Original Article

Surgical and functional outcomes of bilateral synchronous adrenalectomy for functional tumors: A cohort study

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ABSTRACT

Introduction: Bilateral synchronous adrenalectomy has the potential for significant surgical and functional morbidity. We reviewed our 15-year experience with bilateral synchronous adrenalectomy to assess the safety, surgical outcomes, morbidity, and impact on health-related quality of life (QoL).

Materials and Methods: In an IRB-approved study, we reviewed our database of patients who underwent bilateral synchronous adrenalectomy for functional tumors between April 2008 and August 2022. Demographic profile, metabolic and radiological parameters, operative details, and complications were recorded. Follow-up was obtained either in-person or telephonically and analyzed for resolution of symptoms, QoL using the WHO-QoL BREF questionnaire, and complications of chronic steroid intake. Data were reported descriptively and compared between laparoscopic and open approaches.

Results: During the study period, 337 adrenalectomies were performed, of which, 51 were bilateral and in 48 patients both the surgeries were performed synchronously. Thirty-three of these 48 patients had bilateral pheochromocytomas and 15 had Cushing's syndrome. Among patients with Cushing's syndrome, three had life-threatening symptoms requiring urgent bilateral surgery. Forty patients underwent transperitoneal laparoscopic surgery and 8 underwent open surgery. There were two intraoperative and 7 post-operative complications. Forty-three patients were available for follow-up. All had resolution of symptoms and body mass index (BMI) changes, and only two patients continued to receive one antihypertensive medication. Episodes of steroid deficiency occurred in 7 patients while steroid excess occurred in 3 patients. QoL was satisfactory in all the patients in all the domains.

Conclusions: Bilateral synchronous adrenalectomy is safe and feasible for functional adrenal tumors. It leads to symptom resolution with amelioration of hypertension and BMI changes with satisfactory overall QoL.

INTRODUCTION

Bilateral adrenalectomy is an infrequently performed surgery due to its limited indications which include patients with bilateral pheochromocytomas,[1] refractory Cushing's syndrome;[2] and some types of congenital adrenal hyperplasia.[3] The surgery can either be performed synchronously or in two separate sittings. The former has the advantage of a single anesthesia exposure and thus an overall shorter recovery time. With improvements in the anesthetic care, experience in laparoscopy, and establishment of safety and efficacy of laparoscopic adrenalectomy,[4-7] the approach to bilateral adrenalectomy has shifted from staged open surgery to synchronous laparoscopic surgery.

Unlike unilateral surgery, bilateral adrenalectomy has the potential for significant surgical and functional morbidity

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with the need for lifelong steroid replacement. Apart from variability in the symptom resolution, there is potential for both Addisonian crisis and iatrogenic Cushing's syndrome from the under and overtreatment with steroids, respectively, and the metabolic effect of hypercortisolism.

We are a tertiary referral center and have previously reported our outcomes for pheochromocytoma surgery.[8] We reviewed our 15-year experience with bilateral synchronous adrenalectomy for surgical outcomes, long-term morbidity and mortality, and its impact on health-related quality of life (QoL) of patients.

MATERIALS AND METHODS

We reviewed our database for patients who underwent bilateral synchronous adrenalectomy for functional tumors between April 2008 and August 2022. Their clinical profile, operative details, and complications were retrieved from the records. This included details of history, physical examination, family and medication history, metabolic parameters as available (plasma and urinary catecholamines and their metabolites, plasma and urinary cortisol, dexamethasone suppression test, and selective adrenal vein sampling), and radiological parameters (contrast-enhanced computed tomography (CT), magnetic resonance imaging, meta-iodo-benzyl-guanidine scan, and ^{68}Ga-DOTANOC positron emission tomography/CT scans).

All the patients were contacted on the phone numbers on the record, and follow-up was obtained either in-person or telephonically and analyzed for resolution of symptoms, complications of chronic steroid intake, and QoL using the WHO-QoL BREF questionnaire.[9] All the data collected were reported descriptively and also compared between laparoscopic and open surgery groups.

All patients provided written informed consent and were guaranteed confidentiality. The institutional review board, ethics committee study approval number was IEC-461/17.06.2022. The authors confirm the availability of, and access to, all the original data reported in this study.

