

Can Enhancement Pattern and Enhancement Level on Biphasic Enhanced CT Distinguish Homogeneous Pheochromocytomas From Adenomas Without Lipid

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Research

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Abstract

Objective The purpose of our study was to evaluate whether enhancement pattern and enhancement level on biphasic enhanced CT can distinguish homogeneous pheochromocytomas from adenomas without lipid and explore the value of percentage of peak enhancement (PPE) in differentiating the two entities.

Methods We retrospectively analysed pathologically proven 17 pheochromocytomas and 34 adenomas. Both tumors were homogeneous without necro-cystic changes and hemorrhage. The inclusion criteria for adenomas without lipid in our study was that the mean attenuation values were greater than 10 HU and the minimum values were greater than 0 HU on unenhanced CT. Biphasic CT scan protocol consisted of unenhanced phase, arterial phase (25-35 seconds) and venous phase (60-80 seconds). The enhancement pattern, attenuation values on unenhanced and enhanced phases and PPE were compared between the two groups.

Results Enhancement pattern was similar between the two groups ($p>0.99$), persistent enhancement pattern on venous phase was the most common in both tumors. The precontrast CT values of pheochromocytomas were significantly higher than that of adenomas without lipid (41 HU vs 37 HU, $p=0.006$). The enhancement level on arterial and venous phase of pheochromocytomas was greater than that of adenomas without lipid, but no significant differences were found (100 HU vs 85 HU, $p=0.223$; 103 HU vs 96 HU, $p=0.905$, respectively). The distribution of PPE of two entities was different. A range of 100%-240% of PPE can discriminate adenomas without lipid from pheochromocytomas, with sensitivity of 88.2%, specificity of 47.1%.

Conclusion The enhancement pattern and enhancement level on biphasic enhanced CT could not distinguish homogeneous pheochromocytomas from adenomas without lipid. Further studies are needed to prove the potential value of PPE due to its low specificity.

Introduction

Incidental adrenal masses are very common in patients undergoing CT examinations for other reasons, accounting for 4% of all abdominal CT exams.¹ Although the incidence rate increases to 9%-13% in patients with history of cancer, the possibility of metastatic adrenal mass is relatively low, approximately 26%-36%.²⁻⁴ Among these incidental adrenal masses without history of cancer, most are benign and nonfunctional.⁵ Nonfunctional adenoma, myelolipoma, cyst, hemorrhage can be safely left alone, while pheochromocytoma, metastasis and cortical adenocarcinoma warrants further investigation and treatment.⁶ Of these tumors, pheochromocytoma can secrete catecholamine that may lead to lethal hypertensive crisis, and unrecognized pheochromocytoma may cause a potential fatal incident during surgery. Therefore, it is very crucial to make an accurate preoperative diagnosis to exclude pheochromocytoma.

Adenomas are most common in adrenal incidentalomas, accounting for 70%-80% of cases.^{1,7} Lipid-rich adenomas have a low attenuation on unenhanced CT due to the existence of abundant intracytoplasmic lipid. Threshold of 10 HU on unenhanced CT shows excellent diagnostic performance of lipid-rich adenomas.⁸ However, approximately 29% adenomas show attenuation values greater than 10 HU on unenhanced CT, making them indeterminate to diagnose.⁸ These lesions are termed as lipid-poor adenomas. Despite that, Jhaveri et al.⁹ showed that CT histogram analysis at the threshold of more than 5% or 10% negative pixels on unenhanced CT yielded a very high sensitivity and specificity for diagnosis of lipid-poor adenomas. But CT histogram analysis may not work in the case of lipid-poor adenomas without lipid which show absence of negative pixels on unenhanced CT. Those lipid-poor adenomas without lipid on unenhanced CT may be mistaken for non-adenomas.

Pheochromocytomas have diverse imaging appearance due to variable degeneration.¹⁰ Study revealed presence of suspicious morphology (neco-cystic changes and inhomogeneity) was more common in pheochromocytomas compared to adenomas, and absence of suspicious morphology was one of criteria to exclude pheochromocytomas.¹¹ This finding may not apply to the cases of homogeneous pheochromocytomas. Almost all pheochromocytomas have precontrast CT values more than 10 HU and cannot be confused for lipid-rich adenomas.¹² It is challenging to differentiate homogeneous pheochromocytomas from adenomas without lipid on unenhanced CT.

Adenomas typically display rapid washout characteristic on delayed phase after contrast, compared to non-adenomas, including metastases, pheochromocytoma. Several studies found absolute percentage washout (APW) and relative percentage washout (RPW) on delayed phase can distinguish adenoma from non-adenomas.¹³⁻¹⁶ Thus, a dedicated adrenal CT protocol consisted of unenhanced scan, venous and delayed enhanced scan is recommended for indeterminate adrenal mass.⁶ However, washout characteristic was not definitely reliable to distinguish adenoma from pheochromocytoma. A considerable part of pheochromocytomas met the washout criteria of adenomas, leading to misdiagnosis.^{17,18} Some investigators suggested that dual-phase enhancement pattern and enhancement level can provide additional value to distinguish pheochromocytomas from adenomas,¹⁹⁻²¹ although enhancement level varied in studies. But it is not clear whether the aforementioned results can apply to differentiation the cases of homogeneous pheochromocytomas from adenomas without lipid.

