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Spectrum of retroperitoneal and genitourinary paraganglioma: Experience at a North Indian tertiary care center

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Introduction Genitourinary and retroperitoneal paragangliomas are infrequent tumors with bizarre presentation. A high index of suspicion is required to make a diagnosis in young hypertensive individuals. Our aim is to study the varied clinical presentations and management of these paragangliomas. Herein, we share our experience of clinical presentation, diagnosis, and management of these paragangliomas.

Material and methods Seventeen consecutive patients who underwent surgery for paraganglioma at our institute from August 2009 to July 2014 were included. Demographic, peri-operative, surgical, and follow up data were collected and analyzed.

Results Mean age of presentation was 34.8 years with female predominance. The majority of the tumors were located in the retroperitoneum and urinary bladder. Most of them presented with classical symptoms of catecholamine excess and hypertension. Complete surgical resection could be performed in 13 cases. At a median follow up of two years, cases with R0 resection (no microscopic malignant cells) did not show recurrence. Among patients on chemotherapy, one died, another had partial response, and yet another had progressive disease.

Conclusions Genitourinary and retroperitoneal paragangliomas are a disease of a young age group with variable clinical features at presentation. Appropriate pre-operative optimization and complete surgical resection provide the best chance of cure.

Key Words: genitourinary ‹› malignant ‹› paraganglioma ‹› renal ‹› retroperitoneal

INTRODUCTION

Retroperitoneal and genitourinary paragangliomas are rare neuroendocrine tumors arising from sympathetic chain ganglia. They arise from paraganglia, a network of chromaffin producing neural crest tissue that anatomically parallels the sympathetic and parasympathetic ganglia in the head, neck, thorax, abdomen, and pelvis. Clinical presentation is bizarre, requiring a high index of suspicion for diagnosis to avoid catastrophic perioperative complications.

- To study the varied clinical presentations and surgical management of retroperitoneal and genitourinary paragangliomas.
- To identify the role of good perioperative management for optimal outcome of patients who underwent complete surgical resection.
- To address surgical challenges in performing complete surgical resection of these tumors.
- To study post operative course and follow up.

MATERIAL AND METHODS

We analyzed the data of 17 consecutive patients who underwent surgery for abdominal and genitourinary paraganglioma from August 2009 to July 2014 at our institution. All patients were admitted and evaluated by an endocrinologist and a urologist. Serum

