

**ONLINE FIRST PUBLICATION**

Online first papers have undergone full scientific review and copyediting, but have not been typeset or proofread. To cite this article, use the DOIs number provided. Mandatory typesetting and proofreading will commence with regular print and online publication of the online first papers of the *SMJ*.

**A 15-year pheochromocytoma and paraganglioma experience in a single centre: a Singapore perspective**

Yingshan Lee<sup>1</sup>, MBBS, MRCP, Leon Yuan Rui Tan<sup>2</sup>, MBBS,  
Shaikh Abdul Kader Kamaldeen Abdul Shakoor<sup>1</sup>, MBBS, MRCP

<sup>1</sup>Department of Endocrinology, Tan Tock Seng Hospital, <sup>2</sup>Department of Paediatrics, KK Women's and Children's Hospital, Singapore

**Correspondence:** Dr Yingshan Lee, Consultant, Department of Endocrinology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433. [yingshan\\_lee@ttsh.com.sg](mailto:yingshan_lee@ttsh.com.sg)

---

**Singapore Med J 2021, 1–29**

<https://doi.org/10.11622/smedj.2021135>

Published ahead of print: 4 October 2021

Online version can be found at  
<http://www.smj.org.sg/online-first>

**ABSTRACT**

**Introduction:** Pheochromocytomas (PCC) and paragangliomas (PGL) are rare endocrine tumours. The objective of this study was to describe our experience with these two entities in a Singapore population.

**Methods:** We identified patients with positive histopathological confirmations of PCC and PGL who were treated at a tertiary Singapore hospital between January 2000 and December 2015. The results were analysed for clinical presentations, treatment and long-term outcomes.

**Results:** A total of 27 cases (20 PCC, 7 PGL) were identified over a 15-year period. One case of PGL developed bilateral disease on follow-up. There were 17 male and 10 female patients with a median age of 57 (range 24–77) years. A positive family history was uncommon and present in only 3.7% of patients. Uniquely, the top three presenting symptoms were abdominal discomfort, palpitations and diaphoresis. Despite adequate preoperative preparation, intraoperative haemodynamic instability occurred in 70.4% and early postoperative hypotension occurred in 11.1% of patients. After surgery, hypertension was resolved in 41.2% (7/17) and diabetes mellitus in 60% (3/5). Disease recurrence was reported in 22.2% and distant metastases in 14.8%. At the end of the follow-up period (median 35 [range 3–148] months), 70.4% were still alive.

**Conclusion:** PCC and PGL can present with a wide range of symptoms. Intraoperative haemodynamic instability was frequent despite good preoperative preparation. Disease recurrences and metastasis occurred in up to one-fifth of the patients. Genetic screening should be offered to patients with PCC and PGL.

*Keywords:* adrenal incidentaloma, neuroendocrine carcinoma, paraganglioma, pheochromocytoma

## INTRODUCTION

Pheochromocytomas (PCC) are rare catecholamine-producing tumours arising from chromaffin cells of the adrenal medulla. When located in extra-adrenal locations, they are called paragangliomas (PGL). Although the true prevalence of PCC is uncertain, rates of 0.2%–0.6% have been documented in patients with hypertension.<sup>(1-4)</sup> The fascination with this rare tumour is partly attributed to its myriad and, at times, dramatic presentation. These tumours are notoriously known to be great mimickers, and unusual presentations involving almost every organ system have been reported. Traditionally, a classical triad consisting of headaches, diaphoresis and palpitations have been described. In one of the most expansive studies published by Goldstein et al almost 20 years ago, hypertension, headaches and palpitations occurred in 82%, 58% and 48% of all patients, respectively.<sup>(5)</sup> In another epidemiological study, which included 284 patients from the same period, the reported frequencies of hypertension, headaches and palpitations were similar at 71.5%, 51.0% and 58.0%, respectively.<sup>(6)</sup> Interestingly, later studies showed a shift toward PCC/PGL presenting with fewer symptoms and being diagnosed increasingly as incidentalomas.<sup>(7-9)</sup> Two studies that looked at cases after the year 2005 reported PCC/PGL being diagnosed incidentally in up to 65%.<sup>(8,9)</sup> Other characteristics, such as the proportion of intra- to extra-adrenal lesions and malignancy rates, remained largely similar throughout the different time periods. Generally, intra-adrenal lesions were more commonly seen, at reported rates of 61%–95%.<sup>(5-9)</sup> Malignancy rates ranged from 4% to 13%.<sup>(5-9)</sup>

Much less is known of the characteristics of PCC/PGL in Asians. One of the largest PCC/PGL studies was performed in an Indian population. Over a 12-year period, it reported a total of 225 cases, of which one-third were PGL. Of these, 43% presented with adrenergic symptoms and 44% were diagnosed incidentally. Hypertension was seen in 65%, and 37.3% had at least one symptom of headache, palpitations or diaphoresis. The metastasis rate was 15%

in that study.<sup>(10)</sup> In a smaller series from Hong Kong, consisting of only Chinese subjects, 65% were intra-adrenal and 35% were extra-adrenal lesions. The majority were symptomatic, with the top three symptoms being hypertension, headache and palpitations. There were no malignant cases during the mean follow-up period of 7 (range 1–15) years.<sup>(11,12)</sup>

Little is known of the behaviour of PCC/PGL in a multiethnic population such as Singapore. Given the wide variation in modes of presentation and behaviour of this rare condition, we find it important to report our experience in our population. We aimed to methodically investigate the presentation, management, short-term outcomes (surgical complications) and long-term outcomes (recurrence, malignancy and mortality) of cases of PCC/PGL that were surgically managed in our institution over a 15-year period.

## **METHODS**

We conducted a retrospective review of medical records for cases of PCC/PGL that attended our hospital between January 2000 and December 2015. Inpatient database was searched using our institution diagnosis codes for ‘pheochromocytoma’ and ‘paraganglioma’. To avoid missing cases, we also searched using diagnosis codes that included the word ‘adrenal’, such as ‘benign neoplasm of adrenal gland’, ‘second malign neo adrenal’, ‘malign neopl adrenal’, ‘malignant neoplasm of cortex of adrenal gland’, ‘disorder of adrenal gland, unspecified’ and ‘adrenal disorder NEC’. We included only cases with histopathological confirmation of PCC/PGL. Both the inpatient and outpatient medical records of the identified cases were reviewed for demographic data, as well as personal and family medical history. Disease-specific information was collected, including mode of presentation, biochemical and radiological investigations, and tumour size and location. Perioperative events, such as preoperative preparation, intra- and early postoperative complications and length of stay, were evaluated. We looked at anaesthesia records for intraoperative events such as hypotension,

hypertension and blood transfusion rates. For this study, intraoperative hypotension was defined as systolic blood pressure (SBP) < 90 mmHg, and intraoperative hypertension was defined as SBP > 160 mmHg or diastolic blood pressure (DBP) > 110 mmHg. Data was collected for early postoperative complications, defined as occurring in the first 72 hours after surgery. Postoperative complications were classified using the Clavien-Dindo classification.<sup>(13)</sup> Follow-up data included persistence of urinary metanephrines abnormalities, recurrence, metastasis and survival outcomes. Recurrence was defined as biochemical evidence of raised metanephrines and/or radiological evidence of tumour at the original site of disease. Malignant disease was defined as evidence of disease at locations where catecholamine-producing cells are typically not present. Follow-up data was obtained up till December 2016 to allow for at least one year of follow-up for cases identified in 2015.

