World Journal of Surgery

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Published Online: 17 April 2006

World J Surg (2006) 30: 893–898
DOI: 10.1007/s00268-005-0288-2

# Long-term Outcome following Laparoscopic Adrenalectomy for Large Solid Adrenal Cortex Tumors

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**Abstract**

*Introduction:* Laparoscopic adrenalectomy (LA) is the procedure of choice for small benign adrenal tumors. In the absence of local invasion or metastases, the preoperative diagnosis of an adrenocortical carcinoma (ACC) is difficult, often leaving size as the principal predictor of malignancy. Large tumors are resectable laparoscopically, but the long-term outcome and therefore appropriateness of LA for cortical tumors > 6 cm is not known.

*Methods:* We reviewed the LA experience in our institution since its introduction in June 1994. Patients who underwent LA for solid cortical tumors ≥ 60 mm in diameter without preoperative or intraoperative evidence of malignancy were reviewed. Follow-up data, including clinical examination, biochemical analysis, and repeat scans, were reviewed for evidence of local or systemic recurrent disease.

*Results:* Between 1994 and 2004 a total of 462 adrenalectomies were performed, 391 of which were done laparoscopically. Among them, 19 were solid cortical tumors ≥ 60 mm in diameter with no overt malignant preoperative or intraoperative characteristics: 9 nonsecreting tumors, 8 Cushing's syndrome tumors (including 2 virilizing variants), 1 virilizing tumor, and 1 aldosteronoma. The mean age of the patients was 49.9 years (range 22–77 years), and the mean tumor size was 69.0 mm (range 60–80 mm). Histology confirmed a cortical adenoma in eight patients, malignant tumors in three, and indeterminate tumors in eight. The mean follow-up was 34 months (range 4–108 months). Two patients died of systemic recurrent disease (liver metastases) at 10 and 19 months, respectively, following surgery; two other patients died 12 and 21 months, respectively following surgery owing to unrelated cardiovascular and cerebrovascular pathology. One patient underwent surgery for local recurrence 54 months after primary surgery; the remaining 14 patients are well with no clinical or radiologic evidence of recurrent disease.

*Conclusions:* Laparoscopic adrenalectomy for large solid cortical tumors without pre- or intraoperative evidence of malignancy is not contraindicated, and it is unlikely to have a deleterious effect on long-term outcome. Each case should be considered individually. We provide an algorithm for the approach to adrenocortical tumors ≥ 6 cm.

Since Gagner and colleagues' original description of laparoscopic adrenalectomy (LA) for the treatment of Cushing's syndrome due to a adrenocortical adenoma in 1992,[1] this approach to the adrenal gland has become the procedure of choice for benign adrenal disease requiring surgery. The widespread adoption of LA has been partly due to the improvement in laparoscopic instrumentation and technical expertise and partly to the

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accumulation of mainly retrospective data demonstrating that LA is associated with less intraoperative blood loss,[2] lower morbidity, shorter hospital stay[3] more rapid return to work, greater patient satisfaction, and fewer incisional hernias[4] than the open approach.

Small aldosterone-secreting tumors represent the most common indication for LA in published series, with more than one-third of cases performed for this pathology alone.[5] However, as experience with the technique has increased, so have the indications, with reports of large tumors (up to 15 cm in diameter) being successfully removed laparoscopically.[6,7] Although the removal of tumors ≥ 6 cm is technically feasible and associated with morbidity similar to that associated with smaller tumors,[8] large cortical tumors are associated with a higher risk of malignancy; and laparoscopic resection in such cases may lead to a high recurrence rate.[9] The principal concerns surrounding the laparoscopic approach to large adrenal tumors are the hypothetical risk of an inadequately extensive resection and the potential for port-site or peritoneal metastases, which would adversely affect the clinical outcome.[10,11]

The aim of this study was to assess the outcome of patients who have undergone laparoscopic adrenalectomy for cortical tumors ≥ 6 cm in diameter where there were no pre- or intraoperative features of malignancy.

## MATERIALS AND METHODS

We reviewed the consecutive series of laparoscopic adrenalectomies performed in our institution for 10 years beginning in 1994. Patients who had undergone LA for adrenal cortex tumors ≥ 6 cm in diameter were identified. Included were patients who manifested no preoperative radiologic features of malignancy, such as tumor invasion of the surrounding structures, lymphadenopathy, or systemic metastases. Intraoperatively, only patients with no macroscopic features suspicious of malignancy (*e.g.,* local fixity, invasion of surrounding fat, suspicious neovascularization, lymphadenopathy) were included. The presence of mixed hormonal secretion, virilization, or elevated dehydroepiandrosterone sulfate (DHEA-S) in the absence of radiologic evidence of malignancy was not a preoperative contraindication to the laparoscopic approach.

