly (58.2 ± 21.0 HU [range, 21.0–108.0] vs 55.5 ± 21.5 HU [range, 14.0–105.0]; p = 0.582). Skewness and kurtosis did not differ between groups (p = 0.612 and 0.978, respectively), whereas entropy was higher in metastases (p = 0.013). The AUC for entropy to diagnose metastases was 0.65 (95% CI, 0.52–0.77). Tumor margin, rim enhancement, and the central vein sign did not differ between groups (p > 0.05). Metastases were considered more heterogeneous by both radiologists (p = 0.001 and 0.011, respectively), and agreement was satisfactory (κ = 0.51). Likert scores of 4 or 5 (mostly or completely heterogeneous) yielded sensitivity and specificity for diagnosis of metastases of 32.5% and 97.2%, respectively, for radiologist 1 and 22.5% and 97.2%, respectively, for radiologist 2.

**CONCLUSION.** Adrenal metastases cannot be reliably differentiated from adenomas at single-phase contrast-enhanced CT. Increased tumor size and heterogeneity were specific findings but showed unacceptably low sensitivity.

Adrenal nodules are commonly detected in patients undergoing CT examinations. It has been reported in imaging series that the frequency of incidental adrenal adenomas is approximately 4% [1, 2]. When an adrenal nodule measures less than 10 HU at unenhanced CT or shows significant washout of contrast agent at dedicated 15-minute delayed contrast-enhanced CT (> 60% absolute washout or > 40% relative washout) compared with a 70-second contrast-enhanced CT, then a diagnosis of adrenal adenoma can be established with high accuracy [3–5]. There are notable exceptions (e.g., pheochromocytoma and hypervascular metastases such as clear cell renal cell carcinoma and hepatocellular carcinoma) that can show washout in the adenoma range [6–10]; however, in general, unenhanced CT and washout CT can accurately diagnose adrenal adenomas in most cases in clinical practice.

A common clinical scenario occurs when an adrenal nodule is discovered at single-phase contrast-enhanced CT examination. At single-phase contrast-enhanced CT, establishing a diagnosis of adenoma is challenging because of the features of adenomas that overlap with those of metastases and other adrenal masses. In patients with no history of malignancy, adrenal nodules incidentally discovered at contrast-enhanced CT have a negligible risk of malignancy [11] and, thus, can be investigated conservatively, typically with biochemical workup and a follow-up imaging study in 1 year to establish stability, provided the nodule is smaller than 4 cm and homogeneous [6, 12].

References:

