Running Title: Partial vs. Total adrenalectomy-Simforoosh et al.

Symptom Resolution and Recurrence Outcomes after Partial Versus Total Laparoscopic Adrenalectomy: 13 years of Experience with Medium-Long Term Follow up

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Abstract

Background: Partial adrenalectomy (PA) is an emerging modality typically performed for the treatment of hereditary and sporadic bilateral tumors, to reduce the risk of adrenal failure. In this study, we evaluated the recurrence and functional outcomes after partial and total adrenalectomy (TA).

Materials and methods: From March 2005 to July 2018, 284 patients with functional tumor or > 5 cm adrenal mass underwent clipless and sutureless laparoscopic partial or total adrenalectomy (PLA and TLA). Patients with a pathological diagnosis of pheochromocytoma, Cushing or Conn's disease and more than two yea follow up were included in this study. Pre-operative and operative variables were collected retrospectively and functional outcomes and recurrence were gathered prospectively.

Results: One hundred forty patients (mean age: 43±5.1years) were included in the study. PLA and TLA were performed for pheochromocytoma (total n=78; PLA=12 (15%), TLA=66 (85%)), Cushing syndrome (toal n=17; PLA = 4 (24%), TLA = 13 (76%)), and Conn's disease (total n=45; PLA=7 (16%), TLA=38 (84%)). In pheochromocytoma patients, improvement of hypertension, palpitation, and headache was not different between patients who underwent PLA versus TLA (all P > 0.05). Two recurrences were observed in patients with pheochromocytoma and they had undergone TLA. In patients with Cushing disease, central obesity, fascial plethora and hypertension were improved in all patients six months after treatment, muscle weakness was improved one year after surgery, and acne and hyperpigmentation only improved two years after surgery. Length of time for resolution of symptoms was not different in patients who underwent PLA versus TLA. In Conn's disease hypertension was resolved in all patients and no patient required potassium supplements post-operatively. In follow up no recurrence was observed in patients with a pathological diagnosis of Cushing or Conn's disease.

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Conclusion: In our experience, PLA can provide excellent control of the symptoms parallel with TLA and with no statistically significant difference in recurrence making PLA an attractive option in patients with an adrenal mass.

Keywords: adrenalectomy; laparoscopy; partial; adrenal sparing surgery; cortical sparing surgery; recurrence

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INTRODUCTION

Adrenal masses are relatively common among the general population, with an autopsy series of 3–5% (1). Most of these lesions, when they are first detected, are benign nonfunctioning adrenal adenomas, but they can also be functional and secretory (2). Laparoscopic total adrenalectomy—first introduced by Dr. Gagner (3)—is an acceptable method for treating these adrenal masses. Simforoosh et al. (4) reported the first laparoscopic adrenalectomy in Iran. However, the adrenal insufficiency that follows bilateral adrenalectomy results in a lifelong risk of morbidity due to Addisonian crisis (35%), which, in turn, can compromise a patient's quality of life (5).

Consequently, over the last two decades, increasing enthusiasm has been created in partial adrenalectomy (PA). Although PA has produced successful results, the risk of the recurrence of tumor remains a concern, as this risk and the associated efforts to detect recurrences require lifelong clinical and biochemical surveillance. Previous studies have revealed that cases of Conn's adenoma seem to be a reliable indication of PA due to its benign behavior and eccentric location and that curative biochemicals seems to be the result of PA in almost all cases (5, 6).

Compared with Conn's syndrome patients, experiences with PA are minimal in Cushing's syndrome patients. Walz and colleagues (7) evaluated PA in 22 patients with adrenal neoplasia,

including four patients with Cushing's adenoma. Recurrence was not observed in any patients after a median follow up of 6.5 years. Data on the recurrence of inherited pheochromocytoma after PA are inconsistent. Following adrenal sparing surgery, Inabnet et al. (8) reported relapse in three of five patients, and van Heerden et al. (9) observed relapses in two patients. However, others found no relapses or only one relapse in larger series.

