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

Letizia Canu,[1,2] Janna A. W. Van Hemert,[1] Michiel N. Kerstens,[3] Robert P. Hartman,[4] Aakanksha Khanna,[5] Ivana Kraljevic,[6] Darko Kastelan,[6] Corin Badiu,[7] Urszula Ambroziak,[8] Antoine Tabarin,[9] Magalie Haissaguerre,[9] Edward Buitenwerf,[3] Anneke Visser,[10] Massimo Mannelli,[2] Wiebke Arlt,[11] Vasileios Chortis,[11] Isabelle Bourdeau,[12] Nadia Gagnon,[12] Marie Buchy,[13] Francoise Borson-Chazot,[13] Timo Deutschbein,[14] Martin Fassnacht,[14,15] Alicja Hubalewska-Dydejczyk,[16] Marcin Motyka,[16] Ewelina Rzepka,[16] Ruth T. Casey,[17] Benjamin G. Challis,[17] Marcus Quinkler,[18] Laurent Vroonen,[19] Ariadni Spyroglou,[20,21] Felix Beuschlein,[20,21] Cristina Lamas,[22] William F. Young,[5] Irina Bancos,[5] and Henri J. L. M. Timmers[1]

[1]Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, 6500 HB Nijmegen, Netherlands; [2]Department of Experimental and Clinical Biomedical Sciences University of Florence, 59100 Florence, Italy; [3]Department of Endocrinology, University of Groningen, University Medical Center Groningen, 9713 GZ Groningen, Netherlands; [4]Department of Radiology, Mayo Clinic, Rochester, Minnesota 55905; [5]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota 55905; [6]Department of Endocrinology, University Hospital Center Zagreb, Zagreb 10000, Croatia; [7]National Institute of Endocrinology C. I. Parhon, Carol Davila University of Medicine and Pharmacy, 011863 Bucharest, Romania; [8]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, 02-097 Warsaw, Poland; [9]Service d'Endocrinologie Hôpital Haut-Lévêque, CHU de Bordeaux, 33600 Pessac, France; [10]Department of Applied Health Research, University of Groningen, University Medical Center Groningen, 9713 GZ Groningen, Netherlands; [11]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham B15 2TT, United Kingdom; [12]Division of Endocrinology, Center Hospitalier de l'Université de Montréal, Montreal H2X 0A9, Quebec, Canada; [13]Fédération d'Endocrinologie, Groupement Hospitalier Est, Hospices Civils de Lyon, 69500 Bron F-69677, France; [14]Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Wuerzburg, D-97080 Wuerzburg, Germany; [15]Comprehensive Cancer Center Mainfranken, University of Wuerzburg, D-97080 Wuerzburg, Germany; [16]Department of Endocrinology, Jagiellonian University, Collegium Medicum, 31-501 Krakow, Poland; [17]Addenbrooke's Hospital, Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge and NIHR Biomedical Research Center, Cambridge CB2 OQQ, United Kingdom; [18]Endocrinology in Charlottenburg, 10627 Berlin, Germany; [19]Department of Endocrinology, Center Hospitalier Universitaire de Liège, Liège 4000, Belgium; [20]Medizinische Klinik und Poliklinik IV Ludwig-Maximilians-Universität München, 80336 Munich, Germany; [21]Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, UniversitätsSpital Zürich, 8091 Zurich, Switzerland; and [22]Endocrinology Department, Hospital General Universitario de Albacete, Albacete, Spain 02006

ORCiD numbers: 0000-0003-4995-8108 (L. Canu).

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,

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 13 July 2018. Accepted 26 October 2018.
First Published Online 31 October 2018

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.

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)**

Adrenal 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 hereditable 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 χ^2 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 1. Characteristics of Patients (n = 368) and Lesions (n = 382) for Whom Quantitative CT Characteristics Were Available

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

[a] *RET* (n =32), *VHL* (n = 11), *NF1* (n = 11), *SDHB* (n = 2), *SDHD* (n=2), *MAX* (n = 1), and *SDHAF2* (n = 1).

