CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma


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Background: Up to 7% of all adrenal incidentalomas (AIs) are pheochromocytomas (PCCs). In the evaluation of AI, it is generally recommended that PCC be excluded by measurement of plasma-free or 24-hour urinary fractionated metanephrines. However, recent studies suggest that biochemical exclusion of PCC not be performed for lesions with CT characteristics of an adrenocortical adenoma (ACA).

Aim: To determine the proportion of PCCs with ACA-like attenuation or contrast washout on CT.

Methods: For this multicenter retrospective study, two central investigators independently analyzed the CT reports of 533 patients with 548 histologically confirmed PCCs. Data on tumor size, ISSNs: Print 0021-972X, Online 1945-7197, Copyright © 2019 Endocrine Society

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Abbreviations: ACA, adrenocortical adenoma; AI, adrenal incidentalomas; APW, absolute percentage washout; ENSAT, European Network for the Study of Adrenal Tumors; ESE, European Society of Endocrinology; HU, Hounsfield unit; PCC, pheochromocytoma; RPW, relative percentage washout.

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unenhanced Hounsfield units (HU), absolute percentage washout (APW), and relative percentage washout (RPW) were collected in addition to clinical parameters.

**Results:** Among the 376 PCCs for which unenhanced attenuation data were available, 374 had an attenuation of >10 HU (99.5%). In the two exceptions (0.5%), unenhanced attenuation was exactly 10 HU, which lies just within the range of ≤10 HU that would suggest a diagnosis of ACA. Of 76 PCCs with unenhanced HU > 10 and available washout data, 22 (28.9%) had a high APW and/or RPW, suggestive of ACA.

**Conclusion:** Based on the lack of PCCs with an unenhanced attenuation of <10 HU and the low proportion (0.5%) of PCCs with an attenuation of 10 HU, it seems reasonable to abstain from biochemical testing for PCC in AIs with an unenhanced attenuation of ≤10 HU. The assessment of contrast washout, however, is unreliable for ruling out PCC. *(J Clin Endocrinol Metab 104: 312–318, 2019)*

**A**drenal pheochromocytomas (PCCs) and extra-adrenal sympathetic paragangliomas are rare tumors that arise from catecholamine-producing chromaffin cells (1). Up to 40% of chromaffin tumors are associated with hereditary tumor syndromes (2–5). The most accurate diagnostic test for the biochemical diagnosis of these tumors is the measurement of plasma free or 24-hour urinary fractionated metanephrines (6, 7). Typical symptoms and signs include headache, tremors, palpitations, sweating, and anxiety. However, up to 25% of patients do not have signs and symptoms, and up to 30% of PCCs are diagnosed following the discovery of an adrenal incidentaloma (AI) (7, 8).

The prevalence of AI on thoracic, abdominal, and pelvic CT ranges between 1.0% and 8.7% depending on age (9–14). Most AIs are adrenocortical adenoma (ACA) (12). Less prevalent causes are myelolipomas, cysts, adrenocortical carcinoma, and metastases from other malignancies. PCCs account for up to 7% of AIs (7). Unlike in situations when substantial adrenal hormone secretion or malignancy are suspected, no treatment is indicated for benign, nonfunctioning ACA. In 2016, the European Society of Endocrinology (ESE) in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT) published a guideline to provide clinicians with evidence-based recommendations for clinical management of patients with AIs (7). This guideline adapts a generally accepted approach in the evaluation of AI by taking into account quantitative CT characteristics. An attenuation of ≤10 Hounsfield units (HU) on unenhanced CT or an absolute percentage washout (APW) of ≥60% or a relative percentage washout (RPW) of ≥40% on CT with delayed washout after 10 to 15 minutes are considered suggestive of ACA.

