Original Article

Not all adrenal incidentalomas require biochemical testing to exclude pheochromocytoma: Mayo clinic experience and a meta-analysis

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Background: Excluding a pheochromocytoma is important when a patient presents with an incidentally discovered adrenal mass. However, biochemical testing for pheochromocytoma can be cumbersome, time consuming, or falsely positive. Our objective was to determine if unenhanced computed tomography (CT) imaging alone can be used to rule out pheochromocytoma.

Methods: We performed a retrospective study of all patients with a pathologically confirmed pheochromocytoma and unenhanced CT imaging who were treated at the Mayo Clinic between 1998 and 2016. Additionally, we performed a systematic review and meta-analysis of original studies published after 2005 with patients who had adrenal masses, more than 10 patients with pheochromocytomas, and reported attenuation on unenhanced CT imaging in Hounsfield units (HU).

Results: In the Mayo cohort, we identified 186 patients and 199 pheochromocytomas with unenhanced CT imaging. The mean unenhanced CT attenuation was 35±9 HU (range, 15–62), and only 15 tumors had attenuation ≤20 HU. The systematic review identified 26 studies (1,217 tumors), and 23 studies provided a mean unenhanced CT attenuation. The overall mean unenhanced CT attenuation across the studies was 35.6 HU (95% CI, 22.0–49.1 HU). A cutoff of >10 HU had a 100% sensitivity (95% CI, 1.00–1.00) for pheochromocytoma with low heterogeneity between the 21 qualified studies (I^2=0%). Sensitivity for pheochromocytoma was 100% and 99% for an unenhanced CT attenuation cutoff of >15 and >20 HU.

Conclusions: Biochemical testing may not be required to exclude pheochromocytoma if an incidental adrenal mass has low attenuation (<10 HU) on unenhanced CT images.

Keywords: Pheochromocytoma; computed tomography (CT); Hounsfield units (HU); diagnosis

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Introduction

Biochemical exclusion of a catecholamine-producing pheochromocytoma is often recommended for all adrenal incidentalomas (1-3). There have been reports of pheochromocytomas mimicking hypodense adrenal adenomas (4,5). Different tests are used to rule out a catecholamine-secreting pheochromocytoma, including 24-h urine fractionated metanephrines and catecholamines, as well as plasma fractionated metanephrines. The 24-h urine collection is cumbersome and may be performed incorrectly (6). Measuring plasma fractionated metanephrines can avoid the cumbersome 24-h urine collection; however, a false positive rate as high as 15% has been reported (7,8). The question has been raised if the biochemical evaluation for pheochromocytoma can be omitted based on the imaging phenotype of the adrenal mass, resulting in the reduction of unnecessary testing, cost, and potential anxiety or overtreatment (5,9,10). Furthermore, general surgeons can evaluate patients with an indication for abdominal surgery and a newly discovered adrenal mass. Exclusion of a catecholamine-producing pheochromocytoma based on imaging findings alone would simplify patient management and expedite operative treatment in this scenario.

The primary aim of our study was to determine the range of unenhanced attenuation for pathologically proven pheochromocytoma on computed tomography (CT) by combining a systematic review with a large cohort of patients treated at the Mayo Clinic. Finally, this would be used to determine a highly sensitive cutoff value of unenhanced attenuation that can be used to identify adrenal masses not requiring biochemical testing for pheochromocytoma.

Methods

Retrospective review

All patients with a pathologically confirmed pheochromocytoma treated at the Mayo Clinic between 1998 and 2016 were identified. Patients without unenhanced CT images were excluded. The images and radiology reports were reviewed. The axial cut with the greatest diameter of the tumor was identified and was considered to be the region of interest (ROI). The appearance of the mass was qualitatively assessed as either heterogeneous or homogeneous, and ROI was specifically selected in order to avoid inclusion of calcifications, which would result in increased measured attenuation. The average unenhanced attenuation of the ROI was measured within the greatest possible area not including calcifications or tumor periphery.

The study was approved by the Mayo Clinic Institutional Review Board (ID 14-008336) and a waiver of the requirement to obtain informed consent from the study subjects was approved considering the minimal risk of the study.

