Int Surg 2017;**102**:318–323
DOI: 10.9738/INTSURG-D-16-00152.1

The Value of Dual-Phase Enhancement CT as a Predictor of the Preoperative Preparation of Adrenal Pheochromocytoma

Shaoping Cheng[1], Xinghuan Wang[1], Jinbai Huang[2], Jing Luo[2]

[1]*Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, China*

[2]*Department of Radiology, the First Affiliated Hospital of Yangtze University, Jingzhou, China*

The purpose of this study was to evaluate the function of adrenal pheochromocytoma with the value of dual-phase enhancement computed tomography (CT) and to guide the preoperative preparation of adrenal pheochromocytoma. From June 2009 to December 2015, the patients with a diagnosis of pheochromocytoma were divided into 2 groups according to the length of preparation time (group 1, $\leq$2 weeks; group 2, $>$2 weeks). Two experienced radiologists measured adrenal lesion attenuation from dual-phase, contrast-enhanced CT examinations. Student *t*-test analysis was performed to compare arterial and venous phase enhancement levels and the maximum increased enhancement CT value. There were 31 cases of pheochromocytoma that were accepted into the study: 13 cases in group 1 and 18 cases in group 2. At contrast-enhanced CT, the mean arterial enhancement and venous enhancement of pheochromocytoma were 74 $\pm$ 20 Hounsfield units (HU; range, 50–107 HU) and 72 $\pm$ 18 HU (range, 44–109 HU), respectively, in group 1, which were significantly less than those in group 2, with a mean of 101 $\pm$ 26 HU (range, 64–138 HU) and 100 $\pm$ 22 HU (range, 61–131 HU; $P < 0.05$). The average maximum increased attenuation at enhancement CT in group 1 was 41 $\pm$ 12 HU (range, 24–62 HU), significantly less than that in group 2, with a mean of 62 $\pm$ 22 HU (range, 26-102 HU; $P < 0.05$). The preparation time was related to the absolute enhancement level, especially with the maximum increased attenuation of pheochromocytoma at enhanced CT. More preparation time before surgery was needed if the maximum enhancement level during arterial phase and venous phase was greater than 109 HU and the maximum increased attenuation was greater than 62 HU.

Corresponding author: Xinghuan Wang, MD, Department of Urology, Zhongnan Hospital of Wuhan University, Donghu Road 169, Wuhan, 430071 Hubei, China.
Tel.: +86 18971387168; E-mail: wangxinghuan@whu.edu.cn

Key words: Contrast-enhanced CT – Adrenal – Pheochromocytoma – Preoperative preparation

Pheochromocytoma is a rare tumor arising from the chromaffin cell in adrenal medulla or extra-adrenal paraganglia. Extensive research has been focused on strategies to confirm the diagnosis.[1,2] Computed tomography (CT) is suggested as the first-choice imaging adrenal modality.[3] Several studies have addressed the value of nonenhanced CT and contrast-enhanced CT to distinguish adrenal pheochromocytomas from other adrenal diseases.[4–6] A recent study showed that a dual-phase enhancement pattern of CT can be used to differentiate adenoma from pheochromocytoma by comparing the mean arterial and venous enhancement values.[7] To our knowledge, adrenal pheochromocytomas are rarely biochemically silent. Our research is focused on whether the dual-phase enhancement CT value of pheochromocytoma is related to its function, and furthermore, whether it can be used as a possible predictor for preoperative preparation.

