Clinical Utility of Noncontrast Computed Tomography Attenuation Value (Hounsfield Units) to Differentiate Adrenal Adenomas/Hyperplasias from Nonadenomas: Cleveland Clinic Experience


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Radiological characterization of an adrenal tumor as adenoma may decrease the need for follow-up imaging studies, biopsies, and unnecessary adrenalectomies. We retrospectively reviewed 299 adrenalectomies in 290 patients at Cleveland Clinic Foundation over a recent 5-yr period to assess the value of noncontrast Hounsfield units (HU) in characterizing whether an adrenal mass is adenoma or nonadenoma. The mean (± sd) HU value for the adrenocortical adenoma/hyperplasia group was 16.2 ± 13.6 and significantly lower ($P < 0.0001$) than primary adrenocortical cancers (36.9 ± 4.1), metastases (39.2 ± 15.2), and pheochromocytomas (38.6 ± 8.2). The sensitivity and specificity for 10- and 20-HU cutoff values to differentiate adenomas/hyperplasias from nonadenomas were 40.5 and 100% and 58.2 and 96.9%, respectively. The size of the adrenal tumor had less value with only 40.7 and 81.3% sensitivity and 94.7 and 61.4% specificity for 2- and 4-cm cutoff values. A combination of less than or equal to 4-cm adrenal mass size and noncontrast computed tomography HU less than or equal to 20 had 42.1% sensitivity and 100% specificity. Our study, the largest with surgical histopathology as the gold standard for diagnosis, supports a noncontrast computed tomography attenuation value of 10 HU as a safe cutoff value to differentiate adrenal adenomas/hyperplasias from nonadenomas. (J Clin Endocrinol Metab 90: 871–877, 2005)
divided into five groups (Table 1) depending on their pathological diagnosis: group 1, adrenocortical adenoma/hyperplasia; group 2, primary adrenocortical carcinoma (PAC); group 3, metastasis; group 4, pheochromocytoma; group 5, others. There were 28 patients in group 5 with the following histopathological diagnoses: myelolipoma (nine), cyst (four), hematomata (three), lymphoma (two), chronic inflammation (two), ganglieneuroma (two), normal adrenal (two), epithelioid angioma (one), Schwannoma (one), and focal lipomatous change (one). The secretory status of adrenal masses in 156 patients with adrenal adenoma/hyperplasia was obtained through chart review and was as follows: 65 nonfunctional, 76 hyperaldosteronism, eight adrenal Cushing’s syndrome, and seven undetermined.

Noncontrast HU measurement was available in 50.5% of the adrenal masses (151 of 299). Among these, the CT scan images in 60.3% (91 of 151) of adrenal masses were available on picture archive and communication system workstations. These were reviewed by one of our experienced CCF radiologists, who was blinded to the final diagnosis, and the noncontrast HU values were recalculated. Two or more attenuation values were obtained, and measurements included at least two thirds of the diameter of the adrenal mass. Areas of necrosis or cystic changes were excluded from the attenuation measurements. In patients with a heterogeneous adrenal mass, the highest HU measurement was used in our database. The noncontrast HU measurements in 39.7% (60 of 151) of adrenal masses were obtained from the patient’s chart and/or CT scan reports. The CT scans at CCF were performed on a Siemens Somatom plus or Siemens Somatom plus 4 (Siemens Medical Systems, Forchheim, Germany). Only a small number of patients in our series had delayed postcontrast scans from which enhancement washout could be measured. The greatest diameter of adrenal masses measured by CT and not the pathology report were used for data analysis.

**Statistical analysis**

The mean (± sd) and median (range) of age, size, and HU values within each group were calculated using Microsoft Excel software. The groups were compared on continuous variables using two-tailed, unpaired t tests and on categorical variables using \( \chi^2 \), all at the 0.05 significance level. The \( \chi^2 \) tests were carried out using S-Plus (Mathsoft, Inc.). Sensitivity, specificities, positive predictive value (PPV), and negative predictive value (NPV) for any specific cutoff value or a combination of values were calculated. In this study, the sensitivity is defined as the probability that an adrenal mass is classified as an adenoma/hyperplasia, given that it is truly an adenoma/hyperplasia. Specificity is defined as the probability that an adrenal mass is classified as a nonadenoma, given that it is truly a nonadenoma.