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8. Based on a presentation at the ARRS 2018 Annual Meeting, Washington, DC.
9. MATERIALS AND METHODS. Sixty-one consecutive patients from a single-institution lung cancer registry (40 metastases and 36 adenomas) who underwent single-phase contrast-enhanced CT at baseline diagnosis were retrospectively studied by two radiologists (blinded to the diagnoses) who independently evaluated four features previously described in adenomas: smooth margin, rim enhancement, central vein sign (preserved adrenal vein), and homogeneity (using a 5-point Likert scale). A third radiologist measured size and attenuation and performed quantitative texture analysis. Comparisons were performed using chi-square, logistic regression, and ROC analysis.
10. RESULTS. Metastases were larger than adenomas (mean ± SD) 24 ± 11 mm [range, 11–66 mm] vs 19 ± 5 mm [range, 11–34 mm]; p = 0.012), with overlap between groups. Attenuation of metastases and adenomas did not differ significantly (58.2 ± 21.0 HU [range, 21.0–108.0] vs 55.5 ± 21.5 HU [range, 14.0–105.0]; p = 0.582). Skewness and kurtosis did not differ between groups (p = 0.612 and 0.978, respectively), whereas entropy was higher in metastases (p = 0.013). The AUC for entropy to diagnose metastases was 0.65 (95% CI, 0.52–0.77). Tumor margin, rim enhancement, and the central vein sign did not differ between groups (p > 0.05). Metastases were considered more heterogeneous by both radiologists (p = 0.001 and 0.011, respectively), and agreement was satisfactory (κ = 0.51). Likert scores of 4 or 5 (mostly or completely heterogeneous) yielded sensitivity and specificity for diagnosis of metastases of 32.5% and 97.2%, respectively, for radiologist 1 and 22.5% and 97.2%, respectively, for radiologist 2.
11. CONCLUSION. Adrenal metastases cannot be reliably differentiated from adenomas at single-phase contrast-enhanced CT. Increased tumor size and heterogeneity were specific findings but showed unacceptably low sensitivity.
12. Adrenal nodules are commonly detected in patients undergoing CT examinations. It has been reported in imaging series that the frequency of incidental adrenal adenomas is approximately 4% [1, 2]. When an adrenal nodule measures less than 10 HU at unenhanced CT or shows significant washout of contrast agent at dedicated 15-minute delayed contrast-enhanced CT (> 60% absolute washout or > 40% relative washout) compared with a 70-second contrast-enhanced CT, then a diagnosis of adrenal adenoma can be established with high accuracy [3–5]. There are notable exceptions (e.g., pheochromocytoma and hypervascular metastases such as clear cell renal cell carcinoma and hepatocellular carcinoma) that can show washout in the adenoma range [6–10]; however, in general, unenhanced CT and washout CT can accurately diagnose adrenal adenomas in most cases in clinical practice.
13. A common clinical scenario occurs when an adrenal nodule is discovered at single-phase contrast-enhanced CT examination. At single-phase contrast-enhanced CT, establishing a diagnosis of adenoma is challenging because of the features of adenomas that overlap with those of metastases and other adrenal masses. In patients with no history of malignancy, adrenal nodules incidentally discovered at contrast-enhanced CT have a negligible risk of malignancy [11] and, thus, can be investigated conservatively, typically with biochemical workup and a follow-up imaging study in 1 year to establish stability, provided the nodule is smaller than 4 cm and homogeneous [6, 12].
testing is performed to exclude the diagnosis of pheochromocytoma (due to overlap in attenuation values of adrenal adenomas and pheochromocytomas at contrast-enhanced CT performed at approximately 70 seconds) [7, 8] and to identify hormone-secreting adenomas [13]. This approach is not appropriate in patients with a personal history of cancer because the risk of metastatic disease in an incidentally discovered adrenal nodule increases substantially when there is an oncologic history [14]. In the absence of any previous imaging studies (to assess for nodule growth or stability in size over time or the presence of intracytoplasmic lipid on a prior or unenhanced CT or chemical-shift MRI), it remains controversial whether there are imaging features at single-phase contrast-enhanced CT that can reliably differentiate adenomas from metastases. Two previous studies suggest that imaging features at contrast-enhanced CT can reliably distinguish adenomas from nonadenomas [15, 16], with several other studies citing features suggestive of adenomas, including homogeneous texture [17, 18], well-circumscribed or sharply demarcated margin [15, 16], rim enhancement [19–21], and the central vein sign [22]; however, the utility of these features has not been well established. Similarly, quantitative analysis (including texture analysis), which has proven useful in other genitourinary applications on CT [23, 24], has not been well evaluated in adrenal nodules, to our knowledge. The purpose of this study was, therefore, to assess subjective and quantitative imaging features on single-phase contrast-enhanced CT and to determine their ability to differentiate adrenal adenomas from metastatic disease in patients with cancer.

Materials and Methods

Patients

With institutional review board approval, we retrieved a roster of patients at a single institution who received a diagnosis of lung cancer between May 2006 and August 2017 and who had undergone abdominal CT. We searched retrospectively (working backward from December 2015 to May 2006) for consecutive patients who presented with an adrenal nodule at the baseline diagnosis of cancer on single-phase contrast-enhanced CT examinations of the abdomen. The start date of December 2015 was selected to provide a sufficient time interval to establish a diagnosis of adenoma on the basis of the absence of growth on serial scans. Patients who received their diagnosis in January 2016 or later were excluded because of an insufficient time interval to establish benignity or malignancy of masses on the basis of growth parameters. In the same cohort of patients, we also identified patients who presented with adrenal metastases at baseline imaging on single-phase contrast-enhanced CT of the abdomen. The reference standards for diagnosis of adenoma and metastasis are provided in detail later.

