World J Surg (2008) 32:840–844
DOI 10.1007/s00268-007-9327-5

World Journal of Surgery

Safety of Laparoscopic Adrenalectomy in Patients with Large Pheochromocytomas: A Single Institution Review

Giuseppe Ippolito · Fausto F. Palazzo · Frederic Sebag · Abhijit Thakur · Mariya Cherenko · Jean-François Henry

Published online: 7 December 2007

Abstract
Background Laparoscopic adrenalectomy is the procedure of choice for small adrenal tumors, but some concerns have been voiced when this approach is adopted for larger tumors and pheochromocytomas. The aim of this study was to examine the results of the laparoscopic resection of large pheochromocytomas.
Methods A retrospective review of adrenalectomies performed for adrenal pheochromocytomas >6 cm in diameter. We compiled and analyzed the early operative complications, histologic findings, and cure rates with a minimum of 1 year of follow-up after surgery.
Results From 1996 to 2005, a total of 445 laparoscopic adrenalectomies were performed in our institution using the anterolateral transperitoneal approach. From this series we identified 18 procedures for pheochromocytomas with an average diameter on imaging of 78.2 mm (range 60–130 mm). All patients were rendered safe with a standard departmental protocol involving calcium-channel blockade initiated at least 2 weeks prior to surgery. The average peak intraoperative blood pressure was 187 mmHg. Capsular disruption occurred in two cases. One patient required an intraoperative blood transfusion due to intraoperative blood loss. No immediate conversions to an open procedure were required, but one patient underwent a delayed laparotomy for hematoma formation. Histologically, four of the adrenal tumors displayed evidence of vascular invasion. Biochemical cure was achieved in all patients after a median follow-up of 58 months (16–122 months).
Conclusions Laparoscopic adrenalectomy appears to be a safe and effective approach for large pheochromocytomas when no preoperative or intraoperative evidence of local invasion is present.

Adoption of the laparoscopic approach has reduced the morbidity and length of stay following adrenalectomy [1]. Although there are no large randomized controlled trials that have compared open versus laparoscopic adrenalectomy, numerous case series have demonstrated the safety and efficacy of laparoscopic adrenalectomy [2, 3], and it has become the standard of care for the operative treatment of both functioning and nonfunctioning adrenal tumors. Given the technical challenge associated with the surgical excision of large adrenal tumors and pheochromocytomas, initially there were some reservations about using the laparoscopic approach for these tumors. However, as experience with the laparoscopic approach has increased, reports have appeared demonstrating the feasibility of laparoscopic resection of adrenal tumors > 6 cm in diameter, and eventually the same occurred with small pheochromocytomas. However, few reports have documented the laparoscopic approach for large pheochromocytomas with a diameter of ≥6 cm [4, 5].

The concerns surrounding the laparoscopic approach to large pheochromocytomas arise because of the technical challenge they may present, the intraoperative instability that follows the discharge of hormones secondary to manipulating the tumor, and the risk of malignancy in a large pheochromocytoma. The aim of this study was to

Paper Presented at the ISW Congress.

G. Ippolito (✉) · F. Sebag · A. Thakur · M. Cherenko · J.-F. Henry
Department of Endocrine Surgery, La Timone Hospital, 264 Rue Saint-Pierre, 13385 Marseille, France
e-mail: giuseppe_ippolito@yahoo.it

F. F. Palazzo
Department of Surgery, Hammersmith Hospital, London, UK

evaluate the safety and efficacy of a laparoscopic procedure for large pheochromocytomas and the median-term outcomes after surgery.

Methods

A retrospective review was performed on patients who had a pheochromocytoma and underwent surgery in our department between 1996 and 2005. Large pheochromocytomas—tumors with a diameter of ≥6 cm on preoperative imaging—were selected if a minimum of 1 year of follow-up after surgery was available.

