Outcomes of Laparoscopic Adrenalectomy: 19-Year Experience after 500 Cases

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Background: Laparoscopic adrenalectomy, which was first introduced in 1992, is now regarded as the gold standard for treating various forms of adrenal masses. The authors reported their learning curve and the development of surgical techniques, as well as certain drawbacks associated with surgical outcomes.

Materials and Methods: Between March 2000 and March 2019, the data of all patients that underwent laparoscopic adrenalectomy were compiled and examined. The primary outcome covered all the operative parameter, which include operative time and the learning curve, diagnosis with size, conversion rate, and blood loss. Pre-operative, intra-operative, and post-operative data, including all complications, were secondary outcomes.

Results: Five hundred thirteen surgical procedures in a single center were studied during the 19-year period. In 421 cases, hormone-producing tumors were discovered and included Conn's syndrome in 275 cases, Cushing's syndrome in 75 cases, and pheochromocytoma in 71 cases. After the first 50 cases, the mean operative time was significantly lowered. There was also a moderate link between the tumor size and the operational time (Pearson correlation, r=0.315, p<0.05). There were 22 (4.3%) cases of intraoperative complications and 29 (5.7%) cases of postoperative complications. Histopathological reports are available, including adrenocortical carcinoma with the mean tumor size of 3.2cm with a range of 2.5 to 12 cm.

Conclusion: Laparoscopic adrenalectomy has proven to be a safe and successful treatment for most adrenal-related diseases with various sizes. The learning curve should be regarded as a part of training. This method can replace open surgery in a high-volume center, particularly in certain malignant patients.

Keywords: Adrenalectomy; Laparoscopy; Surgical outcomes

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Gagner et al first reported in 1992 that the laparoscopic adrenalectomy (LA) had significant advantages over the conventional open adrenalectomy⁽¹⁾. These advantages included less postoperative pain, shorter hospital stays, a better cosmetic outcome, and a faster recovery. It is now wildly acknowledged as a standard treatment for most adrenal disorders that require surgical intervention⁽²⁻⁴⁾. Transperitoneal approach was the first to be introduced and remains the most prevalent procedure to this day. Furthermore, posterior

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retroperitoneal approach is another procedure that urologists use due to its benefits in minimizing blood loss and shortening the hospital stay⁽⁵⁾. To overcome the learning curve, however, each technique requires extensive training and should be conducted in a highvolume center.

All adrenal procedures in the authors' institute were performed by open approaches in the early 1990s, requiring a large abdominal or flank incision. The authors accomplished the first case of transperitoneal LA in 2000 and have since enhanced both surgical and anesthetic techniques. Endocrinologists and radio-interventionists also played essential roles in achieving the highest diagnostic and preoperative management standards. The authors would like to convey their conclusions from the 500 casesexperience acquired in the present study over a nineteen-year period.

Materials and Methods

The Institutional Review Board (IRB No.052/60, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand) authorized the present study. The data of all patients that underwent LA at King Chulalongkorn Memorial Hospital between April 2000 and March 2019 was reviewed retrospectively. Patients who received open adrenalectomy on the first attempt, were excluded from participating in the present study. Five hundred thirteen consecutive patients, including 185 men and 328 women that received LA primarily performed by two surgeons were included. Hormone-secreting tumors, nonfunctioning incidentalomas larger than 4 cm or rapidly increasing after follow-ups, radiological suspicion of malignancy with nearby organ invasion, and adrenal metastases less than 6 cm were all indications for surgery. The Institute's Ethics Committee allowed data collection through medical chart.

The authors gathered all preoperative information including demographics, comorbidities, indication for LA, operational procedures, estimated blood loss, operating hours, hospital stays, and any postoperative complications. The Clavien-Dindo scoring system was used to record both early as less than 30 days, and late postoperative problems.

Pre-operative evaluation

To determine the position, size, and extent of the adrenal tumor, all patients were evaluated with computed tomography (CT) or magnetic resonance imaging (MRI). Endocrinologists did the pre-operative examination as well as the functional assessment. In case of an aldosterone producing adenoma, the authors used the plasma aldosterone concentration (PAC) and plasma renin activity (PRA) as screening techniques, followed by the saline loading test to confirm the diagnosis. Adrenal venous sampling was also performed in patients above the age of 40 who had adrenal mass less than 1 cm in size, or bilateral adrenal nodules. Before the operation, the electrolyte abnormality or hypokalemia, was treated with spironolactone and potassium chloride elixir and was monitored throughout the treatment. After ruling out exogenous steroids as a reason in patients with Cushing syndrome, the authors examined the cortisol level, ACTH level, and performed the low dose of 1 mg of dexamethasone suppression test. All patients received the perioperative steroid replacement, which was modified over the postoperative period. A 3-time elevation of plasma-free metanephrines led to the diagnosis of pheochromocytoma. The chromogranin A test was performed in borderline cases with ambiguous plasma-free metanephrines level to confirm the diagnosis. All pheochromocytoma patients were admitted for adequate regulation of blood pressure using an alpha-adrenergic blocker with or without beta blockage. Pre-operatively, the intravascular volume was increased using oral fluid and intravenous crystalloid solutions.

