



LAPAROSCOPIC ADRENAL-SPARING SURGERY CASE SERIES: PARTIAL ADRENALECTOMY AND CYST RESECTION

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SUMMARY – The aim is to present our case series documenting indications, laparoscopic technique, surgical and endocrinologic outcomes of laparoscopic partial adrenalectomy. In the period from April 2011 until October 2021, we performed 39 procedures. The patients were divided into three groups: unilateral adrenal gland tumor with a normal contralateral gland (group 1), tumor of the solitary adrenal gland (group 2), and adrenal cysts (group 3). There were 20 patients in group 1, 6 patients in group 2, and 13 patients in group 3. The most common histology in group 1 was adenoma (40%), all tumors in group 2 were renal cell carcinoma metastases, and all cysts in group 3 were benign. There were no major complications (Clavien Dindo grade ≥ 2) in the whole cohort. All patients in groups 1 and 3 had favorable endocrinologic outcomes, and 50% of group 2 patients required lifelong hydrocortisone replacement therapy. The procedure is safe and feasible with favorable outcomes in the hands of a high volume adrenal surgeon.

Key words: *Laparoscopy; Adrenalectomy; Organ sparing treatments; Minimally invasive surgery*

Introduction

More than a century passed from the first reported total adrenalectomy performed by Thornton in 1889¹ to the first reported laparoscopic total adrenalectomy (LTA) by Higashihara in 1992², and then less than a decade for laparoscopy to establish itself as the standard in adrenal surgery³. Further advancement in surgical technique led to organ sparing adrenal surgery and the first retroperitoneoscopic partial adrenalectomy by Walz *et al.* in 1996⁴ and then laparoscopic by Janetchek *et al.* in 1997⁵. Adrenal function preservation increases the quality of life and decreases the need

for supplementation therapy⁶. Laparoscopic partial adrenalectomy (LPA) has been proposed as a feasible option not only in bilateral and solitary adrenal gland tumors, but also for monolateral small adrenal tumors⁶ and metastases⁷.

The first LTA in our institution was performed in January 1997⁸ and the first LPA in January 2008. In this study, we present our case series documenting indications, laparoscopic technique, surgical and endocrinologic outcomes.

Materials and Methods

We performed a retrospective case series study of 39 LPA performed in our center from April 2011 until October 2021. The patients were divided into three groups: unilateral adrenal gland tumor with a normal contralateral gland (group 1), tumor of the solitary

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adrenal gland (group 2), and adrenal cysts (group 3). In our center, every patient with an adrenal tumor is discussed at a multidisciplinary tumor board meeting consisting of endocrinology, urology, oncology and radiology specialists. The optimal treatment modality, based on the best available evidence, is proposed for each patient. The standard diagnostic workup of adrenal pathology consists of patient history, physical examination and radiological examination (computed tomography or magnetic resonance imaging scan) and biochemical tests (such as serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels, urinary free cortisol, catecholamine concentrations, 1 mg overnight or high-dose dexamethasone suppression, renin and aldosterone levels, saline suppression test and ambulatory salt loading test). The decision on LPA in group 1 was based on favorable anatomic tumor location within the adrenal gland preoperatively. This was reevaluated intraoperatively, and if the anatomic relations were still favorable as judging by visual appearance, LPA was carried out. For patients in group 2, LPA was the only option because of the solitary adrenal gland, and for patients in group 3, once the intraoperative diagnosis of a cyst was visually confirmed, LPA was carried out. Contraindication for LPA was high radiological and clinical suspicion of malignancy. All patients underwent endocrinologic reevaluation and follow-up after the procedure. Perioperative and postoperative parameters were recorded and assessed, including postoperative complications. Data were collected from patient medical records. Descriptive statistics were used to analyze and represent the results using Microsoft Excel.

The study was conducted following ethical principles of the Declaration of Helsinki.

