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Laparoscopic adrenalectomy, a safe procedure for pheochromocytoma. A retrospective review of clinical series

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ABSTRACT

Background: Minimally invasive adrenalectomy for pheochromocytoma (PCC) is a complex surgical procedure especially because of the haemodynamic instability due to the excessive secretion of catecholamines, which may result in a considerable risk of conversion and complications.
Aim: By a multicentric retrospective study, the authors reported the results of laparoscopic adrenalectomies in patients operated for adrenal pheochromocytomas with the aim of investigating the role of the laparoscopic approach in managing adrenal disease.
Methods: Sixty patients, preoperatively treated with a selective alpha1-blocker, underwent 61 laparoscopic adrenalectomies for PCC smaller or larger than 6 cm – group A (≤6 cm), group B (>6 cm). We compared the two groups of patients analyzing haemodynamic instability, operative time, conversion rate, incidence of complications, length of hospital stay and medium and long-term outcomes.
Results: In 23 cases tumor was >6 cm in diameter. Average operative time was 165 min, with a 5% conversion rate. There was no mortality and morbidity rate was 8.3%. Intraoperative hypertensive crises were registered in 15% of patients, whereas 5/60 patients had hypotensive crises. After comparing the two groups of patients, no statistically significant differences in terms of haemodynamic instability, operative time, conversion rate, morbidity and length of hospital stay were observed.
Conclusions: As a surgical treatment of pheochromocytomas, laparoscopic adrenalectomy is an effective and safe approach, in selected cases even for PCCs >6 cm in diameter, although patients with such large tumors may have a higher conversion rate and more intraoperative hypertensive crises. Preoperative selective adrenergic blockade does not prevent intraoperative hypertensive crises, but by facilitating the pharmacological management of the perioperative haemodynamic instability, may avoid the onset of major adverse cardiovascular complications.

1. Introduction

Pheochromocytoma (PCC) is a rare neuroendocrine tumor, with a prevalence ranging between 0.1% and 0.6% in patients suffering from arterial hypertension.[1] Minimally invasive adrenalectomy (MA), which is associated with less pain, a lower morbidity rate, a shorter hospital stay, a more rapid recovery and a better cosmetic result than "open" surgery, is the gold standard for the treatment of adrenal tumors ≤6 cm in diameter and weighing <100 g.[2] An analysis of the published studies on PCC surgery, which only rarely involve case series of more than 50 patients, shows that the minimally invasive approach has significant advantages.[3] However, the role of laparoscopy in treating PCC >6 cm in diameter is still controversial for the presumed higher risk of malignancy and of local recurrence rate, and moreover it may be associated with longer operative times, a greater blood loss, a higher conversion rate, and several complications as well. Preoperative blood pressure

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control, a reduced manipulation of the adrenal gland and sparing of the adrenal capsule are the treatment guidelines. Provided that there is no evidence of local invasion or of supposed malignancy, laparoscopic adrenalectomy (LA) is successfully carried out even for patients with PCC >6 cm in diameter, but this indication is at present matter of debate.

We report the results of a multicentric retrospective study of 60 patients with PCC smaller or larger than 6 cm – group A (≤6 cm), group B (>6 cm), who underwent LA after preoperative selective adrenergic blockade with doxazosin. The purpose of the study was to compare haemodynamic instability, operative time, conversion rate, incidence of complications, length of hospital stay and medium and long-term results in both of the groups of patients.

