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**Retrospective evaluation of the outcome of open versus laparoscopic adrenalectomy for stage I and II adrenocortical cancer.**

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Adrenocortical Cancer**

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## Abstract

### Background

Although there is consensus that laparoscopy is the standard of care for the resection of benign adrenal tumours, there is controversy regarding the role of laparoscopy for the resection of adrenocortical cancer (ACC).

### Objective

The aim of the present study was to review the ACC database of the San Luigi Hospital to compare the oncologic effectiveness of open adrenalectomy (OA) versus laparoscopic adrenalectomy (LA) in the treatment of patients with stage I and II ACC.

### Design, setting, and participants

We performed a retrospective analysis involving 43 patients with stage I and II ACC who had undergone radical surgery.

### Intervention

The patients were stratified into two groups according to the surgical procedure. The “open group” consisted of patients treated with OA; the “lap group” consisted of patients treated with LA.

### Measurements

Oncologic effectiveness of the procedures was tested comparing the recurrence-free survival of patients treated with OA versus LA. Secondary outcome measures were differences in terms of type of recurrence and overall survival.

### Results and limitations

The open group consisted of 25 patients and the lap group of 18 patients. The two groups were comparable in terms of demographic data. The median follow-up was 38 mo in the open group and 30 mo in the lap group. Recurrence rate was 64% in the open group and 50% in the lap group. The median recurrence-free survival was 18 mo in the open group and 23 in the lap group ( $p = 0.8$ ). No differences in

terms of pattern of recurrences were recorded. During follow-up, 28% of the open group patients and 5% of the lap group patients died. No differences in terms of survival time were noted ( $p = 0.3$ ).

## Conclusions

The present findings provide interesting evidence that OA and LA may be comparable in terms of recurrence-free survival for patients with stage I and II ACC when the principles of surgical oncology are respected.

## Keywords

- Laparoscopy;
- Adrenocortical cancer;
- Surgery;
- Adrenalectomy

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## 1. Introduction

Adrenal tumours represent a wide spectrum of pathologies ranging from benign adenoma to adrenocortical carcinoma (ACC), and indications for adrenalectomy include hormone secretion and/or perceived risk of malignancy (ie, tumour size, radiographic features, local invasion, lymph node involvement, or distant metastases) [1], [2], [3], [4], [5] and [6].

When the adrenal tumour is small and shows a benign imaging phenotype, there is a general consensus on the type of surgical approach because laparoscopy has become the first option for this kind of lesion [7] and [8]. However, when a malignant tumour is suspected and surrounding tissues are involved, open adrenalectomy is clearly indicated [9] and [10]. But when the lesion is >4–6 cm and/or there are radiologic features that increase the risk of malignancy without a clear involvement of adjacent organs, the optimal surgical approach is still to be defined.

In the case of ACC, which is a rare but extremely aggressive neoplasm, surgery is the only potentially curative treatment, so the choice of surgical strategy is crucial for the patient's outcome. Open surgery is usually considered the best surgical treatment, but some authors have published on the use of laparoscopy; nevertheless, only a few laparoscopic cases have been reported [11], [12], [13] and [14].

The aim of the present study was to review the ACC database of the San Luigi Hospital to compare the oncologic effectiveness of open versus laparoscopic adrenalectomy in the treatment of patients with ACC.

## 2. Patients and methods

### 2.1. Adrenocortical carcinoma database of the San Luigi Hospital

The ACC database was established in 2001 with the development of a structured data form to collect comprehensive information on all patients with ACC who were referred to our Centre for Diagnosis and Treatment of Adrenal Diseases. All data were obtained by reviewing patients' histories, discharge summaries, medical records, and source documents. Data were retrieved by trained medical personnel using specifically tailored data forms. For the purpose of this study, data of patients referred between January 2002 and June 2008 were considered. We included patients who underwent radical surgery either at our centre (operated by a single surgeon, FP) or at other institutions before referral to us. These institutions are secondary centres for adrenal diseases but usually refer patients with ACC to us for postoperative management and treatment. Follow-up for this study was closed in June 2009. The institutional ethics committee of our hospital approved the study, and all patients provided written informed consent.

