Laparoscopic adrenalectomy in urological centres – the experience of the German Laparoscopic Working Group

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Study Type – Practice patterns (retrospective cohort)
Level of Evidence 2b

OBJECTIVE

• To evaluate the safety and feasibility of laparoscopic adrenalectomy (LA) performed in several German centres with different laparoscopic experience, as LA has become the gold-standard approach for benign surgical adrenal disorders; however, for solitary metastasis or primary adrenal cancer its precise role is uncertain.

PATIENTS AND METHODS

• The data of 363 patients who underwent a LA were prospectively collected in 23 centres.

• All centres were stratified into three groups according to their experience: group A (<10 LAs/year), group B (10–20 LAs/year) and group C (>20 LAs/year).

• In all, 15 centres used a transperitoneal approach, four a retroperitoneal approach and four both approaches.

• Demographic data, perioperative and postoperative variables, including operating time, surgical approach, tumour size, estimated blood loss, complications, hospital stay and histological tumour staging, were collected and analysed.

RESULTS

• The transperitoneal approach was used in 281 cases (77.4%) and the retroperitoneal approach was used in 82 patients (22.6%).

• In all, 263 of 363 lesions (72.5%) were benign and 100 (27.5%) were malignant.

• The mean (SD) operating time was 127.22 (55.56) min and 130.16 (49.88) min after transperitoneal and retroperitoneal LA, respectively.

• The mean complication rates for transperitoneal and retroperitoneal LA were 5% and 10.9%, respectively.

CONCLUSION

• LAs performed by urologists experienced in laparoscopy is safe for the removal of benign and malignant adrenal masses. LA for malignant adrenal tumours should be performed only in high-volume centres by a surgeon performing at least >10 LAs/year.

KEYWORDS

adrenal gland, benign and malignant disease, laparoscopy, adrenalectomy, outcomes

INTRODUCTION

Minimally invasive techniques like laparoscopy aim to achieve the same results as open surgical procedures with the same safety and less trauma for the patient [1]. Laparoscopic adrenalectomy (LA) has become the generally accepted standard of care for surgical management of the vast majority of adrenal-related cases in little over the past two decades.

Centre	LA approach	TABLE 1
		Participating centres
Halle/Saale	Transperitoneal	
Heilbronn	Retroperitoneal	
Chemnitz	Transperitoneal	
Brüder Trier	Transperitoneal	
Mainz	Transperitoneal	
Freiberg	Trans- and retroperitoneal	
Coburg	Transperitoneal	
Basel	Retroperitoneal	
Münster	Retroperitoneal	
Berlin-Buch	Transperitoneal	
Berlin-Charité	Transperitoneal	
Lübeck	Transperitoneal	
Flensburg	Transperitoneal	
Pforzheim	Transperitoneal	
Pirna	Transperitoneal	
Straubing	Transperitoneal	
Weiden	Transperitoneal	
Kaiserslautern	Trans- and retroperitoneal	
Dessau	Transperitoneal	
Fulda	Transperitoneal	
Freiburg	Trans- and retroperitoneal	
Wolfsburg	Trans- and retroperitoneal	
Elisabethenkrankenhaus, Leipzig	Retroperitoneal	

Since the initial report by Gagner *et al*. [2] on the laparoscopic approach for adrenalectomy, several authors have reported on the feasibility and effectiveness of the laparoscopic technique for the treatment of adrenal disease [3–8].

The anatomical location of the adrenal gland in the upper retroperitoneal space, cranial and medial of the kidneys and in close proximity to the diaphragm, led to the development of various approaches, including lateral transperitoneal, anterior transperitoneal, lateral retroperitoneal, posterior retroperitoneal, and transthoracic approaches. Nevertheless, the lateral transperitoneal and the retroperitoneal approach are the technique most often used for LA.

In the present study, we investigated the role of laparoscopy for adrenal diseases, to define if LA can be safely performed for benign and malignant adrenal diseases considering the surgeon's experience and the surgical approach.