Table 1. *Summary of 17 cases*

S no.	Age/ Gender	Site	Size (cm)	Comorbidities	Presentation	Hormonal analysis	Imaging	Surgery	Peri- operative	Remark
1	42/F	Urinary bladder	5×3.5	Nil	Gross hematuria	U. Metanephrine 16 µg/day U. Normetanephrine 178 µg/day	CECT	Partial cystectomy	Uneventful	Diagnosis: Shot in BP while TURBT
2	44/F	Urinary bladder	4×5	Nil	Gross hematuria	P. Metanephrine 20.8 pg/ml P. Normetanephrine 81 pg/ml	CECT	Partial cystectomy	Uneventful	Diagnosis: Shot in BP while TURBT
3	52/M	Urinary bladder Metastatic	10×8	HTN	Classical, Gross hematuria	P. Metanephrine 39.8 pg/ml P. Normetanephrine 1100 pg/ml	CECT DOTATATE	RC with IC	Uneventful	Adjuvant chemo therapy
4	14/M	Urinary bladder and inter-aorto-caval	3.8×3	Nil	Classical, Micturitional headache	P. Metanephrine 73.8 pg/ml P. Normetanephrine 1479 pg/ml	CECT DOTATATE	Mid line Partial cystectomy with excision of inter-aortocaval lesion	Uneventful	
5	16/M	Prostate Metastatic	2.4×2.2	HTN	Classical, Micturitional headache, Obstructive uropathy, LUTS	P. Metanephrine 24 pg/ml P. Normetanephrine 1153 pg/ml	CECT DOTATATE ^{123}I MIBG	RC with CCD	Uneventful	Diagnosis: true-cut Trans-rectal biopsy. Adjuvant chemotherapy
6	26/F	Pelvis	8×6.4	DM, HTN	Classical, Micturitional headache	P. Metanephrines 680 pg/ml	CECT DOTATATE	Lower midline Excision with Partial cystectomy	Uneventful	Mimicking Bladder pheochromocytoma
7	45/F	Pelvis	5×5	Nil	Vague pain lower abdomen	P. Metanephrine 15.3 pg/ml P. Normetanephrine 101 pg/ml	CECT DOTATATE	Lower midline transperitoneal Excision	Uneventful	Explored by gynaecologist for tuboovarian mass, intraop shot in BP
8	40/F	Left Intra-Renal	12×10	DM, HTN	Gross hematuria	N/A	CEMRI	Lt Radical nephrectomy by left subcostal transperitoneal	Uneventful	Diagnosis: intraop shot in BP
9	17/F	Para-aortic	12×10	HTN, HCV+	Classical	P. Metanephrine 27 pg/ml P. Normetanephrine 153 pg/ml	CECT DOTATATE	Lap transmesocolic excision	Uneventful	
10	23/F	Left renal hilar	4×3	HTN	Classical	U. Metanephrine 115 µg/day U. Normetanephrine 7218 µg/day	CECT PET CT EC renal scan	Lap Transmesocolic excision	Uneventful	Renal preservation
11	35/M	Right renal hilar	5×4	Nil	Classical	U. Metanephrine 43.5 µg/day U. Normetanephrine 700 µg/day	CECT PET CT DOTATATE EC renal scan	Midline transperitoneal Excision	Posterior segmental renal artery injured → repaired	
12	36/F	Retroperitoneum, metastatic	8.4×6.4	HTN	Flank pain	P. Metanephrines 660 pg/ml	CECT DOTATATE EC renal scan	Midline transperitoneal R2 Excision with right nephroureterectomy	Dense adhesion to great vessels Intraop IVC injured	Rt lower limb DVT in post operative period
13	53/F	Inter-aorto-caval	12×7.5	HTN	Classical	P. Metanephrines 124 pg/ml	CECT PET CT	Midline transperitoneal Excision	Uneventful	
14	21/M	Retroperitoneum Multiple	8×5 2×2 Multiple subcentimetric	HTN	Pain abdomen	U.metanephrines 338 µg/day	CECT DOTATATE	Midline transperitoneal R2 Excision	Dense adhesion to great vessels	H/O seizures and hemiparesis 2 years ago
15	20/F	Retroperitoneum Multiple	6.8×3.8 5.2×3 Multiple subcentimetric		Classical Headache	P. Metanephrine 20 pg/ml U. metanephrine 139 µg/day U. Normetanephrine 667 µg/day	CECT PET SCAN EC renal scan	Midline transperitoneal Excision	Uneventful	Left poorly functioning kidney secondary to poor flow
16	55/M	Retroperitoneum	6×5	HTN	Headache	U. metanephrines 739 µg/day	CECT DOTATATE	Midline transperitoneal Excision	Uneventful	CABG and Excision in single sitting
17	54/F	Para-aortic	6×4	DM, HTN	Pain abdomen Dyspnea	U. Metanephrine 9.09 µg/day U. Normetanephrine 1967 µg/day	CECT PET SCAN DOTATATE EC renal scan	Left subcostal transperitoneal Excision with nephrectomy	Uneventful	Small nonfunctioning left kidney

P: Plasma, U: Urine, Metanephrines: Metanephrine+ normetanephrine, HTN: Hypertension, DM: Diabetes mellitus, HCV: Hepatitis C virus,EC: Ethylenedicysteine, BP: Blood pressure, TURBT: Trans urethral resection of bladder tumour, RC: Radical cystectomy, IC: Ileal conduit, CCD: Continent cutaneous diversion, CECT: Contrast enhanced computed tomography, CEMRI: Contrast enhanced magnetic resonance imaging, PET: Positron emission tomography, MIBG: Meta-iodobenzylguanidine, DOTATATE: An amide of the acid DOTA, CABG: Coronary artery bypass graft, LUTS: Lower urinary tract symptoms, DVT: Deep vein thrombosis, IVC: Inferior vena cava, Lap: Laparoscopic, N/A: Not Available

and/or urinary free and/or total metanephrine levels were measured in 16 patients. Cross sectional imaging was by tri-phasic CECT of abdomen and pelvis or MRI. ^{18}Fluorodeoxyglucose positron emission tomography(^{18}FDG PET) scan was performed on 5 patients, while ^{68}Ga DOTA-TATEPET was performed on 11 patients. Preoperatively, patients were monitored with at least twice-daily blood pressure measurements (both supine and standing). The target blood pressure was achieved in all patients (except one) with use of sequential α and β blocker for two weeks. All patients were infused 2 litres of normal saline the night before surgery to prevent rebound hypotension in postoperative period as per the institution's protocol. All cases were operated by a single surgeon. Two patients underwent laparoscopic surgery, while the rest were operated by open approach. Follow up data was collected from outpatient department (OPD) visits, telephonic consultations, as well as re-admissions.