Systematic review and meta-analysis

Eligibility criteria

Studies meeting the following criteria were included in the review: original study, published after 2005, including patients with an adrenal nodule/mass and at least 10 patients with pheochromocytoma, reporting unenhanced attenuation of the adrenal tumor, written in English. Pheochromocytoma diagnosis was considered to be conclusive if it was based either on pathological findings or biochemical testing (24-h urine or plasma fractionated metanephrines/catecholamines at least 3 times higher than the upper limits of the reference ranges in a patient with an adrenal mass).

Data sources and search strategies

A comprehensive search of several databases using any language was conducted from January 1st, 2005 to May 30th, 2018. The databases included MEDLINE Epub Ahead of Print, Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by a medical reference librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies using unenhanced CT for exclusion of a pheochromocytoma in humans. The actual strategy is provided in the appendix.

Methodological quality assessment

The quality of studies included in the meta-analysis was rated using QUADAS-2 scale (http://www.quadas.org). The risk of bias was rated in four domains: (I) patient selection; (II) interpretation of the index test; (III) reference standard; (IV) flow and timing. Concerns regarding applicability were assessed in the first three domains. The risk of bias and applicability was assessed as high, low or uncertain. The

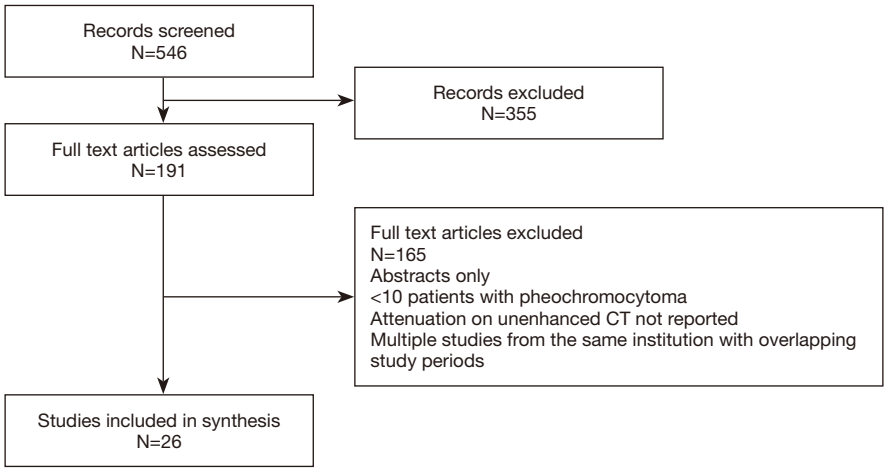

Figure 1 Flowchart of study assessment. CT, computed tomography.

studies were assessed independently by two reviewers, and their assessments were reconciled by a third reviewer.

Data synthesis

The studies were reviewed and the data extracted independently by two reviewers. Conflicts were resolved by consensus. Descriptive statistics of imaging characteristics including unenhanced CT attenuation measured in Hounsfield units (HU) and size were calculated. Random-effect models meta-analysis was then used to estimate the pooled sensitivity and 95% confidence intervals (CIs) for the diagnosis of pheochromocytoma with different cutoffs of unenhanced attenuation: >10, >15 and >20 HU. Sensitivity was defined as a proportion of patients with pheochromocytoma who had a positive test out of all patients with pheochromocytoma. Variance of proportions was stabilized using the Freeman Turkey double arcsine method (11). Weighted mean HU value was pooled from all pheochromocytomas across studies. I^2 statistic was used to estimate heterogeneity. Analysis was conducted using STATA software package (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC).

Results

Retrospective review

We identified 439 pathologically confirmed pheochromocytomas from the Mayo Clinic over the study period. Unenhanced CTs were available for 186 patients and a total of 199 tumors (13 bilateral). Mean tumor diameter was 38±22 (range, 12–150) mm; 124 tumors were ≤40 mm in diameter. Most tumors were homogenous on non-contrast phase CT (n=136, 68%). For the entire cohort, mean unenhanced CT attenuation was 35±9 HU (range, 15–62). Overall, only 15 tumors (8%) had an unenhanced CT attenuation ≤20 HU with 50% of these having attenuation measured at 19 or 20 HU; 8 tumors (53%) had a heterogeneous appearance. A single pheochromocytoma with CT attenuation of 15 HU had a significant cystic component. In the subgroup of homogenous tumors ≤40 mm (n=115), mean CT attenuation was 36±8 (range, 17–58) HU.

