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Applicability of laparoscopic approach to the resection of large adrenal tumours: A retrospective cohort study on 200 patients.

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Author Comments:	Dear Sir, Please find enclosed the manuscript entitled "Applicability of laparoscopic approach to the resection of large adrenal tumours: A retrospective cohort study on 200 patients". This is a multicentre retrospective cohort study with the aims: 1) to compare clinical outcomes of laparoscopic adrenalectomy for large versus small adrenal tumours and 2) to identify risk factors associated to increased duration of the surgical operation and hospital stay in laparoscopic adrenalectomy. Please do not hesitate to contact us if you have any question.

	Looking forward to hearing from you, we remain. Sincerely yours, Mattia Portinari and Carlo V. Feo
Response to Reviewers:	Dear Sir, Please find enclosed the revised manuscript (Version 14_07_2015). As suggested, the conclusion was corrected. Please note that the text inserted in the revised manuscript (page 14) has been highlighted. Please do not hesitate to contact us if you have any question. Looking forward to hearing from you, we remain. Sincerely yours, Mattia Portinari and Carlo V. Feo
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Abstract:	Background: Controversies exist in the best surgical approach (open vs. laparoscopy) to large adrenal tumours without pre- or intraoperative evidence of primary adrenocortical carcinoma. The primary concern is recurrence due to capsular disruption of an unsuspected malignant tumour. In addition, intra-operative blood loss, conversion rate to open adrenalectomy, operative time, and hospital length of stay may be increased with the laparoscopic approach. The aims of our study were: 1) to compare clinical outcomes of laparoscopic adrenalectomy for large versus small adrenal tumours and 2) to identify risk factors associated to increased duration of the surgical operation and hospital stay in laparoscopic adrenalectomy. Methods: This is a multicentre retrospective cohort study in a large patient population (N=200) who underwent laparoscopic adrenalectomy in 2004-2014 at three academic hospitals in Northern Italy. Patients were divided in two cohorts according to tumour size: "large" tumours were defined as ≥5 cm (N=50) and "small" tumours as <5 cm (N=150). Results: The study groups were comparable in age and gender distribution as well as their tumour characteristics. The operative time (p=0.671), conversion rate (p=0.488), intra- (p=0.876) and post-operative (p=0.639) complications, and hospital stay (p=0.229) were similar between groups. The early study period (2004-2009), which included laparoscopic adrenalectomy operators' learning curve, was the only independent factor associated with increased risk of longer operative time [HR 0.57 (95% CI 0.40-0.82), p=0.02], while American Society of Anaesthesiology score ≥3 was the only predictor of prolonged hospital stay [HR 0.67 (95% CI 0.47-0.97), p=0.03]. Conclusions: Surgeons skilled in advance laparoscopy and adrenal surgery can perform laparoscopic adrenalectomy safely in patients with ≥5 cm adrenal tumours with no increase in operative time, hospital stay, or conversion rate. Surgeon' experience and the patients comorbidities have the largest impact on operative time and length of hospital stay in laparoscopic large adrenal tumour resection.

Applicability of laparoscopic approach to the resection of large adrenal tumours:

A retrospective cohort study on 200 patients.

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Abstract

Background: Controversies exist in the best surgical approach (open vs. laparoscopy) to large adrenal tumours without pre- or intraoperative evidence of primary adrenocortical carcinoma. The primary concern is recurrence due to capsular disruption of an unsuspected malignant tumour. In addition, intra-operative blood loss, conversion rate to open adrenalectomy, operative time, and hospital length of stay may be increased with the laparoscopic approach.

The aims of our study were: 1) to compare clinical outcomes of laparoscopic adrenalectomy for large versus small adrenal tumours and 2) to identify risk factors associated to increased duration of the surgical operation and hospital stay in laparoscopic adrenalectomy.

Methods: This is a multicentre retrospective cohort study in a large patient population (N=200) who underwent laparoscopic adrenalectomy in 2004-2014 at three academic hospitals in Northern Italy. Patients were divided in two cohorts according to tumour size: "large" tumours were defined as ≥5 cm (N=50) and "small" tumours as <5 cm (N=150).

