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ORIGINAL ARTICLE

Minimally invasive cortical-sparing surgery for bilateral pheochromocytomas

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Abstract
Introduction Cortical-sparing adrenalectomy in bilateral pheochromocytomas offers a postoperative corticoid-free course and has to be balanced against the risk of local recurrence. In this study we report our experience with the minimally invasive cortical-sparing adrenalectomy in patients with bilateral pheochromocytomas.
Methods From January 1996 to February 2011, 66 patients (45 men, 21 women; mean age 36±16 years) were treated for bilateral pheochromocytomas. Fifty-seven patients (88%) were affected by genetic diseases. In 32 patients surgery was synchronously performed on both side, in 34 cases adrenalectomy followed previous surgery. All in all, 101 operations (47 right, 54 left) were conducted using the retroperitoneoscopic access (n=97) or the laparoscopic route (n=4).
Results The mortality in our series was zero. Postoperative complications included one patient with a bleeding requiring reoperation and one patient developing a cerebral stroke on the fifth postoperative day. The mean operative time was 67±26 min for unilateral adrenalectomy and 128±68 min for bilateral surgery (range 25–300 min). A cortical-sparing resection was possible in 89 procedures resulting in a corticoid-free postoperative course in 60 patients (91%). A postoperative corticosteroid substitution therapy was necessary in six patients. During a median follow-up period of 48 months, one patient showed a persistent disease and needed reoperation, none developed a recurrent disease.
Conclusion Cortical-sparing surgery for bilateral pheochromocytomas has a low recurrence rate and avoids lifelong cortisone substitution therapy in the majority of cases.

Keywords Pheochromocytoma · Adrenalectomy · Cortical-sparing adrenalectomy · Bilateral pheochromocytomas · Bilateral adrenalectomy · Adrenal

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Introduction

The first description of a patient with bilateral pheochromocytoma is dated back to 1886. Felix Fränkel alludes a case of an 18-year-old girl who suddenly collapsed and died. Her symptoms include the classical clinical manifestation of chromaffin tumors: "she had a 1-year history of recurrent episodes of palpitations, headaches, vomiting, pallor accompanied by a strong pulse, and retinitis" [1, 2]. This first patient suffered from multiple endocrine neoplasia type 2A syndrome exemplifying that bilateral pheochromocytomas are most often encountered in the setting of familial diseases [2, 3]. Today, nine genetic diseases that

may cause the development of pheochromocytomas are defined. These are: multiple endocrine neoplasia type 2 (MEN 2), von Hippel–Lindau syndrome (VHL), von Recklinghausen's neurofibromatosis (NF-1), pheochromocytoma–paraganglioma syndromes associated to mutations of the succinate dehydrogenase enzyme complex (SDHA, SDHB, SDHC, SDHD), and pheochromocytomas in conjunction with recently described mutations (TMEM127 and MAX). In these disorders, the penetrance of pheochromocytomas ranges from 14% to 50% [1, 3], and bilateral adrenal pheochromocytomas occur in 10–80% of index patients [4].

In 1918, an experimental study in guinea pigs demonstrated survival after resection of 3/4 to 7/8 of the adrenocortical tissue [5]. The first case of a bilateral partial adrenalectomy in a human was described in 1934 by Decourcy for treatment of arterial hypertension [6]. In 1946, Broster performed partial adrenalectomies on bilateral tumors in a 9-year-old child affected with pseudohermaphroditism [7]. Adrenal hyperplasia was diagnosed intraoperatively, and resection of 2/5 of adrenal tissue on both sides was considered the only hope for relieving the disease. Partial adrenalectomy for bilateral pheochromocytomas even if already performed about 30 years ago [8, 9] never gained a worldwide consent. Indeed, the conventional surgical strategy for patients with bilateral tumors has been bilateral total adrenalectomy [10]. This strategy minimizes the risk of recurrence but is associated with a lifelong corticosteroid therapy and its possible complications, from Addisonian crisis even to death [10, 11]. Partial adrenalectomy offers the advantage of avoiding complications related to excessive catecholamine secretion by removing tumors and at the same time to presumably avoid the postoperative cortisone supplementation therapy. This strategy should be balanced with the risk to develop recurrent disease. Minimally invasive adrenal surgery due to the precise dissection and the magnification of the endoscope offers the best prerequisite for improving the use of cortical-sparing tumor resection [12]. Since 1994, retroperitoneoscopic adrenalectomy has been developed and systematically adopted for removal of adrenal tumors by us [13]. Partial retroperitoneoscopic adrenalectomy has been demonstrated to be safe and effective for hormonally active as well as inactive adrenal tumors [14–17]. In this study we report our experience on patients affected by bilateral pheochromocytomas focusing on the role of cortical-sparing surgery and the risk of local recurrence.