However, the guidelines and an accompanying meta-analysis (15) clearly indicated that unenhanced CT is the only reliable method to differentiate benign from malignant adrenal tumors. In addition, the guideline recommended that an endocrine work-up for AI be performed, including the measurement of plasma-free or 24-hour urinary fractionated metanephrines. However, the guideline also mentioned that it would be reasonable to avoid biochemical testing for PCC in patients who have AI with an unenhanced attenuation of ≤10 HU. Nevertheless, the authors acknowledged that only two small studies were published on this topic (16, 17). The findings in the latter studies require confirmation in more patients before substantiated statements can be made.

Of note, PCCs demonstrating an attenuation of ≤10 HU have been described, albeit rarely, in the literature (18, 19). Hence, in this international multicenter study, we retrospectively evaluated the quantitative CT characteristics of PCCs, as indicated in the radiological reports, to assess the proportion and associated characteristics of PCCs with an ACA-like attenuation on CT, taking into account both unenhanced attenuation and contrast washout measurements.

**Methods**

**Patients**

We included patients with a histologically proven PCC (single or multiple) who had undergone preoperative CT [*i.e.*, unenhanced CT (with or without contrast-enhanced CT) or contrast washout CT]. Patients with only postcontrast CT were not eligible for inclusion. Patients had been diagnosed and treated in centers affiliated with ENSAT. Participating ENSAT centers were the Mayo Clinic, Rochester, Minnesota (n = 153); Radboud University Medical Center, Nijmegen, Netherlands (n = 46); University Hospital Center Zagreb, Zagreb, Croatia (n = 43); Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (n = 42); Medical University of Warsaw, Warsaw, Poland (n = 33); CHU de Bordeaux, Pessac, France (n = 29); University Medical Center Groningen, Groningen, Netherlands (n = 28); University Hospital of Florence, Florence, Italy (n = 21); University of Birmingham, Birmingham, United Kingdom (n = 20); Center Hospitalier de l’Université de Montréal, Montreal, Quebec, Canada (n = 19); Hospices Civils de Lyon, Lyon, France (n = 17); University Hospital of Wuerzburg, Wuerzburg, Germany (n = 17); University Hospital of Krakow, Krakow, Poland (n = 16); Cambridge University Hospitals, Cambridge, United Kingdom (n = 12); Endocrinology
in Charlottenburg, Berlin, Germany (n = 12); Center Hospitalier Universitaire de Liege, Liege, Belgium (n = 10); Medizinische Klinik und Poliklinik IV Ludwig-Maximilians-Universität München, Munich, Germany (n = 10); Hospital General Universitario de Albacete, Albacete, Spain (n = 5). Patients provided informed consent, under ENSAT or local institutional protocol, when required.

Two hundred fourteen patients from the two Dutch centers were also included in a previous study on this topic by Buitenwerf et al. (20). In the latter study, a central re-evaluation of CT images was performed to calculate unenhanced attenuation, whereas in the current study, both unenhanced attenuation and contrast washout were analyzed based on locally generated CT reports. Additional inclusion criteria were age at diagnosis ≥18 years, a diagnosis in or after 2000, availability of the CT report, and clinical annotations (age, sex, and underlying hereditary syndrome).

Biochemical testing and imaging

Biochemical testing, usually by measurement of plasma-free or 24-hour urinary fractionated metanephrines, was performed according to local protocols with corresponding reference values. If metanephrines were not available, 24-hour urine or plasma catecholamines were used, in order of preference. Biochemical phenotypes were categorized as “adrenergic,” “noradrenergic,” or “normal.” The phenotype was classified as “adrenergic” when the increment of metanephrines, relative to the upper limits of normal, exceeded 5% of the combined metanephrine and normetanephrine increments. Patients in whom these criteria were not fulfilled and in whom normetanephrine levels exceeded the upper limits of normal were classified as “noradrenergic” (21). In addition, CT scans were obtained according to local protocols regarding contrast procedure, acquisition and reconstruction parameters, and approach to drawing the region of interest for HU measurements.

