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Long-term outcomes of laparoscopic adrenalectomy for Cushing disease

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ABSTRACT

Introduction: In the surgical management of the patients with Cushing syndrome (CS), minimal invasive adrenalectomy (MA) has become the procedure of choice to treat adrenal tumors with a benign appearance ≤6 cm in diameter. Authors evaluated medium- and long-term outcomes of laparoscopic adrenalectomy (LA) for CS or subclinical CS (sCS), performed for ten years in an endocrine surgery unit.
Methods: We retrospectively reviewed 21 consecutive patients undergone LA for CS or sCS from 2003 to 2013. Postoperative clinical and cardiovascular status modifications and surgical medium and long-term outcomes were analyzed.
Results: In each patient surgery determined a normalization of the hormonal profile. There was no mortality neither major post-operative complications. Mean operative time was higher during the learning curve, there was no conversion, and morbidity rate was 6.3%. Regression of the main clinical symptoms occurred slowly in twelve months.
Conclusions: LA is a safe, effective and well-tolerated procedure for the treatment of CS and sCS reducing arterial blood pressure, body weight and fasting glucose levels. Following the learning curve a morbidity rate similar to that reported in the MA series for other adrenal diseases is observed.

1. Introduction

Hypercortisolism in Cushing's syndrome (CS) caused by an adrenocorticotrophic hormone (ACTH) producing pituitary tumor (Cushing's disease), cortisol secretion (adrenal adenoma/carcinoma), or ACTH hypersecretion by a not pituitary tumor remains a severe and life-threatening disease. An estimated incidence ranging from 2 to 3 per million population per year is reported [1]. Minimally invasive adrenalectomy (MA), thanks to a lower morbidity rate, a shorter hospitalization, and a more rapid recovery than "open" surgery, by increasing patients' satisfaction and comfort, has become the standard of care for the management of functioning and non-functioning adrenal neoplasms with a benign appearance ≤ 6 cm in diameter and weighing < 100 g [2]. Progresses in the fields of anesthesiology and surgery, a better understanding of the pathophysiology of the adrenal diseases, and an appropriate pre-operative blood pressure control, contributed to obtain better outcomes also in the surgical management of CS [3,4]. Moreover, the analysis of the available evidence data demonstrated that MA remains the preferred treatment for subclinical CS (sCS) [4].

We report the results, from the last ten years, of a retrospective analysis of 21 CS and sCS patients with adrenal lesions who had undergone laparoscopic adrenalectomy (LA) in a referral university unit of endocrine surgery. Medium and long-term outcomes were compared with those reported during the same years following LA for other adrenal diseases.

2. Materials and methods

2.1. Study design

Review of all recorded clinical data was performed for patients who underwent LA for adrenal neoplasms, between

