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Adrenals

Laparoscopic Versus Open Adrenalectomy for Adrenocortical Carcinoma: Surgical and Oncologic Outcome in 152 Patients

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Abstract

Background: The role of laparoscopic adrenalectomy in the treatment of patients with adrenocortical carcinoma (ACC) is controversial.
Objective: Our aim was to compare oncologic outcome in patients with ACC who underwent either open adrenalectomy (OA) or laparoscopic adrenalectomy (LA) for localised disease.
Design, setting, and participants: We conducted a retrospective analysis of 152 patients with stage I–III ACC with a tumour $\leq$10 cm registered with the German ACC Registry.
Intervention: Patients were stratified into two groups according to the surgical procedure (LA or OA). For comparison, we used both a matched pairs approach by selecting for each patient from the LA group ($n = 35$) one corresponding patient from the OA group ($n = 117$) and multivariate analysis in all 152 patients.
Measurements: Disease-specific survival was chosen as the predefined primary end point. Secondary end points were recurrence-free survival, frequency of tumour capsule violation and postoperative peritoneal carcinomatosis, and incidence and reasons for conversion from LA to OA.
Results and limitations: LA and OA did not differ with regard to the primary end point using either the matched pairs approach (hazard ratio [HR] for death: 0.79; 95% confidence interval [CI], 0.36–1.72; $p = 0.55$) or multivariate analysis (HR for death: 0.98; 95% CI, 0.51–1.92; $p = 0.92$). Similarly, adjusted recurrence-free survival was not different between LA and OA (HR: 0.91; 95% CI, 0.56–1.47; $p = 0.69$). Frequency of tumour capsule violation and peritoneal carcinomatosis were comparable between groups. In 12 of 35 patients of the LA group, surgery was converted to open surgery with no impact on the clinical outcome.
Conclusions: For localised ACC with a diameter of $\leq$10 cm, LA by an experienced surgeon is not inferior to OA with regard to oncologic outcome.

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1. Introduction

Minimally invasive retroperitoneoscopic or laparoscopic adrenalectomy (LA) has become the accepted gold standard for the treatment of benign adrenal tumours because it leads to fewer complications, a shorter hospital stay, and reduced 30-d morbidity rates [1–5]. Although initially this technique was restricted to small tumours, today experienced surgeons can safely remove benign tumours up to 12 cm [4]. Although in such larger tumours operative time, blood loss, and hospital stay may be increased, the general benefits of LA are maintained [6].

In contrast, for adrenocortical carcinoma (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, localised tumours (stage I/II) with a diameter <10 cm may also be accessible by LA. However, although some surgeons claim that LA for localised ACC may be performed with equal oncologic outcome [7], others believe this approach is contraindicated [4]. Initial reports on LA for ACC described tumour fragmentation and port-site and local recurrences [8,9]. In addition, Gonzalez et al. [10] reported on a high risk of peritoneal carcinomatosis after LA for ACC, and this concern was reiterated in a recent report from France [11]. In contrast, a growing number of reports on laparoscopic surgery for ACC suggest a comparable or even superior oncologic outcome compared with open surgery [12,13]. In most cases the tumour diameter was <8.5 cm [7], but recently laparoscopic surgery for malignant tumours with a size up to 15 cm has been reported [14]. Because ACC frequently recurs after surgery with curative intent [15,16], evaluation of the best surgical strategy requires long-term follow-up in a sufficient number of patients.

Due to the rarity of the disease, the number of ACC cases in these series has been small, the follow-up time was limited, and suitable controls, who underwent open adrenalectomy (OA) for ACC, were frequently lacking [7].

To overcome these limitations, we provide data here from the German ACC Registry on the role of the surgical approach for the oncologic outcome in patients with ACC.

2. Methods

2.1. German Adrenocortical Carcinoma Registry

At the time of the analysis (April 2010), the German ACC Registry (www.nebennierenkarzinom.de) contained 608 patients. All data were collected by trained medical personnel as described previously [17–19]. Follow-up data were obtained approximately every 3 mo. The German ACC Registry was approved by the ethics committee at the University of Würzburg, and patients gave written informed consent. The diagnosis had been confirmed by histopathology [16]. Stage designation was based on the European Network for the Study of Adrenal Tumours (ENSAT) criteria, which are superior to the Union Internationale Contre le Cancer/World Health Organisation staging system [19,20]: stage I, a tumour diameter ≤5 cm; stage II, a tumour diameter >5 cm; stage III, tumour infiltration of neighbouring structures, venous tumour thrombus in vena cava or renal vein, or positive lymph nodes; and stage IV, distant metastases.