Patients and methods

In the period between January 1996 and February 2011, 66 patients with bilateral pheochromocytomas were referred. Fifty-seven patients suffered from inherited diseases (Table 1). Thirty-four patients (21 men, 13 women; mean age 34±14 years) had bilateral tumors at the time of presentation and underwent a synchronous (32 cases) or subsequential (two cases) operation on both sides. Two of them had undergone a previous unilateral partial adrenalectomy (open anterior and open posterior, respectively). Thirty-two patients (23 men, 9 women; mean age 36.5±17 years) had at least one previous operation and 9 of them suffered from ipsilateral persistent or recurrent disease (Table 2). Eight patients of the latter had had an anterior approach previously (laparoscopic or open); two patients had had two and three exploration on the right side, respectively. One patient underwent a previous posterior partial adrenalectomy. In two patients previous histopathology showed a potentially malignant

Table 1 Characteristics of 66 patients with bilateral pheochromocytomas

Age (years)	36±16		
Gender	45 male, 21 female		
	Yes		No
Hereditary disease (*n*)	57	29 VHL 18 MEN 2A 3 MEN 2B 3 SDHD 2 NF-1 2 TMEM127	9
Previous adrenal surgery (*n*)	34	11 ipsilateral 23 contralateral	32

VHL von Hippel–Lindau syndrome, *MEN* multiple endocrine neoplasia, *NF-1* neurofibromatosis type 1, *SDHD* pheochromocytoma–paraganglioma syndrome due to heterozygous mutations of the succinate dehydrogenase enzyme complex (subunit D), *TMEM127* transmembrane protein 127

Table 2 Pattern of previous adrenalectomies in 34 patients with previous ipsilateral (*n*=11) or contralateral (*n*=23) pheochromocytomas

Previous procedure(s)	Total adrenalectomy	Partial adrenalectomy
Open adrenalectomy	13 unilateral 1 bilateral[a]	4 unilateral 4 bilateral[b]
Laparoscopic transabdominal adrenalectomy	10 unilateral 1 unilateral[c]	1 unilateral[c]
Retroperitoneoscopic adrenalectomy	–	1 unilateral

[a] One patient developed a recurrent unilateral pheochromocytoma though total bilateral adrenalectomy had been described as the first surgery

[b] Two patients were operated twice and three times on the right side, respectively

[c] This patient underwent bilateral surgery, partial on one side

disease due to the strong adhesions of the tumor to the surrounding tissue. Fifty-five patients received α-adrenergic blockade (phenoxybenzamine 0.9–4.3 mg/kg body weight p.o.). Since 2008 this strategy was modified as medical pretreatment has been individualized. Therefore, 11 patients have been operated without preoperative α-blockage. Informed consent was obtained prior to surgery in all cases.

Altogether, 101 adrenal procedures were performed (47 right and 51 left). The posterior retroperitoneoscopic approach was used in 97 procedures including the ten patients with ipsilateral recurrent pheochromocytomas. The surgical technique of retroperitoneoscopic adrenalectomy has been described previously [18] and has recently been modified for single-access surgery [19]. In four selected operations, the laparoscopic transabdominal anterior approach was used due to tumor diameter (12 cm, one case), recurrent disease after two previous operations (one case), or concomitant removal of infrarenal paragangliomas (two cases), respectively. Partial adrenalectomy was performed whenever possible and defined as sparing of at least one third of one gland. Partial adrenalectomy was planned based on the preoperative findings of magnetic resonance imaging (MRI) and/or computed tomography (Fig. 1). In six cases the operation was performed simultaneously on both sides by two surgical teams.