A search of 823 consecutive patients identified 34 patients with 36 adenomas (two patients had two adenomas) and 27 patients with 40 metastases (nine patients had two metastases and two patients had three metastases) who met the inclusion criteria. Patient inclusion is shown in the flowchart in Figure 1. The mean (± SD) patient age was 68.0 ± 10.2 years with no differences in age between groups (p = 0.50). There were 28 men and 33 women, with 11 men and 23 women in the adenoma group and 17 men and 10 women in the metastases group (p = 0.03). Nine patients had small cell lung cancers, 37 patients had adenocarcinomas, six patients had non–small cell lung cancer (unclassified), four patients had squamous cell cancers, three patients had large cell lung cancers, one patient had carcinoid tumor, and one patient had an undifferentiated cancer. There was no difference in distribution of cancer type between groups (p = 0.665).

Adrenal Adenomas

Adrenal adenomas were diagnosed when a separate unenhanced CT showed mean attenuation of a nodule measuring less than 10 HU (n = 27) [25], a separate chemical-shift MRI showed intracellular lipid within the nodule subjectively and quantitatively with a chemical-shift index greater than 15% (n = 4) [26], or when a separate multiphase adrenal washout CT showed absolute washout at 15-minute delayed contrast-enhanced imaging of greater than 60% (n = 5) [5, 27] and follow-up imaging performed after at least a 1-year interval showed no change in size of the nodule. The mean time to follow-up for establishing stability in size in this study was 2238 ± 988 days (range, 431–3978 days). Using these standards, 86.1% (31/36) of adenomas were lipid rich (i.e., showed unenhanced CT attenuation < 10 HU or intracellular lipid on chemical-shift MRI), and 13.9% (5/36) were lipid poor (i.e., showed attenuation > 10 HU on unenhanced CT or no detectable intracellular lipid on chemical-shift MRI).

Adrenal Metastases

Adrenal metastases were diagnosed when there was significant growth, defined as a greater than 20% increase in size in [28–30] (in this study, mean growth of 56.1% or 117 ± 7.6 mm [range, 2.2–29.5 mm]) on serial follow-up imaging performed within 1 year (mean, 91 ± 54 days; range, 31–210 days) in the context of progressing metastatic disease elsewhere (n = 22); or when the adrenal nodule measured larger than 10 mm and was unequivocally new compared with a previous examination that could be retrieved from the patient’s medical record, with a mean interval between examinations of 1196 ± 634 days (range, 89–2191 days) (n = 18).

CT Technique

All patients included in the study had undergone single-phase contrast-enhanced CT of the abdomen at the time of cancer diagnosis. The CT protocols varied, but the timing of acquisition was generally in the portal venous phase (timed empirically at approximately 70 seconds after contrast agent administration). Minor differences in

![Flow diagram](file.png)

**Fig. 1—Flow diagram for patient selection used in this retrospective study.**
the timing of the portal venous phase were not considered significant. Every examination included axial images of the adrenal glands (slice thickness, 2.5–5 mm) with coronal reconstructed images (slice thickness, 3 mm). For 79% (48/61) of patients, CT was performed at a single institution: 18 patients underwent CT on a 16-MDCT scanner (LightSpeed Plus, GE Healthcare), 24 patients underwent CT on a 64-MDCT scanner (LightSpeed VCT or Discovery 750, GE Healthcare; Asteion or Aquilion 64, Toshiba Healthcare), and six patients underwent CT on a 320-MDCT scanner (Aquilion, Toshiba Healthcare).

Our institutional CT protocol consisted of a fixed 120-kVp technique with automated tube current modulation and a variable tube current-time product of 100–500 mAs. Acquisition is helical, with a rotation time of 0.8 second and a noise index of 41.4. The timing of the portal venous phase is established empirically in all cases timed to be approximately 70 seconds after the injection of contrast agent. Patients were given 105 mL of nonionic contrast material (iohexol [Omnipaque, GE Healthcare] before 2008 or iopamidol [Isovue, Bracco Healthcare] from 2008 onward) at a fixed IV rate of 3.5 mL/s using a power injector followed by a saline flush.

