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Outcomes and Timing for Intervention of Partial Adrenalectomy in Patients with a Solitary Adrenal Remnant and History of Bilateral Pheochromocytomas

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Summary

Objective—To evaluate the outcomes and timing of intervention for adrenal sparing surgery in patients left with a solitary adrenal remnant after bilateral adrenal surgeries.

Subjects/Patients and Methods—Patients were included in the study if they had undergone bilateral adrenal surgery as a treatment for pheochromocytoma and were left with a solitary adrenal remnant. Perioperative, functional, and oncologic outcomes were evaluated on 21 patients that met the inclusion criteria.

Results—There was minimal perioperative morbidity and no perioperative mortality. After a median follow up of 21 months (range 3–143) there were two cases of persistent disease. Ten patients (48%) required steroid supplementation upon discharge with 4 subsequently discontinuing steroid supplementation. Patients were more likely to require steroid supplementation postoperatively if they underwent simultaneous adrenalectomy and contralateral partial adrenalectomy, rather than staged procedures (86% versus 40%, p=0.02). Additionally, patients who underwent surgery for tumors greater than 4 cm were more likely to require long-term steroids than patients who underwent surgery for lesions less than 4 cm (75% versus 18%, p=0.05).

Conclusions—Patients left with a solitary adrenal remnant after bilateral adrenal surgery have low surgical morbidity, reasonable functional outcomes and low rates of recurrence at an intermediate follow-up period. A staged approach may decrease the immediate postoperative need for steroids, and intervention before the largest tumor reaches 4 cm may decrease the rate of long-term steroid dependence.

Keywords

Adrenal sparing surgery; complications; partial adrenalectomy; treatment outcome

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Introduction

Pheochromocytomas occurs bilaterally in 3–11% of affected patients.[1] Historically, in the setting of bilateral pheochromocytoma, therapeutic recommendations included total bilateral adrenalectomies to minimize the risk of recurrent disease and the sequelae of increased catecholamine production.[2] Although performing total bilateral adrenalectomies minimizes the risk of recurrence, life-long steroid replacement is necessary. Chronic steroid dependence may lead to multitude of problems, such as osteoporosis, weight gain, and decreased quality of life.[3] Additionally, as many as 35% of patients on chronic steroid replacement have been hospitalized with Addisonian crisis with mortality as high as 4% in some series.[3,4]

In an attempt to minimize steroid dependence and its associated morbidities, several authors have recommended partial adrenalectomy as a component of bilateral adrenal surgery.[5–7] Prior reports of surgical and functional outcomes of patients with bilateral adrenal pheochromocytoma included a heterogeneous population of patients with solitary or bilateral adrenal remnants. There is currently limited information available on outcomes of patients left with a surgically treated solitary adrenal remnant.[8,9] Additionally, the timing for intervention has not been previously evaluated. Here we report the surgical and functional outcomes, as well as the timing for intervention, for patients left with a solitary adrenal remnant after bilateral adrenal surgery.

Subjects/Patients and Methods

We reviewed records of all patients who had undergone a partial adrenalectomy for pheochromocytoma at the National Cancer Institute between 1996 and 2009. The patients were included only if they had undergone a partial adrenalectomy on a solitary adrenal gland, or if they had undergone a partial adrenalectomy in the setting of a simultaneous contralateral total adrenalectomy. Therefore, the final cohort consisted of patients with a surgically treated solitary adrenal remnant. Written consent was obtained from all participants according to the National Cancer Institute Institutional Review Board.

Hospital records and operative reports were reviewed for demographics, perioperative and functional outcomes, and recurrences. The diagnosis of pheochromocytoma was confirmed through an assessment of biochemical function and imaging.[10] All operations were performed after at least two weeks of our standard pre-operative blockade with phenoxybenzamine 10 mg BID and metyrosine 250 mg TID. Partial adrenalectomy was performed as previously described.[11] Patients were followed postoperatively for clinical or laboratory evidence of adrenocortical insufficiency. An adrenocorticotropin stimulation test was performed for the patients who had clinical or laboratory evidence of Addisonian crisis. If needed, steroid supplementation was initiated. After discharge, patients were followed with biochemical and imaging studies three to six months after surgery, and yearly thereafter. For those discharged with steroid supplementation, repeat functional studies were performed at three or six months to identify patients with sufficient adrenal function to discontinue steroid replacement therapy. Functional outcomes were determined by the need for replacement steroids at discharge and at the most recent follow-up visit. Recurrence was defined as the new development of elevated catecholamine levels, or the presence of a new lesion in the adrenal remnant on follow-up imaging studies.