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January 2003 and January 2013. An asymptomatic lesion, incidentally discovered, and not associated with a predominant hormonal secretion, was considered as an "incidentaloma". According to Persy [5] in about 5–20% of these cases a sCS, consisting in a subclinical cortisol hypersecretion, associated with subtle alterations of the hypothalamic–pitutitary–adrenal (H–P–A) axis due to the adrenal autonomy, might be present. CS diagnosis was based on blunted diurnal cortisol circadian rhythm (plasma cortisol at 24.00/8.00 percent ratio > 50%), suppressed ACTH concentrations (morning plasma ACTH < 10 pg/ml) and elevated 24 h urinary free cortisol excretion (24 h urinary free cortisol > 100 mg), combined with an abnormal result of at least one other test of the H–P–A axis such as 1 mg dexamethasone, given between 23.00 and 24.00 h, and cortisol measured between 08.00 and 09.00 h the following morning or dexamethasone 2 mg/day orally, 0.5 mg every 6 h for 48 h, plasma cortisol level $\geq$ 1.8 μg/dl with a cut-off value for suppression of 50 nmol/L (1.8 g/dl) [6]. Impaired fasting glucose levels and diabetes were defined according to Alberti et al. [7]. A BMI >25 was classed as obesity, a triglyceride serum levels >150 mg/dl, cholesterol serum levels>220 mg/dl or statine therapy identified hyperlipidemia [8]. All subjects underwent clinical examination preoperatively and post-operatively at 6 and 12 months, recording the presence of arterial hypertension, obesity, dislipidemia and diabetes mellitus type 2. Apart from sCS or CS, surgical indications for LA included pheochromocytomas (PCCs) up to 8 cm in diameter, neoplasms (incidentalomas or adenomas associated with a specific hormonal secretion and clinical syndrome) up to 6 cm, myelolipoma up to 12 cm, adrenal metastases < 6 cm, in patients with an ASA risk not over level III, and age less than 80 years. Suspected primary malignant adrenal tumor was considered as a contraindication to LA. Outcomes measures for our analysis were 30-day mortality and complications rate, and functional medium and long-term results. An experienced endocrine and laparoscopic surgeon, associated with a collaborative team, performed all surgical procedures. In most cases, patients were referred to surgery by regional endocrinology units, following a comprehensive endocrinological assessment. Demographic, surgical, pathological features and data about intraoperative and postoperative blood pressure (BP) levels were retrospectively collected. Diagnostic imaging consisted of ultrasonography, computed tomography (CT), magnetic resonance imaging, metaiodobenzylguanidine scintigraphy in all PCC patients, in whom a genetic study looking for mutations of the RET proto-oncogene was performed as well. Anesthesia charts and pathology reports of each patient were obtained. In presence of a diastolic blood pressure above 90 mmHg and systolic blood pressure (SBP) levels > 150 mmHg hypertension was diagnosed; SBP > 180 mmHg levels were considered hypertensive crises, and levels < 90 mmHg were considered hypotensive crises. Alfa or Beta blockers, calcium antagonists and angiotensin receptor blockers represented the associated previous drug therapy. Postoperatively, patients were not routinely admitted to the Intensive Care Unit. In no patient peridural analgesia was employed. Finally, in SC patients, hydrocortisone was given quickly intraoperatively through an intravenous line (100 mg) and the dose was postoperatively increased if signs of hypocortisolism developed (fatigue, lethargy and fever). Patients were discharged if they had no cardiovascular complains or pain, and had begun oral feeding. Follow-up consisted of 6 month, then yearly testing of blunted diurnal cortisol circadian rhythm (plasma cortisol at 24.00/8.00 percent ratio > 50%), ACTH concentrations and 24 h urinary free cortisol excretion and abdominopelvic CT scans with contrast agent. Data were analyzed using descriptive statistics.

2.2. Anaesthesia

Patients received general anesthesia. All operations were performed using orotracheal intubation, without local anesthesia of the upper airways. Invasive arterial pressure monitoring was routinely used for PCC patients. A central venous catheter was selectively previously placed. No pulmonary catheters were used. Hemodynamic data were recorded. Heart rate, systolic and diastolic blood pressure were recorded before the induction of anesthesia, after CO_2 inflation, before and after adrenalectomy. After induction of anesthesia, by remifentanil (0.25 mcg/kg/min) and propofol (2 mg/kg), cisatracurium besylate (0.2 mg/kg), which was also used as muscle relaxant during surgery, was administered. Anesthesia was maintained by the inhalation of sevoflurane and nitrous oxide 50% in oxygen, supplemented with remifentanil infusion. Muscle relaxation during the operation was maintained with intermittent boluses. Blood loss and infused fluid volume during surgery were also recorded. Intraoperative treatment of hypertensive crises was carried out according to previous reported data [9–11].

2.3. Surgery

Operative time was considered as the period from skin incision to wound dressing. An antibiotic and antithrombotic prophylactic therapy was administered in all cases. Adrenalectomies were performed using a standard transperitoneal lateral laparoscopic approach, with 4 trocars if the tumor was in the right adrenal gland, and usually 3 trocars if it was in the left one [3]. The patients were placed in the left or right lateral decubitus position (on the side opposite to the tumor), of about 30° for right LA and of about 90° for left LA. In each case, pneumoperitoneum was induced by Hasson trocar, according to the "open" technique, and was maintained at 12–14 mmHg with carbon dioxide (CO_2). Harmonic scalpel™ (Ethicon Endo Surgery INC – Johnson & Johnson, NJ, USA) or LigaSure™ vessel sealing system (Tyco, Boulder CO, USA) were routinely employed for adrenal glands dissection. Whenever necessary, a bipolar coagulation was routinely preferred for hemostasis. In the surgical intervention, the first step in most cases was the vascular control of the main adrenal vein by clips. In two PCC cases, a linear stapler was utilized. If required, the lateral and posterior connections of the right hepatic lobe were incised, so retracting liver superiorly and medially, taking particular care in CS patients, in whom liver may be very fragile. During a left LA, a wide left colon mobilization is routinely carried out. The surgical specimens were extracted in retrieval bags through a mini-laparotomy at the site of one of the trocars. An off-suction 20 Fr drain was routinely placed and removed after about 1–2 days. Full mobilization and free eating were recommended on the first postoperative day.