**Results**

**Patient demographics**

The mean (± sd) age of the patients in each group along with their gender ratio is shown in Table 1. The mean (± sd) age of the patients in the adenoma/hyperplasia group was 54 ± 12.3 yr and significantly different from the adrenal metastasis group, 63.6 ± 10.3 yr (P = 0.0007), but not PAC, 53.3 ± 11.5 yr (P = 0.87); pheochromocytoma, 52 ± 15.5 yr (P = 0.36); and others, 50.4 ± 15.5 (P = 0.25) (Table 1). The female gender proportion in adenoma/hyperplasia group was significantly different only from the metastasis group (P < 0.001).

**Size and lateralization**

The median (range) and mean (± sd) size (cm) of the adrenal masses in each group are shown in Table 1. The mean (± sd) size of adrenal masses in the adenoma/hyperplasia group was 2.8 ± 1.4 and significantly smaller than PAC, 10.1 ± 4.2 (P < 0.0001); adrenal metastasis, 4.7 ± 2.8 (P < 0.0001); pheochromocytoma, 5.0 ± 2.4 (P < 0.0001); and others, 6.4 ± 2.6 (P < 0.0001). The size distribution of adrenal masses for different groups are shown in Fig. 1. Adrenal masses were more common on the left side (Table 1).

**Noncontrast HU**

The median (range) and mean (± sd) noncontrast HU measurements of the adrenal masses for each group are shown in Table 1. Noncontrast HU measurements were available in 151 adrenal masses. The mean (± sd) noncontrast HU measurements of adrenal masses in the adrenocortical adenoma/hyperplasia group was 16.2 ± 13.6 and significantly lower than PAC, 36.9 ± 4.1 (P < 0.0001); adrenal metastasis, 39.2 ± 15.2 (P < 0.0001); and pheochromocytoma, 38.6 ± 8.2 (P < 0.0001) but not different from the others group, –2 ± 52.2 (P = 0.31). Among patients with adrenal nonadenomas, there were two patients with adrenal metastasis, who had noncontrast HU values of 12 and 20, and the rest had values more than 20 HU. The distribution of noncontrast HU in different groups are shown in Fig. 2. The means (± sd) HU for nonfunctional adrenal masses (n = 32) and those with hyperaldosteronism (n = 40) in the adrenocortical adenoma/hyperplasia group were 15.1 ± 13.5 and 15.9 ± 13.5, respectively, and were not different (P = 0.79). There were only four patients with adrenal Cushing’s syndrome who had noncontrast HU measurements available ranging from 0–38.

The percentage of adrenal masses with available noncon-

**TABLE 1. Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>Aden/hyper Gr 1</th>
<th>Carcinoma Gr 2</th>
<th>Metastasis Gr 3</th>
<th>Pheo Gr 4</th>
<th>Others Gr 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>156*</td>
<td>15</td>
<td>31</td>
<td>61</td>
<td>28*</td>
</tr>
<tr>
<td>Adrenal masses</td>
<td>157</td>
<td>15</td>
<td>35</td>
<td>63</td>
<td>29</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>54 ± 12.3</td>
<td>53.3 ± 11.3</td>
<td>63.6 ± 10.3</td>
<td>52 ± 15.5</td>
<td>50.4 ± 15.5</td>
</tr>
<tr>
<td>Size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.8 ± 1.4</td>
<td>10.1 ± 4.2</td>
<td>4.7 ± 2.8</td>
<td>5.0 ± 2.4</td>
<td>6.4 ± 2.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.7 (0.6–6)</td>
<td>9.6 (2–16.8)</td>
<td>4.1 (1.5–11.2)</td>
<td>4.1 (2.4–11.4)</td>
<td>5.6 (2–12)</td>
</tr>
<tr>
<td>Female/male</td>
<td>87/69</td>
<td>9/6</td>
<td>7/24</td>
<td>32/29</td>
<td>12/16</td>
</tr>
<tr>
<td>No. of patients with bilateral adrenal masses</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Right/left</td>
<td>62/95</td>
<td>7/8</td>
<td>14/21</td>
<td>30/33</td>
<td>14/15</td>
</tr>
<tr>
<td>Adrenal masses with available HU</td>
<td>79/157</td>
<td>7/15</td>
<td>20/35</td>
<td>29/63</td>
<td>16/29</td>
</tr>
<tr>
<td>HU</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>16.2 ± 13.6</td>
<td>36.9 ± 4.1</td>
<td>39.2 ± 15.2</td>
<td>38.6 ± 8.2</td>
<td>–2 ± 52.2</td>
</tr>
<tr>
<td>Median (range)</td>
<td>19 (–19–43)</td>
<td>36 (31–43)</td>
<td>38.5 (12–83)</td>
<td>39 (22–59)</td>
<td>24.5 (–86–63)</td>
</tr>
</tbody>
</table>