RESULTS

Table 1 gives an overview of 17 cases included in our study. Age of presentation ranged from 16 to 53 years with mean age being 34.8 years. Female preponderance was noted (F:M = 3:1). Ten patients had elevated catecholamine levels. Presentation varied according to the site as shown in table 1. The patient with prostatic paraganglioma presented with hematuria, micturitional headache, and hypertension. On subsequent evaluation (CT, DOTATATE, ^{123}I MIBG), he was found to have obstructive uropathy (serum creatinine 3 mg/dl) and solitary metastasis in the left humerus. After bilateral percutaneous nephrostomy (PCN), the serum creatinine became normal and patient was taken for radical cystoprostatectomy with continent cutaneous diversion (CCD).

Another young female presented with classical symptoms having a past history of eclampsia, in which the

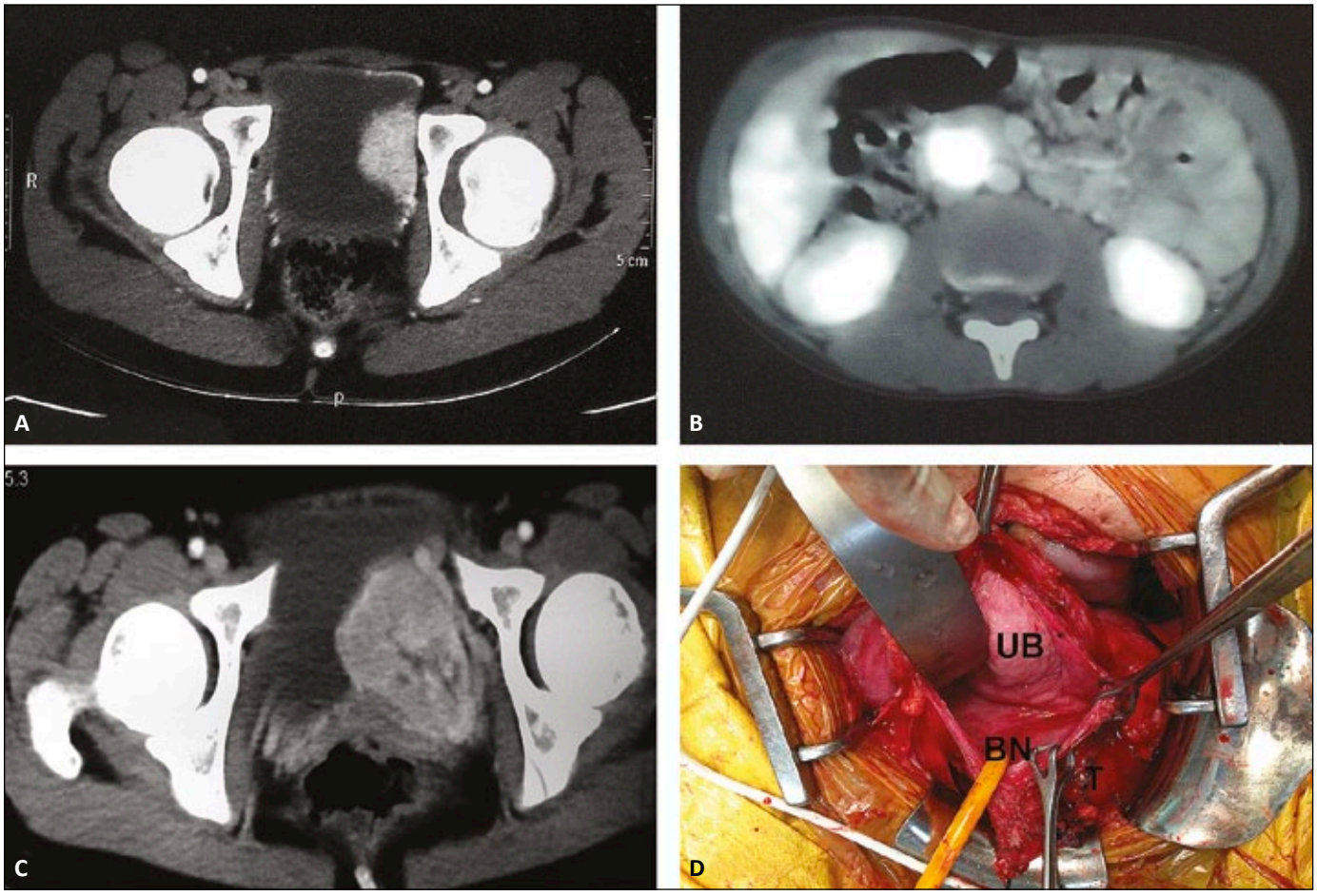

Figure 1. *CECT of abdomen and pelvis showing well enhancing lesion arising from the left lateral wall of the the urinary bladder (a). DOTATATE scan of the same patient showing a second lesion in the inter-aortocaval region (b). Another patient with pelvic paraganglioma mimicking urinary bladder mass on CECT scan (c). Intra-operative photograph of the same patient showing pelvic paraganglioma sparing the bladder wall (d). BN – bladder neck, T – tumor, UB – urinary bladder.*

baby was delivered by caesarean section. On evaluation, she was found to have pelvic paraganglioma seems to involve urinary bladder. This patient was taken up for surgery with the plan of radical cystectomy if needed, but complete excision of lesion could be performed with preservation of the urinary bladder and ureter (Figure 1).