3. Results

3.1. Demographics

Sixteen of 88 (18.2%) observed patients, 12 women and 4 men (M:F = 1:3), with a mean age of 43.6 years (range 22–74), were considered affected by CS, and 5/88 (5.6%) by sCS, 3 women and 2 men, with a mean age of 52.6 years (range 36–68), were enrolled for the analysis (Table 1). Functioning tumors were present in 49/88 cases (55.6%). Seventeen patients (19.3%) were affected by PCC, 16 (18.2%) by Conn's disease, 1 (1.1%) by a voluminous myelolipoma, while in 34 cases (38.6%) an incidentaloma was present. In 2 cases (2.7%) adrenal cysts were reported by definitive pathology. Two metastases (one in the right and one in the left adrenal gland)

Table 1
Demographics and operative time.

	CS	sCS
Age (years)	43.6 (22–74)	52.6 (36–68)
Male/Female ratio	1/3	1/3
Mean size (cm)	2.1 (2–2.5)	1.7 (1.6–2)
Right site	11	2
Left site	8	1
Mean weight (gr)	19.6 (13.5–31.4)	17 (14–20)
Mean operative time (min)	144.3 (120–180)	143 (130–160)
Mean hospitalization (days)	4.1 (3–9)	4.3 (3–5)

CS: Cushing Syndrome; sCS: subclinical Cushing Syndrome.

appeared respectively 13 and 3 years after the surgical treatment of a breast and of a renal cancer, with a tumor mean size of 5.86 cm (range 1.1–12). Aldosteronomas were associated with the smallest size (1.1 cm), while myelolipoma was the largest observed neoplasm (12 cm). A right adrenal gland tumor in 9/16 CS cases (56.2%) and 1 bilateral tumor were reported, similar to that reported in the entire series. Associated diseases in CS patients included hypertension in 10/16 patients (62.5%), obesity in 9/16 patients (56.2%) insulin-dependent diabetes in 4/16 patients (25%) and dilated cardiomyopathy in 3/16 patients (18.7%). Associated pathologies in sCS patients included hypertension in 3/5 patients (60%), insulin-dependent diabetes in 1/5 patients (20%). Pathological examination showed an adrenocortical adenoma in 9/16 CS patients (56.2%) and in 3/5 sCS patients (60%), while a glandular hyperplasia was identified in 7/16 (43.7%) CS cases and in 2/5 sCS patients (40%). In each patient surgery determined a normalization of the pathological hormonal serum levels. Mean follow-up was 56.8 month (6–120). Contralateral gland hyperplasia caused relapsing disease in one female patient undergone left adrenalectomy about twelve months before. Long-term results are summarized in Table 2.

3.2. Surgery

Three of 16 (18.7%) patients underwent previous abdominal surgery, with a laparoscopic or laparotomic approach. No simultaneous laparoscopic procedures were performed. Overall mean operative time was 143.8 min (range 125–180) during the learning curve and 121.3 min (range 100–160) in the further procedures. Mean blood loss was 145.7 ml (range 50–220). In one female patient, muscle relaxation was not sufficient to obtain a wide "working space" by pneumoperitoneum. More technical difficulties and operative time were observed during the surgical operation. No patient required intra or postoperative blood transfusion. Harmonic scalpel™ (Ethicon Endo Surgery INC – Johnson & Johnson, NJ, USA) or LigaSure™ vessel sealing system (Tyco, Boulder, CO, USA) showed a similar efficacy in tissue dissection and hemostasis control. There was no mortality. Two of 21 (9.5%) injuries of the splenic and hepatic capsule, conservatively and successfully treated by Floseal ® Hemostatic Matrix (Baxter Zurich- Switzerland) and oxidized cellulose (Tabotamp Fibrillar Johnson & Johnson, NJ, US), were the most significant observed intraoperative complications. Conversion to open surgery was not reported. Mean hospitalization was 4.2 days (range 3–9) (Table 1).