For 21% (13/61) of patients, CT was performed at outside institutions: nine patients underwent CT on a 64-MDCT scanner (LightSpeed VCT or Discovery 750, GE Healthcare; Asteion or Aquilion 64, Toshiba Healthcare), and four patients underwent CT on a 256-MDCT scanner (iCT 256, Philips Healthcare). Images were retrieved from a central image storing database for the Local Hospital Integration Network. CT protocols from outside facilities were designed to match those from our institution and used similar scanning parameters.

**Subjective Analysis**

Two fellowship-trained abdominal radiologists with 10 and 11 years of experience in urogenital CT independently evaluated each examination while blinded to all patient information and final diagnosis. Each radiologist subjectively evaluated for rim enhancement, which was defined as peripheral enhancement with central lower attenuation in a nodule and has been described elsewhere to be associated with adenoma on MRI [21] (Figs. 2–4); central feeding vessel, which was defined as a central enhancing linear structure connecting with the inferior vena cava on the right side or the left renal vein on the left side and has been described elsewhere to be associated with adenoma on contrast-enhanced CT [22] (Figs. 2 and 3); tumor heterogeneity using a 5-point Likert scale, where 1 denotes completely homogeneous attenuation, 2 denotes mostly homogeneous attenuation, 3 denotes mixed areas of heterogeneous attenuation, 4 denotes mostly heterogeneous attenuation, and 5 denotes completely heterogeneous attenuation, as described elsewhere in stud-
Adrenal Adenoma Versus Adrenal Lung Cancer at CT

Quantitative Analysis

A radiologist with 3 years of experience in urogenital CT measured the size and attenuation of each nodule on CT examinations. The radiologist measured the nodule in three planes (anterior-posterior, transverse, and craniocaudal), and the mean size was recorded in millimeters. ROIs were placed within the center of the nodule on the axial image where it appeared the largest to measure attenuation in Hounsfield units (Fig. 2). For homogeneous nodules, an ROI encompassing two-thirds of the nodule’s surface area on axial CT was placed (carefully avoiding the edges of the nodule so as not to include adjacent retroperitoneal fat in the measurement) [31]. For heterogeneous nodules, an ROI with a diameter of 5 mm was placed within the most hyperattenuating portion of the nodule, again on the axial slice where the nodule appeared the largest [32].

Using the same axial image where ROI measurements were performed, texture and shape analysis was also performed. Patient-identifying information was removed, and images were exported in DICOM format from the PACS to an independent workstation for lesion analysis using ImageJ (version 1.48, National Institutes of Health). Each tumor was manually contoured to encompass as much of the tumor as possible while carefully avoiding extratumoral structures (Fig. 2). A minimum area of 10 mm² was required to obtain accurate measurements, as described elsewhere [33]. First-order texture features, including kurtosis (a measure of histogram flatness), skewness (a measure of histogram asymmetry), and entropy (a measure of histogram irregularity), were extracted by histogram analysis and studied as described elsewhere [34].

Statistical Analysis

Quantitative data are shown as mean ± SD and range. Demographic and subjective variables were compared using the chi-square test of proportions, and quantitative data were compared using multivariable logistic regression analysis. Interobserver agreement for subjective variables was calculated using the Cohen kappa statistic and interpreted according to methods described by Landis and Koch [35] (κ < 0.2, poor agreement; κ = 0.21–0.40, fair agreement; κ = 0.41–0.60, satisfactory agreement; κ = 0.61–0.80, good agreement; and κ = 0.81–1.00, excellent agreement). ROC curve analysis was performed for statistically significant quantitative variables, and diagnostic accuracy was calculated for statistically significant subjective data. Optimal threshold values were selected using the Youden index, as described by Zhou et al. [36]. A threshold p < 0.05 indicated a statistically significant difference. Statistical analysis was performed with STATA data analysis and statistical software (version 13, StataCorp).