### 2.2. Patient cohort

Inclusion criteria were age  $\geq 18$  yr and the availability of preoperative and postoperative computed tomography (CT) or magnetic resonance imaging scans, stage I or II ACC according to the McFarlane-Sullivan classification (tumour without infiltration of neighbouring structures, positive lymph nodes, or distant metastasis) [15] and [16], and complete follow-up information until death or the end of the study period. All histologic diagnoses were confirmed by two experienced pathologists at our centre (EB, MV) according to the Weiss criteria [17] and [18]. Exclusion criteria were incomplete tumour staging or incomplete follow-up data, extensive surgical approach beyond adrenalectomy (eg, nephrectomy, resection of pancreas tail, partial hepatectomy), macroscopically incomplete resection, tumour capsule violation, conversion from laparoscopic to open surgery, concomitant cancers within the previous 5 yr, and clinically significant concomitant diseases. Complete resection was defined as no evidence of macroscopic residual disease on the basis of surgical reports, histopathologic analysis, and postoperative imaging. Follow-up visits, which included imaging of the chest and abdomen, were performed every 6 mo until either disease progression occurred or the study period ended. The first postoperative CT was performed within 1 mo following surgery. For the purpose of this analysis, disease recurrence was diagnosed on the basis of radiologic evidence of a new lesion during follow-up. Recurrence was defined as local when involving the operative site or regional lymph nodes, peritoneal when there was evidence of abdominal carcinomatosis, or distant. Local recurrences were further classified as "single" (neoplastic tissue in a single site) or "multiple" (two or more sites). Moreover, we evaluated port-site recurrences in patients treated laparoscopically. Adjuvant treatment following complete tumour removal and treatment of the recurrence were considered.

Of 56 patients with identified stage I or II ACC, 43 met all entry criteria and were included in the study (Fig. 1); of these, 12 (28%) were treated at our institution. The patients were stratified into two groups according to the surgical procedure. The “open group” consisted of patients treated with open adrenalectomy (OA); the “lap group” consisted of patients treated with laparoscopic adrenalectomy (LA). The surgical approach was based on surgeon preference and expertise, and the referral pattern was the same for patients treated with either methodology.

### 2.3. Statistical analysis

All statistical analyses were performed with Statistica software (StatSoft, Inc, Tulsa, OK, USA). Rates and proportions were calculated for categorical data and medians and ranges for continuous data. Differences in continuous variables were analysed by means of the two-tailed Mann-Whitney *U* test. For categorical variables, differences were analysed by means of the chi-square test. Survival curves were computed according to the Kaplan-Meier method and were compared by means of the log-rank test. A Cox proportional hazards regression analysis was used to assess in univariate and multivariate analyses the predictive role of the treatment (OA vs LA) and of clinical and pathologic variables on disease recurrence. All reported *p* values are two sided. A *p* value of <0.05 was considered to indicate statistical significance.

### 2.4. Study end points

The primary end point of the study was to evaluate the oncologic effectiveness of the procedures comparing the recurrence-free survival of patients treated with OA versus LA. Secondary outcome measures were differences in terms of type of recurrence (ie, single or multiple, local or distant) and overall survival.

## 3. Results

The open group consisted of 25 patients and the lap group consisted of 18 patients. Table 1 summarises the demographic data, characteristics of the lesions, and clinical presentation. As far as surgical details are concerned, all patients in the open group were treated with an anterior transperitoneal approach; all patients in the lap group were treated with a transperitoneal laparoscopic approach. The median follow-up duration of the whole cohort was 35 mo (range: 11–72 mo).

The two groups were comparable in terms of age; sex; size, stage, and secretory status of tumour; and Weiss score. The median follow-up after surgery was 38 mo (range: 11–72 mo) in the open group and 30 mo (range: 12–54 mo) in the lap group. After adrenalectomy, 15 patients of the open group (60%) and 12 patients of the lap group (66%) (*p* = 0.6) were treated adjuvantly with mitotane.

During follow-up, 16 patients of the open group versus 9 patients of the lap group experienced a recurrence. Thus the recurrence rate was 64% in the open group and 50% in the lap group. Median recurrence-free survival was 18 mo in the open group and 23 mo in the lap group and did not differ significantly according to the log-rank test ( $p = 0.8$ ). Fig. 2 depicts the Kaplan-Meier survival curves of the two groups. Local recurrences were recorded in 6 patients of both the open and laparoscopic group ( $p = 0.5$ ); distant recurrences were observed in 10 patients of the open group and 4 patients of the lap group, respectively ( $p = 0.2$ ). Local recurrences were multiple in five patients of the open group and two patients of the lap group, respectively ( $p = 0.4$ ). No peritoneal or port-site recurrences were observed. Among patients in the two groups, recurrences were managed with repeat surgery (26%), mitotane (8%), or cytotoxic chemotherapy (30%); these approaches were often used in combination. During follow-up, seven patients of the open group (28%) and one patient of the lap group (5%) died due to ACC-related causes.

