Laparoscopic treatment of pheochromocytomas smaller or larger than 6 cm
A clinical retrospective study on 44 patients. Laparoscopic adrenalectomy for pheochromocytoma

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Laparoscopic treatment of pheocheomocytoma smaller or larger the 6 cm. A clinical retrospective study on 44 patients

INTRODUCTION: *Laparoscopic adrenalectomy is a gold standard for the treatment of pheochromocytomas less than 6 cm in diameter. Given the difficulty in dissecting the adrenal glands, the presumed increase in the risk of malignancy, and capsular disruption there is controversy regarding minimally invasive surgery for neoplasms greater than 6 cm. The aim of this study was to report laparoscopic adrenalectomy results in 44 patients with pheochromocytomas either larger or smaller than 6 cm.*
METHODS: *The retrospective clinical study was conducted on 44 patients who underwent surgery in the Campania region in Italy, between January 1998 and January 2008. In 30 cases the lesion measured ≤ 6 cm (group A) in diameter and in 15 > 6 cm (group B). The authors compared cardiovascular instability, operative time, conversion rate, incidence of intra and postoperative complications, length of hospital stay, and medium long term follow-up results in the two groups of patients.*
RESULTS: *By comparing group A vs group B no significant differences were observed in operative time, incidence of intra and postoperative complications lenght of hospital stay or medium long term follow-up results. In patients with pheochromocytomas > 6 cm a higher conversion rate, although not statistically significant, was observed. The same occurred with cardiovascular instability shown by intraoperative sudden bouts of hypertension. One patient underwent "open" reoperation for residual retrocaval glandular tissue, not removed during laparoscopic treatment.*
CONCLUSIONS: *Laparoscopic adrenalectomy for pheochromocytoma by experienced laparoscopic surgeon is safe and probably preferable also in selected cases larger than 6 cm. These patients may have a longer operative time, a greater intraoperative blood loss, a higher conversion rate, more intraoperative hypertensive crises than other patients. Adequate preoperative pharmacological therapy and careful anaesthesia monitoring make possible optimal management of cardiovascular instability.*

KEY WORDS: Alpha blockade, Hypertension, Laparoscopic adrenalectomy, Pheochromocytoma

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Introduction

Laparoscopic adrenalectomy (LA) is the procedure of choice for the treatment of tumours < 6 cm in diameter and weighing < 100 g, since it is associated with a lower rate of mortality and complications than open surgery [1]. Given the significant cardiovascular instability involved, the rich vascularization of the area, the tenacious adhesions between the adrenal glands and neighboring structures, and the risk of capsular disruption (followed by tumor seeding and recurrence), surgical treatment of pheochromocytoma (PCC) is a complex procedure. However, over the last decade, the literature has shown LA being preferable in cases of PCC, since the results obtained are similar to those reported for other pathologies of the adrenal glands. Although many authors have shown LA for large PCC to be as safe and effective as laparoscopic or open procedures performed for lesions < 6 cm [2-5], some controversy exists about the indications for laparoscopic treatment of PCC > 6cm in diameter. In this perspective we present a multicentric retrospective study on 44 patients suffering from PCC, regardless of their dimensions, who underwent LA in the Campania region of Italy, between January 1998 and January 2008. Aim of this study remains to identify significant differences between the two groups, to better evaluate the role of LA in the management of PCCs larger than 6 cm.

Table I - *Division of patients based on pheocromocytoma size*

	Group A ≤ 6cm (30 pts)	**Group B > 6cm (14 pts)**
Median age	43 (21-70)	37 (23-77)
Male patients	5	9
Site: right	15	8
left	15	7
Median size (cm)	4 (2,4 -6)	8 (6,3 -11)
ASA score 1-2	18	9
3-4	12	5
Median urinary cathecolamines (pg/dl)	400 (100-1472)	480 (101-3467)

