

BRIEF REPORT

Laparoscopic Adrenalectomy for Potentially Malignant Adrenal Tumors Greater than 5 Centimeters

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Purpose: Laparoscopic adrenalectomy (LA) is controversial for large, potentially malignant tumors. We report a series of LA or hand-assisted LA for large (>5 cm) adrenal tumors.

Patients and Methods: Among 210 LAs performed in 6 yr, 39 patients had potentially malignant tumors greater than 5 cm in diameter. Their perioperative and follow-up data were retrospectively analyzed.

Results: All 39 patients had successful LAs without perioperative mortality, conversion to open surgery, or capsular disruption during dissection. The mean tumor size was 6.2 cm (range, 5–12 cm), operative time 207 min (115–315 min), and blood loss 75 ml (minimal–1400 ml). Complications included one intraoperative diaphragmatic perforation, three mild wound infections, and one pneumonia. Preoperatively there were 27 nonfunctioning tumors, seven pheochromocytomas, three cortisol-secreting tumors, and two virilizing tumors. Final pathology revealed eight malignant (four adrenocortical carcinomas and four metastatic carcinomas) and 31 benign tumors (14 cortical adenomas, eight pheochromocytomas, six myelolipomas, and three ganglioneuromas). Median follow-up was 39 months. Four patients (two adrenocortical carcinomas, one metastatic hepatoma, and one lymphoma) died 24, 10, 9, and 3 months after surgery, respectively. A hand-assisted device was used in 10 patients. Only the tumor size was larger and length of postoperative hospital stay longer for those in the hand-assisted group.

LAPAROSCOPIC ADRENALECTOMY (LA) has become the standard for removing small benign adrenal tumors (1). Despite anticipated difficult dissection and poorer prognosis (2, 3), the application of LA for large adrenal tumors (>5 or 6 cm) with malignant potential and/or adrenal metastasis has been extended in some centers (4–10). However, limited case series can be found in current medical literature. We retrospectively reviewed our 6-yr clinical experience with laparoscopic or hand-assisted LAs for potentially malignant (>5 cm) adrenal tumors.

Patients and Methods

Between 1999 and 2005, 210 patients underwent laparoscopic or hand-assisted LAs in our institute. All patients underwent complete endocrine and image evaluations, which determined the size of the adrenal tumors (the largest diameter of the mass on computed tomography or magnetic resonance imaging). LA was limited to well-encapsulated masses without any radiographic evidence of periadrenal involvement or obvious lymphadenopathy. All of the patients were informed about the benefits and potential risks, including possible open

conversion if difficulties were encountered intraoperatively. All provided informed consent.

There were 39 patients among our 210 cases who had a tumor greater than 5 cm and fulfilled the inclusion criteria for the analysis.

Conclusions: LA is a reasonable option for selected large adrenal tumors when complete resection is technically feasible and there is no evidence of local invasion. Hand-assisted LA is a good alternative to open conversion if a difficult dissection is encountered intraoperatively. (*J Clin Endocrinol Metab* 91: 3080–3083, 2006)

Surgical technique

All operations were performed with the lateral transperitoneal approach (11, 12), and a hand-assisted device (HAD) was used (placed midline for a left LA and in the subcostal area for a right LA with a 7-cm incision) whenever necessary. Special attention was given to achieving an *en-bloc* excision of the tumor with wide surgical margins and as much periadrenal tissue as possible. All of the procedures were performed by a single experienced laparoscopic surgeon to ensure that the principles of oncologic surgery were strictly followed.

Statistical analysis

The data are expressed as mean \pm SEM and range. Comparisons between groups were made by nonparametric analysis (Wilcoxon's rank sum tests). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Preoperatively, the case numbers and initial diagnoses of various tumors are listed in Table 1. The patients' mean age was 45 ± 4.1 (4–75) yr. The tumor measured 6.2 ± 1.2 (5–12) cm. Sixteen left and 23 right LAs were performed. All 39 patients had their tumor excised laparoscopically via *en-bloc* resection. There was no perioperative mortality and no cap-

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Abbreviations: ACC, Adrenocortical carcinoma; HAD, hand-assisted device; HCC, hepatocellular carcinoma; LA, laparoscopic adrenalectomy; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.