Results: The study groups were comparable in age and gender distribution as well as their tumour characteristics. The operative time (p=0.671), conversion rate (p=0.488), intra- (p=0.876) and post-operative (p=0.639) complications, and hospital stay (p=0.229) were similar between groups. The early study period (2004-2009), which included laparoscopic adrenalectomy operators' learning curve, was the only independent factor associated with increased risk of longer operative time [HR 0.57 (95% CI 0.40-0.82), p=0.02], while American Society of Anaesthesiology score ≥3 was the only predictor of prolonged hospital stay [HR 0.67 (95% CI 0.47-0.97), p=0.03].

Conclusions: Surgeons skilled in advance laparoscopy and adrenal surgery can perform laparoscopic adrenalectomy safely in patients with ≥5 cm adrenal tumours with no increase in operative time,

hospital stay, or conversion rate. Surgeon' experience and the patients comorbidities have the largest impact on operative time and length of hospital stay in laparoscopic large adrenal tumour resection.

Key-words: Adrenalectomy, Laparoscopy, Adrenal cancer, Cohort study, Retrospective study, Multivariate Analysis.

Introduction

Laparoscopic surgery has become the technique of choice for the treatment of various benign and malignant diseases in general surgery as well as other surgical specialties. According to the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines for minimally invasive treatment of adrenal pathology released in 2013, large (i.e. >5-6 cm) adrenal tumours without pre- or intraoperative evidence of primary adrenocortical carcinoma (ACC) can be approached laparoscopically by a surgeon skilled in advanced laparoscopy and adrenal surgery[1]. If there is any evidence for carcinoma found intra-operatively, conversion to an open approach is warranted[1].

Two major concerns regarding the laparoscopic approach for large adrenal tumours have been raised: 1) the risk of inadequate removal or capsular disruption of an unsuspected malignant tumour with subsequent increase in the risk of local, peritoneal, and port-site recurrences; and 2) the technical difficulty in tumour dissection. Open adrenalectomy is preferred in tumours with a high risk of being malignant because of increased risk for local recurrence and peritoneal spread with the laparoscopic approach[2, 3]. However, there is evidence in the literature to support the laparoscopic resection of ACC in the absence of local invasion on preoperative imaging and at initial laparoscopic exploration in high-volume centres with experienced surgeons[4, 5]. Additionally, while it has been shown that the risk of adrenal malignancy increases with the size of the tumour, it is controversial whether tumour size by itself should contraindicate a laparoscopic approach for adrenalectomy[6, 7]. Finally, although a laparoscopic approach for large adrenal lesions have been shown to be safe and effective[8-10], it may be associated with increased intra-operative blood loss and rate of conversion to open adrenalectomy, longer operative time, and prolonged hospital length of stay (LOS) due to more difficult dissection of the gland[1, 11, 12].

In light of all such controversies regarding laparoscopic approach for the resection of large adrenal tumours, we aimed to: 1) compare the clinical outcomes of laparoscopic adrenalectomy for large (≥5 cm) versus small adrenal tumours; 2) to identify risk factors associated to increased duration of the

surgical operation, conversion rate, post-operative complications, and prolonged hospital LOS in laparoscopic adrenalectomy; and 3) to evaluate the oncologic outcomes in patients with adrenal malignancy who underwent laparoscopic adrenalectomy.

Material and Methods

This is a multicentre retrospective cohort study carried out on a population composed by consecutive patients undergoing laparoscopic adrenalectomy between 2004 and 2014 at three academic hospitals in Northern Italy.

Data that included details of patients and tumour characteristics, intra- and post-operative variables and outcomes, and prevalence of adrenal malignancies (i.e. ACC, malignant pheochromocytoma, adrenal metastases) were collected from electronic medical records and clinical charts in an electronic database. Peri-operative complications were defined according to the Clavien-Dindo classification[13]. The study period was divided in early (2004-2009), which included the earlier stages of the learning curve when the surgeons were perfecting their skills of laparoscopic adrenalectomy and late study periods (2010-2014) when their learning curve reached a plateau. On the basis of pathology report, patients were divided in two cohorts according to the size of the tumour: 1) "large" tumours were defined as ≥5 cm (large mass group); and 2) "small" tumours as <5 cm (control group).