Materials and Methods

Study Design

The study, endorsed by the LAP (Laparoscopic) Club, founded in Naples, Italy, in 1995 to promote the study and diffusion of minimally invasive surgery, is the result of collaboration between four experienced centres in adrenal surgery (about 20 adrenalectomies/year), where advanced laparoscopic surgery is routinely performed. The retrospective data were obtained from questionnaires whose details are reported in Table I and II. Only patients with a clear preoperative diagnosis of PCC were included in the study (urinary catecholamines elevation or a positive metaiodobenzylguanidine -MIBG- scintigraphy). In case of normal values of urinary catecholamines, preoperative diagnosis was ensured by MIBG scintigraphy and clinical presentation. Because of the presence of paroxysmal arterial hypertension, characterised by systolic blood pressure (SBP) > 160 mm Hg, with an hearth rate (HR) > 100 beats/min (b/m), associated to common symptoms (headaches, palpitations, episodic sweating), all patients were treated preoperatively, for at least 15 days, according to a drug therapy protocol based on alpha blockers, sometimes combined with beta blockers, sartans, and calcium antagonists, until their blood pressure (BP) was stabilized. As regards details of cardiovascular stability, the antihypertensive drugs used and their dosage, as well as BP levels from the preoperative period to one-year follow-up, were recorded. In each case the patient's anaesthesia chart, and the results of the pathologist's examination were obtained. Since our study was multicentric, only in 8/44 patients a

Table II - *Results*

	Group A ≤ 6cm	**Group B > 6cm**
Median operative time (min.)	160 (60-240)	165 (90-250)
Median intraoperative blood loss (ml)	100 (50-300)	100(80-210)
Median hospital stay (days)	4 (3-5)	6 (3-8)
Blood transfusion	1/30 (3.3%)	0
Cardiovascular instability BP>160-90 mmHg (16/44 – 36.36%)	9/30 (30%)	7/15 (46.7%)
BP < 90-60 mmHg (4/44 – 9.09%)	3/30 (10%)	1/15 (6.7%)
Mortality	0	0
Conversion	1/30 (3.3%)	1/15 (6.7%)
Complications	3/30 (10 %)	1/15 (6.7%)

Legend: BP = Blood Pressure; *p was not significant in every parameter

genetic study looking for mutations of the RET protooncogene, was performed using blood samples and sometimes samples from the specimens. The patients were divided according to tumour size. Based on data from preoperative diagnostic imaging, confirmed by the measurements of the surgical specimens, group A consisted of patients with PCC ≤ 6 cm in diameter and group B of those with PCC > 6 cm in diameter. The two groups were compared in terms of the following parameters: cardiovascular intraoperative and postoperative status (until discharge), operative time, conversion rate, intra and postoperative complications, length of hospital stay, and medium long term follow-up results. In case of suspected local infiltration or distant metastases at preoperative imaging (CT scan, MRI, or MIBG whole body scintigraphy) a minimally invasive approach was contraindicated. Statistical analysis was performed with SPSS version 11.5 (SPSS©, Chicago, IL, USA). Significance was assigned at a level of $p < 0.05$.

Patients

The case series included 44 patients who underwent LA for PCC between January 1998 and January 2008. Patient characteristics -29 women and 15 men, with a median age of 40 years (range 21-77 years)- are listed in Table I. Pathologies of interest recorded were insulin-dependent diabetes mellitus in 8 cases (18.18%), and dilated cardiomyopathy in 2 cases (4.54%). One case (2.27%) of multiple endocrine neoplasia (MEN) 2A was the only example of genetically determined polyendocrine disease found in the study. A 37-year-old woman, with a medical history of total thyroidectomy, open left adrenalectomy, laparoscopic right adrenalectomy, and laparoscopic treatment for PCC recurrence on the left + double cervical lymphectomy, was discovered to have the syndrome with triple RET mutation (634, 640, 700), with an incomplete phenotype consisting of medullary carcinoma + bilateral PCC without hyperparathyroidism [6].