Therefore, the purpose of the study was to evaluate whether enhancement pattern and enhancement level on biphasic enhanced CT can distinguish homogeneous pheochromocytomas from adenomas without lipid and explore the value of PPE in differentiating the two entities.

Materials And Methods

This retrospective study was approved by the institutional review board of Tongde Hospital of Zhejiang Province, Sir Run Run Shaw Hospital of Zhejiang University School of Medicine and the Second Affiliated Hospital of Zhejiang University School of Medicine, and informed consent was waived. Patients with

pathological diagnosis of adrenal adenomas and pheochromocytomas were enrolled between January 2008 and July 2019. The inclusion criteria was as follows: (1) presence of preoperative contrast enhanced CT imaging. (2) absence of lipid in lipid-poor adenomas and pheochromocytomas on unenhanced CT. The minimum attenuation values were greater than 0 HU in the regions of interest (ROIs) that covered entire tumor as much as possible. Adenomas with mean unenhanced CT values more than 10 HU were deemed as lipid-poor. (3) the homogeneity within tumor on enhanced CT. Two small ROIs of same size were placed at the lowest and highest enhanced portions of tumor on arterial and venous phase respectively, and the lowest and highest attenuation values of the lesion were recorded. A homogeneous mass was defined as absence of necro-cystic changes and hemorrhage within lesion and the difference between the lowest and highest CT values after contrast less than 20 HU. (4) maximum diameter of tumor more than 1cm to avoid partial volume averaging artifact. Finally, the study population consisted of 51 patients with 34 adenomas without lipid and 17 pheochromocytomas. The flowchart of our study was showed in Fig. 1.

The clinical data was obtained from electronic medical system. Hyperadrenergic symptoms consisted of blood tension surge, sweating, palpitation, severe headache, febrile sense. The presence of hypertension and hyperadrenergic symptoms was recorded.

CT protocol

The images were obtained on multidetector CT (MDCT) scanners (SOMATOM Sensation 16, SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany; LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). All patients underwent unenhanced CT followed by arterial phase (25-35 seconds) and venous phase (60-80 seconds) after infusion of contrast at a rate of 3-5 mL/s. A total of 100-120 mL contrast material (Omnipaque, GE Healthcare) was injected intravenously. The scan parameters were as below: 120 kV, 250-300 mA, 1:1 pitch, 3-5mm slice thickness.

Imaging analysis

Two abdominal radiologists with 2 and 11 years experience respectively evaluated all preoperative CT images. They were blind to pathological result. All lesions were assessed on axial images. The imaging data of adenomas without lipid and pheochromocytomas was recorded as follows: (1) size: longest diameter on axial images. (2) attenuation values measured on unenhanced phase (CTU), arterial phase (CTA) and venous phase (CTV). (3) PPE, we calculated the PPE as $PPE = (CTP - CTU)/CTU \times 100\%$, where CTP was the peak enhancement attenuation on arterial and venous phase. (4) enhancement pattern of tumors, as reported by Northcutt et al.¹⁹ If CTA was 5 HU greater than on CTV, the enhancement pattern was deemed washout. If CTV was 5 HU greater than CTA, the enhancement pattern was deemed persistent. If the level was less than 5 HU different between CTA and CTV, the enhancement pattern was deemed plateau.

As all tumors in our study were homogeneous, a round or ovoid ROI was drawn to cover entire lesion on the level of largest diameter as much as possible and should avoid tumor margin to reduce partial

volume averaging artifact (Fig. 2).

Statistical analysis

All statistical data analysis was performed with SPSS (version 20, SPSS, Chicago, USA) and Matlab (version 9.0, MathWorks, Massachusetts, USA). Continuous data was expressed as mean \pm standard deviation (SD). The differences of patient age and tumor size between two groups were analysed by Student *t* test. The differences of CTU, CTA, and CTV, PPE between two groups were analysed by Mann-Whitney U test and Matlab. Chi-square test was used to compare classified data between two groups. The value of area under curve (AUC) was calculated to evaluate the predictive power of the variables. A two-tailed *p* value < 0.05 was considered statistically significant.

Results

Patient Characteristics

There were no significant differences in patient age, gender and hypertension, tumor size between the two groups. All patients with homogeneous pheochromocytomas had no hyperadrenergic symptoms. Results were summarized in Table 1.

Enhancement pattern

The enhancement pattern of pheochromocytomas and adenomas without lipid was similar ($p > 0.99$) (Table 2). Persistent enhancement pattern was most common in both tumors. 26.5% adenomas without lipid and 29.4% pheochromocytomas demonstrated washout feature on venous phase.