Systematic review and meta-analysis

The initial search identified 546 studies; after screening, full text evaluation was performed for 191 studies. As indicated in *Figure 1*, 165 studies were excluded. A total of 26 studies (1,217 tumors with unenhanced CT attenuation reported) were included in this systematic review, including the present cohort (*Table 1*) (5,9,12-32). Twenty-three studies provided mean unenhanced density of the tumor with overall mean unenhanced CT attenuation of 35.6 HU (95% CI, 22.0–49.1 HU), 21 studies (1,029 tumors) provided sufficient data to calculate the sensitivity for cutoff of >10 HU, 11 studies (468 tumors) for cutoff of >15 HU and 13 studies (400 tumors) for cutoff of >20 HU. Heterogeneity among studies was low with I^2=0% for mean CT attenuation and for sensitivity of >10 and >15 HU cutoffs, and I^2=12% at a cutoff of >20 HU. Overall sensitivities for pheochromocytoma were 100% (95% CI, 1.00–1.00), 100% (95% CI, 1.00–1.00), and 99% (95%

Table 1 Studies included in systematic review and meta-analysis

Author	Year	Country	Years of patient enrollment	All tumors pathologically confirmed?	Total tumors (n)	Tumor diameter, mm, mean ± SD [range]	Unenhanced density reported (n)
Bessell-Browne	2007	Canada	1999–2005	Yes	16	40 [7–135]	16
Buitenwerf	2018	Netherlands	2000–2017	Yes	222	Median 51, IQR: 39–74	222
Cheng, Group 1	2017	China	2009–2015	Yes	13	40±27	13
Cheng, Group 2	2017	China	2009–2015	Yes	18	50±42	18
Jun	2015	South Korea	2011–2012	No	19	Median 40, IQR: 24–52	16
Kannan, Group 1	2014	USA	1997–2012	Yes	93	Median 48, [17–220]	90
Kannan, Group 2	2014	USA	1997–2012	Yes	23	Median 30, [17–50]	22
Kasperlik-Zaluska	2006	Poland	–	Yes	36	[11–133]	–
Kim, Group 1	2017	South Korea	2006–2015	Yes	10	26 [18–22]	10
Kim, Group 2	2017	South Korea	2006–2015	Yes	29	34 [34–140]	29
Liu	2019	China	2010–2016	Yes	13	Median 50.7, IQR: 22.4	13
Marty	2018	France	2000–2013	No	33	42±17 [15–80]	33
Myśliwiec	2013	Poland	2009–2012	Yes	14	44 [15–85]	14
Ohno	2018	Japan	2005–2015	Yes	21	Median 42, IQR: 27–58	21
Park	2007	South Korea	2002–2006	Yes	31	44±24 [16–118]	31
Park	2007	South Korea	2001–2005	Yes	12	–	12
Park	2012	South Korea	2005–2009	Yes	48	57 [28–110]	48
Patel	2013	USA	2000–2011	No	47	39 [6–140]	37
Pitts	2013	USA	2009–2011	Yes	10	33 [18–53]	10
Raja	2013	Canada	2000–2011	Yes	52	40±20 [6–90]	41
Sane	2012	Finland	2007–2009	No	10	40±15 [22–67]	9
Schieda	2016	Canada	2003–2014	Yes	34	50±42 [15–203]	10
Szolar	2005	Austria	1996–2002	Unclear	17	51±19 [47–108]	17
Yi, Group 1	2018	China	2006–2017	Yes	67	Median 52, IQR: 39–68	67
Yi, Group 2	2018	China	2006–2017	Yes	17	Median 46, IQR: 35–59	17
Yip	2010	USA	2000–2008	Yes	44	–	44
Zawadzka-Leska	2016	Poland	2010–2015	Yes	16	Median 31, IQR: 16–49	16
Zhang	2017	China	2014–2016	Yes	98	51±31 [12–163]	98
Zhu	2016	China	2008–2012	No	14	–	14
Mayo Cohort	2020	USA	1998–2016	Yes	439	38±22 [12–150]	199