Multivariate Cox models were fitted to the data, in which age, tumour stage, and number of mitosis were included as covariates together with the treatment group. Table 2 shows the results of the multivariate analyses. As far as recurrence-free survival is concerned, treatment modality was not an independent prognostic factor ( $p = 0.3$ ). Due to the low number of events, multivariate analysis was not applicable for overall survival time.

#### 4. Discussion

Some authors have argued that laparoscopic adrenalectomy can be performed safely in selected patients with malignant cortical tumours [11], [19], [20], [21] and [22]. In a previous retrospective study, we reported six cases of ACC treated with laparoscopy, and we concluded that LA seemed to be a feasible option [23]. In contrast, other authors have urged caution, especially on the basis of anecdotal experience with high rates of locoregional recurrence including the development of carcinomatosis [24], [25] and [26].

Few other series have been reported, but the number of patients is usually small, the population heterogeneous, and the follow-up short. Thus the conclusions are not univocal (Table 3). However, due to the rarity of ACC, a randomised, controlled trial comparing OA and LA will likely never be performed.

This compelled us to study past cases that were retrieved from the ACC database of the San Luigi Hospital to do an exploratory analysis and contribute to the discussion on surgical treatment of stage I and II ACC. We chose to review the entire database of our centre, and we included all patients with stage I or II ACC in whom adrenalectomy was the only surgical treatment, excluding patients in whom nephrectomy or more extensive surgery, or conversion of laparoscopic to open, was performed. From the surgical point of view, we compared two groups of patients in whom the surgical principles were respected (ie, no tumour capsule violation, no residual disease at postoperative imaging), and this, in our opinion, is a strength of

our study. Although we disclose the limitations of a retrospective analysis, which is subject to selection bias, the two groups of patients (OA and LA) were well matched in terms of patient and tumour characteristics, as far as the major prognostic factors and adjuvant therapies are concerned. However, the possibility that patients with different unmeasured characteristics were unevenly distributed between the OA and LA groups cannot be completely excluded. We are also aware that the statistical power of some analyses may be rather low due to the limited number of events. Postoperative follow-up was performed at our centre according to a standardised protocol for all patients, allowing us to choose recurrence-free survival as a valuable study outcome. In addition, we considered that recurrence-free survival is a direct expression of the effectiveness of primary surgical therapy, whereas overall survival may be also influenced by subsequent treatments that are not well standardised [9], [10] and [27].

We have also investigated the pattern of recurrence because some authors have reported a higher rate of carcinomatosis in patients treated with laparoscopy [25] and [26]. We did not compare the perioperative data of the two groups basically because we focused our attention on oncologic results. However, the benefits of laparoscopic adrenalectomy in terms of length of hospital stay, decrease in postoperative pain, time to return to preoperative activity level, and cosmetic results are well known [7].

The present findings of a comparable recurrence-free survival between patients treated with OA or LA do not support that OA is the best surgical treatment in patients with ACC as previously suggested by some authors, provided that ACC is diagnosed at stage I or II. The fact that these patients were treated by different surgeons reflects the usual clinical practice and makes the present results more reproducible. This may have disadvantaged the LA group because LA is more technically demanding and dependent on a surgeon's skill; thus, our results may be strengthened by such a consideration. However, surgical technique was the same within the groups, with OA performed through an open anterior approach and LA with a transperitoneal approach. Also, the comparison between the recurrence patterns observed after OA or LA did not differ significantly. Again, these findings do not support the hypothesis that peritoneal carcinomatosis or multiple recurrences are more frequent in patients treated with LA. To adjust for unintentional bias, multivariate analysis including the factors that more influence ACC recurrence and survival was performed [27], [28] and [29]. Results of this analysis confirm that the type of surgical treatment is not an independent prognostic factor. Finally, although median survival was not reached in the lap group, 3-yr survival rate was not different between the two groups. One should note that the group of deceased patients is small, and survival time may be influenced by the multiple treatment modalities used during the disease. Thus, definitive conclusions cannot be drawn. Nevertheless, this finding could strengthen the hypothesis that the oncologic effectiveness of open and laparoscopic surgery may be comparable.

In our opinion, LA is an effective option for surgical treatment of stage I and II ACC, and an expert surgeon can reasonably offer this approach to patients.



## 5. Conclusions

Despite the limitations of the present analysis, this study may be considered reliable to address the surgical management of a rare tumour like ACC, for which no prospective randomised studies will likely be feasible. Although no definitive statistical conclusions can be drawn, there is at least evidence that the laparoscopic and open approaches are comparable in the treatment of patients with stage I and II ACC when the principles of oncologic surgery are respected.