Attenuation values and PPE

On unenhanced CT, the attenuation values of pheochromocytomas were significantly higher than that of adenomas without lipid (41.4 HU vs 36.5 HU, $p = 0.006$) (Table 3). ROC analysis showed cutoff of CTU > 40.7 HU yielded sensitivity of 70.6% and specificity of 76.5% for pheochromocytomas, AUC was 0.739. But there was considerable overlap between the two groups.

No statistical differences were found ($p = 0.223$, $p = 0.905$ respectively) although CTA and CTV were higher in pheochromocytomas than in adenomas without lipid (Table 3, Fig. 3). 14.7% (5/34) adenomas without lipid and 35.3% (6/17) pheochromocytomas were greater than 110 HU on the arterial phase (Fig. 2 and Fig. 4). 64.7% (22/34) adenomas without lipid and 52.9% (9/17) pheochromocytomas enhanced greater than 85 HU on venous phase. No adenomas without lipid showed enhancement level greater than 130 HU on venous phase, and 4 pheochromocytomas met the level.

Distribution of PPE of two groups was markedly different even though the mean values did not differ significantly (172% vs 180%, $p = 0.145$) (Table 3 and Fig. 5). The distribution of PPE of pheochromocytomas was discrete, from the lowest value of 55% to highest value of 526%, while that of

adenomas without lipid was centralized. The analysis of distribution features of PPE showed that a range of 100%-240% was the optimal cutoff to distinguish adenomas without lipid from pheochromocytomas, and AUC was 0.88. 30 of 34 (88.2%) adenomas without lipid and 9 of 17 (47.1%) pheochromocytomas were within the range of 100%-240% (Fig. 2 and Fig. 6). The PPE >240% was detected in 2 adenomas without lipid (5.9%) and in 5 pheochromocytomas (29.4%) (Fig. 4). The sensitivity and specificity of the range of 100%-240% of PPE for diagnosing adenomas without lipid was 88.2% , 47.1% respectively.

Discussion

The non-functional adenomas are the most common in adrenal incidentalomas, accounting for 70%-80%.^{22,23} It is usually homogeneous and relative smaller. The occurrence rate of incidental pheochromocytomas increased, ranging from 5% to 58% in studies.^{7,24,25} Homogeneous pheochromocytomas without necro-cystic changes and hemorrhage may be mistaken as lipid-poor adenomas, especially those without lipid on unenhanced CT. While classic clinical symptom and biochemical test is of great value to differentiate adenomas from pheochromocytomas, these are not fully reliable. Only 11% adenomas are functional.¹⁹ Likewise, negative results of biochemical test can not exclude pheochromocytomas, up to 40% patients with pheochromocytomas were asymptomatic in a study.¹¹ Hence, preoperative image examination plays a vital role in diagnosis.

Chemical shift MR is sensitive to detect intracellular lipid, image analysis of signal loss in in-phase and opposed-phase characterize lipid-rich adenomas.²⁶ However, for hyperattenuating adrenal masses greater than 10 HU, CT is superior to chemical shift MRI.²⁷ Thus, adrenal CT protocol has been recommended for assessment of adrenal lesions.⁶ It not only demonstrates imaging features of size, morphology, lipid content of the lesion, but also provides attenuation values on different phases and washout characteristic.

Our study showed that tumor size of two groups did not differ significantly. Several studies indicated that pheochromocytomas were usually larger than adenomas,^{11,21} in discordance with our study. Only pheochromocytomas without necro-cystic changes and hemorrhage were included in our study. Generally, incidence rate of heterogeneity increases when tumors get larger. The discrepancy of inclusion criteria contributes to different result.

There were few studies on enhancement pattern of adenomas and pheochromocytomas on dual-phase enhanced CT. In a study that evaluated the time density curve (TIC) of adenomas and non-adenomas at dynamic contrast-enhanced CT, 84% adenomas showed rapidly wash-in in early phase (≤ 1 minute) followed washout feature,²⁸ but the TIC of pheochromocytomas included in non-adenomas group was not present alone. Northcutt et al.¹⁹ found there was difference on enhancement pattern between the two entities. 85% adenomas demonstrated a higher enhancement level on venous phase. No adenomas enhanced greatly on arterial phase, while 25% pheochromocytomas did. In our study, enhancement

pattern was similar in two groups, persistent enhancement pattern was the most common (52.9% in both tumors). 26.5% adenomas enhanced higher on arterial phase, in discordance of study by Northcutt et al.¹⁹ It was dubious whether the enhancement pattern of lipid-rich adenomas, lipid-poor adenomas and adenomas without lipid differed.

Adenoma without lipid showed precontrast values of 36.5 HU (range, 25-48 HU), higher than that of lipid-poor adenoma in a retrospective study consisting of 145 cases (mean, 22.0 HU).²⁹ Still, precontrast CT values in pheochromocytomas were significantly higher than that of adenomas without lipid (41.4 HU vs 36.5 HU, $p=0.006$). A cutoff value of 40.7 HU yielded a sensitivity of 70.6% and specificity of 76.5% for pheochromocytomas, but there was not definitely reliable differentiating adenomas without lipid from pheochromocytomas.