Five patients had a total of eight concomitant non-adrenal surgeries: pancreatectomy (2), thyroidectomy (1), resection of a small bowel mass (1), hernia repair (2), partial nephrectomy (1), and retroperitoneal lymph node dissection (1). Due to the morbidities associated with the surgeries listed above, analysis of perioperative outcomes was performed

only in patients who did not have concomitant procedures (n=16), while all patients were included in the analysis of functional outcomes and recurrences (n=21).

To identify the timing for an intervention that allows for the best functional outcomes, we compared outcomes of patients that underwent simultaneous versus staged bilateral procedures, as well as various sizes of the mass resected from the solitary adrenal gland. Fisher's exact test was used to analyze dichotomous variables.[12] A p value of ≤ 0.05 was considered to be significant. Statistical analysis was performed using publicly available software R 2.81.

Results

Patient characteristics are shown in Table 1. A total of 21 patients were left with a solitary adrenal remnant after bilateral adrenal surgery. Fourteen of these patients had undergone a partial adrenalectomy on a solitary adrenal, while the remaining seven patients underwent a simultaneous partial adrenalectomy with contralateral total adrenalectomy. Ten (48%) of the patients were symptomatic prior to surgery, and the remaining patients had sub-clinical disease detected through biochemical testing or imaging.

Perioperative and functional outcomes are shown in Table 2. As mentioned previously, we chose to exclude five patients who had undergone concomitant non-adrenal surgeries in our assessment of perioperative outcomes. The excluded patients had longer operative times, higher estimated blood loss (EBL), and more complications than those with adrenal surgeries alone. Three (60%) of the five patients excluded had four complications, which included pancreatic leak (1), persistent fluid collection (1), urinary tract infection (1), and cerebral vascular accident (1).

Of the 16 patients who had undergone adrenal surgery alone, there were four (25%) perioperative complications (Table 2). These perioperative complications included pleurotomy (1), diaphragmatic injury (1), caval injury (1), and prolonged intubation (1) for failure to tolerate extubation. The pleurotomy occurred during an open procedure and was repaired intraoperatively. The diaphragmatic injury and caval injuries occurred during laparoscopic procedures and were primarily repaired laparoscopically. No patients required re-operation for intraoperative complications. The patient that required prolonged intubation was extubated three days after surgery, and the rest of the recovery was uneventful.

Two patients (12.5%) required intraoperative transfusion with a median of 1.5 units of packed red blood cells. The median size of tumors removed was 2.0 cm (range 1.0 to 8.0). The median peak intraoperative systolic blood pressure (SBP) was 150 mm Hg. Nine patients had SBP greater than 160 mm Hg and were managed with Nitroprusside drip.

Table 2 also indicates functional outcomes and recurrences for our entire cohort (N=21). With a median follow-up period of 21 months (range 3 – 143), two patients (10%) developed an ipsilateral lesion four and five months after surgery.

A total of 10 (48%) patients were given replacement steroids at discharge. Six of these 10 patients had undergone a partial adrenalectomy in the same setting as a contralateral adrenalectomy, while the other four had undergone a partial adrenalectomy on a solitary adrenal gland. Six of seven patients (86%) that had bilateral (rather than staged) procedures required steroids at the time of discharge from the hospital, whereas only four of 14 (29%) patients who underwent staged procedures required steroids at discharge (p=0.02).

Four of these 10 patients have subsequently been weaned off steroids. All four patients showed symptomatic improvement after weaning and no longer exhibited clinical signs of

adrenal insufficiency. At the most recent follow-up, six (29%) patients required steroid supplementation. Three of four patients (75%) who had tumors greater than 4 cm required long-term steroids, whereas only three of 17 patients (18%) with a tumor less than 4 cm required steroids (p=0.05).