All retroperitoneal cases which underwent open surgery were approached by a midline incision. For two patients with multiple retroperitoneal paragangliomas, small bowel mesentery was lifted up in a manner similar to retroperitoneal lymph node dissection (RPLND). In two patients, lesions were densely adherent to great vessels, retroperitoneum, and sacral promontory, so R2 resection (macroscopic residual tumor) could be performed (Figure 2). In one patient, the lesion was encasing the right ureter with gross hydroureteronephrosis (HDUN) and thinned out renal parenchyma; en-bloc nephroureterectomy was performed (Figure 3).

Mean operative time was 87 minutes (range: 60–240), and 60 minutes in each laparoscopy case. Blood loss ranged from 50 ml to 900 ml, with less loss in both laparoscopy cases. Adjuvant chemotherapy comprising of cyclophosphamide, vincristine, and dacarbazine (CVD) was administered in 3 patients. In the post-operative period, blood sugar level became normal in all functional tumors except one patient with left renal paraganglioma. In the post-operative period, hypertensive drugs were not needed in 5 patients and 6 could be managed with single drug.

Follow up

Follow up data was available for fifteen patients. All patients were advised for follow up with serum/±urine

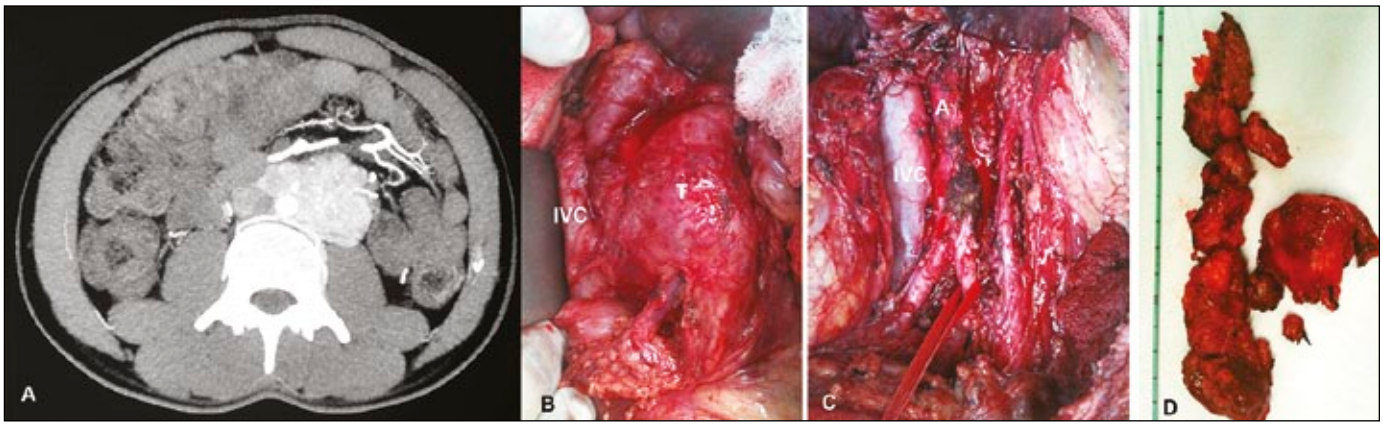

Figure 2. *CECT abdomen showing retroperitoneal paraganglioma with loss of fat planes with aorta (a). Intra-operative photograph showing aortic encasement by the tumor (b). Tumor was densely adherent to the retroperitoneum and aorta and an R_2 resection could be done with preservation of major vessels (c). Gross specimen of the resected tumor (d). A – aorta, IVC – inferior vena cava, T – tumor.*