2. Materials and methods

This study was accomplished by four surgical centers with a wide experience in adrenal surgery (two academic centers and two endocrine-surgery centers). A retrospective analysis was obtained from questionnaires in which patients data were collected, with details of the preoperative laboratory tests and diagnostic procedures for PCC, tumor size, perioperative complications, operative time, length of hospital stay, along with clinical, laboratory, and instrumental examinations after a five years follow-up. The sixty patients included in the study, suffering from either preoperative stable or paroxysmal hypertension associated with other signs or symptoms of cathecolamine excess, underwent laparoscopic adrenalectomy and were grouped according to the tumor size (group A ≤6 cm; group B >6 cm) (Table 1). Whenever malignancy was assumed, for local invasion or distant metastases, a minimally invasive approach was contraindicated. According to Zhu et al.,[4] until blood pressure (BP) and heart rate (HR) stabilization was achieved, (BP <160/90 mmHg for at least 24 h before surgery and HR <100 bpm), in absence of electrocardiographic ST-T changes for at least 1 week, every patient started a preoperative drug therapy, consisting of an alpha1-blocker – doxazosin, at least 15 days before surgery, with a mean daily dose of 4.54 ± 1.65 mg and a mean length of therapy of 21.15 ± 5.91 days. A beta-blocker (atenolol, 50 mg daily) was added in 6 cases with tachycardia (10%). A calcium antagonist (amlodipine besylate, 5 mg daily) in 3 cases (5%), an angiotensin receptor blocker (valsartan, 160 mg daily) in 2 cases (3.3%), and an angiotensin-converting enzyme inhibitor (ramipril, 10 mg daily) in 2 cases (3.3%) represented the associated preoperative drug therapy. Every patient underwent perioperative venous thromboembolism prevention. According to J. Varon,[5] systolic blood pressure (SBP) levels ≥180 mmHg or diastolic blood pressure (DBP) levels ≥120 mmHg were considered hypertensive crises, and levels <90 mmHg were considered hypotensive crises. For each case anesthesia chart and pathologic report were obtained. In 10/60 patients (16.6%), by means of blood samples and sometimes specimen samples, a genetic study looking for mutations of the RET protoncogene was performed. Diagnostic work-up included ultrasonography, CT scanning with contrast agent, Magnetic Resonance Imaging (MRI), whole body metaiodobenzylguanidine (MIBG) scintigraphy in order to confirm PCC diagnosis, and echocardiography. Patients were discharged if they had no cardiovascular complains or pain and had begun oral feeding. Follow-up consisted of 6-monthly, then yearly testing of urinary metanephrine levels and abdominopelvic CT scans with contrast agent.

2.1. Anesthesiological management

In each case, in order to expand plasma volume, intravenous volume loading was carried out in the preoperative holding area. Patients received general anesthesia, with no epidural anesthesia. All operations were undertaken by orotracheal intubation, without anesthetizing upper airway. Invasive arterial pressure monitoring was routinely performed. A central venous catheter was placed before every intervention. No pulmonary artery catheters (Swan-Ganz catheters) were used. Haemodynamic data were recorded. Heart rate, systolic and diastolic blood pressure were recorded before inducting anesthesia, after CO_2 inflation, before and after adrenalectomy. After inducing anesthesia with 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 with inhalation of sevoflurane and nitrous oxide 50% in oxygen, supplemented with remifentanil infusion. Intraoperative muscle relaxation was maintained with intermittent boluses. Blood loss and fluid volume loading during surgery were also recorded. Intraoperative treatment of hypertensive crises consisted of intravenous administration of nitroprusside (initial dose: 0.2 mcg/kg/min, administered by continuous intravenous infusion; maintenance dose was titrated up to a maximum of 10 mcg/kg/min), esmolol (1 mg/kg bolus dose over 30 s, followed by a 150 mcg/kg/min infusion, whenever necessary, adjusting the infusion rate as required up to 300 mcg/kg/min to maintain the desired HR and/or BP), urapidil (starting dose: 0.25–0.4 mg/kg or 25 mg; maintenance dose: 9 mg/h of continuous intravenous infusion), clonidine (single bolus: 75–150 μg in 5 min, or by continuous infusion: 0.4–5 μg/min).

Table 1
Patients data and pheochromocytoma size.

	Group A ≤6 cm 37 patients (61.6%)	Group B >6 cm 23 patients (38.3%)	*p*-value
Mean age (years)	44.16	39.56	0.03
Male patients	8 (21.6%)	13 (56.5%)	0.01
Site			
right	20 (54%)	11 (47.8%)	0.7
left	18 (48.6%)	12 (52.1%)	
Mean size (cm)	3.9	8.3	0.001
ASA score			
1–2	23 (62.1%)	15 (65.2%)	1.0
3–4	14 (37.8%)	8 (34.7%)	
Mean 24 h urinary catecholamines (pg/dl)	585.62 (120–1800)	751.17 (147–3490)	0.1

