Single center experience with laparoscopic adrenalectomy on a large clinical series: Lessons learned from 273 cases: A retrospective cohort study

Sinan Celen, Kadir Omur Gunseren, Hakan Vuruskan, Nurhan Meydan Acimis, Yakup Kordan, Ismet Yavascaoglu

Original Article

Single center experience with laparoscopic adrenalectomy on a large clinical series: Lessons learned from 273 cases: A retrospective cohort study

Sinan Celen[1], Kadir Omur Gunseren[2], Hakan Vuruskan[2], Nurhan Meydan Acimis[3], Yakup Kordan[4], Ismet Yavascaoglu[2]

[1]Department of Urology, Pamukkale Univercity Hospital and Faculty of Medicine, Denizli, Turkey
[2]Department of Urology, Uludag Univercity Hospital and Faculty of Medicine, Bursa, Turkey
[3]Department of Public Health, Pamukkale Univercity Hospital and Faculty of Medicine, Denizli, Turkey
[4]Department of Urology, Koc Univercity Hospital and Faculty of Medicine, İstanbul, Turkey

Address correspondence to:
Dr. Sinan Celen
Çamlaraltı Mahallesi
Pamukkale Ünv. Hastane Yolu
20070 Kınıklı, Pamukkale
Denizli
Turkey.
Tel.: +90 535 3462251
E-mail: sinancelen@hotmail.com

ABSTRACT

Objectives: To evaluate the risk of laparoscopic adrenalectomy (LA) for large adrenal tumors and the risk of learning curve (LC)

Design: Single centre, retrospective study

Setting: Uludag University, Bursa, Turkey

Subjects: A study in a large patient population (N = 273) who underwent laparoscopic adrenalectomy between 2006 and 2017

Interventions: The patients were divided into two study groups according to tumour size as estimated by pathologic specimen maximum diameter, Group A (less than 5 cm) and group B (larger than 5 cm,). In addition, to evaluate LC of LA, the patients were divided into two groups according to time interval: the first period, 2006 to 2011; and the second period, 2012-2017.

Main outcome measures: To evaluate the risk of learning curve and tumour size

Results: There was no statistical difference between the two groups for preoperative and postoperative complications according to tumour size: <5 or ≥5 cm, and there was statistical difference between the two groups for operation time, length of hospital stay, but no statistical difference for postoperative complications according to time interval.

Conclusion: LA in large adrenal masses (5 cm or larger) is not associated with longer operative time, increased blood loss, and longer hospital stay, without affecting perioperative morbidity. Hence, the size of an adrenal mass should not be the only factor in determining whether LA or not. Besides, LC may affect outcomes of LA.

KEYWORDS: adrenal, adrenalectomy, laparoscopy, learning curve, oncology

INTRODUCTION

Since its introduction in 1992, laparoscopic adrenalectomy (LA) has been preferred more, owing to shorter hospital stay, less morbidity, quick recovery, less pain and better cosmesis it provides[1]. Over time and with increasing experience, LA has become the procedure of choice for large adrenal tumors. The Society of American Gastrointestinal and Endoscopic Surgeons guidelines have shown that LA can be safely performed for adrenal masses up to 6 cm except for adrenocortical carcinoma (ACC) or the tumors that show infiltration to surrounding structures on computerized tomography (CT)[2]. Some publications have stated that laparoscopic approaches for ACC can be considered if there are minimal invasive findings[3,4]. This study aimed to evaluate the safety and efficacy of LA for tumors larger than 5 cm by comparing the outcomes. In contrast, performing laparoscopic procedures such as adrenalectomy requires a high level of dexterity and technical skills. Apart from the surgeon's experience; reducing the rate of complications, the rate of conversion, and the operating time also depend on several other factors, such as patient characteristics. Therefore, other purposes of this study also aimed to evaluate the learning curve for LA of experienced laparoscopic urologists.