Preoperative management

All the patients were managed by a multidisciplinary team involving an endocrinologist, an anesthetist, and a urologist. For patients with pheochromocytoma, hypertension was managed using selective alpha-blockers, preferably prazosin along with oral fluid and salt replenishment. Calcium channel and beta blockers were added as required and the usual duration of therapy was 7–10 days. The criteria for acceptance for surgery were control of hypertensive surges in the preoperative period. Intraoperative anesthesia was managed with standard anesthetic drugs with avoidance of histamine-releasing drugs which theoretically have the propensity to cause hypertensive crisis (e.g., succinylcholine and morphine). Patients with Cushing's Syndrome were managed with control of hypertension, hyperglycemia, and dyselectrolytemia using the standard protocols and were accepted for surgery when reasonable control was achieved, keeping in consideration that the continued tumor presence will lead to further deterioration of physiological milieu and early removal of functional tumors is highly desirable. Hypertensive surges, resulting from tumour manipulation (more so with pheochromocytoma) were managed using intravenous nitroprussides and alpha-and beta-receptor blockers.

Operative details

A replacement dose of hydrocortisone and cephalosporin antibiotic prophylaxis was administered to all patients on the morning of surgery. The stomach was decompressed with an orogastric or nasogastric tube.

Open surgery was usually selected for patients with large tumors or those anticipated to require additional procedures and performed either via a Chevron (roof-top) or a midline incision in the supine position. Laparoscopic surgery was performed through a lateral transperitoneal approach with the patient in the lateral decubitus position (at a 75° angle). The position was changed between the two sides for laparoscopy. The pneumoperitoneum was created using a Veress needle. In patients with bilateral pheochromocytomas, the side with the larger tumor was operated first. For Cushing's disease, the right side was usually operated first as a matter of surgeon's choice. Four ports were used for the right side including one port for liver retraction. Ports on one side were closed before turning the patient to the second side. Three separate ports were used for left-side surgeries [Figure 1]. Additional ports were placed if required but this was rare. On the right side, the peritoneum was incised on the lateral border of the inferior vena cava, the undersurface of the liver, and at the lower border of the adrenal gland. The medial margin of the adrenal was separated from the vena cava to identify the adrenal vein at its craniomedial end which was ligated and divided, followed by complete mobilization of the gland. On the left side, the splenic flexure of the colon and the spleen were mobilized completely to expose the diaphragm and the greater curvature of the stomach. This allowed the colon to fall away medially with the spleen. The renal vein was identified and the adrenal vein was clipped on its cranial border before further mobilization of the adrenal gland. Drains were placed selectively and rarely in the more recent procedures.

Postoperative care

Patients with poorly controlled hypercortisolism or those requiring inotropic support after the surgery were managed in the intensive care or high dependency unit till they were stable. Blood glucose and electrolytes were routinely monitored, and antihypertensive and hypoglycemic drugs were added if required.