Evaluation of CT reports

Anonymized imaging reports of preoperative CT scans, generated by local radiologists as part of routine diagnostic evaluation, were submitted for central analysis. The reports were evaluated and scored independently by two observers (L.C. and J.A.W.V.H.) who were blinded to the clinical information. Type of CT examination and field of view, number and location of lesions, tumor size, unenhanced HU, APW and RPW were considered. When multiple unenhanced HU values were mentioned, the highest value was chosen for analysis. When the local report did not mention values for APW/RPW, APW and RPW were calculated according to the formulas below, provided that the required parameters were available.

\[
\text{APW} = \frac{\text{HU portal venous phase - HU delayed phase}}{\text{HU portal venous phase - HU unenhanced}} \times 100\%
\]

\[
\text{RPW} = \frac{\text{HU portal venous phase - HU delayed phase}}{\text{HU portal venous phase}} \times 100\%
\]

PCCs were classified as ACA-like according to quantitative CT characteristics in case one of the following criteria were fulfilled: (i) attenuation on unenhanced CT ≤ 10 HU or (ii) attenuation on unenhanced CT ≥ 10 HU and APW ≥ 60% and/or RPW ≥ 40%.

Data management and statistical analysis

Statistical analysis was performed with SPSS software, version 17.0 for Windows (IBM Inc., Armonk, NY). Clinical characteristics were compared between patients with PCC who had and did not have an ACA-like attenuation based on quantitative criteria. Characteristics were compared by using an unpaired t test if variables were continuous or a χ² test if variables were categorical. A two-sided P value of < 0.05 was considered to indicate a statistically significant difference.

Results

In total, 1011 cases of PCC and extra-adrenal sympathetic paragangliomas were screened for eligibility by the local investigators at the 18 participating centers. Four hundred seven cases were excluded, mainly because of the performance of postcontrast CT only (n = 305). After central review, 71 additional cases were excluded on the basis of a diagnosis of extra-adrenal paraganglioma rather than PCC (n = 25), lack of CT report (n = 21), incomplete CT report (n = 14), age <18 years (n = 5), lack of histological proof of PCC (n = 4), and performance of postcontrast CT only (n = 2). Of the remaining 533 patients with 548 histologically confirmed PCCs, quantitative CT characteristics were available in 368 patients with 382 PCCs (376 unenhanced HU with or without washout and 6 washout only). The clinical characteristics and information regarding HU and maximum diameter of PCCs are given in Table 1. The distribution of unenhanced attenuation (in HU) is reported in Fig. 1. Details on CT scan protocols and availability of quantitative data from radiology reports are given in Table 2.

PCCs with ACA-like attenuation or washout

Of the 376 PCCs for which unenhanced attenuation was available, 374 had an attenuation of >10 HU (99.5%) (Fig. 2). In the two exceptions (0.5%), unenhanced

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Men, n (%)</td>
<td>163 (44.2)</td>
</tr>
<tr>
<td>Mean age at diagnosis ± SD, y</td>
<td>54.01 ± 15.05</td>
</tr>
<tr>
<td>Biochemical phenotype, n (%)</td>
<td>200 (54.3)</td>
</tr>
<tr>
<td>Adrenergic</td>
<td>200 (54.3)</td>
</tr>
<tr>
<td>Noradrenergic</td>
<td>111 (30.1)</td>
</tr>
<tr>
<td>Normal values</td>
<td>18 (4.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>39 (10.5)</td>
</tr>
<tr>
<td>Hereditary syndrome, n (%)</td>
<td>60 (16.3)%</td>
</tr>
<tr>
<td>Mean maximum diameter ± SD, mm</td>
<td>42.73 ± 21.96 (n = 306)</td>
</tr>
<tr>
<td>Mean unenhanced attenuation ± SD, HU</td>
<td>35.04 ± 10.95 (n = 375)</td>
</tr>
</tbody>
</table>

