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Functional and Oncologic Outcomes of Partial Adrenalectomy for Pheochromocytoma in VHL Patients After at Least 5 Years of Follow Up

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Abstract

Purpose—Although the safety and feasibility of partial adrenalectomy in VHL patients has been established, long-term outcomes have not been examined. In this study we evaluate the recurrence and functional outcomes of a VHL cohort treated for pheochromocytoma with partial adrenalectomy with a follow up of at least 5 years.

Methods—We reviewed records of VHL patients treated with partial adrenalectomy for pheochromocytoma at the National Cancer Institute. Demographic, germline mutation status, surgical indication, oncologic and functional outcome data were collected. Local recurrence was defined as radiographic evidence of recurrent tumor on the ipsilateral side of partial adrenalectomy. Patients were considered steroid-dependent if they required steroids at most recent follow up.

Results—Thirty-six partial adrenalectomies for pheochromocytoma were performed in 26 VHL patients between September 1995 and December 2003. Twenty-three cases were performed open and 13 using laparoscopic techniques. Prior surgical history was obtained for all patients. At a median follow up of 9.25 years (5–46 years), no patient has developed metastatic pheochromocytoma. Three patients (11%) developed 5 local recurrences, treated with surgical extirpation or active surveillance. All recurrences were asymptomatic and detected by radiographic imaging on follow up. Additionally, 3 of 26 patients (11%) subsequently required partial adrenalectomy for pheochromocytoma on the contralateral adrenal gland. In the entire cohort, only three patients became steroid dependent (11%).

Conclusion—Outcomes for partial adrenalectomy in VHL patients with pheochromocytoma are encouraging at long-term follow up and should be recommended as a primary surgical approach whenever possible. Adrenal-sparing surgery can obviate the need for steroid replacement in the majority of patients. Local recurrence rates appear to be infrequent and can be managed successfully with subsequent observation or intervention.

Keywords

Pheochromocytoma; VHL; partial adrenalectomy; adrenal sparing surgery; hereditary syndromes

von Hippel-Lindau (VHL) is an autosomal dominant inherited syndrome that predisposes patients to develop tumors in a number of organs, including CNS hemangioblastomas, retinal angiomas, renal cell carcinomas, pancreatic cysts, endolymphatic sac tumors and pheochromocytomas.¹ In comparison to patients with sporadic pheochromocytoma, VHL patients are more likely to develop bilateral and multifocal pheochromocytomas.^{2–3} Up to

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47% of VHL patients with pheochromocytomas will be found to have bilateral adrenal involvement, with many contralateral lesions developing metachronously.⁴⁻⁵

Historically, management of patients with bilateral adrenal pheochromocytomas has involved total removal of adrenal glands, subjecting patients to life-long steroid replacement, risk of addisonian crisis, and other associated complications of steroid dependence.⁶ To avoid or minimize the above issues, partial adrenalectomy has emerged as a feasible alternative to total adrenalectomy in the hereditary pheochromocytoma population.^{4, 7-9} Although the technical feasibility and safety of this procedure has previously been described, the rate of local tumor recurrence, the need for subsequent intervention, and the oncologic efficacy remain unknown at long-term. In this study we report functional and oncologic outcomes in a VHL cohort treated with partial adrenalectomy for pheochromocytoma with a follow up of at least 5 years.

Materials and Methods

We retrospectively reviewed records of VHL patients treated at the Urologic Oncology Branch of the National Institutes of Health (NIH) under an IRB approved protocol, undergoing partial adrenalectomy for pheochromocytoma. Patients who had less than five years follow up and/or who did not have at least one surgery at the NIH were excluded from the study. Demographic characteristics, germline mutation status, surgical indication, functional and oncologic outcome data were collected.

Local recurrence was defined as radiographic evidence of recurrent tumor on the ipsilateral side of partial adrenalectomy. Functional outcome data was determined by the need for steroid replacement upon discharge after surgery. Patients were considered steroid-dependent if they required steroids at last follow up.

Operative Technique

Tumor extirpation was executed as previously described at the NIH for pheochromocytoma in VHL patients using both open and laparoscopic approaches.¹⁰⁻¹¹ Because of the location of pheochromocytoma within the adrenal medulla, we performed a partial or total “demedullation” of the adrenal gland, leaving the majority of cortex intact whenever possible. Open partial adrenalectomy was done through a subcostal or flank approach. Laparoscopic partial adrenalectomy was performed via transperitoneal approach. With either surgical technique, the tumor pseudocapsule was identified and a plane was developed between the tumor and the normal adrenal gland, often leaving only a thin rim of normal adrenal cortex. Manipulation of the remnant gland was minimized during tumor resection. While during our recent cases we have frequently avoided adrenal vein ligation when performing partial adrenalectomy for pheochromocytoma, in this series the adrenal vein was divided in the majority of instances.