Quantitative results were reported as means  $\pm$  standard deviation (SD) or median with interquartile range (IQR). Categorical data was reported as percentages. Differences between groups were assessed using independent *t*-test, Mann-Whitney U test, Kruskal-Wallis test and Spearman's rank-order, as appropriate. Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA). A *p*-value of < 0.05 was considered statistically significant.

Ethics approval for the study was obtained from the National Healthcare Group Domain Specific Review Board (DSRB reference 2014/00822).

## RESULTS

A total of 38 cases were identified from 1,357 cases that were screened using diagnosis codes. 11 cases were excluded, as they did not have histopathological confirmation of the disease. Among these 11 cases, two sought treatment in another hospital, four were non-locals and sought treatment in their own countries, three were diagnosed to have adrenal cortical tumours

after surgery and two elected not to undergo surgery. Finally, 27 cases were included for analysis.

The study population consisted of 17 male and ten female patients. The median age at diagnosis was 57 (range 24–77) years. The largest ethnic group was Chinese (24/27, 88.9%), followed by Malay (2/27, 7.4%) and Filipino (1/27, 3.7%). Pre-existing hypertension was present in 63.0%, diabetes mellitus in 18.5% and ischaemic heart disease in 14.8% (Table I). Among the 27 confirmed cases, 20 were PCC and seven were PGL. Of the extra-adrenal lesions, two were in the para-aortic region, two were bladder lesions and three were glomus tumours. One patient with PGL glomus tumour developed bilateral disease during follow-up. The median size of the tumours was 5.3 (range 1–20) cm. Intra-adrenal tumours were not significantly larger than the extra-adrenal tumours (median 6.0 [range 2–20] cm vs. 3.5 [range 1–6] cm;  $p = 0.60$ ). Two patients (Case 4 and 25) had prior surgeries for PCC/PGL. Positive family history was present in one patient (Case 25), and there was only one case of confirmed syndromic PCC (Case 3, neurofibromatosis type 1).

**Table I. Characteristics of study population.**

Characteristic	No. (%)		
	All (n = 27)	PCC (n = 20)	PGL (n = 7)
Gender			
Male	17 (63.0)	12 (60.0)	5 (71.4)
Female	10 (37.0)	8 (40.0)	2 (28.6)
Race			
Chinese	24 (88.9)	17 (85.0)	7 (100)
Malay	2 (7.4)	2 (10.0)	0 (0)
Filipino	1 (3.7)	1 (5.0)	0 (0)
Age* (yr)	57 (24–77)	60.5 (24–77)	55 (27–67)
Smokers	4 (14.8)	4 (20.0)	0 (0)
Family history	1 (3.7)	0 (0)	1 (14.3)
Pre-existing conditions			
PCC/PGL	2 (7.4)	1 (5.0)	1 (14.3)
Hypertension	17 (63.0)	13 (65.0)	4 (57.1)
Diabetes mellitus	5 (18.5)	3 (15.0)	2 (28.6)
Ischaemic heart disease	4 (14.8)	1 (5.0)	3 (42.9)

\*Data presented as median (range). PCC: pheochromocytomas; PGL: paragangliomas

Among the 27 cases, 85.2% presented with symptoms and 14.8% were diagnosed incidentally. The top two most common symptoms were abdominal pain (11/27, 40.7%) and palpitations (10/27, 37.0%), while diaphoresis (5/27, 18.5%) and labile blood pressure (5/27, 18.5%) were the third most common symptom. Weight loss was present in four patients. The commonly described triad of palpitations, diaphoresis and headache was present in only one patient. PCC was diagnosed through evaluation of new-onset hypertension in one patient. As can be seen from Table II, the presenting symptoms can be vague and wide-ranging.

**Table II. Modes of presentation in patients.**

Mode of presentation	No. (%)		
	All (n = 27)	PCC (n = 20)	PGL (n = 7)
Incidental	4 (14.8)	3	1
Symptomatic	23 (85.2)	17	5
Crisis	6 (22.2)	5	1
Abdominal pain	11 (40.7)	10	1
Palpitations	10 (37.0)	9	1
Diaphoresis	5 (18.5)	5	0
Labile BP	5 (18.5)	5	0
Mass effect*	5 (18.5)	0	5
Weight loss	4 (14.8)	3	1
Pallor	3 (11.1)	2	1
Breathlessness	2 (7.4)	2	0
Flushing	2 (7.4)	2	0
Headache	2 (7.4)	2	0
Lethargy	2 (7.4)	1	1
Diabetes (new)	1 (3.7)	1	0
Hematuria	1 (3.7)	1	0
Hemiparesis	1 (3.7)	1	0
Hypertension (new)	1 (3.7)	1	0
Hypertension (uncontrolled)	1 (3.7)	1	0
Lower urinary tract symptoms	1 (3.7)	0	1
Syncope	1 (3.7)	1	0

\*Mass effect includes: hearing loss (n = 3); multiple craniopathies (n = 1); loss of voice (n = 1) PCC: pheochromocytomas; PGL: paragangliomas

The most common method of radiological imaging for diagnosis was computed tomography (15/27, 55.6%), followed by magnetic resonance imaging (15/27, 55.6%) and ultrasonography (11/28, 40.7%). <sup>131</sup>I-MIBG scintigraphy was performed in only two cases. Of the 27 cases, 15 (55.6%) underwent open surgeries, 10 (37.0%) underwent laparoscopic

surgeries, and 2 (7.4%) cases of bladder paragangliomas had transurethral resection of the bladder tumours. A short median stay of 2 (range 1–6) days in the intensive care unit (ICU) after surgery was required in 85.2% of patients. The median length of hospitalisation was 6 (range 1–31) days, and this was similar between the PCC and PGL cases.

Postoperative metanephrine tests are typically repeated about four weeks after discharge. Two patients had persistent disease, as evidenced by elevated urinary metanephrines. One of them (Case 9) had metastatic disease at the point of entry to the study. The other patient (Case 7) had eventual normalisation of the urinary metanephrines on subsequent repeat testing.