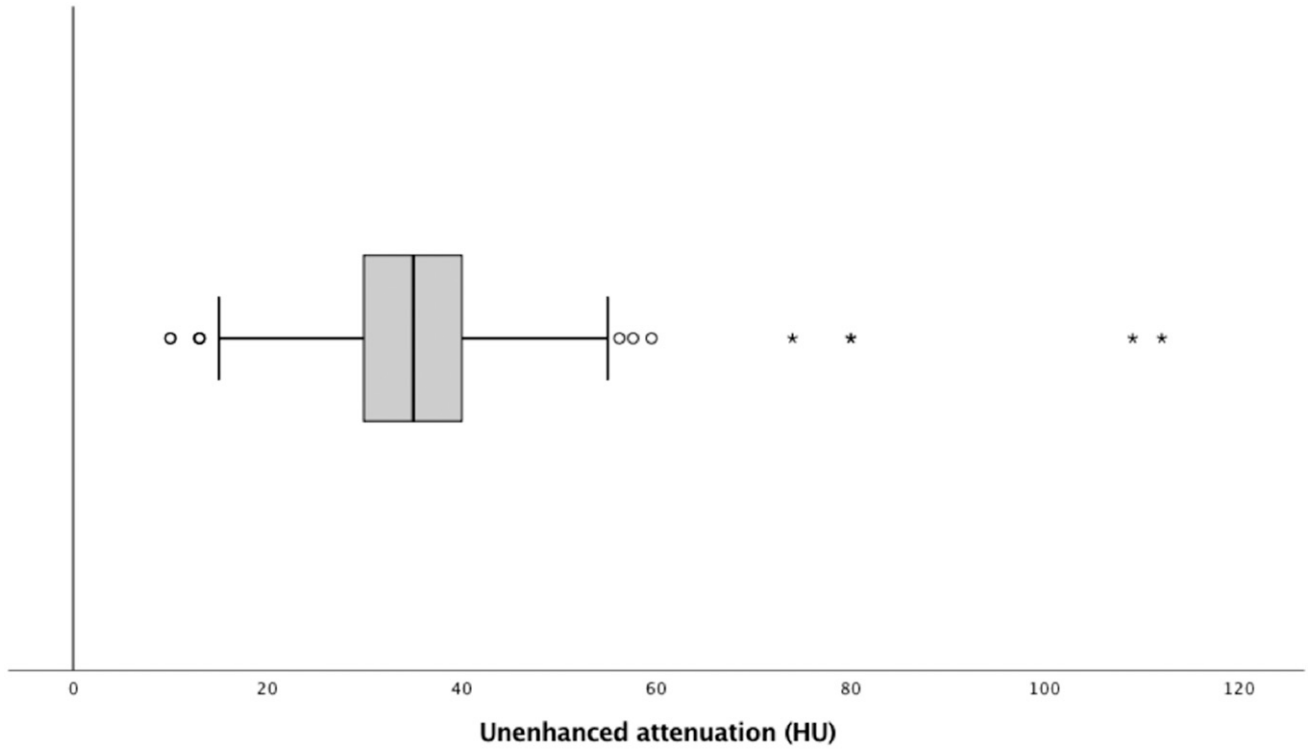

Figure 1. Distribution of unenhanced attenuation (HU, box-and-whiskers plot). Outliers (open circle); extreme values (asterisk); median (vertical line); 25% to 75% (box); 95% CI (whiskers).

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 ≥ 60% and/or an RPW ≥ 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,

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

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

Abbreviation: NA, not available.

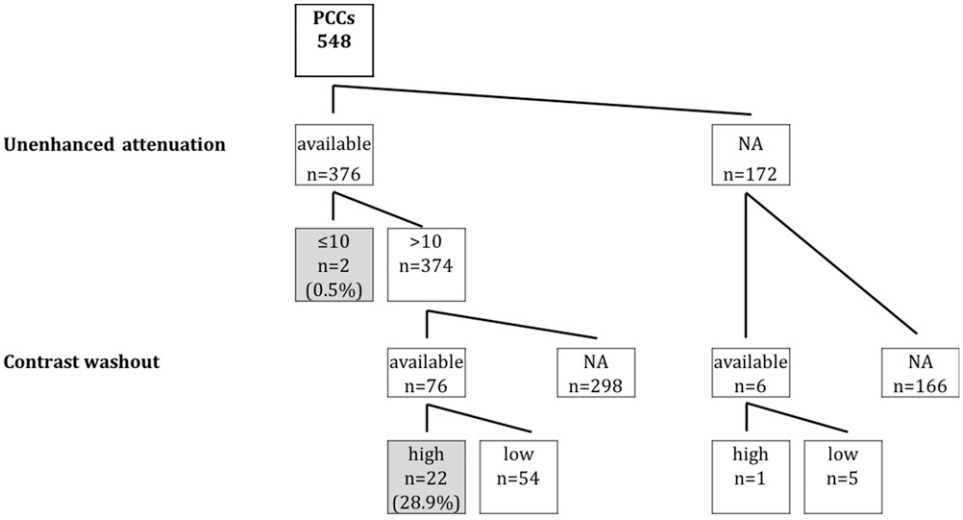

Figure 2. CT characteristics of PCCs. High washout: absolute ≥60% and/or relative ≥40%; low washout: absolute <60% and/or relative <40%. NA, not available.