*Author contributions:* Francesco Porpiglia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Fiori, Porpiglia, Terzolo.

*Acquisition of data:* Terzolo, Daffara, Zaggia.

*Analysis and interpretation of data:* Terzolo, Berruti.

*Drafting of the manuscript:* Fiori, Terzolo.

*Critical revision of the manuscript for important intellectual content:* Berruti, Terzolo.

*Statistical analysis:* Fiori, Berruti.

*Obtaining funding:* Terzolo.

*Administrative, technical, or material support:* None.

*Supervision:* Porpiglia.

*Other (specify):* Bollito, Volante (pathologic review).

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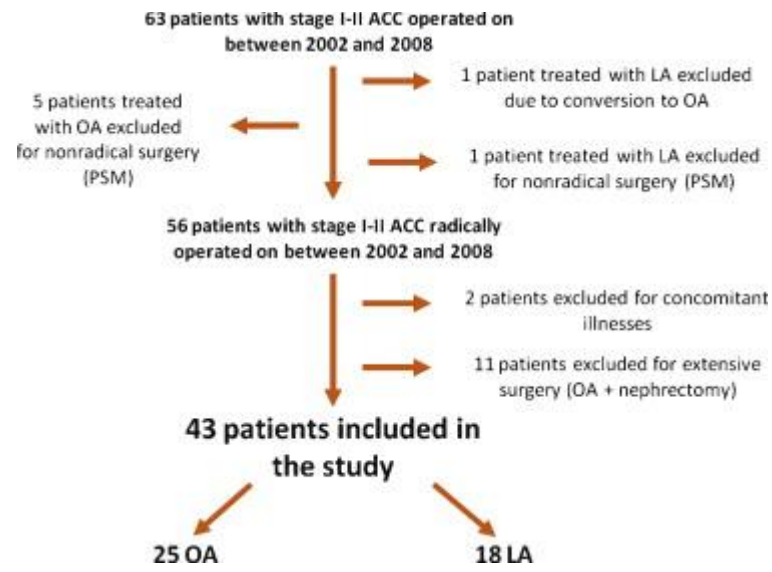


Table 1.

Baseline characteristics of patients

Characteristic	Open group ( <i>n</i> = 25)	Lap group ( <i>n</i> = 18)	<i>p</i> value
Median age, yr (range)	41.3 (24–68)	47 (28–69)	0.16
Sex, No. (%)			
Male	9 (36)	8 (53)	0.8
Female	16 (64)	10 (47)	
BMI (range)	22.2 (15–30)	24.2 (16–32)	0.4
ECOG score			
0	14	9	0.7
1	11	9	
Tumour stage (%)			
I	3 (12)	3 (20)	0.4
II	22 (88)	15 (80)	
Median tumour size, cm (range)			
	10.5 (3–17)	9 (2–15)	0.39
Functional status of tumours, No. (%)			
Secreting tumours	14 (56)	11 (61)	0.5
Glucocorticoids with or without androgens	11	9	
Androgens	2	0	
Aldosterone	0	2	
Estradiol	1	0	
Nonsecreting tumours	13 (44)	7 (39)	0.7
Adrenal incidentalomas, No. (%)	7 (28)	6 (33)	0.3
Weiss score			
Median (range)	6 (3–8)	6 (3–8)	

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group.