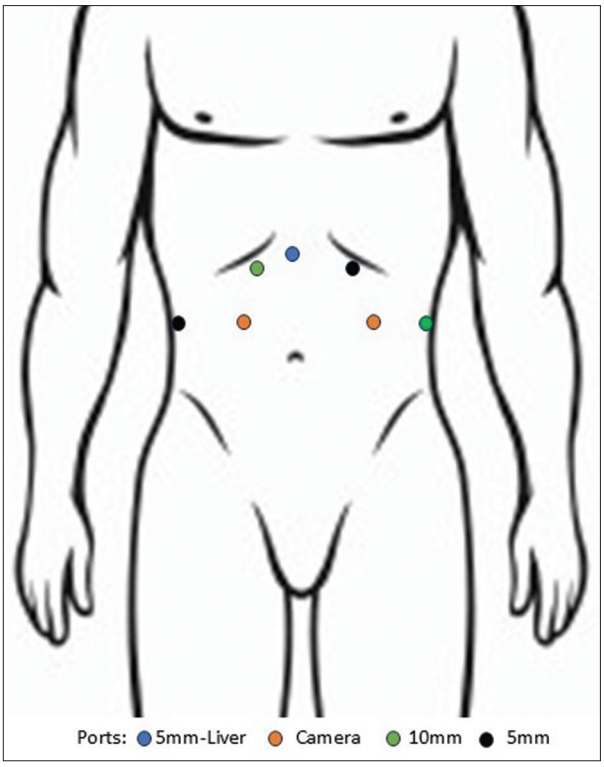

Figure 1: Port positions

Steroid replacement

At the induction of anesthesia, 100 mg iv hydrocortisone was administered. After bilateral adrenalectomy, hydrocortisone was started at 200 mg/day in 4 divided doses and was tapered by 50 mg/day each day if the patient was stable and clinically stable with no postoperative complications. On day 3, if the patient was accepting orally and was hemodynamically stable on a hydrocortisone dose of 100 mg/day, oral prednisolone overlap was started at 15 mg/day in two divided doses (10 mg at 8:00 am, 5 mg at 4:00 pm) followed by discontinuation of hydrocortisone over the next 2 days. Once hydrocortisone infusion was stopped, fludrocortisone 50 mcg daily was added. For adults, the usual maintenance dose of prednisolone was 5 mg and 7.5 mg in two doses or hydrocortisone (15 mg to 25 mg in three divided doses) to be adjusted on the follow-up.

On follow-up, patients were monitored on the basis of clinical assessment, including body weight, postural change in blood pressure, energy levels, and signs of frank glucocorticoid excess. Serum cortisol levels were not monitored. Fludrocortisone replacement was started at 50 –100 mcg/day with *ad libitum* salt intake with monitoring the patient on follow-up with clinical assessment (salt craving, postural hypotension, or pedal edema), blood electrolyte measurements (serum sodium and potassium levels), and direct renin concentration.

Statistical analysis

Data were analyzed using Stata 14.0 statistical software (StataCorp, Texas, USA). Data were tested for normality by Kolmogorov–Smirnov test. Categorical data were expressed as frequency and percentages. Quantitative variables were expressed as mean ± standard deviation. Independent *t*-test was used to compare quantitative variables between the types of diagnosis and operative approach. Chi-square and Fisher's exact test were used to compare categorical variables. Those variables that did not follow normal distribution were expressed as median and quartiles and were compared by rank sum test.

RESULTS

Between April 2008 and August 2022, a total of 337 adrenalectomies were performed on 286 patients at our department. Of these, 51 patients underwent bilateral adrenalectomy. Among these 51 patients, one patient underwent surgery for nonfunctional adrenocortical carcinoma, and in 2 patients, the bilateral adrenalectomy was performed in a staged manner for bilateral pheochromocytomas. The remaining 48 patients underwent bilateral synchronous adrenalectomy for functional adrenal tumors. Thirty-three of these 48 patients had bilateral pheochromocytomas and 15 patients had refractory Cushing's syndrome. Among the patients with Cushing's syndrome, three had life-threatening symptoms requiring urgent bilateral surgery. Clinical details of the patients are presented in Table 1.

Among patients with bilateral pheochromocytomas, 60% presented with the classical triad of headache, palpitations, and hypertension. Thirteen patients had syndromic association (VHL – 4 patients, MEN 2A – 9 patients, and MEN 2B – 2 patients). The median tumor size was 4 cm (range: 1–17 cm). Patients with Cushing's syndrome were predominantly female and all had cushingoid features and hypertension and 53% had diabetes mellitus.

Operative details and complications

Out of the 48 patients, 40 underwent surgery via a laparoscopic approach. One patient required conversion to open surgery on the left side due to dense adhesions with the tail of the pancreas and non-progression of the dissection. Among the 8 patients undergoing open surgery, 1 patient had Cushing's syndrome. The median size (range) of the tumor among patients who underwent open surgery was 6.7 cm (4–17 cm).

The mean operative time (188.2 ± 51.2 vs. 217.5 ± 67.5 min), blood loss (100 vs. 625 ml), and hospital stay (3 vs. 7 days) was shorter for the laparoscopic approach [Table 2]. One patient in each group had a diaphragmatic injury and postoperative complications occurred in 6 patients in the laparoscopic group (seizure, adrenal bed collection, subhepatic hematoma, mastoid abscess, acute retinal necrosis, and pneumothorax in one patient each) and in only one patient in the open group (surgical site infection

