

## Laparoscopic adrenalectomy for large solid cortical tumours - is it appropriate?

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### Rezumat

#### *Este adecvată adrenalectomia laparoscopică pentru tumorile solide de mari dimensiuni ale corticalei suprarenale?*

**Scop:** Adrenalectomia laparoscopică, procedeul de elecție pentru tumorile suprarenaliene benigne de mici dimensiuni, este utilizată și în cazul tumorilor de mari dimensiuni. Studiul nostru dorește să evalueze evoluția postoperatorie a pacienților cu rezecție laparoscopică a unor tumori suprarenaliene de mari dimensiuni.

**Metodă:** Am analizat toți pacienții cu adrenalectomii laparoscopice realizate în perioada 2002-2009, excluzând pe cei cu suspiciune pre- sau intraoperatorie de malignitate. Pe baza datelor de urmărire postoperatorie clinică, biochimică și computer-tomografică, am cercetat semne de recurență a bolii.

**Rezultate:** În perioada menționată, în unitatea noastră au fost 50 de pacienți la care s-a practicat adrenalectomie laparoscopică; dintre ei, 18 au avut tumori solide corticale de peste 7 cm, fără caracteristici pre- sau intraoperatorii de malignitate: 6 tumori cu sindrom Cushing, 8 tumori nesecretante, 4 aldosteronoame. Vârsta medie a pacienților a fost 46.89 ani (22-64 years), iar media diametrului tumoral 7.57 cm (7-9.1 cm). Examenul anatomo-patologic a identificat 10 adeoame corticale, 4 tumori maligne și 4 tumori cu histologie

nedeterminată. Urmărirea postoperatorie medie a fost 28.94 luni (4-58). Trei pacienți au decedat prin recidivă (metastaze hepatice și pulmonare) la 12, 19, respectiv 21 luni după operație. Un pacient a suferit o hepatectomie stângă pentru metastaze la 33 luni postoperator. 14 pacienți nu au manifestări de recidivă

**Concluzii:** Tumorile adrenocorticale cu dimensiuni de peste 7 cm fără caracteristici pre- sau intraoperatorii de malignitate pot fi rezecate laparoscopic. Această abordare nu modifică prognosticul și evoluția pe termen lung. Mortalitatea este legată de malignitate.

**Cuvinte cheie:** laparoscopie, adrenalectomie, adenom de glandă suprarenală, carcinom de glandă suprarenală

### Abstract

**Background:** Laparoscopic adrenalectomy, the procedure of choice for small benign adrenal tumours, is also used for large tumours. Our study aims to assess the outcome of large adrenal tumours laparoscopically resected.

**Methods:** All patients with laparoscopic adrenalectomy performed in between 2002 and 2009, without preoperative or intraoperative malignant characteristics, were reviewed. Clinical, biochemical and CT follow-up data were reviewed for evidence of recurrent disease.

**Results:** Fifty patients underwent laparoscopic adrenalectomies in our unit, 18 of them having solid cortical tumours  $\geq 7$  cm without preoperative or intraoperative malignant features: 6 Cushing's syndrome tumours, 8 non-secreting tumours, 4 aldosteronomas. The mean age of the patients was 46.89 years (range 22-64 years), and the mean tumour size 7.57 cm (range

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7-9.1 cm). Histology identified 10 cortical adenomas, 4 malignant tumours, and 4 indeterminate tumours. The mean follow-up was 28.94 months (range 4-58 months). Three patients died of systemic recurrent disease (liver and lung metastases) at 12, 19 and 21 month, respectively, after operation. One patient underwent a left hepatectomy for liver metastases, 33 months postoperatively. Fourteen patients have no evidence of recurrence.

**Conclusions:** Adrenal tumours  $\geq 7$  cm without pre- or intraoperative evidence of malignancy are resectable laparoscopically. This approach is unlikely to worsen the long-term outcome. The mortality is related to the malignancy.