Patients and Methods

Study population

We retrospectively reviewed the data of the patients with adrenal pheochromocytoma from our institution's pathology database from June 2009 to December 2015. All of the patients included had accepted arterial and venous phase intravenous contrast-enhanced CT images of the adrenal gland and were symptomatic with hypertension, and they also had stable intraoperative and postoperative hemodynamics. The patients were excluded if they had other causes of secondary hypertension, like renovascular disease, obstructive sleep apnea syndrome, and so on. Eventually, there were 31 patients included in the study. One patient with bilateral pheochromocytomas was also excluded for the complexity of preparation and the instability of intraoperative hemodynamics. Patient blood pressure was 140 to 200 mmHg systolic and 90–120 mmHg diastolic (1 mmHg = 0.133 kPa). All patients received preoperative α-blockade prazosin, which is the main α-blockade used in our hospital, to prevent preoperative cardiovascular complications. Prazosin was used in doses of 1 mg three times daily initially, and the dose was increased to the maximal dose of total 12 mg daily to control the hypertension. Calcium channel blockers were added in cases where the blood pressure was out of control. To control tachycardia, β-blockade was indicated. The target blood pressure was 100 to 130 mmHg systolic 70 to 80 mmHg diastolic, and the target heart rate was 60 to 80 bpm. The length of preoperative preparation was defined as the time from beginning the use of the drugs to time of achieving the target blood pressure and heart rate. The treatment of a high-sodium diet and fluid intake was advised for reexpansion of plasma volume. On the preoperative day the patients were given administration of saline (2 L).

Imaging studies

The adrenal CT imaging examinations were conducted in our institution with 64-MDCT scanners (GE Medical Systems, Waukesha, Wisconsin) and the slice thickness was 2.5 mm. First, a nonenhanced scan of the adrenal glands was done, followed by the dual-phase CT protocol, including arterial phase (usually with bolus tracking of the abdominal aorta parallel with the adrenal gland or with a fixed delay of 25 seconds) and venous phase (60 seconds) acquisition after infusion of 60 to 90 mL of 350 mg iohexol per milliliter, low-osmolar contrast material (iohexol, GE Healthcare, Shanghai, China), infused at 2 to 4 mL per second. For the 64-MDCT scanner, the arterial trigger is 100 HU. CT imaging dates were evaluated by 2 radiologists who are especially experienced with adrenal diseases (J.H., with 25 years of experience, and J.L., with 10 years of experience). The 2 radiologists were blinded to the final pathologic results and worked independently. All images were evaluated as axial images at a GE AW4.6 workstation. The density of the mass was expressed as Hounsfield unit (HU) values. A circular region-of-interest cursor was placed over the center of the mass, avoiding edges, calcifications, and cystic or necrotic lesions. One to three region-of-interest measurements were obtained, and the mean value of the measurements was calculated. Nonenhanced and contrast-enhanced CT (including arterial and venous phase) images were measured at the same regions-of-interest. One of the patients' CT images are shown in Figs. 1, 2, and 3. The maximum diameter of the mass was measured. All of the measurements of the 2 radiologists obtained were averaged to give the final results.

Fig. 1 Transverse CT scan obtained in a 42-year-old man with adrenal pheochromocytoma. Nonenhanced CT image shows a 6-cm right adrenal mass that measures 44 HU. Enhanced CT images, including the arterial phase and venous phase, obtained at the same level of the mass. The mass measures 92 HU in arterial phase and 91 HU in venous phase. The maximum increased attenuation is 48 HU.

Fig. 2 Transverse CT scan obtained in a 42-year-old man with adrenal pheochromocytoma. Nonenhanced CT image shows a 6-cm right adrenal mass that measures 44 HU. Enhanced CT images, including the arterial phase and venous phase, obtained at the same level of the mass. The mass measures 92 HU in arterial phase and 91 HU in venous phase. The maximum increased attenuation is 48 HU.

Fig. 3 Transverse CT scan obtained in a 42-year-old man with adrenal pheochromocytoma. Nonenhanced CT image shows a 6-cm right adrenal mass that measures 44 HU. Enhanced CT images, including the arterial phase and venous phase, obtained at the same level of the mass. The mass measures 92 HU in arterial phase and 91 HU in venous phase. The maximum elevated attenuation is 48 HU.

Statistical analyses

All results are given as means ± standard deviation ($\bar{x}$ ± SD). A Student *t*-test of independent samples assuming unequal variances was performed between the groups. This analysis was performed for patient age, local size, blood pressure, and the attenuation of pheochromocytomas at nonenhanced CT and enhanced CT (including arterial and venous phase). In addition, the mean maximum elevated attenuation (using the maximum value during dual-phase CT to subtract the value at nonenhanced CT) also was compared in the 2 groups. Correlation analysis was based on a Pearson correlation test. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

This study was approved by the academic committee and ethics committee of Wuhan University, and all patients signed informed consent forms. The demographic data of the 31 cases are shown in Table 1. Most of the patients were female (22 female and 9 male), and the ages ranged from 37 to 73 years. Of the 31 adrenal masses, 17 were located in the left