Indications to laparoscopic adrenalectomy were: 1) functioning adenoma or macronodular adrenal hyperplasia (i.e. primary aldosteronism, Cushing's syndrome, and pheochromocytoma) regardless of size; 2) non-functioning tumours ≥4 cm in diameter; and 3) non-functioning tumours <4 cm with increasing diameter during follow-up.

Patients with suspected ACC at pre-operative diagnostic imaging (i.e. tumour invasion into surrounding tissues or lymph node enlargement) were operated on using the open surgery approach and were therefore excluded from the study.

All patients were evaluated by an endocrinologist and underwent preoperative biochemical screening for primary aldosteronism, Cushing's syndrome, and pheochromocytoma. All patients underwent pre-operative abdominal imaging by computed tomography (CT) and/or magnetic resonance imaging (MRI), both with intravenous administration of contrast medium. Total body meta-iodobenzylguanidine scintigraphy scan was performed whenever pheochromocytoma was suspected. Peri-operatively, all patients with Cushing's syndrome were prescribed appropriate steroid replacement to compensate for post-surgical hypoadrenalism. All patients with pheochromocytoma received appropriate alpha-adrenergic blockade and, in selected cases, beta-adrenergic blocking agents.

All patients underwent a laparoscopic lateral transperitoneal adrenalectomy (LLTA) with a standardized surgical technique as described by Gagner et al. in 1997[14]. The surgical procedures were performed by a total of three surgeons, one per centre. All surgeons had similar experience with laparoscopic adrenalectomy and similar learning curves.

All patients underwent follow-up to ensure a normal adrenal function following surgery and to monitor for recurrences, especially in the settings of ACC and pheochromocytoma.

Statistical analysis

The Shapiro-Wilk test was used to assess the assumption of normality and data were expressed as mean ± standard deviation or median (interquartile range – IQR 25-75) according to the distribution. Categorical data are presented as number (%). Data were analysed by intention to treat using the Chi-square, ANOVA, and Mann-Whitney tests as appropriate. Logistic regression analysis was employed to assess factors associated with post-operative complications (Clavien-Dindo ≥ grade I), while Cox

regression analysis was performed to evaluate predictors of prolonged duration of both the operation and hospital LOS. We assessed the association between baseline characteristics and length of the surgical operation and hospital LOS in the univariate analysis adopting time to the end of surgical procedure and hospital discharge of patients as the endpoints of interest, respectively. For the time to event analyses, patients were censored at the time of end of surgical procedure and hospital discharge. We then performed multivariate Cox regression analyses to assess independent predictors of increased operating time and hospital LOS. Of note, hazard ratios (HRs) <1 correspond to an association of the factor with longer operation time and hospital LOS, while HRs >1 correspond to shorter operation and earlier discharge.

Significance was considered for values of P <0.05. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp. Released 2011. Armonk, NY: IBM Corp.).

Results

Between January 2004 and December 2014, a total of 200 patients underwent laparoscopic adrenalectomy at the Departments of Surgery of *S. Anna* University Hospital in Ferrara, *Maggiore* University Hospital in Parma, or *S. Maria della Misericordia* University Hospital in Udine, Italy. Of these 200 patients, 50 (25.0%) had adrenal tumours ≥5 cm (large mass group) and 150 (75.0%) had tumours <5 cm (control group).

The patient and tumour characteristics, including indication for adrenalectomy, are illustrated in Table 1. Gender distribution, age, BMI, American Society of Anaesthesiology (ASA) score, tumour side, indications for adrenalectomy, and final pathology were similar between groups. Cushing's syndrome (21.3% vs. 8.0%; p = 0.025) as pre-surgical diagnosis and adrenocortical adenomas (61.3% vs. 44.0%; p = 0.025) at final pathology were more common in patients with small tumour than large tumours, respectively.