MATERIALS AND METHODS

This study was a single-center retrospective cohort study comprising a large patient population (273 patients) that underwent LA between June 2006 and June 2017 at the Department of Urology, Uludag University Hospital. Data were obtained from the electronic medical records and patient data files. All the patients were preoperatively assessed using a CT or magnetic resonance and by an endocrinologist. In addition, if presence of pheochromocytoma was suspected, a total body metaiodobenzylguanidine scintigraphy was performed on all the patients. Indications of LA in our clinic were: (1) functional adenoma; (2) macronodular hyperplasia (primary hyperaldosteronism, Cushing syndrome, pheochromocytoma); and (3) unconfined masses larger than 4 cm, which were identified as masses with rapid size increase and malignancy during the follow-up. All the patients were closely followed up by an endocrinologist after surgery until they regained normal functioning. All the patients were operated using a standard transperitoneal laparoscopic technique by three surgeons (urologists) who had 5 years of surgical training. Six patients were excluded from the study because they underwent bilateral adrenalectomies, while the remaining 273 patients were included in the study. The patients were divided into two study groups based on the tumor size, using the postoperative pathological reports. Group A comprised patients with adrenal tumors smaller than 5 cm and group B comprised those with tumors larger than 5 cm, which was considered as the definition of large adrenal tumors. Although radiological reports were available in our records, the evaluation was based on pathological reports because the imaging modalities were applied by different radiologists, which could have resulted in inaccurate tumor size classification and misinterpretation of study data. Operating time was calculated based on the skin-to-skin time. The hospital stay was defined as the duration from the day of surgery until discharge. Long-term complications were assessed by reviewing the outpatient charts. In addition, the study period was divided into two to analyze the learning curve of this procedure for a large volume set: group A/first period (between 2006 and 2011) and group B/second period (between 2012 and 2017). Age, gender, American Society of Anaesthesiology (ASA) score, preoperative diagnosis, tumor size, operating time, conversion to open surgery, morbidity, and mortality were assessed for all the study groups. Complications were classified based on the Clavien–Dindo score[5]. The college research review committee revised the paper according to the rule and regulation. Accordingly, the study was approved by the Ethics Committees of Pamukkale University.

Statistical analysis

Demographic and clinical characteristics were analyzed in relation to the tumor size. Quantitative variables were summarized as percentiles, median, mean and compared using the Kruskal-Wallis test. Absolute and percentage frequencies were used to summarize qualitative variables, and Chi-square, ANOVA, Mann–Whitney, and Shapiro–Wilk tests to evaluate differences between variable categories and the different surgical approaches.

Cox regression analysis was performed to evaluate the effect of clinical and demographic characteristics on the median values of operating time, study period and hospital stay (dependent variable). Statistical significance was assessed at a level of probability of 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp. Released 2011. Armonk, NY: IBM Corp.).

RESULTS

This study included 273 patients who underwent LA between the years 2006 and 2017 at the University of Uludag Hospital. Patient and tumor characteristics such as gender, age, BMI, ASA score, tumor size, and final pathology features are shown in Table 1, and no significant intergroup differences were observed regarding these characteristics, except for BMI (BMI, p = 0.12, p >0.05). The smallest tumor size was 10 mm, while the largest tumor size was measured as 150 mm. Overall, 113 patients were operated in the first period (group A) and 160 patients in the second period (group B). Intraoperative and postoperative outcomes of the groups are shown in Table 2. Logistic regression analysis could not be performed on these variables because of the low number of postoperative complications. ANOVA *t*-test was performed to evaluate the association between the baseline characteristics and prolonged operative time for large tumors, and only age was found to be a statistically significant factor and not the study period (Table 3). In addition, ANOVA *t*-test was performed to evaluate the association between baseline characteristics and hospital stay for large tumors, and hospital stay was found to be shorter in the second period of the learning curve (Table 4). We compared the first and second periods, group A (between 2006 and 2011) and group B (between 2012 and 2017), respectively. Operation time and hospital stay were found to be significantly shorter in group B, but no statistically significant difference was observed in terms of complications, such as blood loss (Table 5). No significant intergroup differences were observed regarding patient and tumor characteristics.

DISCUSSION

Are large adrenal tumors an obstacle to laparoscopy?

Although LA has increasingly become widespread, its negative results owing to the increase in the size of the tumor make the limit of laparoscopy a controversial topic. As the size of adrenal masses increase the study area becomes more limited and anatomy becomes more complex, which may lead to increased risk of blood loss, vascular injury, organ damage, and prolonged hospital stay. In addition, there is the risk of invasion and spread owing to the risk of cancer that cannot be diagnosed through radiological imaging. Several previous studies have defined the size of the large mass between 3.5 cm and 8 cm, and we identified the size of the largest mass as 5 cm in our study[6]. The literature reported that the large adrenal masses (> 6 cm) were associated with duration of surgery and with an increased risk of intraoperative incident. Many authors reported lesion diameter more than 5 - 6 cm as independent predictive factors for conversion[7,8]. The literature reveals that the rate of complications, conversion rate, and hospital stay increase with the increase in tumor size. Besides, the mean operative time can also get hampered with an increase in the tumor size[9]. But contrary to the literature, our data revealed no significant difference regarding the outcomes of LA, such as hospital stay, operation time, and preoperative and postoperative complications for patients with large tumors compared with those with smaller tumors[10]. Possibly, as the surgeons gained experience, especially in the second period of the learning curve, they began to effortlessly operate on larger adrenal tumors. ANOVA *t*-test was used to evaluate the association between the baseline characteristics and prolonged operative time for larger tumors, and only age was statistically significant, but not the study period. As a result, the tumor size alone is not an absolute contraindication to LA alone. A correct preoperative patient selection and surgical technique could minimize this risk.