Discussion

To decrease the morbidity associated with steroid replacement, some investigators have attempted to preserve adrenal function with subtotal adrenalectomy.[5,7,9,13–15] As demonstrated by Brauckhoff et al., it may be possible to prevent the need for steroid dependence by preserving only a small portion of the total functional adrenal cortex[13]. However, in patients with pheochromocytoma, preserving adrenal tissue increases the risk of recurrence.[8] Graff et al reported a 45% recurrence rate for patients with after subtotal adrenalectomy, which is much higher than the 3% recurrence rate reported after total bilateral adrenalectomy.[5,8] Therefore, the management of these patients involves weighing the risks of steroid replacement necessitated by total adrenalectomy against the risks of recurrence with partial adrenalectomy.

Similar to other studies, we demonstrate that the majority of partial adrenalectomies on a solitary adrenal remnant may be performed safely with acceptable perioperative morbidity.[16] Although our complication rates are slightly higher, and operative times longer, than the recent review of partial adrenalectomy series by Kaye at al, this may be explained by the challenging nature of treating the patients in this study.[17] Fifty-two percent of patients had prior non-adrenal abdominal surgery, which may have contributed to a higher percentage of perioperative complications as well as longer operative times. Of importance, all of the perioperative complications resolved without the long-term sequelae, and the great majority of these patients remained steroid-independent at last follow-up.

Our results indicate that there were two instances (9.5%) of persistent disease in the ipsilateral remnant adrenal gland after surgical intervention. Both of these patients had multifocal disease at the time of partial adrenalectomy, and both had multiple tumors resected at the time of their surgery. According to operative and pathology reports there were four lesions removed in one patient and “multiple” lesions removed in the other patient. Due to the short time to recurrence (four and five months, respectively), these patients most likely had persistent disease rather than true recurrences. One patient underwent a second successful laparoscopic partial adrenalectomy to remove the residual lesion, while the other patient elected to have the adrenal tumor managed with observation; it has remained stable for 12 years.

A comparison of the outcomes of our cohort with other studies is summarized in Table 3. With the results of the present study included, there are now reports of 70 patients with a solitary adrenal remnant after bilateral adrenal surgeries. Overall, using weighted means, 19% of patients required steroid replacement and 6% had recurrences at a median follow-up of 53 months.

To our knowledge, there are no reports interrogating the optimal timing for the intervention for patients with bilateral adrenal tumors. In our cohort, six of seven patients (86%) that had bilateral (rather than staged) procedures required steroids at the time of discharge from the hospital, whereas only four of 14 (29%) patients who underwent staged procedures required steroids at discharge (p=0.024). While there are no studies in humans documenting the physiologic effect of adrenalectomy on residual adrenal tissue, our results may be explained by Nakayama and colleagues who showed compensatory growth and hypertrophy of residual adrenal in rats after surgical resection of one of their adrenal glands.[18] The same

phenomenon may occur in the human adrenal gland, which may explain the higher rate of steroid dependence we observed in patients who had undergone simultaneous bilateral procedures compared to patients who had undergone staged procedures. Additionally, the size of the resected mass appears to have an effect on our ability to successfully perform adrenal-sparing procedure. We noted a significantly higher rate of steroid dependence in patients treated for tumors greater than 4 cm (p=0.05).

Since active surveillance is frequently utilized for patients without symptoms and signs of increased catecholamine secretion, our findings may have direct clinical implications for those trying to avoid unnecessary surgery and steroid dependence. We demonstrate that observing patients with a pheochromocytoma in a solitary remnant until their mass reaches 4 cm may allow avoidance of intervention without compromising functional outcomes. Similar to our findings, Ihara, et al. have recommended reserving partial adrenalectomy for solitary lesions less than 3 cm.[19]

An additional observation from our study is that resection of multiple tumors did not affect steroid dependence. Although our series had a higher rate of steroid dependence than others in Table 3, most patients in our cohort had multifocal disease. Importantly, of those patients left with a solitary adrenal remnant that required resection of multiple tumors (n=8) all but one patient (87.5%) were able to avoid steroid replacement. Therefore, we determined that preoperative or intraoperative identification of multiple pheochromocytomas should not preclude a surgeon from attempting a partial adrenalectomy.