Diagnostic imaging included ultrasonography, CT scanning with contrast agent, in some cases MRI, whole body MIBG scintigraphy (in every patient) and echocardiography in 8 patients. In each case an alpha blocker was administered as preoperative drug therapy (doxazosin, 2-10 mg/die). In 5 cases (11.36%) a beta blocker was added (atenolol 50 mg/die), in 2 cases (4.54%) a calcium antagonist (amlodipine besylate 5mg/die), in one case (2.27%) a sartan (valsartan 160 mg/die) and in one case (2.27%) an ACE inhibitor (ramipril 10 mg/die). Therapy always lasted for at least 15 days. In each case low molecular weight heparin was administered as prophylaxis against deep venous thrombosis. Twenty-three right LA and 22 left LA were performed in 44 patients (including one bilateral LA), by a lateral transabdominal approach. No adrenalectomy was performed using retroperitoneoscopic or submesocolic access. In a case of conversion due to suspected malignant infiltration of the renal vessels, not seen at preoperative imaging, and not confirmed by the definitive pathology report (desmoplastic reaction), right nephrectomy was required. In all cases a drain was positioned and removed early, between postoperative days 1 and 2. Blood pressure stabilization, resumption of gastrointestinal function and the disappearance of pain were the patient discharge criteria used. Follow-up included plasma and urine catecholamine testing or urinary metanephrine testing every 6 months, and possibly a CT scan with contrast agent. Blood pressure was evaluated by means of measurements taken before, during and after surgery and until discharge. The criteria for hypertensive crises were SBP > 160 mm/Hg for >10 min, and criteria for hypotensive crises were SBP < 80 mm/Hg for > 10 min accompanied by tachycardia with a HR of > 100 bm.

Anaesthesia

Patients received general anesthesia without epidural anesthesia. All operations were performed using orotracheal intubation, without local anaesthesia of upper airway. Invasive arterial pressure monitoring was routinely used. A central venous catheter was previously placed. No pulmonary catheters were used. Hemodynamic data were recorded. Heart rate, systolic and diastolic blood pressure were recorded before anesthesia induction, after CO_2 inflation, before and after adrenalectomy. After induction of anaesthesia with remifentanil (0.25 mcg/kg/min) and propofol (2 mg/kg), cisatracurium besylate (0.2 mg/kg), which was also used as a muscle relaxant during surgery, was administered. Anesthesia was maintained with 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 consisted of intravenous administration of nitroprusside (initial dose: 0.2 mcg/kg/min, administered by continuous intravenous infusion; maintenance dose was titrated upward to a maximum of 10 mcg/kg/min), esmolol (1 mg/kg bolus dose over 30 seconds followed by a 150 mcg/kg/min infusion, if necessary, or a loading dosage infusion of 500 mcg/kg/min for one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min, adjusting the infusion rate as required up to 300 mcg/kg/min to maintain desired HR and/or BP), urapidil (starting dose: 0.25-0.4 mg/kg or 25mg; 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).

