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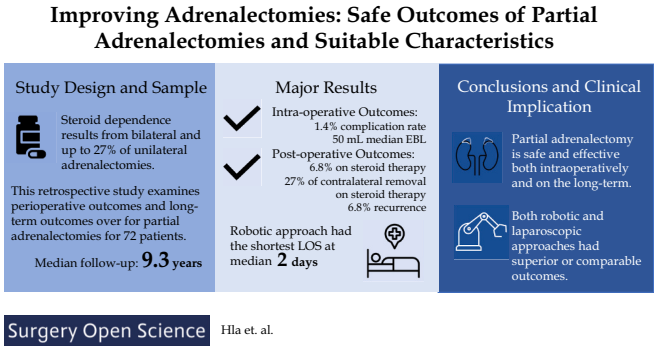
Research Paper

# Improving adrenalectomies: Safe outcomes of partial adrenalectomies and suitable characteristics

Diana A. Hla [a,*], Nafiye Busra Celik [b], Enrique F. Elli [b]

[a] Mayo Clinic Alix School of Medicine, Jacksonville, FL, USA
[b] Department of General Surgery, Mayo Clinic, Jacksonville, FL, USA

## GRAPHICAL ABSTRACT




## ARTICLE INFO

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Partial adrenalectomy
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## ABSTRACT

*Background:* Partial adrenalectomy (PA) is increasingly used to treat benign tumors to lower the probability of adrenal insufficiency and reduce need for lifetime hormone replacement therapy. Currently, two major concerns are increased bleeding and non-functioning adrenal remnants. This paper examines these concerns and compares surgical approaches with novel findings.

*Methods:* Between 1993 and 2023, 72 patients underwent PA for primary adrenal disorders. Demographic, clinicopathologic and outcome data were analyzed for summary statistics, confidence intervals, and heteroscedastic *t*-test statistics.

*Results:* The patients were 17–76 years-old and were 59.7 % female. The PA was on the left 54.2 % and bilaterally 4.2 %. The indications were adrenal adenoma, pheochromocytoma, cyst, hyperplasia, and other. The mean tumor diameter was 2.7 cm (range 0.7-10 cm). 23 were performed open, 43 laparoscopically, and 6 with an intended robotic approach. Median follow-up was 9.3 years.

Robotic had the shortest length of stay (LOS) (*p*-value 0.01), then laparoscopic (p-value 0.00004), then open. The estimated blood loss (EBL) ranged from 5 to 500 mL (median 50 mL). The median LOS was two days.

Intra-operative complication rate was 1.4 % and readmission within 30 days occurred in 2.8 %. Out of 72 patients, 6.8 % needed hormone replacement; of the 14 patients with contralateral adrenalectomy, 28.6 % needed replacement.

* Corresponding author at: Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA.
*E-mail address:* hla.diana@mayo.edu (D.A. Hla).
@DianaHla (D.A. Hla)@MayoJaxGenSurg (D.A. Hla)

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*Conclusion:* PA appears to be safe with both laparoscopic and robotic-assisted techniques with superior perioperative outcomes. The functional results of PA prevent most patients from requiring ongoing steroid replacement treatment and recurrence rates were low. PA should be advised for more frequent use as the preferred treatment method of choice.

*Key message:* Partial adrenalectomies' perioperative and long-term outcomes over a median 9.3 year follow-up emphasized its safety and efficacy with 95 % CI of (2.7 cm, 3.6 cm) for masses with adrenal sufficiency post-resection. Additionally, as healthcare institutions decide whether to invest in surgical robots, robotic approach's outperformance of laparoscopic and open on LOS may be counterbalanced by laparoscopic's strong performance in low EBL.