Due to these limited and controversial data regarding the efficacy and safety of PA versus TA in adrenal masses, this study was conducted to evaluate the efficacy and safety of these surgical approaches in the treatment of pheochromocytoma, Cushing and Conn's disease.

MATERIALS AND METHODS

Patients and settings

This was a retrospective-prospective study conducted from March 2005 to July 2018. All patients with radiologically confirmed adrenal masses underwent clinical examination and biochemical evaluations. Ultrasonography and abdominal CT scan was preoperatively performed for all patients. MRI was performed if CT scan was inconclusive. Routine biochemical tests such as serum sodium and potassium levels, fasting blood sugar, and endocrine analyses such as serum cortisol, ACTH, mineralocorticoids, and 17-hydroxyprogesterone, and 24-hour urinary VMA were also performed when indicated. Patients who had biochemically active adrenal masses or clinically unapparent adrenal mass more than five cm were scheduled for PA or TA. Patients with pathological diagnosis other than pheochromocytome, Cushing or Conn's disease were excluded from the study. Patients were also excluded if surgery was planned as open surgery form the outset or if surgery was converted to open surgery or whether follow up duration was less than two years.

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The study was approved by the Ethics Committee at Shahid Beheshty University of Medical Sciences. All of the surgeries were performed by expert endourologists.

Surgical Procedure

Transperitoneal laparoscopic total adrenalectomy (TLA) was carried out as previously described and is summarized below (10). Patients received oral phenoxybenzamine for adequate alpha blockade in case of high preoperative cathecholamines or when there was preoperative suspicion to pheochromocytoma. Under general anesthesia, the patients were positioned in flank with an angle of about 60 degrees. Small umbilical incision was created under direct visualization to enter the abdominal cavity and pneumoperitoneum was then rapidly created with CO2. Three 5 mm trocars were inserted under direct vision. For right-side adrenalectomy, we inserted another 5 mm trocar to retract the liver. We used bipolar cautery to coagulated adrenal veins and then divided veins by cold scissors. No vascular staplers, clips, or any other energy sources were used for the closure of adrenal vessels as described earlier(10). Adrenal glands were separated from the surrounding tissue by sharp or blunt dissection and use of bipolar cautery. Specimens were retrieved from the abdominal cavity using an Endobag through enlargement of the umbilical or lower quadrant port sites. For partial adrenalectomy the same protocol was used. Adrenal masses were identified and divided from the rest of normal adrenal tissue by cold scissors and bleeding was controlled by bipolar cautery.

Patients' Follow-up

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A retrospective chart review was designed to obtain demographic, biochemical, hormonal, operative, and postoperative parameters, including the length of hospital stay, surgical time, major complications and steroid dependence at follow-up of PA. The size of the resected adrenal mass was determined by pathologic reports. Follow-up consisted of abdominal CT or magnetic resonance imaging, clinic visits, plasma or 24-hour measurement of adrenal hormones as indicated by pathology reports 3-6 months after operation and then annually. In Conn's disease follow-up included the measurement of the blood pressure, and serum potassium.

In Cushing's disease, patients were investigated for Cushing symptoms or signs in each follow up visit. Patients were asked to report symptoms that they experienced before surgery and symptoms that they had at follow up visits. In case of symptom resolution, patients were asked to estimate the duration of symptom presence after surgery. The survey also inquired if patients were on steroids in bilateral cases and for how long steroids were required postoperatively. Specific questions related to the management of diabetes and hypertension were also included, looking specifically at how their disease was currently treated and whether or not they were on medication or dietary modifications for this condition. Diabetes and hypertension resolution were also verified by patient chart review, looking at blood pressure measurements, serum glucose measurements, and medication profiles whenever possible.

Statistical analysis

We used an independent t test for normally distributed data. Chi-squared test was implemented to compare nominal data. Statistical analysis was performed using SPSS version 18.0 software. Statistical significance was set at $P < 0.05$.