Table 1: Demographic characteristics and clinical data

Parameter	Pheochromocytoma (*n*=33)	Cushing's syndrome (*n*=15)
Mean age (years±SD)	31.5±13.7	28.5±8.9
Gender (male:female)	17:16	2:13
Median duration of symptoms (range) (months)	12 (1–180)	24 (2–180)
Symptoms		
Headache	19 (57.6)	3 (20)
Palpitations	21 (63.6)	1 (6.7)
Sweating	20 (60.6)	1 (6.7)
Cushingoid features	1 (3.03)	15 (100)
Abdominal pain	12 (36.4)	0
Hypertension	29 (87.9)	15 (100)
Diabetes	6 (18.2)	8 (53.3)
Cardio/cerebrovascular events	3 (9.1)	0
Family history positive	16 (48.5)	1 (6.7)
Median 24 h urine catecholamines (range)		
VMA (mg/day) (*n*=11)	24.3 (6.96–48.9)	-
Epinephrine (μg/day) (*n*=21)	40.45 (3.38–518.9)	-
Nor-epinephrine (μg/day) (*n*=19)	225 (13.31–2671)	-
Metanephrine (μg/day) (*n*=6)	1102 (68.93–10,040)	-
Normetanephrine (μg/day) (*n*=6)	3321.5 (231.4–10,060)	-
Median serum catecholamines (range)		
Epinephrine (pg/mL) (*n*=2)	59.01 (22.03–96)	-
Nor-epinephrine (pg/mL) (*n*=1)	234	-
Metanephrine (pg/mL) (*n*=2)	3532.85 (1415.7–5650)	-
Normetanephrine (pg/mL) (*n*=2)	9500 (8500–10,500)	-
Median serum cortisol (range) (μg/dL) (*n*=15)	-	40.32 (15.34–73.1)
Median tumor size (range) (cm)		
Right	4 (0.8–16.8)	-
Left	4 (1–17)	-

SD=Standard deviation, VMA=Vanillylmandelic acid

with pancreatic fistula with right popliteal deep venous thrombosis). There were no deaths in the perioperative period.

Long-term morbidity and quality of life

Three patients with bilateral pheochromocytomas and two patients with refractory Cushing's syndrome were lost to follow-up. The median duration of follow-up in patients with bilateral pheochromocytomas and refractory Cushing's syndrome was 72 months (9–157 months) and 51 months (2–102 months), respectively. All 43 patients had resolution of their symptoms [Table 2]. The antihypertensive requirement was reduced in both the groups with only one patient in each group requiring a single antihypertensive medication. Among the patients with diabetes mellitus, the requirement for hypoglycemic drugs declined. Patients with bilateral pheochromocytomas gained weight with an increase in their body mass index (BMI) from 20.2 ± 5.2 to 21.6 ± 4.8 kg/m^2 while those with refractory Cushing's syndrome lost weight with the decrease in BMI from 29.3 ± 7.8 to 25.4 ± 8.0 kg/m^2.

Episodes of steroid deficiency occurred in 7 patients, while iatrogenic Cushing's syndrome was diagnosed in 3 patients with bilateral pheochromocytomas. On follow-up, the QoL in 27 patients (who had a physical visit) was found to be satisfactory in all patients in all the domains [Table 2]. Four patients with bilateral pheochromocytomas died due to unrelated causes, whereas one patient with refractory Cushing's syndrome died due to pneumonia.

DISCUSSION

Bilateral adrenalectomy is a rare surgery, required in a limited number of patients with bilateral adrenal pathologies that are refractory to medical treatment. Current indications include bilateral pheochromocytomas, refractory Cushing's syndrome due to failed intervention for pituitary adenoma (surgery, radiotherapy, or stereotactic radiosurgery), ectopic ACTH-producing tumor with failed pharmacological treatment, inability to localize or remove the primary source, or due to some types of macronodular adrenal hyperplasia, and some types of congenital adrenal hyperplasia.[1-3] In addition, in patients with life-threatening complications from severe hypercortisolism, bilateral adrenalectomy may serve as a life-saving procedure, resulting in immediate and complete normalization of the blood cortisol levels. We found bilateral synchronous adrenalectomy, both by the open and laparoscopic approach, to be safe and effective without significant morbidity.