Table 1 Clinical data of study patients with adrenal pheochromocytoma

	Group 1 (≤2 wk)	Group 2 (>2 wk)
No. of patients	13	18
Age, y	51 ± 6	56 ± 10
Sex, male/female	4/9	5/13
Side, left/right	7/6	10/8
Blood pressure		
Systolic pressure, mmHg	154.6 ± 15.5	165.4 ± 20.9
Diastolic pressure, mmHg	97.7 ± 10.1	97.7 ± 13.7
24-h VMA elevated, n (%)	5 (38.5)	12 (66.7)
Operation, laparoscopic/open	11/2	13/5

adrenal gland and 14 in the right adrenal gland. A total of 24 patients underwent laparoscopic surgery, and 7 patients underwent open surgery, including 1 patient transferred for open surgery because of intraoperative bleeding. The patients were divided into 2 groups according to the length of preparation time (≤2 weeks for group 1 and >2 weeks for group 2). There were 13 patients in group 1 and 18 patients in group 2. There were no significant differences in the mean age and blood pressure between the 2 groups. The 24-hour urinary vanilmandelic acid (VMA) of 17 patients was increased (106.54–206.34 μmol/d).

Imaging results

The maximum diameter of the adrenal masses was 1 to 20 cm. The mean diameters were 4.0 ± 2.7 cm in group 1 and 5.0 ± 4.2 cm in group 2, with $P > 0.05$; there was 1 mass with calcification, 4 masses with necrosis, and 12 masses with heterogeneity. At nonenhanced CT, the mean attenuation was 36 ± 9 HU (range, 27–41 HU) in group 1, which was less than that in group 2, which had a mean attenuation of 41 ± 7 HU (range, 24–50 HU), showing no significant differences ($P > 0.05$). At contrast-enhanced CT, the mean arterial enhancement of pheochromocytomas was 74 ± 20 HU (range, 50–107 HU) in group 1, which was significantly less than that in group 2, which had a mean of 101 ± 26 HU (range, 64–138 HU). The mean venous enhancement of pheochromocytomas was 72 ± 18 HU (range, 44–109 HU) in group 1, which was significantly less than that of group 2, which had a mean of 100 ± 22 HU (range, 61–131 HU). The mean maximum elevated attenuation in group 1 was 41 ± 12 HU (range, 24–62 HU), significantly less than that in group 2, which had a mean of 62 ± 22 HU (range, 26–102 HU). The details are summarized in Table 2

Table 2 Imaging data of study patients with adrenal pheochromocytoma

	Group 1 (≤2 wk)	Group 2 (>2 wk)
Diameter, cm, mean	4.0 ± 2.7	5.0 ± 4.2
Value at nonenhanced CT, HU	36 ± 9	41 ± 7
Value of arterial phase at enhanced CT, HU	74 ± 20	101 ± 22
Value of venous phase at enhanced CT, HU	72 ± 18	100 ± 22
Maximum elevated value, HU	41 ± 12	62 ± 22

Discussion

Most pheochromocytoma is hormonally functional, and the cardiovascular morbidity and mortality are high if untreated.[8,9] These patients with hyperfunctional pheochromocytoma are associated with hypertension, low blood volume, and catecholamine cardiomyopathy, because of high blood concentrations of catecholamine. Therefore, the patients have to receive treatments to control hypertension and improve blood vessel capacity before surgery, and α-blockade is the first choice of these.[9–11] There have been retrospective studies comparing the effectiveness of nonselective α-blockade and α_1-selective blockade, but the results of the studies were inconsistent.[10,12] At our institution, we prefer using prazosin because of its effectiveness and few adverse effects. Lenders *et al*[3] recommend preoperative medical treatment for 7 to 14 days. But a retrospective study reported that at the Mayo Clinic, patients were treated with α-blockade for 1 to 4 weeks to ensure full alpha blockade.[10] The preparation time in our study ranged from 7 to 34 days and more preparation time, more preoperative α-blockade, which is likely to contribute to improving outcomes.[13] Therefore, we divided the patients into 2 groups according to preparation time (≤2 weeks for group 1 and >2 weeks for group 2), with the purpose of analyzing the difference.

