

# Laparoscopy versus open adrenalectomy in patients with solid tumor metastases: results of a multicenter European study

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**Background:** The outcome of adrenalectomy carried out by laparoscopy or open surgery for solid tumor metastases was assessed.

**Methods:** A total of 317 patients with histologically confirmed adrenal metastatic disease collected from 30 centres in Europe underwent adrenalectomy by laparoscopy (n=146) or open laparotomy (n=171). Differences between laparoscopic and open adrenalectomy were assessed by a single Cox analysis for both

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# procedures.

**Results:** The median overall survival was 24.0 [95% confidence interval (CI): 21.4–26.6] months for open adrenalectomy and 45.0 (95% CI: 22.6–67.4) for laparoscopic adrenalectomy (P=0.008). Survival rates were 68%, 49%, 35% and 29% at 1, 2, 3 and 5 years for open surgery *vs.* 88%, 62%, 52% and 46% for laparoscopy, respectively. In the subgroup of R0 resections, the difference in survival in favor of laparoscopy (median 46 *vs.* 27 months) was marginally significant (P=0.073). Renal cancer [hazard ratio (HR) 0.42; 95% CI: 0.23–0.76, P=0.005], surgery of the primary tumor (HR 0.33; 95% CI: 0.19–0.54), and use of chemotherapy (HR 0.62; 95% CI: 0.43–0.88) were associated with a better survival, whereas type of resection (R1/R2 *vs.* R0) was associated with a worse prognosis (HR 2.29; 95% CI: 1.52–3.44, P<0.001).

**Conclusions:** Laparoscopic adrenalectomy patients showed a longer survival than open adrenalectomy individuals, as minimally invasive approach was attempted more common in less advanced disease which led to higher number of R0 resections.

Keywords: Adrenalectomy; open adrenalectomy; laparoscopic adrenalectomy; survival; retrospective study

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## Introduction

Several studies have reported that adrenalectomy improves outcome in selected patients with metastatic disease, particularly in cases of isolated lesions and metachronous metastasis (1-6). In patients with isolated adrenal metastases, a more favourable survival for adrenal resection has been reported as compared with nonoperative approaches (7,8). Adrenal metastasis is often confined within the gland itself, providing more chances to achieve *en bloc* removal. In the context of established indications for surgical extirpation of adrenal masses, laparoscopic adrenalectomy has become the gold standard for removal of most benign tumours and may be used for malignant lesions as well (9-12).

The laparoscopic approach has improved immediate surgical results as compared to the open procedure for the treatment of benign tumours, with the advantages of less blood loss, minimal invasion, quicker recovery, fewer complications, and shorter duration of hospitalization (13-16). However, there is much less experience regarding the use of laparoscopic adrenalectomy in metastatic adrenal disease. Adrenalectomy though the laparoscopic route as compared with open surgery achieves similar oncological results with less morbidity (17,18), but homogeneous patient-based series comparing outcome differences between laparoscopic and conventional open adrenalectomy in patients metastatic adrenal disease are needed.

In a previous study of patients undergoing adrenalectomy

for solid tumor metastasis included in a European multicenter survey, long-term survival in selected patients was shown after operative removal of adrenal metastasis (4). This retrospective study performed in the same population was designed to assess the outcome in oncological terms of removal of adrenal metastasis by laparoscopy or open surgery.

#### **Methods**

The design and characteristics of the study has been previously described (4). Briefly, this was a retrospective and multicenter survey with data provided by Units of Endocrine Surgery of 30 hospitals from UK, Italy, France, Germany, Serbia, and Spain. From 1999 to 2001, all consecutive patients with metastases to the adrenal gland in which adrenalectomy could be successfully performed, with histologically proven malignancy were included. Patients with primary renal tumors involving the adrenal glands and those in which the time elapsed between adrenalectomy to the last follow-up visit was not specified were excluded. This study aimed to assess the outcome of laparoscopic adrenalectomy *vs.* open adrenalectomy.

An *ad hoc* questionnaire was completed over 1-year period (July 2010–2011) with clinical information collected from medical records, including demographics, primary tumor-related data, diagnostic techniques, side of the adrenal

mass, extra-adrenal disease extension, type of surgical approach (laparoscopy *vs.* open laparotomy), completeness of resection (R0, complete resection, R1, microscopic margin involvement, R2, gross macroscopic tumor); isolated adrenalectomy (limited to the adrenal gland), extended adrenalectomy (resection of contiguous organs with lymphadenectomy), duration of surgical procedure, length of hospitalization, postoperative complications, adjuvant chemotherapy, size of the tumor, length of followup, and vital status at the last follow-up control. When the laparoscopic approach was converted to a laparotomy, these cases were considered as open.