Recently, some researches suggested that arterial and venous enhancement level was significantly higher in pheochromocytomas than in adenomas, and it can avoid misdiagnosis combined with washout features.¹⁹⁻²¹ In a study by Northcutt et al.,¹⁹ attenuation on arterial and venous phase in 22 pheochromocytomas was significantly higher than that in 41 adenomas (104 HU vs 37 HU, 119 HU vs 60 HU respectively). No adenomas exceeded 85 HU in the arterial phase, and 58% pheochromocytomas were higher than 110 HU in the arterial phase. Subsequently, Northcutt et al.²⁰ drew the similar conclusion by increasing the sample size with 26 pheochromocytomas and 200 adenomas, the mean venous enhancement values of pheochromocytomas and lipid-poor adenomas were 111 HU and 76 HU respectively. A threshold of 130 HU on venous phase was 38% sensitive and 100% specific for pheochromocytomas. Mohammed et al.²¹ found venous enhancement level greater than 85 HU showed good diagnostic performance for pheochromocytomas, with sensitivity of 88.2%, specificity of 83.7%. There were some differences on findings of ours and theirs. Significant differences were not found between the two groups, although the mean arterial and venous enhancement level of pheochromocytomas was higher than that of adenomas without lipid (100 HU vs 85 HU, $p=0.223$; 103 HU vs 96 HU, $p=0.905$). In our research, 14.7% (5/34) adenomas without lipid and only 35.3% (6/17) pheochromocytomas were greater than 110 HU on the arterial phase. 64.7% (22/34) adenomas without lipid and 52.9% (9/17) pheochromocytomas enhanced greater than 85 HU on venous phase. The main distinction between ours and theirs was inclusion criteria for adenomas and pheochromocytomas. On one hand, the size of homogeneous pheochromocytomas in our study was relatively smaller, however, a study by Kim et al.³⁰ revealed the enhancement level on 1 minute did not differ significantly between small and large pheochromocytomas (the size threshold: 3 cm). On the other hand, all lipid-poor adenomas in our study showed no lipid on precontrast CT, which was different from almost all of studies. The unenhanced CT values of adenomas without lipid were higher than that of lipid-rich and lipid-poor adenomas, which may indicated the decreased ratio of lipid-rich cell.³¹ Researches revealed the attenuation on arterial and venous phase of lipid-poor adenomas was significantly higher compared to lipid-rich adenomas.^{19,20} We noted the enhancement level of adenomas without lipid in our study was greater than that of lipid-poor adenomas in Northcutt's study (arterial phase, 85 HU vs 57 HU; venous phase, 96 HU vs 86 HU).¹⁹ As no study investigated the correlation between enhancement level on arterial

and venous phase and precontrast values of adenomas, inclusion criteria for adenomas without lipid in our study may contribute to the discrepancy of studies. Nevertheless, no adenoma without lipid showed enhancement level greater than 130 HU on venous phase in our study, in line with study by Northcutt et al.,²⁰ but only 4 pheochromocytomas met the level (4/17, 23.5%).

The PPE could reflect the blood supply characteristic of tumors in some degree. Our study demonstrated that distribution of the PPE of adenomas without lipid and pheochromocytomas was discriminative. The distribution of PPE of adenomas without lipid was agminated while that of pheochromocytomas was discrete. This feature may be related to variable imaging appearance of pheochromocytomas, from hypovascular to highly vascular lesion.^{10,12} A range of 100%-240% of PPE yielded sensitivity of 88.2%, specificity of 47.1% for diagnosing adenomas without lipid. Compared to APW and RPW obtained from a relatively long delayed phase, the chief advantage of PPE is that it can be obtained conveniently from biphasic enhanced CT in clinical practice. Additional delayed scan may be avoided for patient if indeterminate adrenal incidentaloma was found with homogeneous density. However, further studies are needed to explore the potential value of PPE due to its low specificity.

There were several limitations of our study. First, the sample size of both tumors was small owing to the strict inclusion criteria. The occurrence rate of pheochromocytomas was low, much less of homogeneous lesions without necro-cystic changes and hemorrhage. Similarly, lipid-poor adenomas without lipid on unenhanced CT were not common. Second, we did not perform delayed scan and washout characteristic was not calculated in the study. Further study are needed to investigate its value in the differentiation of homogeneous pheochromocytomas and adenomas without lipid. Third, the retrospective nature of our study result in some inherent limitations, particularly, contrast volume and infusion rate, which may affect enhancement level.

Conclusion

The enhancement pattern and enhancement level on biphasic enhanced CT could not distinguish homogeneous pheochromocytomas from adenomas without lipid. A range of 100%-240% of PPE can discriminate adenomas without lipid from pheochromocytomas, with sensitivity of 88.2%, specificity of 47.1%. Further studies are needed to prove the potential value of PPE due to its low specificity.

