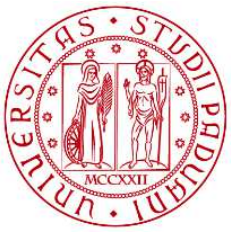

UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Università degli Studi di Padova

Dipartimento di Medicina - DIMED

CORSO DI DOTTORATO DI RICERCA INTERNAZIONALE IN

IPERTENSIONE ARTERIOSA E BIOLOGIA VASCOLARE

XXIX° CICLO

ADRENAL SURGERY: FIVE YEARS OF EXPERIENCE

Coordinatore: Ch.mo Prof. Gian Paolo Rossi

Supervisore: Ch.mo Prof. Maurizio Iacobone

Dottorando: Giovanni Viel

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ABSTRACT

Background

Adrenal disease is a heterogeneous group of diseases characterized by specific peculiarities. The development of diagnostic methods and the use of genetics in recent years have enabled us to better define each of the syndromes that originate from the adrenal gland. Although in literature there are many publications that analyze single aspects of each pathological condition, few publications allow us an overview.

The aim of this study is to analyze 5 years of endocrine surgery experience to highlight the main characteristics of the adrenal disease and the better surgical approach.

Materials and methods

The study is a retrospective analysis of prospectively collected data from January 2012 to October 2016 at the Endocrine Surgery Unit of the University of Padua, Italy. The experience is analyzed in term of diagnostic and surgical approach, in relation to the different adrenal tumors. Biochemical exams, imaging and genetic features are evaluated. The different surgical approaches are described.

Results

Two hundred twelve patients underwent surgical treatment for adrenal tumors. Ninety-four patients (38.7%) came from other regions than Veneto. Primary aldosteronism (PA) was diagnosed in 71 cases, Hypercortisolism in 43 cases (Cushing Sindrome -CS n=16, adrenocorticotropic hormone independent macronodular adrenal hyperplasia -AIMAH n=9, Cushing Disease -CD n=7, Subclinical Cushing Sindrome -SCS n=6, PA and SCS n=2), Pheocromocythoma

(P) in 33 cases, Non Secreting Tumors (NST) in 39 cases, adrenocortical cancer (K) in 9 cases, metastasis in 19 cases, CS in ectopic ACTH secreting tumor in 1 case and virilizing tumor in 1 case.

Genetic analysis reported mutation in ARMC5 gene in 2 patients with AIMAH diagnosis. Mutations in VHL, SDHD, RET, MAX and NF1 were described in patients with P. The surgical approach depends on preoperative diagnosis, genetic analysis and team experience. Cortical sparing adrenalectomy was reserved for a case of familial P. Retroperitoneoscopic procedures were performed in prevalence in patients with PA (20 cases) but also in one patient with K. Two laparoscopic adrenalectomy were performed in presence of K.

Conclusions

Surgical treatment is the final answer to a clinical, endocrinological, radiological, genetics and surgical evaluation. The complexity of the adrenal tumor classification represents itself an indication at multidisciplinary approach exclusively in high-volume centers in order to determine the most appropriate treatment.

RIASSUNTO

Presupposti dello studio

La patologia surrenalica rappresenta un gruppo eterogeno di malattie caratterizzate da specifiche peculiarità. l'evoluzione delle metodiche diagnostiche e l'ausilio della genetica negli ultimi anni hanno permesso di definire meglio ciascuna delle sindromi che originano dalla ghiandola surrenalica. Benché nella letteratura scientifica siano numerose le pubblicazioni che analizzano singoli aspetti di ciascuna condizione patologica, poche sono le pubblicazioni che permettano di avere un visione d'insieme della problematica.

Obiettivo di questo studio è identificare le peculiarità delle patologie surrenaliche sottoposte a chirurgia negli ultimi 5 anni.

Materiali e metodi

Lo studio è un'analisi retrospettiva di dati raccolti in modo prospettico a partire da Gennaio 2012 a Ottobre 2016 presso l'Unità di Endocrinochirurgia dell'Università di Padova, Italia. L'esperienza di un singolo centro è stata analizzata in termini di iter diagnostico e approccio chirurgico in relazione alle differenti diagnosi di tumore surrenalico. Esami di laboratorio, accertamenti radiologici e caratteristiche genetiche sono state considerate. Sono stati descritti i diversi approcci chirurgici.