The diagnosis of pheochromocytoma was confirmed by clinical features combined with evidence of elevated plasma methoxyamines (normal <2000 pg/ml) and urine metanephrines (normal <2000 nmol/24 hr). In addition to radiologic imaging [computed tomography (CT) and/or magnetic resonance imaging (MRI)], we routinely performed scintigraphic studies with ^{131}I-metabenzylguanidine (MIBG) for large pheochromocytomas to rule out multiple lesions and metastases [6]. During the preoperative workup, evidence of malignancy (e.g., local invasion, metastases) was a contraindication to a laparoscopic approach.

Preoperative preparation consisted in a minimum of 2 weeks of calcium-channel blockade (nicardipine 20–90 mg/day), which was continued until the induction of general anesthesia. Intraoperatively, short-acting drugs (including sodium nitroprusside and esmolol) were added to prevent acute hypertensive episodes by vasodilatation and for heart rate control, respectively. Intravenous fluids and epinephrine were given when the systolic blood pressure fell below 90 mmHg after tumor removal.

All procedures were performed via a transperitoneal anterolateral laparoscopic approach. The technique consisted of vascular dissection of the gland without previous control of the adrenal vein aimed at systematic devascularization of the tumor with minimal manipulation of the adrenal gland itself. The adrenal glands were resected with periadrenal fat to allow safe tumor margins. All specimens were placed in an Endocatch bag (U.S. Surgical, Norwalk, CT, USA) and cut into larger fragments to allow excision via a laparoscopic port. Drainage was used selectively.

Postoperatively, all patients received prophylaxis for deep vein thrombosis and were monitored in a high dependency or intensive care unit for the first postoperative day. During follow-up, the criteria of cure were documented by clinical and biochemical evaluation postoperatively and yearly thereafter. In selected patients (e.g., when capsular disruption had occurred or in cases of apparently nonfunctioning pheochromocytoma) radiologic and scintigraphic studies were performed.

Results

From 1996 to 2005 we performed 445 laparoscopic adrenalectomies, 96 of which were pheochromocytomas. Altogether, 18 (19%) large pheochromocytomas were found in 17 patients (7 men, 10 women) with a mean age of 48 years (25–85 years). There were 16 unilateral pheochomocytomas and one bilateral pheochromocytoma. None of the 16 patients who presented with unilateral disease had a history suggestive of inherited disease. The patient with bilateral pheochromocytomas had negative genetic testing for multiple endocrine neoplasia type 2, von Hippel-Lindau disease, and pheochromocytoma/paraganglioma syndrome.

The clinical presentation consisted in hypertension requiring treatment (eight patients), hypotension (two patients), and incidentally identified tumors with no symptoms suggestive of catecholamine excess (seven patients). Hypertensive patients presented an average of 50-fold elevation (range 0–150) above the upper limit of plasma methoxyamines and 13-fold (range 0–35) increase in urinary metanephrines. One patient had negative biochemical screening for catecholamine secretion, and the diagnosis of pheochromocytomas was based on histologic evaluation. Nonhypertensive patients presented an average of 24-fold elevation (range 2–86) above the upper limit of plasma methoxyamines and 18-fold (range 2–52) increase in urinary metanephrines. In total, 7 lesions were left-sided, and 11 involved the right adrenal gland. On imaging, the average size was 78.2 mm (range 60–130 mm). On CT scans, various degrees of cystic parenchymal degeneration were found in 12 patients. In 16 patients MIBG showed results concordant with those of radiologic imaging with no additional foci of disease (Fig. 1).

At surgery, the average highest systolic blood pressure (SBP) was 187 mmHg (range 150– 260 mmHg), and the average lowest SBP was 94 mmHg (range 60–100 mmHg). Intraoperative hypertension (SBP >170 mmHg) occurred in three patients at insufflation and in two during manipulation of the tumor. Three of these patients had preoperative hypertension; the remaining two were normotensive. All were well controlled with intravenous vasodilators and cessation of tumor manipulation. Intraoperative hypotension (SBP <90 mmHg) occurred in three patients, each of whom responded to volume infusion and/or infusion of vasopressors. Capsular disruption occurred in two patients; and intraoperative bleeding required a blood transfusion in one. All these patients had left-sided lesions. No conversions were required. The average operating time was 136 minutes (range 95–305 minutes). There was no mortality. One patient with intraabdominal hematoma secondary to bleeding from the left renal vein required open reexploration. Postoperatively, two patients experienced hypotension