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RESULTS

A total of 284 patients were operated for adrenal mass during the study period. A number of 144 patients were excluded for not having a pathologic report of pheohromoytoma, Cushing or Conn's disease (n=133), or for short follow-up (n=11). Finally, 140 patients were followed for a mean follow-up of 65 months. The demographics of patients, their operative and postoperative parameters is illustrated in **Table 1**.

Pheochromocytoma

Seventy-eight patients underwent laparoscopic surgery due to phaeochromocytoma. Ninety percent of our patients had hypertension (mean: 230±11 mmHg) preoperatively, and 87% of them were improved post-operatively (mean: 130±7 mmHg) (P= 0.001). Patients went from a mean of 2.8 ± 0.7 antihypertensive medications pre-operatively to 0.8 ± 0.2 medications (P<0.001). Eighty seven percent of our patients had palpitation preoperatively, and 83% of them improved post-operatively (P<0.001). Twenty three percent of our patients had headache preoperatively, and 73% of them improved post-operatively (P=0.02). Improvement of hypertension, palpitation, and headache was not statistically different between patients who underwent PLA versus TLA (**Table 1**).

Six cases (4 cases in TA group and 2 cases in PA) in pheochromocytoma underwent bilateral adrenalectomy. None of the patients who underwent PA required permanent steroid supplements post-operatively while patients who underwent bilateral TLA were on steroid replacement.

After a six-year follow-up, two cases who underwent TLA were visited in our clinic because of hypertension and biomarker recurrence. Their images showed recurrence of pheochromocytoma

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in the site of surgery and they were scheduled for tumor resection. After a second operation, they did not have recurrence in a one-year follow-up.

Cushing's Syndrome

Seventeen patients underwent laparoscopic surgery due to Cushing's disease, of these, 4 (24%) underwent PA and 13 (76%) patients underwent TA. After a six-month follow-up, symptoms such as central obesity, fascial plethora and hypertension were improved in all patients. Ninety-two percent reported dramatic changes. But symptoms such as muscle weakness, acne and hyperpigmentation did not improve completely.

After a one-year follow-up, symptoms such as muscle weakness improved in all patients and 90% reported dramatic changes. These changes were not significant between the two study groups (P=0.46). Nevertheless, acne and hyperpigmentation did not resolve completely.

In the second year after surgery, patients were evaluated for symptoms such as acne and hyperpigmentation almost at a similar time interval. Symptoms were resolved in both groups similarly. **Figure 1** outlines the time line of symptom resolution in patients after Cushing surgery. There was no recurrence in patients with a pathology diagnosis of Cushing. Three cases (2 cases in TLA group and 1 case in PLA) in Cushing underwent bilateral adrenalectomy. The case of PLA did not require permanent steroid supplements post-operatively.

Finally, the patients had persistent symptoms including diabetes (81%), hyperpigmentation (89%), obesity (61%) and hypertension (62%). Using a univariate analysis, we compared all of the patients who had unresolved symptoms after adrenalectomy to those that had a complete response, and we were unable to identify any factor that could be a predictive of failure to respond to adrenalectomy. Evaluated factors included age (P = 0.51), gender (P = 0.07), diagnosis (P = 0.24),

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treatment pre-operatively with adrenolytic medication (P = 0.50), serum cortisol level (P = 0.12), and urine cortisol level (P = 0.34).

Time of symptom resolution varied from weeks to up to eighteen months (**Figure 1**). Most changes in physical examination were observed within a mean of six months after operation. However, hyperpigmentation took an average of thirteen months for resolution. There was significant variability among patients in how long it took for symptoms to resolve.

Conn's syndrome

Forty-five patients underwent laparoscopic surgery due to Conn's syndrome; 7 (16%) underwent PA and 38 (84%) patients underwent TA. The maximum mean systolic blood pressure measured was 207 ±25.7 mmHg and the maximum mean diastolic pressure was 114±18.7 mmHg. Elevated blood pressure had first been diagnosed 6.5 ±2.5 years before the operation. Thirty-two patients (71%) suffered from hypokalemia with a mean minimal level of 2.6 ±0.3 mmol/L. In a retrospective analysis, hypokalemia was first detected 1.8 ± 2.1 years before surgery.