Surgical technique and perioperative management

We use a conventional laparoscopic lateral transperitoneal approach. Patient positioning, pneumoperitoneum achievement, trocar placement and the initial steps are identical as that of LTA, as we have previously published⁸, up to the point of adrenal gland dissection. With the use of minimal dissection, we expose the adrenal vein. Vascular control of the adrenal vein is very important for LPA because if uncontrolled bleeding starts from the edge of resection, it is necessary to double clip and cut the vein and perform total adrenalectomy. The next step is tumor differentiation from normal tissue so that only the part of the gland where the tumor is situated can be dissected. This step is taken for the preservation of blood supply for the remnant of the adrenal gland. Resection of the tumor is done with an ultrasonic dissector (SonoSurg, Olympus), the resected surface of the gland is first cauterized with bipolar, then sutured with Vicryl 4-0, and in the end, oxycellulose hemostatic agent is applied if needed (Fig. 1). The specimen is removed using a laparoscopic retrieval bag by extending one trocar incision, usually the one in the lower lateral abdominal quadrant. All patients had a drain that was removed when the secretion was less than 100 mL, usually on the second postoperative day.

Perioperative endocrinologic management depends on the underlying pathology. Patients with a solitary adrenal gland require perioperative manage-

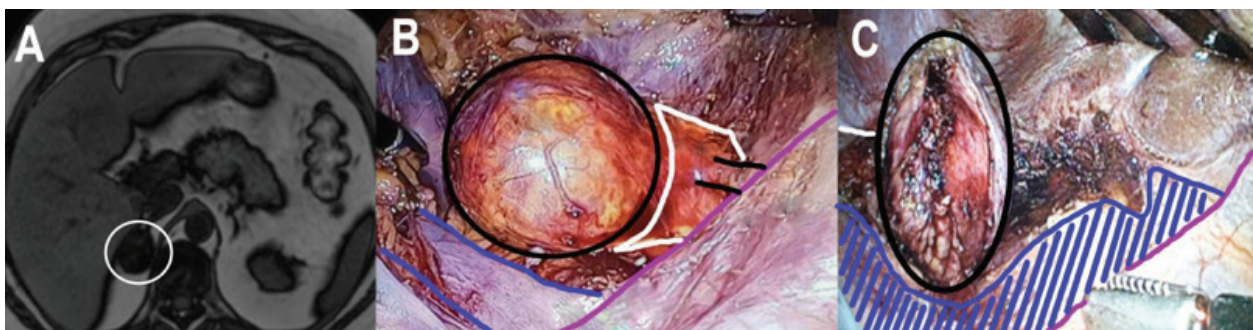


Fig. 1. Preoperative diagnostic magnetic resonance imaging, photographs of intraoperative anatomic relations and adrenal gland after partial adrenalectomy for right-sided adrenal tumor.

(A) T1 weighted MR image showing favorable anatomic position (white circle); (B) tumor (black circle), adrenal vein (black lines), normal adrenal tissue (white lines), inferior vena cava (pink line), renal vein (purple lines); (C) resected tumor (black oval), adrenal gland remnant (purple area), liver held with a retractor (white line), inferior vena cava (pink line).

ment of intravenous corticosteroid administration one day before and after surgery. Oral corticosteroids are administered on the second day after surgery, tapered and discontinued after the ACTH stimulation test which determines the need for lifelong hormonal substitution therapy. Patients with pheochromocytoma are given phenoxybenzamine *per os* (p.o.) for 7 days before surgery. The need for subsequent therapy depends on postoperative metanephrine values. Patients with aldosterone-producing adenomas (APA) are followed-up clinically and antihypertensive drugs were discontinued in case of blood pressure normalization, and biochemically with a saline suppression test.

Results

Demographic and perioperative data are shown in Table 1. There were no conversions to either LTA or open surgical approach. There were no major complications (Clavien Dindo grade ≥ 2) during the early and late postoperative period in the whole cohort. Median hospital stay was 4 days (interquartile range (IQR) 3-5) for the whole cohort.

Detailed histology of the resected tumors in group 1 is presented in Table 2. There were 12 hormonally active tumors, 6 APA, 4 pheochromocytomas and 2 adenomas causing Cushing syndrome.

All tumors in group 2 were renal cell carcinoma (RCC) metastases after contralateral radical nephrectomy and adrenalectomy.

In group 3, six patients had incidental cyst diagnosis (46.1%), five patients had nonspecific abdominal pain (38.5%) and two patients had cyst recurrence after laparoscopic marsupialization (15.4%). All cysts were histologically confirmed as simple adrenal cysts.

