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Partial Adrenalectomy: An Underutilized First Line Therapy for Small Adrenal Tumors

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Abstract

Purpose—Many patients with small adrenal masses undergo total adrenalectomy. We evaluate the outcomes of partial adrenalectomy by performing a comprehensive literature review.

Materials and Methods—We performed a Pubmed search of literature published in the English language using the following queries: “partial adrenalectomy” and “adrenal sparing surgery”, and identified 317 and 155 articles, respectively. We excluded case reports or series containing less than 5 patients, articles not focused on surgical management, and those that did not indicate perioperative outcomes. The remaining articles were cross-referenced by author and institution in order to eliminate studies with redundant cases. Demographics, diagnosis, tumor characteristics, perioperative and functional outcomes, as well as recurrence data was collected when available.

Results—Twenty-two articles from 22 first authors met our inclusion criteria describing outcomes of 417 patients. There is an increasing trend towards utilization of partial adrenalectomy worldwide over the past 20 years. Partial adrenalectomy is most commonly performed for Conn's Syndrome, followed by pheochromocytoma. Most of the procedures are performed laparoscopically with minimal morbidity. The recurrence rate is only at 3% and over 90% of patients remain steroid independent.

Conclusions—Surgical outcomes and perioperative complications of partial adrenalectomy are similar to those reported for total adrenalectomy. When partial adrenalectomy is performed for small adrenal lesions, the rate of malignancy is negligible, the recurrence rate is low, and the vast majority of patients remain steroid independent at long-term follow up. These data strongly support acceptance of partial adrenalectomy as a first line treatment for small adrenal masses.

Keywords

adrenalectomy; outcomes; review

In the last 20 years the rate of adrenal surgical procedures in the United States has increased by one third¹. This trend is at least partly explained by the modern use of cross-sectional imaging which has resulted in an increased detection of incidental adrenal masses.^{2, 3} While most adrenal tumors are small and non-functional, studies have found that up to 15 percent may be biochemically active.² Historically, total adrenalectomy has been the standard approach for masses found within the gland, regardless of size or location. However, in recent years there has been a growing advocacy for performing partial adrenalectomy in order to avoid the side effects of potential adrenal insufficiency and steroid replacement in select cases.^{3–8}

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Adrenal tumors may be found in certain hereditary syndromes where bilateral adrenal involvement is common. In such cases, bilateral adrenalectomy would result in lifelong steroid dependence. While some patients tolerate chronic steroid replacement well, others experience serious medical consequences. It has been shown that a third of patients after bilateral adrenalectomy experienced a major medical problem requiring hospitalization related to the lack of endogenous steroid production.⁹ In another study from patients post bilateral adrenalectomy, Addisonian crisis has been reported to be as high as 35%, with a mortality rate of 3%.¹⁰ Steroid dependence is also associated with a decreased quality of life, increased fatigue, decreased resistance to stress and infection, increased risk of osteoporosis, and uncontrolled weight gain.^{11–15}

Additionally, there are many scenarios when a normal contralateral adrenal gland may be threatened in patients with unilateral adrenal masses and no hereditary syndromes. Because of the risks and potential complications associated with adrenal insufficiency, some recommend partial adrenalectomy even in patients not affected with familial syndromes.^{11, 12} Other clinicians perform total adrenalectomy for any adrenal tumor.

In an attempt to address the above disparate clinical approaches and to evaluate current trends as well as outcomes of partial adrenalectomy, we have conducted this analysis.

Materials and Methods

We performed a Pubmed search of the literature published in the English language using the following queries: “partial adrenalectomy” and “adrenal sparing surgery,” and identified 317 and 155 articles, respectively. An additional 30 articles not found in the original search were identified via bibliography review of the most relevant publications. We excluded case reports or series containing less than 5 patients; articles not focused on surgical management; articles reviewing partial adrenalectomy solely for renal cell carcinoma; studies where data from partial and complete adrenalectomies were not reported separately; and those that did not indicate peri-operative outcomes. A total of 32 articles met our initial inclusion criteria.