**Key words:** laparoscopy, adrenalectomy, adrenocortical adenoma, adrenocortical carcinoma

## Introduction

Laparoscopic adrenalectomy (LA) has become the gold standard for the treatment of adrenal disorders requiring surgery, in most centres, since Gagner and colleagues have originally described it in 1992 (1). What makes this procedure feasible by laparoscopy is the relatively small size of most adrenal tumors, the low rate of malignancy and the easy access to the gland.

The widespread adoption of LA has been partly due to the improvement of laparoscopic instrumentation and technical expertise, and partly to data proving that LA is associated with less intraoperative blood loss (2), low morbidity, less hospital stay, lower cost (3), shorter recovery time, better quality of life and fewer postoperative hernias (4) compared with the open approach.

In most series, more than one third of cases performed consist in small size aldosterone secreting tumours (5). Whereas technical expertise has increased, so have the indications, with laparoscopic removal of large tumours (up to 20 cm in diameter) (6,7,8). Laparoscopic resection of adrenocortical tumours  $\geq 7$  cm is technically possible and associated with morbidity similar to that associated with smaller tumours (9,10). Nevertheless, large adrenal tumours are in relationship with a higher risk of malignancy, therefore laparoscopic resection may lead to a higher recurrence rate (11). When no local involvement or distant metastases are observed, it is difficult to diagnose preoperatively the adrenocortical carcinoma (ACC), therefore tumour size remains the main predictor of malignancy (8,12).

The main debate around the laparoscopic approach to large adrenal tumours is related to an insufficient extension of the resection and to the potential risk of port site or peritoneal metastases, which would worsen the outcome.

Our present study aims to assess the outcome of patients who have undergone LA for adrenocortical tumours  $\geq 7$  cm in diameter, to whom no pre- or intraoperative findings of malignancy were noticed. In our experience, the median

tumor size in the fifty patients who underwent LA was close to 6 cm, and none of the tumor less than 6 cm in diameter proved to be malignant. That justifies why we established the 7 cm as a cut off size for a seeming benign tumor that can be removed by laparoscopy, being aware that none of our patients had preoperative biopsy to prove the tumor as benign.

## Materials and Methods

The 50 consecutive patients, who underwent LA in our unit since 2002, were reviewed. Among them, those who had undergone LA for adrenal tumours  $\geq 7$  cm were identified. We selected only patients with no preoperative, clinical or imaging features of malignancy such as involvement of surrounding structures, lymphadenopathy or systemic metastases. Patients to whom we had identified during surgery macroscopic findings of malignancy (involvement of surrounding fatty tissue, suspicious neovascularization, lymph node involvement, tumour fixity) were not included and they were all converted to open surgery.

All operations were performed by a transperitoneal lateral laparoscopic approach and the adrenalectomy consisted in resection of adrenal glands with their surrounding fat. Minimal gland manipulation has been had in view during the procedure. The follow-up was every 4 months for the first year, every 6 months for the second and yearly thereafter. It consisted in a clinical examination, biochemical analysis, and ultrasonography. CT scan was performed yearly to detect local or systemic recurrent disease.

## Results

Between 2002 and 2009, a total of 65 adrenalectomies were performed in our unit, 50 of them being performed by laparoscopic approach. The other 15 were done by open approach, based on preoperative unequivocal evidence of malignancy, conversion from laparoscopy in case of intraoperative features of malignancy or presence of adhesions as a result of one or more previous laparotomies. There were 18 patients with solid adrenal tumours  $\geq 7$  cm in diameter. None overt malignant preoperative or intraoperative features were detected in any of the 18 cases who underwent laparoscopic adrenalectomy. The group included 6 Cushing's syndrome tumours, 8 non-secreting tumours, 4 aldosteronomas (Table 1).