Table 2
Laparoscopic adrenalectomy: long-term results (%).

	Pre surgical data (CS + sCS)	Follow up data (CS + sCS)	
		Persistence	Regression
Hypertension	61.9 (13/21)	23.1	61.5
Obesity	31.7 (9/21)	33.4	66.6
IDDM	23.8 (5/21)	60	40
Dilated cardiomyopathy	14.2 (3/21)	66.6	33.4

IDDM: insulin-dependent diabetes mellitus.

3.3. Morbidity

No postoperative mayor complication occurred. Thirty-day morbidity rate was 18.7% (3/16 patients), and consisted of one case of abdominal wall hematoma, one case of port site hernia, and one intra-abdominal collection spontaneously resolved. Morbidity rate was similar to that reported in the entire series. Pulmonary embolism, acute renal failure, bleeding requiring transfusion, deep venous thrombosis and sepsis were not observed during the 30 postoperative days.

3.4. Follow-up

LA was efficacious in determining a normalization of the endocrine profile after 56.8 month long-term follow-up. Hypertension was persistent in 3/13 cases (23.1%), disappeared in 8/13 patients (61.5%), while in 2/13 (15.4%) a reduction of number and dose of antihypertensive drugs were observed. Obesity disappeared in 6/9 patients (66.6%) and diabetes disappeared in 2/5 cases (40%), while glucose intolerance was not reported. Cardiomyopathy persisted in 2/3 cases (66.6%) (Table 2).

4. Discussion

During the last decades, advances and diffusion of diagnostic imaging have determined a higher rate of incidentally discovered adrenal masses, defined as incidentalomas [3,12]. Most of these are unsecretive, benign lesions, while in approximately 5–20% of the cases a subclinical cortisol hypersecretion might be present, associated with subtle alterations of the hypothalamic–pituitary–adrenal axis due to adrenal autonomy, a disorder that has also been described as sCS [5]. Accordingly, corticotrophin ACTH producing pituitary tumor – Cushing's Disease – adrenal adenoma/carcinoma or ACTH hypersecretion by a non-pituitary tumor may cause severe and life-threatening hypercortisolism in CS. In 10–20% of patients an ectopic ACTH secretion and rarely, ectopic corticotropin-releasing hormone (CRH) secretion can be identified. The syndrome may be caused by a wide spectrum of tumors, ranging from undetectable tumors to widespread metastatic disease. However, in the majority of patients with ectopic CS, a disseminated malignant disease is diagnosed [13]. In untreated patients, significant morbidity and potential mortality related to life-threatening infections, diabetes mellitus, hypertension, and increased risk associated with surgery have been reported [14]. Surgery, determining a reduction of arterial blood pressure, body weight and fasting glucose was considered the treatment of choice for clinical and subclinical SC [15–17]. Because of the high incidence of co-morbidities in CS patients, surgical and perioperative management has become challenging for surgeons. Fortunately, thanks to a better management, physiopathologic knowledge and technological progress during the last decades mortality decreased totally [16]. Lower morbidity (3–20%) and mortality rates, decreased postoperative pain, analgesic administration, ileus and costs, shorter hospitalization, earlier return to work and a better cosmetic result than those reported following open surgery, are the main advantages of the retroperitoneoscopic or laparoscopic adrenalectomy, largely established as the gold standard for small benign adrenal lesions [2]. Previous laparotomic surgery may be not considered as contraindication. Recovery from clinical

syndromes associated with excessive hormonal secretion is the major objective of surgery, but the large acceptance of the mini-invasive approach extended the indications to the treatment of incidentalomas >3.5–4 cm, cysts, glandular hyperplasia and metastases [2,18–20].

In our experience, thanks to the improvement of surgical skills and the technologic assistance (i.e. new dissection tools or intra-operative ultrasound, very useful during a sparing adrenalectomy), LA could be considered as the gold standard for the treatment of benign adrenal diseases, in such cases with a diameter up to 12 cm (myelolipoma) [4,21,22] with a very low morbidity rate similar to that reported in other endocrinological diseases [23–25]. This surgical approach was effective, safe and well tolerated in most cases, with a very low morbidity rate, also following sCS, CS or PCC treatment, considered at high risk for hemodynamic disorders [9,21,22].