2.2. Study cohort

To be included patients had to fulfil the following criteria: surgery between 1996 and 2009, age ≥16 yr, no distant metastases at the time of primary diagnosis, tumour size ≤10 cm, and detailed information on surgical procedures and follow-up available. Ninety-one patients were excluded due to surgery before 1996, 38 due to age <16 yr, 138 due to distant metastases, and 160 due to tumour size >10 cm. For 29 patients, missing information on the surgical procedure or follow-up led to exclusion. Therefore, a total of 152 patients fulfilled all inclusion criteria.

2.3. Outcomes

The predefined primary end point was disease-specific (overall) survival. Secondary end points were recurrence-free survival, perioperative complications (including violation of the tumour capsule), frequency of peritoneal carcinomatosis, frequency and reasons for conversion of LA to OA, and outcome of patients in whom surgery had or had not been converted from LA to OA.

2.4. Statistics

Patient characteristics between subgroups were compared with the Fisher exact test and χ^2 test. Disease-specific survival was defined as the time elapsed from primary surgery to death from ACC. Patients who were alive or who had died ($n = 1$) from other causes were censored. We chose two different methodological approaches for analysis. First, for each patient with LA, one patient with OA was matched according to the following criteria: tumour stage, tumour size, adjuvant therapy, age, and presence of glucocorticoid excess. Matching was performed by an investigator (DB) who was not aware of patient outcome. Second, in a multivariate approach using the Cox proportional hazards model, disease-specific and recurrence-free survival was analysed after adjustment for the following factors: surgical approach, tumour stage, tumour size, adjuvant therapy, age, and presence of glucocorticoid excess.

Survival analysis was calculated using the Kaplan-Meier method, and differences between groups were assessed with log-rank statistics. Recurrence-free survival was defined as time from the date of tumour resection to the first evidence of relapse or last follow-up without evidence of disease. The Cox proportional hazards model was used for multivariate analysis to adjust for surgical approach, tumour stage, tumour size, adjuvant therapy, presence of glucocorticoids, and age. Data were analysed using SPSS v.18.0 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Surgical outcome

Table 1 lists patient characteristics. In 35 of 152 patients (23%), LA was performed. In 33 patients, a laparoscopic transperitoneal approach was used (94%); two patients had undergone retroperitoneoscopic adrenalectomy. In the OA group, 85 patients (73%) had transperitoneal, 31 patients (26%) had retroperitoneal, and 1 patient (1%) had thoracoabdominal surgery. In 12 cases the surgeons converted from LA to open surgery due to bleeding ($n = 4$), adhesions ($n = 4$), bowel perforation ($n = 1$), or other technical problems ($n = 2$). In one case intraoperative evidence of malignancy led to conversion ($n = 1$).

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Table 1 – Baseline characteristics of 152 patients treated with open or laparoscopic adrenalectomy for adrenocortical carcinoma between 1996 and 2009