## Introduction

Bilateral adrenalectomies have historically been the preferred treatment for genetic syndromes involving the adrenals, including von Hippel-Lindau, multiple endocrine neoplasia type 2, and neurofibromatosis 1 [1]. Although bilateral adrenalectomies prevent the possibility of recurrence, the adrenals produce glucocorticoids (cortisol), mineralocorticoids (aldosterone), androgens (DHEA), epinephrine, and norepinephrine. Thus, the loss of both glands necessitates lifelong steroid replacement therapy, and even unilateral adrenalectomy has been shown to cause insufficiency in up to 27 % of patients [2,3]. The numerous and significant side effects of long-term steroid therapy can significantly affect patients' lives after the procedure. Additionally, medication compliance becomes essential. Noncompliance— whether due to financial difficulties, patient forgetfulness, or international travel—can precipitate adrenal insufficiency crises that have the potential to be lethal. Telenius-Berg, et al. found that about 44 % of patients' status-post bilateral adrenalectomy considered themselves more or less handicapped, and a third reported chronic fatigue and constant psychological pressure [4].

With the advancements in surgery and radiologic surveillance, partial adrenalectomies (PA) have been gaining in popularity in the past decade. Partial adrenalectomy, also called cortical-sparing adrenalectomy, was first performed by Irvin et al. in 1983. and submitted by Walz et al. in which they used a retroperitoneal laparoscopic technique and obtained helpful results of surgical outcome and kept the cortical function as well as avoid life-long steroid usage in 1996 [5–8].

Recommendations for tumor sizes suitable for partial adrenalectomy typically vary from 2 to 5 cm, though >5 cm is also suggested by some [9–12]. Multiple papers that helped establish the safety of partial adrenalectomies set size guidelines based on author discretion [11,13,14]. This paper thus seeks to gain insight into the sizes for which partial adrenalectomy is both safe and prevents adrenal insufficiency, especially for patients who have the contralateral gland completely removed.

Laparoscopic transperitoneal or retroperitoneal, and robot-assisted laparoscopic transperitoneal or retroperitoneal techniques can all be used for performing partial adrenalectomy [15]. As time went on, the idea of minimally invasive surgery (MIS) partial adrenalectomy was significantly accepted in patients with benign or even metastatic disease of the adrenal gland. It was also taken into consideration in patients who had previously undergone contralateral total adrenalectomy and who might otherwise become permanently dependent on hormonal replacement [16].

Partial adrenalectomy (PA) may eliminate the requirement for steroid replacement and offers very low local recurrence, according to a systematic review, which suggests that PA may be regarded as a primary option treatment when technically possible [17]. Furthermore, the suggested standard therapy for small benign and hormonally active adrenal tumors may change to minimally invasive partial adrenalectomy [18].

A 2015 meta-analysis found an overall recurrence rate of 8 % and 15 % steroid dependence rate post-partial adrenalectomy [6]. We hypothesized partial adrenalectomy would have both safe perioperative and postoperative outcomes, with improved recurrence and steroid dependence rates given the context of improved surgical and radiologic performance over time. Laparoscopic and robotic approaches were hypothesized to have similarly improved perioperative outcomes over the open approach.

## Methods

### *Study population and data collection*

A retrospective analysis of all patients who underwent partial adrenalectomy between January 1, 1993, and May 3, 2023, were identified from the maintained Mayo Clinic surgical database across the three campuses: Jacksonville, Fl; Rochester, MN; and Scottsdale, AZ. Overall, 21 surgeons performed the included operations. Recorded data included patient demographics, preoperative studies, surgical procedure details, related pathology, length of stay, and postoperative outcomes. Data from the patients and the surgical and medical outcomes were retrospectively reviewed after obtaining IRB approval.

### *Patient qualifications for inclusion*

Out of the 233 patients collected, 143 patients were excluded on the basis that the partial adrenalectomy was performed as either part of an en-bloc resection or for metastasis. Of the 84 patients who had primary adrenal disease, 12 were excluded due to the follow-up period being shorter than a week. The remaining 72 patients were analyzed in this paper.

### *Surgical approach*

Approaches included open, laparoscopic, and robotic. Additionally, both transabdominal and retroperitoneal approaches were included. Patient selection for approaches varied throughout the years, but all cases in the last four years have been done robotically. In the nine cases where the estimated blood loss was described as “negligible” or “minimal” without a quantity assigned, it was analyzed as 5 mL, consistent with the minimum blood loss recorded. Transection was done by vessel sealer and suturing as needed.