Intraoperative management

All the patients were given generalized anesthesia with endotracheal intubation. A nasogastric tube and a Foley catheter were also inserted. Except for individuals with big tumors with the risk of open conversion, the bowel preparation was not frequently performed. Preoperatively, prophylactic antibiotics were administered to all patients. Following antibiotic prophylaxis, the patient was placed in the lateral decubitus position, affected side up. To broaden the operative field, the kidney rest was elevated, and the operating table was flexed slightly. With the shoulder in a neutral position, the ipsilateral arm rested on a floating armrest above the body. The lower leg was flexed at 90 degrees while the upper leg was straight. To avoid neuromuscular damage, the cushion pads and pillow were positioned between the legs.

For all LA, the authors used a lateral transabdominal technique. The open Hasson method was used to achieve the pneumoperitoneum. The CO2 was compressed and kept at a constant level of 12 to 15 mmHg. Three trocars were frequently used in the left LA; however, one additional trocar was required in the right LA to retract the liver. The 12 mm Hassan trocar was used to introduce the camera port. All hand instrument ports were made up of 5 mm trocars that were inserted using a triangle technique under direct vision. After the surgeon completed the first position of a bilateral adrenalectomy, the patients were turned to the opposite side. The mobilization of the colon at the line of Toldt was the first step in the surgical operation. The adrenal vein was identified and controlled sequentially using surgical clips or vascular closing devices. The adrenal tumor was then separated from the surrounding structures, placed in a retrieval bag, and removed through the camera port incision. The authors have always used vascular sealing devices instead of clips to ligate all blood vessels supplying adrenal tumors in recent years. Closed suction drains were not commonly used unless the surgeons were afraid that they could meet a significant volume of collection or blood loss while resecting huge adrenal tumors.

Post-operative management

Following surgery, all patients' vital signs were monitored, and they were given IV crystalloids. On the first postoperative day, an intravenous opioid was prescribed prn, followed by acetaminophen or NSAIDS on the next days. Oral fluid was permitted since day one postoperatively to encourage early feeding and mobilization. When patients began to ambulate, the Foley catheter was removed, and the drain was usually removed on the first or second postoperative day. Complications, both major and minor, were documented. Patients were followed up for clinical evaluation and pathological results 2 weeks after they were discharged.

Statistical analysis

The IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY, USA) was used for the analysis. Continuous data were reported as mean (standard deviation) for normally distributed data and median (interquartile range) for non-normally distributed data. Categorical variables were reported as a number (percentage). If there were some missing data, Pearson chi-square test was performed to compare the information between groups.

Results

Between April 5, 2000 and March 13, 2019, five surgeons in the present study institute performed 513 laparoscopic adrenalectomies, the majority of which were performed by two surgeons. Table 1 displays the demographic data. The study involved 513 patients, with 185 males and 328 females. The average age was 48 years old with a range of 11 to 92 years of age. The average body weight, height, and body mass index (BMI) were 64.5 kg with a range of 30 to 127 kg, 160 cm with a range of 138 to 182 cm, and 25.8 kg/m² with a range of 15 to 40.2 kg/ m². Two hundred twenty-seven (44.3%) surgeries were conducted on the right side, 268 (52.2%) on the left side, and 18 (3.5%) bilaterally. The average size of the tumor was 3.1 cm with a range of 0.4 to 22 cm. Hormone-producing tumors were diagnosed in 421 patients (82%), with 275 (53.6%) aldosteroneproducing adenomas, 75 (14.6%) Cushing syndromes, and 71 pheochromocytomas. Seventy (13.7%) of the patients had non-functioning tumors, while 13 (2.5%) had adrenal metastases from colon cancer, breast cancer, or renal cell carcinoma. Six of the remaining nine patients were diagnosed with histoplasmosis, while the other three were identified with adrenal myelolipoma.