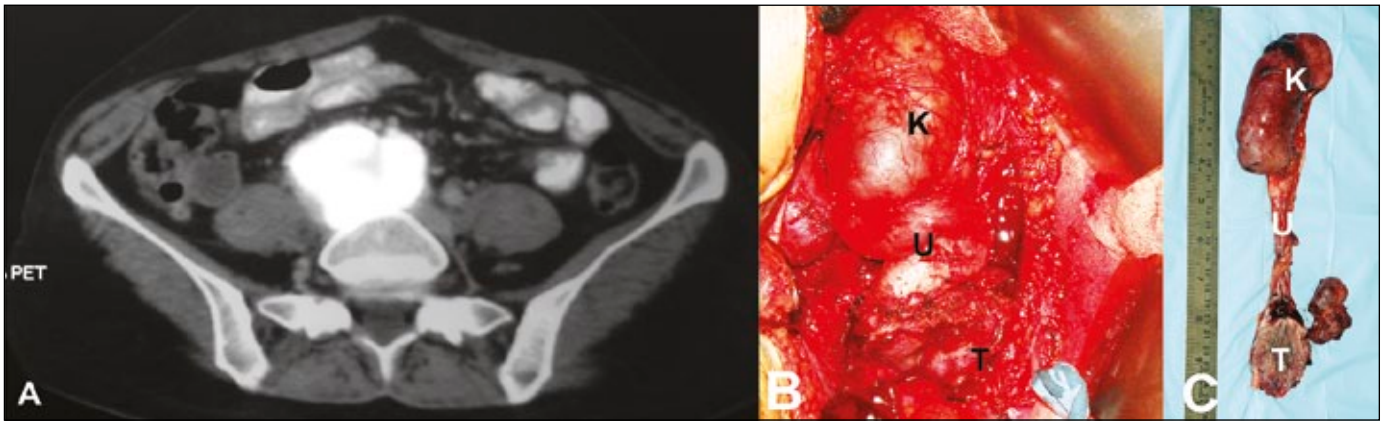

Figure 3. *DOTATATE PET scan of retroperitoneal paraganglioma in pelvis showing good uptake (a). Intraoperative photograph showing gross hydroureteronephrosis on right side secondary to ureteric encasement by the tumor (b). Gross specimen (c). K – kidney, T – tumor, U – ureter*

metanephrines levels yearly and cross-sectional imaging when required. The patient who underwent radical cystoprostatectomy with focal radiotherapy for humeral metastasis and adjuvant chemotherapy, showed partial response at 4 months of follow up. Two other patients on chemotherapy showed disease progression, with one dying a year after radical cystoprostatectomy. Patients who had undergone R0 resection did not show tumor recurrence at a median follow up interval of 2 years.

DISCUSSION

The classic symptoms in functional paragangliomas occur secondary to episodic release of excess catecholamine into circulation. They include headaches, palpitations, anxiety, and diaphoresis. Hypertension can be paroxysmal (48%) or persistent (29%). Blood pressure may be normal in up to 13% of patients. Non-specific symptoms, such as weakness and chronic fatigue, are also quite common confounding the diagnosis of paraganglioma. Due to their bizarre clinical manifestations with a low prevalence, the timely and accurate diagnosis of paragangliomas may be challenging [1–5]. Urologic symptoms, such as episodic hematuria with characteristic headache, hypertension, palpitations, diaphoresis, syncope, or blurred vision after voiding or during cystoscopy, are characteristic of urinary bladder paraganglioma [6, 7, 8]. In this study, the presentations were variable (Table 1). Emphasis on pre-operative diagnosis is needed because in the past, reported mortality rates were up to 50%, when surgery was usually done without prior catecholamine blockade. In the current era, it is less than 3% [9]. Paragangliomas usually occur in the third to fifth decades with equal gender distribution. In our patients, the average age of presentation was 34.8 years, which is same as reported in literature; however, female predominance was noted in a ratio of 3:1. Age of presentation may predict the tumor's catecholamine phenotype and underlying genetic mutation. Patients with an established mutation or hereditary syndrome may manifest at a younger age with an average age of presentation in the third decade, in contrast to those with sporadic disease, who usually present in the fifth decade. Also, epinephrine secreting tumors tend to manifest at a later age [3, 10]. Pelvic paraganglioma can rarely present as non-functioning kidney with accelerated hypertension [11].