Results

We have identified 36 partial adrenalectomies performed in 26 patients between September 1995 and December 2003. Twenty-three cases were performed via an open approach and 13 were approached laparoscopically. Partial adrenalectomy was successfully completed in all instances. Five of 36 procedures (14%) underwent ipsilateral renal surgery prior to or at the time of the partial adrenalectomy. The median follow-up of the entire cohort from the time of first adrenal surgery was 9.25 years (5–46 years). Patient and tumor characteristics are displayed in Table 1.

No patients developed metastatic pheochromocytoma at most recent follow-up. At the time of these analyses all but one patient are alive. One patient succumbed to metastatic renal cell carcinoma. A total of three patients (11%) have developed 5 local recurrences. Additionally, 3 of 26 patients (11%) subsequently required partial adrenalectomy on the contralateral adrenal gland. In all instances, the patients were asymptomatic and the recurrence was detected by surveillance imaging only. There were no significant differences observed regarding either local recurrence or steroid dependence between patients undergoing open and laparoscopic surgery. Patients with recurrences are summarized in Table 2.

Germline VHL mutations were detected in all patients. Missense mutations were the most common type of mutation detected in 22 of 26 patients (84.6%), followed by three patients with partial deletions (11.5%) and one patient (3.8%) with a frame-shift mutation. The missense mutation at codon 167 of the VHL gene was most commonly found, occurring in fourteen of 26 patients (53.8%). A complete list of mutations seen in this patient cohort is displayed in Table 3.

Long-term steroid replacement therapy was required in three patients (11%). Two of 3 patients became steroid-dependent immediately following surgery, while the third patient required steroids 4 years after partial adrenalectomy. Two patients who became steroid dependent had solitary adrenals: one having had prior total adrenalectomy and the second having contralateral total adrenalectomy at the time of his partial adrenalectomy. The third patient had history of prior contralateral adrenal sparing surgery. None of the five additional patients in our cohort with solitary adrenal glands required steroid replacement. No patients that required steroid replacement at long-term follow up developed local recurrence.

Discussion

Patients with hereditary forms of pheochromocytomas commonly develop bilateral and multifocal pheochromocytomas.^{4, 12} Historically, these patients would undergo total adrenalectomy, putting them at risk for steroid-dependence and its associated morbidity. A review by Asari *et al* noted a 15% risk of Addisonian crisis in patients who underwent bilateral adrenalectomy.¹² Telenius-Berg *et al* reported decreased quality of life in 40% of MEN2 patients who underwent bilateral adrenalectomy.¹³ By analyzing our long term outcomes of adrenal-sparing surgery for pheochromocytoma in the setting of VHL, we aimed to critically evaluate the role of adrenal sparing surgery in the cohort of patients with a highest risk for development of bilateral pheochromocytomas, oncologic efficacy of the procedure, and potentially identify risk factors for disease recurrence.

Few papers have addressed pheochromocytoma recurrence risk in the VHL patient population following partial adrenalectomy. Walther *et al.* described a 7.7% local recurrence risk (1 of 13 patients) after partial adrenalectomy at a median follow-up of 18 months.⁴ Neumann *et al.* reported tumor recurrences in 3.4% (1 of 29 patients) of VHL patients after adrenal-sparing surgery at a mean follow-up of 6 years.¹⁴ The slightly higher recurrence rates in our most updated cohort (11%) can probably be attributed to our longer median patient follow-up (9.25 years). Evidence of delayed recurrence (41 years in our cohort) after initial partial adrenalectomy emphasizes the importance of life-long surveillance in this patient population.