### *Post-operative outcomes*

The number of weeks from the surgery to the last record relating to the patient adrenal function and medications were recorded. While a significant number of patients were given adrenal replacement therapy immediately post-op prophylactically, the postoperative outcome of whether a patient required adrenal replacement was recorded based on medication status at the last follow up.

### *Statistical analysis*

Continuous variables were reported with median and interquartile ranges (IQR) while categorical variables were reported as absolute values and proportions. Statistical calculations were done in Microsoft Excel. Confidence intervals were calculated at 95 %, and all tests were

two-sided and heteroscedastic utilizing $p$ values of $<0.05$.

## Results

We identified 72 patients who underwent partial adrenalectomy for a primary adrenal mass who met the inclusion criteria during the study period. The ages of these patients ranged from 17 to 76, with a median of 51 (IQR: 41, 61). 59.7 % of the patients were assigned female sex at birth. 81.9 % self-identified as Caucasian, 4.2 % as African American, 2.8 % as Hispanic, and 2.8 % as Asian (Table 1).

The indications for going through partial adrenalectomy were represented by adrenal adenoma in 42 cases (58.3 %), pheochromocytoma in 19, cyst in 3, hyperplasia in 3, and other (paraganglioma, cortical carcinoma, etc.) in 5. The mean tumor diameter was 2.7 cm (2.1, 4) with a range of 0.7 cm - 10 cm. The partial adrenalectomy was done on the left 54.2 %, on the right 41.7 %, and bilaterally in 4.2 % of the cases.

Of these partial adrenalectomies, 23 were performed with an open approach, 43 with a laparoscopic approach, and six with a robotic approach. The trans-abdominal approach was used in 60 (83.3 %) and the retroperitoneal approach in 12.

The median follow-up length was 484.9 weeks, equivalent to 9.3 years, with IQR 100.3 to 833.0 weeks, equivalent to 16.0 years.

14 patients (19.4 %) had complete adrenalectomy either before (7, 9.6 %) or concurrently with (7, 9.6 %). Bilateral partial adrenalectomies were performed in 3 patients.

### *Perioperative outcomes*

Within this series, there were no intended partial adrenalectomies that were converted to total adrenalectomies, and all procedures were successfully completed. There was one conversion from a robotic to laparoscopic adrenalectomy.

For surgeries that were only adrenal, the operative time ranged from 78 to 390 min with a median of 184 (IQR 152, 218). There was one intraoperative complication reported—a hepatic laceration. The estimated blood loss ranged from 5 mL to 500 mL with a median of 50 mL (IQR 152, 218). The median length of admission was two days (IQR 2, 3) with a minimum length of one day and a maximum length of 9 days (Table 2).

Comparing the open, laparoscopic, and robotic approaches, the laparoscopic approach was found to be superior in the perioperative outcome of estimated blood loss (EBL); with a heteroscedastic two-tailed $t$-test $p$-value of 0.006, the EBL was lower for the laparoscopic approach compared to the open approach (Table 3). There was no other statistically significant difference found between the approaches in perioperative outcomes. There was also no significant difference found between transabdominal and retroperitoneal approaches in EBL and operative time.

### *Postoperative outcomes overall*

The postoperative outcomes examined were the length of admission, complications, and readmissions in the following month, the need for adrenal hormone replacement, and recurrence.

The mean length of admission was 2.9 days. 2 patients were readmitted within 30 days post-procedure, with one due to ileus and the other unknown due to incomplete records. 6.8 % of patients who underwent partial adrenalectomy developed adrenal insufficiency.

The mean length of stay (LOS) for open partial adrenalectomies was 5.8 days whereas the mean for laparoscopic was 2.4 days. Robotic partial adrenalectomies had a mean of 2.0 days. The $p$-value for the difference between the admission lengths between open and laparoscopic was 0.00004 with laparoscopic performing better. The $P$ value for the difference between the LOS between laparoscopic and robotic was 0.01 (Fig. 1).

