Original Article

Diagnostic value of pre-operative imaging for pheochromocytoma

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Abstract

Objective: This study aims to investigate the predictive value of preoperative imaging findings for pathological outcomes by comparing preoperative imaging findings with pathological results.

Material and Method: From 2006-2018, 58 adrenal PCC patients underwent adrenalectomy at King Chulalongkorn Memorial Hospital (KCMH). Patients were divided into PCC and non-PCC groups by pathological results. Preoperative imaging (CT and/or MRI) was retrospectively reviewed by a uro-radiologist who classified patients into imaging suggested PPC (group 1) and imaging non-suggested PCC (group 2). Imaging criteria for suggested PCC in this study were defined as 1. hypervascularity on CECT scan: detected focus of high attenuation more than 140 HU on portovenous phase; 2. high SI on T2W as compared to adjacent renal cortex SI and 3. hypervascularity mass with uptake MIBG scan. Diagnostic value of preoperative imaging for PCC diagnosis was reported in sensitivity, specificity, PPV, NPV, and ROC area.

Result: Forty-six patients (79%) were PCC and 12 patients (21%) were non-PCC. According to imaging findings, 38 patients (66%) were group 1 and 20 patients (34%) were group 2. In group 2, 8 patients were PCC and 12 patients were non-PCC. Sensitivity of preoperative imaging to the diagnosis of PCC was 82.6% (95% CI, 0.68-0.92), specificity was 100% (95% CI, 0.73-1.0), PPV was 100% (95% CI, 0.9-1.0), NPV was 60% (95% CI, 0.36-0.8) and ROC area was 0.91% (95% CI, 0.86-0.9).

Conclusion: Preoperative imaging with a new threshold of HU offers excellent specificity and PPV to detect PCC.

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Introduction

Pheochromocytoma (PCC) is a rare catecholamine-secreting tumor derived from chromaffin cells in the adrenal medulla. Prevalence of PCC in hypertensive patients is 0.1-0.6%[1,2]. Autopsy series found an undiagnosed tumor rate of 0.05-0.1%[3-5]. Untreated PCC has high morbidity and mortality from cardiovascular events as the result of catecholamine hypersecretion.

Biochemical tests and imaging studies are the standard diagnostic tools for PCC. Biochemical test for the diagnosis of PCC is the measurement of serum and urine catecholamine and their products. After a positive biochemical test, tumor localization is performed by imaging study, mainly computed tomography (CT) scan or magnetic resonance imaging (MRI) study[6-8].

From CT scan, PCC typically has rapid enhancement after contrast injection and has variable washout pattern. However, in routine clinical practice, most PCC has a non-adenoma criteria, which is Hounsfield units (HU) >10 in unenhanced CT scan, absolute percentage washout [APW] <60% and relative percentage washout [RPW] <40%)[8-11]. From a systematic review and meta-analysis, only 35% of PCC met the criteria for adrenal adenoma[12]. A threshold criterion such as HU >110 or >130 in the venous phase has been reported for a more specific diagnosis of PCC in recent studies[12-16].

From MRI scan, PCC usually has hyposignal intensity in T1-weighted images and hypersignal intensity in T2-weighted images. However, 35% of PCC had atypical or nonspecific signals in T2-weighted images. Classical homogeneous high signal intensity, which is isointense to cerebrospinal fluid (CSF), was found in only 11%[18].

Treatment of PCC is mainly the surgical removal of the tumor, which is a minimally invasive adrenalectomy at present. Preoperative patient preparation and postoperative care are also important steps in PCC treatment[6,7].

In our practice, we have occasionally found that the pathological report was not PCC after adrenalectomy. The purpose of this study is to investigate the predictive value of preoperative imaging studies for pathological outcome by comparing imaging findings with pathological results.

Material and Method

This retrospective study was approved by the Institutional Review Board of Research Affairs, Faculty of Medicine, Chulalongkorn University. We reviewed medical data from patients who were diagnosed with adrenal PCC and underwent adrenalectomy from all surgical approaches at King Chulalongkorn Memorial Hospital (KCMH).

From 2006-2018, 68 patients were diagnosed with PCC by positive biochemical tests and imaging study. Ten patients were excluded from this study because of incomplete imaging data. Therefore, 58 patients were included in this study; 24-hrurine metanephrine and normetanephrine levels were measured by the High Performance Liquid Chromatography (HPLC) technique. All patients were well-prepared due to discontinuing the medication associated with false positive results before the test.