Several factors have been reported to influence the risk of recurrence including age at presentation, sidedness (right more common than left) and tumor size.¹⁵ Patients undergoing adrenal-sparing surgery at a young age appear to be at higher risk for local recurrence. Walther *et al.* noted the only pheochromocytoma recurrence in a patient originally diagnosed with disease at age 8.⁴ Al-Sobhi *et al.* described local recurrence in a 10 year old

VHL boy undergoing bilateral partial adrenalectomy.¹⁶ In the largest series published on 192 patients with sporadic and familial pheochromocytoma and paraganglioma, Amar *et al.* described similar pattern of tumor recurrence in patients of younger age.¹⁵ Our findings are in accordance with these earlier reports. The average age of initial diagnosis in patients who developed pheochromocytoma recurrences was significantly lower than in the group that did not recur (12.3 vs. 30.5 years $P=0.039$, chi square test). The relationship between age and recurrence may be secondary to the increased time for the remnant adrenal chromaffin cells to form and develop new tumors after surgery, or differences in the disease phenotype, where earlier penetrance potentially influences individual's propensity to form pheochromocytomas throughout life. On the other hand, those patients treated earlier may have had longer follow up time to develop new tumors. This concept is supported in our cohort because patients with and without recurrence demonstrate statistically significant differences in follow up time (24 vs. 10 years $P<0.05$ chi-square test).

In addition to the patient's age at diagnosis, the inherited germline mutation may predetermine the aggressiveness and recurrence risks of pheochromocytoma in certain families. Chen *et al.* demonstrated that patients with VHL harbor different mutations which affect their phenotype, including the likelihood of developing pheochromocytoma.¹⁷ In their cohort, ninety-one of 92 (99%) VHL patients who developed pheochromocytomas had a missense mutation in the VHL gene. Our group has reported similar findings in the past.³ In our present cohort 84.6% of patients had a missense mutation. Fifty-four percent of patients had a missense mutation at codon 167 and, similar to previous reports, this may represent a genetic "hot spot" in VHL patients for developing pheochromocytoma.³ Of our patients who formed recurrent disease, all had missense mutations and two of the three patients had the identical missense mutation. Of importance, these patients were members of unrelated families (although the possibility of founder's effect cannot be excluded). While the significance of these findings is unknown, the potential relationship of mutation status and risk of tumor and tumor recurrence may be important and warrants investigation in the future.

The ability to preserve adrenal function and avoid long-term steroid replacement after partial adrenalectomy has been described in the literature. Baghai *et al.* reported on two VHL patients undergoing partial adrenalectomy, neither requiring steroid replacement at a 3-month follow up.¹⁸ Neumann *et al.* described normal cortisol response to ACTH stimulation testing in 4 patients following bilateral adrenal-sparing surgery out to 2 years post-operatively.⁹ Walther *et al.* noted the absence of steroid replacement therapy in his VHL cohort with up to 3 years of follow-up.¹¹ The higher 11% rate (3 of 26) of life-long steroid replacement in our series may be explained by our larger cohort of patients, longer follow up, and our higher rate of solitary adrenal glands. Notably, one patient in our cohort developed the need for replacement therapy four years after partial adrenalectomy. Although pheochromocytoma recurrence seems to be independent of steroid replacement (no patient who recurred has required steroid replacement), the potential for recurrence and the delayed need for steroid supplementation underscore the importance of life-long surveillance in this patient population.

There has been suggestion in the literature that the main adrenal vein preservation during partial adrenalectomy may impact preservation of the adrenal remnant and ultimately lead to steroid dependence.¹⁹ Because the adrenal vein was ligated in the majority of patients in this series we are unable to comment on its potential impact on function. Recently, however, because of an adequate preoperative blockade we have avoided division of the adrenal vein in select patients without increasing complications risk while maintaining excellent outcomes. In this series, two of three patients who developed steroid dependence had ligation of their adrenal vein intraoperatively.

Management of pheochromocytoma recurrences can be a therapeutic challenge for the practicing surgeon. The hazards of repeat retroperitoneal surgery have been well documented in our VHL population undergoing repeat or salvage partial nephrectomy for recurrent renal cell carcinoma.^{20–21} Unlike kidney cancer in VHL patients, management strategies for pheochromocytoma based on tumor size have not been well established.²² The role for initial surveillance of pheochromocytomas in VHL patients may be supported by the low rates of metastatic pheochromocytoma in the VHL population, our personal observation of a slow growth rate, as well as the fact that catecholamine elevation can be independent of tumor size.³

In our series patients with recurrences were treated with repeat surgery or observation. Amongst the five recurrences, 2 were treated with successful repeat partial adrenalectomy, 1 with total adrenalectomy, and 2 with surveillance. Patients who elected surveillance had solitary adrenal glands, were hemodynamically stable and asymptomatic, and therefore elected a non-operative approach. Observation of tumors that are asymptomatic, low catecholamine producing, and relatively stable in size may potentially be a reasonable strategy in some patients with recurrent pheochromocytoma but should be weighed against the potential risk of development of metastatic disease, repeat surgery, and the potential need for steroid-replacement therapy.