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. A disclaimer was made that the evidence to support this exception was minimal, with two studies that showed a low likelihood of a PCC among adrenal lesions that were radiologically suggestive of ACA (16, 17). Sane *et al.* (16) examined whether PCC could be ruled out as cause of AIs on the basis of unenhanced attenuation values only. They retrospectively evaluated a cohort of 174 patients with AI. Unenhanced attenuation was available for 115 tumors. Nine patients had a PCC, and in none of these tumors was the unenhanced HU < 10. They concluded that routine measurement of metanephrines is unnecessary in an asymptomatic patient with AI, provided that the lesion is of low attenuation, small, and homogenous. Schalin-Jäntti *et al.* (17) performed a 5-year prospective follow-up study of 56 patients with 69 lipid-rich (*i.e.*, low attenuation) AIs. They found that 24-hour urinary metanephrines were normal at baseline as well as during follow-up. In addition, Jun *et al.* (19) studied 251 patients with AI and had similar results, leading to the conclusion that for small lesions (AI size ≤ 3 cm), noncontrast CT can substitute for biochemical testing for PCC. Nevertheless, all of the conclusions and recommendations made in these previous studies are based on small subsets of PCCs among cohorts of patients with AIs.

Rather than taking AI as a starting point, 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.

Acknowledgments

We thank professor Jacques W.M. Lenders for his critical appraisal of the manuscript.

Correspondence and Reprint Requests: Henri J.L.M. Timmers, MD, PhD, Department of Internal Medicine, Section of Endocrinology (471), Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, Netherlands. E-mail: henri.timmers@radboudumc.nl.

Disclosure Summary: The authors have nothing to disclose.

References

1. Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr; Endocrine Society. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;**99**(6):1915–1942.
2. Berends AMA, Buitenwerf E, de Krijger RR, Veeger NJGM, van der Horst-Schrivers ANA, Links TP, Kerstens MN. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. *Eur J Intern Med*. 2018;**51**:68–73.
3. Dahia PL, Hao K, Rogus J, Colin C, Pujana MA, Ross K, Magoffin D, Aronin N, Cascon A, Hayashida CY, Li C, Toledo SP, Stiles CD; Familial Pheochromocytoma Consortium. Novel pheochromocytoma susceptibility loci identified by integrative genomics. *Cancer Res*. 2005;**65**(21):9651–9658.
4. Vicha A, Musil Z, Pacak K. Genetics of pheochromocytoma and paraganglioma syndromes: new advances and future treatment options. *Curr Opin Endocrinol Diabetes Obes*. 2013;**20**(3):186–191.
5. Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. *Nat Rev Endocrinol*. 2015;**11**(2):101–111.
6. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *Lancet*. 2005;**366**(9486):665–675.
7. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2016;**175**(2):G1–G34.
8. Kopetschke R, Slisko M, Kilisli A, Tuschy U, Wallaschofski H, Fassnacht M, Ventz M, Beuschlein F, Reincke M, Reisch N, Quinkler M. Frequent incidental discovery of phaeochromocytoma: data from a German cohort of 201 phaeochromocytoma. *Eur J Endocrinol*. 2009;**161**(2):355–361.
9. Arnold DT, Reed JB, Burt K. Evaluation and management of the incidental adrenal mass. *Proc Bayl Univ Med Cent*. 2003;**16**(1):7–12.