* One patient was present in both groups with a right adrenal adenoma and left myelolipoma.
Contrast HU in each group were as follows: adenoma/hyperplasia, 78 of 156 (50%); PAC, 7 of 15 (46.7%); pheochromocytoma, 29 of 63 (46%); metastasis, 20 of 35 (57%); and others, 17 of 30 (56.7%). There was no statistically significant difference between the group of patients with and without noncontrast HU measurements in regard to age, 53 ± 13.3 yr vs. 55.5 ± 13.6 yr ($P = 0.34$); tumor size, 4.2 ± 2.9 cm vs. 4.5 ± 2.7 cm ($P = 0.12$), and female/male sex ratio 77/71 vs. 79/74 ($P = 0.95$).

### Sensitivity and specificity

The sensitivity, specificity, PPV, and NPV for 10- and 20-HU noncontrast CT attenuation values, tumor size, and a combination of HU and tumor size to distinguish adrenocortical adenoma/hyperplasia from nonadenomas are shown in Table 2. Patients with myelolipomas were excluded from analysis, because they usually have characteristic CT image findings and mostly had a noncontrast CT attenuation value less than –40 HU. The sensitivity, specificity, PPV, and NPV for 10- and 20-HU threshold cutoff values to differentiate adenal adenomas/hyperplasias from nonadenomas were 40.7% and 82% sensitivity, 94.7% and 61.4% specificity, 89.3% and 69.4% PPV, and 59.7% and 75.3% NPV for 2- and 4-cm cutoff values (Table 2 and Fig. 3). A combination of tumor size less than or equal to 4 cm and HU less than or equal to 10 had a specificity and PPV of 100%, similar to the 10-HU cutoff value (Table 2). Three patients in group 5 (others) had malignant adrenal masses, including two lymphomas and one epithelioid angiosarcoma, but no HU measurement was available.

### Discussion

Since the first report from Schaner et al. (33) in 1978 about unusually low HU in four adrenal masses, there has been accumulating literature about the value of noncontrast HU in differentiation between adrenal adenomas and nonadenomas (11, 13–26, 34). The majority of studies on the value of noncontrast HU relies on radiological features or clinical observation that can be as short as 6 months in duration in some reports (11, 15, 18, 20, 22, 34, 35).

Our series based on surgical histopathology as the gold standard for diagnosis supports the thesis that an adrenal mass with noncontrast HU value less than or equal to 10 is extremely unlikely to be nonadenoma, excluding myelolipoma. The sensitivity for a 10-HU cutoff value in our data is only 40.5%. This is likely because of the presence of a large proportion of surgically removed lipid-poor adenomas in our database. Studies that have used clinical observation or CT characteristics as proof of a benign nature of adrenal masses have reported a sensitivity of 68–83% for a 10-HU cutoff value (17, 18, 22).

Although CT findings in functional adrenocortical tumors with hyperaldosteronism or Cushing’s syndromes have been described in the literature, there is little information about the value of HU measurement in their differentiation from nonfunctional adrenocortical tumors (13, 17, 27, 36). Among hyperfunctioning adrenocortical adenomas, those secreting aldosterone tend to have the lowest HU density (16, 27, 37). Our data suggest that HU value may not be used to differentiate aldosterone-producing adrenal tumors from nonfunctional adrenocortical tumors. There are only four patients in our series with adrenal Cushing’s syndrome who had noncontrast HU measurement available, and therefore no meaningful comparison with nonfunctional adrenocortical tumors could be made.

None of the patients in the pheochromocytoma group had
a HU less than 22. The majority of studies have shown higher noncontrast HU in patients with pheochromocytoma compared with adrenocortical adenomas because of their low lipid content (13, 15–17, 20, 28, 31, 38, 39). Karstaedt et al. (11) described four cases of pheochromocytoma with low attenuation values (5–10 HU), which were attributed to the necrotic areas. No information was given about the methodology of HU measurement or whether areas with higher attenuation values were present. Ramsay et al. (40) reported an unusual case of bilateral pheochromocytoma with lipid degeneration exhibiting gross and microscopic features resembling adrenal cortical nodules. Blake et al. (41) has recently reported two patients with pheochromocytoma, including one with medullary hyperplasia, who had noncontrast CT HU less than 10. Based on current literature, although the presence of a pheochromocytoma with noncontrast CT attenuation value less than 10 HU is very unlikely, the rare cases with low attenuation values should be kept in mind.