Results

By considering normal a value within 0 and 115 pg/dl, preoperative median 24-hour urinary catecholamine concentration was 400 pg/dl (range: 100-1472 pg/dl) in group A and 480 pg/dl (range: 101-3467 pg/dl) in group B. Paroxysmal arterial hypertension was observed in all patients. No cases of stroke were reported. By comparing parameters such as operative time, blood loss, mean hospital stay, cardiovascular instability, mortality, conversion rate to open surgery and complications in group A vs group B, a significant difference was never found, see Table II for details. The instances of morbidity were the following; one (2.27%) fluid collection of the surgical site, associated with hyperpyrexia (40°C), which resolved after treatment with percutaneous drainage under ultrasound guidance, one (2.27%) case of pneumothorax cured with pleural aspiration, one (2.27%) case of delayed wound healing in a diabetic patient, and one (2.27%) case of abdominal wall haematoma. Conversion to open surgery was 3.3% in group A, (a 73-year old woman, in whom tenacious adherences between gallbladder and the right colon were found during right LA) and 6.7% in group B, (a 54-year–old woman for suspected invasion of the right renal vessels - p=0.6 Chi^2). The sudden bouts of hypertension occurred during induction of anaesthesia and manipulation of the adrenal glands, in 16/44 patients (36.36%). More specifically, there was a greater incidence of hypertensive crises in group B than in group A (46.7% vs. 30%, p=0.2 Chi^2). During induction of anaesthesia, 4/44 patients (9%), had transitory crises with a median BP of 200/100 mmHg (range:165/88-260/180 mmHg) and a median HR of 90 bm (range: 65-92). All these episodes resolved after medical treatment and the patients were stabilized after about 10 min. Other hypertensive crises occurred during manipulation of the adrenal glands in 12/44 patients (27.27%) with a median BP of 180/90 mmHg (range:160/80-320/150 mmHg) and a median HR of 100 bm (range: 65-130) resolved after removal of the glands. There were no sudden bouts of hypertension postoperatively. Upon waking from anaesthesia, 2/44 patients (4.54%), 1/2 in group A, had arterial hypotension (70/40-80/60 mmHg) which required administration of colloids. On postoperative day 1 2/44 patients (4.54%), 2/2 in group A, were hypotensive (70/40-80/60 mmHg) and they were treated with hydrocortisone and plasma volume expansion; by evaluating hypotensive crises we found 3 cases in group A and 1 in group B, (10% vs. 6.7%, p=0.7 Chi^2). In conclusion, by comparing group A vs group B, cardiovascular instability was similar and statistically not significant (40% vs. 53.3%, p=0.3 Chi^2). There were no complications such as stroke, myocardial infarction, pulmonary or cerebral edema, associated with the sudden bouts of hypertension. No hyperglycemic crises were observed. In every case the definitive histology report confirmed the diagnosis of PCC, without evidence of malignancy [no patient with malignancy at five years follow-up (3-13 years)]. As regards the relationship between size > 6 cm and malignancy, there was no disease recurrence observed in the study, at five years follow-up, and there were no criteria of suspected malignancy in the definitive histology reports. The search for the RET mutations identified a triple mutation (634, 640, 700) in the patient suffering from MEN 2A, but no mutations in the other patients. A male patient of group A, with a large cystic PCC, underwent "open" reoperation for residual retrocaval glandular tissue, not removed during laparoscopic treatment. At five years follow-up (3 – 13 years) no complications and/or disease recurrence were observed.

Discussion

Pheochromocytoma is a rare tumor. In the United States the incidence ranges between 1.55 and 2.1/100, 000 people/year, with a female predominance and a peak age of occurrence in the fourth or fifth decade [7, 8]. The hyperkinetic, vasoconstrictive, and hypovolemic hypertension caused by PCC, is paroxysmal in 48% of patients, and persistent in 29%, while 13% of PCC patients are normotensive [9] Before alpha blockers were introduced, perioperative mortality, now limited to 0-6%, ranged from 24-50% [10, 11]. Although some authors maintain that there is a relationship between PCC size > 6 cm, catecholamine concentration, duration of anaesthesia, and complications, functional activity seems to be independent of size. In other words, small PCC can cause severe cardiovascular crises [3, 12] as well. In this connection continuous monitoring by anaesthesiologist and reduced tumour manipulation, is recommended. Fernandez-Cruz [13] has demonstrated that during open adrenalectomy the plasma catecholamine concentration is more elevated. Preoperative treatment is recommended by the majority of endocrine surgery centres [13-15]. The most widely used protocols are based on therapy with alpha blockers [16], and calcium antagonists [2], associated with an expansion of plasma volume. Literature data demonstrate that pharmacological therapy cannot prevent intra and postoperative cardiovascular disturbances, as confirmed by our study, but do permit better resolution of such disturbances and, probably, prevents the most greatly feared adverse effects (stroke, pulmonary edema). Over the last 10 years LA has become the gold standard for the treatment of benign adrenal tumours, including PCC < 6cm in diameter [1, 17-19] . During the past 5 years interest in the literature was firmly focused on extending the use of LA to PCC > 6 cm in diameter [2, 3, 5]. Cardiovascular instability, a higher risk of malignancy, reported to reach 13-14%, and capsular disruption with seeding, were the relative contraindications to LA in these cases [20, 21]. In the light of these considerations, our study reports the results of 15/45 LA for PCC > 6 cm in diameter, and