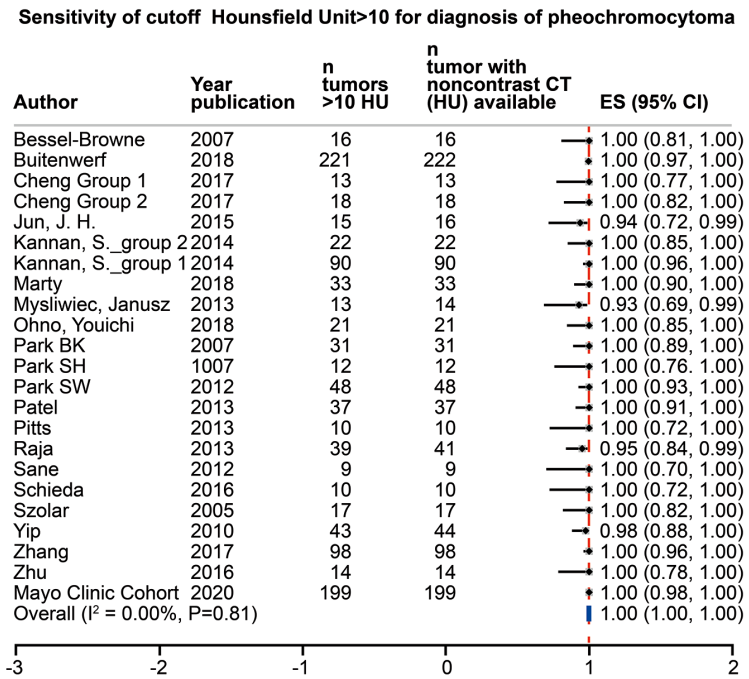

Figure 2 Meta-analysis of the sensitivity for diagnosis of pheochromocytoma, unenhanced density on CT imaging >10 HU. CT, computed tomography; HU, Hounsfield units; CI, confidence interval.

CI, 0.96–1.00) for unenhanced CT attenuation cutoffs of >10, >15 and >20 HU, respectively. Further results of the meta-analysis are presented in *Figures 2-4*. Using the crude numbers from the included studies, in 1,000 patients cutoffs of >10, >15 and >20 HU would lead to missing the diagnosis of 3, 5 and 44 pheochromocytomas, respectively.

Methodological quality of included studies

The methodological quality assessment of included studies is shown in *Figure 5*. Overall, risk of bias for domain 1 (patient selection) was low for 21 studies (81%) since all studies had consecutive rather than a random sample, and most studies had pathologic confirmation of the diagnosis. The risk of bias was assessed as high for the majority of studies (n=20, 77%) for domain 2 (index test), since the persons interpreting the images were either not blinded to the diagnosis or this was not clearly stated, and/or there was no preset cutoff for unenhanced attenuation. The risk of bias for domain 3 (reference standard) was assessed as low for 26 (100%) of the included studies. For domain 4 (flow and timing), the risk of bias was low for 18 (70% of the studies). Studies with high risk of bias for this domain included patients who did not have non-contrast CT and exclusion of patients for unclear reasons or due to the presence of certain imaging characteristics. All studies were rated as low for concerns regarding applicability for domain 1 (patient selection), and 20 studies (77%) were rated as low for domain 2 (index test). The studies were rated as high for concerns regarding applicability for this domain if the authors did not specify the number of patients with non-enhanced CT or if the range or cutoffs were not provided for unenhanced attenuation. Low concerns regarding applicability were assessed for the majority of the included studies (n=25, 96%) for domain 3 (reference standard).

Certainty in the evidence

The certainty in the reported sensitivity is at least moderate. Despite increased risk of bias in some QUADAS-2 domains, there were overall adequate ascertainment of the exposure and outcomes in these studies and limited concerns about heterogeneity or imprecision (33).