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TABLE 1. Final pathology report on all patients

Preoperative diagnosis	Final pathology report	n
Nonfunctioning tumors	Cortical adenoma	9
	Pheochromocytoma	1
	Myelolipoma	6
	Ganglioneuroma	3
	Primary ACC	4
	Malignant lymphoma	1
	Metastatic RCC	1
	Metastatic HCC	1
	Metastatic SCC	1
	Pheochromocytoma	Pheochromocytoma
Cortisol-secreting tumors	Cortical adenoma	3
Virilizing tumors	Cortical adenoma	2

sular disruption during dissection. Mean operative time was 207 ± 53 (115–315) min, and mean blood loss was 75 ± 79 (minimal–1400) ml. No patient required a conversion to conventional open surgery, whereas a HAD was used in 10 patients. All of the patients resumed oral intake within 24 h after surgery.

Postoperatively, patients required 5.2 ± 5.9 mg morphine sulfate. Diaphragmatic perforation occurred in one of the left LAs because of severe adhesions after a previous ipsilateral nephrectomy for renal cell carcinoma (RCC). The resulting pneumothorax healed after laparoscopic suture repair of the diaphragm and chest tube drainage. Postoperative complications included three mild wound infections and one pneumonia. All healed uneventfully with conservative managements.

Pathology results and prognosis

Table 1 details the pathological diagnosis on all tumors. Preoperatively malignancy could not be ruled out in all these patients because of the large size and/or heterogeneous enhancement in imaging studies. The tumor resection margins were negative in all of the patients with adrenal metastasis or primary adrenocortical carcinoma (ACC). The median follow-up time was 39 (3–68) months. Four patients [two with ACC, one with metastatic hepatocellular carcinoma (HCC), and one with malignant lymphoma] died 24, 10, 9, and 3 months after surgery, respectively.

Six of the 39 patients had past histories of extraadrenal malignancies, but no other metastasis had been detected preoperatively. Two patients with RCC had undergone ipsilateral nephrectomy. Pathology revealed a benign adenoma in the one with diaphragmatic perforation and metastatic RCC in the other. One patient with bladder transitional cell carcinoma had an adrenal mass noted during staging work-up, which turned out to be a nonfunctioning benign

adenoma. Metastasis was also confirmed in the patients with past history of lymphoma, HCC, and esophageal squamous cell carcinoma.

Table 2 depicts follow-up information on eight patients with pathologically proven malignancies. The patient with metastatic RCC had inoperable mediastinal and pulmonary metastasis 6 months later, and immunotherapy was administered. The patient with metastatic HCC died 9 months after operation due to rupture of a new hepatic recurrence. In the patient with relapsing lymphoma, contralateral adrenal metastasis and multiple lymphadenopathy were found 1 month after surgery. He died due to sepsis after chemotherapy. The patient with metastatic squamous cell carcinoma (SCC) was still alive after 9 months with further chemotherapy. No local recurrence or port seeding was noted in all these four metastatic patients.

Primary ACC was confirmed in four patients (no. 5–8 in Table 2). In patient 5, a metastatic lymph node in the resected *en-bloc* mass, tumor invasion to capsules, and tumor emboli in a few vessels were reported. Local recurrence was found 5 months later, and she died after 24 months despite chemotherapy. Patient 6 had multiple metastases 3 months after surgery and died 10 months after. Patient 7 had a previous history of endometriosis. Her preoperative images showed a fat-containing tumor favoring myelolipoma, but pathology reports showed a cortical adenoma with a high mitotic figure yet not meeting the malignant criteria for a carcinoma. She had an ovarian tumor rupture 22 months after LA, and metastatic ACC was reported.

Hand-assisted LA

Ten patients had hand-assisted LA. Operative time, blood loss, postoperative narcotic requirements, and incidence of wound infection were comparable between the hand-assisted LA group and those who had pure LA ($n = 29$). Only the mean tumor size was larger (7.33 ± 1.5 vs. 5.84 ± 1.7 cm, $P = 0.01$), and postoperative hospital stay was longer for those in the hand-assisted group (6.9 ± 2.1 vs. 4.2 ± 1.8 d, $P = 0.03$).

Discussion

Despite absolute contraindication of LA for a large ACC with local periaxial invasion or venous thrombus (1), there is still no consensus regarding the maximum tumor size for LA. Whereas the size of an adrenal tumor is an important indicator of its malignant risk, many, if not most, large adrenal tumors are benign. In this series, only eight of 39 adrenal tumors greater than 5 cm were malignant, whereas

TABLE 2. Follow-up on eight patients with adrenal malignancies

Patient no. and cancer	Tumor size (cm)	Local recurrence	Distant metastasis	Survival (months)
1. Metastatic RCC	6		Lung and mediastinum	44 (alive)
2. Metastatic HCC	6		Hepatic	9 (death)
3. Lymphoma	5.5		Multiple	3 (death)
4. Metastatic SCC	6			9 (alive)
5. Primary ACC	8.5	+, 5 months	Multiple	24 (death)
6. Primary ACC	5		Multiple	10 (death)
7. Primary ACC	5.5		Ovarian	38 (alive)
8. Primary ACC	6			6 (alive)

almost 80% of these large tumors were benign. If size is the sole criterion on which the operative approach is based, many patients with benign large adrenal tumors will have an unnecessary open adrenalectomy that might increase their morbidity.