on average 8.1 cm, comparing them with the results of patients who underwent surgery for smaller PCC. Analysis of the data shows that, although a higher incidence rate of hypertensive crises in patients treated for large PCC than in those with PCC < 6 cm (46.7% vs 30%) and a higher conversion rate (6.7 % vs 3.3%) were found, the differences were not statistically significant. Operative time, intra-and postoperative complications, mortality rate, and long-term results, were similar in the two groups, resembling the data reported in the literature [2, 3, 5]. The experience of Wilhelm [5], Henry [2], and Perry [3] shows that LA for PCC > 6 cm, in selected cases, is characterized by well contained operative times, minimal blood loss, short hospital stays and virtually no long-term recurrence. The complication rate is like that reported for smaller PCC. Because of tenacious adhesions involving the viscera or, more often, blood vessels, (the renal veins – as in our experience- and the vena cava) the conversion rate is sometimes higher: 12% according to Wilhelm [5], 37% according to Perry [3], and 6.7% in the present series. Toniato [4], with his personal experience of 64 patients observed in 15 years, after confirming the advantages of laparoscopy and reporting more blood loss in PCC > 6 cm than PCC < 6 cm, concludes that tumor size does not influence surgical outcome. Kercher [14] with an experience of 18 PCC > 6 cm in 10 years, reports longer operative times than in cases of smaller PCC, but similar blood loss, cardiovascular instability, and length of hospital stay. The immediate and long-term results of laparoscopic surgery for PCC > 6 cm or < 6 cm in diameter are therefore, very similar due to technological progress, honing of experience, and better pre-and postoperative pharmacological management, perfected over the years in referral centers. Given the rarity of PCC, the small number of case series, and the possibility of recurrence after more than 5 years, it is difficult to determine its malignant potential [22, 23]. The malignancy incidence rate ranges from 6.5 % to 13.1% [23, 24], and even though large PCC are usually associated with higher risk of malignancy [25], no clear association has been found with size [4, 5]. The incidence of malignancy in large PCC is in fact lower than reported in other adrenal tumours of the same size [26]. In case of suspected malignancy, prompt conversion is recommended and open surgery remains the only effective therapy for malignant PCC [27, 28].

Conclusions

Laparoscopic adrenalectomy is an ideal approach in the treatment of pheochromocytoma. Preoperative pharmacological therapy is recommended, and, although in association with careful intraoperative anesthesia monitoring it does not prevent sudden bouts of hypertension, it allows to manage them effectively. In our study, by comparing group A vs group B, a higher although not significant rate of hypertensive bouts and conversion to open surgery was observed. In spite of the complexity of manipulating and dissecting the adrenal gland, laparoscopic treatment for PCC > 6 cm in diameter remains safe, reliable and, in well selected cases, associated with the same complications and long-term results as smaller PCC. Minimally invasive adrenalectomy for pheochromocytoma is a complex, but elective procedure, that is sometimes a challenge to treat and should therefore be in the hands of multidisciplinary specialist teams (that include endocrinologists, cardiologists, surgeons, and anaesthesiologists), in referral centres. Based on these considerations, LA for PCC 6-8 cm in diameter would be acceptable, if performed by an expert surgeon, with great circumspection and with care taken to avoid capsular disruption.