The mean age of the patients was 46.89 years (range 22-64 years), and the mean tumour size 7.52 cm (range 7-9.1 cm). Histology identified 10 cortical adenomas, 4 malignant tumours, and 4 indeterminate tumours. The mean-follow-up was 28.94 months (range 4-58 months). Three patients with adrenocortical carcinoma (one with Cushing's and the other two with nonsecreting tumors) died of systemic recurrent disease (liver and lung metastases) at 12, 19 and 21 month, respectively, after operation (Table 1). The last patient with adrenocortical carcinoma and nonsecreting tumor underwent a left hepatectomy for liver metastases, 33 months postoperatively. The other 14 patients have no clinical or radiologic

**Table 1.** Clinical-pathological characteristics of the patients

Age at operation (years)	Clinical findings	Tumour size (mm)	Histology	Follow-up (months)
46	Non-secreting tumour	70	Cortical adenoma	58; wr
62	Non-secreting tumour	74	Cortical adenoma	22; wr
62	Aldosteronoma	75	Cortical adenoma	4; wr
36	Cushing's	79	Cortical adenoma	25; wr
49	Non-secreting tumour	71	Cortical adenoma	48; wr
44	Non-secreting tumour	75	Cortical adenoma	56; wr
62	Aldosteronoma	70	Cortical adenoma	24; wr
29	Aldosteronoma	72	Cortical adenoma	32; wr
37	Cushing's	89	Cortical adenoma	54; wr
43	Cushing's	80	Cortical adenoma	35; wr
42	Aldosteronoma	88	Indeterminate	30; wr
31	Cushing's	70	Indeterminate	10; wr
59	Non-secreting tumour	91	Indeterminate	8 ;wr
60	Cushing's	72	Indeterminate	30 ;wr
64	Cushing's	70	Adrenocortical carcinoma	12; D
61	Non secreting tumour	71	Adrenocortical carcinoma	19; D
22	Non-secreting tumour	72	Adrenocortical carcinoma	21; D
35	Non-secreting tumour	74	Adrenocortical carcinoma	33; HR

Wr - without recurrence; D - deceased; HR - hepatic recurrence

evidence of recurrence (Table 1). The 5 patients with benign Cushing's syndrome were cured after unilateral adrenalectomy. The four patients with aldosteronoma were cured after surgery with normotension and normal levels of blood potassium.

## Discussion

LA has become the gold standard for the surgical treatment of adrenal diseases, proving to be a safe and highly effective procedure. It has been well established that the laparoscopic approach provides overt advantages over open adrenalectomy such as less intraoperative blood loss (2), lower morbidity, shorter hospital stay (3), shorter recovery time, better quality of life, fewer incisional hernias (4) and lower overall costs (13). These benefits make the LA the procedure of choice for adrenal tumours in most centres.

Despite the general acceptance and widespread of LA, there is still controversy in some aspects. The first controversial aspect is in connection with the surgical approach for the suspected or well established malignant tumours. LA has not proved to be safer or more effective than the open procedure for the adrenocortical carcinoma (14). Nevertheless, as the incidence of adrenal carcinoma is relatively low (~ 1 %) (15), we prefer laparoscopic over open approach for the treatment of adrenal tumours unless we operate well established malignant lesions with involvement of neighbouring anatomic structures.

The second aspect of controversy is the cut-off size for a seeming benign tumour that can be removed by laparoscopy. Initially, most surgeons have recommended this approach only for tumours smaller than 6 cm, but removal of tumours as large as 20 cm has been reported (6,7,8). In our experience, we have increased the limit size of removed tumours, as more

experience was acquired. In our current series, the largest tumour we removed laparoscopically was 91 mm in diameter. Open adrenalectomy is therefore now reserved in our unit for proved malignant adrenal tumours, because in this case an extended resection, including lymphadenectomy and possibly splenectomy, nephrectomy or distal pancreatectomy, is required. Thus, we think that the appropriate surgical approach depends on our ability to distinguish benign from malignant adrenal disease.

When no tumour invasion or metastases are identified, no clinical, biochemical or radiologic finding can enable the identification of malignant adrenal tumours. Clinical presentation such as virilisation, mixed hormonal secretion and elevated dihydroxyepiandrosterone sulfate (DHEA-S) levels are suggestive, but rarely certifies the presence of malignancy (15). Low attenuation on CT scans and rapid enhancement after contrast injection followed by rapid washout, cannot unequivocally exclude malignancy. Iodine-cholesterol (NP 59) scans have equally failed to live up to their expectancy. Positron emission tomography scanning which has been increasingly adopted in some centres for the investigation of large adrenal tumours seems to be useful for identifying metastases to the adrenal gland, but is less reliable for primary adrenal malignancies. As a matter of fact, when clear malignant characteristics such as metastases or local invasion are absent, size remains the main predictor of the nature of adrenal tumours. Although the risk of cancer increases statistically with the size of the tumour, most adrenal tumours are nevertheless benign (16).