In all cases, histopathologic reports were reviewed. Metastases detected at  $\leq 6$  and >6 months after treatment of the primary tumor were classified as synchronous and metachronous, respectively. In patients treated with bilateral adrenalectomy in different procedures, the type of surgery and outcome of the first adrenalectomy was analyzed. Overall survival was defined as the time from adrenalectomy up to the date of the last follow-up or death.

## Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables as mean and standard deviation (± SD). Follow-up time and survival time are expressed as median values and interquartile range (IQR) (25th-75th percentile). The Kaplan-Meier method was used to estimate survival, with median values and 95% confidence intervals (CIs) for 1, 2, 3, and 5 years survival rates. Survivals for the different surgical procedures (laparoscopy vs. open laparotomy) and for the subset of patients who underwent R0 resections were also estimated with the Kaplan-Meier method, with differences analyzed with the log-rank test. Bivariate Cox analysis was used to assess the relationship between each variable with survival. Data are expressed as hazard ratio (HR) and 95% CI. Variables statistically significant or marginally significant in the bivariate analysis were analyzed in a Cox proportional hazards regression model with backward stepwise selection. Statistical significance was set at P<0.05. Data were analyzed using the SPSS statistical program (version 18.0) (IMB Corp.).

#### **Results**

The study population included 317 patients, 171 (53.9%) undergoing open adrenalectomy and 146 (46.1%) laparoscopic adrenalectomy. *Table 1* shows relevant

characteristics of patients in the two study groups. Statistically significant differences in the laparoscopic adrenalectomy group as compared to the open adrenalectomy group included higher percentages non-small cell lung cancer (NSCLC) and colorectal cancer patients; chemotherapy treatment; use of computed tomography (CT) scan only or positron emission tomography (PET) for diagnosis; a lower percentage of bilateral adrenal metastases; higher percentages of isolated adrenalectomy, R0 resections; shorter duration of operation and hospitalization; smaller tumor size; and higher percentage of adjuvant-treated patients. The median (IQR) length of follow-up was 21 [8–36] months for open adrenalectomy and 20 [10–35] for laparoscopic adrenalectomy.

As shown in Table 2, in the bivariate analysis, renal cancer as the type of primary tumor and surgical treatment were significantly associated with a better survival, whereas the presence of synchronous adrenal metastasis, extra-adrenal disease, extended adrenalectomy, R1/R2 resections, duration of surgery, tumor size, length of hospital stay, and open surgery (or converted) were associated with poor survival. In the multivariate Cox proportional hazards regression model (Table 2), risk factors for better survival were renal cancer (HR 0.42; 95% CI: 0.23-0.76, P=0.005), surgery of the primary tumor (HR 0.33; 95% CI: 0.19-0.54), and use of chemotherapy (HR 0.62; 95% CI: 0.43-0.88), whereas type of resection (R1/R2 vs. R0) was associated with a worse prognosis (HR 2.29; 95% CI: 1.52-3.44, P<0.001). Open adrenalectomy (or converted) almost reached statistical significance (HR 1.37; 95% CI: 0.971-1.925, P=0.073).

The median (IQR) survival for the laparoscopy group was 45.0 (22.6-67.4) months as compared with 24.0 (21.4-26.6) months for the open adrenalectomy group (log-rank test, P=0.008) (*Figure 1*). In patients treated with laparoscopic adrenalectomy, the survival rates at 1, 2, 3, and 5 years were 88.4%, 62.4%, 52.0%, and 46.0%, respectively. In patients treated with open adrenalectomy, the survival rates were 67.9% at 1 year, 49.0% at 2 years, 35.3% at 3 years, and 29.2% at 5 years.

The median survival analysis in the subset of patients undergoing R0 resections was 46 (95% CI: 13.695–78.305) months for laparoscopy-treated patients and 27.0 (95% CI: 18.063–35.937) for laparotomy-treated patients (log-rank test, P=0.073).

