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The change in the principle of performing laparoscopic adrenalectomy from small to large masses

Yeşim Erbil*, Umut Barbaros, Gülay Karaman, Alp Bozbora, Selçuk Özarmağan

Istanbul University, Istanbul Medical Faculty, Department of General Surgery, 34340 Capa/Istanbul, Turkey

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ABSTRACT

Background: Laparoscopic adrenalectomy has become the gold standard in most patients with adrenal tumors. It is unclear; however, at what size an adrenal neoplasm should be resected by means of an open or a laparoscopic approach. The aim of the present study was to compare the outcomes of laparoscopic adrenalectomy for large tumors with smaller tumors.

Methods: A prospective study of patients who underwent adrenalectomy during the period 2006–2009 was undertaken. The patients were divided into 2 groups according to the tumor size. Group 1 ($n = 29$) consisted of patients presenting tumors smaller than 5 cm in diameter; group 2 ($n = 31$) consisted of patients with tumors larger than 5 cm in diameter.

Results: Two of the 29 tumors in group 1 (6.8%) were malignant at final histology. However, 11 of the 31 tumors in group 2 (35.4%) were malignant. There were no significant differences between operating time and complications of groups 1 and 2. The intra-operative blood loss was significantly lower in group 1 than in group 2.

Conclusion: 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.

1. Background

Since the initial description of laparoscopic adrenalectomy (LA) in 1992 by Gagner et al.,[1] LA is today considered the first-choice treatment of most adrenal diseases and the indications of this technique have been greatly expanded.[2–5] Retrospective comparison studies have consistently shown the laparoscopic approach to have lower complication rates, less operative blood loss, less postoperative pain, less narcotic requirements, shorter hospital stays, earlier return to activity and diet, and lower overall costs than open adrenalectomy.[6–10]

Tumor size is usually considered an indicator of malignancy. Tumors larger than 5 cm in diameter are likely to be malignant but remain relatively insensitive and nonspecific.[11–13] It is uncertain if the laparoscopic resection of large potentially malignant adrenal tumors is appropriate due to concern over incomplete resection and local recurrence. For this reason, selection of those suitable for laparoscopy is practiced by many surgeons and this may bias outcomes. Some authors still suggest that patients with benign adrenal lesions larger than 5–6 cm should not be treated with LA because of the longer operative time, the elevated risk of bleeding due to the numerous vessels surrounding the neoplasia, and the risk of capsular disruption.[14–16] Several centers, on the other hand, demonstrate that large potentially malignant adrenal tumors with no radiological evidence of invasion may be treated safely and effectively through a laparoscopic approach.[11–13,17–19]

2. Aim of the study

The aim of the present study was to assess the safety of LA for large adrenal tumors and to compare the results of LA for tumors $\geq$5 cm with those <5 cm from a consecutive series of patients.

3. Patients and methods

3.1. Patients

In our Department of Surgery at the Istanbul Faculty of Medicine between June 2006 and January 2009 a total of 68 consecutive LA were performed in 60 patients: 52 unilateral and 8 bilateral. There were 44 women and 16 men with a mean age of 44.1 years (range 23–76 years). The patients were divided into 2 groups according to the tumor size. Group 1 ($n = 29$) consisted of patients presenting

* Corresponding author. Tel.: +90 212 5331784; fax: +90 212 6319771.
E-mail address: yerbil2003@yahoo.com (Y. Erbil).

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tumors smaller than 5 cm in diameter; group 2 ($n = 31$) consisted of patients with tumors larger than 5 cm in diameter. The study plan was reviewed and approved by our institutional ethical committee, and informed consent was obtained for all patients.

3.2. Pre-operative evaluation

Body mass index (BMI) was calculated as the ratio of weight (kg) divided by height (m^2). All patients underwent the following endocrine workup aimed to screen for pheochromocytoma, hyperaldosteronism, hypercortisolism, and virilizing or feminizing tumors. Computed tomography (CT) was used routinely to predict the benign or malignant status and size of the lesion. Tumor size was measured with the largest diameter of the mass on CT or magnetic resonance imaging (MRI). When local invasion was suspected on CT, MRI angiography was used to test for major vascular involvement. A diagnosis of possible adrenal carcinoma was based on the patient history and radiology findings. Radiological characteristics of malignancy included: tumor size larger than 6 cm, local invasion, irregular margins or tumor heterogeneity.