PATIENTS AND METHODS

On behalf of the Laparoscopic Working Group of the German Urological Association, we sent a questionnaire focusing on operative data after LA for benign and malignant conditions of the adrenal gland to 41 German urological centres with laparoscopic experience. In all, 23 urological departments participated on this multi-centre study, prospectively collecting the data after LA.

From 2003 to 2009, 363 patients underwent a transperitoneal or retroperitoneal LA at the participating urological centres. The centres were stratified into three groups according to their experience: group A (<10 LAs/year), group B (10–20 LAs/year) and group C (>20 LAs/year). Group A included 13 centres; group B included four; and group C included six. In all, 15 centres used a transperitoneal approach, four a retroperitoneal approach and four both approaches (Table 1).

Imaging via CT or MRI was the method of choice for securely diagnosing adrenal masses and assessing their size. Further evaluation of serum and urine metabolic parameters was performed to identify functional masses of the adrenal cortex and medulla, which would have required specifically adjusted preoperative management or postoperative hormonal substitution. Generally, cooperation with an endocrinologist is recommended in the preoperative management of these patients.

Demographic data, perioperative and postoperative variables, including operating time, surgical approach, tumour size, estimated blood loss (EBL), complications, hospital stay and histological tumour staging, were collected and analysed. Complications were defined according to the Clavien classification [9].

The data were recorded in a Microsoft Excel database (Microsoft Inc., Redmond, WA, USA). Data are expressed as the mean (SD) and statistical significance was assumed with a $P < 0.05$. For comparison of unpaired values among different groups, the nonparametric Kruskal–Wallis test (one-way ANOVA by ranks) was used. Intergroup analysis of means between two groups was performed using unpaired two-tailed t-test (Mann–Whitney). Between groups comparison of gender ratios and surgical-side ratios was performed using Fisher's Exact Test. For the multivariate analysis linear regressions analysis and Pearson correlation analysis were used. The CI was set on 95%.

RESULTS

TRANSPERITONEAL LA (Table 2)

A transperitoneal approach was used in 281 operations (77.4%); 153 were women (54.4%) and 128 were men (45.6%) with a mean (SD) age of 48.5 (34.5) years. Tumours were located in the right adrenal gland in 127 patients (45.2%) and in the left adrenal gland in 154 patients (54.8%).

The mean operative time was 159.85 ± 66.43 min, 116.46 ± 54.82 min and 105.35 ± 45.44 min for groups A, B and C respectively. The mean estimated blood loss was 158.72 ± 270.41 mL, 142.84 ± 204.63 mL and 108.27 ± 106.80 mL in the three groups respectively $(P = 0.012)$. Overall mean hospital stay was 7 ± 2 days $(P = 0.94)$.

Transperitoneal LA was completed successfully in 270 of 281 patients with a mean complication rate of 5%. In all, 11 patients (3.9%) presented with complications that required surgical interventions (Clavien grade 3). Of these patients, three (1.1%) required conversion for excessive bleeding of the vena cava during the laparoscopic mobilization of the right adrenal mass and two (0.7%) required conversion for bleeding