# Discussion

Results of the present study show a better survival for

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<b>Table 1</b> Sanche data of 517 parents with aurenal inclastate disease dicated with open aurenalectomy and iaparoscopic aurenalector	Table 1 Salient data of 317 patients with adrenal metastatic disease treated	ed with open adrenalectomy and laparoscopic adrenalector	ıv
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Variable	Open surgery (n=171)	Laparoscopy (n=146)	P value	
Gender			0.750	
Men	119 (69.6)	104 (71.2)		
Women	52 (30.4)	42 (28.8)		
Age, years, median (IQR)	58 [50-67]	60 [54-65]	0.427	
Type of primary tumor			0.027	
Non-small cell lung cancer	69 (40.4)	79 (54.1)		
Colorectal cancer	21 (12.3)	22 (15.1)		
Renal cancer	23 (13.5)	14 (9.6)		
Breast cancer	2 (1.2)	9 (6.2)		
Melanoma	5 (2.9)	6 (4.1)		
Other*	51 (29.8)	16 (10.9)		
Treatment of the primary tumor				
Surgery	155 (90.6)	128 (87.7)	0.394	
Chemotherapy	54 (31.6)	92 (63.0)	<0.001	
Radiation therapy	29 (17.0)	43 (29.5)	0.008	
Synchronous adrenal metastasis (n=310)	44 (26.5)	29 (20.1)	0.188	
Metachronous adrenal metastasis (n=310)	122 (73.5)	115 (79.9)		
Diagnostic method of adrenal mass			<0.001	
CT scan only	147 (86.0)	105 (72.4)		
MRI only	10 (5.8)	3 (2.1)		
PET only	3 (1.8)	9 (6.2)		
FNA	1 (0.6)	0		
CT and/or MRI and/or PET	10 (5.8)	28 (19.3)		
Extra-adrenal disease (n=296)	46 (30.3)	37 (25.7)	0.382	
Site of the adrenal metastasis (n=314)			0.006	
Right adrenal gland	70 (41.2)	81 (56.2)		
Left adrenal gland	89 (52.4)	61 (42.4)		
Bilateral	11 (6.5)	2 (1.4)		
Surgical-related data				
Type of resection (n=281)			<0.001	
Isolated adrenalectomy	100 (71.9)	131 (92.3)		
Extended adrenalectomy	39 (28.1)	11 (7.7)		
Completeness of resection			0.014	
R0	139 (81.3)	135 (92.5)		
R1 <sup>†</sup>	10 (10.5)	7 (4.8)		
R2 <sup>†</sup>	14 (8.2)	4 (2.7)		
Duration of surgery, min, median (IQR) (n=225)	135 [110–185]	120 [90–150]	<0.001	
Length of hospital stay, days, median (IQR) (n=297)	7 [5–11]	3 [2–4]	<0.001	
Tumor size, mm, median (IQR)				
Preoperative studies (n=256)	5.0 (3.9–7.1)	3.6 (3.0–5.0)	<0.001	
Pathologic studies (n=289)	6.8 (4.0–9.0)	5.0 (3.0–7.0)	<0.001	
Postoperative complications	21 (12.3)	9 (6.2)	0.064	
Adjuvant treatment (n=315)	83 (49.1)	100 (69.5)	<0.001	

Data as frequencies and percentages in parenthesis unless otherwise stated. \*, for the purpose of analysis breast cancer and melanoma are included in the "other" category; <sup>†</sup>, R1 and R2 analyzed in a single category (R0 *vs.* R1 or R2).

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Table 2 Bivariate Cox analysis and multivariate Cox proportional hazard regression analysis

