Feasibility of Laparoscopic Adrenalectomy for Large Pheochromocytomas

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ABSTRACT

Background and Objectives: The majority of surgeons consider large and potentially malignant pheochromocytomas an absolute contraindication for laparoscopic adrenalectomy (LA). The aim of this study was to evaluate the risks and outcomes of LA in patients with this anomaly.

Methods: Five patients (2 males, 3 females) with large (>6 cm) pheochromocytomas were selected. Preoperative investigation demonstrated no evidence of invasive carcinoma. All patients received alpha-blocker preparation for at least 20 days. Laparoscopic adrenalectomy via a lateral transperitoneal approach was performed in all cases.

Results: Patient’s median age was 48 years, and the median tumor size was 10.8 cm. No capsular disruption and no hypertensive crises occurred during the operation. The median operating time was 148 minutes and blood loss was <150 mL. Conversion to open adrenalectomy occurred in 2 patients owing to intraoperative evidence of carcinoma. No postoperative morbidity or mortality occurred. All patients are disease free after a median follow-up of 13 months.

Conclusions: In experienced hands, LA can be proposed for large and potentially malignant pheochromocytomas. Conversion to open adrenalectomy is mandatory if local invasion, capsular disruption, or technical difficulties are observed during the operation.

Key Words: Laparoscopic adrenalectomy, Pheochromocytoma, Large adrenal tumors.

INTRODUCTION

Since its introduction in 1991, laparoscopic adrenalectomy (LA) has rapidly become the procedure of choice for the surgical management of most adrenal tumors, and the indications for LA have expanded since its first description. However, the use of LA for pheochromocytomas is still controversial, and the role of this procedure continues to be undefined. Furthermore, surgeons were initially hesitant to resect pheochromocytomas laparoscopically because of the potential hemodynamic effects of catecholamine secretion during pneumoperitoneum and tumor manipulation. The development of preoperative localization, the improvement of pre- and perioperative pharmacologic and anesthetic management, combined with maturation of laparoscopic techniques have led to more patients with pheochromocytoma being safely cured laparoscopically.

On the other hand, for more surgeons, invasive adrenal carcinoma is an absolute contraindication for LA, and whether LA should be proposed for large (>6 cm) or potentially malignant tumors is questionable. The risk of malignancy increases with the size of pheochromocytomas, but the size does not reliably predict malignancy in pheochromocytomas with local disease only. The role of laparoscopic resection for pheochromocytoma remains to be examined. Some authors have demonstrated that the laparoscopic approach for pheochromocytomas yields results comparable to those of open resection. Others have reported series demonstrating the feasibility or results of LA for large and potentially malignant tumors. The aim of this study was to evaluate the risks and outcome of LA performed in our department with large (>6 cm) and potentially malignant pheochromocytomas.

METHODS

During the last 8 years, 48 adrenalectomies, 36 of which were LA, have been performed in our department in 47 patients. We selected 5 patients with large pheochromocytomas. In none of these patients did a preoperative investigation demonstrate invasive carcinoma or preoperative evidence of extraadrenal disease. The following data
were recorded: patient's age and sex, preoperative diagnosis, final size of tumor, intra- and postoperative complications, operation time, final histological diagnosis, and length of postoperative stay. All patients underwent a full endocrine and imaging evaluation.

The diagnosis of pheochromocytoma was based on elevated levels of vanillylmandelic acid and unexpected high levels of metanephrin or normetanephrin. The localization of the lesions was accomplished with high-resolution computed tomography (CT), magnetic resonance imaging (MRI), and radio-labeled meta-iodobenzylguanidine (MIBG) to exclude extraadrenal disease. All 5 patients received preoperative preparation with alpha-blockers (phenoxybenzamine), and in 3 of them a combination of beta-blockers was administered for treatment of tachycardia. Preoperatively, phenoxybenzamine was administered in a daily dose of 20 mg to 40 mg. The minimal duration of preoperative administration was 20 days, and the maximum was 30 days to obtain sufficient hemodynamic correction and blood volume expansion. Restoration of intravascular volume was determined by the stabilization of arterial pressure for at least 2 weeks plus the absence of orthostatic hypotension and a 10% decrease in hematocrit (Hct) values.

