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ORIGINAL ARTICLE

Re-operative Surgery for Pheochromocytoma-Paraganglioma: Analysis of 13 Cases from a Single Institution

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Abstract Re-operative adrenal surgery for recurrent pheochromocytoma/paraganglioma (PCC/PGL) is a therapeutic situation not commonly encountered. The recurrence rate of pheochromocytoma is estimated to be 6.1–16.5% of patients from published retrospective series; there are no reports from the Asian continent. A retrospective analysis of the departmental database was performed on patients who had undergone surgery for PCC/PGL from January 2004 to December 2014 at the Christian Medical College Hospital, Vellore, India. Among 99 patients identified during the study period, there were 14 recurrent tumours and 13 patients underwent re-operative surgery. We located eight recurrences on the right side, three on the left side and three in the midline. All 14 recurrences were functioning, and the biochemical analysis as well as imaging studies were positive in 13 of them. The mean duration to recurrence from the time of the primary surgery was 76.3 months (range 6–180 months). Of the 89 patients who underwent their first operation at our centre, 67.4% reported for follow-up for a mean period of 25 months (range 4–132 months). Four of these required re-operation with a recurrence rate of 4.5% (4/89). The open approach was used for all but one of the recurrent tumours. Recurrence following surgery for PCC/PGL is a rarely studied though significant problem. Right adrenal tumour recurrences were most common, and all these recurrences were in the retrocaval region; this typical phenomenon may be dubbed the 'right retrocaval trap'. The reason for this was presumably due to difficult access and inadequate exposure of this area in open and laparoscopic surgery, resulting in incomplete dissection.

Keywords Re-operation · Pheochromocytoma · Paraganglioma · Adrenal · Surgery · Recurrence

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Introduction

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are neuroendocrine tumours that secrete excess catecholamines that cause hypertension and other effects which require specialized skills in diagnosis and treatment. The tumours are typically well defined and benign though the remote anatomical location can present a challenge for operative access. Currently, laparoscopic transperitoneal or posterior retroperitoneoscopic approaches are the standard of care except for the rarer large, infiltrative tumours when the open approach is preferred. Familial syndromes may cause multiple tumour formation in adrenal and extra-adrenal sites which need to be assessed carefully on preoperative imaging and at surgery. Re-operative surgery for recurrent PCC/PGL is an uncommon situation that presents with unique difficulties and is infrequently reported in the literature; this is the first known report from a centre in Asia.

Many early publications prior to 1980 have reported outcomes of surgery for a small series of pheochromocytoma. We reviewed six reports published after 1980 wherein the recurrence rate of PCC/PGL ranged between 6.1 and 16.5% [1–5]. Amar et al. from the Pompidou Hospital, Paris, reported a 16.5% recurrence at 10 years in 192 patients; familial, right adrenal and extra-adrenal tumours in younger patients were

more frequently recurrent [1]. Plouin et al. analysed 129 patients with pheochromocytoma at the Broussais Hospital, Paris, and found seven benign and nine malignant recurrences (14%) in their series of 114 patients at risk [2]; recurrence was more common in large (>5 cm), bilateral and extra-adrenal and familial tumours. Van Heerden et al. from the Mayo clinic in Rochester identified six local and distant recurrences (6.1%) in 98 patients who were followed up after excision of PCC/PGL [3]. The recurrences occurred 5 to 13 years following initial resection. Shen et al. identified seven recurrences in 102 patients who were treated for pheochromocytoma, estimating their recurrence rate to be 6.8% [4]. The mean time between primary operation and the development of recurrence was 6 years. Three patients with recurrences died of the disease. Press et al. had eight recurrences (5.9%) in 135 patients with adrenal pheochromocytoma [5]. On multivariate analysis, a tumour size more than 5 cm was an independent factor for recurrence. Pruszczyk et al. from Warsaw identified four benign and four malignant recurrences (13.1%) from 61 patients available with a mean follow-up of 79 months [6].

Methods

We analysed the retrospective records of patients who underwent surgery for PCC/PGL from December 2004 to December 2014 at the Christian Medical College Hospital, Vellore. These patients were diagnosed to have PCC/PGL based on biochemical tests and cross-sectional and nuclear imaging before surgery. Details of demographics, clinical presentation, biochemical assessment, imaging tests, pathology and follow-up were reviewed. For the study, a cure was defined as normalisation of symptoms or biochemical tests after resection at a 1-year follow-up; it is well recognized, however, that recurrences can occur many years after surgical resection and apparent cure. The review was approved by the institutional review board of our hospital (Ref: IRB No. 8907 [RETRO], dated 23 April 2014).