We divided the patients into the PCC group and the non-PCC group, according to the pathological results. Preoperative imaging (CT and/or MRI) was retrospectively reviewed by a uro-radiologist who classified patients into imaging suggested PPC (group 1) and imaging non-suggested PCC (group 2). Imaging criteria of the mass that suggested PCC in this study was defined as 1. hypervascularity on CECT scan: detected focus of high attenuation more than 140 HU on portovenous phase; 2. high SI on T2W as compared to adjacent renal cortex SI, and 3. hypervascularity mass with uptake MIBG scan.

Statistical Analysis

Continuous variables were presented by median (25^{th} percentile - 75^{th} percentile) and categorical data were presented by number (%). Wilcoxon rank sum test was used to compare the median between the groups and Chi square test or Fisher's exact was used to compare the categorical data. The sensitivity, specificity, positive predictive value (PPV), negative predictive value and area under Receiver Operating Characteristic (ROC) curve for PCC imaging diagnostics were evaluated.

Statistical significance was defined as $p<0.05$. STATA version 15.1 (Stata Corp LP, Texas 77845 USA) was used to perform all statistical analyses.

Result

Patient demographic data are presented in Table 1. There were 46 PCC patients (79%) and 12 non-PCC patients (21%) who were followed up to pathological results. The PCC group had significantly lower BMI (p=0.002) and larger tumor size (p=0.03) than the non-PCC group. There was no significant difference in level of 24-hr urine metanephrine and normetanephrine between the groups.

Pathological outcomes in the non-PCC patients are shown in Table 2. Preoperatively, CT scan was performed in 39 patients, MRI was performed in 7 patients, CT scan and MRI were performed in 4 patients, CT scan and MIBG scan were performed in 7 patients, and MRI and MIBG scan were performed in 1 patient.

According to imaging criteria, 38 patients (66%) were classified into group 1 (suggested PPC) and 20 patients (34%) were classified into group 2 (non-suggested PCC). In group 2, 8 patients were PCC and 12 patients were non-PCC (Table 3). Sensitivity of preoperative imaging findings to detect PCC was 82.6% (95% CI, 68-92), specificity was 100% (95% CI, 73-100), positive predictive value was 100% (95% CI, 90-100), negative predictive value was 60% (95% CI, 36-80), and ROC area was 0.91% (95% CI, 0.86-0.90) (Figure 1) (Table 4).

Discussion

Pheochromocytoma (PCC) has a wide range of clinical presentations, from asymptomatic disease (29-57%) to uncontrolled hypertension and hypertensive crisis[17]. Nearly 5% of PCC was detected as adrenal incidentaloma6.

Current clinical guidelines recommend all patients with suspected PCC are initially evaluated by biochemical tests. Although plasma free metanephrines and urine fractionated metanephrines have high diagnostic accuracy, these tests are strongly influenced by many factors, such as postures or medications6. Therefore, false positive biochemical results in adrenal incidentaloma will be diagnosed as PCC and lead to unnecessary surgery.

We investigated the diagnostic value of pre-operative imaging for PCC. CT and MRI scan are the first-choice imaging modality for locating tumors after biochemical test. The unenhanced CT scan and washout pattern are most commonly used for diagnosis PCC with 90-100% sensitivity and 70-80 specificity%[6]. Recent studies have reported that venous enhancement with HU greater than 110 or 130 offers more specificity than the washout criteria. For MRI scan, the overall sensitivity is 90-95% and specificity is 50-97%[15,17].

In this study, both BMI and tumor size were also related with PCC. PCC diagnosis was significantly higher in thinner patients (median BMI 23 vs 27.7) and large tumor size (5 vs 3.1 cm). Levels of metanephrines and normetanephrines were not associated with PCC diagnosis. For CT scan, we used a new level of HU>150 in the portal venous phase instead of 110 or 130. This offers 100% specificity and PPV to detect PCC but low NPV to exclude PCC (60%). These findings may lead to further prospective studies to identify the predictive factors for surgical outcomes by using the preoperative imaging data combined with other preoperative factors.

Table 1. Patient characteristics.