All procedures were performed via a transperitoneal lateral laparoscopic approach. The technique consisted of resecting the adrenal glands with the periadrenal fat and with minimal manipulation of the adrenal gland itself. Follow-up was typically every 6 months for the first 2 years and yearly thereafter. It included a clinical examination, biochemical analysis, and repeat scans to identify evidence of local or systemic recurrent disease.

## RESULTS

Between 1994 and 2004, a total of 462 adrenalectomies were performed, 391 of which were performed laparoscopically. Altogether, 71 open adrenalectomies were performed because a laparoscopic approach was contraindicated either by the disease (unequivocal evidence of malignancy) or the presence of adhesions secondary to one or more previous laparotomies. There were 19 patients with solid cortical tumors ≥ 60 mm diameter without overt malignant preoperative or intraoperative characteristics who underwent laparoscopic adrenalectomy (Table 1). The tumors included 9 nonsecreting tumors, 8 Cushing's syndrome tumors (including 2 virilizing variants), 1 virilizing tumor, and 1 aldosteronoma. The mean age of the patients was 49.9 years (range 22–77 years), and the mean tumor size was 69.0 mm (range 60–80 mm). Histology confirmed a cortical adenoma in eight patients, categorically malignant tumors in three patients, and indeterminate tumors in eight. The mean follow-up was 34 months (range 12–108 months). Two patients died of systemic recurrent disease (liver metastases) at 10 and 19 months, respectively, following surgery. Two other patients died 12 and 21 months, respectively, following surgery from unrelated cardiovascular pathology. One patient developed a local recurrence 54 months after surgery that required right adrenal bed resection and nephrectomy. The remaining 14 patients are well, with no clinical or radiologic evidence of recurrent disease.

## DISCUSSION

Laparoscopic adrenalectomy has become the procedure of choice for benign adrenal disease because it is associated with less blood loss,[2] lower morbidity, shorter hospital stay,[3] more rapid return to work, fewer incisional hernias,[4] and lower cost[12] than open surgery. Open adrenalectomy is therefore now reserved for malignant adrenal tumors because this disease requires compartmental resection including lymphadenectomy and possibly splenectomy, nephrectomy, or distal pancreatectomy. The appropriate surgical approach therefore appears to be implicitly dependent on our ability to distinguish benign from malignant adrenal disease.

**Table 1.**
Synopsis of the patients

| Age at surgery (years) | Clinical features | Tumor size (mm) | Histology | Follow-up (months) |
|---|---|---|---|---|
| 47 | Nonsecreting tumor | 60 | Cortical adenoma | 108; NSR |
| 77 | Nonsecreting tumor | 65 | Cortical adenoma | 21; RIP, MI |
| 71 | Nonsecreting tumor | 65 | Cortical adenoma | 12; RIP, CVA |
| 36 | Cushing's | 80 | Cortical adenoma | 14; NSR |
| 49 | Nonsecreting tumor | 60 | Cortical adenoma | 24; NSR |
| 44 | Nonsecreting tumor | 65 | Cortical adenoma | 46; NSR |
| 61 | Aldosteronoma | 60 | Cortical adenoma | 72; NSR |
| 65 | Nonsecreting tumor | 75 | Cortical adenoma | 8; NSR |
| 43 | Cushing's | 60 | Indeterminate | 54; Local recurrence |
| 64 | Virilizing Cushing's tumor | 62 | Indeterminate | 81; NSR |
| 29 | Cushing's | 80 | Indeterminate | 35; NSR |
| 39 | Nonsecreting tumor with flank pain | 80 | Indeterminate | 28; NSR |
| 44 | Cushing's | 80 | Indeterminate | 10; RIP, 2° liver metastasis |
| 42 | Virilizing Cushing's tumor | 75 | Indeterminate | 5; NSR |
| 32 | Cushing's | 60 | Indeterminate | 25; NSR |
| 60 | Cushing's | 80 | Indeterminate | 32; NSR |
| 22 | Nonsecreting tumor | 70 | Adrenocortical carcinoma | 13; NSR |
| 72 | Nonsecreting tumor | 70 | Adrenocortical carcinoma | 19; RIP, 2° liver metastasis |
| 31 | Virilizing tumor | 65 | Adrenocortical carcinoma | 32; NSR |

NSR: no signs of recurrence; RIP: deceased; MI: myocardial infarction; CVA: cerebrovascular accident.