The median follow-up in group 1 was 36 months (IQR 13.75-61.25). Two patients died, one due to non-small-cell lung carcinoma and the other from sarcoma progression, at 18 and 12 months after LPA, respectively. Two patients with APA were lost to follow-up, and the remaining four had clinical and biochemical remission, as did two patients with Cushing syndrome. Three patients with pheochromocytoma had clinical and biochemical remission, and one had the disease as part of the MEN2 syndrome, who underwent ipsilateral adrenalectomy due to tumor recurrence 4 years after LPA. One patient with lymphoma received chemoradiotherapy and is in remission during 5 years of follow-up. Three patients with hemangioma, myelolipoma and lymphangioma had normal endocrinologic function, while the myelolipoma patient had nonfunctional recurrence of 8 mm in diameter in the adrenal remnant, which has been under surveillance. One patient with renal cell carcinoma metastasis later underwent contralateral adrenalectomy due to disease recurrence, and subsequently developed partial adrenal insufficiency, requiring glucocorticoid supplementation only during stress, and is still alive after 3 years of follow-up. The patient with adrenal cell carcinoma

Table 1. Demographic and perioperative data

	Group 1	Group 2	Group 3	Total
Patients	n=20	n=6	n=13	N=39
Male/ Female	4/16 (20%/80%)	3/3 (50%/50%)	4/9 (30.7%/69.3%)	11/28 (28.2%/72.8%)
Age (years)	Median 50.5 (IQR 41.75-59.75)	Median 65 (IQR 62.25-70.75)	Median 38 (IQR 36-44)	Median 47 (38-63.5)
Side, left/right	12/8 (60%/40%)	3/3 (50%/50%)	7/6 (53.8%/46.2%)	22/17 (56.4%/43.6%)
Tumor size (mm)	Median 25.5 (IQR 22.25 - 36.5)	Median 19.5 (IQR 18-27.75)	Median 100 (IQR 70-120)	Median 35 (IQR 23-71.5)
Procedure duration (min)	Median 90 (IQR 71.25-107.5)	Median 107.5 (IQR 87.5-126.25)	Median 75 (IQR 60-85)	Median 82.5 (IQR 70-100)
Estimated blood loss (mL)	Median 35 (IQR 25-50)	Median 45 (IQR 35-52.5)	Median 17.5 (IQR 13.75-20)	Median 27 (IQR 20-47.5)

IQR = interquartile range

Table 2. Histology in group 1

Histology report	
Adenoma	n=8 (40%)
Pheochromocytoma	n=4 (20%)
Non-small-cell lung carcinoma metastasis	n=1 (5%)
Renal cell carcinoma metastasis	n=1 (5%)
Lymphoma	n=1 (5%)
Sarcoma	n=1 (5%)
Hemangioma	n=1 (5%)
Lymphangioma	n=1 (5%)
Myelolipoma	n=1 (5%)
Adrenal cell carcinoma, Weiss score 4	n=1 (5%)

(ACC) did not receive any adjuvant treatment and is recurrence-free after 6 years of follow-up.

The median follow-up in group 2 was 35.5 months (IQR 30-53.75). Two (33.3%) patients died due to disease progression. Three (50%) patients required lifelong hydrocortisone replacement therapy because of adrenal insufficiency.

The median follow-up in group 3 was 6 months (IQR 1-19.25) and one patient was lost to follow-up. The remaining patients had normal endocrinologic function, and one patient had a minor cyst residue, 3 cm in diameter (preoperatively it was 10 cm), with no progression during 83 months of follow-up.

Discussion

Laparoscopic total adrenalectomy is the standard procedure in benign adrenal surgery because of the minimally invasive surgery benefits with excellent surgical and clinical outcomes. LTA can also be performed using a robotic approach with similar results^{9,10}. However, LPA has gained popularity in the era of organ sparing surgery because of the potential of independence from chronic steroid replacement therapy. The indication for LPA in cases with a solitary adrenal gland and bilateral tumors, especially in familial pheochromocytoma, is unquestionable if we want to avoid the morbidity associated with chronic steroid substitution therapy. The controversy has always been whether LPA is indicated for tumors in patients with normal contralateral adrenal gland^{6,11}. Two arguments support LPA in this setting. First, it has been reported that patients with a solitary adrenal gland after adrenalectomy do not respond equally to stress as normal controls¹².