Authors analyzed their results throughout the discussion and performed a literature review inhering mini invasive adrenalectomy for SC. Although our study confirms the previous published data, it has several limitations. A single team composed by experienced endocrine and laparoscopic surgeons, in a tertiary referral centre, operated patients mostly selected by referral endocrine units. No patient underwent a retroperitoneal approach. Finally, data were retrospectively evaluated and no comparison with an "open" series was carried out.

4.1. Demographics

The presented series includes patients mostly affected by a clinical syndrome presenting complex clinical pictures and needing often a preoperative medical treatment. CDs were associated with cardiovascular disease, but nevertheless their morbidity rate was similar to that observed in patients with sCDs or incidentalomas, that were less frequently observed in our series. Regarding the regression of clinical symptoms, it was observed in more than 50% of the reported cases, with great satisfaction for patients.

4.2. Surgical details

We considered the first 30 operations as part of the learning curve, but about 40 cases are needed before mastering the surgical procedure. A higher risk of conversion to open surgery is identifiable in patients affected by adrenal lesions greater than 8 cm and needing concomitant surgical procedures that should be not managed during the first phase of experience without a tutor [4]. Our low rate of conversion, similar during the learning curve and after this time for the entire series reflects the high proficiency in advanced laparoscopic surgery of the operative team, as well as confirming the appropriate indications to LA.

A lateral position of about 30° is actually preferred in performing a right LA, as well as, during a left LA, a wide left colon, spleen and pancreatic tail mobilization is routinely carried out. Finally, an ultrasonic dissector of recent conception (Harmonic Ace® Ethicon Endo-Surgery INC – Johnson & Johnson, NJ, USA) is considered as the preferred adrenal gland dissection instrument, and resulted very useful in maintaining a near bloodless field, as well as reported in the management of other endocrine diseases [23,24]. Robotic approach showed several advantages -the 3-dimensional view, wristed instrument, and stable camera platform- more useful for removing large adrenal tumors [25–27]. Training and cost are the two major concerns for robotic adrenalectomy, and more prospective studies are needed to exactly define the role of robotics in adrenal surgery [28].

4.3. Morbidity and outcomes

Large indeterminate adrenal neoplasm, carcinoma, tumor size >6 cm, and the need for concomitant surgical procedures are considered the major variables predicting the 30-day morbidity [4]. By analyzing the available literature data, mortality was reported during the postoperative period in high-risk patients, and a careful multidisciplinary and long-term management is recommended [16]. According to our experience, in Cushing's diseases, a higher post-operative infectious complication rate was not observed. In no patient pancreatitis or torsion of splenic vessels were observed. Considering CS as a bilateral adrenal disease, the role of ultrasound assisted sparing adrenalectomy should be carefully considered, especially in young patients. However, its indication remains controversial. In case of intraoperative complications, a conversion to open surgery was not necessary, and a "conservative" management of the splenic and hepatic capsule injuries was easily performed, without excessive risks for the patients.

4.4. Learning points

Regression of CS or sCS symptoms is mostly slow, but clinical advantages following surgery are undeniable and so an operative treatment is mandatory. LA is safe and feasible also for large adrenal lesions and an additional port may be very useful, especially in case of complications. According to the available evidence data CS surgery may be associated with higher operative time, complications and conversion rate, and an experienced operative team is needed. Previous laparotomic surgery might be not considered as a contraindication to the laparoscopic approach, moreover, the surgical skill required is proportional to the tumor size. A collaborative management, between endocrine physician, surgeon and anaesthesiologist is recommended in referral high volume units, especially in the treatment of CS or PCC patients, considered at high risk of morbidity. To enhance the surgical performance, the operative team should be composed by individuals usually performing jointly a LA. In order to reduce patient risks, major intraoperative complications may be laparoscopically managed only if great care is adopted and a prompt conversion is considered in case of technical difficulties.

Ethical approval

This is a retrospective study based only on the analyses of recorded data and then no Ethical Approval was necessary.

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Author contribution

Giovanni Conzo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Piero Giorgio Calò: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Claudio Gambardella: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Ernesto Tartaglia: Participated substantially in conception, design, and execution of the study and in the analysis and

interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Claudio Mauriello: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Cristina Della Pietra: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Fabio Medas: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Rosa Santa Cruz: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Francesco Podda: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Luigi Santini: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Giancarlo Troncone: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflicts of interest

All Authors have no conflict of interests.

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