In the absence of local tumor invasion or metastases, there is no clinical, biochemical, or radiologic test that enables preoperative identification of malignant adrenal tumors. Clinical presentation such as virilization, mixed hormonal secretion, and elevated dihydroxyepiandrosterone sulfate (DHEA-S) levels are suggestive but rarely allow absolute prediction of malignancy.[13] Equally, low attenuation on computed tomography and magnetic resonance imaging scans, which demonstrates rapid enhancement after gadolinium contrast followed by rapid washout, cannot unequivocally exclude malignancy. Iodocholesterol (NP 59) scans have also failed to live up to their promise; and positron emission tomography scanning, which we have increasingly adopted in the investigation of large adrenal tumors, is useful for identifying metastases to the adrenal gland[14] but is less reliable for primary adrenal disease. As a consequence, when unequivocal malignant features such as metastases or local invasion are absent during the preoperative evaluation, size remains the principal predictor of the nature of adrenal tumors. However, although the risk of adrenal malignancy increases with the size of the tumor[15]—with most adrenal cortex adenomas tending to be small and adrenocortical carcinomas (ACCs) tending to be 5 to 6 cm[16]—most large tumors are nevertheless benign.

The intraoperative features indicative of the malignant nature of an adrenal tumor include local fixity; invasion of the pancreas, spleen, or superior pole of the kidney; venous thrombosis; and lymphadenopathy. Such findings should be an indication for open surgery given the need for a compartmental resection. However, an occult ACC may be present in the absence of all such features and therefore may be inadvertently removed, whether laparoscopically or via open surgery.

Despite the developments in molecular biology, even the histologic diagnosis of ACC can be a challenge given that no single microscopic feature enables an unequivocal diagnosis.[17] This is reflected by the fact that as many as eight of our series of 19 patients had equivocal pathologic findings. The most widely used histologic scoring system, the Weiss score, may be predictive of malignancy,[18] but it is operator-dependent and its reliability may be limited by tumor heterogeneity.[19] When immunohistochemical analysis of the markers p53, mdm-2, p21, bcl-2, cyclin D1, and Ki-67 were correlated with histology, they appeared to do no more than complement the traditional histologic features that predict malignancy, such as tumor necrosis, atypical and numerous mitoses, and sinusoidal invasion.[20] Although gene expression profiling may offer a reliable method for differentiating benign from malignant disease[21] in the future, at the present time the two most reliable pathologic criteria for diagnosis remain the presence of metastatic disease and possibly tumor weight.[22] Because size and weight may be correlated, the size of an adrenal tumor may be correlated with the risk of malignancy. Nevertheless, most heavy (therefore large) adrenal tumors are benign histologically and behaviorally[23]; and a small diameter is no

guarantee of benign behavior because as many as 13.5% of resected ACCs are <5 cm in diameter at diagnosis.[24]

Hence small tumor size does not guarantee that an adrenal tumor is benign, and large size is not necessarily indicative of malignancy. This is underlined by Copeland's calculations concerning adrenal incidentalomas. He stated that if the 6 cm rule were applied across the board, as many as 60 adrenalectomies for incidentally found tumors >6 cm in diameter would have to be performed to identify and remove one carcinoma.[25] When added to the fact that benign adrenal tumors are not uncommon and indeed can be identified in 1.4% to 8.9% of autopsies[23,25] and that the incidence of malignant adrenal tumors may be as low as two per million per annum,[26] it is clear that the ideal surgical approach to large adrenal tumors is controversial.

The treatment of ACCs is surgical because in the absence of efficacious adjuvant therapy the completeness of surgical resection is paramount to prolonging the disease-free interval and long-term patient survival.[27] Open surgery is the procedure of choice for known ACCs[28]—but what of those tumors that are large but without unequivocal signs of malignancy? In the absence of unequivocally preoperative or intraoperative malignant features, the appropriate procedure is simple adrenalectomy with removal of the gland and its surrounding fat. As the size of the adrenal gland increases, there is a small but not insignificant risk that an occult ACC may be removed. Capsular disruption in such cases would lead to suboptimal oncologic management, increasing the risk of local recurrence and of peritoneal carcinomatosis.[9,10] Our series suggests that capsular disruption is unlikely to be more frequent than with open surgery. Indeed, it is our opinion that the excellent magnified view, fine dissection, and minimal manipulation of the adrenal gland possible with the laparoscopic approach offers as a good if not better a chance of complete resection of the adrenal gland than does the open approach and therefore a lower risk of recurrence in the event of inadvertent removal of an ACC. We have therefore adopted a simple management algorithm for the surgical management of adrenal tumors radiologically ≥ 6 cm that uses laparoscopic assessment as an integral part of the evaluation of an adrenal tumor (Fig. 1).