Corticoid administration was not used during surgery. Postoperatively, corticoid supplementation was administered after complete bilateral adrenalectomy or if clinical signs of hypocortisolism developed. This scheme has been published previously [17]. Postoperatively, patients were treated at the intensive care unit (n=7) or the normal ward (n=59) depending on general experiences or individual comorbidities. Oral intake as well as mobilization were started immediately after the operation. Postoperatively, intravenous fluids administration was not used routinely. Blood pressure was controlled five times a day and a clinical examination performed twice daily to exclude Addisonian symptoms.

A prospectively maintained database including age, gender, previous medical history, tumor size and side, operating time (defined as skin incision to skin closure) and type or surgery (total or partial resection), intra- and postoperative complications, histopathology, postoperative therapy, and duration of hospital stay. Follow-up data were obtained by contacting the general physician or the referral endocrinologist. Persistent and recurrent diseases were defined as biochemical and/or radiological evidence of pheochromocytoma within or after 3 years following surgery, respectively. For statistical analysis continuous variables were expressed as means±standard deviations. Between group differences were assessed by the Mann–Whitney test. The significance level was set at $p<0.05$. Data were analyzed using Prism 5® (Graph Pad Software, Inc.).

Results

All procedures were completed by the minimally invasive approach without mortality. Postoperative complications included one bleeding after partial adrenalectomy requiring re-retroperitoneoscopy to evacuate hematoma on the first postoperative day, two cases of segmental relaxation, two cases of hypoesthesia of the abdominal wall, and one case of cerebral stroke which developed on the fifth postoperative day.

Eighty-nine partial and 12 total adrenalectomies were performed (Table 3). In five patients the estimated adrenal remnants was <15% (range 0–100) of the complete bilateral tissue, in 45 patients the remnants' size was between 15% and 50%, and in 16 patients above 50%. The main adrenal vein was preserved in 27 (30%) partial adrenalectomies. Eight patients (12%) underwent synchronous resection of a retroperitoneal paraganglioma. The mean operative time

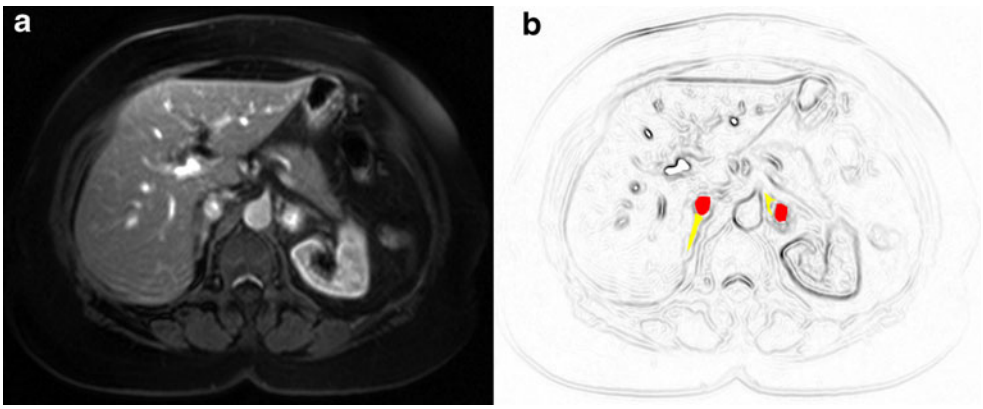

Fig. 1 Bilateral pheochromocytomas prior bilateral partial adrenalectomy (VHL patient). **a** MRI (T2 weighted). **b** *Red* tumors, *yellow*, normal adrenal tissue (from [31])