Declarations

Ethical approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and

with the 1964 Helsinki Declaration and its later amendments or comparable ethical Standards.

Consent for publication: All authors have read and approved the final version of the manuscript.

Availability of data and materials: This data and materials came from Tongde Hospital of Zhejiang Province, Sir Run Run Shaw Hospital of Zhejiang University School of Medicine and the Second Affiliated Hospital of Zhejiang University School of Medicine.

Competing Interest: The authors declare no conflict of interest.

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Author contributions : Guarantor of integrity of the entire study: J. Wang; Study concepts and design: Y.Y An, J. Wang; Literature research: F.J. Tian, M.H. Shao, B. Lin; Clinical studies: Y.Y An, F.J. Tian, M.H. Shao, B. Lin, J. Wang; Data analysis: Y.Y An, F.J. Tian, B. Lin, J. Wang; Statistical analysis: H.L. Ji, L.Y. He, Q.X. Hu; Manuscript editing: Y.Y An

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Tables

Table 1 Comparison of clinical data between homogeneous pheochromocytomas and adenomas without lipid

Clinical data	Adenomas without lipid	Pheochromocytomas	P
No. of the subjects	34	17	–
Age	50.6 ±11	52.1±12.7	0.672
Sex (male/female)	15/19	9/8	0.552
Hypertention	14 (41.2%)	9 (52.9%)	0.318

Note: Dash (–) indicated that statistical analysis was not performed.

Table 2 Comparison of CT imaging features between homogeneous pheochromocytomas and adenomas without lipid

Imaging features	Adenomas without lipid	Pheochromocytomas	P
Location (left/right)	14/20	7/10	1.0
Tumor size (mm)	23.8 ± 11.4	24.3 ± 11.9	0.885
Shape			1.0
regular	33 (97.1%)	16 (94.1%)	
irregular	1 (2.9%)	1 (5.9%)	
Enhancement pattern			0.476
persistent	15 (44.2%)	8 (47.1%)	
plateau	13 (38.2%)	4 (23.5%)	
washout	6 (17.6%)	5 (29.4%)	

Note: numbers in parentheses are percentages.

Table 3 Comparison of attenuation values and PPE between homogeneous pheochromocytomas and adenomas without lipid

CT parameters	Adenomas without lipid	Pheochromocytomas	P
CT _{pre} (HU)	37 ± 6 (25-48)	41 ± 6 (29-50)	0.006
CT _a (HU)	85 ± 24 (43-147)	100 ± 36 (61-174)	0.223
CT _v (HU)	96 ± 17.8 (62-133)	103 ± 34.3 (72-180)	0.905
PPE (%)	172 ± 48 (82-271)	180 ± 130 (55-526)	0.145

Note: numbers in parentheses are ranges.