10. Zeiger MA, Siegelman SS, Hamrahian AH. Medical and surgical evaluation and treatment of adrenal incidentalomas. *J Clin Endocrinol Metab*. 2011;**96**(7):2004–2015.
11. Terzolo M, Bovio S, Pia A, Reimondo G, Angeli A. Management of adrenal incidentaloma. *Best Pract Res Clin Endocrinol Metab*. 2009;**23**(2):233–243.
12. Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med*. 2007;**356**(6):601–610.
13. Bülow B, Ahrén B; Swedish Research Council Study Group of Endocrine Abdominal Tumours. Adrenal incidentaloma—experience of a standardized diagnostic programme in the Swedish prospective study. *J Intern Med*. 2002;**252**(3):239–246.
14. Barzon L, Sonino N, Fallo F, Palu G, Boscaro M. Prevalence and natural history of adrenal incidentalomas. *Eur J Endocrinol*. 2003; **149**(4):273–285.
15. Dinnes J, Bancos I, Ferrante di Ruffano L, Chortis V, Davenport C, Bayliss S, Sahdev A, Guest P, Fassnacht M, Deeks JJ, Arlt W. Management of endocrine disease: imaging for the diagnosis of malignancy in incidentally discovered adrenal masses: a systematic review and meta-analysis. *Eur J Endocrinol*. 2016;**175**(2):R51–R64.
16. Sane T, Schalin-Jäntti C, Raade M. Is biochemical screening for pheochromocytoma in adrenal incidentalomas expressing low unenhanced attenuation on computed tomography necessary? *J Clin Endocrinol Metab*. 2012;**97**(6):2077–2083.
17. Schalin-Jäntti C, Raade M, Hämäläinen E, Sane T. A 5-year prospective follow-up study of lipid-rich adrenal incidentalomas: no tumor growth or development of hormonal hypersecretion. *Endocrinol Metab (Seoul)*. 2015;**30**(4):481–487.
18. Blake MA, Krishnamoorthy SK, Boland GW, Sweeney AT, Pitman MB, Harisinghani M, Mueller PR, Hahn PF. Low-density pheochromocytoma on CT: a mimicker of adrenal adenoma. *AJR Am J Roentgenol*. 2003;**181**(6):1663–1668.
19. Jun JH, Ahn HJ, Lee SM, Kim JA, Park BK, Kim JS, Kim JH. Is preoperative biochemical testing for pheochromocytoma necessary for all adrenal incidentalomas? *Medicine (Baltimore)*. 2015;**94**(45):e1948.
20. Buitenwerf E, Korteweg T, Visser A, Haag CMSC, Feelders RA, Timmers HJLM, Canu L, Haak HR, Bisschop PHLT, Eekhoff EMW, Corssmit EPM, Krak NC, Rasenberg E, van den Bergh J, Stoker J, Greuter MJW, Dullaart RPF, Links TP, Kerstens MN. Unenhanced CT imaging is highly sensitive to exclude pheochromocytoma: a multicenter study. *Eur J Endocrinol*. 2018;**178**(5):431–437.
21. Eisenhofer G, Pacak K, Huynh TT, Qin N, Bratslavsky G, Linehan WM, Mannelli M, Friberg P, Grebe SK, Timmers HJ, Bornstein SR, Lenders JW. Catecholamine metabolomic and secretory phenotypes in phaeochromocytoma. *Endocr Relat Cancer*. 2010;**18**(1):97–111.
22. Canu L, Van Hemert JAW., Kerstens M, Hartman RP, Khanna A., Kraljevic I, Kastelan D, Badiu C, Ambroziak U, Tabarin A, Haissaguerre M, Buitenwerf E, Visser A, Mannelli M, Arlt W, Chortis V, Bourdeau I, Gagnon N, Buchy M, Borson-Chazot F, Deutschbein T, Fassnacht M, Hubalewska Dydejczy H. A, Motyka M, Rzepka E, Casey R T, Challis B G, Quinkler M, Vroonen L, Spyroglou A, Beuschlein F, Lamas C, Young W F, Bancos I, Timmers H J L M. Canu_SupdataTab1.pdf.
23. Hasassri ME, Pandian TK, Bobr AA, Bancos I, Young WF Jr, Richards ML, Farley DR, Thompson GB, McKenzie TJ. Pheochromocytoma with Synchronous Ipsilateral Adrenal Cortical Adenoma. *World J Surg*. 2017;**41**(12):3147–3153.
24. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Pheochromocytoma as a frequent false-positive in adrenal washout CT: A systematic review and meta-analysis. *Eur Radiol*. 2018;**28**(3):1027–1036.
25. Cropp RJ, Seslija P, Tso D, Thakur Y. Scanner and kVp dependence of measured CT numbers in the ACR CT phantom. *J Appl Clin Med Phys*. 2013;**14**(6):4417.