In the first follow up after surgery, no patient required potassium supplements and all patients in the two groups showed improvement in hypertension. After an eight-year follow up, there was no recurrence in the two groups.

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DISCUSSION

In this series, we observed no statistically significant differences between the PLA and TLA groups in terms of the mean operative time, intra-operative blood loss, duration of hospital stay, complications, or postoperative morbidity. Also, the functional results for PA and TA were

comparable in the treatment of adrenal tumors. While no recurrences were detected at the 65-month (on average) follow-up for patients with Cushing's adenoma and Conn's syndrome, two recurrences were observed in patients in the pheochromocytoma group who underwent TA.

Most of the time, pheochromocytoma is a non-familial sporadic tumor. However, it can present itself as a genetic disease with an autosomal dominant inheritance of high penetrance that can occur either in isolation or in combination with other pathologies (11). Patients with bilateral pheochromocytomas are treated with total bilateral adrenalectomy. Despite the fact that cortical-sparing adrenalectomy was introduced in 1999, it is still a relatively underutilized procedure (12, 13). A recent meta-analysis (14) reported that PA can reduce the need for steroid replacement therapy and has a low risk of recurrence. However, this knowledge is based mainly on retrospective case series with small sample size.

Overall, there is little evidence supporting the use of partial adrenalectomy in treatment of bilateral pheochromocytomas, leading to a paltry recommendation in the recent guidelines on the management of pheochromocytoma (14, 15). However, we have shown that the functional outcomes of PLA and TLA were comparable in the treatment of pheochromocytoma.

Indeed, while functional outcomes of surgery are encouraging, the data regarding recurrences need to be critically evaluated. In our cohort, tumors recurred in two patients. Recurrence in pheochromocytoma ca be a true recurrence due to positive surgical margins, recurrence due to multifactorial nature of disease in PLA surgeries, or a de novo lesion. A relatively high rate of "recurrence" in a hereditary pheochromocytoma population might merely reflect the multifocal nature of the disease rather than a "true" recurrence at the site of resection (16).

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Hereditary pheochromocytomas have recurrence rates ranging from 0–100% (17, 18). Walz et al. suggest that this wide range may be due to the different follow-up times employed in different studies, as recurrences are often seen more than 10 years after the initial tumor is removed (13). The rate of recurrence in the hereditary disease might also be a result of detection and screening biases, as these patients are likely to undergo periodic radiographic surveillance. The small number of recurrences in our study (two out of 78 patients) limit our ability to identify patients who are at risk for recurrence. It is unclear if any specific tumor type or lesion size is more likely than others to be associated with recurrences within the ipsilateral gland.

The adverse side effects associated with chronic steroid dependence have led the surgeons to endorse a PA procedure in the treatment of adrenal tumors. Too little steroid replacement can lead to Addisonian crisis and death and too much can cause osteoporosis, diabetes and hypertension. The amount of residual adrenal cortical tissue to be left in situ to maintain acceptable cortical functioning while ensuring adequate tumor clearance is a topic of debate. Most authors suggest that a margin of at least 3-5 mm is necessary to attain good results (16). A recently published review indicates that 5.3% of patients require long-term steroid replacement therapy (16). Most patients who require steroid replacement therapy had suffered from bilateral disease, although some had only unilateral adrenal involvement.

Although only 5.3% of patients require long-term steroid replacement, Yip et al. found that approximately 35% of patients undergoing PA for bilateral resection were steroid dependent (19). Nevertheless, our findings related to steroid dependence agree with the data presented in a recently published review article (16). This meta-analysis showed that patients in PA groups were less dependent on steroids than TA patients.

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Cushing's syndrome is a result of excess cortisol, which lead to devastating metabolic, physical, and mental changes. In our study, we included only those patients who underwent adrenalectomy as part of their treatment. Therefore, our patient population might not be generalizable to all patients with Cushing's syndrome. Specifically, our findings might not be relevant to patients with pituitary Cushing's syndrome who underwent successful transsphenoidal resection treatment.