TABLE 2 Transperitoneal LA

Variable	Group A	Group B	Group C	P, A–B*	P, A–C*	P, B–C*	P overall†
N	62	70	149				
Mean (SD) age, years	56.12 (1.98)	62.24 (12.28)	54.66 (12.65)	0.019	0.281	0.007	0.018
Ratio male/female	0.82	0.67	0.92	0.812‡	0.923‡	0.721‡	–
Ratio left/right adrenal gland	1.21	1.27	1.08	1.000‡	0.761‡	0.824‡	–
Mean (SD) operating time, min	159.85 (66.43)	116.46 (54.82)	105.35 (45.44)	0.016	0.009	0.010	<0.001
Mean (SD) EBL, mL	158.72 (270.41)	142.84 (204.63)	108.27 (106.80)	0.659	0.0128	0.042	0.013
Mean (SD) hospital stay, days	7.38 (2.99)	7.08 (2.06)	6.89 (2.06)	0.760	0.777	0.923	0.942
Mean (SD; range) tumour size, cm	2.96 (1.78; 0.5–6)	3.46 (1.34; 2.5–7)	3.77 (1.51; 1.8–10)	0.165	<0.001	0.026	<0.001
Mean (SD; range) size for malignant tumours, cm	1.82 (1.54; 0.5–3.5)	2.72 (1.83; 2.5–6.5)	4.64 (2.36; 2.5–10)	0.043	0.022	0.045	0.016
Number of ACCs	2	3	19	0.840	<0.001	<0.001	<0.05
Number of malignant phaeochromocytoma	0	0	3	NA	0.03	0.03	0.03

Two-tailed unpaired t-test (Mann–Whitney); † Kruskal–Wallis test; ‡ Fisher's exact test; NA, not applicable.

of the vena lienalis during LA on the left side, while in another two patients (0.7%) conversion was necessary because of adhesions. Three patients (1.1%) presented with a lesion of the spleen and in another patient (0.3%) a lesion of the pancreas occurred intraoperatively.

One 75-year-old patient (0.4%) had a pulmonary embolism on the fifth postoperative day but fully recovered (Clavien grade 2). Two patients (0.7%) developed a postoperative haematoma in the right and left adrenal areas, which did not require intervention (Clavien grade 1). Postoperative complications are listed in Table 3.

RETROPERITONEAL LA

In all, 82 operations (22.6%) were performed with a retroperitoneal approach; 34 were women (41.5%) and 48 were men (58.5%) with a mean age of 53 (40) years. Tumours were located in the right adrenal gland in 46 patients (56.1%) and in the left adrenal gland in 36 patients (43.9%).

The mean operating time was 143.95 (6.12) min, 126.82 (50.91) min and 119.72 (42.61) min for groups A, B and C respectively *(P* = 0.332*)*. The mean EBL was 145.14 (150.72) mL, 127.50 (162.12) mL and 107.61 (104.93) mL in the three groups respectively *(P = 0.019)*. Overall the mean hospital stay was 7 (2) days *(P* = 0.277; Table 4).

Retroperitoneal LA was completed successfully in 76 of 82 patients with a mean complication rate of 10.98%. Six patients (7.3%) presented complications that required surgical interventions (Clavien grade 3), with conversion for excessive bleeding of the vena cava in two patients (2.44%), for lesion of the spleen in another two patients (2.44%), and for the development of a marked hypotension with an unclear origin in one patient (1.22%). In another patient (1.22%) a conversion to open surgery was necessary because of an intraoperative detection of a pancreas tumour. One 54-year-old patient (1.22%) had an increase in serum creatinine on the second postoperative day but fully recovered after pharmacological treatment (Clavien grade 2). Two patients (2.44%) developed a postoperative haematoma in the adrenal areas, which did not require intervention (Clavien grade 1). Postoperative complications are listed in Table 5.

ONCOLOGICAL RESULTS

In all, 263 (72.5%) of 363 lesions were benign. Of these, 193 were adenomas of the adrenal gland, 48 were phaeochromocytomas and 15 myelolipomas. There were also three benign adrenal cysts, one ganglioneuroma and two haemangiomas.

In all, 100 (27.5%) of 363 lesions were malignant. The final histology reported primary malignant disease of the adrenal gland in 37 patients. The remaining patients had metastases from other primary

TABLE 3 Complications after transperitoneal LA

Complication	%
Bleeding	1.1
Conversion	3.9
Injury of the spleen	1.1
Injury of the pancreas	0.3
Haematoma	0.7
Pulmonary embolism	0.4
Adhesions	0.7

cancers: 26 from a RCC, 15 from a lung cancer, nine from a mamma carcinoma, eight from a melanoma and four from a colon cancer. In one 33-year-old patient and in one 54-year-old, the adrenal tumour represented a metastasis from testicular cancer.