Limitations of our analysis include the retrospective nature of our study and the relatively small cohort size. Although we have not performed quality of life analysis in our cohort of patients undergoing adrenal-sparing surgery, much of the historical morbidity associated with total extirpation appears to have been eliminated with partial adrenalectomy.¹¹ Additionally, the use of radiographic imaging (CT or MRI) and biochemical studies to detect pheochromocytoma relapses may have underestimated true rates of local recurrence, especially if the recurrences are microscopic and cannot be detected by modern imaging. Challenges with detection, especially in the setting of recurrent disease, have been well documented in the literature.^{23–25} Lastly, the requirements for steroid replacement were not standardized and were frequently prescribed at the discretion of outside physicians. Despite these limitations our study represents the largest cohort evaluating VHL patients undergoing partial adrenalectomy with the longest follow-up in the literature, and documents excellent oncologic and functional outcomes of adrenal sparing procedures in this cohort.

Conclusions

With at least five years of follow-up, partial adrenalectomy carries a low risk of recurrence and affords steroid independence to the majority of patients. Patients who are diagnosed with pheochromocytoma at a young age and have a germline missense mutation of the *VHL* gene may be at a higher risk of tumor recurrence. Late recurrences and the potentially delayed need for steroid supplementation underscore the importance of life-long surveillance. In the VHL population adrenal sparing surgery, rather than total adrenalectomy, should be the treatment of choice, when technically feasible.

Acknowledgments

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Abbreviations

VHL   von Hippel-Lindau

CNS	Central nervous system
ACTH	Adrenocorticotrophic hormone
CT	Computed tomography
MRI	Magnetic resonance image

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Table 1

Demographics of the Study Cohort

Parameters		No.
Total Partial Adrenalectomies, number (%)		36 (100)
Total number of patients, number (%)		26 (100)
Caucasian patients, number (%)		26 (100)
Mean age at initial diagnosis, years (range)		27 (10–62)
Tumor site (%)	Right	11 (31)
	Left	11 (31)
	Bilateral	7 (38)
Indications for surgery, number (%)	Pheochromocytoma-related symptoms	4 (11)
	Mass on CT or MRI	20 (56)
	Elevated catecholamines	9 (25)
	Concurrent Abdominal Surgery	2 (6)
Mean tumor size, cm (range)	Elective Surgery	2.5 (0.3–5)

Table 2

Characteristics of Patients with Recurrences

Characteristics	Patient 1	Patient 2	Patient 3
Age at initial diagnosis, yrs	13	12	12
Size of pheochromocytoma, cm	3.8	NA	3.2
Side of partial adrenalectomy	Lef	Bilateral	Left
Approach of initial surgery	Laparoscopic	Open	Open
Time to recurrence, yrs	4	5, 39, 41	1
Size of largest recurrent mass, cm	1.2	NA (L), 2 (R), 3.9 (L)	2.2
Management of recurrence	RPA	left RPA, right TA, left S	S
Total follow-up since diagnosis, yrs	13.5	46	13
Status	Alive, NED	Alive, stable left 3.9cm	Alive, stable left 2.2cm
Steroid-dependent (Yes/No)	No	No	No

NA= not available; RPA= repeat partial adrenalectomy; TA= total adrenalectomy; S= surveillance; NED= no evidence of disease

Table 3**Mutations of Patients with Pheochromocytoma**

Type of Mutation	Mutation	No. families (%)	No. individuals (%)
MS	R167Q	4 (22)	12 (46.1)
MS	R167W	2 (11)	2 (7.7)
MS	G114R	1 (5.6)	1 (3.8)
MS	F136C	1 (5.6)	1 (3.8)
MS	L118P	1 (5.6)	1 (3.8)
MS	Y112H	1 (5.6)	1 (3.8)
MS	Y98H	1 (5.6)	1 (3.8)
MS	L128F	1 (5.6)	1 (3.8)
MS	L129P	1 (5.6)	1 (3.8)
MS	R161Q	1 (5.6)	1 (3.8)
PD	Exons 2 and 3	3 (16.7)	3 (11.5)
FS	delA at 696	1 (5.6)	1 (3.8)

MS= Missense; PD= partial deletion; FS= frame shift; R= arginine; Q= glutamine; W= tryptophan; G= glycine; F=phenylalanine; C= cysteine; L= lysine; P= proline; Y= tyrosine; H= histidine