The median follow-up duration was 35 (range 3–148) months in this study. Local tumour recurrence occurred in 22.2% of patients (PCC 15%, PGL 42.9%). Metastasis occurred in 25% of PCC cases but none in PGL. Metastatic disease was diagnosed at initial presentation or at surgery in two patients. In the other two patients, metastasis was detected between 18 and 48 months after diagnosis. The most commonly affected site was the lymph nodes, but metastases were also found in the lung, liver and bone. Table III summarises the cases that developed recurrences and/or metastases. At the end of the study period, 70.4% of the patients were alive, 11.1% had died and 18.5% were lost to follow-up. Among the patients who died during the follow-up period, two (Case 9 and 11) died from metastatic PCC and one (Case 19) from metastatic ovarian cancer. None in the PGL group died during the study period (Table III & Appendix)

6 (22.2%) patients presented in crisis (Table IV). Not unexpectedly, these patients were more symptomatic than the rest of the study cohort who presented with symptoms ( $p = 0.04$ ). There were, however, no significant differences in age, size of tumour, degree of catecholamines and metanephrines elevation, preoperative blood pressure, surgery waiting time, frequency of intraoperative haemodynamic instability, transfusion rates, early



postoperative events, length of stay or frequency of recurrence and metastasis. Only one patient received surgery in the same admission. All six patients were adequately alpha-blocked, and 5 (83.3%) received additional beta blockade. Their mean maximal single dose of phenoxybenzamine was higher compared to the rest of the study cohort (median 30 [range 20–40] mg vs. 20 [range 0–60] mg;  $p = 0.05$ ). Despite achieving good preoperative haemodynamic stabilisation (mean SBP  $119 \pm 7$  mmHg, mean DBP  $74 \pm 9$  mmHg, mean pulse rate  $75 \pm 6$  beats per minute), intraoperative hypo- and hypertensive episodes were present in all five patients with available anaesthesia charts (one patient's anaesthesia chart was not available). Five patients were still alive at the end of the study period, and one patient was lost to follow-up. No recurrence or malignancy was detected in any of the cases. This experience highlighted the priority placed in achieving adequate preoperative stabilisation even in cases that present in crisis, as opposed to emergency surgery.<sup>(14)</sup>

Four patients who were diagnosed incidentally had undergone imaging for unrelated causes. Three patients (Case 2, 14 and 19) were diagnosed with PCC and the fourth patient (Case 6) was diagnosed with a para-aortic PGL. Incidentalomas were smaller (median 3.25 [range 2–4] cm vs. 6.25 [range 1–20] cm;  $p = 0.04$ ) and had lower urinary normetanephrines (NM) ( $p = 0.03$ ). They did not differ in levels of urinary metanephrines, waiting time for surgery, maximal single dose of phenoxybenzamine, preoperative blood pressure, surgery approach, intraoperative haemodynamic instability, postoperative complications, duration of stay in the ICU and length of hospitalisation. None of the incidentalomas developed recurrences or metastasis.

Positive family history was present in only one patient (Case 25) – one sister was diagnosed with PCC and another with PGL. This patient presented with loss of voice and hearing, and was diagnosed with a glomus tumour on the left side. Seven years prior, he had undergone excision for bilateral para-adrenal tumours. He had an open surgery for the left

glomus tumour and received radiosurgery six months later for tumour recurrence diagnosed on magnetic resonance imaging. During follow-up, for which there were periods of non-attendance, he was diagnosed to have a new glomus tumour on the contralateral side ten years later. Unfortunately, no genetic testing was done.

There were six patients who developed recurrence – three PCC and three PGL glomus tumours. The time taken for disease recurrence ranged from 6 months to 15 years for PCC. Case 4 was a patient who had prior surgery for PCC and presented 15 years later with recurrence of a large 13-cm tumour at the ipsilateral side. He had normalisation of urinary metanephrines and NM after surgery to remove the recurrent PCC but developed metastasis four years later. Cases 11 and 15 were both diagnosed to have recurrence of PCC from positive symptoms and raised urinary NM. Both had normal urinary metanephrines and NM after their initial surgery. For the three patients with glomus tumours, two were not able to achieve complete tumour excision during the initial surgery, while the third patient (Case 25) has been described above.

There were four patients with metastasis. Case 9 was a 47-year-old Chinese man who presented with weight loss and abdominal discomfort. He was found to have a large, 15-cm PCC with widespread disease to the bone, liver and lung at diagnosis; he died ten months later. Metastasis for the other three patients was detected either at the point of surgery or up to 48 months later. The most common site of metastasis is the lymph node. Other than Case 9, the rest were either asymptomatic or had very mild symptoms when they were diagnosed with advanced disease. Raised urinary NM was common to all (Table III).

In our centre, 24-hour urine collection for catecholamines and metanephrines is performed with high-performance liquid chromatography. Urinary catecholamines and metanephrines have a high sensitivity and specificity of between 84% and 100% in the biochemical diagnosis of PCC/PGL in published studies.<sup>(15,16)</sup> In our study, the results were

available in 23 out of 27 patients before surgery. The results were unavailable for four of the seven patients with PGL, three of whom had a diagnosis of glomus tumour.

All patients with PCC had functional tumours, and the mean elevation of urinary epinephrine and norepinephrine levels were both 5.7 times above the upper range. Mean metanephrine and NM levels were elevated 14.9 times and 16.7 times, respectively. Two out of 20 patients had normal urinary metanephrine levels, while all PCC cases had elevated urinary NM levels. We considered adrenergic-predominant PCC as having an increase in urinary metanephrines of at least 10% over the total urinary increases in metanephrine and NM combined.<sup>(12)</sup> Seven out of 20 patients were predominantly NM-producing. NM-producing and metanephrine-producing PCC did not differ in size, intra- or postoperative blood pressure instability, and frequency of recurrence or metastasis.

In the three cases of PGL with available urinary results, two (para-aortic PGL) had elevated norepinephrine and NM, with levels raised three times above the upper limit of normal. Urinary epinephrines were normal in all three cases, and urinary metanephrines were raised maximally to 1.1 times only. This pattern of hormonal secretion is unsurprising, as phenylethanolamine-N-methyltransferase, the enzyme responsible for the conversion of norepinephrine to epinephrine, is specific to the adrenal medulla and absent in the peripheral sympathetic ganglions.

According to the 2014 Endocrine Society clinical practice guidelines, it is recommended that patients receive at least 7–14 days of medical treatment, including alpha blockade, prior to surgery.<sup>(17)</sup> Our institution's practice includes alpha blockade and liberal salt and fluid intake, with the aim to achieve target blood pressure below 130/80 mmHg and the presence of postural drop. Phenoxybenzamine is preferred in our institution, and patients are admitted at least one day before surgery for intravenous hydration.

In this study, 63% of patients received a combination of alpha and beta blockers; 18.5% received alpha blockers alone, 3.7% received beta blockers alone, and 14.8% of patients (all with PGL) were not on either preoperatively. All patients with PCC received at least alpha blockers and 75% of them required additional beta blockade. Other antihypertensives used included angiotensinogen converting enzymes inhibitors (4/27, 14.8%) and calcium channel blockers (5/27, 18.5%). Mean blood pressure was  $125/76 \pm 11/10$  mmHg and mean pulse rate was  $79 \pm 11$  beats per minute prior to surgery, suggesting that preoperative blood pressure and pulse rate were at the recommended targets.<sup>(17)</sup> Magnesium sulphate infusion was given for 70% of PCC and 28.6% of PGL patients.

There were 15 (55.6%) open surgeries, 10 (37.0%) laparoscopic surgeries and 2 (7.4%) transurethral resection of bladder tumours. Due to the location of PGL, all patients with PGL underwent open surgery. Half of patients with PCC underwent surgery via a laparoscopic approach. Those with PCC who underwent open surgery had larger tumours ( $> 5$  cm) than those who underwent laparoscopic surgery ( $p = 0.01$ ). This was not unexpected, since the Endocrine Society guidelines recommended open resection for large tumours  $> 6$  cm or invasive PCC to ensure complete tumour resection and to avoid intraoperative tumour rupture.<sup>(17)</sup> Patients who underwent open surgery required more transfusion ( $p = 0.01$ ), stayed longer in the ICU (2 days vs. 4 days;  $p = 0.01$ ) and had longer overall length of hospitalisation (4 days vs. 17 days;  $p < 0.01$ ). There were no significant differences between the frequency of intraoperative blood pressure fluctuations between the two surgical approaches.