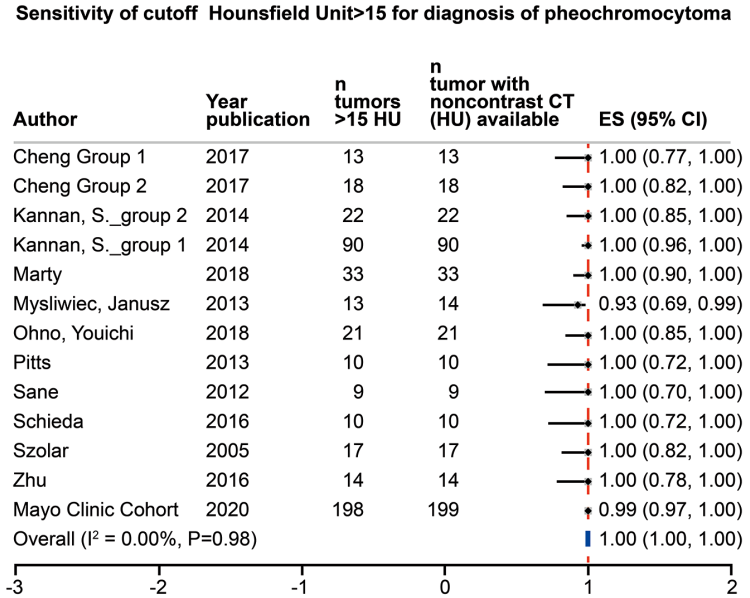

Figure 3 Meta-analysis of the sensitivity for diagnosis of pheochromocytoma, unenhanced density on CT imaging >15 HU. CT, computed tomography; HU, Hounsfield units; CI, confidence interval.

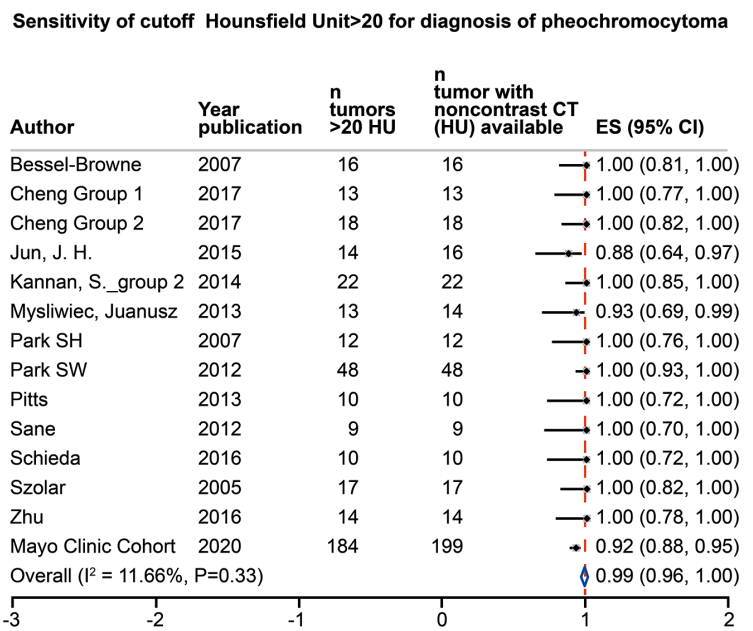

Figure 4 Meta-analysis of the sensitivity for diagnosis of pheochromocytoma, unenhanced density on CT imaging >20 HU. CT, computed tomography; HU, Hounsfield units; CI, confidence interval.

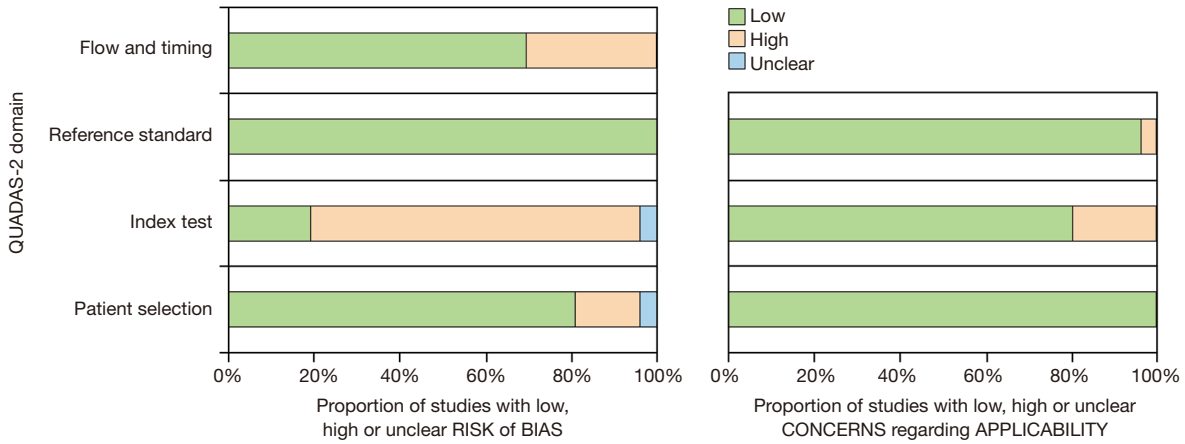

Figure 5 QUADAS-2 assessment of bias and applicability.