Patients with Cushing's lesions were prescribed appropriate steroid replacement to compensate for hypofunction of the adrenal gland(s). Patients with pheochromocytomas received appropriate pre-operative blockade with phenoxybenzamine and a β-blocker.

3.3. Inclusion and exclusion criteria

Indications for adrenalectomy included: hormone secreting tumors and all tumors >6 cm. Resection of non-functioning adrenal tumors (<6 cm) was indicated for patients with evidence of tumor growth on serial imaging. The presence of mixed hormonal secretion, virilization, or elevated dehydroepiandrosterone sulfate (DHEA-S) in the absence of radiologic evidence of malignancy was not a pre-operative contraindication to the LA. Patients who manifested pre-operative radiologic features of malignancy, such as tumor invasion of the surrounding structures, lymphadenopathy, or systemic metastases were performed open adrenalectomy and were excluded this study. Two open adrenalectomies were performed in the same period because of the evidence of extension into adjacent tissues necessitating a wide excision of adjacent infiltrated structures (adrenalectomy + nephrectomy + splenectomy).

3.4. Surgery

All adrenalectomies were performed by two surgeons. The LAs were performed by a transperitoneal flank approach in the lateral decubitus position. Access was achieved through 3 port sites in left-sided lesions and 4 in right-sided lesions, the fourth port needed for liver retraction. For right adrenalectomy, the right lobe of the liver is fully mobilized by division of the triangular ligament. With the liver retracted cephalad and medially rotated, the peritoneum overlying the right adrenal gland is dissected using electrocautery, showing the right adrenal vein. After the right adrenal vein is located, it is doubly clipped and cut. Occasionally, a vascular stapling device is used to control the adrenal vein. The remaining dissection is performed with vessel sealing system. All tumors were extracted in their entirety, along with the adrenal gland and the surrounding fatty (Fig. 1). They were collected in a plastic bag to allow detailed histomorphological classification. For left-sided resection, the splenophrenic, splenocolic, and splenorenal ligaments are divided using electrocautery. The spleen and pancreatic tail are then rotated medially. The peritoneal dissection is performed until the left renal vein is reached, exposing the adrenal gland and vasculature. The resection then proceeds as previously described for the right adrenal gland. Drainage was used routinely. Fragmentation of the gland was recorded. Operative time was defined as the time from skin preparation to closure of the skin incisions. Operative blood loss was measured from that collected in the suction device. All patients received prophylaxis for deep vein thrombosis. Nasogastric suction was not used postoperatively. Oral fluids were given on the next day.

Age, gender, BMI, indications for adrenalectomy, clinicopathological tumor characteristics, operating time, intra-operative blood loss, intra-operative complications, and conversion from laparoscopic to open adrenalectomy, postoperative complications, and hospital stay were recorded and compared these parameters in both groups.

3.5. Statistics

Data were analyzed using SPSS 11.0 for Windows. Results were expressed as means ± SD. Data comparisons were performed by Mann Whitney-*U* and chi-squared tests. Correlation analyses were performed using non-parametric Spearman's correlation and two-way analysis of variance tests. Study parameters that had non-Gaussian distributions were transformed to square root values. Results were considered statistically significant, when the two-tailed *p*-value was less than 0.05.

