INTRODUCTION
The incidence of pheochromocytomas, a neuroendocrine tumour, is around 1.9% occurring equally in men and women. Clinical presentation is highly variable but most commonly it presents with episodes of headaches, sweating, palpitations, and hypertension. Most of pheochromocytomas are benign but some are malignant. The prevalence of malignant pheochromocytoma is about 10%, and is somewhat higher for paraganglioma. Malignant pheochromocytoma is reported to be rare, and its prognosis is poor. The only reliable evidence of malignancy is the presence of metastasis in non-chromaffin tissues as histopathological evaluation cannot distinguish between benign and malignant tumours. Plasma or urinary metanephrines are approximately 98% sensitive for detecting pheochromocytomas. Tumour localization with Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or 131I or 123I-MIBG radionuclide scanning is nearly always possible.

Once malignancy is diagnosed, therapy is generally directed at controlling blood pressure and debulking of tumour. Surgical removal is usually curative; chemotherapy and radiotherapy are palliative for malignant pheochromocytomas. Although the survival rate is less than 50%, malignant pheochromocytomas can be slow growing. Patients may have minimal morbidity and survive for as long as 20 years. Recurrences and malignancy are more frequent in cases with large or extra-adrenal tumours.

CASE REPORT
A 40-year-old male presented with fluctuating blood pressure associated with attacks of headache and raised urinary VMA levels. The headache was episodic and global in distribution, associated with profuse sweating, palpitation, facial flushing and feeling of dizziness. He had prior admission to hospital a year ago, where he was found to have fluctuating blood pressure and was diagnosed as a case of pheochromocytoma on the basis of raised urinary VMA levels. He also had history of rheumatic heart disease and had undergone mitral and aortic valve replacement in 1993. He was on oral Coumadrin 5 mg once daily since 1993 and Labetalol 100 mg once daily for past one year.

On examination, he had pallor with pulse rate of 96 beats/minute and blood pressure of 110/75 mmHg. On cardiovascular examination, ejection systolic murmur was audible. Rest of the systemic examination was normal.

On investigations, complete blood count revealed hemoglobin of 6.8 g/dL and platelet count of 435x10^9/L. Urine analysis, serum urea, serum creatinine and liver function tests were normal. Coagulation profile including prothrombin time and partial thromboplastin time with kaolin were elevated. A urinary VMA level done a year ago was 283 µmol/dL with reference range of 10-35 µmol/dL. Colour Doppler ultrasound of abdomen identified a highly vascular, 9.0 x 6.0 x 5.0 cms, homogenous, echogenic, oval shaped mass above and anterior to the upper segment of right kidney displacing the fascia around it. A CT scan done a year ago showed 7.0 x 6.0 x 5.5 cms fairly well-defined lobulated mass of soft tissue attenuation in right suprarenal area displacing the inferior vena cava anteriorly and right kidney downwards. Another separate small 1.5 cm soft tissue attenuation mass was noted along the posterior abdominal wall on right side (Figure 1).
Before surgery, Coumadin was stopped and Clexane 40 mg injected subcutaneously 12 hourly was started. He was also given oral Phenoxybenzamine 5 mg 6 hourly besides continuing Labetalol for control of blood pressure with regular charting. He had two units of red cell concentrate transfused pre-operatively. He had complete evaluation of his cardiovascular status including ETT by cardiologist besides pre-anaesthesia assessment by anaesthesiologist. Injectable Phentolamine was made available for use in emergency during operation.

A large adrenal tumour was excised through right thoraco-abdominal 10th rib bed approach. In addition, two other nodules were excised from aortocaval groove and posterior abdominal wall separate from the main tumour. Whole of the abdominal cavity was explored for other extra-adrenal tumours. Intra-operative hypertension was controlled by intravenous Nitroglycerine and Phentolamine infusion and hypotension on removal of tumour was controlled by intravenous adrenaline infusion.

Histopathological examination of specimen revealed 8 x 7.5 x 5 cm tumour in adrenal gland weighing 131 grams. Cut surface had variegated appearance with yellow, white and brown colours with areas of haemorrhages in it. Microscopic examination revealed compressed adrenal gland and tumour forming Zellballin patterns and composed of variable sized cells with abundant finely granular basophilic cytoplasm and round nuclei with prominent nucleoli (Figure 2). Nuclear inclusions are also seen. Findings were consistent with malignant pheochromocytoma. Similar microscopic findings were found in the aortocaval lymph node (Figure 3) and in metastatic deposit of posterior abdominal wall lesion confirming metastatic malignant pheochromocytoma originating in right adrenal gland.