We then cross-referenced the above 32 articles by author and institution in order to eliminate studies with redundant cases. Ten studies were excluded because of redundant data. To decide which of the remaining 32 articles would be included in our final analysis, we used the following criteria in decreasing order of importance: 1) studies with the most data of interest reported for partial adrenalectomy, 2) the greatest number of patients, and 3) the most recent articles. A total of 22 articles describing the outcomes of 417 patients were used for final data collection and analysis (Figure 1).

The following data were collected when available: demographics, diagnosis, tumor characteristics, peri-operative and functional outcomes, and recurrence. Only data from partial adrenalectomy cases were extracted and tabulated. Patients whose surgery was converted from a partial to a total adrenalectomy were included in our final analysis.

To attain uniformity among authors, we have grouped patients based on either clinical or pathological diagnosis into the following categories: 1) Pheochromocytoma, 2) Conn's syndrome (aldosterone producing tumor), 3) Cushing's Syndrome (cortisol producing adenomas), and 4) Other lesions. We have tabulated our data based on the number of patients (not the number of tumors). However, in situations when the patient had multiple clinical or pathological diagnoses, each was tabulated as a separate entity. Because some authors used “minimal” for estimated blood loss of 0 to 50 milliliters, we assigned a value of 50 milliliters to procedures indicating “minimal” blood loss. If both pre-operative imaging and pathology data were indicated for tumor size, we reported the value based on pre-

operative imaging. We chose to do so because more studies reported radiographic size rather than pathologic size.

The articles were carefully reviewed for peri-operative complications and outcomes. Because it was not possible to discern whether the complications occurred in separate patients or more than one complication occurred in a single patient, we tabulated all of the complications and reported them as a percentage of the entire cohort. Only complications related to the partial adrenalectomy were included, while those from concomitant procedures were not. In order to accommodate for variations in study size we have employed weighted averages.

Long-term outcomes were assessed for recurrences and steroid dependence. Follow up was reported as the longest interval from the time of surgery to either the most recent appointment or recurrence. Recurrences were considered as tumors identified on the ipsilateral adrenal gland after prior partial adrenalectomy. Cases with a new tumor on the contralateral adrenal gland were not considered to be local recurrences. Additionally, only those patients that required long-term daily exogenous steroid replacement (beyond the immediate peri-operative period) were considered steroid-dependent in the analysis.

Results

Twenty-two articles from 22 first authors and multiple institutions describing outcomes of 417 patients met our inclusion criteria. The distribution of articles by the year of publication is shown in Figure 2. All of the articles with the corresponding Pubmed reference numbers used in our review are listed in Table 1.

Patient characteristics are indicated in Table 2. Mean age was 44 years (10–82) and 42% of tumors occurred in males. Mean tumor size was 2.6 cm (0.04–9.0) affecting each adrenal gland equally. Adrenal-sparing surgery was performed most commonly for Conn's Syndrome, with pheochromocytoma a close second, followed by non-functional adrenal tumors and Cushing's syndrome.

Table 3 describes surgical characteristics, peri-operative and long-term functional outcomes. Seventy-six percent of cases were performed laparoscopically with less than 1% requiring conversion to an open procedure. Three percent of patients originally undergoing partial adrenalectomy were converted to a total adrenalectomy. Estimated blood loss was 72 ml (0–1500) and operative time was 130 minutes (37–516). Seven percent of patients experienced a peri-operative complication. Mean follow-up time was 56 months (3–331). Tumor recurrence occurred in 3% of patients, with a mean time to recurrence of 113 months (36–324). Ten studies reported data on long-term requirement for steroid replacement. Seven out of 133 patients (5.3%) required long-term exogenous steroid supplementation.

Details of peri-operative complications are listed in Table 4. A total of 16 studies described peri-operative complications in 363 patients with a total complication rate of 7%. The five most common complications were abdominal wall laxity and hemorrhagic complications (1.4% each), followed by pneumonia, pneumothorax, and wound infections (0.8% each).

Figure 3 demonstrates the utilization of partial adrenalectomy in published literature across the span of the past 2 decades. The number of partial adrenalectomies has increased nearly 10 fold from 1991–1995 compared to 2001–2005. The vast majority of partial adrenalectomies are now being performed laparoscopically.