Figures

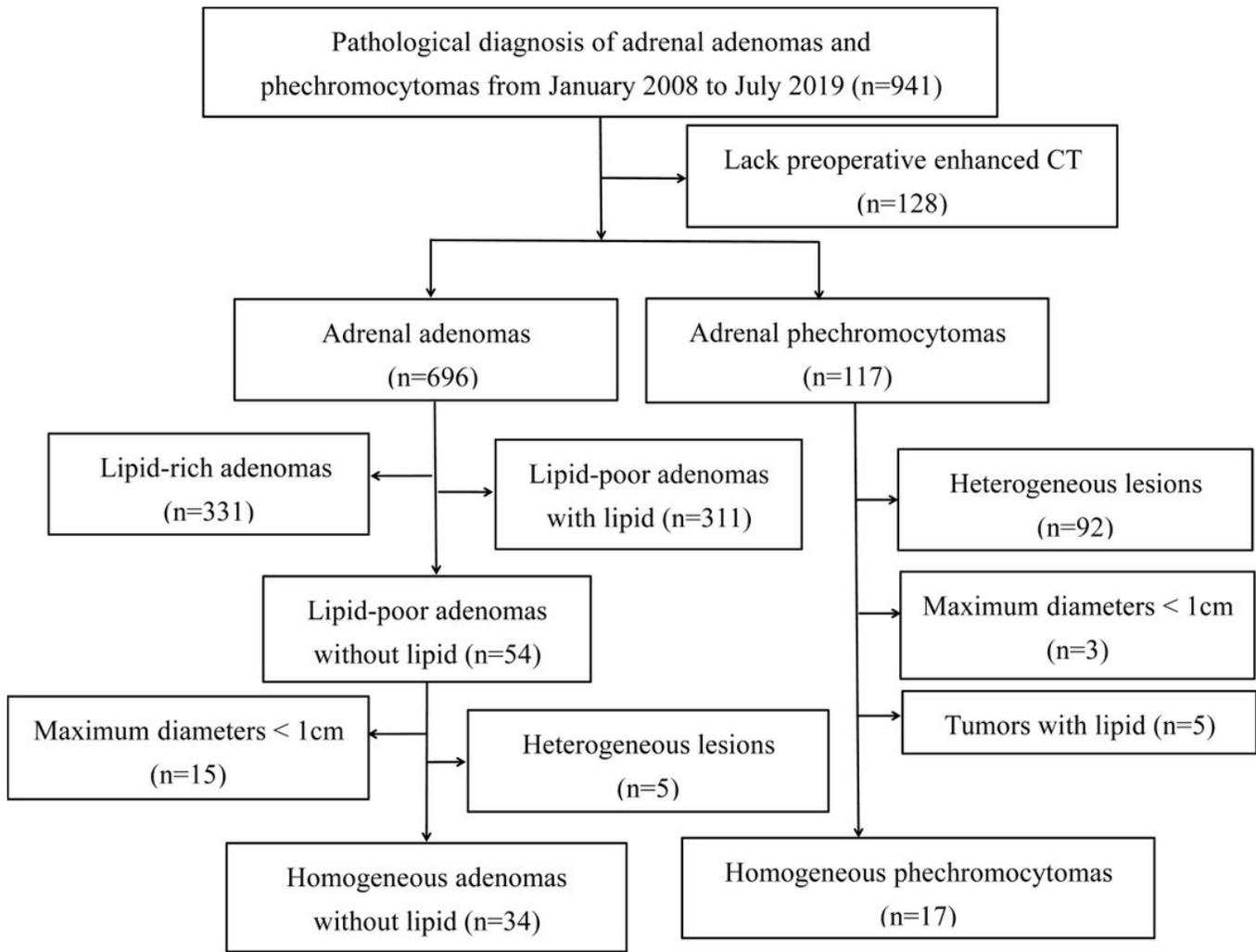


Figure 1

Flowchart of study cohort.

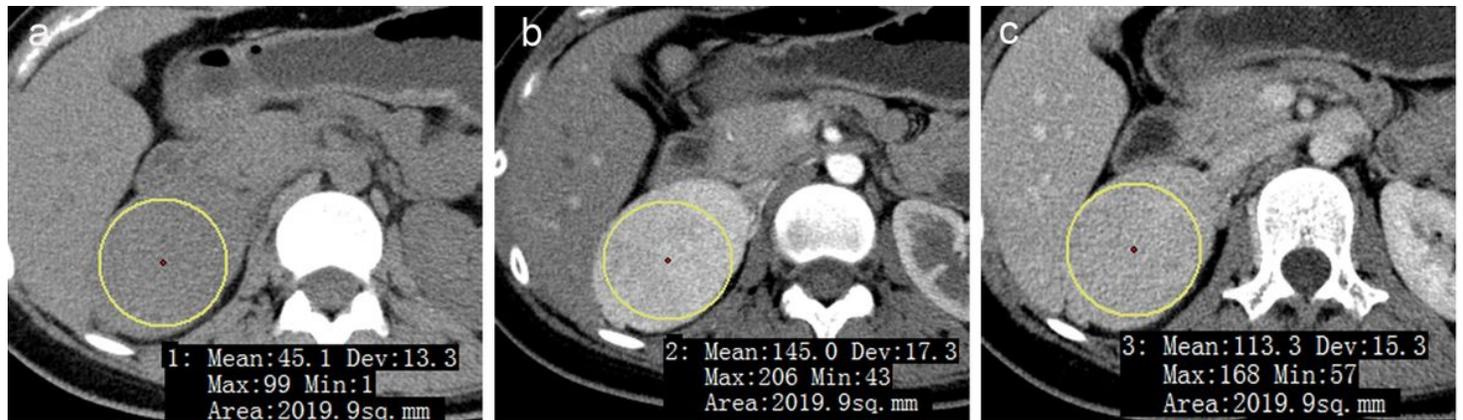


Figure 2

A 20-year-old woman with homogeneous adrenal lesion measuring 72 mm. A round ROI was drawn to cover entire lesion on the level of largest diameter as much as possible. The lesion showed absence of lipid on unenhanced CT with minimum values greater than 0 HU. Attenuation values were 45 HU, 145 HU and 113 HU on unenhanced, arterial and venous phase respectively. The lesion showed washout on venous phase. PPE was 222%. Pathology showed adenoma.