In our opinion, the intraoperative data suggesting the malignant nature of an adrenal tumour include local fixity, involvement of the spleen, pancreas, and upper pole of the

kidney, lymphadenopathy and venous thrombosis. Findings as above have been considered indications for open surgery in our patients, given the world-wide accepted requirement for a compartmental resection (17). An occult adrenocortical carcinoma (ACC) may be identified postoperatively on the resected specimen even in the absence of all features of malignancy, as we encountered in four cases. Therefore, in such cases the tumor may be inadvertently removed, either by laparoscopic or open approach.

Despite the recent advances in molecular biology, the diagnosis itself of the ACC can be challenging, taking into account that no single macroscopic feature enables a diagnosis of certitude (18). This is reflected by the fact that as many as 4 of our cases had equivocal pathologic findings. The most widely accepted histological scoring system, the Weiss score, may be predictive for malignancy (19), but is operator-dependent and its reliability may be limited by tumour heterogeneity (20). Some immunohistochemical markers as mdm-2, p53, p21, bcl-2 and Ki-67, were correlated with histological data (tumour necrosis, number of mitoses and sinusoidal invasion) (21), but that didn't appear to improve the malignancy prediction. Gene expression profiling might provide a reliable method for differentiating benign from malignant disease (22) in the future. At the present time, the most reliable pathologic criteria for diagnosis are the presence of metastatic disease and tumour size and weight. Whereas size and weight may be correlated, the size of an adrenal tumour may be correlated with the risk of malignancy. However, most large size adrenal tumour are benign histological and behaviourally (23), so large size is not necessarily a malignancy criterion. Moreover, small tumour size is no guarantee of benign behaviour because about 13 % of resected ACC are  $\leq 5$  cm diameter at the moment of diagnosis. When we take into account that benign adrenal tumours are not uncommon and can be identified in 1.4% to 8.9% of autopsies (23,24) and that the incidence of malignant adrenal tumours may be as low as 2/one million/year (25), it is certain that the ideal surgical approach to large size adrenal tumours is controversial.

Surgery is the best treatment of ACC because in the absence of efficacious adjuvant therapy the completeness of surgical resection is of paramount importance to prolonging the disease-free interval and the long-term survival (26). For proved ACC, we think that open surgery is the procedure of choice, but what about those tumours which are large but with no certain signs of malignancy? In the absence of unequivocally preoperative or intraoperative malignant findings the appropriate procedure is simple laparoscopic adrenalectomy with removal of the gland and its surrounding fat. As the size of the adrenal tumour increases, there is a small but not insignificant risk that an occult ACC may be removed. In such cases, capsular disruption would lead to suboptimal oncologic management, increasing the risk of local recurrence and of peritoneal carcinomatosis (11,12). According to our experience, it is unlikely that capsular disruption during the tumour manipulation should be more frequent than in open surgery. The difficulties we encountered during LA for large adrenal tumors were related in several cases to the

laparoscopic instruments that abraded tumors, penetrated (grossly or macroscopically) or even teared the capsule. We had also difficulties to extract some of the largest tumors in our series, faithful to the spirit of small incisions. We think that the excellent magnified view, fine dissection and minimal manipulation of the adrenal gland possible in the laparoscopic approach offer a good if not even a better chance of a complete resection of the adrenal gland than usually does the open approach and therefore a lower risk of recurrence in the event of inadequate removal of an ACC. We usually employ in our practice an algorithm for the surgical management of adrenal tumours  $\geq 7$  cm diameter, which includes laparoscopic assessment as an integral part of the evaluation of an adrenocortical tumour (Fig. 1). The median tumor size in our fifty patients who underwent LA, was close to 6 cm and none of the resected tumors smaller than 6 cm proved to be malignant. That encouraged us to establish the 7 cm as a limit size for the seeming benign tumors that can be resected laparoscopically.