Table 2 displays the peri-operative parameters. The median surgical time for unilateral adrenalectomy was 90 minutes with a range of 30 to 420 minutes and

Table 1. Demographic data

Variables	
Number of patients	513
Sex; n (%)	
Male	185 (36.1)
Female	328 (63.9)
Tumor laterality; n (%)	
Right	227 (44.3)
Left	268 (52.2)
Bilateral	18 (3.5)
Age (year); mean (SD) [range]	48 (13.70) [11 to 92]
Tumor size (cm); mean (SD) [range]	3.1 (2.4) [0.4 to 22.0]
Preoperative diagnosis; n (%)	
Aldosterone producing adenoma	275 (53.6)
Cushing syndrome	75 (14.6)
Pheochromocytoma	71 (13.8)
Nonfunctioning tumor	70 (13.7)
Adrenal metastasis	13 (2.5)
Other (e.g., histoplasmosis etc.)	9 (1.8)
SD=standard deviation	

Table 2. Peri-operative outcomes

Variables		
Operative time (minute)		
Unilateral adrenalectomy; median (IQR) [range]	90 (50) [30 to 420]	
Bilateral adrenalectomy; mean (SD) [range]	197.1 (48.9) [120 to 295]	
Estimated blood loss (mL); median (IQR) [range]		
Unilateral adrenalectomy	40 (30) [10 to 2,500]	
Bilateral adrenalectomy	175 (337) [50 to 500]	
Open conversion; n (%)	8 (1.6)	
Intraoperative complications; n (%)	18 (3.5)	
Postoperative hospital stays (day); mean (SD) [range]	4.3 (2.8) [2 to 30]	
Overall postoperative complications; n (%)	29 (5.7)	
Minor (Clavien-Dindo grade 1-2)	18 (3.5)	
Major (Clavien-Dindo grade 3-5)	11 (2.1)	

IQR=interquartile range; SD=standard deviation

the mean surgical time was 197.1 minutes with a range of 120 to 295 minutes for bilateral adrenalectomy. When the first 50 cases were compared to the rest, there was a considerable decreased in mean operating time from 126 minutes with a range of 70 to 240 minutes to 83.2 minutes with a range of 30 to 175 minutes (p<0.05). Following this period, the operative time tended to descend to a plateau phase, as seen in Figure 1. As shown in Figure 2, there was a moderate

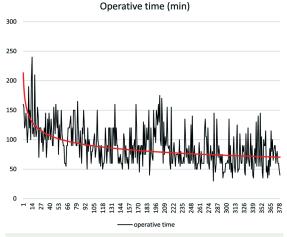
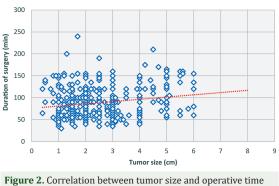


Figure 1. Trend of operative time.



(Pearson correlation).

association between tumor size and operating time (Pearson correlation, r=0.315, p<0.05). However, the tumor size in the present study for the first 50 patients was not different from the rest at 2.9 versus 3.2 cm (p=0.620).

In unilateral adrenalectomy, the median estimated blood loss was 40 mL with a range of 10 to 2,500 mL, but in bilateral cases, it was increased to 175 mL with a range of 50 to 500 mL. In eight (1.6%) cases, conversion to open surgery was required. Table 3 shows the reasons for conversion. Bleeding was the most common reason for conversion. Adhesions to neighboring organs was the other explanation, and an unintentional tear of tumor capsules in one case.

Intraoperative complications occurred in 22 (4.3%) of the cases (Table 4), including nine small liver injuries, one spleen injury, one pancreatic injury, one duodenal serosa tear, one diaphragmatic tear, one colon serosa tear, one IVC tear, five tumor capsule rupture, and two hypertensive crises while manipulating the pheochromocytoma. Except for two

Table 3. Reasons for conversion

Definitive diagnosis	Size	Reason for conversion	
1. Pheochromocytoma	9 cm	Bleeding	
2. Pheochromocytoma	8 cm	Bleeding	
3. Metastasis	2.5 cm	Bleeding	
4. Pheochromocytoma	8 cm	Severe adhesion	
5. Pheochromocytoma	8.4 cm	Bleeding and adhesion	
6. Metastasis	6.8 cm	Adhesion with liver and IVC	
7. Leiomyoma	6.1cm	Tear of IVC	
8. ACC	8.8 cm	Tear of tumor capsule	
ACC=adrenocortical carcinoma; IVC=inferior vena cava			