2.2. Surgery

Every adrenalectomy was performed using transperitoneal laparoscopy, with the patient positioned in the lateral decubitus. Four trocars were inserted in the case of a right PCC and three in the case of a left one, while one supplementary trocar was used in 11/60 cases (18.3%). In one case of bilateral adrenalectomy, after removing the first gland, the patient was repositioned on the table for the second, separate procedure. Carbon dioxide pneumoperitoneum was kept at 12–14 mmHg. According to "vein first" technique, at the beginning of the operation, the main adrenal vein was identified and divided between clips. In the cases of right PCC >6 cm, procedure began with superior and lateral mobilization of the adrenal gland to facilitate identification of vena cava and right renal vein, followed by the section of the main adrenal vein. In most patients adrenal gland dissection was carried out by ultrasonic or bipolar shears. Surgical specimens were always extracted through a mini-laparotomy at the site of a trocar, using a specimen extraction bag. A drainage tube, usually preferred by the surgeons participating to this study, was routinely placed and then removed after 1–2 days. Postoperatively, patients were not routinely referred to the Intensive Care Unit. No patient received epidural analgesia.

3. Statistical analysis

Data were expressed as mean ± SEM, unless otherwise specified. Statistical analysis was performed with SPSS version 11.5 (SPSS©, Chicago, IL, USA). Significance was assigned with a *p*-value <0.05.

4. Results

4.1. Patient demographics

Our series consisted of 60 patients, 39 women and 21 men, with a mean age of 42.4 ± 14.38 years, who underwent a total of 61 LAs, between January 1998 and December 2011. No cases of preoperative stroke were reported. Associated diseases of interest included insulin-dependent diabetes mellitus in 13 cases (21.6%) and dilated cardiomyopathy in 4 cases (6.6%). There was one case (1.66%) of a genetically determined polyendocrine syndrome: multiple endocrine neoplasia (MEN) 2A with a triple RET mutation (634, 640, 700).[6] Urinary catecholamines were elevated in 58/60 patients. Preoperative 24-h mean concentration was 649.08 ± 548.885 pg/dl (n.v. = 0–115 pg/dl), respectively 585.62 ± 395.44 in group A and 751.17 ± 740.28 in group B. Thirty cases of PCC in the right adrenal gland, 29 in the left adrenal gland and 1 bilateral tumor were reported with an average diameter of 5.6 cm (3.9 cm group A–8.3 cm group B) (range 2.4–11 cm). In 23/60 patients (38.3%) the tumor was larger than 6 cm, in 37/60 (61.6%) the PCC was equal to or smaller than 6 cm (Table 1). Preoperative treatment with doxazosin was well tolerated without important side effects, allowing an efficacious BP and HR control.

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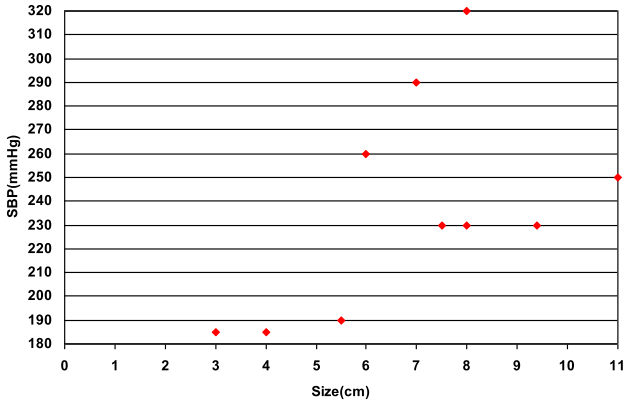
4.2. Surgical outcomes