Recurrence of adrenal disease occurred in 5 patients (Table 4). The diseases that recurred were focal adrenocortical hyperplasia in two patients, adrenal adenoma, Cushing's, and a malignant adrenocortical carcinoma that had already metastasized prior to resection (resection performed in order to control the secondary Cushing's syndrome). No pheochromocytomas recurred. PA can be a good option for patients with pheochromocytomas. Out of the 72 patients, five needed adrenal hormone replacement with fludrocortisone, hydrocortisone, and/or prednisone.

### *Postoperative outcomes for patients with contralateral adrenal operation*

Concurrent or past adrenalectomy of the other adrenal gland had been performed in four of these five patients that required adrenal hormone replacement therapy, while the last had a mass size of 6 cm. Out of 14 patients who had complete adrenalectomy either prior to or concurrently with, long-term steroid therapy was needed for four (28.6 %).

For the 3 patients who had concurrent bilateral partial adrenalectomies, none needed steroid therapy or had a recurrence.

**Table 1**
Description of cohort.

| Variable | Proportion or median with IQR as applicable |
|---|---|
| Age (IQR) | 51 years (41, 61) |
| Follow-up length | 484.9 weeks (100.3, 833.0) |
| Sex | |
| Male | 29 (40.3 %) |
| Female | 43 (59.7 %) |
| Race | |
| White | 59 (81.9 %) |
| Black or African-American | 3 (4.2 %) |
| Hispanic | 2 (2.8 %) |
| Asian | 2 (2.8 %) |
| Unknown | 6 (8.3 %) |
| Type of Adrenal Disease | |
| Hyperplasia | 3 (4.2 %) |
| Cyst | 3 (4.2 %) |
| Adenoma | 42 (58.3 %) |
| Pheochromocytoma | 19 (26.4 %) |
| Other | 5 (6.9 %) |
| Laterality | |
| Left | 39 (54.2 %) |
| Right | 30 (41.7 %) |
| Bilateral | 3 (4.2 %) |
| Surgical approach | |
| Open | 23 (31.9 %) |
| Laparoscopic | 43 (60.0 %) |
| Robotic | 6 (8.3 %) |
| Transabdominal | 60 (83.3 %) |
| Retroperitoneal | 12 (16.6 %) |
| Contralateral Adrenalectomies | |
| Complete prior to partial adrenalectomy | 7 |
| Complete concurrent with partial adrenalectomy | 7 |
| Bilateral partial adrenalectomies concurrently | 3 |

**Table 2**
Perioperative outcomes.

| Variable | Proportion or median with IQR as applicable |
|---|---|
| Conversion from robotic to laparoscopic | 1 (1.4 %) |
| Intraoperative complications | 1 (1.4 %) |
| Duration of surgery | 184 min (152, 218) |
| Estimated Blood Loss | 50 mL (5 mL, 200 mL) |
| Length of Admission | 2 days (2,3) |

**Table 3**
Perioperative measures by surgical approach.

| Surgical Approach | Estimated Blood Loss (Median with IQR) |
|---|---|
| Open * | 200 mL (50, 400) |
| Laparoscopic * | 12.5 mL (5, 87.5) |
| Robotic | 100 mL (50, 125) |
| **Surgical Approach** | **Operative Time (Median with IQR)** |
| Open | 195 min (162.3, 231.8) |
| Laparoscopic | 174 min (152.5, 205) |
| Robotic | 212 min (108, 245) |

* Statistically significant difference with $p = 0.0058$.

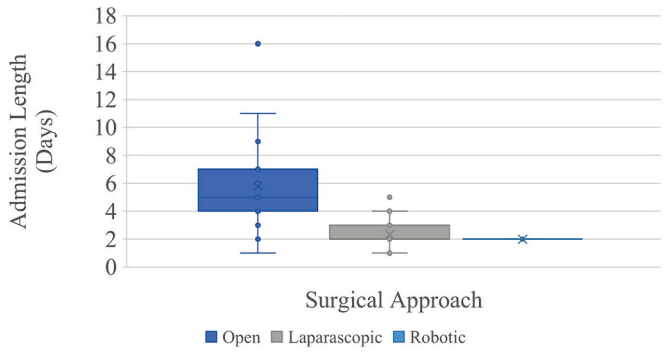


**Fig. 1.** Length of stay by surgical approach. This box-and-whiskers plot displays the distribution of the length of admission by surgical approach. Laparoscopic had superior outcomes over open by $p = 0.00004$, and robotic had superior outcomes over laparoscopic by $p = 0.01$.