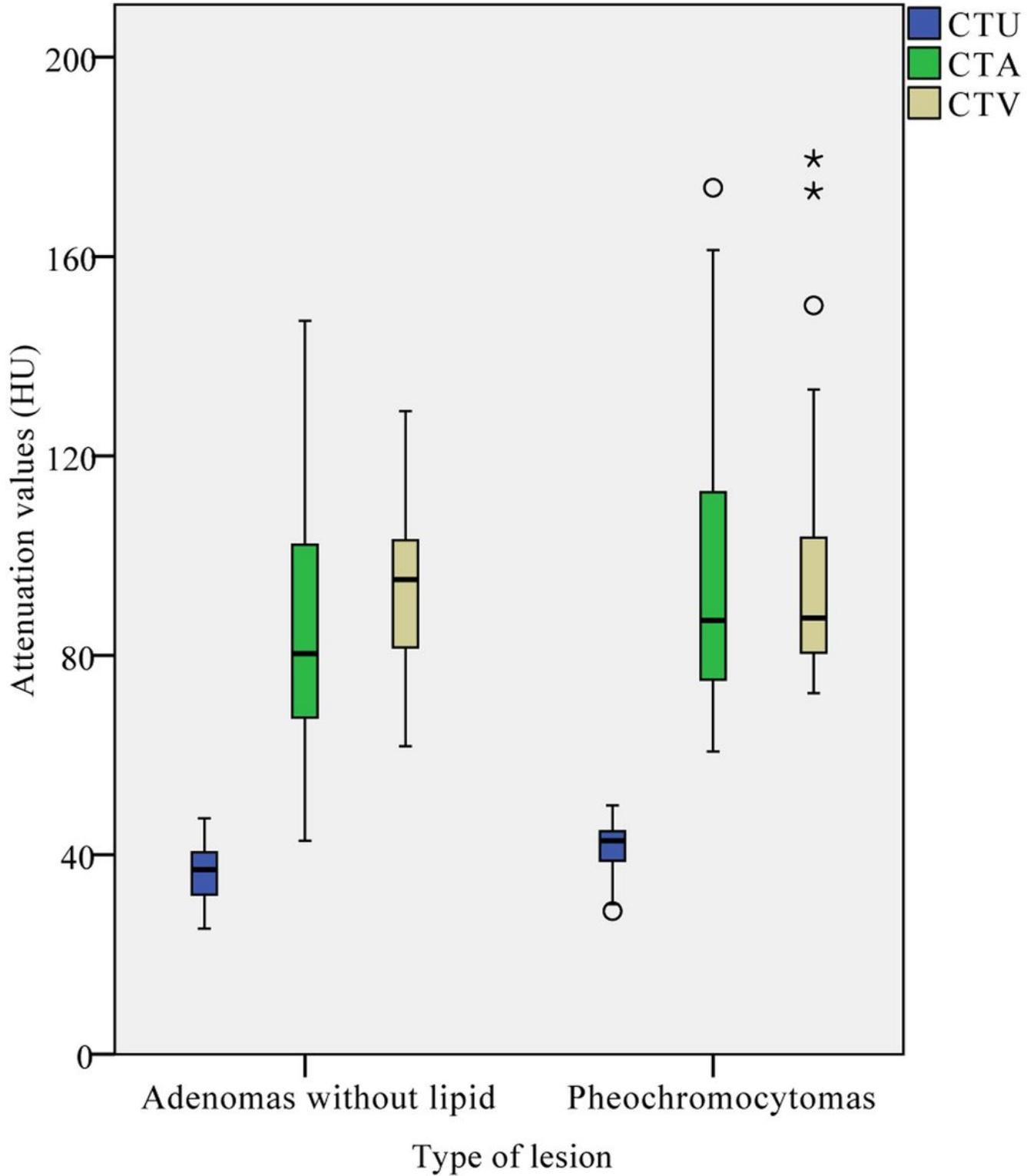


Figure 3

Boxplot of CTA and CTV of homogeneous pheochromocytomas and adenomas without lipid. No statistical differences were found although CTA and CTV were higher in pheochromocytomas than in adenomas without lipid.



Figure 4

A 70-year-old woman with homogeneous adrenal lesion measuring 17 mm. Attenuation values were 43 HU, 161 HU and 133 HU on unenhanced, arterial and venous phase respectively. The lesion showed washout on venous phase. PPE was 274%. Pathology showed pheochromocytoma.