Three patients in the fifth group (others) who had malignant adrenal masses, two with lymphoma and one with epithelioid angiosarcoma, did not have the HU measurement available. We could not find any study specifically addressing noncontrast HU values in such patients. Review of CT and magnetic resonance imaging (MRI) images and attenuation values of a few cases reported in the literature suggests that both of these conditions have low lipid content and therefore would be expected to have higher HU values when compared with lipid-rich adenomas (42–47). Additional studies to evaluate noncontrast HU in such patients are needed.

Adrenal tumor size has been proposed by many authors as one of the important determinants to differentiate adrenal adenomas from nonadenomas (1, 3, 17, 30, 48–51). There is a significant increase in the frequency of malignancy with increase in adrenal tumor size (1, 3, 48, 52, 53). Different cutoff values ranging from 4–6 cm have been proposed for surgical resection of adrenal masses (1, 7, 25, 30, 50, 51, 53, 54). Our data and others suggest that the noncontrast HU is superior to adrenal size in differentiating adrenal adenomas from nonadenomas (Fig. 4) (17, 18, 20, 22, 26, 31). Although there was a statistically significant difference in tumor size between the adrenocortical adenoma/hyperplasia group and all other groups, there was a wide variation in tumor size. A cutoff value for adrenal masses at 2 and 4 cm had only 94.7 and 61.4% specificity to rule out adrenal nonadenomas (Table 2). There are four patients with adrenal metastasis and one with PAC in our series who had an adrenal mass less than or equal to 2 cm. These observations suggest that although the incidence of adrenal malignancy increases with an increase in size of the tumor, the size by itself may not

![Fig. 3. Receiver operating characteristics (ROC) curves for noncontrast CT attenuation value (HU) and tumor size for distinguishing adrenal adenoma/hyperplasia from nonadenomas.](image-url)
serve as an absolute criterion because the size is, to some extent, a function of time (2, 22, 53).

The lack of change in the size of an adrenal mass has been accepted by many experts as a reliable indicator of the benign nature of the tumor (30, 53). This may delay the surgical intervention in a highly aggressive adrenocortical carcinoma, and there have been very rare cases of adrenal metastasis with no change in CT appearance followed for up to 18 months (19). The prognosis of PAC is greatly improved by early diagnosis and surgical resection of the adrenal mass (30, 55, 56). On the other hand, follow-up of patients with nonfunctioning adrenal masses suggests that 5–25% of adrenal masses increase in size by at least 1 cm (30, 57, 58).

In addition to lipid content there have been a variety of other CT characteristics that may differentiate adrenal adenomas from nonadenomas. Such characteristics include smooth border, round or oval shape, sharp margins, maintenance of adrenal configuration, lack of calcification within or on the edge of the tumor, homogeneity of the mass, and lack of enhancement after contrast (3, 6, 13, 15, 35, 48, 59). Although these features are helpful in decision making and further characterization of a mass, none of them individually is able to rule out malignancy with a great confidence (6, 15, 60).

Some studies have reported the value of delayed enhanced and percentage change in attenuation value during CT scan of adrenal glands to differentiate adrenal adenomas from nonadenomas (31, 34, 61, 62). This may be particularly helpful in lipid-poor adrenal tumors with a noncontrast HU of more than 10. Calculation of percentage washout post contrast has been shown by some authors to be promising in the differentiation of lipid-poor adrenal adenomas from nonadenomas (28, 32, 39–63). A washout of less than 60% at 15 min post contrast had 95% specificity in identifying nonadenomas (28, 32, 39). Because percentage washout was available in only a small proportion of our patients, we cannot comment on the value of such measurement in our series. This needs evaluation and confirmation by additional studies.

MRI and adrenal scintigraphy are among other noninvasive methods used to differentiate benign and malignant adrenal masses. Opposed-phase chemical-shift MRI is one of the most promising ones. Its sensitivity and specificity for diagnosis of a benign adrenal mass seems to be close to noncontrast CT attenuation value (30, 42, 43, 66). The decrease in signal intensity during chemical-shift MRI depends on the amount of lipid present in an adrenal tumor. Most benign adrenocortical tumors have a low signal intensity during T2-weighted MRI. A limited number of patients with PAC have undergone opposed-phase chemical-shift MRI, and for this reason more experience in such patients has been recommended (6). The CT seems to be superior to MRI because of its widespread availability, high speed, and low cost. Adrenal scintigraphy using 131I-69-iodomethyl-19-norcholesterol (NP-59) is another method reported to be promising in differentiating benign and malignant adrenal masses larger than 2 cm in size. Adrenal nonadenomas have absent or significantly reduced uptake compared with adenomas, but the lack of widespread availability limits its usefulness (7, 29, 67).