	Total (N=58)	PCC (N=46)	Non-PCC (N=12)	P
Median (IQR) Age	47 (36 - 57)	46 (34 - 55)	53 (39.5 - 67)	0.14
Gender		0.36		
Male	27 (46.55)	20 (43.48)	7 (58.33)	
Female	31 (53.45)	26 (56.52)	5 (41.67)	
Median (IQR) BMI	23.3 (20.8 - 25.6)	23 (20.8 - 24.5)	27.7 (24.8 - 29.4)	0.002
BMI group				0.001
• < 18.5	7 (12.07)	7 (15.22)	0 (0)	
• 18.5-22.9	18 (31.03)	16 (34.78)	2 (16.67)	
• 23-24.9	17 (29.31)	16 (34.78)	1 (8.33)	
• ≥ 25	16 (27.59)	7 (15.22)	9 (75)	
Median (IQR) Size	4.4 (3 - 7)	5 (3.4 - 7)	3.1 (1.6 - 3.9)	0.03
Side				0.86
• Right	25 (43.86)	20 (44.44)	5 (41.67)	
• Left	32 (56.14)	25 (55.56)	7 (58.33)	
Median (IQR) Metanephrine	231.2 (131.6 - 405.7)	257 (137 - 406.4)	216 (111 - 316.2)	0.20
Median (IQR) Normetanephrine	621.6 (423.61 - 987.2)	565.2 (420.51 - 1103)	738.7 (509.31 - 911)	0.75

Table 2. Pathologic outcomes in the non-PCC group.

Pathology report	N
Adrenal cortical adenoma	6
Adenomatoid tumor	2
Intra-adrenal medulla organizing hematoma	1
Adrenal medullary hyperplasia	1
Neoplasm with necrosis	1
Poorly differentiated neuroblastoma	1

Table 3. Preoperative imaging and pathological diagnosis.

Pheochromocytoma (n)	Imaging suggest PCC (n)		Total
	Yes	No	
• Yes	38	8	46
• No	0	12	12
Total	38	20	58

P-value <0.001

Table 4. Performance of imaging suggested for diagnosis of pheochromocytoma.

	%	95%CI	
Sensitivity	82.6	68.6	92.2
Specificity	100	73.5	100
Positive predictive value	100	90.7	100
Negative predictive value	60	36.1	80.9
ROC area	0.91	0.86	0.97

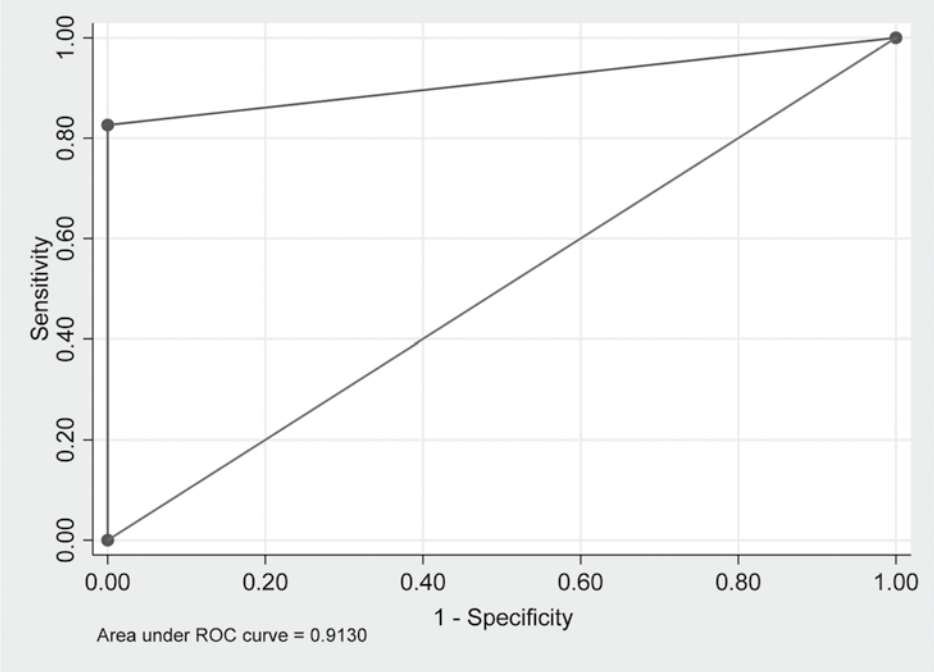

Figure 1. Shows sensitivity and area under ROC curve for the imaging suggested for pheochromocytoma diagnosis.

The limitations of this study include its retrospective design. The imaging studies were interpreted by a single uro-radiologist, resulting in a lack of interobserver reliability. Lastly, there was a small number of patients due to the low incidence of PCC. A multicenter study with a high volume of patients would have more powerful results.

Conclusion

Preoperative imaging with a new threshold of HU offers excellent specificity and PPV to detect PCC.

Conflict of interest

The authors declare no conflict of interest.

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