The overall low risk of proven malignancy and the fact that in the absence of malignant features one would perform the same surgical procedure with the same risks whether open or laparoscopic suggests that automatically adopting a 6 cm tumor diameter threshold for open surgery is unjustified. Indeed, this approach would prevent a large proportion of patients from benefiting from an operation that has many well documented advantages. Indeed, with the proviso that the necessary surgical expertise is available, the laparoscopic approach should be the default operation for large adrenal tumors of the adrenal medulla and cortex.[29] However, each case should be treated on its individual merits. For example, extremely large tumors for which there is a question about laparoscopic resectability and tumors for which there is a higher than usual index of suspicion of malignancy, such as large Cushing's tumors, should be treated with caution.

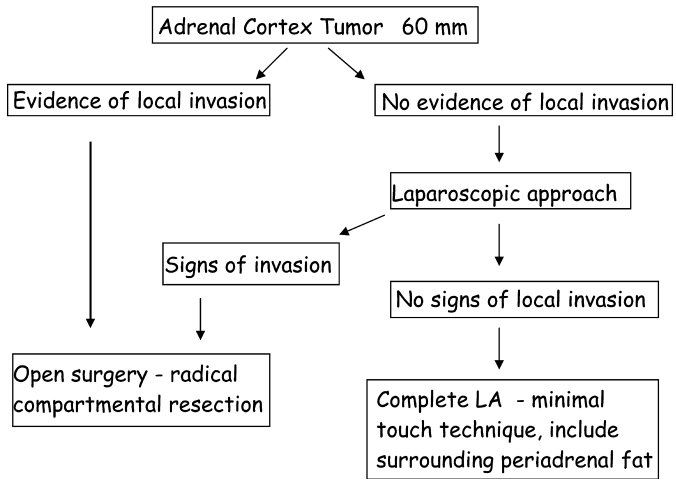


**Figure 1**. Algorithm for the surgical management of adrenal tumors ≥ 60 mm in diameter. LA: laparoscopic adrenalectomy.

Local tumor recurrence, which may appear more than a year and a half following LA even in the absence of tumor spillage, was seen prior to the introduction of LA. However, the incidence of local recurrence following open adrenalectomy for large adrenal tumors is unknown, and therefore no reliable historical comparison with the laparoscopic approach is possible. Equally, no comparison with the 71 open adrenalectomies performed in our department is appropriate because the patients with large tumors, by definition, had evidence of local invasion, which contraindicated a minimal access approach. Within the limitations of a case series, our study suggests that the laparoscopic approach is oncologically sound in patients with an occult ACC given that of the three patients with proven ACCs and the eight with tumors of indeterminate histology only one has had a local or peritoneal recurrence. Furthermore, local and systemic recurrence is seen with tumors < 6 cm as well as with larger tumors.[30] This finding implies that if the counterargument to the laparoscopic approach is applied it would limit the use of LA to adrenal tumors with the lowest malignant risk, such as the smallest Conn's tumors.

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

The medium to long-term follow-up of patients with clinically and radiologically benign large adrenal tumors suggests that a laparoscopic approach is not contraindicated for oncologic reasons alone. We therefore believe that when the appropriate surgical expertise is available a laparoscopic approach for adrenal tumors > 6 cm that are not overtly malignant should be the initial approach of choice. If there are any intraoperative features of malignancy, the procedure should be converted to an open approach because an extensive radical compartmental resection that may involve local organs is required and is best performed by open surgery. Conversely, if intraoperative findings support the preoperative clinical and radiologic findings—no fixity, no local invasion, no gross lymphadenopathy, no venous thrombosis—regional resection and therefore conversion are not needed, and the operation should be completed laparoscopically. This approach (Fig. 1) allows patients with tumors ≥ 6 cm to reap the benefits of a minimal access approach rather than condemning them to an obligatory open approach with its associated greater morbidity.

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