Biochemical testing is the first step in the evaluation of patients suspected of pheochromocytoma/paraganglioma. If biochemical tests are positive for high metabolic activity, appropriate imaging is undertaken to localize the source. Though functional imaging is not necessary in the preoperative workup of all paragangliomas, it may be needed to differentiate a paraganglioma from a neurogenic tumor, lymph node disease, or a mesenchymal tumor in the retroperitoneum. Moreover, since genetic status is often not available before surgery, biochemical testing may be considered for large lesions (>5 cms), young age (<40), and multiple lesions [12–16].

On plain CT images, lesions may show uniform attenuation, but in general, they are non-uniform with solid or cystic complex masses and may contain calcification. In contrast phase, these lesions typically enhance avidly, although the cystic area, if any, may remain unenhanced. Urinary bladder paraganglioma appears as a well-defined nonpapillary, well enhancing heterogenous lesion. Paragangliomas usually demonstrate low signal on T1-weighted and high signal on T2- based contrast agents. Cystic degeneration and hemorrhage within these lesions can cause further diagnostic challenges on MR imaging. Intra-renal paragangliomas may mimic renal cell carcinoma on pre-operative imaging [17]. The molecular structure of MIBG resembles that of norepinephrine, showing high affinity for the norepinephrine transporter system. ^{123}I- MIBG causes low radiation dose, superior image quality, and high sensitivity in comparison to ^{131}I-MIBG. Still, because of low sensitivity and specificity, this modality is valuable for familial syndromes with multiple neuroendocrine tumors at different sites, multifocal tumors, and relapsing and metastatic disease [18]. PET provides images with high spatial and contrast resolution, and improved image quality allows for detection of small lesions anywhere in the entire body. The most commonly used radiopharmaceutical for PET is 2-[fluorine18] fluoro-2-de-oxy-D-glucose (FDG)which has poor specificity for pheochromocytomas. To overcome this, noradrenergic transporter systems were targeted by PET tracers. This involves the use of ^{18}F-fluorodopamine (^{18}F-DA), 18F-dihydroxy phenylalanine (DOPA), ^{11}C-epinephrine, ^{11}C-hydroxyephedrine (HED), ^{68}Ga-DOTA compounds, and somatostatin receptor (SSTR) analogues. All these functional imaging studies have shown higher sensitivity and specificity in their initial experiences; however, metastatic lesions could not be picked up well. Data with ^{68}Ga-labeled agonists are still in infancy, but have bee found to be sensitive in the detection of rapidly progressing metastatic paraganglioma, especially in those with no or little avidity for MIBG. We performed ^{18}FDG PET in 5 patients and ^{68}Ga-DOTA PET in 11 patients and lesions were picked up by both. In 2 patients, FDG-PET and DOTATATE PET both were performed and latter was superior for localization [4, 12, 13, 19, 20].

To rule-out cardiomyopathy, preoperative cardiac evaluation and echocardiography is recommended. For catecholamine blockade, sequential α and β antagonists are the most commonly used drugs, alternatives being calcium channel blockers and the tyrosine hydroxylase inhibitor metyrosine. Preoperatively, patients should be monitored with at least twice-daily blood pressure measurements (both seated and standing to evaluate for orthostatic hypotension). In our patients, we used sequential α and β blocker. With regard to anesthetic care, fentanyl, ketamine, and morphine should be avoided because of their potential to stimulate catecholamine release. The use of atropine is discouraged because of its potential to cause tachycardia. Anesthetic gases with the least amount of cardiac depressant effects are preferred, while halothane and desflurane are generally avoided. Higher plasma norepinephrine concentrations, large tumor size (>4 cm) and postural hypotension following α-adrenergic blockade are associated with an increased risk of intraoperative hemodynamic instability. Intraoperative acute hypertensive crises can be managed with intravenous administration of esmolol, sodium nitroprusside, phentolamine (short acting α-blocker), or nicardipine. We used esmolol and sodium nitroprusside infusion because of the rapid onset of vasodilatory properties and shorter duration of action. In cases of atrial and ventricular arrhythmias, intravenous esmolol and lidocaine, respectively, are the agents of choice [2, 3, 7, 21].