Overall mean operative time was 165.66 ± 70.48 min and was similar in the two groups (Table 2). Conversion to open surgery was necessary in 3/60 patients (5%), in one case (PCC >6 cm) due to suspected infiltration of renal vessels, not confirmed by pathology, which found a desmoplastic reaction, and in the remaining two cases (1 PCC >6 cm and 1 PCC <6 cm) because of the tenacious adhesions between PCC and the surrounding structures, and between the right colon and the gallbladder. Mean blood loss was 143.16 ± 63.33 ml and was similar in the two groups of patients (Table 2). Blood transfusion was required for an adrenal capsular hemorrhage, in one case of PCC <6 cm in diameter. There was no mortality. Morbidity was 8.3% (5/60 patients) and consisted of one abdominal wall hematoma (group B), one case of delayed wound healing in a diabetic patient (group A), one serosanguineous fluid collection in the suprarenal space, and treated by US guided percutaneous drainage (group B), one pneumothorax treated by pleural aspiration (group A), and an infection of the urinary tract (group A). There was no relationship between preoperative doxazosin dose and intraoperative hypertensive crises. These were of short duration and occurred at induction of anesthesia and during manipulation of the adrenal glands in 10/60 patients (16.6%) (Fig. 1), with a higher incidence in patients with PCC >6 cm in diameter than in other patients, (26% vs 18.9% $p = 0.4$), not statistically significant (Table 2). At induction, 3/60 patients (5%) had paroxysmal hypertension with peaks of 180/90, 180/120 and 190/110 mmHg, with HR of 85, 90 and 110 bpm, resolved after drug therapy. Further episodes of hypertension, with a median BP of 250/180 mmHg (range 220/160–320/150 mmHg) and a mean HR of 99 ± 9.41 bpm, were observed during manipulation of adrenal glands in 7/60 patients (11.6%), and ceased after adrenalectomy. Hypertensive crises were not associated with any significant complication, such as cerebral vascular accident, pulmonary edema, myocardial infarction or ischemia, cardiac arrhythmia and multiorgan failure, and no postoperative mechanical ventilation was required. Fig. 1 reports the relationship between hypertensive crises and PCC size. The highest BP levels were observed in a patient who underwent laparoscopic adrenalectomy to remove a PCC 8 cm in diameter (320/150 mmHg), and the 24-h preoperative urinary catecholamine concentration was 655 pg/dl. No intraoperative hypotensive episodes were observed.

4.3. Postoperative outcomes

After awakening from anesthesia, 2/60 patients (3.3%) were hypotensive (70/40 mmHg, 80/65 mmHg) and were treated by crystalloids and hydrocortisone. On postoperative day 1, 3/60 patients (5%) had hypotension which was successfully treated in the same way. Mean hospital stay was 3.96 ± 0.85 days and was similar in the two groups of patients (Table 2). One male patient, after laparoscopic resection of a PCC <6 cm in diameter, was openly reoperated via a posterior approach, due to disease persistence associated with adrenal retrocaval remnants. Surgical pathology did not report any malignancy. Testing for RET mutations identified a triple mutation (634, 640, 700) in a 37 years old female patient suffering from MEN 2A, but no mutations were found in other patients. Postoperative levels of urinary catecholamines were normal at five years follow-up (12 months – 13 years), except one young male patient who, one year after LA, underwent "open retroperitoneal" reoperation for disease persistence due to remnant retrocaval glandular tissue (group B).



*Statistically significant relationships between PCCsize (> or ≤ 6 cm) and hypertensive crises were not observed.
SBP: systolic blood pressure (mmHg)
PCC: pheochromocytoma

Fig. 1. Relationship between PCC size and hypertensive crises (SBP >180 mmHg). *Statistically significant relationships between PCC size (> or ≤6 cm) and hypertensive crises were not observed. SBP: systolic blood pressure (mmHg). PCC: pheochromocytoma.

Table 2
Perioperative results.

	Group A (≤6 cm) 37 patients	Group B (>6 cm) 23 patients	*p*-value
Mean operative time (min)	170.54 ± 71.99	157.82 ± 70.45	0.7
Intraoperative blood loss (ml)	155.67 ± 60.98	123.04 ± 64.55	0.4
Blood transfusion	1 (2.7%)	0	1.0
Hypertensive crises (SBP >180 mmHg)	4/37 (18.9%)	6/23 (26%)	0.4
Hypotensive crises (SBP <90 mmHg)	3/37 (8.1%)	2/23 (8.6%)	1.0
Mortality	0	0	1.0
Conversion to open procedure	1/37 (2.7%)	2/23 (8.6%)	0.5
Complications	3/37 (8.1%)	2/23 (8.6%)	1.0
Hospital stay (days)	4.05 ± 0.84	3.82 ± 0.88	

* Statistically significant differences were not observed between the two groups of patients.
SBP = systolic blood pressure.