Selection of patients who will benefit most from partial adrenalectomy as a component of bilateral adrenal surgery is critical for ensuring good outcomes. Although our series is a small and retrospective review from a single institution, it has allowed us to make the following adjustments in our management strategy: First, in the presence of bilateral adrenal pheochromocytomas when the contralateral adrenal gland may be lost, we now choose to proceed in a staged rather than simultaneous approach. Second, patients on surveillance with pheochromocytoma in a solitary gland are advised to undergo surgery before their tumor approaches 4 cm. Finally, the presence of multifocal lesions appreciated preoperatively or intraoperatively does not dissuade us in proceeding with an adrenal sparing procedure.

This series has limitations inherent to any retrospective study. We did not address variability of surgical expertise, technique, and available technology in treating the patients over a span of 12 years. Furthermore, with a median follow-up of 21 months, there is the possibility that additional patients will develop recurrences not detected at the time of our analysis. Nevertheless, to our knowledge, this is the largest study assessing the outcomes and timing for intervention in patients left with a surgically treated solitary adrenal remnant.

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Table 1

Patient characteristics

	All patients (N=21)		Adrenal surgery only (N=16)	
Patients (%)	21	100	16	(100)
Median Age, years (range)	40	(13–79)	42.5	(13–79)
Male (%)	9	(43)	6	(38)
Right side (%)	10	(48)	9	(56)
VHL (%)	13	(62)	10	(62)
MEN II (%)	3	(14)	3	(19)
NF-1 (%)	1	(5)	0	(0)
Without known hereditary disorder (%)	4	(19)	3	(19)
Prior non-adrenal abdominal surgery (%)	11	(52)	8	(50)
Open (%)	6	(29)	4	(25)
Laparoscopic or robotic (%)	15	(71)	12	(75)
Simultaneous contralateral total adrenalectomy (%)	7	(33)	5	(31)
Concomitant non-adrenal procedure (%)	5	(24)	0	(0)
Symptomatic prior to surgery (%)	10	(48)	8	(50)
Median years since contralateral adrenal surgery (range)*	10.5	(2–31)	10.5	(2–29)

* For 14 patients with prior contralateral adrenalectomies

Table 2

Perioperative outcomes, functional outcomes, and recurrences

Perioperative Outcomes (N=16)		
Periop complications (%)	4	(25)
Intraop complications (%)	3	(19)
Postop complications (%)	1	(6)
Median hrs procedure (range)	5.5	(3–10)
Median ml intraop blood loss (range)	200	(25–800)
Patients receiving intraop transfusions (%)	2	(13)
Median peak intraop systolic blood pressure (range)	150	(120–260)
Median cm tumor size (range)	2	(1–8)
Patients with multinodular tumors (%)	4	(25)
Median length of stay (range)	7	(4–14)
Functional Outcomes (N=21)		
Median months follow-up (range)	28	(3–143)
Patients discharged on steroid replacement (%)	10	(48)
Patients requiring steroids at most recent follow-up (%)	6	(29)
Recurrences (N=21)		
Patients with persistent disease after initial surgery (%)	2	(10)
Recurrences (%)	2	(10)

Table 3

Outcomes of patients after unilateral adrenalectomy with contralateral partial adrenalectomy

First author	Institution	Year	N	Median follow-up (mo.)	Steroid requirement (%)	Recurrence (%)
Albanese	University of Pittsburgh	1993	4	84	0	0
de Graff	Netherlands	1999	4	46	0	0
Neumann	Freiberg, Germany	1999	6	73	0	NA
Brauckhoff	Martin-Luther, Germany	2002	2	24	0	0
Walz	Freiberg, Germany	2004	12	40	1 (8)	1 (8)
Yip	M.D. Anderson, Houston	2004	22*	71	6 (27)	1 (5)
Present Study	N.I.H.	2010	21	28	6 (29)	2 (10)
Total			**71**	**51****	**13 (18)**	**4 (6)**

N.I.H., National Institutes of Health

NA, Not Available

* 16 of 22 had partial with contralateral total adrenalectomy, while 6 other patients had bilateral partial adrenalectomy

** weighted mean