4. Results

4.1. Patient characteristics

Indications for laparoscopic adrenalectomy were nonfunctional tumor ($n = 28$), Cushing's syndrome ($n = 12$), pheochromocytoma ($n = 8$), aldosteronoma ($n = 6$), and Cushing's disease ($n = 6$). The mean tumor size was 5.4 ± 2.8 cm (range 2–17 cm). Twenty-five tumors were on the right side and twenty-seven on the left. The mean operating time was 91.7 ± 33 min (range 45–210 min) for unilateral LA and 199.4 ± 61 min (range 155–255 min) for bilateral LA. Intra-operative blood loss and postoperative hospital stay were 79 ± 109 ml (range 20–750) and 3.3 ± 2.3 days (range 2–15). The mean operating time of left-sided adrenalectomies (114.5 ± 37 min) was significantly higher than that of right-sided adrenalectomies (73.3 ± 31 min), ($p = 0.001$). The LAs were performed by the two surgeons experienced in endocrine and laparoscopic surgery. There was not a significant difference in intra-operative blood loss (70.4 ± 47 ml vs. 77 ± 144 ml) and operating times (87.6 ± 32 min vs. 93.2 ± 25 min) between the two surgeons. Twenty of our patients had previous abdominal surgery. No patient required a conversion to conventional open or hand-assisted surgery. There was no postoperative mortality. Complications occurred in 5 (8.3%) patients: pancreatic fistula (1), wound infection (1), respiratory infection (1), hemodynamic change (1) and capsular disruption (1).

4.2. The evaluation of the patients according to the tumor size

The mean ages were 45.4 ± 12 years in group 1 and 42.8 ± 12 years in group 2. The female/male ratios were 23/6 and 21/10 in groups 1 and 2, respectively. Mean tumor size was 3.5 cm in group 1 (2–5 cm) and 7.2 cm in group 2 (5–17 cm). There were no significant differences between age, gender, tumor localization, operating time, prior abdominal surgery, and complications of groups 1 and 2. The intra-operative blood loss was significantly lower in group 1 (52.7 ± 64 ml) than in group 2 (93.3 ± 130 ml) ($p = 0.001$) (Table 1).

Complications developed in 2 patients in the group with tumor size more than 5 cm. Capsular disruption in one patient with a 12 cm nonfunctional adenoma occurred at the end of the dissection and on final pathology, that patient found to have an adrenocortical

Fig. 1. Resected adrenal tumor with surrounding fatty (A) liposarcoma; (B) adrenocortical carcinoma; (C) malignant pheochromocytoma.

carcinoma. Hemodynamic change (labile intra-operative blood pressure) occurred in one patient with pheochromocytoma despite adequate pre-operative blockade with phenoxybenzamine and propranolol and blood transfusion was required for intra-operative bleeding. Three of 5 complications which were occurred were in the patient with tumor size less than 5 cm. These were pancreatic fistula, wound and respiratory infection. The patient developed pancreatic fistula that resolved spontaneously after 2 weeks.

Two of the 29 tumors in group 1 (6.8%) were malignant at final histology. However, 11 of the 31 tumors in group 2 (35.4%) were malignant. Malignant tumors were bilateral malignant pheochromocytoma in one case, adrenocortical carcinoma in three cases, liposarcoma in one case and adrenal metastases in eight patients. Twelve patients were classified as having nonfunctional adrenal tumors. No patient underwent pre-operative fine needle aspiration biopsy.

Table 1
Comparison of the groups.

Variable	Group 1 (5 cm<)	Group 2 (5 cm≥)	*p*
No. patients	29	31	–
Tumor size (cm)	3.5±	7.2 ± 2.9	0.001
Mean age (years)	45.4 ± 12	42.8 ± 12	NS
Male/female	23/6	21/10	NS
BMI (m^2/kg)	32.7 ± 6.2	27.5 ± 5.1	0.001
Left/Right	14/8	13/17	NS
Prior abdominal surgery (*n*)	7	5	NS
Operating time (min)	95.7 ± 38	85.6 ± 36	NS
Blood loss (ml)	52.7 ± 64	93.3 ± 130	0.001
No. complication (*n*)	3	2	NS
Hospital stay (day)	3.6 ± 2	3 ± 2	NS

Eight of the 13 patients had past histories of extra-adrenal malignancies (from lung carcinoma in seven cases and esophageal squamous cell carcinoma in the one patient). The difficulty of dissection, dense adhesions, and unusual and numerous retroperitoneal feeding vessels were not observed intraoperatively. At operation there was no evidence of local invasion or adenopathy. All of the adrenal glands were removed intact and had negative margins on pathologic examination. However, the one patient with ACC in whom there was capsular disruption of the tumor during dissection underwent.