**Table 4**
Postoperative outcomes.

| Outcome | Days/Frequency |
|---|---|
| Mean length of admission | 2.9 days |
| Readmissions within 30 days | 2 (2.7 %) |
| Developed adrenal insufficiency | 5 (6.8 %) |
| Recurrence of adrenal mass | 5 (6.8 %) |

## Discussion

Although partial adrenalectomies have been gaining in popularity over the past two decades, the decision between a total adrenalectomy and a partial adrenalectomy is still somewhat nebulous, as the desire to avoid adrenal insufficiency and prevent recurrence must be balanced. Additionally, since partial adrenalectomies are not considered the first-line surgical treatment for adrenal masses, the amount of data available to examine perioperative and postoperative outcomes has not been particularly strong.

In the prior literature, shorter follow-up lengths presented difficulties in the power of studies to shed light on postoperative outcomes like adrenal insufficiency and disease recurrence. With a follow-up length of median 484 weeks which is equivalent to 9.3 years, adrenal sufficiency or recurrence would be likely to be seen.

### *Perioperative outcomes*

The results of this study suggest that partial adrenalectomies have safe perioperative outcomes. Adrenalectomies have several intraoperative challenges. For pheochromocytoma, hemodynamic liability during adrenalectomy must be anticipated and managed [19]. In contrast, aldosterone or cortisol-secreting tumors may cause hypotension immediately after adrenalectomy, so steroids are recommended in the post-operative period to compensate for the possibly transient adrenal insufficiency [20]. Cortisol-secreting tumors may also cause increased friability of the tumors and increased bleeding intraoperatively. In the literature, the perioperative complication rate for adrenalectomy varies from 1.7 to 30.7% [21].

As perioperative complications only occurred in 1.4 % of cases and were not related to the adrenal gland directly, these results suggest that partial adrenalectomy does not increase the risk of perioperative adverse events. A recent study on laparoscopic total adrenalectomies found a mean operative time of 145 min and a mean estimated blood loss of 95 mL, and this study's findings of a median operative time of 184 min and a median estimated blood loss of 50 mL are comparable [22]. As a major concern with partial adrenalectomy has been blood loss, these results are reassuring. The longer operative time for a partial adrenalectomy is not surprising, given that choosing the margin for transaction must also be done carefully. As a result, partial adrenalectomies are unlikely to worsen the perioperative outcomes for patients compared to total adrenalectomies.

### *Effect of surgical approach on operative outcomes*

Multiple surgical techniques for adrenalectomies have been described, including open transperitoneal, laparoscopic transperitoneal, posterior retroperitoneal, and robotic surgery [23,24]. The findings of this study on the different surgical approaches to partial adrenalectomy suggest that all these approaches have safe outcomes. Robotic adrenalectomies have been shown to be safe and have similar, or even better, perioperative outcomes compared to laparoscopic adrenalectomy [23,25].

For operative time, the open approach was the longest, at 195 min, followed by laparoscopic at 174, and robotic at 212 min. While there was no statistically significant difference of $P$ value $<0.05$, this is in line with past studies suggesting that the robotic approach has the longest operative time [23].

For estimated blood loss, a statistically significant difference was found between the open approach and laparoscopic approach with laparoscopic being associated with a lower blood loss with a P value of 0.006. While this finding could be biased by selection, it suggests that the laparoscopic approach could lead to superior perioperative outcomes.

Between these three surgical approaches, the length of stay in the hospital showed the largest differences. The robotic approach led to the shortest admission time, followed by laparoscopic then open. The $p$-values for these respective differences were 0.00004 and 0.01, emphasizing that laparoscopic and robotic approaches can lead to shorter hospital stays for patients. This finding is in line with the previous literature for total adrenalectomies, which found that robotic approach led to a significantly shorter LOS compared to laparoscopic [26].