Table 5 is a summary of the various etiologies possibly causing surgical or medical loss of adrenal function.

Discussion

The impetus behind performing this review was to evaluate the current state of partial adrenalectomy, assess the feasibility of the procedure, and to address the controversy regarding recommendations in performing this procedure. While the argument for adrenal sparing surgery is easier in those patients with either a solitary adrenal gland or bilateral adrenal involvement, the practice of incorporating partial adrenalectomy in the routine care of patients with a normal contralateral gland is still quite controversial.

The argument for adrenal preservation in those with a solitary adrenal gland or bilateral disease is supported by the benefits derived from independence from chronic steroid replacement. Despite the clinician's best attempts to keep exogenous steroid administration at physiologic levels, fixed dosing schedules result in under or over-dosing and an inability to adjust for a patient's physiologic demands. Furthermore, steroid replacement often requires frequent dose adjustments. Notably, up to 30% of patients are under-dosed, which especially occurs during stressful events.⁸ In a report by Telenius-Berg, et al., 33% of patients post bilateral adrenalectomy for MEN2 had significant medical problems related to a lack of endogenous steroid production and required hospital admission.⁹ Furthermore, Addisonian crisis has been reported in up to 35 percent of patients after bilateral adrenalectomy, with a 3 percent mortality rate.^{10, 13-15}

While too little steroid replacement can lead to Addisonian crisis and death, too much is associated with premature osteoporosis, complications of hypertension and diabetes.¹⁰ Post-adrenalectomy steroid dependence is also associated with a decreased quality of life, increased fatigue, decreased resistance to stress and infection, increased risk of osteoporosis, and weight gain.^{11, 13, 14} Other common side effects include: mood changes, diarrhea, abdominal distention, nausea, dyspepsia, increased appetite, peptic ulcers, adrenal suppression, candidiasis, hirsutism, increased intraocular pressure, immunosuppression, hypertension, edema, and hypokalemia.¹⁶ Furthermore, many common medications interact with exogenous steroids.¹⁶

In light of the multitude of adverse side effects commonly encountered with chronic steroid dependence, some have adopted an adrenal sparing procedure in patients with bilateral adrenal tumors or a solitary adrenal gland. While steroid independence may allow avoidance of "common" side effects, steroid dependence may be particularly devastating for patients with certain familial syndromes, such as VHL and MEN2. These patients often have to undergo additional surgeries for different components of their disease, and are thus at risk for increased physiologic stress.

This review indicates that adrenal sparing surgery is gaining popularity and is being performed more commonly at institutions worldwide. The trend of publications and number of patients undergoing this procedure has increased over the past two decades (Fig 2 and 3) and is likely to continue to rise. Of interest, partial adrenalectomy is not only being performed in patients with bilateral adrenal involvement or a solitary gland, but also in those with a normal contralateral gland. In over 400 patients included in the final cohort, partial adrenalectomy was utilized for treatment of a variety of conditions. The most common reason for partial adrenalectomy was Conn's syndrome (aldosterone producing adenomas), with surgery for pheochromocytomas a close second.

One of the possible reasons that Conn's tumors were the most common lesions removed by partial adrenalectomy may be due to the fact that aldosterone producing adenomas are particularly amenable to adrenal preserving procedures as they are often small and solitary, oftentimes located at the margin of the gland.¹⁷ Indeed, tumor location is an important criterion in deciding whether or not to undertake an adrenal-sparing approach. Some authors

noted that tumors located anteriorly and on the margin of the gland are removed relatively easily, while those located posteriorly may be more complex.¹⁸ However, the large proportion of pheochromocytoma cases in this review argue that even those tumors that are surgically challenging, originating in the adrenal medulla and less likely on the periphery of the gland, can still be safely and successfully resected with a partial adrenalectomy. While location may indeed be an important factor in the decision to perform adrenal sparing surgery, the more likely explanation for Conn's tumors being the most common tumor removed by partial adrenalectomy is either due to the overall higher incidence of aldosterone producing adenomas compared to other adrenal tumors or selection bias based on our methodology. Of more importance, however, is the fact that the distribution of clinical diagnosis in this article is broad, and is likely to be representative of the adrenal pathology encountered by in practice.