Intraoperative hypotensive (18/27, 66.7%) and hypertensive (19/27, 70.4%) events occurred in more than two-thirds of all cases, and the frequency of occurrence was similar in both PCC and PGL. Patients with PCC more frequently required intraoperative antihypertensives (75% vs. 28.6%,  $p = 0.03$ ). Blood transfusions were required in about one-quarter of all patients. Despite the high frequency of intraoperative haemodynamic instability,

none developed postoperative circulatory events such as strokes or cardiac events. Postoperative complications were categorised using the Clavien-Dindo classification. There were three cases in Clavien I, 12 cases in Clavien II, and no cases in Clavien III or IV. The most common postoperative complications were hypertension (8/27, 29.6%) and hypotension (3/27, 11.1%). Glycaemic disturbances, postoperative fever, delirium and bacteraemia are some of the other postoperative complications reported (< 5%).

We performed univariate analysis to identify factors associated with intraoperative and early postoperative hypotension or hypertension. Patients who experienced intraoperative hypotension had larger tumours (7.2 cm vs 2.7 cm,  $p = 0.002$ ). Those with early postoperative hypotension were more likely to have tumour size > 10 cm ( $p = 0.002$ ). Patients with intraoperative hypertension were more likely to have metanephrine levels that are elevated by more than two times ( $p = 0.009$ ), while those with early postoperative hypotension were more likely to have higher NM levels ( $p = 0.04$ ). The number of blood pressure-lowering medications required before surgery correlated with that for intraoperative hypertension (if more than two medications,  $p = 0.05$ ) and persistent postoperative hypertension ( $p = 0.004$ ).

We also looked at the post-surgery status of hypertension and diabetes mellitus among patients with these conditions prior to diagnosis. Resolution was defined as not requiring medications, improvement if fewer medications were prescribed, unchanged if the same number of medications were prescribed, and worsened if more medications were prescribed. There were 17 patients with pre-existing hypertension. The median age was 62 (range 31–75) years. All except two patients were on blood pressure-lowering medications before surgery: eight patients received a single agent, while seven required two or more agents. We did not have information on the duration of hypertension. At the final follow-up, 41.2% had resolution while 11.8% had improvement in hypertension (Table V). There were only five patients with pre-existing diabetes mellitus (age range 48–68 years). We did not have data on the duration

of diabetes mellitus. All were receiving oral hypoglycaemic agents, and two also received insulin treatment before surgery. The glycated haemoglobin was between 6% and 12%. Glycaemic control resolved or improved in all patients with pre-existing diabetes mellitus in the immediate postoperative period. Both patients on insulin treatment were able to cease insulin postoperatively. At the end of the study follow-up, 3 (60%) patients did not require any glucose-lowering medication. The remaining two required only oral hypoglycaemic agents. Repeated glycated haemoglobin was between 4.7% and 7.8% (Table V).

Only one patient underwent genetic testing: Case 25, a 25-year-old Malay woman who presented with headaches, diaphoresis, palpitations and newly diagnosed hypertension. She had undergone laparoscopic surgery to remove a 3-cm right PCC. Five years later, she experienced recurrence at the ipsilateral side and had two further open surgeries. Despite that, she had persistent elevated NM, and remnant soft tissue at the right adrenal bed was present on imaging. Genetic testing for *MAX*, *NF*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SDHA*, *TNEM* and *VHL* all returned negative. She remained on conservative management with phenoxybenzamine and close surveillance.

## DISCUSSION

In this study, we described the behaviour and outcome of PCC and PGLs in a tertiary hospital in Singapore over a 15-year period. In our study, the prevalence of PCC/PGL, using a denominator of all diagnosis-coded inpatient adrenal lesions seen in the same period, was 1.9%. It is difficult to estimate the actual prevalence of PCC/PGL, as the methodology differed in the different studies. Two recent studies, based on large Danish and Dutch pathology registries, reported the age-standardised rates of PCC/PGL to be 0.4–4.65 per million person-years.<sup>(18,19)</sup> Other recent retrospective studies conducted in cohorts of adrenal incidentalomas have reported prevalence rates of 0.8%–1.4% in Western populations<sup>(20,21)</sup> and 5.9%–11.7% in Asian

populations.<sup>(22-25)</sup> Of note, from the Danish and Dutch registries, the incidence of PCC/PGL has doubled over the past two decades, with patients being diagnosed at an older age and presenting with smaller tumours.<sup>(18,19)</sup> It is proposed that the increased use of radiological imaging and greater awareness among clinicians have contributed to this trend. In our study, the median age of PCC/PGL was 57 years, which was older than that of other reported cohorts by almost a decade.<sup>(5,6,10,11)</sup> In our study cohort, 85.2% were symptomatic and 14.8% were asymptomatic. The median tumour size was 5.3 cm. One developed bilateral disease, one had metastasis at diagnosis and two had prior diagnosis of PCC/PGL. At the end of a median follow-up period of 35 months, 70.4% were alive, 22.2% had recurrence and 14.8% had metastasis.

The symptomatology in our study population differed from that of other published case series. Commonly reported symptoms, such as headaches, palpitation, and diaphoresis,<sup>(5-7,26,27)</sup> were only present in 7.4%, 37.3% and 18.5% of our cohort, respectively, with the 'classical triad' seen in only one patient. In our cohort, abdominal pain was the most common complaint (40.7%), and five out of six patients presenting in crisis had abdominal pain. All patients with abdominal pain were eventually found to have intra-abdominal lesions (ten PCC and one para-aortic PGL). All except one patient had lesions that were larger than 4 cm. Comparing within the study population, the size of the lesion in the group presenting with abdominal pain was similar (median 5.5 cm vs. 5.3 cm). This different pattern of symptomology was not observed in other Asian studies. A study conducted in a West Indian cohort reported abdominal pain in 29%, although paroxysmal symptoms remained the most common.<sup>(10)</sup> A smaller cohort of Chinese patients did not report such a shift in symptomology.<sup>(11)</sup> Abdominal pain is a common yet vague complaint. It may be related to the space-occupying effect of an underlying tumour or due to gut ischaemia, although none of the patients had associated symptoms of diarrhoea.

It highlights the importance of being aware of this condition given its notoriety for presenting with myriad and at times vague symptoms.