All these operations were performed by a single surgeon. The preferable surgical approach was the lateral transperitoneal laparoscopic procedure, placing the patient in the lateral decubitus position with the affected side up. This approach offers a large working space, easier removal of large tumors, and a facile conversion to open adrenalectomy if necessary, according to our department experience, which is over 130 adrenalectomies in the last 25 years. The incision in case of conversion was placed at the line formed by the 3 anterior trocar sites. During surgery, blood pressure was strictly monitored by arterial line, and intravenous alpha- and beta-blockade was administered as necessary. An abdominal drain was placed in all patients for 20 hours to 24 hours on the adrenal bed.

RESULTS

Five patients with large pheochromocytomas were analyzed (Table 1). The cohort included 2 males and 3 females with a median age of 48 years (range, 29 to 64). The localization of pheochromocytomas was 4 in the right side and 1 in the left, the smallest located left. The procedures included 4 right and 1 left laparoscopic adrenalectomies.

| No | Sex | Age | Date  | Tumor Localization | Tumor Size (cm) | Operation Time (Min) | Conversion to Open | Pathology Report | Pathology Report | Postop Stay (Days) |
|----|-----|-----|-------|-------------------|-----------------|----------------------|-------------------|------------------|-----------------|------------------|
| 1  | ♂   | 48  | 9/03  | right            | 8.8             | 160                  | no                | benign           |                 | 2                |
| 2  | ♀   | 44  | 10/03 | right            | 10.8            | 170                  | no                | benign           |                 | 2                |
| 3  | ♀   | 54  | 5/04  | left             | 6.5             | 115                  | yes               | Ca              |                 | 5                |
| 4  | ♀   | 64  | 8/04  | right            | 15              | 110                  | yes†              | benign           |                 | 5                |
| 5  | ♂   | 29  | 3/05  | right            | 13              | 185                  | no                | benign           |                 | 3                |

*The adrenal gland had brown pigmentation, and the tumor was paraganglioma with local invasion behind the tail of the pancreas.
†Conversion to open was decided upon after ligation of the adrenal vein because of intraoperative evidence of retroperitoneal invasion.

| Table 2. Tumor Characteristics |
|-------------------------------|
| No   | Patient | CT or MRI Size (cm) | Postexcision Size (cm) | Pathology Report Size (cm) | Postexcision Weight (g) | Pathology Report Weight (g) |
|-----|---------|---------------------|------------------------|--------------------------|------------------------|---------------------------|
| 1   | ♂       | 7×5.5               | 8.8×6.5                | 6.2×5                    | 90                     | 65                        |
| 2   | ♀       | 8.5×6               | 10.8×7.5               | 7.3×5.5                  | 110                    | 75                        |
| 3   | ♀       | 5.5×4.5             | 6.5×5.2                | 4.5×3.7                  | 65                     | 50                        |
| 4   | ♀       | 13×9.5              | 15.2×12.1              | 12×8.5                   | 265                    | 205                       |
| 5   | ♂       | 10.5×8.2            | 13×9.5                | 10×8                     | 215                    | 168                       |
Postexcision tumor size measured 6.5 cm to 15.2 cm (median, 10.8), which represents the real one, but the maximal diameter at CT or MRI and on histological examination was significantly different. So, at CT and MRI the size of the lesions was estimated from 5.5 cm to 13 cm, which means a difference of 20% especially for the right-sided ones. On the other hand, the maximum diameter on histological examination was about 15% to 25% smaller (4.5 cm to 12 cm) due to severe blood loss after tumor removal and dehydration due to formaldehyde solution (Table 2).

The first step of LA in all patients with right-sided lesions was dissection of the adrenal vein from its medial attachment from the inferior vena cava and then successful ligation of the adrenal vein with staples, which was rather easily recognized at the front surface of the mass. The diameter of the adrenal vein was about 2 mm to 5 mm, which is very small for these large pheochromocytomas.

On the contrary, the veins of the adrenal bed formed a network of very large vessels draining behind the vena cava prespinally or to the renal vein. Accordingly, this was the most difficult step of the excision with the highest risk of hemorrhage or capsular disruption. The mobilization of the gland from the inferolateral site to its anteromedial boundaries was very helpful and time saving, with minimal blood loss.