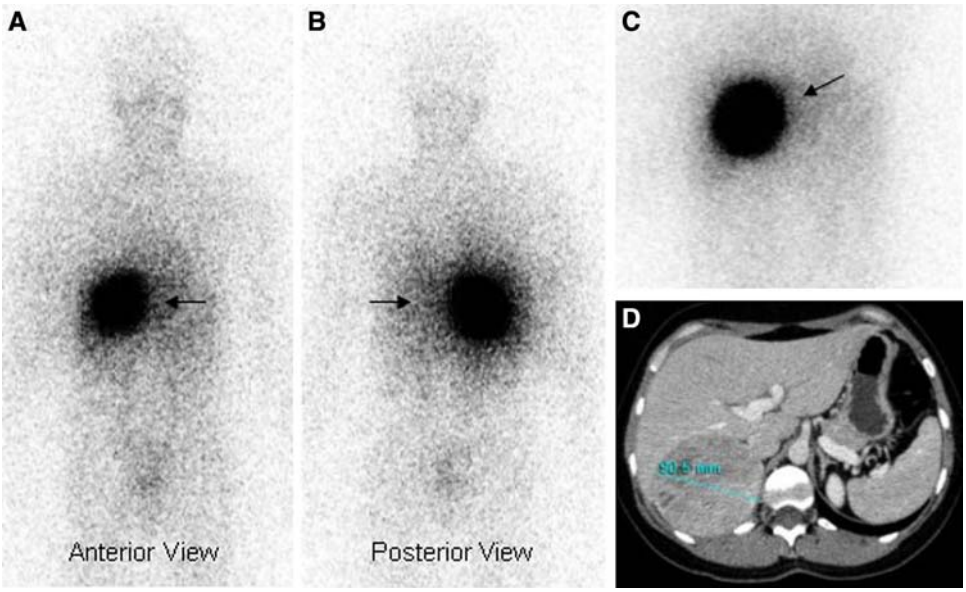

Fig. 1 Preoperative workup for a large pheochromocytoma. Abdominal computed tomography (CT) scan (**D**) identified a right-sided large pheochromocytoma in a 44-year-old man, and ^{131}I-MIBG scans (**A**–**C**) ruled out other associated localizations. *Arrows*, right adrenal tumor uptake

(SBP <90 mmHg) and required administration of intravenous fluids.

The specimens had a median weight of 105 g (range 39–222 g). Histologically, pheochromocytoma was confirmed in all cases. Cystic parenchymal degeneration (e.g., cyst, hemorrhage, or necrosis) was found in 12 patients. Four lesions displayed vascular invasion: Direct extension into the lumen of a capsular vessel was identified in two patients. Tumor nests covered by endothelium were identified in two other patients in whom no capsule was identified; and the pathologist was unable to categorize this criterion.

The average length of hospital stay was 5.5 days (range 4–10 days).

Seven patients taking antihypertensive drugs before operation were completely withdrawn by a month following surgery. One patient remained hypertensive but needed a single antihypertensive drug instead of three. Biochemical cure was achieved in all patients, as reflected by normal urinary metanephrines after a median follow-up of 58 months (16–22 months). One year after surgery, the two patients with capsular disruption (Fig. 2) and the patient with a nonsecreting pheochromocytoma underwent investigations by CT and MIBG that confirmed the completeness of the resection and the absence of macroscopic recurrences. The patients displaying vascular invasion at histology showed no evidence of recurrence at 2 to 8 years of follow-up.