We noticed a high prevalence of haemodynamic instability (70.4%) in our study. This was despite good preoperative preparation, which included adequate preoperative blood pressure and pulse rate control with alpha and/or beta blockers, in addition to ad libitum salt and fluid intake. Studies that aimed to identify predictive factors of intraoperative haemodynamic instability during PCC surgeries had different definitions of haemodynamic instability.<sup>(28-37)</sup> Most studies used a cut-off for SBP, ranging from 160 mmHg to 200 mmHg for the upper limit and 80 mmHg to 110 mmHg for the lower limit. Some studies defined haemodynamic instability using a mean arterial pressure < 60 mmHg.<sup>(28,33)</sup> Intraoperative blood pressure variability, duration spent in hypotension or hypertension, and a percentage rise above or below baseline blood pressure are some of the other indices used.<sup>(29,35-37)</sup>

Large tumour size<sup>(28,30,31,34,36)</sup> and higher catecholamine level<sup>(29-32,37)</sup> were most often predictive of intraoperative haemodynamic instability. Jiang et al observed that a tumour size > 5 cm was an independent predictor of intraoperative haemodynamic instability (odds ratio [OR] 2.526, 95% confidence interval [CI] 1.039–4.768;  $p = 0.019$ ).<sup>(28)</sup> Namekawa et al, who used a higher cut-off of > 6 cm, observed that it was predictive of intraoperative hypotension and vasopressor use (OR 24.9, 95% CI 2.85–591.5;  $p < 0.01$ ).<sup>(31)</sup> Brunaud et al, who investigated the predictive factors of cardiovascular morbidity (defined in part as hypertensive and hypotensive episodes requiring pharmacologic management) in 225 patients who underwent laparoscopic adrenalectomy, found that tumour size was predictive of postoperative cardiovascular morbidity ( $5.0 \pm 2.7$  vs.  $4.2 \pm 1.8$ ;  $p = 0.032$ ).<sup>(34)</sup> Kiernan et al retrospectively evaluated a cohort of 91 PCC cases and found, on multivariate analysis, that increasing tumour size was associated with a significant rise in the number of episodes of SBP 30% above



baseline (relative risk 1.40,  $p = 0.041$ ) and increased postoperative vasopressor requirement (OR 1.23,  $p = 0.039$ ).<sup>(36)</sup>

Higher levels of catecholamines and metanephrines have been shown to be predictive of haemodynamic instability<sup>(29-32,37)</sup>. Gaujoux et al reported an OR of 15.63 (95% CI 3.74–65.21;  $p < 0.0001$ ) of haemodynamic instability when urinary metanephrines were above ten times the upper limit.<sup>(32)</sup> Weingarten et al reported that, although intraoperative haemodynamic variability was observed in all groups in their study, it was significantly greater when urinary catecholamines and metanephrines levels were increased ( $p < 0.001$ ).<sup>(37)</sup> Namekawa et al observed that urinary norepinephrine  $> 600$  mcg/day ( $p = 0.02$ ) and epinephrine  $> 200$  mcg/day ( $p < 0.01$ ) were independent predictors of prolonged hypotension requiring inotropic support.<sup>(31)</sup> Using a definition of haemodynamic instability that is most similar to that of our study, Chang et al identified 24-hour urinary norepinephrines as an independent risk factor for haemodynamic instability (OR 1.02, 95% CI 1.01–1.03;  $p = 0.046$ ).<sup>(29)</sup>

Jiang et al and Gaujoux et al both identified predictive factors of haemodynamic instability using multivariate analyses. In Jiang et al's study, the independent predictive risk factors were tumour size  $> 5$  cm, presence of diabetes mellitus and preoperative SBP fluctuation  $> 50$  mmHg.<sup>(28)</sup> In the study by Gaujoux et al, only two risk factors were identified – high pre- preoperative blood pressure and ten times elevation of urinary metanephrine and/or NM.<sup>(32)</sup> In both studies, the incidence of haemodynamic instability increased by about five-fold when any single risk factor was present. When two or more risk factors were present, the incidence of haemodynamic instability was about 50%. Some other predictive factors that have been inconsistently reported included age, preoperative blood pressure, presence of diabetes mellitus, number of blood pressure-lowering medications, phenoxybenzamine dosage and use of selective alpha-blockers.<sup>(28-37)</sup>

With good preoperative alpha blockade and perioperative care, surgical mortality from PCC/PGL resection is now uncommon. Nonetheless, perioperative morbidity remains a concern, and this is reflected in the high rates of intraoperative haemodynamic instability in our study. Our study suggests that patients with larger tumours and urine metanephrines levels that are raised by more than two times have higher risks of intraoperative haemodynamic instability. In the early postoperative period, those with tumour sizes > 10 cm and elevated NM prior to surgery are at higher risks of hypotension. Finally, patients who are on more than two antihypertensive medications are more likely to have persistently raised blood pressure intra- and postoperatively. Identifying and communicating these factors to the surgical and anaesthesia team will be crucial.

Despite a tumour recurrence and metastasis rate of 22.2% and 14.8%, respectively, over a relatively short median period of follow-up (35 months), only one patient reported having a positive family history of PCC/PGL. Another patient underwent genetic testing, which returned negative. As recommended by the 2014 Endocrine Society guidelines,<sup>(17)</sup> genetic testing should be offered to all patients with PCC/PGL. While most PCC/PGL have low risk for malignancy, germline mutations can be found in up to 40% of nonsyndromic PCC/PGL, and in about 11% of patients without a positive family history.<sup>(38-43)</sup> Some of these germline mutations include *SDHAF2*, *SDHD*, *VHL*, *RET* and *TNEM127*. Germline mutations that are linked to a higher risk of malignancy include *SDHB*, *MAX* and *EPAS/HIF2A*.<sup>(44)</sup> Family history is unreliable in detecting nonsyndromic germline mutations due to possible gaps in history and varying penetrance of mutations. Chew et al reported a referral rate for genetic testing in PCC/PGL of 21.8% in a large local national centre. In that study of 124 patients, all syndromic cases were referred but only 3.8% of nonsyndromic PPGL were referred. Subsequently, only 44% of referred patients agreed to proceed with genetic testing.<sup>(45)</sup> To identify the barriers to genetic testing, Chieng and Lee surveyed cancer-affected patients, cancer-free patients and their

cancer-free family members. The most common reasons against genetic testing were cost, the unwillingness to bear the emotional burden of the results, and the impression that management will not change.<sup>(44)</sup> Subsidies on genetic testing did lead to an improved uptake in testing.<sup>(46)</sup> We did not evaluate the reasons behind our low prevalence of genetic testing in the current study. We postulate that in addition to the above stated patient-related factors, clinician-related factors may be responsible for the low uptake. These included time factor in a busy outpatient clinic and a lack of resources for dedicated genetic counselling in our centre. At the point of writing, a clinic for genetic counselling has been set up. Directed genetic testing in PCC/PGL should be guided by syndromic features, family history and biochemical phenotype. This will provide guidance in the prognostication of disease in the patients, as well as opportunity for screening and early diagnosis in their relatives.

This study was not without limitations. As this was a retrospective medical records review study, we cannot exclude potential selection and observer bias. Certain data was missing, such as preoperative blood pressure readings in five cases and anaesthetic charts in one case. Cases managed medically and those managed in the recent five years were not included. With increased awareness of this condition, as well as the trend towards more PCC/PGL being diagnosed incidentally, the availability of these cases may alter our result.