Table 4. Intra-operative complication

No. of patients (n=513)	Intra-operative complications
9 (1.8%)	Small liver injury
5 (1.0%)	Rupture of tumor capsule
2 (0.4%)	Hypertensive crises while manipulation of the pheochromocytoma
1 (0.2%)	Spleen injury
1 (0.2%)	Pancreatic injury
1 (0.2%)	Duodenal serosa tear
1 (0.2%)	Diaphragmatic tear
1 (0.2%)	Colon serosa tear
1 (0.2%)	IVC tear
IVC=inferior vena cava	

cases, all cases could be managed by laparoscopy and the adrenalectomy procedure could be performed. The first conversion was an IVC tear, which was difficult to control the bleeding using laparoscopic equipment, necessitating conversion to open surgery. The second case involved the rupture of the tumor capsule in a patient who had Cushing syndrome but was also concerned about adrenocortical carcinoma (ACC). The conversion was required to resect the entire tumor margin.

Postoperative problems were discovered in 29 (5.7%) of the patients. There were 18 (3.5%) mild problems (grade 1-2) according to the Clavein-Dindo classification, including wound infection, hypoglycemia, atelectasis, bowel ileus, and subcutaneous emphysema. Major complications (grades 3-5) were detected in 11 (2.1%) of the cases, including ischemic stroke, vocal cord edema necessitating reintubation, congestive heart failure, intestinal hernia, post-operative bleeding, and pleural effusion, all of which necessitated additional procedures. Table 5 shows a detailed analysis of the types and rates of complications. The average length of postoperative hospitalized was 4.3 days with a range of 2 to 30 days. Table 5. Post-operative complications

	n (%)
Overall postoperative complications	29 (5.7)
Minor (Clavien-Dindo grade 1-2)	18 (3.5)
Infected wound	5
Hypoglycemia	4
Bowel ileus	3
Subcutaneous emphysema	2
Atelectasis	2
Hematoma at flank	1
Intraabdominal collection >> conservative	1
Major (Clavien-Dindo grade 3-5)	11 (2.1)
Ischemic stroke	1
Vocal cord edema >> re-intubation	2
Congestive heart failure	2
Pneumonia	1
Post-op bleeding >> re-explore lap	1
Pleural effusion >> pleural tapping	2
Intestinal hernia >> repair	2

Table 6. Histopathological reports

No. of patients (n=513)	Pathology
337 (65.7%)	Cortical adenoma
57 (11.12%)	Pheochromocytoma
52 (10.14%)	Cortical hyperplasia
12 (2.34%)	Myelolipoma
10 (1.95%)	Adrenocortical carcinoma
10 (1.95%)	Metastasis
9 (1.75%)	Histoplasmosis
5 (0.97%)	Schwannoma
5 (0.97%)	Adrenal cyst
4 (0.78%)	Adrenal hemorrhage
3 (0.58%)	Ganglioneuroma
2 (0.39%)	Paraganglioma
2 (0.39%)	Inflammation
1 (0.2%)	Cryptococcosis
1 (0.2%)	Leiomyoma
1 (0.2%)	Cavernous hemangioma
1 (0.2%)	Diffuse large B cell lymphoma
1 (0.2%)	Angiosarcoma

Table 6 summarizes the histopathological reports. The cortical adenoma was the most common, with other benign tumors including pheochromocytoma, myelolipoma, and ganglioneuroma. There were eight ACCs, with a mean tumor size of 3.2 cm and a range of 2.5 to 12 cm, with three larger than 6 cm. Among these ACC patients, all surgical margins were negative. During the follow-up period, no port site tumor recurrence, local recurrence, or metastasis occurred. The present study discovered three high-risk cases for malignant pheochromocytoma with a PASS score greater than 6, and ten cases of intermediate risk with a PASS score of 4 to 6. Adrenal metastases from HCC, RCC, breast, colorectal, and cervical cancer were reported in seven cases.

Discussion

Gagner performed the first successful LA in 1991⁽¹⁾. Studies have demonstrated the benefits and safety of this technique. As a result of those studies, it has become the standard procedure for benign adrenal tumors⁽²⁻⁴⁾. The authors reported one of the largest groups of patients that underwent transperitoneal LA at a single center. This operation was started by the authors' institute in 2000. Two surgeons performed the first 100 cases (SA and RS). Followed by three surgeons (PK, UM, and SD) who learned and practiced this procedure. The technique was developed and passed on to young surgeons by more experienced ones.