Of the 37 primary malignant diseases, 34 were adrenocortical carcinomas (ACCs) and three were malignant phaeochromocytomas. The ACCs included 20 stage I tumours and 14 stage II tumours, according to the McFarlane-Sullivan classification (tumour without infiltration of neighbouring structures, positive lymph nodes, or distant metastasis) [10].

All malignant specimens had negative margins at histopathology. Three patients (3%) developed a postoperative port-site metastasis after retroperitoneal LA. One patient had metastases from melanoma, one

TABLE 4 Retroperitoneal LA

Variable	Group A	Group B	Group C	P, A–B*	P, A–C*	P, B–C*	P, Overall*†
N	11	21	50				
Mean (SD) age, years	54.12 (13.32)	41.71 (13.25)	56.37 (16.14)	0.087	0.349	0.015	0.047
Ratio male/female	1.0	0.6	1.7	0.614‡	0.699‡	0.699‡	–
Ratio left/right adrenal gland	0.33	0.33	0.80	1.430‡	0.449‡	0.449‡	–
Mean (SD) operating time, min	143.95 (56.12)	126.82 (50.91)	119.72 (42.61)	0.674	0.204	0.674	0.332
Mean (SD) EBL, mL	145.14 (50.72)	127.50 (162.12)	107.50 (104.93)	0.079	0.188	0.030	0.0187
Mean (SD) hospital stay, days	7.63 (1.73)	6.21 (1.66)	6.82 (1.75)	0.204	0.199	0.423	0.277
Mean (SD; range) tumour size, cm	2.62 (1.12; 0.5–5)	3.71 (0.91; 2–7)	3.98 (1.83; 1.5–10)	0.033	0.014	0.475	0.073
Mean (SD; range) size for malignant tumour, cm	1.82 (1.54; 0.5–3.5)	2.84 (1.94; 2–5)	3.98 (2.76; 2.5–7)	0.041	0.024	0.040	0.012
Number of ACCs	2	3	5	0.082	0.021	0.04	0.015
Number of malignant phaeochromocytoma	0	0	0	NA	NA	NA	NA

Two-tailed unpaired t-test (Mann–Whitney); † Kruskal–Wallis test; ‡ Fisher's Exact Test; NA, not applicable.

TABLE 5 Complications after retroperitoneal LA

Complications	%
Bleeding	2.5
Conversion	7.3
Injury of the spleen	2.5
Significant hypotension	1.2
Postoperative increase of the serum creatinine	1.2
Haematoma	2.4
Intraoperative detection of a pancreas tumour	1

FIG. 2. Tumour size vs hospital stay.

FIG. 3. Tumour size vs EBL.

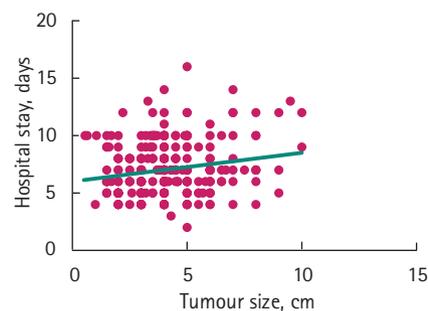*FIG. 1. Tumour size vs operating time.*
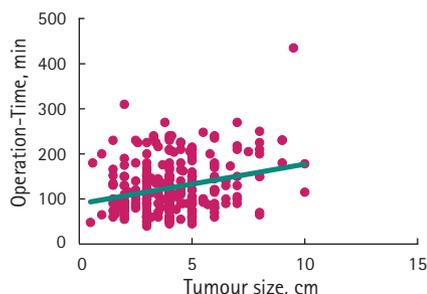
patient from lung cancer and one patient had a primary adrenocortical mass.