Discussion

The approach to adrenal disorders requiring surgical resection was revolutionized in 1992 with the introduction of laparoscopic adrenalectomy [7]. Numerous reports have consistently demonstrated a decreased hospital stay and an earlier return to normal activities as well as a decrease in postoperative analgesics and lower late morbidity in

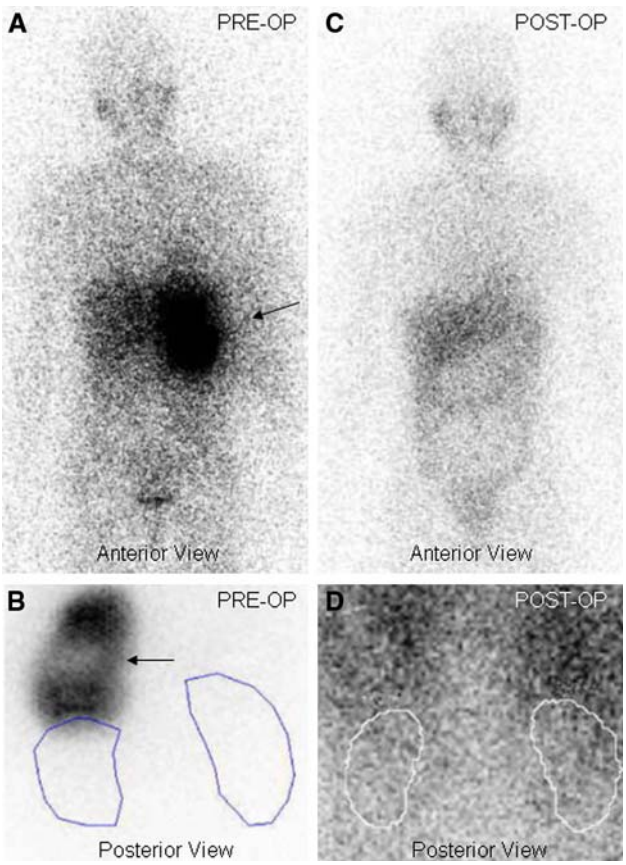

Fig. 2 Follow-up of a patient with intraoperative capsular disruption. The patient, operated on for a left-sided large pheochromocytoma (**A, B**, *arrows*), experienced intraoperative capsular disruption. At 1 year after surgery, an MIBG scan did not identify any residual tumor uptake (**C**, **D**)

patients who have undergone the laparoscopic procedure [2, 3]. Although laparoscopic adrenalectomy is now widely accepted as the procedure of choice for lesions <6 cm in diameter, its adoption for large pheochromocytomas has raised some concerns. The contentiousness revolves around the technical challenge of the procedure, the intraoperative hemodynamic instability due to the discharge of hormones during manipulation of large pheochromocytomas, and a higher rate of malignancy associated with large pheochromocytomas.

The technical feasibility of laparoscopic adrenalectomy for large pheochromocytomas is beyond doubt [4, 5]. Right-sided tumors may be technically more challenging because of the operating space, which is limited by the liver with the inferior vena cava compressed and displaced anteriorly by the tumor. However, our complications occurred in patients with left-sided tumors. No significant difference in complication rates have been reported in small compared to large laparoscopically resected pheochromocytomas [5]. However, capsular disruption, which is a reflection of technical difficulty, occurred twice in our series. The same can also be said of intraoperative bleeding, which occurred in one patient. An internal audit has shown the departmental complication rate for all adrenal surgery to be 7.5% and 10.7% for endoscopic and open procedures, respectively, and up to 10.3% in patients following a laparoscopic adrenalectomy for a pheochromocytoma <6 cm in diameter [8, 9].

In the current study of large pheochromocytomas, complications occurred in 4 of the 17 patients. Although conversion to an open procedure may not be considered a complication, it is more likely to occur in patients with a large tumor and with pheochromocytomas than in those with other pathologies [10].

Management of hemodynamic instability in patients with a large pheochromocytoma can be particularly problematic. Preoperatively, no differences are reported between patients taking antihypertensive drugs before surgery for small or large pheocromocytomas [5]. We observed hypertension in 8 of 17 patients with large pheochromocytomas (the same incidence reported for small pheochromocytomas [5]), and in most cases plasma methoxyamine and urine metanephrine values in large pheochromocytomas of hypertensive and normotensive patients were indistinguishable. It is reported that about 70% of pheochromocytomas >6 cm in diameter are cystic, confirming that cystic degeneration correlates with tumor diameter [11]. In these series, cystic parenchymal degeneration estimated by preoperative CT scanning were found in 12 of 17 patients. It has been hypothesised that central necrosis leads to a loss of functioning tumor tissue in large pheochromocytomas [12]. Large cystic tumors may present with large quantities of urinary catecholamine metabolites but with near-normal circulating plasma catecholamines, a reflection of the tendency of these tumors to release mainly metabolized catecholamines into the circulation; this is reflected by a relatively high ratio of metabolites to free catecholamines found in the urine [13].