Discussion

Our data show that imaging alone can be sufficient to rule out pheochromocytoma in many patients. We suggest a cutoff of <10 HU on unenhanced CT to rule out a pheochromocytoma. Pheochromocytomas with unenhanced CT attenuation ≤20 HU appear to be quite rare (4% of tumors). However, the majority of studies in our meta-analysis used a cutoff of >10 HU (19 studies, 963 tumors) and resulted in a pooled sensitivity of 100%. The consequence of missing a pheochromocytoma diagnosis is also potentially catastrophic. Therefore, a conservative cutoff of <10 HU is reasonable.

Several recent studies have shown similar results. A multicenter retrospective study from the Netherlands (n=222 tumors) showed hypodense pheochromocytomas on CT imaging being exceedingly rare (<0.5%) (13). Additionally, a multicenter study (n=376 tumors), which includes some of our cohort, showed only two tumors (0.5%) with an unenhanced attenuation of 10 HU and no tumors with <10 HU (34). A recent meta-analysis (n=1,167 tumors) also proposed a cutoff of <10 HU to rule out pheochromocytoma and showed this method is cost effective (35).

"Hypodense pheochromocytoma" is a poorly documented phenomenon. A study from 1987 (4) gives a pathologic description of lipid infiltration of a pheochromocytoma, however, no details regarding attenuation of the tumor were provided. Our cohort did not have any pheochromocytomas with an unenhanced CT attenuation of <15 HU, even when heterogeneous masses were examined, and pheochromocytomas ≤20 HU were rare (8%), with about a half of such tumors (53%) being heterogeneous. Only 3 pheochromocytomas with unenhanced CT attenuation <10 HU were identified in the systematic review. No potential explanations for this phenomenon were offered in the series by Jun *et al.* (5) or by Myśliwiec *et al.* (20). Buitenwerf *et al.* describe a single low attenuation tumor (–4 HU) as an ACTH-secreting lesion causing Cushing syndrome, but without obvious necrosis, cystic parts or calcifications (13).

It is of concern that potential inclusion of hypodense areas of partially cystic or necrotic masses into ROI may result in a measurement below our proposed cutoffs, thus leading to false exclusion of a pheochromocytoma. However, even when heterogeneous masses from our cohort were included in analysis, the lowest unenhanced CT attenuation was 15 HU in a predominantly cystic tumor. Therefore, it appears that the technique of measurement applied in our study can avoid the pitfall, and the unenhanced attenuation remains >10 HU even in such extreme cases. It should be pointed out that heterogeneity of the mass in our study was assessed qualitatively, as a visual impression of the observer, rather than using a particular algorithm. Caution should be exercised when approaching adrenal lesions with cystic components, calcifications or hypodense areas possibly associated with areas of necrosis or hemorrhage since these features make a lipid-rich adenoma unlikely and about 7% of cystic adrenal lesions can be associated with a pheochromocytoma (36).

There are certain limitations to our study. The majority of articles included in this review are retrospective single institution series, with relatively small numbers of patients. The data were not reported consistently across the

studies, since their objectives varied and only a minority of studies focused on the hypothesis presented in our study. Two studies including a total of 80 tumors (16,31) did not clearly report if all patients had unenhanced CT performed. An important but unlikely source of bias would be utilization of unenhanced CT attenuation for exclusion of pheochromocytoma during study enrollment periods. This would then falsely decrease the proportion of hypodense pheochromocytoma, as those tumors would go undiagnosed. This scenario seems very unlikely and to our knowledge this approach to biochemical testing for pheochromocytoma in patients with adrenal masses was not a routine part of clinical practice at the Mayo Clinic during the study period.

Conclusions

Patients with an incidentally discovered adrenal mass do not require biochemical testing to exclude pheochromocytoma if the neoplasm has low attenuation (<10 HU) on unenhanced CT images.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs.2020.03.04). Dr. Bancos reports grants from HRA Pharma, other from ClinCor, other from Corcept, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Mayo Clinic Institutional Review Board (ID 14-008336) and a waiver of the requirement to obtain informed consent from the study subjects was approved considering the minimal risk of the study.

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