The tumour size ranged from 0.6 cm to 14 cm. Among patients with large tumours, 35 had tumour size between ≥5 cm and <8 cm, 10 patients between ≥8 cm and <10 cm, and 5 patients ≥10 cm.

One hundred eighteen (59%) patients were operated on in the early period (2004-2009) of the study while the surgeons were gaining experience with laparoscopic adrenalectomy. Among them, 19 of 118 patients (16.1%) had a large tumour (≥5 cm) as compared to 31 out of 82 patients (37.8%) operated on in the late period (2010-1014) ($p < 0.0001$).

No between-group difference in the operative time ($p = 0.671$), both conversion rate ($p = 0.488$) and reason ($p = 0.854$), intra- ($p = 0.876$) and post-operative ($p = 0.639$) complications, or hospital LOS ($p = 0.229$) was found (Table 2).

Logistic regression analysis to identify factors associated to increased risk of conversion rate and post-operative complications could not be performed due to the low number of events (N = 10 and N = 21, respectively)[15].

Unadjusted Cox regression analysis showed that left tumour side was associated with a reduced risk of prolonged operative time and this association was maintained after adjusting for potential confounders (HR 1.69; 95%CI 1.22-2.33). Full-adjusted Cox regression model also revealed that early period (2004-2009) as opposed to late period (2010-2014) of the study was the only independent factor associated with an increased risk of prolonged operative time (HR 0.57; 95%CI 0.40-0.82) (Table 3).

Full-adjusted Cox regression analysis adopting a tumour size cut off point of ≥8 cm showed that the early study period (HR 0.58; 95%CI 0.41-0.81) and the tumour size ≥8 cm (HR 0.47; 95%CI 0.24-0.94) were independent predictors of prolonged operative time (Table 4). The association between left tumour side and reduced operative time was maintained using ≥8 cm as a cut off (Table 4).

Cox regression analysis showed that ASA score ≥3 was the only factor that was associated with prolonged hospital LOS and adjusting for potential confounders strengthened the association (HR 0.67; 95%CI 0.47-0.97) (Table 5). This association (HR 0.69; 95%CI 0.48-1.00; p = 0.05) was maintained also in the full-adjusted Cox regression analysis for the tumour size cut off point of ≥8 cm, that was not associated to prolonged hospital LOS (HR 0.57; 95%CI 0.28-1.16; p = 0.122).

Twenty-one patients (10.5%) had adrenal malignancies based on pathological findings: 5 had ACC, 10 had adrenal metastases, and 6 had malignant pheochromocytoma. Of the 11 patients with primary malignancy, three had tumours ≥5 cm (large mass group) while 8 had tumours <5 cm (control group). Post-operative follow up was available in 6 patients with an average duration of 40 ± 24.4 months. Data on initial diagnosis, tumour size, rate of conversion to open procedure, and data on adrenal malignancies that were available at follow up are illustrated in Table 6.

Discussion

The present study confirmed the feasibility and safety of laparoscopic adrenalectomy for tumours with a diameter ≥5 cm using operative time, conversion rate, peri-operative complications, and hospital LOS as endpoints. The early period of the study, which included the steep part of the learning curve for the surgeons who performed laparoscopic adrenalectomy, was the only independent factor associated with an increased risk of longer operative time, while ASA score ≥3 was the only predictor of prolonged hospital LOS.

The definition of a large size adrenal tumour varies greatly among different authors, ranging from ≥3.5 cm to ≥8 cm[9, 11, 16-19]. We defined large tumours as ≥5 cm based on final pathology report using the recent SAGES guidelines[1]. Diagnostic imaging studies (i.e. CT, MRI) may underestimate the actual size of adrenal masses by 18% to 20%[20].

Laparoscopic large tumour resection doesn't necessary lead to bad outcome.