In conclusion, we analysed a cohort of 27 patients diagnosed with PCC/PGL seen over a 15-year period. Our data reaffirmed our understanding that this tumour presents in a varied manner and that the classical triad described in textbooks is most often absent. We identified two gaps in our current management, namely the ability to predict those who are at risk of perioperative complications and inadequate knowledge on underlying germline mutation associated with PCC/PGL in our population. Despite maintaining a high standard of preoperative preparation with alpha and beta blockade without any surgical mortality, the incidence of intraoperative haemodynamic instability was 70.4% and early postoperative

hypotension occurred in 11.1% of patients. We found that larger tumour sizes and urinary metanephrine levels elevated by more than two times were associated with intraoperative haemodynamic instability, while tumour sizes > 10 cm and elevated urinary NM were associated with early postoperative hypotension. Despite the incidence of recurrence (22.2%) and metastasis (14.8%) observed in our study, little is understood about germline mutations in our population. Only one of our patients underwent genetic testing. Genetic testing should be offered to all patients with PCC/PGL. We propose that dedicated studies be performed to target these gaps.

## REFERENCES

1. Sinclair AM, Isles CG, Brown I, et al. Secondary hypertension in a blood pressure clinic. *Arch Intern Med* 1987; 147:1289-93.
2. Anderson GH Jr, Blakeman N, Streeten DH. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens* 1994; 12:609-15.
3. Arlton M, Juan CS, AvRuskin TW. Pheochromocytoma: clinical observations from a Brooklyn tertiary hospital. *Endocr Pract* 2000; 6:249-52.
4. Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res* 2004; 27:193-202.
5. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, et al. Clinical experience over 48 years with pheochromocytoma. *Ann Surg* 1999; 229:755-66.
6. Mannelli M, Ianni L, Cilotti A, Conti A. Pheochromocytoma in Italy: a multicentric retrospective study. *Eur J Endocrinol* 1999; 141:619-24.

7. Baguet JP, Hammer L, Massuco TL, et al. Circumstances of discovery of pheochromocytoma: a retrospective study of 41 consecutive patients. *Eur J Endocrinol* 2004; 150:681-6.
8. Gruber LM, Hartman RP, Thompson GB, et al. Pheochromocytoma characteristics and behavior differ depending on method of discovery. *J Clin Endocrinol Metab* 2019; 104:1386-93.
9. Falhammar H, Kjellman M, Calissendorff J. Treatment and outcomes in pheochromocytomas and paragangliomas: a study of 110 cases from a single center. *Endocrine* 2018; 62:566-75.
10. Jaiswal SK, Sarathi V, Memon SS, et al. Sympathetic paraganglioma: a single-center experience from western India. *Endocr Pract* 2019; 25:211-9.
11. Yau JS, Li JK, Tam VH, et al. Pheochromocytoma in the Hong Kong Chinese population. *Hong Kong Med J* 2010; 16:252-6.
12. Eisenhofer G, Lenders JW, Goldstein DS, et al. Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. *Clin Chem* 2005; 51:735-44.
13. Daniel D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240:205-13.
14. Scholten A, Cisco RM, Vriens MR, et al. Pheochromocytoma crisis is not a surgical emergency. *J Clin Endocrinol Metab* 2013; 98:581-91.
15. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 2003; 88:553-8.

16. Boyle JG, Davidson DF, Perry CG, Connell JM. Comparison of diagnostic accuracy of urinary free metanephrines, vanillyl mandelic acid, and catecholamines and plasma catecholamines for diagnosis of pheochromocytoma. *J Clin Endocrinol Metab* 2007; 92:4602-8.
17. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99:1915-42.
18. Berends AMA, Buitenwef E, de Krijger RR, et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. *Eur J Intern Med* 2018; 51:68-73.
19. Ebbehøj AL, Sondergaard E, Christian Trolle, Stochholm K, Poulsen PL. The epidemiology of pheochromocytoma: increasing incidence and changing clinical presentation. A population-based retrospective study 1977-2015. *Endocr Abstracts* 2017; 49.
20. Patrova J, Jarocka I, Wahrenberg H, Falhammar H. Clinical outcomes in adrenal incidentaloma: experience from one center. *Endocr Pract* 2015; 21:870-7.
21. Goh Z, Phillips I, Hunt PJ, Soule S, Cawood TJ. Characteristics of adrenal incidentalomas in a New Zealand centre. *Intern Med J* 2018; 48:173-8.
22. Kim J, Bae KH, Choi YK, et al. Clinical characteristics for 348 patients with adrenal incidentaloma. *Endocrinol Metab (Seoul)* 2013; 28:20-5.
23. Ahn SH, Kim JH, Baek SH, et al. Characteristics of adrenal incidentalomas in a large prospective computed tomography-based multicenter study: the COAR Study in Korea. *Yonsei Med J* 2018; 59:501-10.
24. Ichijo T, Ueshiba H, Nawata H, Yanase T. A nationwide survey of adrenal incidentalomas in Japan: the first report of clinical and epidemiological features. *Endocr J* 2020; 67:141-52.

25. Li L, Yang G, Zhao L, et al. Baseline demographic and clinical characteristics of patients with adrenal incidentaloma from a single center in China: a survey. *Int J Endocrinol* 2017; 2017:3093290.
26. Cotesta D, Petramala L, Serra V, et al. Clinical experience with pheochromocytoma in a single centre over 16 years. *High Blood Press Cardiovasc Prev* 2009; 16:183-93.
27. Loh KC, Shlossberg AH, Abbott EC, Salisbury SR, Tan MH. Pheochromocytoma: a ten-year survey. *QJM* 1997; 90:51-60.
28. Jiang M, Ding H, Liang Y, et al. Preoperative risk factors for haemodynamic instability during pheochromocytoma surgery in Chinese patients. *Clin Endocrinol (Oxf)* 2018; 88:498-505.
29. Chang RY, Lang BH, Wong KP, Lo CY. High pre-operative urinary norepinephrine is an independent determinant of peri-operative haemodynamic instability in unilateral pheochromocytoma/paraganglioma removal. *World J Surg* 2014; 38:2317-33.
30. Aksakal N, Agcaoglu O, Sahbaz NA, et al. Predictive factors of operative hemodynamic instability for pheochromocytoma. *Am Surg* 2018; 84:920-3.
31. Namekawa T, Utsumi T, Kawamura K, et al. Clinical predictors of prolonged postresection hypotension after laparoscopic adrenalectomy for pheochromocytoma. *Surgery* 2016; 159:763-70.
32. Gaujoux S, Bonnet S, Lentschener C, et al. Preoperative risk factors of hemodynamic instability during laparoscopic adrenalectomy for pheochromocytoma. *Surg Endosc* 2016; 30:2984-93.
33. Chen Y, Scholten A, Chomsky-Higgins K, et al. Risk factors associated with perioperative complications and prolonged length of stay after laparoscopic adrenalectomy. *JAMA Surg* 2018; 153:1036-41.