Riassunto

La surrenectomia mininvasiva per feocromocitoma (Feo) inferiore ai 6 cm di diametro, rappresenta uno standard per innumerevoli e riconosciuti vantaggi. Tuttavia, date le notevoli difficoltà nella dissezione, il rischio di effrazione capsulare e di malignità, tale chirurgia, nelle lesioni maggiori di 6 cm, resta di notevole complessità ed oggetto di controversie. Gli autori presentano un lavoro multicentrico e retrospettivo circa il ruolo della surrenectomia laparoscopica (SL) nel trattamento di feocromocitomi con diametro maggiore od inferiore ai 6 cm. I dati, relativi a 44 pazienti, operati di SL per Feo, tra il '98 ed il '08, sono stati raccolti in maniera retrospettiva mediante un questionario proposto a quattro centri specialistici della regione Campania. In 30 casi le lesioni erano ≤ 6cm (gruppo A), in 15 risultavano > 6 cm (gruppo B). La durata dell'intervento, la stabilità cardiovascolare, il tasso di conversione, l'incidenza di complicanze intra e postoperatorie, l'ospedalizzazione ed i risultati a medio e lungo termine venivano esaminati e confrontati nei due gruppi di pazienti. Dalla valutazione statistica non risultavano differenze significative nei parametri esaminati, tuttavia nel trattamento di lesioni > 6 cm veniva osservata una maggiore incidenza di pousse' ipertensive intraoperatorie ed un piu' elevato tasso di conversione.Dall'analisi dei risultati è possibile concludere che la SL per Feo, rappresenta una metodica sicura ed affidabile, talora anche per neoplasie > 6 cm, in casi selezionati. Un adeguata preparazione preoperatoria con litici selettivi, associata ad un attento monitoraggio anestesiologico consentono un agevole gestione dell'instabilità cardiocircolatoria.

References

1. Murphy MM, Witkowski ER, Ng SC, McDade TP, Hill JS, Larkin AC, Whalen GF, Litwin DE, Tseng JF: *Trends in adrenalectomy: A recent national review*. Surg Endosc, 2010; 2:2518-526.

2. Ippolito G, Palazzo FF, Sebag F, Thakur A, Cherenko M, Henry JF: *Safety of laparoscopic adrenalectomy in patients with large pheochromocytomas: A single institution review*. World J Surg, 2008; 32:840-44.

3. Perry KA, El Youssef R, Pham TH, Sheppard BC: *Laparoscopic adrenalectomy for large unilateral pheochromocytoma: experience in a large academic medical center*. Surg Endosc, 2010; 24(6):1462-467.

4. Toniato A, Merante Boschin I, Opocher G, Guolo A, Pelizzo M, Mantero F: Is *the laparoscopic adrenalectomy for pheochromocytoma the best treatment?* Surgery, 2007; 141:723-27.

5. Wilhelm SM, Prinz RA, Barbu AM, Onders RP, Solorzano CC: *Analysis of large versus small pheochromocytomas: Operative approaches and patient outcomes*. Surgery, 2006; 140(4):553-59; discussion 559-60.

6. Conzo G, Circelli L, Pasquali D, Sinisi A, Sabatino L, Accardo G, Renzullo A, Santini L, Salvatore F, Colantuoni V: *Lessons to be learned from the clinical management of a MEN 2A patient bearing a novel 634/640/700 triple mutation of the RET proto-oncogen*e.Clin Endocrinol (Oxf). 2012 Apr 16. doi: 10.1111/j.1365-2265.2012.04412.x.

7. Greene JP: *New perspectives in pheochromocytoma*. Urol Clin North Am, 1989; 16:487-503.

8. Bornstein SR, Gimenez-Roqueplo A: *Genetic testing in pheochromocytoma. Increasing importance for clinical decision making.* Ann. N.Y. 2006; Acad. Sci, 1073:94-103.

9. Bravo EL, Tagle R: *Phaeocromocytoma: state-of-the-art and future prospects*. Endocr Rev, 2003; 24:539-53.

10. Emerson CE, Rainbird A.: *Use of a "hospital-at-home" service for patient optimization before resections of pheochromocytoma*. Br J Anaesth, 2003; 90:380-82.

11. Pullerits J, Ein S, Balfe JW: *Anaesthesia for phaeochromocytoma*. Can J Anaesth, 1988; 35:526-34.

12. Levine SN, McDonald JC: *The evaluation and management of pheochromocytomas*. Adv Surg, 1984; 17:281-313.

13. Fernandez-Cruz L, Taura P, Saenz A, Benarroch G, Sabater L: *Laparoscopic approach to pheochromocytoma: Hemodynamic changes and catecholamine secretio*n. World J Surg, 1996; 20:762-68.