5. Discussion

The results of our retrospective study show that laparoscopic adrenalectomy is an effective and safe approach, even for PCCs >6 cm in diameter, although patients with such large tumors may have a higher conversion rate and more intraoperative hypertensive crises. We reported a low perioperative morbidity and successful medium and long-term outcomes. Preoperative selective adrenergic blockade with doxazosin is recommended in the management of sporadic and hereditary forms[7] because it does not prevent intraoperative hypertensive crises, but by facilitating pharmacological management of the perioperative haemodynamic instability, may avoid the onset of major adverse cardiovascular events such as myocardial infarction or ischemia, reversible myocardial depression, stroke, pulmonary or cerebral edema, respiratory distress syndrome and multiorgan failure. These were not observed in our series. According to literature data we propose a laparoscopic approach also for PCC 6–8 cm only if great care is adopted to avoid capsular disruption and, if necessary, a prompt conversion to open technique is cautiously considered to reduce patient risks. Pheochromocytoma is an endocrine rare tumor, most common in women in their 40s and 50s, with an incidence in the United States between 2 and 8 cases per million per year.[8] In the last decade, following work-up of adrenal incidentalomas or familial syndromes, an increasing number of patients with

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subclinical PCC has been diagnosed.[9] The "rule of 10" is used to describe PCC; 1/10 patients, mostly with a sporadic form of the tumor, may have malignant PCC, in 1/10 cases the tumor is bilateral, in 1/10 extradrenal and in 1/10 familial.[10,11]There are hereditary forms of PCC and extraadrenal PCC, i.e. paragangliomas (PGL), that can be found in multiple endocrine neoplasia 2 (MEN 2), von Hippel-Landau disease (VHL), neurofibromatosis (NF), and the PCC-PGL syndromes (PGL 1–4),[12] which are generally benign and currently under study. Pheochromocytoma occurs in 30–50% of cases of MEN 2 and in 15–20% of cases of VHL. After the 2000s it has been shown that MA (laparoscopic and retroperitoneoscopic) is associated with lower morbidity and mortality rates than traditional surgery, especially because it allows to reduce postoperative pulmonary infections and thromboembolic complications.[13,14] However, there are still more risks associated with the surgical treatment of PCC, either open or laparoscopic, in spite of lower mortality (0.0–3.8%) and less complications (5–22%) – blood pressure variations, intraoperative blood loss, visceral lesions, and adverse cardiovascular events (stroke, pulmonary or cerebral edema, myocardial infarction) – than in the past.[15–19] According to Bruynzeel, a high plasma norepinephrine concentration, tumor size >4 cm, a high preoperative mean BP and a more pronounced postural drop after α-blockade are risk factors of haemodynamic instability.[20] Pheochromocytoma surgery is still a challenge, especially for large lesions, because of the excessive secretion of catecholamines, the extensive vascularization of this kind of tumor, the difficulties in mobilization and dissection of the adrenal gland, the tenacious adhesions to adjacent structures, often to major blood vessels (renal vein). So the role of laparoscopic approach for neoplasms >6 cm is still controversial. During the past decade, increased laparoscopic experience has made possible to reduce mortality, morbidity, conversion rates, operative time, blood loss and the length of hospital stay also for large PCC, as reported in the rare series of patients with tumors >6 cm in diameter, demonstrating the efficacy and safety of the laparoscopic approach (Table 3). In case of technical difficulties, prompt conversion to reduce patients risks must be recommended, as well as great care in sparing adrenal capsule. In case of capsular disruption, open or hand assisted approach has been suggested to prevent "iatrogenic pheochromocytomatosis".[9] Even though Toniato observed higher blood loss in PCC >6 cm, he concluded that PCC dimensions do not affect surgical outcome.[21] On the contrary, Kercher reported longer operative times in 18 cases of PCC >6 cm treated during 10 years.[22]The risk of malignancy, which was reported to be as high as 13.4%[23] and of local recurrence of laparoscopically resected tumors were considered in the past as contraindication to laparoscopic treatment of PCC >6 cm. The definition of malignancy should be based especially on clinical observation of metastases, which can appear more than 5 years after surgery, and consequently follow-up of patients who have undergone PCC surgery should therefore last more than 10 years. Furthermore, in case of familial forms, in which bilateral PCC is common, a lifetime follow-up is necessary.[9] Nevertheless, it is important to note that PCC >6 cm in diameter become malignant less frequently than other adrenal lesions of the same size do, and probably size cannot itself be an absolute contraindication for LA, provided that there is no evidence of local invasion.[24] Finally, about the role of laparoscopic surgery in large PCC, literature is still divided between experienced endocrine surgeons supporters[9,21,24–27] and detractors.[28–31] Improved perioperative management, advances in anesthesiology and surgery, and a better understanding of pathophysiology have allowed a significant reduction in mortality and morbidity associated with perioperative adverse cardiovascular events. Preoperative BP management with the most common drugs – alpha blockers (phenoxybenzamine, doxazosin), or calcium antagonists (nicardipine) – do not prevent intraoperative hypertensive crises but improve both their control and the patient postoperative haemodynamic profile, reducing the risk of major perioperative adverse cardiovascular complications.[4,7,19,32,33] In our experience, irrespective of the preoperative medical treatment, a notable perioperative haemodynamic instability was observed (hypertensive crises: 13.8%; hypotensive crises: 8.3%). However, hypertensive crises were of short duration and their intraoperative pharmacological management was immediate. Moreover, no cases of major adverse cardiovascular complications such as myocardial infarction or ischemia, cardiac arrhythmias, stroke, pulmonary or cerebral edema in neither group of patients were observed, confirming the efficacy of preoperative α-blockade. The reasonable operative times, limited blood loss, low morbidity (8.3%), low conversion rate (5%) and short hospital stay, observed in the study, even in cases of a tumor size >6 cm in diameter, confirm the effectiveness and safety of LA in the surgical treatment of PCC. Provided that there is no pre- or intraoperative evidence of local invasion, it is possible to treat cautiously even PCC 6–8 cm in diameter by LA, and results appear to be similar to those generally reported in the treatment of neoplasms of a smaller size. However, it should be noted that in our study there was a relationship between hypertensive crises, conversion rate and PCC size >6 cm in diameter, but differences statistically significant were not found.