Intraoperatively, we observed hemodynamic instability in both hypertensive and normotensive patients. The intraoperative instability follows the discharge of hormones secondary to manipulation of the tumor, which occurs during both open and laparoscopic procedures [14]. In laparoscopic procedures, tumor manipulation and intraabdominal insufflation may increase plasma norepinephrine and epinephrine levels at least 10-fold [14, 15], causing hemodynamic instability in pheochromocytomas. Hemodynamic instability may occur despite early adrenal vein ligation [15], probably due to the extensive vascularity of pheochromocytomas. In large pheochromocytomas, our surgical strategy is to perform a vascular dissection of the gland without previous control of the adrenal vein, aimed at the systematic devascularization of the tumor with minimal manipulation of the adrenal gland itself. Indeed, spontaneous or evoked crises in blood pressure can occur without additional increases in the already elevated norepinephrine in pheochromocytomas [16, 17]. This underlines the importance of preoperative preparation with vasodilatory drugs in all patients with pheochromocytomas and the input of an experienced anesthesia team.

Malignancy is reported in 6.5% to 13.1% of pheocromocytomas [18, 19]. A trend toward a higher rate of malignancy has been suggested for large pheochromocytomas [20]. In a large series with long-term follow-up, large tumors have been shown to have a significant tendency to exhibit malignant behavior [19]. Recurrences following open resections have been reported in previously diagnosed benign pheochromocytomas after decades [19, 21]. Because morcellation reduces the available information about capsular and vascular invasion, it has been suggested that the specimen be inked prior to morcellation and extraction [22]. However, malignant behavior is in any case difficult to predict histologically in pheochromocytomas; and in the absence of recurrence, the diagnosis of malignancy is challenging. As in other endocrine tumors, malignant features such as vascular and capsular invasion, nuclear atypia, and hyperchromatism can be found in benign as well as in malignant pheochromocytomas [23]. Spread of tumor cells into anatomic areas where there should be no embryologic residue of chromaffine tissue is the most reliable criterion of true malignancy. Indeed, distant and nodal metastases are most frequently the cause of recurrence following pheochromocytoma surgery [21, 24]. The incidence of local recurrence in laparoscopically resected malignant pheochromocytomas is not known. In large solid adrenal tumors without pre- or intraoperative evidence of malignancy,

laparoscopic resection is unlikely to have deleterious effects on long-term outcome even when malignancy is later diagnosed or suggested by histologic analysis of the specimen [25]. Indeed, it may be argued that the excellent magnified view, fine dissection, and minimal manipulation provided by the laparoscopic approach offers a chance of complete resection of adrenal tumors and therefore a lower risk of recurrence in the event of resection of a preoperatively undiagnosed malignant lesion.

Postoperative biochemical cure is reported to be the same for both small and large pheochromocytomas, and lifetime follow-up is advised with yearly biochemical screening in both cases [21]. Pheochromocytoma specimen size over the last 50 years appears to be decreasing with a statistically significant decrease of more than 50% in tumor volume probably due to earlier diagnosis [21]. Hence, it can be envisaged that the earlier diagnosis and resection of pheochromocytomas should decrease the rate of malignancy in pheochromocytomas over the next few years [21]. For the remaining late diagnoses of large pheochromocytomas, laparoscopy remains a reasonable option on the proviso that complete resection is technically feasible and there is no evidence of local invasion. Because pheochromocytomas remain the most challenging adrenal tumor to approach laparoscopically, independent of its size, it would be appropriate that the surgery be performed by an appropriately trained and experienced surgeon, and lifetime follow-up is recommended.