Our study cohort included 9 male and 22 female patients, and the female predominance differed from the study previously reported.[5] Of all 31 adrenal masses, 17 were located in the left adrenal gland, and this finding was consistent with the study previously reported.[5] In addition, there were more patients in group 2 with increased 24-hour urinary VMA, and we may conclude that the longer the preparation time, the higher the function of the mass.

Currently, the qualitative and localization diagnosis of adrenal pheochromocytoma is relatively mature, and CT plays an important role. There may be cystic, necrotic, or hemorrhagic area and calcification in pheochromocytoma at CT and at enhanced CT, and pheochromocytoma may increase obviously with heterogeneous enhancement.[5,7] In the literature, the attenuation of pheochromocytoma at nonenhanced CT is more than 10 HU.[4–6,14] In this study, some of the pheochromocytoma showed the signs of necrosis, calcification, and heterogeneity at CT, and all the pheochromocytomas showed these signs with attenuation at more than 10 HU (range, 24–50 HU).

At delayed enhanced CT, the percentage change in contrast material washout has been evaluated in studies regarding distinguishing pheochromocytomas from adrenal adenomas.[4,6,14] Northcutt *et al*[7] used the dual-phase enhancement patterns of enhanced CT to differentiate adrenal adenoma from pheochromocytoma. But these studies mainly used the attenuation of the mass at differently timed CT scan to calculate washout or compare the enhanced pattern for diagnosis. There was no report about the use of the attenuation to evaluate the function of adrenal carcinoma and to guide clinical work, including the nonenhanced CT and enhanced CT.

Can the attenuation of lesions at CT be used to guide treatment? In a prospective study, the value of noncontrast CT was assessed regarding its use as a possible predictor of renal stone disintegration by shock wave lithotripsy, and the result showed that if the value of the stone is larger than 1000 HU, an alternative treatment should be devised, especially for obese patients.[15] The previous study showed different pheochromocytomas with different values for nonenhanced CT or enhanced CT at different phases.[4–7,14] Therefore, we designed the study to assess whether attenuation can be a possible predictor to guide the clinical job.

In this study, we found the mean value of the mass at nonenhanced CT between the 2 groups was not significantly different. A previous study compared the mean values of masses at nonenhanced CT between 2 groups with differing levels of plasma or urinary metanephrine or normetanephrine, and there was no significant difference.[16] Maybe we can conclude that the mean attenuation at nonenhanced CT is not strongly associated with the function of pheochromocytoma.

Regarding absolute enhancement level, a mass greater than 110 HU in the arterial phase is most likely a pheochromocytoma.[7] In this study, the greatest values for arterial phase and venous phase in group 1 were 107 HU and 109 HU, respectively. The greater enhancement of pheochromocytomas was variable, sometimes in the arterial phase, sometimes in the venous phase, and sometimes equal across phases.[7] If the maximum value of dual-phase CT was greater than 109 HU, we suggested more preparation time be given before surgery. However nearly 50% of patients in group 2 had a dual-phase maximum value of less than 109 HU.

Because different tumors would have different CT values at nonenhanced scan, the absolute value of enhancement CT (the maximum enhancement CT value directly measured) could not exactly describe the effect of enhancement. We chose the maximum increased attenuation (using the maximum value during dual-phase CT to subtract the value at nonenhanced CT) to describe it. To the best of our knowledge, there are no reports discussing maximum increased attenuation. But the pheochromocytomas typically enhanced avidly, and this reflects the capillary-rich framework of the tumor,[17] which may be means for the tumor's hyperfunction. From our data, the maximum increased attenuation ranged from 24 to 62 HU in group 1, and there were 9 patients with maximum increased attenuation greater than 62 HU in group 2. We conclude that the preparation time should exceed 2 weeks if the mass has a maximum increased attenuation of greater than 62 HU. However, like the absolute enhancement level, there was overlapping of maximum increased attenuation in groups 1 and 2.