4.3. Correlations

Strongly positive correlations were found between tumor size and intra-operative blood loss ($r = 0.521$, $p = 0.0001$). There were no correlations between tumor size and operating time. Significant positive correlations were also found between operating time and BMI ($r = 0.610$, $p = 0.0001$), Fig. 2.

4.4. Follow-up

The median follow-up for the entire group of patients was 18 months (range, 4–30 months). Table 2 depicts follow-up information on thirteen patients with pathologically proven malignancies. One patient with metastatic carcinoma presented with local recurrence and liver metastases 14 months after surgery and died. One patient with ACC had multiple metastases 6 months after surgery and died 12 months after. In both cases there was no evidence of tumor capsular rupture or spillage of tumor cells (Table 2).

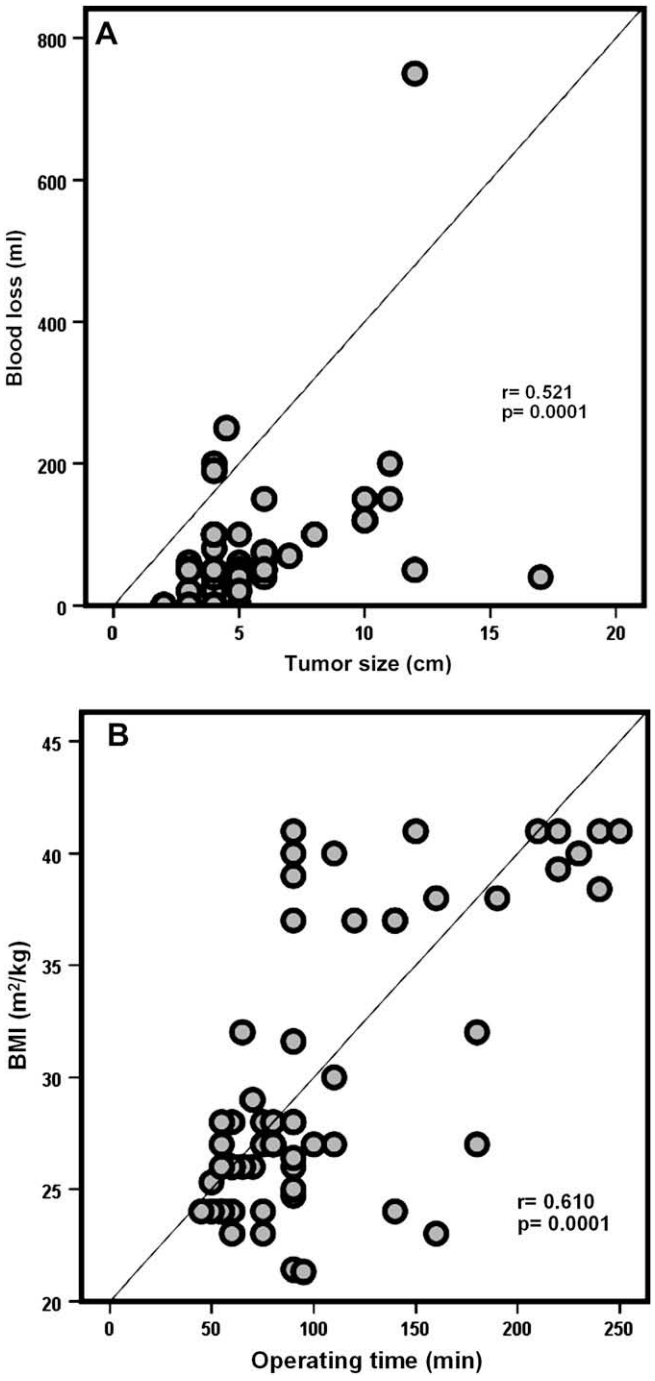

Fig. 2. Relationship between intra-operative blood loss and tumor size (A); BMI and operating time (B).