Dissection of large adrenal lesions may be more challenging by laparoscopy due to the limited space to perform a wide dissection, leading to increased intra-operative blood loss, rate of conversion to open adrenalectomy, and longer operative time as well as hospital LOS as compared to small lesions. Walz et al. reported on 33 patients who underwent endoscopic adrenalectomy for large lesions (≥6 cm)[12]. The operative time, intra-operative blood loss, and conversion rate were increased in patients with large tumour as compared to those with small tumours [12]. It is difficult to compare these results with ours since retroperitoneal adrenalectomy rather than LLTA was used in the resection of large adrenal tumours in this report (24 vs. 9, respectively). Castillo and colleagues published the largest cohort study on surgical outcomes in 227 patients who underwent LLTA tumour resection based on tumour size: <6 cm (N = 140), 6-7.9 cm (N = 47), and ≥8 cm (N = 40), respectively[11]. The rate of conversion to open adrenalectomy and peri-operative complications were similar between groups. By contrast, increased operative time, intra-operative blood loss, and hospital LOS were also reported in patients with large adrenal masses as opposed to small lesions[11]. Similar results have been reported by some authors[9, 17, 21, 22] but not by others[8, 10, 23-25]. The discrepancies in the literature could be due to the different definitions used to define tumour size. In our study, the size of the tumour did not seem to affect the clinical outcome of the patients. Similarly, the operative time, conversion rate, intra- and post-operative complications, and hospital LOS did not differ in patients who underwent LLTA for a large lesion (N = 50) as opposed to small lesion (N = 150) (Table 2).

Surgeon's experience matters more than tumour size.

The size of the adrenal tumour is not the only variable affecting the clinical outcome following LLTA[9, 26, 27]. The BMI of the patient has been shown to positively correlate with operating time in LLTA, and patients with Cushing's disease are generally overweight with increased adipose tissue[9]. Recently, Tiberio et al. showed that the early versus late study period influenced the operating time, and a duration of the surgical procedure >140 minutes was associated with longer

hospital LOS[27]. Of note, the large size of the tumour was not associated with prolonged neither operative time nor hospital LOS. In our investigation, the early period (2004-2009) versus late period (2010-2014) of the study was the only independent factor associated with an increased risk of prolonged operative time (Table 3). Also, ASA score ≥3 was the only factor associated with prolonged hospital LOS (Table 4). In accordance to other authors, the size of the tumour (≥5 cm) did not have any impact on the operative time or the hospital LOS[9, 27]. Tiberio et al. did not include the operator's early learning phase in their study and speculated that the reduction of operative time between the study periods might be due to the availability of advanced dissecting and sealing devices, which were employed only in the late period[27]. In our investigation, ultrasound or radiofrequency dissecting and sealing devices were used throughout the study period, but the skills and experiences of the surgeon differ between the early and late study periods and this difference may have contributed to the decrease in operating time in the late versus early period. In addition, fewer patients with large tumour were operated on in the early as opposed to the late period, which suggests that the learning curve (i.e. experience of the surgeon) rather than tumour size is a major determinant of the duration of the surgical procedure.

Castillo et al. reported increased operative time and hospital LOS in patients with ≥8 cm tumours.[11] In our study, regression analysis adjusted for potential confounders showed that tumour size ≥8 cm was associated to prolonged operative time (Table 4), but it did not affect the hospital LOS. However, due to our low number of patients with a tumour size ≥8 cm (n = 15), these results should be interpreted with caution, but may support the need for a prospective study focusing on this particular group of patients.

Side of the lesion matters too.

The side of the adrenal tumour (left or right) was included in the risk analysis with the hypothesis that left adrenalectomy may have longer operating time as compared to right adrenalectomy, due to the need for an extensive mobilization of the colonic splenic flexure, spleen, and tail of the pancreas.

However, full-adjusted Cox regression analysis showed that having a tumour in the left adrenal gland reduced the likelihood of increased operative time, and this association was maintained also when a tumour size cut off point of ≥8 cm was adopted for the risk analysis. Two reasons may contribute to explain this result: 1) dissecting and sealing devices facilitate the greater mobilization needed to expose the left adrenal space and 2) the dissection and closure of the right adrenal vein is probably more difficult and time consuming than on the left side.

Tumour size alone should not dictate the choice of surgical approach.