Results

There was no significant difference in distribution of adenomas or metastases by laterality, with 38.9% (14/36) of adenomas and 45.0% (18/40) of metastases located in the right adrenal gland (p = 0.590). Metastases were larger than adenomas (mean, 24 ± 11 mm [range, 11–66 mm] vs 19 ± 5 mm [range, 11–34 mm]; p = 0.012); however, there was overlap between groups (Fig. 5). There was no significant difference in the attenuation values of metastases and adenomas (mean, 58.2 ± 21.0 HU [range, 21.0–108.0 HU] vs 55.5 ± 21.5 HU [range, 14.0–105.0 HU]; p = 0.582).

A summary of results comparing adrenal adenomas to metastases using subjective analysis by both radiologists is provided in Table 1. There was no significant difference in tumor margin, presence of central vein sign, or rim enhancement between groups for either radiologist (p > 0.05 for all findings), and interobserver agreement was satisfactory to good. For both radiologists, heterogeneity was rated higher in metastases compared with adenomas (p = 0.001 for radiologist 1 and p = 0.011 for radiologist 2). Likert scores of 4 or 5 (mostly or completely heterogeneous) maximized accuracy for the diagnosis of metastatic disease for both radiologists; however, although the Likert score was specific, it lacked sensitivity. The sensitivity and specificity of subjective nodule heterogeneity for diagnosis of metastases were 32.5% (95% CI, 18.6–49.1%) and 97.2% (95% CI, 85.5–99.9%), respectively, for radiologist 1 and 22.5% (95% CI, 10.2–38.5%) and 97.2% (95% CI, 85.5–99.9%), respectively, for radiologist 2 (Fig. 6). Interobserver agreement for subjective assessment of heterogeneity was satisfactory (κ = 0.51).

Results for quantitative texture analysis are summarized in Table 2. There were no

Fig. 5—Box-and-whisker plot of adrenal nodule size comparing adenomas and metastases. In this study, metastases were larger than adenomas but there was overlap between groups. Whiskers denote 95% CIs, and circles denote outliers.

Fig. 6—Box-and-whisker plot of adrenal nodule entropy comparing adenomas and metastases. In this study, entropy was higher in metastases compared with adenomas but there was overlap between groups. Whiskers denote 95% CIs, and circle denotes outlier.
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TABLE 1: Subjective Imaging Features Independently Assessed by Two Blinded Radiologists in Consecutive Patients With Lung Cancer Comparing Adrenal Adenomas and Metastases

<table>
<thead>
<tr>
<th>Feature</th>
<th>Radiologist 1 (n = 36)</th>
<th>Metastases (n = 40)</th>
<th>Radiologist 2 (n = 36)</th>
<th>Metastases (n = 40)</th>
<th>Interobserver Agreement (κ)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rim enhancement present</td>
<td>36 (13)</td>
<td>45 (18)</td>
<td>22 (8)</td>
<td>43 (17)</td>
<td>0.78</td>
<td>0.431</td>
</tr>
<tr>
<td>Central feeding vessel</td>
<td>17 (6)</td>
<td>8 (3)</td>
<td>22 (8)</td>
<td>15 (6)</td>
<td>0.64</td>
<td>0.217</td>
</tr>
<tr>
<td>Irregular or spiculated margin</td>
<td>3 (1)</td>
<td>15 (6)</td>
<td>0 (0)</td>
<td>10 (4)</td>
<td>0.32</td>
<td>0.066</td>
</tr>
<tr>
<td>Texture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.001</td>
</tr>
<tr>
<td>1 = Completely homogeneous</td>
<td>22 (8)</td>
<td>3 (1)</td>
<td>25 (9)</td>
<td>10 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Mostly homogeneous</td>
<td>19 (7)</td>
<td>28 (11)</td>
<td>31 (11)</td>
<td>28 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Mixed areas of heterogeneity in a nodule that is mostly homogeneous</td>
<td>56 (20)</td>
<td>38 (15)</td>
<td>42 (15)</td>
<td>40 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Mostly heterogeneous</td>
<td>3 (1)</td>
<td>10 (4)</td>
<td>3 (1)</td>
<td>10 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 = Completely heterogeneous</td>
<td>0 (0)</td>
<td>23 (9)</td>
<td>0 (0)</td>
<td>13 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note—Data are percentage (number) of lesions.

