

# Open vs laparoscopic adrenalectomy for localized adrenocortical carcinoma

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**Title:** Open versus laparoscopic adrenalectomy for localised adrenocortical carcinoma

**Running title:** Laparoscopic surgery for adrenal carcinoma

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## **Abstract**

**Objective:** The purpose of the study was to compare the long-term outcomes of patients with localized adrenocortical carcinoma (ACC) subjected to open versus laparoscopic surgery.

**Design:** Retrospective study. **Patients:** This retrospective study included 46 patients with the ACC ENSAT stage I-III of whom 23 underwent open surgery (OA group) whereas 23 were subjected to laparoscopic adrenalectomy (LA group). The main outcomes analysed in the study were differences between the OA and LA groups in recurrence free survival (RFS) and overall survival (OS). **Results:** Patients in OA group had larger tumours (120 (70-250) mm vs. 75 (26-110) mm;  $p < 0.001$ ), higher Ki-67 index (16 (1-65) % vs. 10 (1-25) %;  $p = 0.04$ ) and higher disease stage ( $p = 0.01$ ) compared to the patients in the LA group. The median duration of follow-up for patients underwent OA and LA was 51 (12-174) and 53 (5-127) months, respectively. Eight patients (5 OA, 3 LA) experienced recurrent disease whereas six patients (3 OA, 3 LA) died during follow-up. No differences in RFS and OS were found between patients who underwent open or laparoscopic surgery. **Conclusion:** The study demonstrated that in patients with localised ACC and without invasion of extra-adrenal tissues LA is a plausible treatment option in terms of RFS and OS. However, our results are limited to referral centres with large experience in the management of patients with ACC and may not necessarily apply to nonspecialised centres.

**Keywords:** adrenocortical carcinoma, adrenocortical hyperfunction, Cushing syndrome, laparoscopic surgery, mitotane, survival, disease-free survival

## **Introduction**

Adrenocortical carcinoma (ACC) is a rare but aggressive endocrine malignancy with a 5-year survival rate ranging from 13% to 81%, depending on the tumour stage<sup>1</sup>. Given the unfavourable prognosis of the disease and limited benefit of medical treatment, complete surgical resection of the tumour provides the only chance for long-term cure.

Open adrenalectomy (OA) has traditionally been the preferred surgical approach for ACC allowing en-bloc resection of the tumour, regional lymph nodes as well as the surrounding retroperitoneal fat which is sometimes infiltrated by microscopic extensions of the tumour. However, in the last two decades laparoscopic adrenalectomy (LA) rather than OA has been increasingly used in the treatment of adrenal tumours. It has been shown that LA is associated with shorter duration of operation and hospital stay as well as lower blood loss, perioperative morbidity and costs<sup>2</sup>.

Despite many advantages, the role of LA in the treatment of ACC is a matter of debate. Several early studies demonstrated that LA was associated with incomplete tumour resection, increased risk of peritoneal carcinomatosis and shorter time to tumour recurrence<sup>3-5</sup>. Accordingly, joint guidelines of the European Society of Endocrinology and European Network for the Study of Adrenal Tumours on the management of ACC recommend open surgery as a standard surgical approach for confirmed or highly suspected ACC<sup>6</sup>. On the other hand, parallel to technological advancements and increased experience in laparoscopic surgery, a few recent studies showed more encouraging results demonstrating that the outcome of LA was not inferior to that of OA when surgery was performed in expert centres and when principles of oncologic resection were respected<sup>7-11</sup>. The conflicting results of different studies addressing this issue might be related to their retrospective nature, a limited number of patients, particularly in the laparoscopic group, a relatively short follow-up period and potential referral bias.

To expand this knowledge, we retrospectively analysed all patients that were referred to our specialised adrenal centre with the diagnosis of ACC. The purpose of the study was to compare the long-term outcomes of patients with localized ACC subjected to open versus laparoscopic surgery.

## Methods

In this observational retrospective study, medical records were reviewed for all the patients referred to the Croatian Referral Centre for adrenal gland disorders with the diagnosis of ACC between 2004 and 2018. Data on demographics, imaging results, hormonal work-up, surgery and pathology reports, adjuvant therapy and follow-up were collected. Only patients with R0 tumour resection who were referred for evaluation before the ACC surgery (n=37) or within three months after the surgery (n=9) were included. After patient referral to our centre, all further decisions regarding the management of the disease were made by a multidisciplinary team of experts. Criteria for selecting patients to LA or OA were not predetermined, but all patients with tumours larger than 11 cm were selected to open surgery. The study was approved by the University Hospital Centre Zagreb ethical committee.