Variable	OA $n = 117$ (77%)	LA $n = 35$ (23%)	p value OA vs LA	Matched OA controls ($n = 35$)	p value (matched groups)
Age, yr					
Mean	52.3	50.7	0.6*	52.7	0.6*
Range	(20–87)	23–78*		20–87	
Sex, *n* (%)					
Male	35 (30)	9 (26)	0.67‡	12 (34)	0.6‡
Female	82 (70)	26 (74)		23 (66)	
Hormonal excess, *n* (%)					
Glucorticoids	31(26)	20 (57)	0.001‡	9 (26)	0.015‡
Androgenes/precursors	21 (18)	8 (23)	1‡	6 (17)	0.8‡
Estrogenes	3 (2.6)	2 (6)	0.3‡	1 (3)	1‡
Mineralocorticoids	8 (7)	4 (11)	0.5‡	2 (6)	0.7‡
No hormonal workup performed	43 (37)	3 (9)	0.001‡	1 (3)	0.6‡
Incidentalomas, *n* (%)	23 (20)	8 (23)	0.64‡	9 (26)	1‡
Localisation, *n* (%)					
Right	49 (42)	26 (74)	<0.001‡	17 (49)	0.048‡
Left	68 (58)	9 (26)		18 (51)	
Median tumour size, cm	8	6.2		7.0	
Range, cm	2.5–10	3–10	<0.001‡	2.5–10	0.6‡
ENSAT tumour stage *n* (%)					
I	9 (8)	12 (34)	<0.001†	9 (26)	0.7†
II	70 (60)	19 (55)		22 (63)	
III	38 (32)	4 (11)		4 (11)	
Surgical approach					
Retroperitoneal	30 (26)	2 (6)		16 (46)	0.002
Transperitoneal	85 (73)	33 (94)		19 (54)	
Thoracoabdominal	1 (1)	–			
Perioperative mortality, *n*	0	0	1	0	1
Violation of the capsule					
Yes, *n* (%)	18 (15)	3 (9)	0.4‡	4 (11)	0.74‡
No, *n* (%)	98 (85)	32 (91)		31 (89)	
Resection status, *n* (%)					
R0	64 (55)	24 (69)	0.45†	21 (60)	0.26†
R1	10 (9)	2 (6)		0	
R2	3 (3)	0		1 (3)	
Rx	40 (33)	9 (26)		13 (37)	
Adjuvant mitotane, *n* (%)					
Yes	27 (23)	8 (23)	1‡	7 (20)	1‡
No	90 (77)	27 (77)		28 (80)	
Adjuvant irradiation, *n* (%)					
Yes	11 (10)	1 (3)	0.29‡	1 (3)	1
No	99 (90)	34 (97)		34 (97)	1‡
Weiss score					
Median (range)	5 (2–9)	6 (2–9)	0.24§	4 (2–9)	0.032§
Ki67					
Median (range)	10 (1–60)	10 (1–50)	0.95§	10 (1–60)	0.89§
Recurrent disease at the time of registration	71 (61)	19 (54)	0.56‡	21 (60)	0.8‡
Follow-up of patients alive, mo					
Median	32	64	0.02§	32	0.002§
Range	6–131	22–109		6–131	

* Student *t* test.
† χ^2 test.
‡ Fisher exact test.
§ *U* test.
ENSAT = European Network for the Study of Adrenal Tumours; LA = laparoscopic adrenalectomy; OA = open adrenalectomy.

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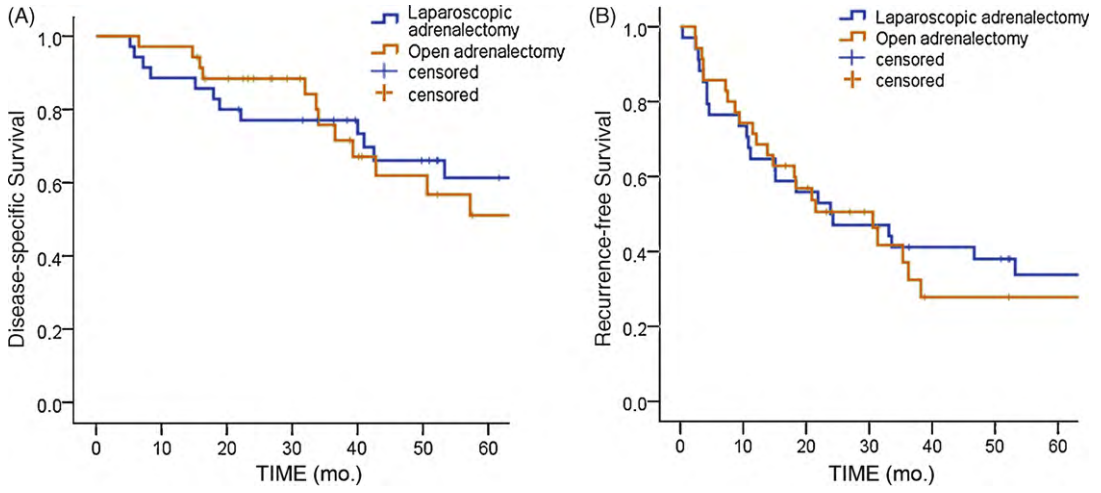

Fig. 1 – Kaplan-Meier estimates of (A) disease-specific survival and (B) recurrence-free survival of 35 patients with laparoscopic adrenalectomy versus 35 matched patients with open adrenalectomy (OA). In 12 of 35 patients, minimally invasive adrenalectomy was converted to OA (see Fig. 2).