Historically, bilateral adrenalectomies were performed by an open approach. However, this approach was associated with high morbidity (40%) and mortality (5.6%).[10] With the establishment of safety and benefits of laparoscopy for adrenalectomy with oncological outcomes similar to open

Table 2: Operative and follow-up data

Operative data	Laparoscopic (*n*=40)	Open (*n*=8)
Median tumor size (cm) (range)	3.9 (1–8.7)	6.7 (4–17)
Mean operative time (min)	188.2±51.2	217.5±67.5
Median blood loss (mL) (range)	100 (50–1000)	625 (350–1000)
Median units of blood transfusion (range)	0 (0–2)	1 (0–3)
Mean preoperative hemoglobin (g/dL)	11.96±1.54	11.73±1.90
Mean postoperative hemoglobin (g/dL)	10.82±1.45	10.82±1.60
Median duration of hospital stay (range) (days)	3 (1–27)	7 (3–11)
Complications	7	2
Intraoperative	1	1
Postoperative (Clavien–Dindo grade)		
<3	1	1
3a	4	0
3b	1	0
Follow-up data (*n*=43)	**Pheochromocytoma (*n*=30)**	**Cushing's syndrome (*n*=13)**
Median duration (range) (months)	72 (9–157)	51 (2–102)
Symptom resolution, *n* (%)	30 (100)	13 (100)
Mean number of antihypertensive drugs (range)		
Preoperative	2 (1–4)	1 (0–4)
Discharge	0 (0–1)	0 (0–1)
Follow-up	0 (0–1)	0 (0–1)
Patients receiving hypoglycemic drugs		
Preoperative	6	8
Discharge	3	5
Follow-up	2	2
Known episodes of iatrogenic steroid excess	3	0
Known episodes of steroid insufficiency	5	2
Physical follow-up	*n*=15	*n*=12
Preoperative BMI (kg/m^2)	20.23±5.20	29.38±7.85
Follow-up BMI (kg/m^2)	21.66±4.88	25.40±8.0
Quality of life (WHO-QoL Bref)		
Overall	80±15.12	73.33±13.02
Physical	79.83±13.14	74.37±15.99
Psychological	81.33±14.25	71.12±18.06
Social	85.33±13.15	81.1±11.67
Environmental	83.16±17.10	77.91±16.61

BMI=Body mass index, QoL=Quality of life

surgery,[4-7] it is expected that the same benefits would accrue for bilateral surgeries. Synchronous bilateral surgeries decrease the overall anesthesia and operative time and allow a quicker overall return to normal activity without the intervening waiting period. With growing experience and evolving technologies, synchronous bilateral surgeries are performed in diverse circumstances including endourological management of renal and ureteric calculi with bilateral percutaneous nephrolithotomy[11] and ureteroscopy[12,13] and the management of solid renal masses with bilateral partial nephrectomies.[14]

One of the arguments against laparoscopy could be the need to reposition the patient between surgeries. Open surgery can be performed in the supine position, bilaterally. However, the length of the incision and amount of dissection required for such bilateral surgeries are visibly larger than the 7 ports required for bilateral laparoscopy. It could also be argued that the dissection and length of incisions would be shorter in the prone position with bilateral lumbar access surgeries[15,16] but these are extremely unfamiliar approaches to most of the surgeons and limit the ability to manage intraoperative complications. Outcomes between retroperitoneal and transperitoneal laparoscopic approaches are similar[15,16] and both would require repositioning since they use the lateral approach. A supine transperitoneal approach could theoretically be used[17,18] but is not common and we prefer the transperitoneal laparoscopic lateral approach owing to its familiarity, larger working space, and the ability to deal with diverse pathologies. Repositioning of the patient takes <15 min. We usually operate on the right side first (surgeon preference) and often leave a 10Fr feeding tube in the abdomen through the liver retraction port (with right-sided ports *in situ*) and use this for re-insufflation for the left side, thus saving time and preventing complications of access on the second side. With this approach, we did not encounter any pneumoperitoneum leak or surgical emphysema.

Our mean operative time for the laparoscopic approach was slightly over 3 h. This is significantly shorter than the 260 min reported in a systematic review of outcomes of bilateral adrenalectomy in patients with Cushing's syndrome that included 6 studies with 129 patients.[19] Chow *et al*.[20]

and Takata *et al*.[21] also reported a similar mean operative time of 264 min and 290 min, respectively. We would attribute this to the experience of the surgeon as well as the overall team involved in the care of these patients. Our experience of over 300 laparoscopic adrenalectomies has enabled fine-tuning of the operative steps and the assistance provided by the anesthesia team aids in quicker surgery and turnaround. Our overall surgical complication rate was 18.7% (9/48) with five being Clavien-Dindo grade 3 or higher. Surgery-related morbidity has been reported to vary from 6% to 31% (median 18%).[19] Chow *et al*.[20] reported an overall complication rate of 20% (3 intraoperative and 11 postoperative) in a retrospective review of 68 patients with Cushing's syndrome. Takata *et al*.[21] reported the overall rate of complication to be 13% in 30 cases where infectious and thromboembolic events comprised 41% and 18% of the complications, respectively.