Should tumor size affect the surgical approach because of the risk of malignancy?

Despite advances in radiological imaging, the risk of malignancy in adrenal masses cannot be determined before surgery. However, some of the radiological imaging techniques have been allowed to underestimate benign tumors, that is, poor lipid nonfunctioning adenomas with atypical features on CT scan. Therefore, the main challenge in the management of adrenal incidentalomas is the selection of appropriate cases by distinguishing between malignant lesions and non-malignant lesions. The risk of adrenocortical carcinoma increases with tumour size and becomes significant for lesions over 4 cm in diameter as previously reported. This is why adrenalectomy is recommended for all adrenal lesions larger than 4 cm with atypical biochemical or imaging features[11,12]. Suspected primary malignant adrenal tumors are considered as contraindication to laparoscopic approach because of the poor oncological outcome and the high risk of peritoneal dissemination of primary adrenal cancer[13-15]. The National Institutes of Health consensus statement reported that the ACC risk was 2% in adrenal masses below 40 mm, 6% between 41 and 60 mm, and 25% above 60 mm[16]. Notably, there are several reasons to avoid a laparoscopic approach in case of suspected cancer, such as peritoneal tumor dissemination and local recurrence because of incomplete removal of the primary malignant lesion[1]. In our study, ACC was observed in seven patients, three of them were in group A and four in group B. Contrary to the literature, we believe that open surgery should not be preferred depending on the tumor size because even though the tumor size is a useful index, it is insufficient for decision making and should not be the only predictor of malignancy[7].

How important is the learning curve?

Laparoscopic surgery was also more difficult to learn than open surgery because it required different psychomotor skills. This study comprised 273 patients who underwent LA over a period of 12 years. This study is one of the largest cohorts in which the learning curve of LA was evaluated. Operating times of LA significantly decreased in the second period, which is comparable to the results reported in the literature[17,18]. With respect to the operating times and hospital stay, the learning curve in this study shows a similar pattern to that reported in the literature. Barczynski *et al* showed that operating times which were described for the first period were much longer (110 min after the introduction, 75 min after 20 patients, and 65 min after 40 patients)[19]. Cabalag *et al* showed that a learning curve of 10 patients in RPA was shorter (110 - 60 min) after an intensive training course with an expert[17]. ANOVA *t*-test was used to evaluate the association between baseline characteristics and hospital stay for larger tumors, and hospital stay was shorter in the second period of the learning curve. However, because of the small number of complications, advanced analysis techniques could not be applied to determine which factors were effective

Strengths and Limitations of the Study

Nonetheless, this study has some limitations. This study is limited by its retrospective nature, and three surgeons having a similar level of skill performed the surgery in a high-volume center. Moreover, all the baseline characteristics were comparable, except for the parameter of ASA, which did not seem to influence the outcomes in univariate analysis.

CONCLUSION

The size of an adrenal mass should not be the only factor used to determine malignancy. Therefore, the laparoscopic technique is safe and feasible for large adrenal tumors regardless of the suspicion of malignancy. Moreover, LA can be performed by general surgeons with experience in laparoscopic techniques after an intensive training course with an expert.

ACKNOWLEDGMENT

SC conceived, designed and did statistical analysis, editing of the manuscript, did data collection and manuscript writing. KÖG, HV, YK did data collection and NMA did statistical analysis and lastly Professor Dr. IY did the review and final approval of manuscript takes the responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. No potential conflict of interest was reported by the authors.