Table 3 Surgical procedures in 66 patients with bilateral pheochromocytomas

Extent of adrenalectomy	Bilateral tumors (n=34)	Unilateral tumors[a] (n=32)
Bilateral total	–	–
Unilateral total and contralateral partial	9	–
Bilateral partial	25	–
Unilateral total	–	3[b]
Unilateral partial	1[c]	29[d]

[a] After previous contralateral (n=26) or bilateral surgery

[b] After previous partial adrenalectomy

[c] Persistent disease after previous bilateral partial adrenalectomy

[d] Two patients were operated twice and three times on the right side, respectively

was 67±26 min (range 40–120 min) for unilateral adrenalectomy and 143±73 min (range 55–385 min) for consecutively removed bilateral pheochromocytomas; the median operative time for simultaneously removed bilateral pheochromocytomas was 85±43 min (range 40–155 min). The mean intraoperative blood loss was 22±43 ml (range 0–300 ml).

Histopathology showed benign pheochromocytomas in all cases (tumor diameter 2.7±1.6 cm; range 0.4–12 cm) including in those two patients with prior suspicion of malignancy. Mean tumor size was larger in total adrenalectomies (4.3 cm, range 1.5–12 cm) compared to partial adrenalectomies (2.8 cm, range 0.4–8 cm; p=0.1). In the subgroup of ipsilateral persistent or recurrent pheochromocytomas (n=11), the mean interval between the first and the second surgical procedures was 15.3±11.5 years. In two VHL patients, a persistent disease has to be assumed as the second ipsilateral tumor was diagnosed within the first 3 years. The other nine defined as recurrent lesions were removed in five VHL patients after 9, 12, 19, 27, and 28 years and in three MEN 2A patients after 12, 17, and 37 years; in one case (unknown genetic disorder), the recurrence was diagnosed 4 years after previous surgery. A second partial adrenalectomy was possible in 7 of 11 patients. In ten cases retroperitoneoscopic removal was used and required an operating time of 77±35 min. One tumor was removed by laparoscopy.

Postoperative corticosteroid substitution therapy was necessary in six patients (9%). Two of these patients underwent bilateral surgery (cortical sparing on one side), three patients underwent completion unilateral adrenalectomy after bilateral surgery, and one patient underwent partial adrenalectomy after previous total adrenalectomy on the contralateral side. During a median follow-up period of 48 months (range 3–183 months), one patient showed a persistent disease and needed reoperation, none developed a recurrent disease.

Discussion

To the best of our knowledge, this study presents the largest cohort of patients with bilateral pheochromocytomas treated with the intention to preserve adrenocortical function. Finely, corticoid supplementation could be avoided in 60 of 66 patients (91%). For maintaining adrenocortical function, one third of one gland (about 15% of both the adrenal glands' cortical tissue) had to be preserved. This threshold has been described by others [20, 21] and us [22] and has been confirmed with the presented data. Only 1 of 61 patients with more than 15% preserved tissue developed signs of hypocortisolism postoperatively but all 5 patients with less than 15% adrenal tissue needed corticoid supplementation. During the hospital stay, a postoperative plasma cortisol measurement or a stimulation test with tetracosactrin has not been performed routinely. The latter can be proposed for selected cases if clinical symptoms are equivocal and during the follow-up to evaluate the stress competence of the patients, even if interpretation of the results is often controversial [24].

An observed but up to now not explained phenomenon is that most pheochromocytomas arise near the origin of the main adrenal vein. Therefore, partial adrenalectomy in pheochromocytomas often means dissection of the main vein as we experienced in 70% of our operations.

Up to now it is not known whether partial adrenalectomy may include an increased risk of recurrence in malignant pheochromocytomas. In our series we did not notice any malignant case as others did in bilateral pheochromocytomas [23, 24]. As “partial adrenalectomy” basically means complete extirpation of the pheochromocytoma (without cell spillage by rupture of the tumor capsule), an increased rate of local recurrence seems extremely hypothetical.