Of interest, there were no reports of adrenal cortical carcinomas in the patients whose pathology was reported in our cohort. It is possible that the absence of this malignant adrenal mass is due to the fact that the incidence of adrenocortical carcinomas is extremely rare and is seen in one per million population per year.^{19–21} The more likely explanation, however, is that the risk of a primary adrenal malignancy is low, and is even lower in those with an adrenal lesion that is less than 4 cm.²²

Size plays a dual role in the decision to perform adrenal sparing surgery: it is an indicator of potential malignancy and a limiting factor in preserving functional adrenal tissue. In a study of adrenal incidentalomas by Angeli, et al., size most closely correlated with malignancy risk. The authors found that 4 cm was an appropriate cut-off to differentiate adrenal carcinomas from other histologies.²² In our review, average tumor size for adrenal-sparing surgery was 2.6 cm, and further supports the low likelihood for adrenocortical carcinoma and a surgeon's decision to perform adrenal sparing procedures for small adrenal tumors. The importance of size is further emphasized by the observation of Diner, et al., who found a statistically significant difference in the size of tumor removed in patients requiring post operative steroid replacement.⁴

This review demonstrates that the peri-operative outcomes for partial adrenalectomy are as good as those seen with total adrenalectomy.^{23–26} Estimated blood loss during a partial adrenalectomy in our cohort was 72 ml (range, 0–1500) and only 2 out of 231 patients (0.87%) required a transfusion. Although we assigned “minimal” blood loss as 50cc, our methodology has not altered the results. The calculation without this designation included a fewer number of studies, but provided a similar estimate (data not shown). Operative time for partial adrenalectomy was 130 minutes (range, 37–516 minutes), which is comparable to total adrenalectomy reports.^{23, 24, 26} The comparable times are seen even in cases of bilateral intervention, where operative time would be expected to be increased. Ishidoyo, et al., demonstrated a shorter operative time (115 minutes for partial and 199 minutes for total, $p < 0.01$) and less blood loss (30.1 ml for partial and 57.3 ml for total, not statistically significant) for partial adrenalectomy when compared to total.²⁷ In a study on total adrenalectomy, Jacobs, et al., demonstrated a mean EBL of 109 cc for laparoscopic and 263 cc for open cases and a mean operative time of 164 and 151 minutes for laparoscopic and open adrenalectomy, respectively.²⁶ Most complications in our cohort were minor and there were no deaths in any series describing surgical outcomes of partial adrenalectomy. Overall, it does not appear that a partial adrenalectomy carries significant additional morbidity when compared to a total adrenalectomy. In fact, partial adrenalectomy compares favorably to total adrenalectomy for some peri-operative outcomes in those studies that performed head to head comparisons between partial and total adrenalectomy.^{31, 32}

Certainly, while surgical outcomes are encouraging, the recurrence data needs to be critically evaluated. In our cohort, three percent of patients had a tumor recurrence, occurring at a mean of 113 months after the initial surgery (range 36–324 months). While there may be a “true” recurrence because of a positive margin, the other type of “recurrence” may be explained by the presence of multifocal disease within the gland or may simply be a *de novo* lesion or a site of microscopic disease not resected at the time of the original surgery. Indeed, a relatively high rate of “recurrence” in a hereditary pheochromocytoma population may only be representative of the multifocal nature of disease rather than a “true” recurrence at the site of resection. Hereditary pheochromocytomas have recurrence rates ranging from 0–100%.^{7, 13, 28–30} Walz, et al., suggests that this wide range may be due to the length of follow-up, as recurrences are often only seen more than 10 years after the initial tumor removal.²⁸ The rate of recurrence in the hereditary population may also be a result of the detection and screening bias, as these patients are likely to undergo periodic radiographic surveillance. Additionally, some argue that partial adrenalectomy does not carry a recurrence risk that is higher than for a total adrenalectomy.⁷ Lee, et al., found that the tumor recurrence rate of 21% after partial adrenalectomy (at a median follow-up of 11.5 years) was lower than that for unilateral adrenalectomy for unilateral disease, and that the tumor recurrences were amenable to surgery.⁷