LA can now be performed using either a lateral transperitoneal or a retroperitoneal approach. Both procedures produce outstanding results and have no advantage over one another⁽⁵⁻⁸⁾. A study by van Uitert et al found that the retroperitoneal technique was superior in terms of blood loss, operating time, and hospital stays in patients with small benign adrenal tumors of 7 cm and a BMI of 35 kg/m²⁽⁹⁾. The authors used the lateral transperitoneal approach in all patients in their investigation since the anatomical landmark was more familiar and the operating space was greater. The authors did, however, agree on the clear benefit of the retroperitoneal approach in patients who had previous abdominal surgery or bilateral adrenalectomies due to the omission of shifting the patients' posture between both sides.

According to certain research, the laparoscopic single-site adrenalectomy (LESS-A) procedure is safe and has comparable surgical outcomes to the standard laparoscopic technique⁽¹⁰⁻¹³⁾. LESS-A gives outstanding cosmetic results, but it has more technical obstacles and takes longer to learn. The complexity of this method is caused by the need to manipulate surgical equipment in small space. Despite the invention of a crossover approach with bent instruments, which make this procedure easier, LESS-A remains difficult in cases of big adrenal tumors and visceral obesity⁽¹³⁾.

In some medical institutes, robotic adrenalectomy is currently considered a possibility. This approach has

shown prospective benefits, particularly in individuals with tumors size of 6 cm or greater, a BMI of 30 kg/m² or greater, and a history of abdominal surgery^(14,15). However, high-level evidence of its advantages over the traditional laparoscopic method is still missing. The docking process, which may add 15 to 60 minutes to the operative time, is a disadvantage of robotic surgery⁽¹⁶⁾. Furthermore, the cost-effectiveness of the robotic approach for uncomplicated adrenal tumors remains questionable⁽¹⁷⁾. The authors believe that this approach is safe and reliable, and it may be used as an alternative for an open adrenalectomy in complicated circumstances.

The learning curve for LA was suggested to be around 30 to 40 cases^(8,9,18-20). Following that time, the operation time would be reduced, as well as the rate of perioperative complications⁽²¹⁾. According to certain research, high-volume centers with more than 40 adrenalectomies per year, had a reduced complication and morality rate^(22,23). As a result, a better outcome should be expected from more experienced surgeons who operated on adrenal tumors on a regular basis. According to the present study findings, after the first 50 cases, the operative time was dramatically reduced from 126 to 83.2 minutes (p=0.05). The average operational time of 98.5 minutes was comparable to other studies that used the same lateral transperitoneal technique^(18,20,21). Pedziwiatr et al discovered a substantial increase in operating time associated with high tumor size in their investigation. However, it does not appear to influence clinical outcomes⁽²¹⁾. The authors discovered a similar link between operation time and tumor size in the present study investigation. The enormous tumor not only complicated surgical technique, but the unexpected collateral vessels also made controlling the bleeding more challenging. Most LA procedures, in the authors' experience, could be accomplished using vascular sealing devices. As previously stated, this procedure was safe and effective, and it might minimize surgical time without raising complications⁽²⁴⁾.

In the present study investigations, eight patients were converted to open adrenalectomy. The cause for conversion in the first few cases was owing to hemorrhage or significant adhesion to the neighboring organs. As the surgeons become more familiar with the technique, they began doing LA in more complex patients, such as adrenocortical cancer. In these cases, the tumor capsule tear necessitated an open conversion to obtain negative margins. The peri-operative complications were compared to those observed in other research. They also documented a statistically significant difference in complication rates between the learning period and the future procedures^(20,21).

There are limitations to the present study. First, because it is a retrospective and descriptive study, there was no comparison of operative result with open surgery. Second, the authors only used the lateral transperitoneal approach, which may have different results than the alternative procedures such as the retroperitoneal approach, LESS-A, or robotic adrenalectomy. Finally, because the present study was conducted by a single team in a tertiary referral facility, the results may not represent the overall outcome in general hospitals. Nonetheless, the present study findings suggest that laparoscopic procedures are safe and beneficial in all adrenal pathologies.

Conclusion

LA, in the authors' opinion, was a safe and effective treatment for most adrenal disorders of varied sizes. The learning curve should be regarded as a component of training. This approach can replace open surgery in a high-volume center, particularly in certain malignant patients. However, careful patient selection, as well as a multidisciplinary team approach during the perioperative phase, are essential for improving surgical outcomes.

What is already known about this topic?

LA is widely acknowledged as the standard treatment for most adrenal diseases that necessitate surgical intervention. The operating time and perioperative complications would be minimized after the learning curve.

What this study adds?

LA is regarded as a safe and effective operation for various sizes of adrenal tumors, including selected malignant patients, at King Chulalongkorn Memorial Hospital.

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Conflicts of interest

The authors declare no conflicts of interest.

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