LA for large and/or potentially malignant adrenal tumors was first proposed by Henry *et al.* (4), who chose 4 cm as a cut-off point and performed 48 such LAs. Their perioperative results were comparable with those for small benign tumors. Hobart *et al.* (5), Novitsky *et al.* (7), and Tsuru *et al.* (10) also reported successful LAs performed in patients with adrenal tumors greater than 5 cm. They concluded that LA is safe and effective for large tumors but cautioned that strict oncological surgical principles must be observed. Moreover, other surgeons who chose 6 cm as the cut-off point (6, 8, 9) had similar conclusions. Data from our series also confirm that LA for selected tumors greater than 5 cm can be performed successfully without obvious morbidities or mortality. One important reason for the 5-cm-size cut-off was to include two of our four primary ACCs that were diagnosed at the sizes of 5–5.5 cm.

Primary ACC is a rare malignancy and has a 5-yr survival, ranging from 16 to 60% (13). Even when patients have localized disease and complete tumor resection, recurrences occur in at least two thirds of cases (13). Cobb *et al.* (14) reviewed LA for primary ACCs and found 10 of 25 (40%) had local recurrence. Porpiglia *et al.* (15) reported the outcome of six primary ACCs in 205 LAs with no intraoperative complications and one open conversion. In a mean follow-up of 30 months, only one died of stroke and the other five were disease free. Moynadeh and Gill (16) recently reported three of the seven patients with primary ACCs receiving LA remained alive in a 26-month follow-up. In contrast, all six ACCs excised laparoscopically in the series by Gonzalez *et al.* (3) had local recurrences. Another review (2) concluded that any tumor greater than 6 cm has a greater risk of being malignant and should be resected by an open approach.

In our series, only one of four patients with ACCs had local recurrence, corroborating the feasibility of LA for *en-bloc* local resection. However, these patients still had an ominous prognosis. Cancer-specific survival was 50% and three of four patients had distant metastasis during follow-up. From our data and those just reviewed, it is difficult to conclude whether LA offers the same therapeutic efficacy for ACCs. One reason is that ACCs are so rare that most other contemporary papers contained five to seven cases at most in their series. It is very difficult to conduct a comparative study of open *vs.* laparoscopic adrenalectomy for large tumors or cancers in a single center. A metaanalysis to compare all LAs *vs.* open adrenalectomies for ACCs or a multicenter prospective comparative study of the two operative approaches might address this important issue.

There is still no reliable preoperative diagnostic test to determine the malignant potential of adrenal tumors (17). In our series, one of six myelolipomas was not diagnosed preoperatively because of no obvious fat-containing part in that tumor. Two patients in our series whose tumors had fat-containing parts (thought to be myelolipomas preoperatively) had a final diagnosis of ACC and ganglioneuroma, respectively.

Several investigators (16, 18, 19) documented that aggressive laparoscopic resection of adrenal metastasis, when done in patients with a solitary resectable disease, can result in prolonged patient survival without significant risk of port-site metastasis. In our series, none of the four patients with metastatic cancers had local recurrence after LA, which proved that LA is feasible for *en-bloc* local resection.

Hand-assisted LA is a minimally invasive surgical alternative (20). The series by Walz *et al.* (8) and Naya *et al.* (9) noticed that LA for patients with larger tumors (>6 and 7.5 cm, respectively) had longer operating time and greater intraoperative blood loss. Hence, we used a HAD whenever the tumor was greater than 8 cm, dissection was difficult, or uncontrollable bleeding was encountered with pure laparoscopic technique. The addition of tactile sensation and better exposure provided a more rapid and direct dissection. It also ensured intact specimen removal at the end of surgery, especially for cases with high malignant potential.

Conclusions

Laparoscopic adrenalectomy is a reasonable procedure for selected large adrenal tumors when a complete resection is technically feasible and there is no evidence of local invasion. A hand-assisted laparoscopic procedure is a good option before an open conversion is considered, especially when difficult dissections are encountered intraoperatively.

Acknowledgments

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