REFERENCES

1. Gagner M, Lacroix A, Bolté E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. N Engl J Med 1992; 327:1033.
2. Stefanidis D, Goldfarb M, Kercher KW, Hope WW, Richardson W, Fanelli RD. SAGES guidelines for minimally invasive treatment of adrenal pathology. Surg Endosc 2013; 27:3960–3980
3. 3-Donatini G, Caiazzo R, Do Cao C, Aubert S, Zerrweck C, El- Kathib Z, *et al*. Long-term survival after adrenalectomy for stage I/II adrenocortical carcinoma (ACC): a retrospective comparative cohort study of laparoscopic versus open approach. Ann Surg Oncol 2014; 21:284–291.
4. Porpiglia F, Miller BS, Manfredi M, Fiori C, Doherty GM. A debate on laparoscopic versus open adrenalectomy for adrenocortical carcinoma. Horm Cancer 2011; 2:372–377.
5. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, *et al*. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg 2009:187–196.
6. Erbil Y, Barbaros U, Karaman G, Bozbora A, Ozarmagan S. The change in the principle of performing laparoscopic adrenalectomy from small to large masses. Int J Surg 2009; 7:266–271.
7. Parnaby CN, Chong PS, Chisholm L, Farrow J, Connell JM, O'Dwyer PJ. The role of laparoscopic adrenalectomy for adrenal tumours of 6 cm or greater. Surg Endosc. 2008 Mar;22(3):617–21.
8. Ramacciato G, Mercantini P, La Torre M, Di Benedetto F, Ercolani G, Ravaioli M, *et al*. Is laparoscopic adrenalectomy safe and effective for adrenal masses larger than 7 cm? J Surg Endosc 2008; 22:516–21.
9. Conzo G, Gambardella C, Candela G, Sanguinetti A, Polistena A, Clarizia G, *et al*. Single center experience with laparoscopic adrenalectomy on a large clinical series. BMC Surg. 2018;18(1):2.
10. Hemal AK, Singh A, Gupta NP. Whether adrenal mass more than 5 cm can pose problem in laparoscopic adrenalectomy - An evaluation of 22 patients? World J Urol 2008; 26:505–8.
11. Kebebew E, Reiff E, Duh QY, Clark OH, McMillan A. Adrenokortikal karsinom için sunum ve sonuçta hastalığın yaygınlığı: ilerleme kaydettik mi? World J Surg 2006 ; 30: 872 – 878

12. Abiven G, Coste J, Groussin L, *et al*. Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab 2006;91:2650-2655
13. Prager G, Heinz-Peer G, Passler C, Kaczirek K, Scheuba C, Niederle B. Applicability of laparoscopic adrenalectomy in a prospective study in 150 consecutive patients. Arch Surg. 2004;139:46–49. doi: 10.1001/archsurg.139.1.46.
14. Lombardi CP, Raffaelli M, De Crea C, Boniardi M, De Toma G, Marzano LA, *et al*. Open versus endoscopic adrenalectomy in the treatment of localized (stage I/II) adrenocortical carcinoma: results of a multi institutional Italian survey. Surgery. 2012;152:1158–1164. doi: 10.1016/j.surg.2012.08.014
15. Lombardi CP, Raffaelli M, Boniardi M, De Toma G, Marzano LA, Miccoli P, *et al*. Adrenocortical carcinoma: effect of hospital volume on patient outcome. Langenbeck's Arch Surg. 2012;397:201–207. doi: 10.1007/s00423-011-0866-8.
16. Nih C. NIH state-of-the-science statement on management of the clinically inapparent adrenal mass (‘‘incidentaloma’’). NIH Consens State Sci Statements 2002; 19:1–25.
17. Cabalag MS, Mann GB, Gorelik A, Miller JA. Posterior retroperitoneoscopic adrenalectomy: outcomes and lessons learned from initial 50 cases. ANZ J Surg 2015; 85:478–482. doi: 10.1111/ans.12508
18. Lin Y, *et al*. Experience of retroperitoneoscopic adrenalectomy in 195 patients with primary aldosteronism. Int J Urol 2007; 14:910–913. doi: 10.1111/j.1442-2042.2007.01860.
19. Barczynski M, *et al*. Posterior retroperitoneoscopic adrenalectomy: a comparison between the initial experience in the invention phase and introductory phase of the new surgical technique. World J Surg 2007; 31:65–71. doi: 10.1007/s00268-006-0083-8.