Ultimately, these outcomes highlight laparoscopic and robotic approaches to partial adrenalectomy should be considered when indicated.

Retroperitoneal and trans-abdominal approaches were not found to have any significant differences amongst these variables, suggesting that both are safe approaches. *Trans*-Abdominal is currently more commonly used for unilateral adrenalectomies [27].

### *Postoperative outcomes*

When involving patients in informed decision-making to decide between a partial or total adrenalectomy, a major concern is the impact that the need for steroid replacement therapy would have on the patient's life. However, recurrence of the mass is also a concern when not performing total adrenalectomies. As a result, finding a balance between these concerns is important.

As a size threshold to consider partial adrenalectomy is not previously prevalent in the literature, this study examined the distribution of mass sizes for which partial adrenalectomy did not cause adrenal insufficiency. The 95 % confidence interval on mass diameters with

adrenal sufficiency post-resection was (2.7 cm, 3.6 cm), centered at 3.2 cm.

Overall, only 6.8 % of patients needed steroid replacement therapy at last follow-up, which is improved from a previous measure of 15 % with a similar patient mix [6].

Additionally, 71.4 % of the 14 patients who had contralateral adrenalectomy prior to or at the time of surgery did not need long-term steroid therapy. Only one patient of the five who needed steroid therapy did not have the contralateral adrenal gland removed and had a mass size of 6 cm—a finding that, while not statistically powered, is in line with this threshold. This would help increase the likelihood that patients do not develop adrenal insufficiency in the postoperative period and that if the contralateral gland were to need resection in the future, the patient can maintain steroid independence. A previous study on MEN2 bilateral adrenal procedures found a need for supplementation in 65 % of patients, which is significantly higher than the finding in this study—possibly due to larger resections [28].

With a recurrence rate of 6.8 % over the follow-up period (median 9.3 years), partial adrenalectomy has acceptable outcomes. The one adrenocortical carcinoma included in this study had a local recurrence, though it had already metastasized prior to surgery and the decision to operate was to control the symptoms of Cushing's disease that the patient had been experiencing severely. The lack of recurrence in patients with pheochromocytoma is encouraging for partial adrenalectomy to be considered for this type of mass. A 2015 meta-analysis of partial adrenalectomies had found an overall recurrence rate of 8 %; our finding is slightly improved, and given the prolonged follow-up period, further strengthen the low recurrence [6].

### *Limitations*

A few limitations should be considered in interpreting this data. First, partial adrenalectomy has not been adopted as a first line surgical treatment for adrenal masses over total adrenalectomies, and thus a head-to-head comparison could not be performed. Direct comparison of outcomes could better clarify a size threshold for steroid independence and possibly recurrence. Additionally, these surgeries were performed primarily at three campuses of Mayo Clinic by senior attending surgeons, which could reduce the generalizability and reproduction of these results to a more geographically diverse population. Additionally, the perioperative outcomes could be biased by the initial choice to do an open, laparoscopic, or robotic approach as more complex cases may be more likely to have been performed open.

While this study was not adequately powered to examine the size differences within the patients who had contralateral adrenal surgery due to sample size, this is a topic that should be further studied.

## Conclusion

The partial adrenalectomy procedure appears to be safe and practical when done by minimally invasive surgery with both laparoscopic and robotic-assisted techniques based on our findings. The EBL and length of stay outcomes highlight laparoscopic and robotic approaches to partial adrenalectomy should be considered when indicated. The functional results of partial adrenalectomy prevent most patients from requiring ongoing steroid replacement treatment and recurrence rates were low. Partial adrenalectomy should be advised to be used more frequently as the preferred treatment method of choice.

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## Ethics approval

This study was deemed exempt by the IRB approval board with application number #23–004746.

## CRediT authorship contribution statement

**Diana A. Hla:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nafiye Busra Celik:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Enrique F. Elli:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

## Declaration of competing interest

None.

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