aData RET (n =32), VHL (n = 11), NF1 (n = 11), SDHB (n = 2), SDHD (n =2), MAX (n = 1), and SDHA F2 (n = 1).
attenuation was exactly 10 HU, which lies just within the range of the ≤10 HU cutoff that would suggest a diagnosis of ACA (22). Of these two PCCs, the histology reports were re-evaluated. The first lesion was a 42-mm right adrenal PCC with extensive central hemorrhage. Preoperative urine catecholamine values were reported to be in the normal range; however, metanephrines were not measured. The second lesion was a 48-mm left adrenal PCC that contained areas of prominent nodular adrenocortical hyperplasia besides PCC. No information on the biochemical phenotype could be retrieved.

Of 76 PCCs with unenhanced HU ≤10 and available washout, 22 (28.9%) had an APW $\geq 60\%$ and/or an RPW $\geq 40\%$, suggestive of ACA. In one additional PCC, APW/RPW was high as well, but unenhanced attenuation was unavailable. The local radiologists reported on six additional lesions with characteristics of ACA. The reasons for this, however, could not be verified because washout data were unavailable; in the two cases where unenhanced attenuation was mentioned, it was >10 HU.

The PCCs with an unenhanced attenuation of >10 HU and high APW and/or RPW (n = 22) did not differ from those with an unenhanced attenuation of >10 HU and low washout (n = 54) with respect to sex, tumor size, and hereditary syndrome (data not shown).

Of 548 PCCs, 282 (51.4%) were initially discovered as AI in 276 patients. One of 199 lesions [lesion 1 in online repository (22)] with available quantitative data was among the two lesions with 10 HU. In this subgroup,

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**Table 2. CT Protocols and Availability of Quantitative Data From Radiological Reports for PCCs**

<table>
<thead>
<tr>
<th>Quantitative Data</th>
<th>All CT Scans</th>
<th>Unenhanced</th>
<th>Unenhanced and Postcontrast</th>
<th>Contrast Washout</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>94 (17.2)</td>
<td>117 (21.4)</td>
<td>148 (27.0)</td>
<td>189 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Unenhanced HU only</td>
<td>298 (54.4)</td>
<td>55 (58.5)</td>
<td>40 (34.2)</td>
<td>24 (16.2)</td>
<td>179 (94.7)</td>
</tr>
<tr>
<td>Unenhanced HU and APW/RPW</td>
<td>78 (14.2)</td>
<td>NA</td>
<td>NA</td>
<td>77 (52.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>APW/RPW only</td>
<td>6 (1.1)</td>
<td>NA</td>
<td>NA</td>
<td>6 (4.1)</td>
<td>NA</td>
</tr>
<tr>
<td>None</td>
<td>166 (30.3)</td>
<td>39 (41.5)</td>
<td>77 (65.8)</td>
<td>41 (27.7)</td>
<td>9 (4.8)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
of 29 PCCs with unenhanced HU > 10 and available washout, 10 (34.4%) had a high APW and/or RPW.

Discussion

We retrospectively evaluated the CT characteristics of PCC in the largest international cohort to date. Our main goal was to determine the proportion of PCCs with an ACA-like appearance based on a low unenhanced attenuation or a high contrast washout. The analysis was based on locally generated radiological reports. Unenhanced HU values were available for 376 of 548 histologically confirmed PCCs, two of which (0.5%) exhibited an attenuation of exactly 10 HU, consistent with an ACA-like attenuation according to recent ESE/ENSAT guidelines. In addition, among 76 PCCs with unenhanced HU > 10 and available washout, 22 (28.9%) showed a high APW and/or RPW, incorrectly suggesting ACA.