Discussion

This study evaluated the usefulness of single-phase contrast-enhanced CT to differentiate between adrenal adenomas and metastases in patients with lung cancer. Our results show that, among subjective findings, only tumor heterogeneity was associated with metastatic disease; however, this imaging finding was specific but lacked sensitivity. The other subjective variables assessed, including tumor margin, rim enhancement, and the central vein sign, were not useful. Metastases were larger than adenomas; however, there was overlap between groups. The attenuation of nodules on contrast-enhanced CT was not useful to differentiate adenomas from metastases. Quantitative CT texture analysis showed higher entropy in metastases, although overall accuracy was only modest. Our results confirm that, when an adrenal nodule is incidentally discovered in patients with an oncologic history at single-phase contrast-enhanced CT, a diagnosis of adenoma or metastatic disease cannot typically be established. In these instances, prompt follow-up imaging (with unenhanced CT, chemical-shift MRI, or adrenal washout CT) should be performed unless previous examinations can be made available. In cases of large adrenal masses that are markedly heterogeneous, a presumptive diagnosis of metastatic disease can be provided, although they may also require confirmatory testing.

Characteristics of benign adenomas at contrast-enhanced CT or MRI previously described in the literature include rim enhancement, spiculated or irregular margins, the central vessel sign, and homogeneous enhancement [15, 16, 21, 22, 37]. Rim enhancement observed in adenomas on contrast-enhanced MRI examinations is thought to be due to rapid contrast agent washout from the central portion of an adenoma, with persistent enhancement in the peripheral adrenal capsule and compressed normal adrenal tissue [21]. Previous studies evaluating this finding on MRI have shown very high specificity for the diagnosis of adenoma [20, 21]. Meanwhile, in studies evaluating rim enhancement using contrast-enhanced CT, the presence of a thick continuous enhancing rim was a feature associated with malignancy, although there was overlap between groups [15, 16]. In our study, there were no differences between adenomas and metastases using rim enhancement. Our own results, combined with the disparity in reported results on CT and MRI, suggest that this imaging finding is likely not useful. Studies previously evaluating tumor margin as a feature to differentiate malignant adrenal masses from adenomas have shown this feature to be specific for malignancy but insensitive [15, 16]. Our study confirms these previous results because a spiculated or irregular margin was almost exclusively seen in metastases; however, the frequency of the finding was very low, which resulted in an insignificant association. The central vein sign is a new sign described in adenomas and is based on preserved visualization of the normal adrenal vein draining into the inferior vena cava or left renal vein. In its original description, it was identified in adenomas only, and other masses studied did not show the finding [22]; however, in our study, we found the central vein sign to be present in both adenomas and metastases, with no difference between the two groups. To our knowledge, no other study has reevaluated this newly described finding. Subjectively, metastases were considered more heterogeneous by both radiologists in our study.

TABLE 2: Quantitative Texture Analysis of Adrenal Metastases and Adrenal Adenomas in Consecutive Patients With Lung Cancer Evaluated With Single-Phase Contrast-Enhanced CT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenoma</th>
<th>Metastases</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurtosis</td>
<td>0.084 ± 0.086</td>
<td>0.026 ± 0.047</td>
<td>0.612</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.074 ± 0.256</td>
<td>0.075 ± 0.254</td>
<td>0.978</td>
</tr>
<tr>
<td>Entropy</td>
<td>5.819 ± 0.501</td>
<td>6.064 ± 0.331</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Note—Data are mean ± SD.
and marked heterogeneity was specific for the diagnosis of metastatic disease. This confirms what prior investigators have shown—namely, that adenomas tend to appear homogeneous at CT [15, 16, 37]. Nevertheless, adenomas can appear heterogeneous on CT (particularly at larger sizes) [38], and overall accuracy for the diagnosis of metastases in our study on the basis of subjective evaluation of texture was only modest.