Vessel ligation performed through ultrasound scissors or endoscopic gastrointestinal approximator (endoGIA) stapler or laparoscopic clips even with monopolar electro diathermy wherever appropriate. No capsular disruption occurred during the tumor dissection, and the lesions were resected en block with the adrenal cortex. The median operating time was 148 minutes (range, 100 to 185). The median blood loss was >150 mL (range, 80 to 300). No hypertension storm (systolic blood pressure >220 mm Hg), tachycardia (>110 beats/min), before tumor removal, or severe hypotension, after vessel ligation, occurred, which was the result of the prolonged (>20 days) and sufficient hemodynamic correction.

Conversion to open adrenalectomy was performed in 2 patients due to intraoperative evidence of malignancy. In the first patient after the adrenal excision, which was large (6 cm) and macroscopically had brown pigmentation, a coexisting invasive large paraganglioma was identified (3rd in Table 1). Histological examination revealed brown pigmentation of the adrenal gland, and malignant pheochromocytoma of resected paraganglion with a small invasion of the capsule and attached fat. In the second patient after ligation of the adrenal vein, there was evidence of vena cava and retroperitoneal invasion with major technical difficulties, so conversion to open adrenalectomy was decided upon (4th in Table 1). Surprisingly, the pathology report provided no signs of malignancy in the latter case.

There was no postoperative morbidity or mortality. All patients were postoperatively normotensive, and intravenous administration of fluids lasted from 24 hours to 36 hours. The median length of stay was 3.5 days (range, 2 to 5). All patients are disease free after a median follow-up of 13 months.

**DISCUSSION**

Since its initial report, laparoscopic adrenalectomy has become the preferred approach for surgical adrenal disease. Although pheochromocytoma was initially considered a contraindication to laparoscopy, LA is evolving as the standard of care. Increasing numbers of series support the safety and efficacy of LA for pheochromocytoma. The combination of pneumoperitoneum and the catecholamine effects of pheochromocytomas during laparoscopy present a unique perioperative management challenge to maintain hemodynamic stability. It is well known that during laparoscopy carbon dioxide pneumoperitoneum increases intraabdominal pressure and thus reduces systemic venous return. Furthermore, pneumoperitoneum may increase sympathetic tone and thus increase peripheral vascular resistance and operative risk of hemodynamic instability.

Inabnet et al directly compared intraoperative hemodynamic parameters for 22 patients undergoing adrenalectomy for pheochromocytoma by open and laparoscopic approaches. There was no significant change in cardiac index or left ventricular work, but they found increased numbers of intraoperative hypertensive events for patients undergoing laparoscopy. The majority of authors agreed that the adequate preoperative preparation with alpha-blockers, for sufficient blood volume correction, combined with careful manipulation of the tumor, correct regulation of gas pressure (8 to 13 mm Hg) and successful management of problems by an experienced anesthetic team can reduce the release of adrenergic substances.

It appears that a period of 10 days to 12 days for preoperative preparation with alpha-blockers is inadequate to restore blood volume. In large pheochromocytomas, we tried phenoxybenzamine administration for at least 20 days in low doses (20 mg to 40 mg). Surprisingly, a significant drop in Hct occurred (8% to 10%) in all cases, indicating intravascular volume restoration.
We believe that the importance of adrenal vein early ligation in large and right-sided pheochromocytomas is a myth. The adrenal vein in these lesions was always found at the front side of the mass and surprisingly not large in size (2 mm to 5 mm). So after the recognition and dissection of the inferior vena cava, the preparation and ligation of the adrenal vein was rather easy. But it was not the sole vein. Particularly in all right-sided tumors, we observed that veins of the adrenal bed formed a remarkable network of very large vessels draining behind the vena cava prespinally or to the renal vein. This was the most difficult step of the excision with the highest risk of hemorrhage or capsular disruption. The mobilization of the gland from the inferolateral site to its anteromedial boundaries was very helpful and time saving, with minimal blood loss, and no capsular disruption. On the other hand, no severe hypotensive episode occurred after the total mass excision due to adequate intravascular volume expansion.