Results

There were 99 patients identified who underwent surgical treatment for PCC/PGL from a total of 230 patients operated for adrenal tumours in the study period. There were 56 male and 43 female patients. The mean age of the patients was 35.6 (16–68) years. The tumours were located in the adrenal gland in 74 patients, in the extra-adrenal paraganglia in 20 patients and in the adrenal and extra-adrenal paraganglia in 5 patients. Of the unilateral tumours, 45 were right sided and 32 were left sided. The tumour was malignant in nine patients. Open surgical approach was used in 64 patients, and minimally invasive techniques were used in 35 patients. Laparoscopic transperitoneal adrenalectomy was introduced in 2007 and posterior retroperitoneoscopic adrenalectomy in 2011. Sixty patients out of the 89 who had the index operation at our centre were available for follow-up (mean 25 months; range 4–132 months) with four observed recurrences (4.5%). Ten patients had a recurrence after an operation at another centre, making a total of 14 patients who presented with a recurrence of PCC/PGL (Table 1). The mean duration to recurrence from the time of the first operation for all recurrent lesions was 76.3 months (range 6–180 months). All patients with recurrent lesions had functioning PCC/PGL. The cross-sectional and nuclear imaging was positive in all patients with recurrence.

The right adrenal gland was the commonest site of recurrence with eight in the right adrenal bed/retrocaval region, three on the left side and three in the midline. Right-sided recurrence was more common than left, as reported earlier [1]. There was no documentation of breached capsule or tumour spillage in the operative records available.

Four of the 14 patients had a recurrence of malignant disease. Two patients expired at surgery or in the immediate postoperative period; one had an invasive recurrent aortocaval paraganglioma, and the second patient had a large 20-cm left-sided adrenal bed malignant invasive tumour. Two other patients with malignant disease recurred with distant metastasis after re-operation. Ten out of the 14 patients had benign disease. Six patients were apparently cured after re-operation with normal urinary metanephrines at 1 year or more. Three were lost to follow-up. One had an inoperable disease and was managed non-operatively.

Discussion

Various factors were identified to have led to recurrence. The major finding of the study was right-sided recurrence of benign disease, which occurred in eight of the 14 cases. On review of the imaging and operative details, there was a residual adrenal tumour in the retrocaval region in all eight cases; the phenomenon could be aptly named ‘the right retrocaval trap’. This problem is potentially avoidable by careful assessment of anatomical relationships and extent of tumour on cross-sectional imaging in the preoperative planning and adequate surgical access ensuring good visual assessment of the posterior tumour during dissection to ensure complete dissection. Though some concerns could be raised about the minimally invasive approach with regard to completeness of dissection, this analysis shows that all ipsilateral recurrences occurred after open surgery. This may reflect the fact that visualization is better with the magnified view through the endoscope, and often, adrenal surgery is undertaken by the more experienced surgeons and, possibly, the temporal profile of the study with longer follow-up in open cases. The adrenal gland tends to enlarge behind the inferior vena cava (IVC) as the

Table 1 Recurrent pheochromocytoma characteristics, treatment and outcome

Age/sex	Genetic syndrome/ mutation	Primary operative approach	Location of recurrence	Time to recurrence (months)	Present size (cm)	Current treatment	Current operative approach	Outcome
26/M (Fig. 1)	Not done	Right open	Retrocaval	18	3.7	Portal vein embolization followed by surgery	Right open	Cured
26/M (Fig. 2)	Absent	Right open	Retrocaval with IVC infiltration	144	7	Surgery	Right open	Recurrence in retrocaval region 4 years later
55/M (Fig. 3)	SDHB exon 2 c.200+ 33 G>A	Right open	Retrocaval	156	3	Surgery	Bilateral subcostal	Cured
53/F	RET 16 mutation codon 918 ATG-ACG (MEN IIB)	Bilateral open	Retrocaval	168	6	Surgery	Right open	Lost to follow-up
27/F	Not done	Right open	Retrocaval, extra-adrenal (right thorax)	11	4	Surgery	Right open	Cured
68/F	Absent	Right laparoscopic	Retrocaval, extra-adrenal	24	2	Surgery	Bilateral subcostal	Lost to follow-up
41/M	Not done	Right open	Retrocaval	180	6	Surgery	Bilateral subcostal	Cured
58/F[a]	Absent	Right laparoscopic	Missed opposite adrenal	6	1.5	Surgery	Left laparoscopic	Cured
23/M[a]	Absent	Left open	Aortocaval between two duplicate IVC	12	2.5	Surgery	Open	Lost to follow-up
58/M	Absent	Right open	Retrocaval, multiple extra-adrenal, retroperitoneal, distant metastasis	60	2	Ablation followed by surgery	Laparoscopy converted to open	Metastasis that was excised 5 months later; recurrence 20 m later in the abdominal wall
32/M[a]	Not done	Right open	Retrocaval, Opposite extra-adrenal	72	5	Surgery	Bilateral subcostal	Metastasis
22/M	Not done	Laparotomy	Aortocaval	36	7	Surgery	Open	Died
39/F	Not done	Left open	Adrenal bed	60	14	Surgery	Left open	Died
50/M[a]	Not done	Bilateral subcostal	Left adrenal bed	122	3.3	Inoperable, planned for ablation	NA	Awaited