The small numbers of recurrences in this review (9 out of 303 patients) limit our ability to identify those patients at risk for recurrence. It is unclear if any specific tumor type or size of lesion is more likely to be associated with a later recurrence within an ipsilateral gland. While recurrence is still a major concern in partial adrenalectomy, it is reassuring that of the patients in this collective cohort developed metastatic disease. Additionally, recurrences have been successfully resected before by others,⁷ and at our institution, where we have successfully performed repeat adrenal surgeries (unpublished data). The presence of a tumor in the contralateral gland was not considered a recurrence, but was rather attributed to a relatively high incidence of bilateral adrenal lesions.

This review indicates that 5.3% of patients require long-term steroid replacement therapy. To assess the rate of steroid dependence we only included patients for whom exogenous long-term steroid replacement was explicitly stated. Most of the patients requiring steroid replacement in our review had bilateral disease, although some had only unilateral adrenal involvement. Although the number of patients requiring long-term steroid replacement is only 5.3%, a study by Yip, et al., (which was not included in the data analysis of this review) found that as many as 35% undergoing cortical-sparing adrenalectomy for bilateral resection were steroid dependent.³¹ Similar to these findings, we have recently presented outcomes of adrenal sparing surgery for pheochromocytoma in patients with a solitary adrenal remnant and reported a long-term steroid dependence rate of 26%.³² While our finding of steroid dependence may be lower than some others (either because of our methodology or due to underreporting in the included studies), it is still possible to conclude that at intermediate follow up, most patients remain steroid independent.

Controversy still exists as to whether adrenal sparing surgery is a viable alternative to total adrenalectomy for treatment of adrenal masses, especially in the sporadic tumor population. Some argue that malignant tumors should be surgically resected by total adrenalectomy, because the risk of microscopic recurrence and metastatic potential outweigh the risks associated with long-term exogenous steroid-dependence. Others consider adrenal preserving surgery for a variety of lesions, including: weak-functioning adrenocortical adenomas, small aldosterone-producing adenomas, a solitary mass, <5cm in diameter^{22, 38}, as well as for those with hereditary syndromes and a high incidence of bilateral and often benign disease.

With data pooled on over 400 patients, we conclude the following:

1. Surgical outcomes and peri-operative complications of partial adrenalectomy are similar to those reported for total adrenalectomy;
2. When partial adrenalectomy is performed for small adrenal lesions, the rate of malignancy is negligible and the recurrence rate is only 3 % (although may be higher in patients with hereditary or bilateral multifocal lesions)
3. Over 90% of patients undergoing partial adrenalectomy will remain steroid independent (although the number may be lower in those with bilateral disease or a solitary adrenal).

So, is it worth performing partial adrenalectomy routinely, especially in those patients with a normal contralateral gland? It appears that the surgical risks of a partial adrenalectomy and the low rate of recurrence favor maximal organ preservation. Although some have demonstrated that leaving at least 15–30% of residual adrenal tissue is necessary for sufficient function,²⁹ others have shown that patients with a unilateral adrenalectomy do not respond equally to stressful situations as do normal controls.³³ This certainly would argue in favor of maximal adrenal preservation. Additionally, the long-term sequel of “subclinical” adrenal insufficiency rate is unknown.

The notion of organ sparing is continuing to gain more widespread use. Radical surgeries have started to yield to more organ sparing resections. As adrenals are a paired organ, a similar organ preservation approach is being used in the treatment of renal tumors. While function of a single kidney may be considered to be adequate and clinically unappreciated by the patient, recent studies have shown that renal insufficiency is associated with an increased risk of cardiovascular disease and mortality.^{40–42} Although organ preservation is being increasingly utilized, as of today, there is still no strong evidence that maximal adrenal preservation is paramount. Nevertheless, there are a number of potential threats to a contralateral adrenal gland throughout an individual's life (Table 5). These potential possible threats, together with the low surgical risks and small possibility for recurrence associated with adrenal preserving surgery, as well as the potential danger of adrenal insufficiency and the need for steroid dependence, support the use of maximal adrenal preservation.