As expected, the frequency of stage III patients was higher in the OA group compared with the LA group (32.5% vs 11.4%; $p < 0.001$) because in the LA group all tumours were considered as stage I/II prior to surgery. However, there was no significant difference in baseline characteristics between the 35 LA patients and their 35 matched counterparts except for tumour localisation, with more tumours on the right side in the LA group (Table 1). A similar rate of R0 resections was found in both LA patients (24 of 35) and OA patients (21 of 35) (Table 1). Violation of the tumour capsule occurred in 3 of 35 patients with LA (8.6%) and in 4 of 35 patients in the matched OA group (11.4%) versus 18 of 117 patients in the entire OA group (15.4%).

3.2. *Oncologic outcome*

Recurrence occurred in 27 patients in the LA group (77%) and in 81 patients with OA (69%; $p = 0.36$). Sixty-one patients died from ACC: 13 in the LA group (37%) and 48 in the OA group (41%) ($p = 0.68$). Median follow-up in patients still alive is 39.3 mo (range: 6.3–131 mo).

Peritoneal carcinomatosis at the time of the first recurrence was documented in one patient in the LA group (3%) and four patients in the OA group (3%; not significant). In three of these patients, violation of the tumour capsule was documented in the surgical report.

3.3. *Survival analysis using matched pairs*

Disease-specific and disease-free survival was not different between LA and OA (Fig. 1a and b) with a hazard ratio (HR) for death of 0.79 (95% confidence interval [CI], 0.36–1.72; $p = 0.55$) and for recurrence of 1.07 (95% CI, 0.61–1.87; $p = 0.82$).

Clinical outcome of the 12 patients in whom surgery had been converted to open surgery was not different from the 23 patients in whom LA was completed (HR for death: 1.07; 95% CI, 0.32–3.58; $p = 0.91$). Similarly, overall and

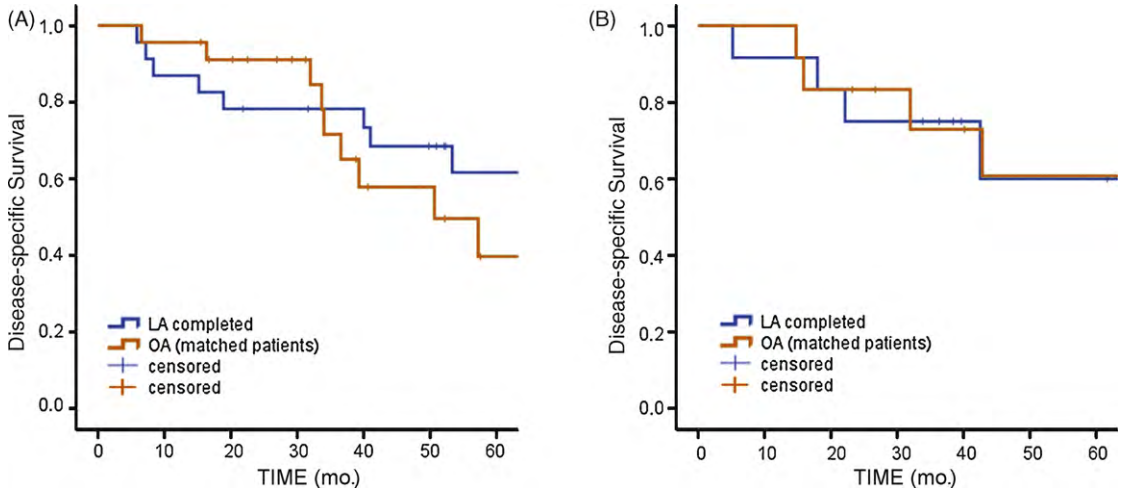

Fig. 2 – (A) Kaplan-Meier estimates of disease-specific survival of the 23 patients in whom laparoscopic adrenalectomy (LA) was completed versus 23 matched patients with open adrenalectomy (OA). (B) Kaplan-Meier estimates of disease-specific survival of the 12 patients in whom LA was converted to OA versus 12 matched patients with OA.