In our study, metastases were larger than adenomas; however, there was overlap between groups. The risk of malignancy increases with adrenal mass size [25, 39]; however, adenomas may also be atypically large [38, 40]. There was no difference in attenuation of adrenal adenomas or metastases measured at portal venous phase contrast-enhanced CT in our study. This is concordant with prior studies that have shown a poor ability to discriminate between malignant and benign lesions at approximately 70 seconds to 5 minutes after the administration of contrast agent [41–43].

Quantitative texture analysis is a technique that can objectively evaluate gray-level patterns of tumors not perceptible to the human eye [44, 45]. Our study showed higher entropy in metastases compared with adenomas, which is concordant with prior studies that have consistently shown increased entropy in malignant compared with benign masses and in more aggressive tumors [9, 34, 45–49]. To our knowledge, only one previous study evaluated texture analysis of adrenal masses using CT [50], and the authors’ preliminary results in a small cohort of patients showed that texture analysis was specific for the diagnosis of malignancy but with low-to-moderate sensitivity. These results are comparable to those from our study, where entropy had high specificity but low-to-moderate sensitivity and reduced overall accuracy for the diagnosis of metastatic disease.

Our study has limitations. The single-center retrospective study design using patients with lung cancer introduces population bias into our conclusions, and our results may not necessarily be applied to other malignancies and should theoretically be validated in the context of different primary cancers. We minimized this risk by performing a consecutive search of patients that included a large number of variably sized metastases. Our study had a slightly lower number of lipid-poor adenomas than the 30% cited in the literature [12], which may be related to the reference standard for diagnosis of adenomas because we required both characteristic imaging features and absence of growth on serial follow-up examinations. It could be argued that the inability to show significant differences between adenomas and metastases for most of the subjective and quantitative variables studied may be related to an insufficient sample size; however, we performed a post hoc power analysis using the reported frequency of adrenal adenomas in patients undergoing CT of 4% [1, 2], the reported frequency of adrenal metastases in patients with lung cancer of 8% [51], and the number of consecutive patients evaluated in our cohort (n = 823) and showed that our study was powered to over 95% with an alpha error of 0.05. Finally, the reference standard for metastatic disease and adenomas was not established by histopathologic analysis in our study, but rather by previously described imaging thresholds on unenhanced CT, chemical-shift MRI, and adrenal washout CT; as well as stability or greater than 20% interval growth on follow-up imaging studies. Previous studies have similarly used these imaging reference standards to diagnose adenomas and metastases because the accuracy of unenhanced CT, chemical-shift MRI, and adrenal washout CT to differentiate metastases from lung cancer and adenomas approaches 100% [5, 30, 52, 53].

In conclusion, our study evaluating a large cohort of patients with lung cancer who underwent baseline single-phase contrast-enhanced CT at the time of cancer diagnosis confirms that it is generally not possible to differentiate between adrenal adenomas and lung metastases at single-phase contrast-enhanced CT. Subjective findings, such as tumor margin, rim enhancement, and the central vein sign, were not useful for diagnosis. Attenuation of metastases and adenomas did not differ significantly, and, although metastases were larger, there was overlap between groups. Metastases were more heterogeneous than adenomas both subjectively and quantitatively; however, texture showed only modest accuracy for diagnosis. Tumor heterogeneity was generally specific when tumors were markedly heterogeneous, but had unacceptably low sensitivity. Our results confirm that when an incidental adrenal nodule is discovered at single-phase contrast-enhanced CT in patients with a personal history of cancer, a diagnosis of adenoma or metastatic disease cannot be made. Prompt follow-up investigations with unenhanced CT, chemical-shift MRI, or adrenal washout CT should be initiated in the workup of the nodule to establish a diagnosis unless prior imaging examinations can be made available. In cases where nodules are large and markedly heterogeneous, a provisional diagnosis of metastatic disease can be offered; however, unless there is evidence of metastatic disease elsewhere, then confirmatory testing is generally also required.

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