MULTIVARIATE ANALYSIS (Table 6)

There was a strong correlation between tumour size and operating time ($r = 0.264$, $r^2 = 0.06$, $P < 0.001$; Fig. 1) as well as the duration of hospital stay ($r = 0.18$, $r^2 = 0.35$,

$P = 0.01$; Fig. 2). Further, there was a moderate correlation between tumour size and the amount of estimated blood loss (Fig. 3). Furthermore, an inverse relationship was found between the tumour entity (benign/malignant) and the duration of hospital stay ($r = -0.10$, $r^2 = 0.10$, $P = 0.07$), as well as operating time ($r = -0.05$, $r^2 = 0.003$, $p = $ ns) (Fig. 1).

DISCUSSION

The advantage of any laparoscopic approach for the adrenal glands for blood loss, operative time, cosmesis and convalescence compared with open surgery is undisputed. Because of its proven efficacy, LA is indicated for the removal of nonfunctional and functional solid small-to-intermediate adrenal masses.

The experience of the surgeon, the location of the mass in relation to other structures and
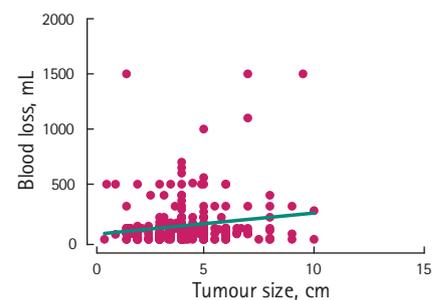
the size of the mass should influence the decision-making process for open adrenalectomy (OA) vs LA. The upper size limit in very experienced hands may be as high as 10–14 cm; however, tumours of >6–7 cm should be seen as the upper limit in the earlier stages of laparoscopic experience [3–8]. Special indications are the removal of malignant tumours or metastases [8,9,11].

The larger operative field of the transperitoneal approach aids in a better orientation and visualization of familiar landmarks known to us from open surgery [11,12]. In particular, this is an advantage in the early learning curve of LA. The more extensive working space is also useful for removal of larger adrenal masses of >6–7 cm [13–15]. In contrast, retroperitoneal LA has gained in popularity because it allows direct access to the adrenal gland and avoids potential injury to intra-abdominal organs [16].

To a large degree, slight differences reported by groups advocating either approach are more likely to represent preference and therefore will be the more commonly applied technique. In experienced hands there were no differences between the transperitoneal and retroperitoneal approach for clinical outcomes [16–18].

In the present study, 281 operations (77.4%) were performed with a transperitoneal approach and 82 operations (22.6%) were retroperitoneal. To our knowledge the present series is the largest published series to date. The reported results did not show significant differences in morbidity between the two approaches. The main problem was not represented by the surgical approach (transperitoneal or retroperitoneal) but it was associated with the peri- and postoperative morbidity, which was greatly influenced by the experience of the surgeon who performed the procedure. The experience of the surgeon and of the centre should influence the decision-making process for OA vs LA.

Although in LA the approach is minimally invasive, the complexity of the procedure is generally at least equal to its traditional OA counterpart. This is reflected in the scope of possible complications, e.g. vascular injury, bowel injury, injury of the liver or of the spleen, pleural injury and pancreatic injury [19]. In the present study, vascular injuries were the most common (3.5%) as well as injury of the spleen (3.5%), followed by conversion occurring due to the presence of massive adhesions (2.6%) and injury of the pancreas (0.3%).

The mean complication rate was 5% and 10.98% after transperitoneal and retroperitoneal LA, respectively. Comparing with the data reported by two recent studies performed by general surgeons, where the mean complication rate was 5.2–17.2% [20,21], the complication rates were similar in the present study.

LA has become the gold-standard approach for benign surgical adrenal disorders such as aldosteronoma, Cushing's syndrome and phaeochromocytoma. However, LA for solitary metastasis or primary adrenal cancer remains a matter of considerable controversy, even if some authors support the safety of the laparoscopic procedure for malignant adrenal cancer [10,22,23].