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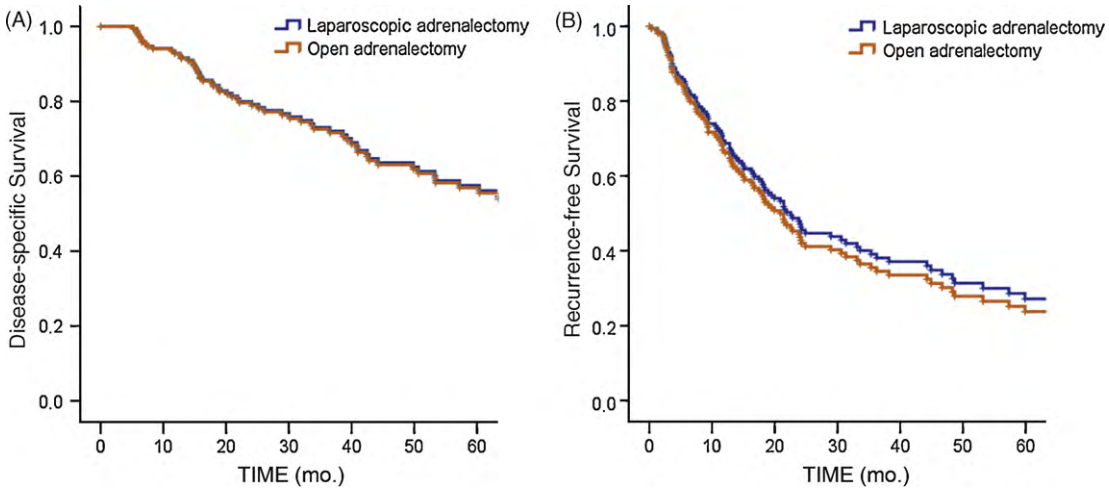

Fig. 3 – Survival analyses using multivariate Cox regression analysis: (A) disease-specific survival; (B) recurrence-free survival. Laparoscopic adrenalectomy (35 patients) and open adrenalectomy (117 patients). Adjusted for age, tumour stage, tumour size, adjuvant therapy, and presence of glucocorticoid excess.

recurrence-free survival were not different in the 23 patients in whom LA was completed compared with their respective matched OA controls (HR for death: 0.68 (0.28–1.77); $p = 0.42$) (Fig. 2a and b).

3.4. *Survival analysis after multivariate adjustment*

Similar results were derived when all 152 patients were included in a multivariate analysis (Fig. 3a and b). After adjustment for surgical approach, age, ENSAT tumour stage, tumour size, adjuvant therapy, and presence of glucocorticoid excess, disease-specific and recurrence-free survival was virtually identical between the 35 patients in the LA group and the 117 patients in the OA group (HR for death: 0.98; HR for recurrence: 0.91; Table 2).

4. Discussion

The major finding of our analysis is a similar outcome after minimally invasive and open surgery for localised ACC with a diameter $\leq$10 cm. This result was consistently derived both by a matched pairs approach and by multivariate analysis. It relates both to oncologic outcome parameters like disease-specific survival and recurrence-free survival as well as to surgical complications like tumour capsule violation and occurrence of peritoneal carcinomatosis. Compared with previous investigations, our study has important strengths: availability of suitable controls including adjustment for prognostic factors, the largest sample size to date, and the longest follow-up (especially in the LA group).

Until 2009 no report on LAs included more than seven patients with ACC, and in these studies suitable controls who had undergone OA were almost completely absent. The first two larger studies on this topic have been published in 2010 and came to opposite conclusions. Porpiglia et al reported on 18 patients who underwent LA and 25 patients who had OA [14]. The authors found OA and LA comparable in terms of recurrence-free survival for patients with stage I and II ACC. This agrees with our findings. However, patients with a conversion from laparoscopic to open surgery were excluded from their analysis. Importantly, 28% of the patients were treated at the reporting institution, the majority with LA potentially inducing a bias favouring LA. Miller et al. [21] retrospectively studied 88 patients with ACC who underwent surgical resection with intent to cure; 17 underwent LA and 71 underwent OA. Recurrent disease was similar in both groups (63% vs 65%). However, mean

Table 2 – Predictors of disease-specific and recurrence-free survival in 152 patients with adrenocortical carcinoma*

	Disease-specific survival				Recurrence-free survival			
	HR	95% CI		*p*	HR	95% CI		*p*
Surgical approach	0.98	0.50	1.92	0.96	0.91	0.56	1.47	0.69
Tumour stage (ENSAT)	1.59	1.01	2.52	0.046	1.18	0.84	1.66	0.34
Tumour size	1.16	0.99	1.36	0.05	1.08	0.97	1.21	0.16
Age	1.00	0.99	1.02	0.49	1.01	0.99	1.02	0.31
Adjuvant therapy	0.98	0.53	1.84	0.97	0.81	0.50	1.31	0.39
Glucocorticoid excess	1.04	0.60	1.82	0.88	1.66	1.10	2.52	0.02

CI = confidence interval; ENSAT = European Network for the Study of Adrenal Tumours; HR = hazard ratio.
* Using a Cox regression multivariate analysis.