5. Discussion

LA has become the preferred method for the removal of benign functioning and non-functioning tumors of the adrenal gland. Despite the success of LA in patients with small adrenal tumors, there has been a reluctance to use this approach in patients with large adrenal tumors.[2–4]

Size is an important variable in predicting malignancy of an incidentally discovered adrenal mass. Tumors larger than 6 cm in diameter are likely to be malignant, however many adrenal adenomas are larger than 6 cm.[17–19] According to the NIH consensus statement for the management of the incidentally adrenal mass, the incidence of adrenocortical carcinomas increases from 2% in tumors <40 mm, to 6% in tumors 41–60 mm in size, to 25% in tumors >60 mm.[20] 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.[11–13] In our series, 11 of 31 adrenal tumors greater than 5 cm were malignant, whereas almost 64.6% of these large tumors were benign.

Larger tumor size, primary and metastatic disease, bilateral lesions or previous surgery in the adrenal region have been suggested limitation for laparoscopy by some investigators,[2,4,21] but these limitations depend on the surgeon's experience and skill. Although it is well known that the size cannot be considered as an absolute contraindication for LA, the maximum tumor size above which a laparoscopic approach is contraindicated has not been determined.[17–19] Several studies in the literature report removal of masses as large as 15 cm; however, because of the increased incidence of malignancy at this size and technical limitations of extraction, this surgery is rarely done.[18,19]

A diagnosis of possible adrenal carcinoma was based on the patient history and radiology findings. Imaging studies can help the surgeons to evaluate a malignant lesion; abdominal ultrasounds, CT and MRI can demonstrate irregular tumor margins, local invasion of the periadrenal tissue, heterogeneity, and hyperdensity.[22,23] CT was used routinely to predict the benign or malignant status and size of the lesion. Tumor size was measured with the largest diameter of the mass on CT or MRI. When local invasion was suspected on CT, MRI or CT angiography was used to test for major vascular involvement. None of the patients had pre-operative imaging studies that irregular tumor margins, tumor invasion of the surrounding structures, lymphadenopathy, or systemic metastases. However, 8 of the 13 patients had past histories of extra-adrenal malignancies. Our patients with ACC had pre-operative imaging studies that suggested malignant potential and pre-operative diagnosis was nonadenomatous lesions. We have used the pre-operative imaging rather than tumor size and selected our patients for laparoscopic adrenalectomy.

Today absolute contraindications for LA include tumors with gross local invasion and invasive adrenocortical carcinomas.[2,21] Computed tomography (CT) scan and CT angiography, as well as magnetic resonance (MR) imaging are recommended in the pre-operative workup of adrenal lesion to assess the presence of signs of malignancy or local invasion. These modalities can demonstrate irregular tumor margins, local invasion of the periadrenal tissue, heterogeneity, and hyperdensity, but these predictors of malignancy may also be seen in benign tumors. CT can predict a malign lesion when it has a high attenuation values (>10 HU units). MRI T2-weighted signal intensity is low in adenoma. CT and MRI characteristics of adrenal tumors are also used to help to determine their risk of malignancy but are not always conclusive.[22,23] The intra-operative 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.[17–19] If evidence of local invasion is present, it is recommended that the procedure be converted to a hand-assisted procedure, or the open technique can be used.[2,17,18] Our data show that patients with large tumors with no preoperative or intra-operative evidence of malignancy can undergo successful laparoscopic adrenalectomy.

With improved imaging techniques, only a small proportion of adrenal masses require percutaneous biopsy for diagnosis.[22,23] In a recent study by Harisinghani et al.,[24] the negative predictive value (NPV) of adrenal biopsies was shown to be between 98 and 100%. Percutaneous CT-guided adrenal biopsy is a relatively safe procedure in patients with a known extra-adrenal malignancy.