This study may have had several limitations. First, it was a retrospective study. Second, we set up several inclusion criteria that may lead to verification bias. We only included patients with pathologic proven pheochromocytoma, excluding bilateral pheochromocytoma and ectopic pheochromocytoma. All patients in our study had intraoperative and postoperative hemodynamic stability, which was evidence of adequate preparation before surgery, and some factors, including different surgeons and anesthesias, may generate different results. Although, based on experience, most patients in our institution mainly receive prazosin to control hypertension, other medicines might have different effects. Third, as we know, the biochemical test includes plasma and urinary metanephrine and methoxynorepinephrine, 24-hour urinary VMA, and 24-hour urinary catecholamine, but only 24-hour urinary VMA can be detected in our institution.

Conclusion

This is the first study using the value of enhanced CT to evaluate the function of pheochromocytoma.

From our data, the preoperation time was related to the value of absolute enhancement level, especially with the enhanced degree of pheochromocytoma at enhanced CT. If the maximum enhanced value is greater than 109 HU and the maximum increased value is greater than 62 HU, which means the pheochromocytoma is highly functional, we need more preparation time before surgery.

Acknowledgments

This study was supported by the Wuhan Clinical Cancer Research Center of Urology and Male Reproduction, grant number 303-230100055.

References

1. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Pheochromocytoma. *Lancet* 2005;**366**(9486):665–675
2. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002;**287**(11):1427–1434
3. Lenders JW, Duh QY, Eisnehofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;**99**(6):1915–1942
4. Caoili EM, Korobkin M, Francis IR, Cohan RH, Platt JF, Dunnick NR. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. *Radiology* 2002;**222**(3): 629–633
5. Motta-Ramirez GA, Remer EM, Herst BR, Gill IS, Hamrahian AH. Comparison of CT findings in symptomatic and incidentally discovered pheochromocytomas. *Am J Roentgenol* 2005;**185**(3):684–668
6. Szolar DH, Korobkin M, Reittner P, Berghold A, Bauernhofer T, Trummer H *et al*. Adrenocortical carcinomas and adrenal pheochromocytomas: mass and enhancement loss evaluation at delayed contrast-enhanced CT. *Radiology* 2005;**234**(2):479–485
7. Northcutt BG, Raman SP, Long C, Oshmyansky AR, Siegelman SS, Fishman EK. MDCT of adrenal masses: can dual-phase enhancement patterns be used to differentiate adenoma and pheochromocytoma? *Am J Roentgenol* 2013;**201**(4):834–839
8. Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of pheochromocytoma. *J Hypertens* 2011;**29**(11):2049–2060
9. Plouin PF, Duclos JM, Soppelsa F, Boublil G, Chatellier G. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. *J Clin Endocrinol Metab* 2001;**86**(4):1480–1486
10. Weingarten TN, Cata JP, O'Hara JF, Prybilla DJ, Pike TL, Thompson GB. Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. *Urology* 2010;**76**(2):508.e6–e11
11. Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab* 2007;**92**(11):4069–4079
12. Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg* 2002;**26**(8):1037–1042
13. Livingstone M, Duttchen K, Thompson J, Sunderani Z, Hawboldt G, Sarah Rose M. Hemodynamic stability during pheochromocytoma resection: lessons learned over the last two decades. *Ann Surg Oncol* 2015;**22**(13):4175–4180
14. Park BK, Kim CK, Kwon GY, Kim JH. Re-evaluation of pheochromocytomas on delayed contrast-enhanced CT: washout enhancement and other imaging features. *Eur Radiol* 2007; **17**(11):2804–2809
15. El-Nahas AR, El-Assmy AM, Mansour O, Sheir KZ. A prospective multivariate analysis of factors predicting stone disintegration by extracorporeal shock wave lithotripsy: the value of high-resolution noncontrast computed tomography. *Eur Urol* 2007;**51**(6):1688–1693
16. Kannan S, Purysko A, Faiman C, Remer EM, Shah L, Bena J. Biochemical and radiological relationships in patients with pheochromocytoma: lessons from a case control study. *Clin Endocrinol (Oxf)* 2014;**80**(6):790–796
17. Blake MA, Kalra MK, Maher MM, Sahani DV, Sweeney AT, Mueller PR *et al*. Pheochromocytoma: an imaging chameleon. *Radiographics* 2004;**24**(suppl 1):s87–s99