ACC and malignant pheochromocytoma are uncommon, whereas benign adrenal tumours are common[10]. In an historical series, Copeland et al. found one ACC for every 60 adrenalectomies performed in patients with adrenal tumours >60 mm[28]. According to the National Institute of Health (NIH) consensus statement for the management of clinically unapparent adrenal mass, the incidence of ACC increases from 2% in tumours ≤40 mm, to 6% in tumours 41-60 mm in size, to 25% in tumours >60 mm[6]. Barnett et al., however, reported a 13.5% prevalence of ACC among patients with tumours <50 mm[29]. In a recent retrospective study on 289 patients who underwent laparoscopic adrenalectomy, Asari and colleagues found that of 14 patients with primary malignancy at final pathology, 7 (50%) were ≤60 mm in size, whereas 30 out of 37 (81.1%) patients with a tumour >60 mm had a benign lesion. These data suggest that if size is the only criterion guiding the operative approach, up to 80% of benign large adrenal tumours would have an unnecessary open approach, losing the advantage offered by a minimally invasive adrenalectomy [7]. In our study, among 11 patients with primary malignancy, three (27.3%) had a large tumour and 8 (72.7%) patients had a small tumour, while 46 out of 50 (92.0%) patients with a large tumour had a benign lesion at final pathology. These data seem to support that tumour size itself should not contraindicate a laparoscopic approach for adrenalectomy, when the risk of ACC is taken into account.

May malignant adrenal tumours be resected by LTTA in the absence of extra-adrenal extension?

It is still debatable whether laparoscopic adrenalectomy should be elected to treat ACC. The issue has been extensively reviewed and discussed during the 3rd International adrenal cancer symposium in Wurtzburg (Germany) in 2011 (http://www.endokrinologie.net/download/veranstaltungen/10122306.pdf).

In the present study, only 6 (54.5%) patients with primary malignancy were available for follow up (40 ± 24.4 months; Table 6): four patients were disease free, one patient with ACC presented with liver and paracaval lymph nodes metastases 14 months after LTTA, and another patient with malignant pheochromocytoma developed a recurrence 6 months after LLTA. Due to the limited number of patients available for follow up and to the absence of an open adrenalectomy comparison group, we could draw no firm conclusions on whether malignant adrenal tumours can be safely resected by LTTA in the absence of any pre-operative and intra-operative evidence of extra-adrenal extension.

Strengths and limitations of the study.

This is one of the largest studies that evaluate the outcomes of laparoscopic resection of large adrenal tumours. It is a multicentre study in which only three surgeons performed the LTTA adopting the same standardized technique at academic hospitals located both in the same geographic area and type of environment. In addition, greater variability in the patient population due to different participating centres may improve the external validity of our study. It should be considered, however, that the presence of three different centres may represent a potential confounding factor on the analysed outcomes and a possible source of bias. Other limitations also exist. Firstly, like most published studies comparing LTTA for large tumours versus small tumours, this is a retrospective study. Secondly, a standardized, universally accepted size cut-off to define a large adrenal tumour was not available. Lastly, a limited number of patients who underwent LTTA for primary malignancy were accessible for follow up and no open adrenalectomy group was available for comparison.

In conclusion, surgeons skilled in advance laparoscopy and adrenal surgery can perform LTTA safely in patients with ≥5 cm adrenal tumours with no increase in ~~operative time,~~ hospital LOS~~,~~ and conversion rate, although increased operative time may be expected with tumour size ≥8 cm. The experience of the surgeon and the comorbidities of the patients are the only factors that affect duration of the surgical procedure and hospital LOS, respectively, in laparoscopic large adrenal tumour resection.

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Disclosure

Drs. Carlo V. Feo, Mattia Portinari, Umberto Maestroni, Paolo Del Rio, Silvia Severi1, Lorenzo Viani, Riccardo Pravisani, Giorgio Soliani, Maria Chiara Zattelli, Maria Rosaria Ambrosio, Jenny Tong, Giovanni Terrosu, and Vittorio Bresadola have no conflicts of interest or financial ties to disclose.

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Table 1. Patient and tumour characteristics.