14. Kercher KW, Novitsky YW, Park A, Matthews BD, Litwin DEM, Heniford BT: *Laparoscopic curative resection of pheochromocytomas*. Ann Surg, 2005; 241:919-28.

15. Pacak K, Ilias I, Adams KT, Eisenhofer G: *Biochemical diagnosis, localization and management of pheochromocytoma: focus on multiple endocrina neoplasia type 2 in relation to other hereditary syndromes and sporadic forms of the tumour*. Journal of Internal Medicine, 2005; 257:60-68.

16. Lee C Pederson, Lee JE: P*heochromocytoma*. CurrTreat Opt i Oncol, 2003; 4:329-37.

17. Conzo G, Tricarico A, Belli G, Candela S, Corcione F, Del Genio G, Ferulano GP, Giardiello C, Livrea A, Marzano LA, Porcelli A, Sperlongano P, Vincenti R, Palazzo A, De Martino C, Musella M: *Adrenal incidentalomas in the laparoscopic era and the role of correct surgical indications: Observations from 255 consecutive adrenalectomies in an Italian series*. Can J Surg, 2009; 52: 281-85.

18. Neri V, Ambrosi A, Fersini A, Valentino TP: *Laparoscopic adrenalectomy: Transperitoneal approach. Cases study*. Ann Ital Chir, 2005; 76(2):123-26.

19. Saldutti L, Romano GGA, Romano F: *Open adrenalectomy surgery: an obsolete technique? About a case of Conn's syndrome*. Ann Ital Chir, 2008; 79:47-52.

20. Henry JF, Sebag F, Iacobone M, Mirallie E*: Results of laparoscopic adrenalectomy for large and potentially malignant tumors*. World J Surg, 2002; 26:1043-47.

21. Gonzalez RJ, Shapiro S, Sarlis N, Vassilopoulou-Sellin R, Perrier ND, Evans DB, Lee JE: *Laparoscopic resection of adrenocortical carcinoma: A cautionary n*ote. Surgery, 2005; 138:1078-85.

22. *Thompson LD: Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasm: A clinicopathologic and immunophenotypic study of 100 cases.* Am J Surg Pathol, 2002: 26:551-56.

23. Pasquali D, Rossi V, Conzo G, Pannone G, Bufo P, De Bellis A, Renzullo A, Bellastella G, Colao A, Vallone G, Bellastella A, Sinisi AA: *Effects of somatostatin analog SOM230 on cell proliferation, apoptosis, and cathecolamin pheocromocitoma cells.* J Mol Endocrinol, 2008; 40(6):263-71.

24. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJM, Lombardi G, Mannelli M, Pacini F, Ponder BAJ, Raue F et al.: *Guidelines for diagnosis and therapy of MEN Type 1 and Type* 2. J Clin Endocrinol & Metabol, 2001; 86(12):5658-5671.

25. Goldstein RE, O'Neill JA, Jr, Holcomb GW 3rd, Morgan WM 3rd, Neblett WW 3rd, Oates JA, Brown N, Nadeau J, Smith B, Page DL, Abumrad NN, Scott HW Jr.: *Clinical experience over 48 years with pheochromocytoma*. Ann Surg, 1999; 229:755-64.

26. Lombardi CP, Raffaelli M, De Crea C, Traini E, D'Amore AM, Bellantone R: *Pheochromocytoma: role of preoperative diagnosis in the assessment of malignancy risk and in the choice of surgical approach*. Suppl Tumori, 2005; 4(3):S211.

27. Cobb WS, Kerker KW, Sing RF, Heniford T: *Laparoscopic adrenalectomy for malignancy.* Am J Surg, 2005; 189:405-11.

28. Conzo G, Grillo M, Campione M, Amore A, Di Marzo M, Santini L: *The role of surgery in the treatment of adrenocortical carcinoma*. Ann Ital Chir, 2002; 73(6):619-22.