This study was performed as a comprehensive review rather than a meta-analysis. Our goal was to provide a description of the current trends and outcomes of partial adrenalectomy, not to do a head-to-head comparison of partial and total adrenalectomy.

There are several limitations to our review. As in any other review, we are only able to extract the available data. Many studies did not include all of the variables of interest and studies had different areas of focus. We are unable to comment on long-term steroid dependence and recurrence risk in all 417 patients as many authors did not report recurrence data and/or had a relatively short follow-up. In addition, since many reports focused on short-term surgical outcomes rather than medical management, the data on long-term steroid dependence was not available.

Despite the limitations to the present review, this report provides the most up-to-date and comprehensive status of partial adrenalectomy. Additionally, because of a rarity of adrenal lesions and adrenal surgeries, a randomized prospective study is unlikely. In fact, the results of this study would raise the question of whether removal of the entire adrenal gland in a randomized prospective trial is ethical. Although this report does not prove or disprove the use of partial adrenalectomy, it provides data for clinicians to be able to weigh the risks and benefits appropriately and strong data towards entertaining the possibility of preserving the adrenal gland and reconsidering the paradigm of total adrenalectomy as the treatment of

choice for small adrenal masses. This study should also raise awareness among health-care providers about the feasibility of this largely underutilized procedure.

Conclusions

Surgical outcomes and peri-operative complications of partial adrenalectomy are similar to those reported for total adrenalectomy. When a partial adrenalectomy is performed for small functional lesions, the rate of malignancy is negligible and the recurrence rate is low. The great majority of patients undergoing partial adrenalectomy will remain steroid independent. These data strongly support the acceptance of partial adrenalectomy as a first line treatment for small adrenal masses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Methodology for Selection of Partial Adrenalectomy Series

Figure 2.
Number of Studies per Year

Figure 3.
Number of Partial Patients in Published Literature per Year by Procedure Type

Summary of Studies

Table 1

1 st Author	Institution	Year	Total Number of Patients	Number of Partial Adrenalectomy Patients	Accession Number
Al-Sobhi, S ³⁴	University of Innsbruck, Austria	2000	7	7	10954306
Brauckhoff, G ³⁵	Martin-Luther-University Halle/Wittenberg, Halle/Saale, Germany	2003	14	14	12734728
Castillo, V ³	Clinica Santa Maria, Santiago de Chile, Chile	2007	22	7	17941786
Diner, F ⁴	National Cancer Institute, Bethesda, Maryland, USA	2005	33	33	15961144
Edstrom, G ⁵	Karolinska Hospital, Stockholm, Sweden	1999	5	5	10391158
Iihara, S ³⁶	Tokyo Women's Medical University, Tokyo, Japan	2003	9	5	14668742
Ikedo ³⁷	Teikyo University School of Medicine, Tokyo, Japan	2002	10	10	12487268
Imai ¹⁷	Nagoya University School of Medicine, Nagoya, Japan	1999	5	5	10094744
Inabnet ³⁰	Mount Sinai Medical Center, New York, NY, USA	2000	32	5	11114636
Ishidoya ²⁷	Tohoku University Graduate School of Medicine, Sendai, Japan	2005	92	29	15947573
Ishikawa ³⁸	Osaka City University Medical School, Osaka, Japan	2000	55	11	10915020
Jeshke ⁶	General Hospital Klagenfurt, Klagenfurt, Austria	2003	13	13	12559268
Kok ¹⁸	Ripas Hospital, Bandar Seri Begawan BA	2002	8	8	11961617
Lee ⁷	University of Texas M. D. Anderson Cancer Center, Houston, USA	1996	15	15	8957496
Liao ³⁹	National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan	2006	8	8	16979699
Meria ⁴⁰	St-Joseph Hospital, Paris, France	2003	212	20	12478096
Nakada ³³	Yamagata University, School of Medicine, Japan	1995	48	26	7752314
Nambirajan ⁸	Elisabethinen Hospital, Linz, Austria	2005	7	7	15826753
Neumann ⁴¹	Albert-Ludwigs-University, Freiburg, Germany	1999	39	39	10027369
Roukounakis ⁴²	Polyclinic Hospital, Athens, Greece	2007	7	7	17761083
Walz ²⁸	Klinik für Chirurgie und Zentrum für Minimal Invasive Chirurgie, Kliniken Essen-Mitte, Akademisches Lehrkrankenhaus der Universität Essen, Essen, Germany	2004	318	96	15517476