References

1. Dudley NE, Harrison BJ (1999) Comparison of open posterior versus transperitoneal laparoscopic adrenalectomy. Br J Surg 178:50–53
2. Jacobs JK, Goldstein RE, Geer RJ (1997) Laparoscopic adrenalectomy: a new standard of care. Ann Surg 225:495–501
3. Gagner M, Pomp A, Heniford BT, et al. (1997) Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. Ann Surg 226:238–246
4. Kercher KW, Novitsky YW, Park A, et al. (2005) Laparoscopic curative resection of pheochromocytomas. Ann Surg 241:919–926
5. Wilhelm SM, Prinz RA, Barbu AM, et al. (2006) Analysis of large versus small pheochromocytomas: operative approaches and patient outcomes. Surgery 140:553–559
6. Taïeb D, Sebag F, Hubbard JG, et al. (2004) Does iodine–131 meta-iodobenzylguanidine (MIBG) scintigraphy have an impact on the management of sporadic and familial phaeochromocytoma? Clin Endocrinol (Oxf) 61:102–108
7. Gagner M, Lacroix A, Bolte E (1992) Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. N Engl J Med 327:1033
8. Henry JF, Sebag F, Iacobone M, et al. (2002) Lessons learned from 274 laparoscopic adrenalectomies. Ann Chir 127:512–519
9. Henry JF, Defechereux T, Raffaelli M, et al. (2000) Complications of laparoscopic adrenalectomy: results of 169 consecutive procedures. World J Surg 24:1342–1346
10. Shen WT, Kebebew E, Clark OH, et al. (2004) Reasons for conversion from laparoscopic to open or hand-assisted adrenalectomy: review of 261 laparoscopic adrenalectomies from 1993 to 2003. World J Surg 28:1176–1179
11. Ito Y, Obara T, Yamashita T, et al. (1996) Pheochromocytomas: tendency to degenerate and cause paroxysmal hypertension. World J Surg 20:923–926
12. Atuk NO, Teja K, Mondzelewski P, et al. (1977) Avasucular necrosis of pheochromocytoma followed by spontaneous remission. Arch Intern Med 137:1073–1075
13. Crout JR, Sjoerdsma A (1964) Turnover and metabolic of catecholamines in patients with pheochromocytoma. J Clin Invest 43:94–102
14. Fernandez-Cruz L, Taura P, Saenz A, et al. (1996) Laparoscopic approach to pheochromocytoma: hemodynamic changes and catecholamine secretion. World J Surg 20:762–768
15. Flavio Rocha M, Faramarzi-Roques R, Tauzin-Fin P, et al. (2004) Laparoscopic surgery for pheochromocytoma. Eur Urol 45:226–232
16. Bravo EL, Tarazi RC, Gifford RW, et al. (1979) Circulating and urinary catecholamines in pheochromocytoma: diagnostic and pathophysiologic implications. N Engl J Med 301:682–686
17. Bravo EL, Tagle R (2003) Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev 24:539–553
18. Thompson LD (2002) Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol 26:551–566
19. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, et al. (1999) Clinical experience over 48 years with pheochromocytoma. Ann Surg 229:755–764
20. Shen WT, Sturgeon C, Clark OH, et al. (2004) Should pheochromocytoma size influence surgical approach? A comparison of 90 malignant and 60 benign pheochromocytomas. Surgery 136:1129–1137
21. Van Heerden JA, Roland CF, Carney JA, et al. (1990) Long-term evaluation following resection of apparently benign pheochromocytoma(s)/paraganglioma(s). World J Surg 14:325–329
22. Meng MV, Koppie TM, Duh QY, et al. (2001) Novel method of assessing surgical margin status in laparoscopic specimens. Urology 58:677–681
23. Scott HW Jr, Halter SA (1984) Oncologic aspects of pheochromocytoma: the importance of follow-up. Surgery 96:1061–1066
24. Harrison TS, Freier DT, Cohen EL (1974) Recurrent pheochromocytoma. Arch Surg 108:450–454
25. Palazzo FF, Sebag F, Sierra M, et al. (2006) Long-term outcome following laparoscopic adrenalectomy for large solid adrenal cortex tumors. World J Surg 30:893–898