TABLE 6 *Multivariate analysis for tumour size and tumour entity vs operating time, EBL and hospital stay*

Variable	Operating time	*P*	EBL	*P*	Hospital stay	*P*
Tumour size						
$r_{pearson}$	0.264	*<0.001*	0.161	*0.006*	0.187	*0.001*
r^2	0.069	*<0.001*	0.026	*0.006*	0.035	*0.001*
F	21.31		7.59		10.37	
Tumour entity						
$r_{pearson}$	−0.057	*0.163*	0.076	*0.092*	−0.103	*0.036*
r^2	0.003	*0.322*	0.006	*0.185*	0.107	*0.073*
F	0.962		1.765		3.226	

Moreover, for ACC the role of LA is controversial. Surgery is of utmost importance in the treatment of ACC because a margin-free complete resection (R0 resection) provides the only means to achieve long-term cure. Although evidence of invasive disease before surgery requires an open approach, localized tumours (stage I/II) with a diameter of <10 cm, may also be accessible by LA [11,22]. This theory has been also confirmed by Porpiglia *et al.* [23]. In their recent study of 43 patients with stage I and II ACC, they reported comparable oncological outcomes between patients treated with OA or LA, with a recurrence rate of 64% after OA and 50% after LA, and a median recurrence-free survival of 18 months in the OA group and 23 months in the LA group ($P = 0.8$).

At the same time Brix *et al.* [11] suggested that LA is not inferior to OA in localized ACC with a diameter of <10 cm for oncological outcome. The authors reported the outcomes in 152 patients affected by ACC who underwent OA or LA. Recurrence rate was 69% after OA and 77% after LA and the median recurrence-free survival was not different between the groups with a hazard ratio for death of 0.79.

Nevertheless, Miller *et al.* [23] concluded that although feasible in many cases and tempting, laparoscopic resection should not be attempted in patients with tumours suspicious for or known to be ACCs.

In the present study, with 37 patients who underwent LA for ACC (34 patients) and for malignant phaeochromocytoma (three), LA was safe and feasible only when performed by surgeons experienced in LA in high-volume centres (>10 LAs/year). In fact, three patients (3%) developed a port-site metastasis

associated with tumour spillage after violation of the capsule. This might appear a high rate for port-metastasis; however, it is important to recognise that all these cases occurred in group A, the group with minor LA experience.

Resection of metastatic processes to the adrenal has a higher incidence of port-site metastasis, if the primary tumour is in a very advanced stage and grade. An international survey showed that in 336 adrenalectomy reports there were four cases of tumour seeding (0.9%). Three of the four cases had metastases from lung cancer and one had a primary adrenocortical mass causing Cushing's syndrome [10].

Port-site metastasis has been hypothesized to occur from the dispersion of malignant cells by CO_2 gas, tumour spillage from inadvertent violation of the involved organ, extraction site contamination by tumour cells and the questionable immunosuppressive effect of pneumoperitoneum [24]. Avoiding these conditions that accelerate the formation of port-site metastases and respecting surgical principles laparoscopy can reproduce the same results as open surgery even in the treatment of malignancies.

A limitation of the present study was the lack of an oncological follow-up, because of the differences in expertise of the participating centres, which could influence the oncological outcomes.

In conclusion, transperitoneal and retroperitoneal LA performed by urologists experienced in laparoscopy is safe for the removal of benign and malignant adrenal masses. According to the present study, LA for malignant adrenal tumours should be performed only in high-volume centres

by a surgeon performing >10 LAs/year. Consequently, surgeons with little laparoscopic experience should avoid, at the beginning of their learning curve, performing LA on malignant disease because of the high risk of inducing port-site metastasis.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **EBL**, estimated blood loss; **(O)(L)A**, (open) (laparoscopic) adrenalectomy; **ACC**, adrenocortical carcinoma.