In 2016, ESE/ENSAT provided clinical practice guidelines for the management of patients with AIs. The guidelines recommended that, as part of the endocrine workup, PCC should be excluded by measurement of plasma free or 24-hour urinary fractionated metanephrines in all AIs. However, the guidelines stated that an exception could be made for cases in which a non-contrast-enhanced CT attenuation was ≤10 HU, consistent with an ACA-like attenuation according to recent ESE/ENSAT guidelines. In addition, among 76 PCCs with unenhanced HU > 10 and available washout, 22 (28.9%) showed a high APW and/or RPW, incorrectly suggesting ACA.

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In the current study and in one previous report, primarily patients with PCC were selected. Buitenwerf et al. (20) recently conducted a retrospective study including 214 patients with 222 histologically proven PCCs. Two expert radiologists independently re-evaluated the CT scans. Only 1 PCC of 222 demonstrated an attenuation value of <10 HU. This was a rare case of ACTH-dependent Cushing disease caused by a PCC. In the current study, we found a similarly low proportion (0.5%) of PCCs with an unenhanced attenuation of ≤10 HU. In fact, none of the PCCs had an unenhanced attenuation <10 HU; in only two PCCs it was exactly 10 HU. In these two cases, histology possibly provided some explanation. Hemorrhage, necrosis, and additional adrenocortical changes (23) may result in intralesional heterogeneity, emphasizing the importance of selecting the proper region of interest for the assessment of attenuation.
In ~70% of AIs, attenuation values are ≤10 HU. This illustrates the large number of patients who might benefit from implementing radiological selection to determine in which patients biochemical screening is needed as a second-line test to rule out PCC (15). Approximately 2000 patients with adrenal incidentaloma and an attenuation value ≤10 HU would need to be biochemically screened to diagnose one case of PCC, assuming a 7% prevalence of PCC in the AI population, 70% frequency of attenuation ≤10 HU, and a false-negative rate of 0.5% of radiological classification as determined in the current study [2857 AIs in total, including 2000 AIs with ≤10 HU (70% of 2857) and 200 PCCs (7% of 2857), of which one (0.5% of 200) is misclassified by CT]. In our opinion, this observation justifies omitting biochemical screening in low-attenuation AIs to prevent false-positive test results and unnecessary costs. In the given example of 2000 low-attenuation AIs, based on $50 cost of metanephrine measurement, omitting biochemical testing would result in an immediate cost reduction of $100,000. In the context of a specificity of plasma metanephrines of ~80% to 90% (1), the true cost reduction is expected to be (much) higher when taking into account follow-up investigations prompted by false-positive biochemical testing results that could have been prevented.

Besides unenhanced HU, contrast washout rates are routinely used for the evaluation of adrenal lesions. Most ACAs with an unenhanced HU > 10 exhibit a high washout. Conversely, a high washout does not rule out PCC. We found that in almost one third of PCCs with available APW/RPW data, washout was high. This is in line with a previously meta-analysis of 10 studies by Woo et al. (24). They reported a rate of PCCs with a high washout pattern of 35%. Washout data for AI should therefore not be used to determine whether biochemical testing should be done.

This study had several limitations. It was a retrospective study of locally generated radiology reports from different centers using different CT machines, settings, and contrast protocols. Drawing of the region of interest for the calculation of radiodensity was done at the discretion of the local radiologist. The impact of these potential confounders, however, is probably limited, inducing minimal variations in attenuation, estimated at 1 to 2 HU (20, 25). In addition, many cases were excluded because of the availability of postcontrast CT scans only. The detail with which different quantitative parameters were reported varied considerably, leading to missing data. On the other hand, the data were extracted directly from clinical practice and thus are representative of "real life."

**Conclusion**

On the basis of the lack of PCCs with an unenhanced attenuation of <10 HU and the low proportion (0.5%) of PCCs with an attenuation of 10 HU, it seems reasonable to abstain from biochemical testing for PCC in AIs with an unenhanced attenuation ≤10 HU. The assessment of contrast washout, however, is unreliable for ruling out PCC.

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**Disclosure Summary:** The authors have nothing to disclose.

**References**