	Control group (< 5 cm) N=150	**Large mass group (≥ 5 cm) N=50**	**p**
Gender [N (%)]			0.189
Male	61 (40.7)	25 (50)	
Female	86 (57.3)	25 (50)	
Age (years)	56.6 ± 12.2	56.1 ± 14.8	0.813
Body mass index* (kg/m^2)	25 (23-29)	24 (21-27)	0.051
American Society of Anaesthesiology score† [N (%)]			0.782
1	32 (22.9)	9 (20.9)	
2	59 (42.1)	20 (46.6)	
3	48 (34.3)	13 (30.2)	
4	1 (0.7)	1 (2.3)	
Tumour size (cm)	3.3 (2.5-3.9)	6.5 (5.8-8.0)	<0.0001
Tumour side [N (%)]			0.752
Right	79 (52.7)	29 (58.0)	
Left	69 (46.0)	21 (42.0)	
Bilateral	2 (1.3)	0	
Indications for adrenalectomy [N (%)]			0.143
Non functioning Adenoma	59 (39.3)	27 (54.0)	
Pheochromocytoma	25 (16.7)	9 (18.0)	
Cushing's syndrome	32 (21.3)	4 (8.0)	
Conn's syndrome	15 (10.0)	2 (4.0)	
Adrenal metastasis	9 (6.0)	2 (4.0)	
Adrenocortical Carcinoma	0	0	
Other‡	10 (6.7)	6 (12.0)	
Final pathology [N (%)]			0.077
Adrenocortical Adenoma	92 (61.3)	22 (44.0)	
Benign Pheochromocytoma	18 (12.0)	6 (12.0)	
Malignant Pheochromocytoma	5 (3.3)	1 (2.0)	
Adrenal Metastasis	9 (6.0)	1 (2.0)	
Adrenocortical Carcinoma	3 (2.0)	2 (4.0)	
Other‡	23 (15.3)	18 (36.0)	

*The data was not available in 15 patients in the control group; † The data was not available in 10 patients in the control group and in 7 patients in the large mass group; ‡ It includes nodular hyperplasia, para-adrenal paraganglioma, ganglioneuroma, myelolipoma, and cysts.

Table 2. Intra- and post-operative variables and outcomes: comparison between groups.

	Control group (< 5 cm) N=150	**Large mass group (≥ 5 cm) N=50**	**p**
Operation time (min)	120 (103-150)	120 (108-153)	0.671
Conversion to open [N (%)]	7 (4.7)	3 (6.0)	0.488
Reason for conversion [N (%)]			0.854
Bleeding due to vascular injury	3 (2.0)	1 (2.0)	
Bleeding due to organ injury	1 (0.7)	0	
Adhesions	1 (0.7)	1 (2.0)	
Suspected cancer	1 (0.7)	0	
Difficult dissection	1 (0.7)	1 (2.0)	
Intra-operative complications [N (%)]			0.876
Bleeding due to vascular injury	4 (2.7)	1 (2.0)	
Bleeding due to organ injury	5 (3.3)	1 (2.0)	
Bowel perforation	1 (0.7)	0	
Post-operative complications (Clavien-Dindo) [N (%)]			0.639
No complications	135 (90.0)	44 (88.0)	
Minor (I-II)	10 (6.7)	6 (12.0)	
Major (III-IV)	5 (3.3)	0	
Death (V)	0	0	
Hospital length of stay (days)	4 (3-5)	4 (3-6)	0.229

Table 3. Association between baseline characteristics and prolonged operative time according to Cox regression analysis adjusted for potential confounders.

	Prolonged operative time			
	Unadjusted Model		**Full Adjusted Model**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Gender (male)	1.01 (0.76-1.35)	0.926	0.91 (0.65-1.26)	0.549
Age (≥65 years old)	1.17 (0.87-1.59)	0.304	1.15 (0.81-1.63)	0.423
Body Mass Index (≥25 kg/m^2)	1.06 (0.79-1.42)	0.691	1.14 (0.82-1.57)	0.439
American Society of Anaesthesiology score (≥3)	1.12 (0.82-1.53)	0.492	0.82 (0.57-1.18)	0.278
Indications for adrenalectomy (Cushing's syndrome)	1.07 (0.74-1.54)	0.739	1.48 (0.98-2.24)	0.063
Tumour size (≥5 cm)	0.92 (0.67-1.28)	0.621	0.74 (0.50-1.08)	0.117
Tumour side (left)	1.42 (1.06-1.89)	0.019	1.69 (1.22-2.33)	0.001
Study period (2004-2009)	0.83 (0.62-1.10)	0.192	0.57 (0.40-0.82)	0.002

Table 4. Association between baseline characteristics and prolonged operative time according to Cox regression analysis adjusted for potential confounders using tumour size cut off point of ≥8 cm.