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time to recurrence was shorter for those who underwent LA (9.6 vs 19.2 mo; $p < 0.005$). Of note, 50% of patients who underwent LA had positive margins or intraoperative tumour spill compared with 18% in the OA group ($p = 0.01$). The authors concluded that LA is inappropriate in known or suspected ACC. These results differ profoundly from our findings and those of Porpiglia et al. [14]. More specifically, in our patients, tumour capsule violation, R0 resection, and recurrence-free survival were similar after OA and LA, indicating that our laparoscopic group compares favourably with their patients. Again, a selection bias may have contributed to their findings because all patients in the laparoscopic group underwent surgery at an outside institution, whereas 18 of 71 open surgeries were performed at the reporting institution. Most of the other patients contacted this centre only after disease recurrence.

Selection bias may be of extraordinary relevance in the comparison between OA and LA. For example, Gonzalez et al reported on peritoneal carcinomatosis after LA [10]. None of their patients was operated at the reporting institution, strongly suggesting a referral bias because successfully operated patients without recurrence were unlikely to contact their centre. An opposite effect may be observed in surgical series reporting on LA. A review of LA for ACC [7] found 13 recurrences in 42 malignancies, which compares favourably with reports from reference series in patients who underwent OA [10,22,23]. However, these reference series predominantly included patients only after recurrence and thus with poor outcome [24]. Such an effect is absent in series from centres reporting only their own experience with LA for ACC and likewise in series on open surgery from a single centre [25] leading to a seemingly superior outcome. In our study both groups were highly comparable concerning disease status at the time of registration, a finding that excludes a major selection bias.

In general, more recent reports on LA for ACC found more favourable results, suggesting that improvements in technology and increasing personal experience are of great relevance for surgical outcome. A recent analysis of 3144 adrenalectomies [26] indicates that adrenal volume and laparoscopic expertise are of key importance for optimum outcome in patients with adrenal tumours. These parameters may be of even greater relevance in radical LA for ACC. A review on trends in adrenalectomy in the United States [27] revealed that adrenalectomy is increasingly performed for both benign and malignant indications. Although perioperative mortality remained low, postoperative complications increased. Furthermore, 65% of adrenal surgeons perform fewer than six adrenalectomies per year. Accordingly, lack of surgical experience may have contributed to the poor outcome in the series reported by Miller et al. [21].

Our findings may resolve a long-standing inconsistency in surgical practice. Although many surgeons experienced in LA for benign disease indicate that they refuse to use LA for ACC, they often use it for potentially malignant masses. For example, hormonally inactive incidentally discovered adrenal masses with evidence of growth during follow-up are currently often removed [28]. The only reason to do so is a perceived risk of malignancy. Yet many surgeons remove these tumours today by LA. Our findings justify this approach.

Our study has important limitations. Because it is a retrospective analysis, unknown confounders may have affected the results. Furthermore, the sample size is still relatively small, and additional series would be of great value. Ideally a randomised prospective trial should settle this important issue. However, it is highly unlikely that in the foreseeable future such a trial will be performed.

5. Conclusions

Our study suggests that LA is not inferior to OA in localised ACC with a diameter $\leq$10 cm with regard to oncologic outcome. Therefore, LA performed by an experienced adrenal surgeon is justified for potentially malignant adrenal incidentalomas and for selected cases of stage I and II ACC.

Author contributions: Martin Fassnacht and Bruno Allolio had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fassnacht, Allolio, Brix.
Acquisition of data: Brix, Fassnacht, Allolio, Fenske, Agha, Dralle, Jorowich, Langer, Mussack, Nies, Spahn, Riedmiller, Weismann, Hahner.
Analysis and interpretation of data: Fassnacht, Brix, Allolio, Fenske, Weismann.
Drafting of the manuscript: Allolio, Brix, Fassnacht.
Critical revision of the manuscript for important intellectual content: Brix, Fassnacht, Allolio, Fenske, Agha, Dralle, Jurowich, Langer, Mussack, Nies, Spahn, Riedmiller, Weismann, Hahner.
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