The most appropriate follow-up of a nonfunctional adrenal mass with a noncontrast HU less than 10 is not known, but some authors performed no routine follow-up imaging study in such patients (28, 32). The transformation rate of nonfunctional adrenal masses to functional tumors seems to be higher in adrenal masses more than 3 cm in size (58). A consensus panel organized by the National Institutes of Health recommended limited follow-up for nonfunctional adenomas less than 3 cm with no specific recommendations (30). The likelihood of developing primary adrenocortical carcinoma from an adenomatous or hyperplastic adrenal mass is not known but seems to be extremely rare (58, 68–72).

Our approach to incidentally discovered adrenal masses is shown in Fig. 4. We do not routinely obtain any follow-up imaging study in nonfunctional adrenal masses with a noncontrast CT HU less than 10. Such patients, especially those with an adrenal mass greater than 3 cm, undergo annual follow-up evaluations for any excess hormone hypersecretion (58, 73). The optimal duration of follow-up is not known, and more long-term studies are needed. Once HU has been taken into consideration, our data support that 6-cm tumor size is a reasonable cutoff for surgical resection, because none of the patients in the adenoma/hyperplasia group had a tumor size more than 6 cm. If one considers surgical resection of adrenal masses based only on their size, even the 2-cm cutoff value may miss some malignancies as presented in our study. Adrenal masses less than 6 cm with a noncontrast HU greater than 10 need to be closely monitored and resected if necessary.
found to be functional or increase in size during a follow-up imaging study in 6–12 months. In patients with adrenal masses less than 6 cm but clinically suspicious for adrenocortical carcinoma, a 3-month follow-up image is reasonable to avoid any significant delay in surgical approach. There is no good evidence supporting continued radiological surveillance if the follow-up study at 6–12 months shows no change in the adrenal tumor size (30). We obtain percentage of washout at 15 min for adrenal masses with noncontrast HU greater than 10 and those with a washout percentage less than 60% are recommended to have their adrenal mass removed. This needs to be further evaluated and confirmed by studies looking at a large number of patients. We recommend biopsy of adrenal tumors to rule out a metastatic adrenal mass once pheochromocytoma has been ruled out, keeping in mind that biopsy may not differentiate adrenocortical carcinoma from adenomas (7, 50). Although the surgical resection of the adrenal mass is usually considered for patients with functional or malignant adrenal masses, medical therapy may be acceptable in the case of primary hyperaldosteronism secondary to adrenocortical adenoma/hyperplasia. Surgery in those with widespread malignancy is usually not indicated (70).

There are several limitations to our study. First, the noncontrast CT attenuation value was available in only 50.5% of adenalectomies. The ratio of patients with HU measurement was approximately 50% in each of five groups. There was no statistically significant difference between adrenal masses with and without HU measurement in regard to sex ratio, age, and tumor size. Second, some of the HU measurements were done in other facilities with different CT machines. The comparison of CT attenuation values on helical and nonhelical CT scanners has been reported to be comparable and seems to be minimally influenced by the position of the patient in the scan field (34). For this reason, it is likely that there should not be a significant change in HU measurements between different CT machines. Third, the CT collimation used for scanning was variable because of the retrospective nature of the study, and there was no report of the region of interest in some of the unavailable CT scans. This may have affected some of the measurements. Fourth, the functional status of adrenocortical adenoma/hyperplasia cases was determined through chart review. Biochemical evaluations were not the same in all patients and depended on the preferences of the evaluating physician, but this does reflect real-life clinical assessment scenarios. Thus, any conclusion about the relation between HU and functional status of adrenocortical tumors should be reached with caution.

Our study of 151 adrenal masses, the largest published study with data based on surgical histopathological diagnosis, supports the proposal that 10 HU in a noncontrast CT is a safe cutoff value to differentiate adrenal adenomas/hyperplasias from nonadenomas. Our data also suggest that 20 HU may be an acceptable cutoff value if the mass is 4 cm or smaller, particularly in those without a history of malignancy. There is a need for additional studies looking at the postcontrast CT attenuation values in patients with noncontrast CT HU greater than 10.

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