Tumor size is usually considered an indicator of malignancy.[11–15] It is unclear, however, at what size an adrenal neoplasm should be

Table 2
Follow-up of the patients with adrenal malignancies.

Patient no. and carcinoma	Initial diagnosis	Tumor size (cm)	Local recurrence	Distant metastasis	Survival (months)
1. Primary ACC	Nonfunctional tumor	10	–	–	alive (28)
2. Primary ACC	Nonfunctional tumor	6	+ (6 mo)	liver, lung	death (12)
3. Primary ACC	Nonfunctional tumor	13	–	–	alive (4)
4. Liposarcoma	Myelolipoma	17	–	–	alive (11)
5. Malign pheochromocytoma	Pheochromocytoma	8	–	–	alive (24)
6. Metastatic lung carcinoma	Nonfunctional tumor	5	+ (7 mo)	liver	death (14)
7. Metastatic lung carcinoma	Nonfunctional tumor	3	–	–	alive (24)
8. Metastatic lung carcinoma	Nonfunctional tumor	4	–	–	alive (18)
9. Metastatic lung carcinoma	Nonfunctional tumor	8	–	–	alive (20)
10. Metastatic lung carcinoma	Nonfunctional tumor	5	–	–	alive (12)
11. Metastatic lung carcinoma	Nonfunctional tumor	5	–	–	alive (30)
12. Metastatic lung carcinoma	Nonfunctional tumor	6	–	–	alive (22)
13. Metastatic SCC	Nonfunctional tumor	5	–	–	alive (5)

ACC: adrenocortical carcinoma; SSC: squamous cell carcinoma.

resected by means of an open approach or a laparoscopic approach. The fears that laparoscopic resection of large adrenal tumors may result in inadequate removal or capsular disruption of a malignant tumor and an increase in the risk of a local or port-site recurrence of the disease. Recurrences may due to the incomplete resection or capsular disruption of the tumor during dissection. These intra-operative complications are also observed during open surgery. What is most important is the ability of the surgeon to perform a safe and complete resection of the adrenal tumor, regardless of the size of the tumor.[11–15]

LA for primary and metastatic adrenal tumors is controversial. Some authors consider malignancy to be an absolute contraindication to laparoscopy.[2,11–14] However, for selected cases, some studies have demonstrated results similar to those for open surgery. Primary ACC is a rare malignancy and has a 5-year survival, ranging from 16 to 60%.[25–27] Even when patients have localized disease and complete tumor resection, systemic metastasis and local recurrences occur in at least two thirds of cases. One must keep in mind that recurrences are also observed after open adrenal surgery for stage I and II tumors. The main risk during laparoscopic or open adrenalectomy for ACC is capsular disruption. Once the capsula has been violated, there is a high risk of intra-abdominal neoplastic dissemination. LA is not yet considered standard treatment for ACC and metastases of the adrenal gland because of concerns regarding long-term outcome and the risk of tumor cell spillage.[2,25–28] We believe that longer follow-up is mandatory before definitive recommendation can be drawn about laparoscopic adrenalectomy in primary or metastatic adrenal malignant masses.

The laparoscopic resection of a large adrenal tumor can be technically challenging. Larger tumors have a larger surface to dissect and can require a longer operative time. The exposure also is trying because the space available in this area is limited. In our study, tumor size was not significant variable of operating time, whereas BMI was only independent significant variable of operating time. The patients who are overweight as in the patients with Cushing disease have an increased incidence of adipose tissue; excessive operating time is necessary to remove adrenal glands. Frequently, large masses have unusual and numerous retroperitoneal feeding vessels that require tedious dissection and result in more intra-operative blood loss. We also found that larger adrenal tumors are significantly associated with intra-operative blood loss.

6. Conclusion

There is still no consensus regarding the maximum tumor size for LA. If there is no evidence of the local invasion, large and potentially malignant adrenal tumors can be safely removed laparoscopically provided that the oncological surgical principles are observed.

Conflict of interest
The authors have no conflict interest.

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Ethical approval
Local ethical committee, Istanbul medical Faculty.

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