Our study has several limitations. First of all, as most published papers in PCC surgery, it was retrospective and also multicentric, comprising a small number of treated patients. Nevertheless, the

Table 3
Results of minimally invasive adrenalectomy in patients with pheochromocytomas.

Authors	Patients (number)	Operative time (min)	Blood loss (ml)	Conversion (%)	Morbidity (%)	Mortality (%)
M Gagner ('96)	23	230	–	0	22	0
MK Walz ('02)	52	116 ± 52	100	0	23	0
DE Jaroszewski ('03)	47	140	80	11	4.8	0
AW Kim ('04)	26	191	276	4	23	0
KW Kercher ('05)	80	169	97	0	7.5	0
Y Naya ('05)	23	192.7	130	4.34	0	0
A Toniato ('07)	40	78	100	3	2.5	0
MJ Mellon ('08)	11	181.4	–	1.4	10	0
KA Perry ('09) PCC <6 cm	22	189	68	9.1	13.6	0
KA Perry ('09) PCC >6 cm	8	212	130	37.5	12.5	0
GY Meyer-Rochow ('09)	36	183	–	2.7	13.9	0
LN Castilho ('09)	24	126	–	0	16.7	0
P Nau ('10)	33	142	–	12.1	6	0
WT Shen ('12)	102	186	–	3	13.7	0
YM Carter ('12)	25	–	–	0	0	0
Present series ('12)	60	165	130	5	8.3	0

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results were similar to those reported in the larger experience of a single institution referral center, based on the laparoscopic management of a higher number of cases.[9] Moreover it must be considered the absence of a control group of patients submitted to "open" adrenalectomies, but this issue has been widely evaluated in literature data, demonstrating the advantages of MA.[3,21,34]

6. Conclusions

According to our results, LA was effective and safe for most patients with PCC without preoperative suspicion of malignancy. Moreover, it was associated with acceptable morbidity rate, similar to those previously reported for other adrenal diseases.[14] There was a higher incidence of hypertensive crises and of conversion to open surgery in PCC larger than 6 cm (statistically not significant), while blood loss, operative time, incidence of complications and long-term outcomes did not seem to be affected by PCC size. Preoperative selective adrenergic blockade with doxazosin did not guarantee haemodynamic stability but allowed an optimal pharmacological control of hypertensive episodes. Given the difficulties related to the dissection of adrenal glands and the risk of perioperative adverse cardiovascular events, LA for patients with PCC remains a complex procedure and great caution is needed, especially in case of large neoplasms. Experienced multidisciplinary teams in specialized referral centers obtain the best results in treating this rare disease.

Ethical approval

No.

Funding

No.

Author contribution

All authors 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.

Conflict of interest

No.

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