34. Brunaud L, Nguyen-Thi PL, Mirallie E, et al. Predictive factors for postoperative morbidity after laparoscopic adrenalectomy for pheochromocytoma: a multicenter retrospective analysis in 225 patients. *Surg Endosc* 2016; 30:1051-9.
35. Livingstone M, Duttchen K, Thompson J, et al. Hemodynamic stability during pheochromocytoma resection: lessons learned over the last two decades. *Ann Surg Oncol* 2015; 22:4175-80.
36. Kiernan CM, Du L, Chen X, et al. Predictors of hemodynamic instability during surgery for pheochromocytoma. *Ann Surg Oncol* 2014; 21:3865-71.
37. Weingarten TN, Welch TL, Moore TL, et al. Preoperative levels of catecholamines and metanephrines and intraoperative haemodynamics of patients undergoing pheochromocytoma and paraganglioma resection. *Urology* 2017; 100:131-8.
38. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002; 346:1459-66.
39. Jafri M, Whitworth J, Rattenberry E, et al. Evaluation of SDHB, SDHD and VHL gene susceptibility testing in the assessment of individuals with non-syndromic pheochromocytoma, paraganglioma and head and neck paraganglioma. *Clin Endocrinol (Oxf)* 2013; 78:898-906.
40. Gupta G, Pacak K, AACE Adrenal Scientific Committee. Precision medicine: an update on genotype/biochemical phenotype relationships in pheochromocytoma/paraganglioma patients. *Endocr Pract* 2017; 23:690-704.
41. Neumann HP, Young WF Jr, Eng C. Pheochromocytoma and paraganglioma. *N Engl J Med* 2019; 381:552-65.
42. Mannelli M, Castellano M, Schiavi F, et al. Clinically guided genetic screening in a large cohort of Italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. *J Clin Endocrinol Metab* 2009; 94:1541-7.



43. Amar L, Bertherat J, Baudin E, et al. Genetic testing in pheochromocytoma or functional paraganglioma. *J Clin Oncol* 2005; 23:8812-8.
44. Chieng WS, Lee SC. Discrepancy between initial high expression of interest in clinical cancer genetic testing and actual low uptake in an Asian population. *Genet Test Mol Biomarkers* 2012; 16:785-93.
45. Chew WH, Courtney E, Lim KH, et al. Clinical management of pheochromocytoma and paraganglioma in Singapore: missed opportunities for genetic testing. *Mol Genet Genomic Med* 2017; 5:602-7.
46. Li ST, Yuen J, Zhou K, et al. Impact of subsidies on cancer genetic testing uptake in Singapore. *J Med Genet* 2017; 54:254-9.

**Table III. Summary of essential clinical features in cases that developed recurrence and/or metastasis (n = 8).**

Case	Histology, site	Initial surgery	Normal cats/mets postop	Recurrence (Rec)					Metastasis (Mets)					Outcome
				Rec	Time from initial presentation to Rec	Presentation of Rec	Site of Rec	Treatment for Rec	Mets	Time from initial presentation to Mets	Presentation of Mets	Site of Mets	Treatment for Mets	
4	PCC, L	Open	Yes	Yes	15 yr from first surgery	Palpitations, sweatiness, raised NM	Adrenal, L	Surgery	Yes	48 mth from study entry	Asymptomatic, raised NM	Lymph nodes	Surgery	Normal NM, alive
9	PCC, R	Open	No	No	–	–	–	–	Yes	Present at diagnosis	Abdominal discomfort, weight loss	Bone, liver, lung	AE, RT	Died
11	PCC, L	Open	Yes	Yes	18 mth	Mild headache, palpitations, raised NM.	Adrenal, L	PBZ, PRRT	Yes	18 mth	Mild headache, palpitations, raised NM	Bone, liver, lung, lymph nodes	PBZ, PRRT	Died
15	PCC, R	Lap	Yes	Yes	5 yr	Hypertension in pregnancy, raised NM	Adrenal, R	Surgery, PBZ	No	–	–	–	–	Persistent raised NM, alive
20	PCC, L	Open	Yes	No	–	–	–	–	Yes	At surgery	Positive lymph nodes at surgery	Lymph nodes	Surgery	Persistent raised NM, alive
25	PGL, glomus tumour, L	Open	No info	Yes	6 mth* 10 yr†	Asymptomatic Positive MRI	Ipsilateral* Contralateral†	Radiosurgery* Open surgery†	No	–	–	–	–	Lost to follow-up
26	PGL, glomus tumour, R	Open	No info	Yes	Since surgery	Residual tumour on MRI	Ipsilateral	RT	No	–	–	–	–	Alive
27	PGL, glomus tumour, R	Open	No info	Yes	Since surgery	Residual tumour on MRI	Ipsilateral	SurSeillance	No	–	–	–	–	Lost to follow-up

Summary of cases in Supplementary Table II. \*First recurrence; †Second recurrence

AE: angio-embolisation; L: left; MRI: magnetic resonance imaging; NM: normetanephrines; PBZ: phenoxybenzamine; PCC: pheochromocytomas; PGL: paragangliomas; PRRT: peptide receptor radionuclide therapy; R: right; RT: radiotherapy

**Table IV. Summary of cases presenting with critical conditions (n = 6).**

Case	Condition	Presenting symptoms	Age (yr)	Type	Size (cm)	Surgery during same admission	Admission to surgery time (day)	Recurrence/metastasis at last follow-up	Follow-up (mth)
3	Acute Ischaemic stroke	Hemiparesis x 2 days Diaphoresis x a few months	50	PCC	20.0	No	46	No	101
5	Haemorrhage into adrenal tumour	Abdominal pain x 1 day Labile BP on admission	67	PCC	6.5	No	64	No	121
16	Acute myocardial infarction with cardiogenic shock and acute pulmonary oedema	Breathlessness x 1 day Syncope x 1 day Abdominal pain x 1 day Newly diagnosed DM and labile BP on admission Flushing x 3 years	71	PCC	5.5	No	76	No	73
18	Hypertensive crisis with acute myocardial infarction	Abdominal pain x 4 days Palpitations x 3 years Weight loss x 3 years	69	PCC	9.0	Yes	23	No	4 (lost to follow-up)
21	Septic shock	Abdominal pain x 4 days Lethargy x 4 days Weight loss x 1 month	62	PGL	5.5	No	41	No	13
24	Intestinal obstruction with hypertensive urgency and pulmonary embolism	Abdominal pain x 5 days Breathlessness x 5 days Newly diagnosed DM on admission	56	PCC	4.8	No	109	No	28

BP: blood pressure; DM: diabetes mellitus; PCC: pheochromocytomas; PGL: paragangliomas

**Table V. Resolution of hypertension at follow-up in patients with pre-existing hypertension or diabetes mellitus.**

	No. (%)			
	Resolved	Improved	Unchanged	Worsen
<b>Hypertension (n = 17)</b>				
First postoperative follow-up	6 (35.3)	4 (23.5)	5 (29.4)	2 (11.8)
Final follow-up	7 (41.2)	2 (11.8)	3 (17.6)	5(29.4)
<b>Diabetes mellitus (n = 5)</b>				
First postoperative follow-up	4 (80)	1 (20)	0 (0)	0 (0)
Final follow-up	3 (60)	1 (20)	1 (20)	0 (0)

## APPENDIX

Supplementary Table I. Summary of clinical parameters.