Table 2

Patient Characteristics

	# of Patients	# of Studies
Total patients	417	22
Mean age, years (range)	44 (10–82)	18
Male (%)	42	16
Mean tumor size, cm (range)	2.62 (0.04–9)	17
Right side location (%)	50	16
Clinical Diagnosis	422 (100)	22
Conn's Syndrome/APA (%)	174 (42)	14
Pheochromocytoma (%)	157 (37)	12
Non-functional tumors (%)	51 (12)	6
Cushing's Syndrome/CPA (%)	40 (9)	5

Table 3**Surgical Characteristics**

	# of Patients	# of Studies
Patients with a description of surgical approach	417	22
Patients treated laparoscopically (%)	319(76)	17
Patients treated via open approach (%)	98 (24)	6
Laparoscopic to open conversion (%)	2 out of 308 (0.7)	16
Partial to total adrenalectomy (%)	7 out of 281 (2.5)	12
Perioperative Outcomes		
Mean estimated blood loss, ml (range)	72 (0–1500)	12
Number of transfusions (%)	2 out of 231(0.9)	7
Mean operative time, minutes (range)	130 (37–2516)	14
Mean post-operative hospital stay, days (range)	7.8(2–18)	8
Perioperative complications (%)	27 out of 363 (7.4)	16
Long-term Functional Outcomes		
Mean follow-up, months (range)	56	15
Recurrence (%)	9 out of 303 (3.0)	15
Mean time to recurrence, months (range)	113(36–324)	4
Long-term daily steroid requirement (%)	7 out of 133 (5.3)	10

Table 4**Complications**

Total patients (%)	363 (100)
Complications	27 (7.4)
Abdominal wall laxity	5 (1.4)
Hemorrhage	5 (1.4)
Pneumonia	3 (0.8)
Pneumothorax	3 (0.8)
Wound infection	3 (0.8)
Hyperesthesia	2 (0.6)
Sepsis	1 (0.3)
Ileus	1 (0.3)
Migrated drain tube post-surgery	1 (0.3)
Omental herniation	1 (0.3)
Hypertension	1 (0.3)
Renal vein injury	1 (0.3)

Table 5**Etiologic Factors of Acquired Adrenocortical Insufficiency⁴³⁻⁴⁵**

I.	Idiopathic
a.	Autoimmune
i.	Polyglandular autoimmune syndrome type 1
ii.	Polyarteritis nodosa
b.	True idiopathic
II.	Infectious
a.	Bacterial
i.	Meningococcemia, acute fulminating
b.	Granulomatous
i.	Tuberculosis
c.	Protozoal & Fungal
i.	Histoplasmosis
ii.	Blastomycosis
iii.	Coccidioidomycosis
iv.	Candidiasis
v.	Cryptococcosis
d.	Viral
i.	Cytomegalovirus
ii.	Herpes simplex virus
iii.	HIV/AIDS
III.	Infiltrative
a.	Sarcoidosis
b.	Metastatic disease
c.	Lymphoma/Leukemia
d.	Hemochromatosis
e.	Adrenoleukodystrophy
f.	Amyloidosis
g.	Iron Deposition>
IV.	Neoplastic
a.	Primary adrenal neoplasm
b.	Secondary adrenal neoplasm
c.	Loss of adrenal during treatment of Renal Cell Carcinoma
V.	Hemorrhage
a.	Waterhouse-Friderichsen syndrome
b.	Heparin-induced thrombocytopenia
c.	Antiphospholipid syndrome
d.	Trauma
VI.	Drug related
a.	Activation of cortisol metabolism
b.	Inhibition of enzymes responsible for cortisol synthesis

VII. Endocrine disorders

- a. Hashimoto's disease
- b. Pernicious anemia
- c. Diabetes Mellitus

VIII. Other

- a. POEMS syndrome
- b. Irradiation
- c. Anorexia-Nervosa