	Prolonged operative time			
	Unadjusted Model		**Full Adjusted Model**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Gender (male)	1.01 (0.76-1.35)	0.926	0.92 (0.66-1.27)	0.591
Age (≥65 years old)	1.17 (0.87-1.59)	0.304	1.07 (0.75-1.52)	0.707
Body Mass Index (≥25 kg/m^2)	1.06 (0.79-1.42)	0.691	1.07 (0.78-1.47)	0.684
American Society of Anaesthesiology score (≥3)	1.12 (0.82-1.53)	0.492	0.87 (0.60-1.26)	0.462
Indications for adrenalectomy (Cushing's syndrome)	1.07 (0.74-1.54)	0.739	1.53 (1.02-2.30)	0.041
Tumour size (≥8 cm)	0.84 (0.50-1.43)	0.530	0.47 (0.24-0.94)	0.032
Tumour side (left)	1.42 (1.06-1.89)	0.019	1.83 (1.32-2.54)	<0.001
Study period (2004-2009)	0.83 (0.62-1.10)	0.192	0.58 (0.41-0.81)	0.002

Table 5. Association between baseline characteristics and prolonged hospital length of stay according to Cox regression analysis adjusted for potential confounders.

	Prolonged hospital length of stay			
	Unadjusted Model		**Fully Adjusted Model**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Gender (male)	0.99 (0.75-1.31)	0.942	1.02 (0.75-1.40)	0.895
Age (≥65 years old)	1.01 (0.74-1.36)	0.967	1.16 (0.81-1.67)	0.412
Body Mass Index (≥25 kg/m^2)	0.78 (0.58-1.05)	0.097	0.85 (0.62-1.17)	0.327
American Society of Anaesthesiology score (≥3)	0.73 (0.53-0.99)	0.049	0.67 (0.47-0.97)	0.034
Indications for adrenalectomy (Cushing's syndrome)	0.70 (0.48-1.01)	0.055	0.67 (0.45-1.02)	0.059
Tumour size (≥5 cm)	0.85 (0.61-1.18)	0.324	0.73 (0.50-1.07)	0.102
Tumour side (left)	1.29 (0.97-1.71)	0.085	1.25 (0.91-1.73)	0.170
Study period (2004-2009)	1.03 (0.77-1.38)	0.822	0.89 (0.63-1.26)	0.513
Duration of the surgical operation	0.99 (0.99-1.00)	0.226	0.99 (0.99-1.00)	0.539

Table 6. Initial diagnoses, tumour size, conversion to open procedure, and follow up data of patients with adrenal malignancies (adrenocortical carcinoma, adrenal metastasis, malignant pheochromocytoma).

Patient and malignancy	Initial diagnosis	Tumour size (cm)	Conversion to open procedure for intraoperative suspected malignancy	Local recurrence	Distant metastasis	Interval (months)	Re-operation	Follow up (months)
1 ACC	Cushing's syndrome	3.5	No	No	No	--	No	29
2 MP	Pheochromocytoma	2.0	No	Yes	No	6	Yes	50
3 ACC	Adrenocortical Adenoma	5.5	No	No	No	--	No	6
4 MP	Pheochromocytoma	1.8	No	No	No	--	No	79
5 MP	Pheochromocytoma	2.8	**No**	No	No	--	No	44
6 ACC	Adrenocortical Adenoma	8.0	**No**	No	Yes	14	Yes	32

ACC – AdrenoCortical Carcinoma; MP – Malignant Pheochromocytoma.

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