The diagnosis of ACC was based on the Weiss scoring system<sup>12</sup> in all patients except those with oncocytic adrenocortical tumour in whom the Lin-Weiss-Bisceglia scoring was applied<sup>13-14</sup>. Tumour staging classification was done using the European Network for the Study of Adrenal Tumours (ENSAT) classification system<sup>6</sup>. In all subjects pathology reports were reviewed by a single pathologist (MC).

Postoperative surveillance consisted of biochemical and radiological (thoracic CT, abdominal and pelvic CT/MRI) investigations performed every 3-6 months in the first two years after the surgery, every 6-9 months in the following three years and every 1-2 years thereafter.

The main outcomes analysed in the study were differences between the OA and LA groups in recurrence free survival (RFS) and overall survival (OS). RFS was calculated from the date of the ACC surgery to the date of tumour recurrence or the last imaging follow-up, whereas OS was calculated from the date of the ACC surgery to the date of death or the last follow-up visit.

## **Statistical analysis**

Statistical analysis was carried out using the SPSS version 17.0 for Windows. The differences between the variables were tested using the Mann-Whitney test or  $\chi^2$  test, as appropriate. Survival analysis was performed using the Kaplan-Meier method and differences were assessed with the log-rank test. Cox regression model was used for multivariate analysis. Significance level was set at  $P < 0.05$ .



## Results

A total of 46 patients (14 males, 32 females; median age 48 (17-74) years) with the ACC ENSAT stage I-III were identified and enrolled in the study. The median tumour size was 92.5 mm (26-250) and Ki-67 index 12% (1-65). Twenty-one patient (46%) had signs and symptoms of hormone hypersecretion of which 14 (30%) had Cushing's syndrome. The median duration of follow-up was 52 months (5-174).

The OA group comprised 23 patients among which 14 were operated at our centre and the remaining 9 patients (39%) underwent the ACC surgery in other centres. In all 23 patients from the LA group, laparoscopic surgery using the transabdominal approach was performed at our centre by a single surgeon (NK). In none of the patients laparoscopic operation needed to be converted to the open one. Patients in OA group had larger tumours (120 (70-250) mm vs. 75 (26-110) mm;  $p < 0.001$ ) and a higher Ki-67 index (16 (1-65) % vs. 10 (1-25) %;  $p = 0.04$ ). In addition, patients who underwent open surgery had a higher disease stage compared to the patients in the LA group ( $p = 0.01$ ).

Twenty-seven patients (11 LA, 16 OA) received adjuvant mitotane treatment. In 26 of them the treatment was initiated within one month after the surgery, whereas in the one remaining patient it was started two months following surgery. Three patients refused mitotane treatment, and in one patient mitotane was discontinued after two months due to liver toxicity. Duration of mitotane treatment was 24 months in patients with the Ki-67 index  $\leq 20\%$  and 36 months when Ki-67 was  $> 20\%$ . Twenty-two patients reached and maintained the target mitotane concentration of more than 14 mg/L, whereas data on mitotane concentration were not available for five patients who had the ACC surgery in the period from 2004-2009. At the moment of data extraction, 17 patients (6 LA, 11 OA) discontinued mitotane after the completion of 24 or 36 months of adjuvant treatment. Patient demographics and clinical characteristics are shown in Table 1.

In terms of disease recurrence, no difference in RFS was found between patients who underwent open or laparoscopic surgery ( $p=0.556$ ; Figure 1). Overall, eight patients (17%) experienced recurrent disease. Of them, three recurrences (13%) were observed in the LA group after 11, 28 and 45 months of follow-up, whereas five recurrences (22%) were recorded in the OA group after 4, 19, 22, 30 and 43 months of follow-up. Three patients (1 LA, 2 OA) had local tumour recurrence, and five patients (2 LA, 3 OA) had distant metastases. Patients with recurrent disease tended to have a higher Ki-67 index (18 (10-40)% vs. 11 (1-65)%), but the difference was not significant ( $p=0.07$ ). The mean RFS was 109 and 129 months for LA and OA, respectively.

With regard to survival, six patients (13%) died during follow-up including three (13%) in the LA group and three (13%) in the OA group. Three of them died due to disease recurrence (1 LA, 2 OA), and the other three died of causes unrelated to ACC (pneumonia, sepsis caused by urinary tract infection and stroke). The mean OS was 109 months and 149 months for LA and OA, respectively and was not different between the groups ( $p=0.767$ ; Figure 2). In the multivariate model, after adjusting for Ki-67 and adjuvant mitotane treatment, mortality was associated with older age ( $p=0.047$ ).