[a] Patients who had their primary operation in our department

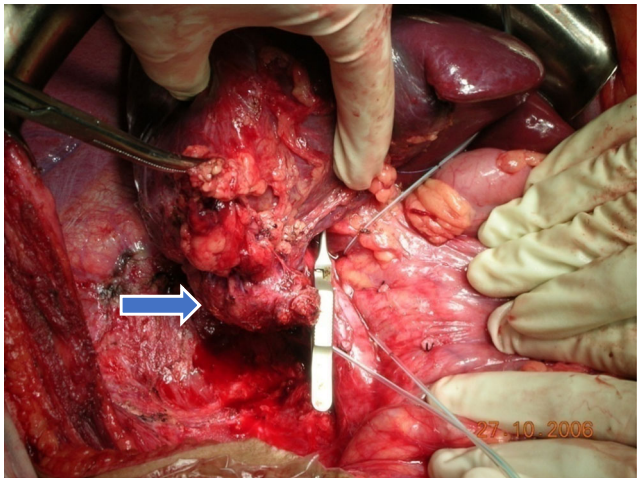

Fig. 1 Intra-operative finding after mobilising the right lobe of the liver. The *blue arrow* shows the tumour adherent the inferior vena cava and the right lobe of liver

IVC is collapsible and allows a plane of the least resistance in a space enclosed by a less compliant liver and kidney. This retrocaval area is difficult to access in open surgery, and the capsular breach is difficult to recognize intra-operatively; hence, incomplete dissection is the likely cause of recurrence rather than missed extra-adrenal tumour or invasive malignant disease (Figs. 1, 2 and 3).

All patients who presented with an apparently unilateral lesion were assessed for the presence of a contralateral lesion. This was not detected on nuclear imaging in one patient with a dominant functioning adrenal gland that suppressed the contralateral uptake, and a small 1.5-cm lesion which was overlooked on initial CT scan. Later, it was made out on a review of the original CT scan taken at the time of the first follow-up when urinary metanephrines were noted to be still elevated. Interestingly, this patient had no features of familial disease and therefore reinforces the need for careful assessment of cross-sectional imaging in all cases.

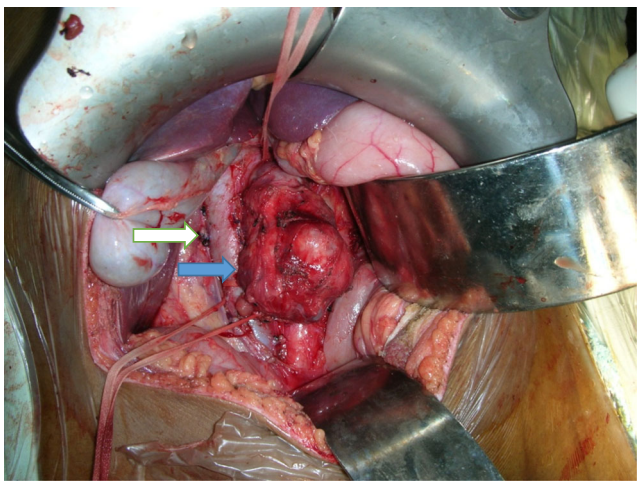

Fig. 2 Intra-operative photograph of the mass in the retrocaval region after mobilization (*blue arrow*). The IVC and the left renal vein are taped