Second, there are a multitude of potential threats to the remaining adrenal gland, such as the need for surgery, infections, idiopathic and other etiologic factors of acquired adrenal insufficiency⁶. LPA has proven to be safe and feasible in the treatment of nonhereditary unilateral functional adrenal adenomas¹³, and there is a proposition to use it as the first-line treatment for small adrenal masses⁶. In our case series, the most common tumor in group 1 was APA, reflecting an overall higher incidence of this pathology compared to other adrenal tumors. The debate over LPA indication for the APA treatment is ongoing, mainly regarding its endocrinologic effectiveness because it is questionable whether the detected adenoma really is the source of excessive aldosterone, even after confirmation of the side with adrenal vein sampling. There can be multiple adenomas in the same gland in 10.1%¹⁴ and APA can coexist with adrenal hyperplasia in 10% of cases¹⁵. Although therapeutic noninferiority of LPA compared to LTA has been reported in several publications^{13,15,16}, LTA is still considered the standard for APA. In our case series, of the 6 APA patients in group 1, four underwent LPA because of inconclusive adrenal vein sampling results, and two because they were younger than 35 years with serious primary aldosteronism and radiologically confirmed small adenoma and for such patients, surgery is the reasonable option without adrenal vein sampling¹⁷. All our APA patients had clinical and biochemical remission, which is in concordance with the previously mentioned series of LPA noninferiority^{13,15,16}. LPA is contraindicated if there is suspicion of malignancy¹¹. One of the radiological criteria for malignant potential in incidentalomas is tumor size, and

4 cm was proposed as the appropriate cut-off¹⁸. The median tumor diameter in our group 1 was 2.5 cm, which implies a low risk of ACC, but still we encountered one case in our series, which is extremely rare⁶. Ko *et al.* also report on one case of incidental ACC in their LPA group of 54 patients, and their patient was recurrence free after 24 months¹⁹, while our patient has been recurrence free without any adjuvant therapy for 60 months. This is an outlier and exception that proves the rule that LTA must be performed in case of ACC suspicion²⁰. All other tumors in group 1 are sporadic and rare, but the favorable endocrinologic and surgical outcomes concur with the proposal that LPA could be the first-line treatment for small adrenal masses⁶.

The preferred treatment for adrenal RCC metastases is total adrenalectomy because it can prolong survival²¹. Adrenal sparing metastasectomy is generally rarely performed, let alone laparoscopically, since bilateral synchronous or metachronous adrenal RCC metastasis is extremely rare²². The first minimally invasive adrenal sparing surgery for RCC metastasis was done by robot-assisted procedure, published by Kumar *et al.* in 2009²³, and there is only one more reported case of retroperitoneoscopic partial adrenalectomy by Kaneko *et al.* 2019⁷. Kaneko reports a recurrence-free survival after 9 months of follow-up and both cases reported no need for cortisol supplementation therapy after surgery^{7,23}. To the best of our knowledge, our case series is the largest yet published LPA series for adrenal RCC metastasis treatment published in English literature. We performed the procedure for metachronous contralateral solitary adrenal RCC metastasis after previous radical nephrectomy and adrenalectomy in 6 cases (group 2) and 1 for metachronous ipsilateral adrenal RCC metastasis after previous radical nephrectomy (group 1). In the solitary adrenal group, 50% of cases required supplementation therapy and during the median follow-up of 36 months, the survival rate was 66.7%. One patient from group 2 later developed RCC metastasis in the contralateral adrenal gland and had to undergo LTA, after which he developed partial adrenal insufficiency. In the light of these results, we can conclude that LPA should be performed in patients with RCC metastasis in the adrenal gland to preserve adrenal function and prolong survival.

Cysts present a rare adrenal pathology, with an incidence of 5.4%–8.7% of all adrenal masses^{24–26}, and in around 60% of cases, they are diagnosed after non-specific abdominal complaints²⁶. In 15% of cases, they

accompany hormonally active adrenal syndromes²⁴. Malignant potential increases with size and is reported in up to 7% of cases²⁷. The preferred treatment is resection/partial adrenalectomy because this way a part of adrenal tissue can be sent for pathologic evaluation to exclude malignancy²⁸. Total adrenalectomy was advocated in the past, but in the era of organ-sparing surgery, this is too aggressive for a lesion that is mostly benign. The median size of cysts in the case series was 10 cm and the pathology report confirmed benign characteristics in every case, reflecting the low incidence of malignancy and justifying the LPA approach. Besides that, in our experience, partial adrenalectomy had almost no recurrences, as opposed to marsupialization, with which we had 2 recurrences in 2 cases (100%), which we then treated with LPA and included in group 3.