Table 1: Patient and tumour characteristics

Patient and tumour characteristics	Control group (<5 cm)	Large mass group (≥5 cm)	p-value
Gender [n (%)]	182	91	
Male	69 (37.9)	39 (42.9)	
Female	113 (62.1)	52 (57.1)	p= 0.431 p >0.05
Age (years) (Mean ± S.D)	52.13±11.56(24-82)	48.35±12.68(21-88)	p=0.067 p >0.05
Body mass index (kg/m^2)[1]	31.03±6.74(182)	30.03±6.75(91)	
BMI group			
<18.49	3(42.9)	4(57.1)	
18.5-24.99	40(70.3)	17(29.8)	p=0.12
>25	139(66.5)	91(33.3)	p >0.05
American Society of Anaesthesiology scores (ASA) (%)			
1	10 (5.5)	20 (22.0)	
2	165 (90.7)	69 (75.8)	
3	7 (3.8)	2 (2.2)	p=0.000 p<0.05
Tumour size (cm)	28.04 ± 8.92 (Min:10.00-45.00)	59.40±17.39 (Min.32.0-130)	
Tumour side [N (%)]			
Right	89 (48.9)	47 (51.6)	p=0.69
Left	93 (51.1)	44 (48.4)	p>0.05
Final pathology [N (%)]			
Adrenocortical adenoma	112 (61.5)	29 (31.9)	
Adrenal hyperplasia	2 (1.1)	1 (1.1)	
Benign pheochromocytoma	17 (9.3)	24 (26.4)	
Malignant pheochromocytoma	0 (0)	1 (1.1)	p=0.000
Adrenal metastasis	24 (13.1)	10 (11.0)	p<0.05
Adrenocortical carcinoma	3 (1.6)	4 (4.39)	
Other [3]	24 (13.1)	22 (24.17)	

[1]The data were not available in 12 patients in the control group, and in 13 patients in the large mass group; [2]the data were not available in 11 patients in the control group and in 7 patients in the large mass group; [3] it includes nodular hyperplasia, para-adrenal, ,paraganglioma, ganglioneuroma, myelolipoma, oncocytoma and cysts

Table 2: Intraoperative and postoperative outcomes between groups

Intraoperative and postoperative outcomes	Control group (<5 cm) n = 182	Large mass group (≥5 cm) n = 91	p-value
Operation time (min)	98.35 (30-180)	103.46 (40-210)	p>0.05
Convertion to open (n (%))	0 (0)	1 (1.09)	p>0.05
Bleeding due to vascular injury	0 (0)	1 (1.09)	
Bleeding due to organ ınjury	0 (0)	0 (0)	
Adhesions	0 (0)	0 (0)	
Suspected cancer	0 (0)	0 (0)	
Intra-operative complications (n (%))	6 (3.29)	4 (4.39)	p>0.05
Bleeding due to vascular injury	4 (2.19)	2 (2.19)	
Bleeding due to organ ınjury	2 (1.09)	2 (2.19)	
Bowel perforation	0	0	
Post-operative complications(clavien-dindo)(n (%))			p>0.05
No complications	175 (96.1)	82 (90.1)	
Minor (1-2)	7 (3.84)	6 (6.59)	
Major (3-4)	1 (0.005)	3 (3.29)	
Death (5)	0	0	
Hospital length of stay (days)	2.92 (1-9)	2.98 (1-26)	p>0.05
Blood loss (cc)	47.6 (10-300)	51.59 (10-350)	p>0.05

Table 3: Association between baseline characteristics and prolonged operative time according to tumour size cut-off point of ≥5 cm

Baseline characteristics	T	DF	Sig2 tailed	p-value
Age	2.257	14 /38/52	0.023	p<0.05
Bodymass index	1.477	14 /38/52	0.157	p>0.05
Study period	0.740	14 /38/52	0.722	p>0.05
Gender (male)	1.381	14 /38/52	0.220	p>0.05

Table 4: Association between baseline characteristics and hospital stay according to tumour size cut-off point of ≥5 cm

Characteristics	T	DF	Sig2 tailed	p-value
Age	1.248	6 /48/52	0.30	p>0.05
Body mass index	0.483	6 /48/52	0.817	p>0.05
Study period	2.715	6 /48/52	0.024	p<0.05
Gender (male)	0.435	6 /48/52	0.852	p>0.05

Table 5: Association between peroperative and postoperative changes according to study period

Peroperative and Postoperative changes	First period (2006-2011)	Second period (2012-2017)	p-value
Operation time (min)	110.39 (45-210)	92.75 (30-205)	p<0.001
Post-operative complications(clavien-dindo)(n (%))			p>0.05
No complications	105 (92.9)	151 (94.3)	
Minor (1-2)	8 (7.07)	6 (3.7)	
Major (3-4)	0 (0.005)	3 (1.87)	
Death (5)	0	0	
Hospital length of stay (days)	3.54 (1-9)	2.52 (1-26)	p<0.001