Variables	Bivariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age, years	0.997 (0.983–1.012)	0.732		
Gender (male vs. female)	1.105 (0.785–1.554)	0.567		
Type of primary tumor				
Non-small cell lung cancer (reference category)	1			
Colorectal cancer	0.847 (0.513–1.399)	0.516		
Renal cancer	0.494 (0.279–0.873)	0.015	0.420 (0.231–0.764)	0.005
Other	1.222 (0.861–1.735)	0.262		
Treatment of the primary tumor				
Surgery (yes <i>vs.</i> no)	0.350 (0.215–0.570)	<0.001	0.328 (0.197–0.545)	<0.001
Chemotherapy (yes vs. no)	0.743 (0.543–1.016)	0.063	0.618 (0.435–0.879)	0.007
Radiotherapy (yes vs. no)	0.956 (0.660–1.384)	0.811		
Synchronous adrenal metastasis vs. metachronous	1.436 (1.014–2.033)	0.041		
Extra-adrenal disease (presence vs. absence)	1.460 (1.030–2.070)	0.033		
Site of adrenal metastasis				
Left adrenal gland (reference category)	1			
Right adrenal gland	0.957 (0.701–1.306)	0.781		
Bilateral involvement	0.813 (0.329–2.007)	0.653		
Extended adrenalectomy (yes vs. isolated adrenalectomy)	1.549 (1.063–2.257)	0.023		
Type of resection (R1/R2 vs. R0)	2.810 (1.896–4.166)	<0.001	2.288 (1.520–3.443)	<0.001
Duration of surgery (per min)*	1.003 (1.000–1.006)	0.026		
Tumor size*				
Preoperative (per mm)	1.087 (1.022–1.157)	0.008		
Pathological (per mm)	1.062 (1.016–1.110)	0.008		
Length of hospital stay (days)*	1.022 (1.001–1.044)	0.041		
Postoperative complications (yes vs. no)	1.272 (0.788–2.055)	0.325		
Adjuvant treatment after adrenalectomy (yes vs. no)	0.881 (0.645–1.202)	0.424		
Open surgery (or converted)	1.538 (1.114–2.124)	0.009	1.367 (0.971–1.925)	0.073

Risk factors for survival in patients undergoing adrenalectomy for solid tumor metastasis. \*, increased risk for each year of age, each minute of operative time, 1 mm of the tumor, and day of hospital stay.

patients with adrenal metastatic disease undergoing adrenalectomy via the laparoscopic route as compared to open surgery. Resection of adrenal metastasis through open surgery was a significantly associated with a poor survival in the bivariate analysis, although this variable was marginally significant in the multivariate Cox proportional hazards regression model.

Better outcomes were associated with laparoscopic adrenalectomy than those obtained after open operations. These results may be explained by different factors, including a reduced tumor size (both at preoperative and histopathological studies), fewer patients requiring extended S164



**Figure 1** Differences in survival according to the surgical procedure (open surgery or laparoscopic adrenalectomy).

adrenalectomy, a higher number of primary tumors treated surgically and patients given chemotherapy for the primary malignant lesion, and a higher rate of complete resections (R0) in the laparoscopic group as compared to the open method. In relation to the effect of completeness of removal of adrenal metastasis, analysis of the subset of patients who underwent R0 resections, the length of surgical was longer for the laparoscopic approach (46 *vs.* 27 months) but the difference was marginally significant. The wellknown benefits of minimally invasive operations already reported by other authors (13-15), such as prompt recovery, a reduced rate of postoperative complications, and shorter length of hospitalization were also documented in our study.

Laparoscopic adrenalectomy for malignancy is still controversial. Although data from small series of patients have shown that laparoscopic radical adrenalectomy is feasible and can be performed with acceptable outcomes in the carefully selected patients with metastases (17,19-22), the present study presents a comparison of oncologic results in a large cohort of patients undergoing adrenalectomy for adrenal metastatic disease, 46% of which were operated on through the laparoscopic approach, using the transperitoneal route in most cases. Of note, strict homogeneous selection criteria and the long follow-up period are strengths of the study. However, because this was a retrospective, multicenter survey study, no specific hypothesis was pre-established Also, laparoscopic or open adrenalectomy was performed according to decision of the attending endocrine surgeon.

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In relation variables associated with survival, renal cancer as the type of primary tumor and surgical treatment were significantly associated with a better survival, whereas survival was negatively affected by synchronous adrenal metastasis, extra-adrenal disease, extended adrenalectomy, R1/R2 resections, duration of surgery, tumor size, length of hospital stay, and open surgery (or converted). In the multivariate analysis, risk factors for better survival were renal cancer, surgery of the primary tumor, and use of chemotherapy, whereas type of resection (R1/R2 *vs.* R0) was associated with a worse prognosis.

On the other hand, the survival rates at 1, 2, 3, and 5 years after surgery were better for patients treated with laparoscopic adrenalectomy than for those undergoing open adrenalectomy. However, we found a favorable 5-year survival rate of 46% of patients in the laparoscopy group and 29.2% of patients in the open surgery group, although our series included more than one third of patient with extra-adrenal disease at the time of adrenalectomy.

In summary, results of this retrospective multicenter review show that laparoscopic adrenalectomy was feasible for the treatment of selected patients with metastatic adrenal disease. Most importantly, this surgical approach was associated with a significantly longer survival as compared to open adrenalectomy, probably in relation to a higher number of R0 resections.

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# Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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