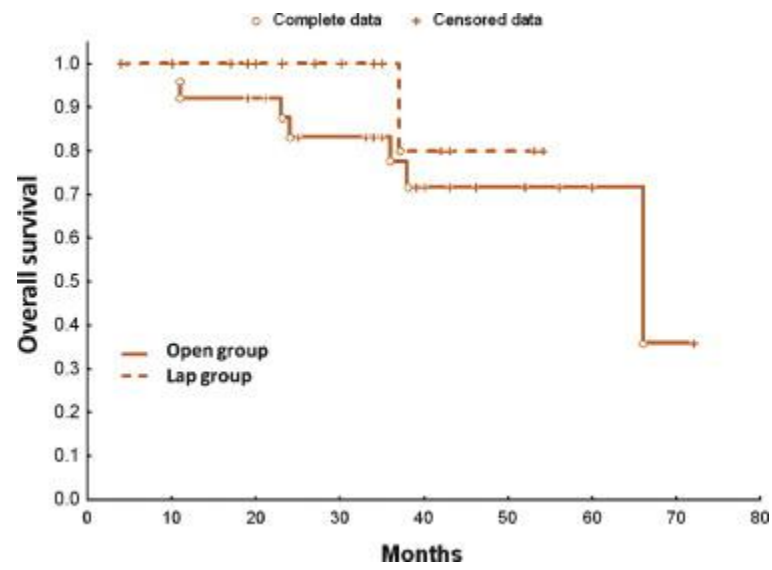
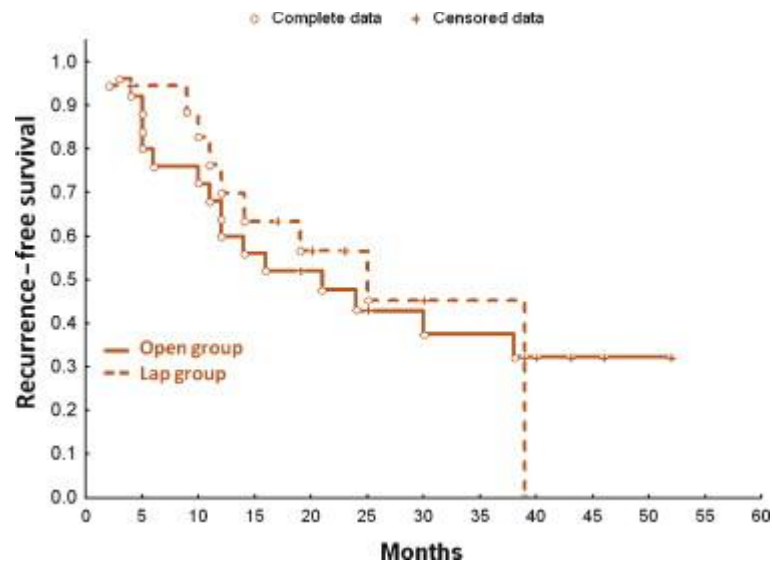




Table 2.

Multivariate analyses\*

	Disease-free survival		
	HR	95% CI	<i>p</i>
Age†	0.98	0.93–1.03	0.34
Stage	0.75	0.09–6.08	0.79
Type of surgery			
Open/Laparoscopic	0.57	0.18–1.80	0.34
Mitosis number†	1.04	1.01–1.07	0.003

CI = confidence interval; HR = hazard ratio.

\* Independent prognostic role of type of surgery and clinical and biological parameters. The same analyses were not applicable for overall survival.

† Continuous variables.

Table 3.

Summary of series of laparoscopic and open adrenalectomies for primary adrenal malignancies

Reference	Yr	Surgical approach	No. of cases	Mean/median size, cm	Mean/median follow-up, mo	Recurrence (local or distant), %	Port site or peritoneal recurrence	Survival
Lombardi et al. [13]	2006	Lap	4 ACC	5.9	23	2 (28)	0	4 alive DF
			3 malignant ph					2 alive with disease
								1 dead (not ACC related)
Gill [14]	2005	Lap	6 ACC	5	26	3 (42)	0	3 alive DF
			1 malignant ph					2 dead for ACC
								1 dead (unknown reasons)
Porpiglia et al. [23]	2004	Lap	5 ACC	6.9	30	0	0	5 alive DF
			1 mixoid ACC					1 dead (not ACC related)
Liao et al. [12]	2006	Lap	4 ACC	6.2	39	3 (75)	0	1 alive DF
								2 alive with disease
								1 dead for ACC
Henry et	2002	Lap	6 ACC	7.4	47	1 (16)	0	5 alive DF

								1 dead of disease
Gonzales et al. [26]	2005	Lap	6 ACC	5.3	21	6 (100)	5 (83)	2 alive with disease
								4 dead for ACC
Gonzales et al. [26]	2005	Open	133 ACC	NR	28	68 (51)	–	Median surv duration: 34 mo
Crucitti et al. [10]	1996	Open	91 ACC	NR	NR	14 (15)	–	Median surv duration: 28 mo
Terzolo et al. [27]	2007	Open	55 ACC	10	67	50 (90)	–	Median surv duration: 52 mo
			75 ACC	10	43	55 (73)		Median surv duration: 67 mo
Icard et al. [9]	2001	Open	253 ACC	12	NR	NR	–	5-yr surv: 38%
Kendrick et al. [30]	2001	Open	58 ACC	12.5	53	30 (51)	–	5-yr surv: 37%

ACC = adrenocortical cancer; DF = disease free; NR = not reported; ph = pheochromocytoma; surv = survival.