Complete surgical excision is central to addressing paragangliomas. In the current era, most of pheochromocytomas and many paragangliomas are being treated with minimally invasive procedures whenever feasible. Laparoscopy is not advisable for locally invasive and/or large tumors or where organ resection is required. Unfortunately, open surgical approaches, although extremely effective, are associated with significant postoperative discomfort and recuperation. Minimally invasive surgical approaches were born out of the desire to address secondary issues related to surgery, including incisional pain, convalescence, and cosmesis. In our patients, only two could be removed laparoscopically, while the rest needed open surgery because of their size, location, and complexity. One patient with left intrarenal lesion was planned for laparoscopy, but attendants and the patient opted for open radical nephrectomy. Trans-mesocolic excision has been reported in literature. In our series, two patients (left renal hilar and paraaortic) were operated laparoscopically by trans-mesocolic approach with great caution to prevent renal vessels and ipsilateral ureter injury. Three ports were placed in each patient. In cases of locally invasive and/or metastatic lesions, options include palliative tumor resection to reduce tumor burden and excess catecholamine related symptoms [22]. Involvement of adjacent organ may require en bloc removal such as in one of our case, where right nephro-ureterectomy was performed because of invasion of the ureter with upstream hydroureteronephrosis and adhesion to the great vessels and retroperitoneum. Left nephrectomy was performed for one patient with left para-aortic paraganglioma with a small nonfunctioning kidney. Bladder tumors with classical symptoms and radiological suspicion should be worked up for paraganglioma. Endoscopically, these tumors appear well circumscribed, solid looking, and solitary, with normal overlying mucosa anywhere in the bladder. In our patients, lesions were solid looking, solitary, and located in the base and trigone region in one, left lateral wall in one, and in the dome region. One was metastatic. For bladder paraganglioma, partial or radical cystectomy with pelvic lymph node dissection is the treatment depending upon size and location of lesion. We were able to save the bladder in two patients. Pelvic paragangliomas may appear arising from the urinary bladder on pre-operative imaging. Intra-operative identification of this scenario shall prevent inadvertent injury to urinary bladder with complete surgical excision [23]. In females, it is a rare, but very important, differential diagnosis of a tubo-ovarian mass [24]. Retroperitoneal multiple lesions are among the most difficult cases for surgery in the view of vicinity and adherence to great vessels and their branches. In our series, two retroperitoneal tumors could not be removed completely [4, 8].

Hypotension and hypoglycemia are the most common immediate postoperative complications. Patients need continuous intraoperative vital and blood sugar monitoring and for at least 48 hours following surgery.

Data regarding follow up is scarce. Recent reviews suggest lifelong follow-up of patients with extra-adrenal pheochromocytoma, with yearly follow up in the initial 10 years [3]. Evaluation at follow up includes history and physical examination, blood pressure measurement, catecholamine level testing, and cross sectional imaging.

For patients with metastatic disease or incomplete excision, options include CVD regimen (cyclophosphamide 750 mg/m^2 body surface on day 1, vincristine 1.4 mg/m^2 body surface on day 1, and dacarbazine 600 mg/m^2 body surface on day 1 and 2, repeated every 21 days). However, benefits of CVD therapy for metastatic pheochromocytoma appears to be short-term and do not include an increase in patient survival. Other options are temozolomide, temozolomide with thalidomide, or targeted radio-

therapy with ^{131}I-MIBG. Treatment of metastatic and inoperable paragangliomas with mTOR inhibitor, tyrosine kinase inhibitors, and interleukins are under trial [2, 25].

CONCLUSIONS

1. Paragangliomas are very infrequent lesions with bizarre presentation and wide area of location. If taken for surgery without diagnosis and preparation, high risk of catastrophic events may happen secondary to hypertensive crisis.
2. One should have high index of suspicion for paraganglioma in cases of retroperitoneal lesions with hypertension in young middle age
3. In case, clinical presentation and imaging suggestive of bladder paraganglioma, complete workup for paraganglioma is advised.
4. Chemotherapy has guarded efficacy in these cases.
5. Complete surgical resection by experienced surgeon provides the best chance of cure.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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