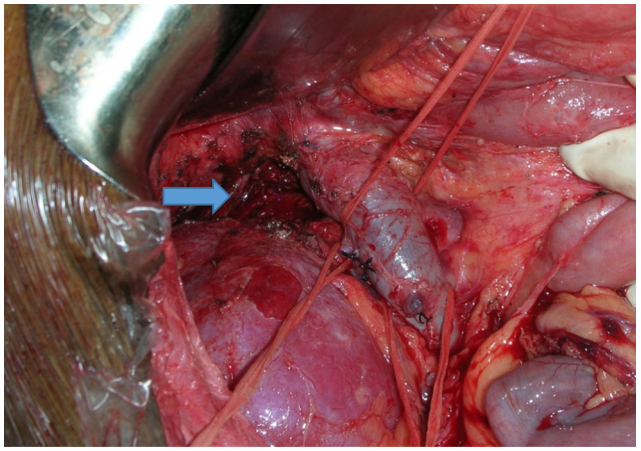

Fig. 3 Tumour bed after excision of mass (*blue arrow*). The aortocaval region was explored for paraganglioma, but no tumour was found

The recurrence was diagnosed in all except one patient by clinical presentation and biochemical analysis and subsequently confirmed by imaging. Only one patient had normal biochemical levels. This is a lower rate than that of a previous study that showed that up to 25% of the recurrences had normal biochemical levels [5].

Six out of the ten patients with recurrent benign lesions were apparently cured by the re-operation on follow-up; three patients were lost to follow-up and one was managed non-operatively.

One patient underwent re-operation for local recurrence after prior debulking surgery on three occasions and ^{131}I-MIBG ablation therapy twice at other centres for a pre-aortic

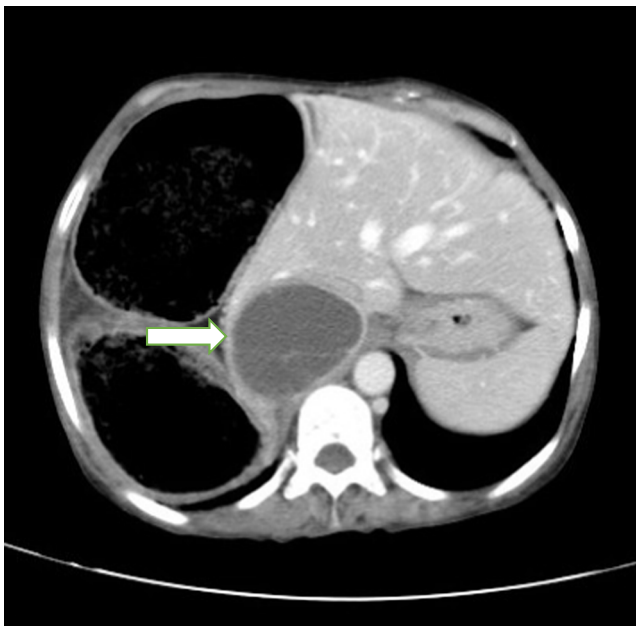

Fig. 4 Fifty-three-year-old lady, diagnosed to have MEN 2B, with a 6-cm cystic lesion in the retrocaval region with enhancing septa and wall enhancement (*white arrow*); also seen are grossly dilated large bowel due to the aganglionic segment

large paraganglioma. He sustained IVC injury and air embolism with intra-operative mortality. A second patient had a 14-cm malignant pheochromocytoma infiltrating the liver that was deemed hazardous to attempt resection. The abdomen was packed, and the procedure was abandoned. The pack was removed after 4 days. Subsequently, that patient was offered palliation alone and expired 3 days after the second laparotomy due to fulminant sepsis. These two cases highlight the potential perils of redo surgery for malignant disease.

We calculated our own recurrence rate to be 4.5% (4/89) which is possibly artificially low with only a 62.5% follow-up including one local recurrence and two contralateral recurrences. Although all patients are advised yearly follow-up, long distances and financial constraints prevent regular follow-up.

Genetic analysis for familial syndromes has been available since 2009 at our institute. We have published the results in an earlier paper [7]. We analysed the rate of familial syndromes by genetic analysis for seven of the 14 cases with recurrence and identified two—SDHB and MEN 2—syndromes. On closer analysis, the recurrence in both cases was of the right retrocaval origin (Fig. 4). Thereby, this indicated that technical causes, and not new lesions because of genetic predisposition, were the cause of recurrence.

The limitations of the study were its retrospective nature, non-uniform genetic screening and suboptimal follow-up at our institution, which may reflect on the apparently low recurrence rates.

Conclusions

Recurrence is a common complication of surgery for PCC/PGL though rarely reported. However, the incidence can be reduced by careful planning and meticulous dissection. Contralateral or extra-adrenal lesions must be carefully looked for on imaging. The retrocaval extension of a right-sided pheochromocytoma must be handled carefully, by excising the lesion completely after adequate exposure, to avoid local recurrence. Malignant disease is a challenging clinical situation, though fortunately uncommon and recurrence appears inevitable with the current available therapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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