In a follow-up, we found that after six months, measurable symptoms, such as central obesity, facial plethora, and hypertension, had improved in all patients. After a one-year follow-up, symptoms such as muscle weakness had improved. Acne and hyperpigmentation were resolved after two years.

Fu et al. (20) conducted a randomized trial on Conn's disease by comparing PA and TA. They demonstrated that PA had a shorter operative time than TA, but this difference was not statistically significant. However, the intraoperative blood loss observed in the PA group was significantly higher than in the TA group. For the PA cohort, a decreased dose of antihypertensive medication was prescribed at the final follow-up. We found that the levels of intraoperative blood loss were comparable between the two groups. Perhaps this is because of the experience in laparoscopic adrenalectomy procedure. Adrenal surgical expertise is not widespread, as less than 30 percent of all surgeons perform more than four adrenalectomies per year (21). Partial adrenalectomy needs even higher surgical expertise and, therefore, should be performed by very experienced adrenal surgeons.

Ishidoya et al. (22) recommended the use of TA over PA for patients with unilateral aldosterone-producing adenoma and primary hyperaldosteronism. All patients who underwent TA recovered from hypertension, suppressed plasma renin activity, and high plasma aldosterone. However, two of the 29 patients treated with PA or enucleation still experienced hypertension with high plasma

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aldosterone. Nevertheless, our results agree with the data provided in a recently published meta-analysis that demonstrated an aldosterone-producing adenoma recurrence rate of 2%. Also, 97% of the considered patients were steroid independent, indicating that PA is efficacious in alleviating Conn's syndrome.

The present study had several limitations. The retrospective portion of the study did not allow for uniform data collection for some variables. However, the design employed enabled us to perform a longitudinal follow-up and include a large sample size, which would be impossible in a purely prospective study of this rare disease. Moreover, our survey study design had limitations, including the potential for patient recall bias and response bias in the evaluation of Cushing's syndrome symptoms and their resolution time after surgery. Also, because of the small number of recurrences, it was not possible for us to determine which factors are likely associated with recurrences. Furthermore, the non-randomized nature of this study renders if prone to selection bias. Patients with larger tumors or more aggressive tumors could have a higher chance of undergoing TLA. Nonetheless, this series is a large series with a moderate-long term follow up indicating the safety of PLA for pheochromocytoma, Cushing and Conn's disease.

CONCLUSIONS

In our experience, PLA can provide excellent control of the symptoms parallel with TLA and with no statistically significant difference in recurrence making PLA an attractive option in patients with an adrenal mass.

CONFLICT OF INTEREST

No competing financial interests exist.

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Figure legendS

Figure 1. Symptom resolution after adrenalectomy in Cushing disease.

Table 1. Comparison of demographic, operative, and post-operative data in patients who underwent partial versus total adrenalectomy.

Variables	Partial Adrenalectomy	Total Adrenalectomy	P-Value
Total pathologies, N=140	N=23	N-117	
Age (Years)	39.05 ± 12.26	41.18 ± 13.38	0.78
Gender, Male/Female	13 / 10	52 / 65	0.56
Side, Right/left	12 / 11	83 / 34	0.08
Tumor Size (Cm)	4.32 ± 3.09	5.44 ± 3.08	0.12
Operative Time, min	103 ± 15	112 ± 10	0.23
Pheochromocytome, N=78	N=12	N=66	
HTN improvement, N(%)	11(89)	60(91)	0.62
Palpitation improvement, N(%)	11(89)	57(86)	1.0
Headache resolution, N(%)	8(66)	48(72)	0.73
Recurrence, N(%)	0(0)	2(3)	1.0
Cushing syndrome, N=17	N=4	N=13	
Bilateral adrenalectomy, N(%)	1(25)	2(15)	1.0
Recurrence, N(%)	0(0)	0(0)	1.0
Conn's Syndrome, N=45	N=7	N=38	
HTN improvement, N(%)	4(100)	38(100)	1.0
Potassium supplement, N(%)	0(0)	0(0)	1.0
Recurrence, N(%)	0(0)	0(0)	1.0

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