Parameter	All (n = 27)	PCC (n = 20)	PGL (n = 7)	p-value	
<b>24-hour urine catecholamines and metanephrines</b>					
24-hour urine epinephrine (RI 9.3–122)	607.6 ± 1,041.6	692.7 ± 1102.0	97.1 ± 58.3	0.71	
24-hour urine norepinephrine (RI 72–505)	2,698.9 ± 3,741.6	2,869.2 ± 3,960.3	1,564.0 ± 1,136.3	0.86	
24-hour urine metanephrine (RI 264–1,729)	22,088.5 ± 31,501.0	25,764.8 ± 32,821.9	1,255.8 ± 5,13.3	0.10	
24-hour urine normetanephrine (RI 480–2,424)	36,367.2 ± 50,232.4	40,549.5 ± 52,572.8	8,500.50 ± 5,112.1	0.31	
<b>Pre-op medications</b>					
Alpha Blockers (PBZ)	22/81.5%	20/100%	2/28.6%	–	
Beta Blockers	18/66.7%	15/75%	3/42.9%		
Calcium channel blockers	5/18.5%	5/25%	0		
ARB/ACEi	4/14.8%	3/15%	1/14.3%		
None	4/14.8%	0	4/57.1%		
PBZ maximal single dose (mg)	20 (0–60)	20 (10–60)	0 (0–20)	<b>0.001*</b>	
<b>Preoperative Blood pressure and pulse rate</b>					
Preop SBP (mmHg)	125 (11)	124 (11)	131 (12)	–	
Preop DBP (mmHg)	76 (10)	75 (10)	78 (10)	–	
Pulse rate (bpm)	79 (11)	78 (10)	81 (15)	–	
<b>Surgical approach and wait times</b>					
Surgery waiting time (day)	59 (8–205)	56 (12–205)	70 (8–138)	–	
Open	15/55.6%	10/50%	5/71.4%	–	
Laparoscopic	10/37.0%	10/50%	0		
TURBT	2/7.4%	0	2/28.6%		
<b>Tumour</b>					
Size (cm)	5.3 (1–20)	6.0 (2–20)	3.5 (1–6)	0.60	
<b>Intraoperative events</b>					
Hypotension	18/66.7%	15/75.0%	3/42.9%	0.66	
Hypertension	19/70.4%	15/75.0%	4/57.1%	0.37	
Use of intraop inotropes	18/66.7%	15/75.0%	3/42.9%	0.66	
Use of intraop antihypertensives	17/63.0%	15/75.0%	2/28.6%	<b>0.03*</b>	
Magnesium sulphate infusion	16/59.3%	14/70.0%	2/28.6%	0.06	
Transfusion	7/25.9%	5/25.0%	2/28.6%	0.85	
<b>Early postoperative events (first 72 hours)</b>					
Clavien I	3	3	0	–	
Delirium	1/ 3.7%	1/ 5.0%	0		
Hypoglycaemia	1/ 3.7%	1/ 5.0%	0		
Postop fever	1/ 3.7%	1/ 5.0%	0		
Clavien II	12	11	1	–	
Hypertension	8/29.6%	7/35.0%	1/14.3%		0.30
Hypotension	3/11.1%	3/15.0%	0		0.23
Bacteremia	1/3.7%	1/5%	0		–
<b>Admission</b>					
ICU stay (day)	2 (0–6)	2 (1–6)	1 (0–3)	–	
Length of hospitalisation (day)	6 (1–31)	5.5 (3–31)	5 (1–10)	–	
<b>BP and PR at first postoperative follow-up</b>					

SBP (mmHg)	126 (20)	125 (19)	130 (24)	–
DBP (mmHg)	78 (12)	79 (12)	77 (11)	–
PR (bpm)	82 (16)	83 (18)	80 (10)	–
<b>BP and PR at final postoperative follow-up</b>				
SBP (mmHg)	127 (20)	127 (19)	129 (9)	–
DBP (mmHg)	70 (12)	73 (10)	70 (3)	–
PR (bpm)	73 (14)	75 (11)	61 (6)	–
<b>Follow-up</b>				
Duration (mth)	35 (3–148)	43 (3–121)	15 (3–148)	–
<b>Outcome</b>				
Recurrence	6/22.2%	3/15%	3/42.9%	0.13
Metastasis	4/14.8%	4/25%	0	0.20
Alive	19/70.4%	15/75%	4/57.1%	0.17
Died	3/11.1%	3/15%	0	
Lost to follow-up	5/18.5%	2/10%	3/42.9%	

\*Relationships are tested between PCC and PGL groups.  $P < 0.05$  is considered statistically significant. Data presented as mean  $\pm$  standard deviation, number of patients/%, median (range) or median (interquartile range).

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; DBP: diastolic blood pressure; ICU: intensive care unit; PBZ: phenoxybenzamine; PCC: pheochromocytomas; PGL: paragangliomas; PR: pulse rate; SBP: systolic blood pressure; TURBT: transurethral resection of bladder tumour

Case	Age (yr)/ gender/race	Symptoms	Surgical approach	Tumour size (cm)	Histology, site	Recurrence	Metastasis	Alive	Lost to follow-up
1	60/M/M	Yes	L	6	PCC, R	No	No	–	1
2	75/M/C	No	L	3	PCC, R	No	No	Yes	–
3	50/F/C	Yes	O	20	PCC, L	No	No	Yes	–
4	39/M/C	Yes	O	13	PCC, L	Yes	Yes	Yes	–
5	67/M/C	Yes	O	6.5	PCC, R	No	No	Yes	–
6	48/M/C	No	O	3.5	PGL, para-aorta	No	No	–	1
7	77/M/C	Yes	O	6.5	PCC, R	No	No	Yes	–
8	63/F/C	Yes	L	8	PCC, R	No	No	Yes	–
9	47/M/C	Yes	O	15	PCC, R	No	Yes	No	–
10	67/M/C	Yes	T	1	PGL, bladder	No	No	Yes	–
11	68/M/C	Yes	O	*	PCC, L	Yes	Yes	No	–
12	57/F/C	Yes	T	6	PGL, bladder	No	No	Yes	–
13	62/F/C	Yes	O	11	PCC, R	No	No	Yes	–
14	75/F/C	No	L	4	PCC, L	No	No	Yes	–
15	25/F/M	Yes	L	3	PCC, R	Yes	No	Yes	–
16	71/M/C	Yes	L	5.5	PCC, R	No	No	Yes	–
17	38/M/F	Yes	L	4.5	PCC, L	No	No	Yes	–
18	69/F/C	Yes	O	9	PCC, R	No	No	–	1
19	53/F/C	No	O	2	PCC, R	No	No	No	–
20	31/F/C	Yes	O	10.5	PCC, L	No	Yes	Yes	–
21	62/M/C	Yes	O	5.5	PGL, para-aorta	No	No	Yes	–
22	46/M/C	Yes	L	2.5	PCC, R	No	No	Yes	–
23	61/M/C	Yes	L	4.5	PCC, L	No	No	Yes	–
24	56/M/C	Yes	L	4.8	PCC, L	No	No	Yes	–
25	27/M/C	Yes	O	1.2	PGL, glomus tumour, bilateral	Yes	No	–	1
26	55/F/C	Yes	O	5	PGL, glomus tumour, R	Yes	No	Yes	–
27	31/M/C	Yes	O	3.5	PGL, glomus tumour, R	Yes	No	–	1

**Supplementary Table II. Summary of clinical features of study cohort (n = 27).**

\*Missing information. Gender: Male (M), Female (F); Race: Malay (M), Chinese (C), Filipino (F); Surgical approaches: Laparoscopic (L), Open (O), Transurethral resection of bladder tumour (T); L: left; PCC: pheochromocytomas; PGL: paragangliomas; R: right