The overall low risk of well established malignancy and the fact that in the absence of malignant features someone would perform the same surgical procedure with the same risk whether open or laparoscopic, suggest that automatically adopting a 7 cm tumour diameter limit, this approach would prevent a lot of patients from benefiting from an operation that has many well documented advantages. Nevertheless, each case should be evaluated and treated according to its individual features. For instance, extremely large tumours for which there is an interrogation about laparoscopic resectability and tumours for which there is a higher than usual reason of suspicion of malignancy, such as large Cushing's tumours, should be treated with caution.

Local tumour recurrence, which may appear after a disease-free period of more than 18 month following LA, even in the absence of tumour spillage, was observed before the introduction of LA.

Within the limitations of a case series, our study suggests that the laparoscopic approach is oncologic sound in patients with an occult ACC, given that of the four patients with proven ACC and the six with indeterminate histology,

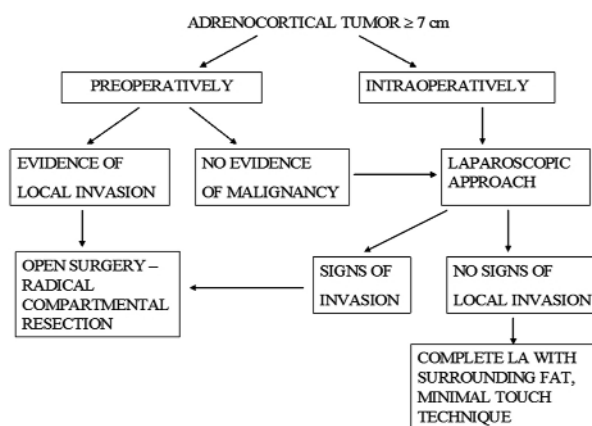


Figure 1.

none has had a local or peritoneal recurrence. Furthermore, local or systemic recurrence is seen with tumours  $\leq 7$  cm as well as with larger tumours (27). This finding implies that if the counterargument to the laparoscopic approach is applied it would limit the use of LA to adrenal tumours with the lowest malignant risk, such as small Conn's tumours.

Systemic recurrence of ACC was also identified prior the introduction of LA. Therefore, although it cannot be demonstrated that the three patients in our series who developed liver and lung metastases and subsequently died of their disease would have had a better outcome if their operative procedure had been performed by an open approach, in the absence of local recurrence this alternative seems somewhat unlikely.

The medium to long-term follow-up of patients with clinic and radiologic benign large adrenocortical tumours suggests that a laparoscopic approach is not contraindicated for oncologic reasons alone. We therefore believe that if a good surgical expertise is available, a laparoscopic approach for adrenocortical tumours  $\geq 7$  cm with no overt malignant features should be the initial approach of choice. In case of any intraoperative signs of malignancy, the procedure should be converted to an open approach because an extended radical compartmental excision (that may involve neighbouring organs) is required and is best achieved by open surgery. If intraoperative findings strengthen the preoperative clinical and radiologic data (no tumour fixity, no local invasion, no large lymphadenopathy, no venous thrombosis) regional excision and therefore conversion, are not required, and the procedure should be completed laparoscopic.

Recurrent or persistent disease as a consequence of incomplete resection or tumour seeding has been a concern in laparoscopic surgery for many years. A delicate surgical technique can avoid this complication, as laparoscopic adrenalectomy has high proven cure rates, similar to those reported with the open approach.

In summary, we conclude that LA is a safe and effective procedure. It allows even patients with adrenocortical tumors  $\geq 7$  cm in diameter to drive the benefits of a minimal access approach rather than undergo an obligatory open approach associated with its greater morbidity. Surgeon experience with both endocrine and laparoscopic surgery is mandatory and each case should be evaluated and treated according to its individual features.

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