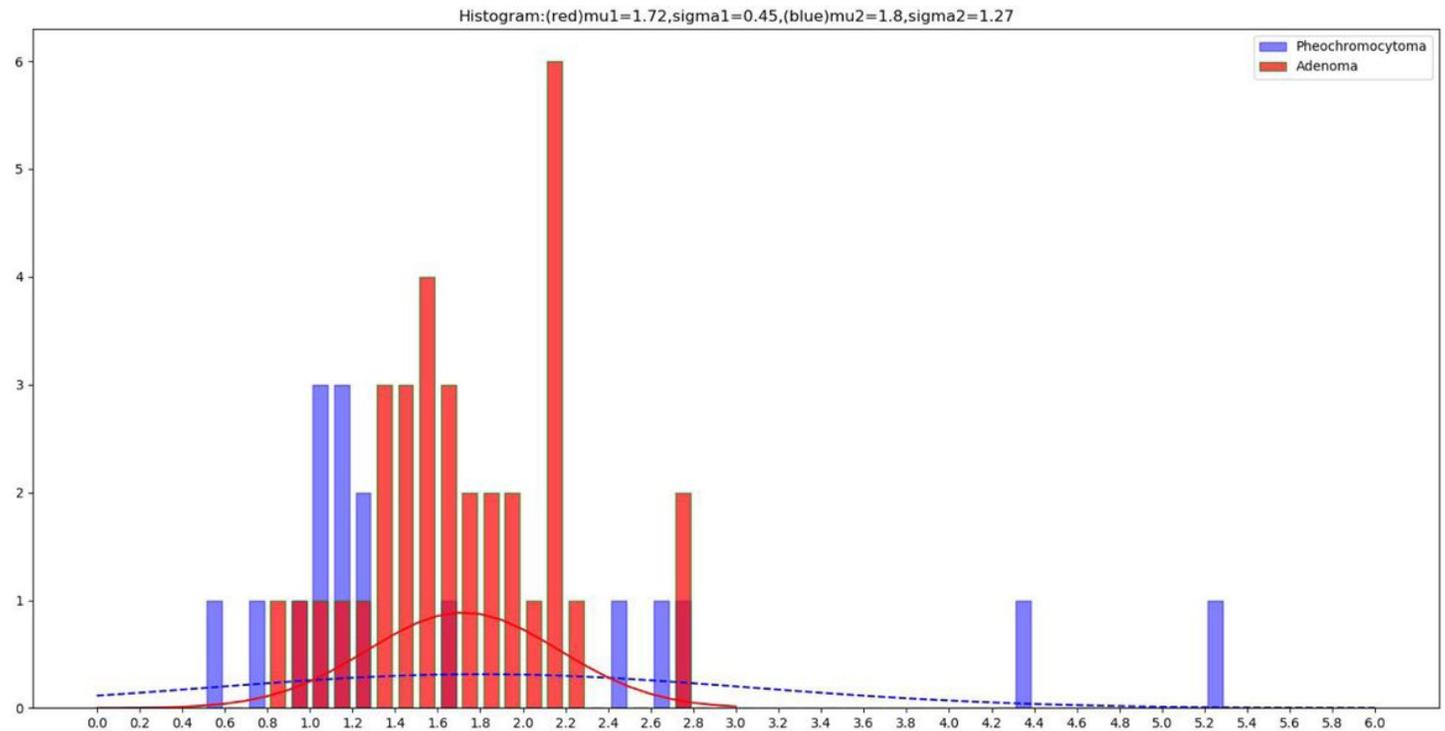


Figure 5

Histogram of PPE of homogeneous pheochromocytomas and adenomas without lipid. The distribution of PPE of pheochromocytomas was discrete, while that of adenomas without lipid was centralized. A

range of 100%-240% of PPE was the optimal cutoff to distinguish the two entities, with sensitivity of 88.2%, specificity of 47.1%. AUC for diagnosis of adenomas without lipid was 0.88.

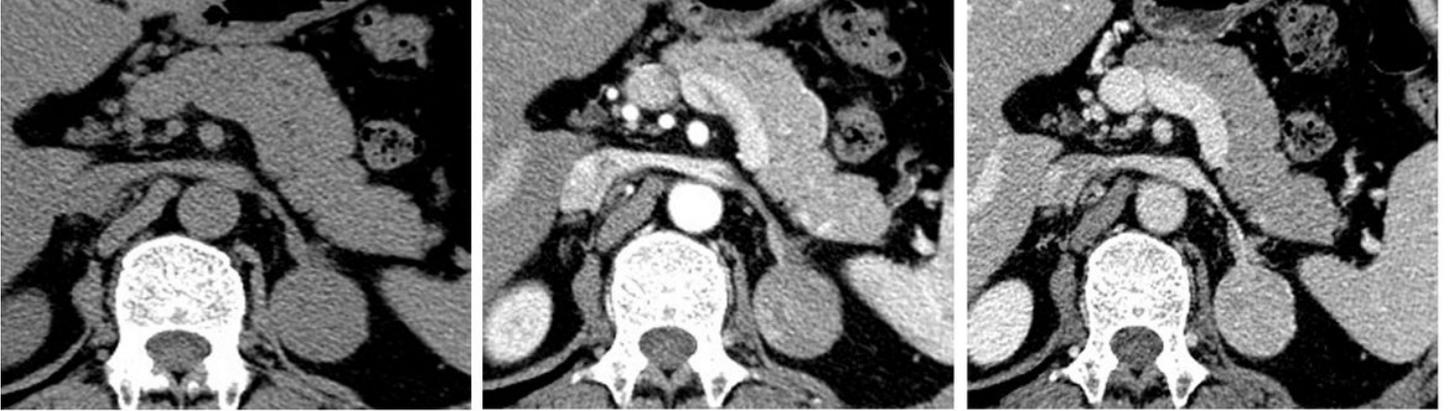


Figure 6

A 49-year-old man with homogeneous adrenal lesion measuring 35 mm. Attenuation values were 38 HU, 69 HU and 100 HU on unenhanced, arterial and venous phase respectively. The persistent enhancement pattern on venous phase was most common in both tumors. PPE was 163%. Pathology showed adenoma.