Our favorite approach for adrenal surgery is the posterior retroperitoneoscopic access. It offers short operating times and minimal postoperative morbidity [18, 25]. In bilateral tumors repositioning is not necessary and even single-access techniques are part of the repertoire [19, 26]. Furthermore, two-team simultaneous surgery is possible with the patient in a prone position [27]. As a side effect, iatrogenic peritoneal pheochromocytomatosis can be avoided by staying in the extraperitoneal space [28]. Another technical aspect concerns the dissection of the adrenocortical tissue. By using monopolar hooks as well as bipolar clamps or ultrasound-driven shears, one postoperative bleeding occurred. The latter had to be treated by retroperitoneoscopic reoperation on the first postoperative day. The site of bleeding was an arterial branch of the adrenal remnant. Other surgical-related complications were not observed.

The concept to preserve adrenocortical function by partial adrenalectomy in bilateral pheochromocytomas has

been introduced about three decades ago [8, 9, 29]. Afterwards, cortical-sparing adrenal surgery was reported in small series [24, 30] followed by our first report of two cases treated by a minimally invasive approach in 1996 [13]. Meanwhile it could be demonstrated in a collective series of 179 patients (including our first 24 patients) that the success rate of function-preserving surgery in bilateral pheochromocytomas is about 86% [31]. Certainly, the eventuality of ipsilateral recurrence in the adrenal remnant has to be taken into account after partial adrenalectomies as most patients suffer from genetic diseases.

Today, data are still confusing regarding ipsilateral or contralateral recurrences and their relation to the underlying genetic disorders. Nevertheless, patients with MEN 2A syndrome have been the most intensively studied group. In 1983, Tibblin and colleagues reported the results after total unilateral adrenalectomy in 13 patients affected by MEN 2A. Four of them (31%) developed contralateral recurrence after a mean follow-up of 6 years. Laimore et al. reported a risk of 52% (12 out of 23 patients) to develop a contralateral tumor a mean of 11.8 years after unilateral complete surgery [10]. Asari and coworkers estimated the 5- and 10-year cumulative risk for developing recurrence by 39% [11]. Considering these data, the period between unilateral surgery and contralateral recurrence has been assessed between 6 and 12 years. Due to limited experience, an estimation of the risk of ipsilateral recurrence following partial adrenalectomy in MEN 2A patients is currently difficult. In the present series, three patients affected by MEN 2A underwent reoperation 12–37 years after previous partial adrenalectomy. Similar data have been described by Jansson and colleagues who reported a completion adrenalectomy 17 years after bilateral partial resection on three patients treated by partial adrenalectomy [32]. Assessment of the eventuality of ipsilateral recurrence is more difficult for patients affected by VHL. Baghai et al. described no recurrence in 4 out of 13 patients that underwent partial adrenalectomy after a mean follow-up of 24 months, Diner and coworkers found two recurrences in 26 patients after 36 and 52 months. In the present study, five patients with VHL syndrome underwent surgery for ipsilateral recurrent pheochromocytoma a mean of 18.6 years (9–28 years) after previous surgery. These data show that ipsilateral recurrences are rare and in case of development occur after about a decade or even later. Moreover, in case of ipsilateral recurrence, redo surgery is still feasible by the posterior minimally invasive approach [33]. Even if the short follow-up of the present series does not allow definitive conclusions about the assessment of risk of recurrence disease, we recommend sparing as much adrenocortical tissue as possible based on the data actually available in the literature [10, 11, 32] and on the personal experience with recurrent tumors presented in this study. Therefore, partial adrenalectomies should be aimed on both sides in synchronous bilateral pheochromocytomas. If possible, the adrenal remnants should be distant from the big vessels to allow a safe second operation.

In conclusion, cortical-sparing adrenal surgery is the treatment of choice option for patients with bilateral pheochromocytomas. It is associated with a high success rate and allows a cortisone-free postoperative management in the vast majority of the cases.

Conflicts of interest None.

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