We use a multidisciplinary approach in treating patients with adrenal tumors and our department is a high-volume center for laparoscopic adrenalectomy. We performed more than 900 laparoscopic adrenalectomies since starting this program in 1997. The guidelines on the treatment of adrenal incidentaloma propose laparoscopic adrenalectomy to be performed in high-volume, experienced centers²⁹. The surgeon's volume and experience become even more important for LPA since it is a technically demanding procedure. There are a few technical aspects that need to be pointed out. The location of the tumor within the gland has a major influence on the ability to perform partial adrenalectomy. Tumors anterior to and on the margin of the gland are generally more amenable for LPA than those on the posterior surface³⁰ and those centrally located³¹. The arterial supply of the gland consists of small arteries, accompanied by small veins, originating from three sources, i.e., the aorta, the inferior phrenic and the renal artery. That is why the remnant of the adrenal gland must not be mobilized off the surrounding retroperitoneal tissue, especially if the adrenal vein cannot be preserved, to ensure adequate arterial supply and venous drainage¹¹. Another important aspect is the residual adrenal volume. It has been suggested that at least 15% to 30% of adrenal tissue is necessary for normal gland function^{32–34}, although some report steroid-independence with less than 15% tissue³⁵. Nevertheless, there is an unanimous agreement that if the proposed minimal remnant tissue cannot be achieved, LTA should be performed³⁶. When talking about the remnant volume, the resection margin should also be

taken into account. The proposed 3-5 mm margin is considered enough for an adequate outcome³⁴. The final aspect is preservation of the adrenal vein. It has been shown that preservation is not essential either for the safety of the procedure or the functional outcome^{30,37}. But we believe that the intraoperative preparation and preservation of the adrenal vein is mandatory for several reasons. First, venous drainage of the adrenal stump contributes to better cortical remnant function^{38,39}. Second, preservation of the adrenal vein leads to better venous drainage with less congestion and less bleeding⁴⁰. Third, in the case of uncontrolled bleeding during tissue resection, the exposed vein can be instantly clipped for hemostasis.

One of the major concerns of LPA compared to LTA is the potential for more bleeding because of the rich adrenal vascular supply, but numerous studies have shown that the perioperative outcomes of LPA are as good as of LTA⁶. Estimated blood loss, operative time and complication rates do not differ significantly between LPA and LTA, and the procedure is considered safe and feasible⁶. Our cohort shows minimal blood loss, reasonable operative time and no complications, the same as other published series, confirming the safety and feasibility of the procedure.

This is a case series of a heterogeneous LPA cohort including patients with different adrenal pathology, limiting conclusions to low levels of evidence, but reflecting real-life situations. The major limiting factor of this study was the lack of randomization and control group, but most of the published reports have the same bias. The debate on LPA indications is still ongoing¹¹, but from our experience, we can conclude that, although technically challenging, the procedure can easily and safely be performed in a variety of indications, especially by a high-volume adrenal surgeon.

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Sažetak

LAPAROSKOPSKA PARCIJALNA ADRENALEKTOMIJA: SERIJA SLUČAJEVA

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Cilj je predstaviti našu seriju slučajeva koja dokumentira indikacije, laparoskopsku tehniku, kirurške i endokrinološke ishode laparoskopske parcijalne adrenalectomije (LPA). U razdoblju od travnja 2011. do listopada 2021. godine učinili smo 39 zahvata. Bolesnici su podijeljeni u tri skupine: jednostrani tumor nadbubrežne žlijezde s normalnom kontralateralnom žlijezdom (skupina 1.), tumor solitarne nadbubrežne žlijezde (skupina 2.) i ciste nadbubrežne žlijezde (skupina 3.). U skupini 1. bilo je 20, u skupini 2. šest i u skupini 3. trinaest bolesnika. Najčešća patohistološka dijagnoza u skupini 1. bio je adenom (40%), svi tumori u skupini 2. bili su metastaze karcinoma bubrega, a sve ciste u skupini 3. su bile benigne. U cijeloj kohorti nije bilo značajnijih komplikacija (Clavien Dindov stupanj ≥ 2). Svi bolesnici u skupinama 1. i 3. imali su povoljan endokrinološki ishod, a 50% bolesnika u skupini 2. zahtijevalo je doživotnu nadomjesnu terapiju hidrokortizonom. LPA je učinkovit i siguran zahvat s povoljnim ishodima u rukama urologa s iskustvom u kirurgiji nadbubrežne žlijezde.

Ključne riječi: *Laparoskopija; Adrenalectomija; Zahvati s poštedom organa; Minimalno invazivna kirurgija*