More than 95% of the patients are expected to achieve symptom remission after the surgery for Cushing's syndrome.[19] In 7 studies, hypertension improved in 80%, diabetes mellitus improved in 75%, and patients with obesity experienced weight loss in 79% of the cases. Chow *et al*.[20] reported biochemical resolution in all the patients and resolution of hypertension, diabetes, and obesity in 64%, 29%, and 35% of the patients, respectively. Takata *et al*.[21] reported no signs of recurrent hypercortisolism in 17 of the 25 patients with Cushing's syndrome and biochemical cure in 5 patients with bilateral pheochromocytoma at a mean follow-up of 31 months. The median duration of follow-up in our cohort was 68 months. All 43 patients had resolution of their symptoms on follow-up with amelioration of hypertension and diabetes mellitus. Catecholamine excess leads to severe wasting, whereas hypercortisolism induces weight gain. After the surgery, BMI in both the groups of patients (pheochromocytomas and Cushing's syndrome) improved, reflecting the reversal of metabolic effects induced by hormone excess.

Three studies in patients with bilateral adrenalectomy for Cushing's syndrome with 97 patients specifically addressed QoL by standardized questionnaires.[22-24] Thompson *et al*.[22] examined 39 patients with a Cushing-specific questionnaire and the SF-12 v2 health survey and found that 86% of the patients were satisfied, whereas 11% felt no overall improvement in symptoms after the surgery. Hawn *et al*.[23] and Smith *et al*.[24] utilized SF-36 QoL questionnaire and found that 82% and 86% of the patients reported an overall improvement in their health status after the surgery. We found that the QoL in our 27 patients who had a physical visit on the follow-up was satisfactory in all the patients for all the domains. Satisfaction could be significantly related to symptom resolution and expectations from the surgery. The short hospitalization, single surgery, and near complete symptom resolution may have contributed to the satisfaction among our patients.

Patients requiring bilateral surgeries have the option of partial adrenalectomy which reduces the need for steroid replacement with its attendant risks of adrenal crisis and iatrogenic Cushing's syndrome at the cost of increased chances of recurrence of the primary pathology. Given the high risk of recurrence, it is an inappropriate option for patients with refractory Cushing's syndrome. For patients with bilateral pheochromocytomas, given the paucity of high-quality evidence, there is only a weak recommendation for partial adrenalectomy.[25,26] Neumann *et al*.[1] reported a multicentre cohort study evaluating the outcomes of partial versus total bilateral adrenalectomies for pheochromocytomas. Among 625 patients with bilateral pheochromocytomas, 401 were synchronous. 193 of these were planned to undergo partial adrenalectomy, but this could be achieved in only 141 (73%). Among the overall 248 patients who received cortical-sparing adrenalectomy, 13% developed another pheochromocytoma within the remnant adrenal after a median of 8 years, whereas 23% required hormone replacement despite adrenal-sparing surgery. On the other hand, all the patients who underwent total adrenalectomy required hormone replacement, and 31% developed either adrenal crisis or cushingoid features. Some of our patients had episodes of steroid deficiency and excess, both of which may occur due to under-dosing or over-dosing or change in the requirement such as during infections. In the study by Neumann *et al*., patients who underwent partial adrenalectomy had a smaller tumor size (median size 30 mm) compared with total adrenalectomy (median size 35 mm) and there was no survival benefit of partial adrenalectomy. In out study, the tumors were larger (median size 40 mm). None of the patients had a recurrence at follow up, whereas 23% developed symptoms of hormone deficiency or excess. While the tumor size may impact the decision to choose partial versus total adrenalectomy, we believe the issue remains unresolved.

This is one of the largest contemporary cohorts of patients undergoing bilateral adrenalectomy in a single center. It is limited by the retrospective nature of the evaluation. However, given the rarity of the procedure, a prospective evaluation with a prolonged follow-up does not seem to be feasible. Another limitation is the lack of baseline preoperative data on the QoL of patients undergoing the surgery to assess the impact of surgery.

Bilateral synchronous adrenalectomy is safe and feasible in patients with functional adrenal tumors. It leads to symptom resolution with amelioration of hypertension and BMI changes with a satisfactory overall QoL.

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