## **Discussion**

Open adrenalectomy (OA) has been well established as a standard approach in the surgical management of ACC. However, in the last two decades laparoscopic adrenalectomy (LA) has been increasingly used for the treatment of patients with adrenal tumours, including those with ACC. Despite the fact that LA is associated with favourable outcomes in terms of perioperative morbidity, there is a concern that patients who have undergone LA for ACC are at higher risk of disease recurrence. Nevertheless, the results of the present study, which included 46 patients with ACC ENSAT stage I-III, demonstrated that laparoscopic surgery did not compromise the long-term outcome of patients with ACC as both RFS and OS were similar between patients subjected to OA compared to those operated by laparoscopic approach.

In general, surgical techniques have impact mostly on the risk of local and peritoneal cavity recurrence. Due to limited tactile sensation, application of endoscopic instruments may increase the risk for tumour capsule rupture during surgery and subsequent dissemination of tumour cells into the peritoneal cavity. In our cohort, three patients (6.5%), one in LA and two in OA group, had local tumour recurrence whereas none of the patients had peritoneal carcinomatosis.

The literature data on preferred surgical techniques in patients with ACC are mostly restricted to retrospective studies, with a limited number of patients, particularly in the laparoscopic group, and with ambivalent results. The majority of initial studies suggested that the laparoscopic approach was associated with unfavourable outcomes in terms of higher rates of local recurrence and peritoneal carcinomatosis<sup>3-5</sup>. However, with advancements in operation techniques and increasing experience in laparoscopic surgery, recent reports showed comparable oncological outcomes between patients subjected to OA or LA<sup>9,10,15</sup>. In addition, the most recent systematic review which included 13 studies with 1,171 patients with ACC ENSAT stage I-III observed no differences between the open and laparoscopic approaches in

terms of R0 tumour resection, tumour overall recurrence or postoperative RFS and OS<sup>11</sup>. Furthermore, a study based on the data from the German Adrenocortical Carcinoma Registry analysed the influence of operation technique on long-term outcomes in 152 patients (35 LA, 117 OA) with ACC ENSAT stage I-III and tumour diameter  $\leq 10$  cm and it showed no difference in disease specific survival and RFS between the OA and LA approaches using either the multivariate analysis or the matched pairs approach<sup>7</sup>.

In addition to surgeons' experience, the size of the tumour is another important determinant of the surgical approach. The recently published guidelines on the management of ACC suggest that laparoscopic adrenalectomy is acceptable in tumours smaller than 6 cm<sup>6</sup>. However, several studies demonstrated that in specialised referral centres laparoscopic surgery for ACC represents the appropriate surgical approach in patients with a tumour diameter of up to 10 cm if the principles of oncologic surgery are respected<sup>10, 16</sup>. In support of these data, in the present study, the majority of patients in the LA group (57%) had a tumour larger than 6 cm (7-11 cm) and only one of them experienced tumour recurrence, 28 months after the laparoscopic surgery. In contrast, another 2 patients with disease recurrence in the LA group had tumours smaller than 6 cm.

In our cohort, during the median follow-up of 52 months the overall ACC recurrence rate (17%) was substantially lower than in a number of other published studies<sup>3-5, 7, 15, 17-19</sup>. This might be due to the fact that 80% of our patients (23/23 LA and 14/23 OA) were operated by a single surgeon who is experienced in adrenal surgery. Moreover, the administration of adjuvant mitotane treatment to most of our patients with a high risk of tumour recurrence (i.e. Ki-67 > 10%) probably had beneficial impact on the rate of tumour recurrence. This is in accordance with the recent study by Calabrese et al. who demonstrated that adjuvant mitotane treatment might prolong RFS in ACC patients after radical tumour resection<sup>20</sup>. Furthermore, all patients from our cohort for whom the data on blood mitotane level were available reached and

maintained the target mitotane concentration >14 mg/L which has been shown to be associated with a favourable response to adjuvant mitotane treatment<sup>21</sup>.

The results of our study are to some extent affected by an inherent bias as the patients selected for laparoscopic surgery had smaller tumours, earlier stages of disease and lower Ki-67 index. Similar limitations have also been present in other studies. A randomized trial would probably be the best method to compare the outcomes between different surgical approaches, but, given the rarity of ACC, it is not likely that such a study will be performed.

Another limitation refers to the retrospective nature of the study. However, despite this limitation, the fact that all the patients were managed in a single centre using a standardized protocol regarding the adjuvant mitotane treatment and patients' follow-up, represents the major strength of the study. Furthermore, in some patients, the follow-up time was limited, but the majority of the patients were still followed for more than three years, a period during which most of the ACC recurrences are likely to happen. Finally, our centre is a high-volume referral centre for adrenal tumours, performing 50-60 laparoscopic procedures per year, and the results of the present study may not necessarily apply to nonspecialised centres.