The diagnosis of malignant pheochromocytoma can only be made reliably by the findings of local invasion, nodal or distal metastasis.\textsuperscript{13} No accurate histologic criteria for the diagnosis existed, and 2.5% to 26% of pheochromocytomas are malignant and are only identified during follow-up.\textsuperscript{10} Malignant pheochromocytoma is more likely in extraadrenal locations (30% to 40%) and tumors of 6 cm or larger.\textsuperscript{14} Many surgeons have traditionally used a size greater than 6 cm as a contraindication to laparoscopic resection. Other groups have resected lesions up to 12 cm without problems.\textsuperscript{3,4} Some studies favor the opinion that laparoscopy can also be indicated for large and potentially malignant tumors.\textsuperscript{5}

Our data support this theory, and the size of the tumor has not been used as a criterion for exclusion of LA. In cases with no preoperative evidence of extraadrenal disease, the possibility of malignancy can be proved only intraoperatively, if evidence of local invasion is found. So, in our series, all patients underwent LA, and in 2 patients there was evidence of local invasion (of the smaller and larger lesions). The pathology report proved malignancy in the smaller lesion (paraganglioma).

**CONCLUSION**

In experienced hands, LA can be proposed for large pheochromocytomas without preoperative signs of malignancy with no difference in postoperative morbidity or mortality. Conversion to open adrenalectomy should be performed if local invasion is observed during surgery or technical difficulties are encountered.

**References:**

1. Gagner M. Laparoscopic adrenalectomy. *Surg Clin North Am.* 1991;76:523–537.
2. David G, Yoav M, Gross D, Reissman P. Laparoscopic adrenalectomy. Ascending the learning curve. *Surg Endosc.* 2004;18:771–773.
3. Kalady MF, McKinlay R, Olson JA, et al. Laparoscopic adrenalectomy and pheochromocytomas. *Surg Endosc.* 2004;18:621–625.
4. Brunt LM, Lairmore TC, Doherty GM, Quasebarth MA, DeBenedetti M, Moley JF. Adrenalectomy for familial pheochromocytoma in the laparoscopic era. *Ann Surg.* 2002;235:713–720.
5. Henry JF, Sebag F, Jacqbone M, Mirallie E. Results of laparoscopic adrenalectomy for large and potentially malignant tumors. *World J Surg.* 2002;26(8):1043–1047.
6. Shen WT, Sturgeon C, Clark OH, Duh QY, Kebebew E. Should pheochromocytoma size influence surgical approach? A comparison of 90 malignant and 60 benign pheochromocytomas. *Surgery.* 2004;136(6):1129–1137.
7. Mobius E, Nies C, Rotdmund M. Surgical treatment of pheochromocytomas: laparoscopic or conventional? *Surg Endosc.* 1999;13:35–39.
8. Wells SA, Merke DP, Cutler Jr GB, Norton JA, Lacroix A. Therapeutic controversy: the role of laparoscopic surgery in adrenal disease. *J Clin Endocrinol Metab.* 1998;83:3041–3049.
9. Novitsky YW, Czerniach DR, Kercher KW, Perugini RA, Kelly JJ, Latwin DE. Feasibility of laparoscopic adrenalectomy for large adrenal masses. *Surg Laparosc Percutan Tech.* 2003;13(2):106–110.
10. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing’s syndrome and pheochromocytoma. *N Engl J Med.* 1992;327:1035.
11. Kazaryan AM, Kuznetsof NS, Shulutko AM, Beltsevich DG, Edwin B. Evaluation of endoscopic and traditional open approaches to pheochromocytoma. *Surg Endosc.* 2004;18:937–941.
12. Inabnet WB, Pitre J, Bernard D, Chapuis Y. Comparison of the hemodynamic parameters of open and laparoscopic adrenalectomy for pheochromocytoma. *World J Surg.* 2000;24:574–578.
13. Sturgeon C, Kebebew E. Laparoscopic adrenalectomy for malignancy. *Surg Clin N Am.* 2004;84:755–774.
14. Linnoila RI, Keiser HR, Steinberg SM, et al. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol.* 1990;21(11):1168–1180. Vol. 11, No. 1