Postoperatively, hypotension required dopamine infusion for initial 24 hours, later, he had stable blood pressure. At 3 weeks follow-up, he had well healed scar with normal blood pressure on oral Coumadin 5 mg once daily. Repeat urinary VMA level was 29 µmol/24 hours which was well within the reference range. $^{131}$I MIBG scan to treat micrometastasis was not done due to its non availability in this setup. Till the time of last follow-up, 4 months after surgery, he has remained in good health with stable blood pressure without antihypertensives.

DISCUSSION

The WHO classification of endocrine tumours defines pheochromocytoma as a tumour arising from chromaffin cells in the adrenal medulla. Closely related tumours in extra-adrenal sympathetic and parasympathetic paraganglia are classified as extra-adrenal paraganglionomas. A pheochromocytoma is an extra-adrenal sympathetic paraganglionoma.

Most pheochromocytomas are benign but approximately 10% of them are malignant either at initial surgery or during follow-up. The incidence of metastatic pheochromocytoma is 13-26% with a 5-year survival rate of 50% after the diagnosis is made. Although most cases of pheochromocytomas are sporadic, approximately 20% are part of Multiple Endocrine Neoplasia type II, Von Hippel-Lindau disease or Neurofibromatosis type I (Von Recklinghausens disease). Clinical presentation is highly variable but hypertension is the most consistent manifestation of pheochromocytoma. The hypertension in pheochromocytoma is hyperkinetic, vasoconstrictive and hypovolaemic type. The serious and potentially lethal cardiovascular complications of these tumours are due to the potent effects of secreted catecholamines.

Once pheochromocytoma is suspected, biochemical testing can establish the diagnosis in more than 95% of patients. Readily available biochemical tests include 24-hours urinary fractionated metanephrines (normetanephrines and metanephrines), 24-hours urine catecholamines, plasma concentrations of catecholamines and 24-hours urinary Vanillyl-mandelic acid (VMA). Biochemical confirmation of the diagnosis should be followed by radiological evaluation to locate the tumour.
CT and MRI have 98 and 100% sensitivity respectively, with lower specificities of 70 and 67% respectively. Scintigraphy with $^{131}$I MIBG provides both anatomical localization and functional characterization of the tumour. It has 100% specificity with sensitivity of around 88%.$^{1,6}$ Recently other localization studies have been evaluated including somatostatin receptor scintigraphy with $^{[111}$In DTPA-D-Phe] pentetreotide (Octreoscan) and $^{6}$-[18F] fluorodopamine Positron Emission Tomography (PET) scanning that show less than perfect sensitivity but are superior in detecting metastatic lesions.$^{7}$

There are no reliable histopathological methods for distinguishing benign from malignant tumours. Although extensive invasion of adjacent tissues can be considered an indicator of malignant potential, the presence of metastasis at a non-chromaffin site is the only currently widely accepted means to define malignant pheochromocytoma.$^{3}$ The most common metastatic sites are lymph nodes, bone, lung and liver.

Once malignancy is diagnosed, therapy is generally directed at controlling blood pressure and tumour debulking by surgical excision. Appropriately used calcium channel antagonists and selective $\alpha_1$-receptor blockers are effective and safe. Labetalol, a $\alpha$ and $\beta$ adrenergic blocker is reported to be effective in the control of blood pressure and clinical manifestations of pheochromocytoma$^{8}$ as was used in this case.

Surgery for malignant pheochromocytoma is rarely curative, but resection of a primary mass or metastases can reduce exposure of the cardiovascular system and organs to toxic levels of circulating catecholamines. Alternatives to surgical resection include external beam radiation, cryoablation, radiofrequency ablation and radiopharmaceutical therapy.$^{9}$ To-date the best adjunct to surgery in malignant pheochromocytoma is radionuclide therapy using $^{131}$I-MIBG which is transported into the cell via the cell membrane norepinephrine transporter present on most neoplastic chromaffin cells. Overall about 75% of patients treated with $^{131}$I-MIBG showed improvement, 50% had reductions in hormonal activity and 22% showed objective tumour responses. Its use in combination with chemotherapy may result in additional benefit.$^{10}$

Biochemical testing should always be repeated after surgical resection of a primary mass to exclude any remaining disease or metastases. Normal levels of 24 hours, urinary VMA level excludes presence of metastases or remaining disease as was in present case, however, urinary or plasma fractionated metanephrines estimation is more superior than urinary VMA levels.

It is generally agreed that follow-up should be long-term with yearly biochemical screening.$^{3}$ With emerging molecular markers of malignant disease, optimal extent and approach for surgical treatment and appropriate extent of follow-up can be established based on specific tumour behaviour and need of additional systemic therapy.

REFERENCES