In conclusion, our study demonstrated that in patients with localised ACC and without invasion of extra-adrenal tissues LA is a plausible treatment option in terms of RFS and OS. Moreover, laparoscopic operation is feasible and safe in patients with even larger tumours than previously suggested, if principles of oncologic surgery are respected. However, this type of surgery should be limited to specialised referral centres with large experience both in laparoscopic surgery and in the management of patients with ACC.

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**Table 1. Demographics and clinical characteristics of patients with ACC**

Variable	OA (n=23)	LA (n=23)	p value
Age (year)	51 (17-66)	43 (18-74)	0.24
Female gender (n, %)	18 (78)	14 (61)	0.2
Tumour size (mm)	120 (70-250)	75 (26-110)	<0.001
ENSAT tumour stage (n, %)			0.01
Stage I	0 (0)	6 (26)	
Stage II	14 (61)	14 (61)	
Stage III	9 (39)	3 (13)	
Excess hormone secretion (n, %)	11 (48)	10 (43)	0.77
Excess glucocorticoid 8 (35) secretion (n, %)		6 (26)	0.52
Ki-67 (%)	16 (1-65)	10 (1-25)	0.04
Weiss score	6 (3-9)	6 (3-9)	0.19
Adjuvant mitotane (n, %)	16 (70)	11 (48)	0.13
Follow-up (months)	51 (12-174)	53 (5-127)	0.26
Recurrence (n, %)	5 (22)	3 (13)	0.44
Death (n, %)	3 (13)	3 (13)	1.0

**Figure 1. Recurrence free survival**

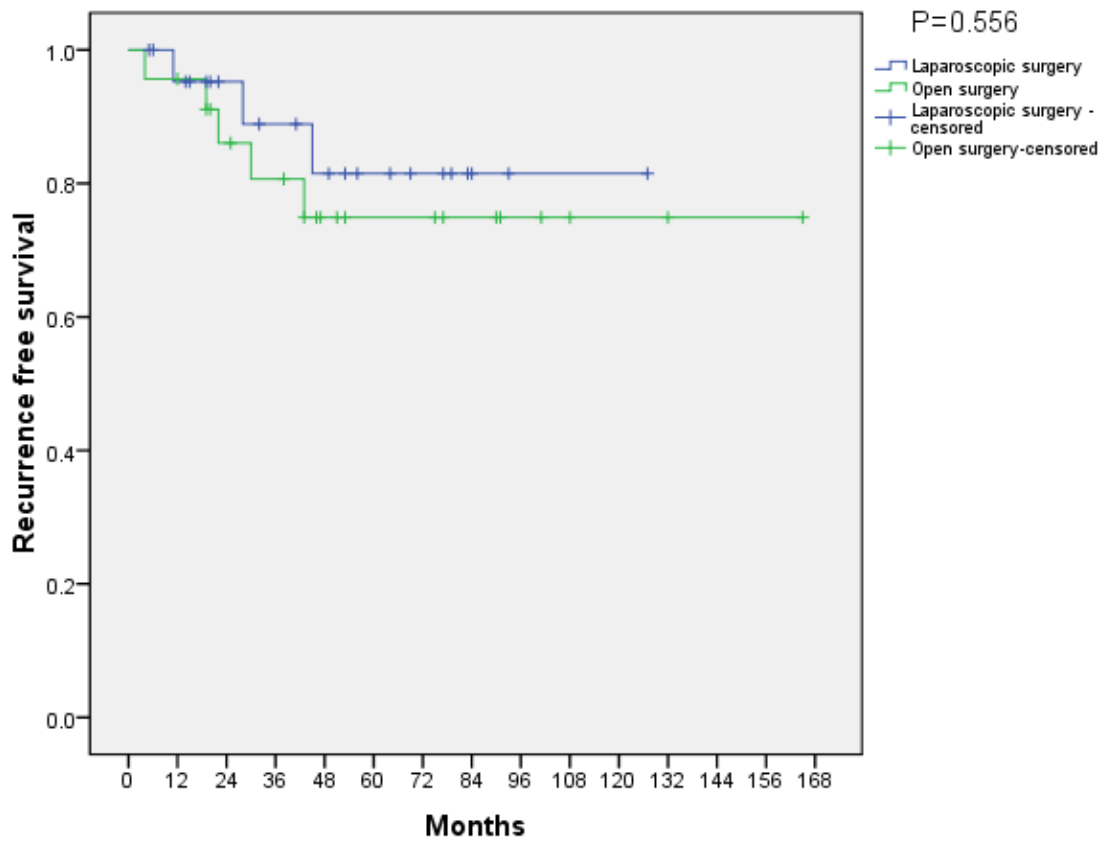


Figure 2. Overall survival