Risultati

212 pazienti provenienti da tutta Italia, 94 (38.7%) dei quali provenienti da regioni diverse dal Veneto, sono stati sottoposti a trattamento chirurgico per neoplasie surrenaliche. In 43 casi è stato diagnosticato ipercortisolismo (16 Cushing Sindrome -CS, 9 iperplasia surrenalica macronodulare ACTH indipendente, 7

malattia di Cushing -CD, 6 Sindrome di Cushing Subclinica -SCS, 2 Iperaldosteronismo primitivo -PA and SCS), 71 PA, 33 Feocromocitoma (P), 39 Tumori non secernenti (NST), 9 carcinoma corticosurrenalico (K), 19 Metastasi, 1 CS da ACTH ectopico, 1 tumore virilizzante. Le analisi genetiche hanno riportato mutazioni di ARMC5 gene in 2 pazienti con diagnosi di AIMAH. Mutazioni in VHL, SDHD, RET, MAX e NF1 sono state descritte in P. La surrenectomia "cortical sparing" è stata riservata ad un caso di feocromocitoma familiare. L'accesso retroperitoneoscopico è stato utilizzato prevalentementee in pazienti con PA (20 casi) ma anche in un caso di K. Inoltre 2 surrenectomie laparoscopiche sono state eseguite in presenza di diagnosi di K.

Conclusioni

Il trattamento chirurgico rappresenta la risposta finale ad una valutazione clinica, endocrinologica, radiologica, genetica e chirurgica. La complessità della classificazione dei tumori surrenalici, rappresenta di per se stessa un'indicazione all'approccio multidisciplinare, esclusivamente in centri ad alto volume al fine di garantire il trattamento più appropriato.

1.INTRODUCTION

1.1 THE ADRENAL GLAND

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The adrenal cortex arises from the coelomic mesoderm of the urogenital ridge, and the medulla arises from neural crest tissue (1-3).

The cortex is divided into three zones: the zona glomerulosa**,** the zona fasciculata, and the zona reticularis. Each region secretes its own set of hormones. The adrenal cortex, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The adrenal medulla is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

Different types of tumor can arise from each part of the gland and they can be identified on the basis of characteristic symptoms. At autopsy the adrenal glands

have been found to contain grossly visible nonfunctioning adenomas in about 2%-9% of adult patients. Microscopic examination of these organs, in addition, may reveal non-uniform adrenal cortices with multiple small rounded nodules in up to 50% of patients (4).

1.2 ADRENAL INCIDENTALOMA

Adrenal tumors can identify incidentally or in relation to symptoms suggesting some type of secretion. The first case is defined adrenal incidentaloma (AI), term coined in 1982 (5): an adrenal lesion that is discovered when a radiological study is performed for indications other than suspected adrenal disease. This definition should exclude patients undergoing imaging studies as part of staging and workup of an underlying malignancy unless the radiological features are consistent with a benign lesion, and patients who had medical history or physical exam that was inadequate but that would have led to a suspicion of an underlying adrenal disorder if taken or performed.

In a report on 25 studies (6), the overall frequency of adrenal adenomas in 87.065 autopsies was 6% (range, 1 to 32). The mean prevalence of AI using high-resolution computed tomography (CT) scans is about 4% (6). The prevalence of adrenal adenomas increases with increasing age (7,8): the probability of finding an unsuspected adrenal adenoma on abdominal CT in a patient between 20 and 29 years of age would be approximately 0.2%, as compared with approximately 7% in a patient over 70 years of age (7,8).

Adrenocortical neoplasms account for less than 0.5% of all clinically significant tumors; however, autopsy studies indicate that as many as 10% of adults over the age of 40 years may have an adrenocortical tumor, usually a simple nodule that is

not larger than 1 cm; up to 36% may have micronodular hyperplasia. Cushing syndrome is a manifestation of approximately one third of all adrenal tumors. In children, a significant number of adrenocortical neoplasms presenting with Cushing's Syndrome are malignant, but the opposite is true in adults. There is a female-to-male predominance for adrenal tumors in all ages (although this is probably not true for infants and toddlers) (9).

1.3 SECRETING ADRENAL TUMORS

The adrenal cortex is a major site of steroid hormone production. Two hormones are of particular importance: aldosterone, which is produced in the zona glomerulosa in response to volume depletion and hyperkalemia, and cortisol, which is produced in the zona fasciculata in response to stress. The excess of hormones productions is responsible of characteristics syndromes.

1.3.1 Hypercortisolism

Endogenous Cushing Syndrome (CS) is a rare disease, and usually characterized by hypertension, diabetes, obesity, osteoporosis, facial rounding, dorsocervical fat pad, thin skin, purple striae, hirsutism, and mood disorders. CS is classified as ACTH-dependent in 85 % of patients, whose cortisol excess is stimulated by an uncontrolled pituitary or ectopic ACTH secretion; the former is known as Cushing’s disease (CD), and occurs in about 70 % of cases of CS, while the latter is a paraneoplastic syndrome. Adrenal (ACTH-independent) CS is secondary to the autonomous secretion of cortisol due to a benign lesion (usually adenoma (Figure 1) or primary micro or macronodular adrenal hyperplasia), or to a malignant node (cortisol-secreting adrenal carcinoma) (10,11).

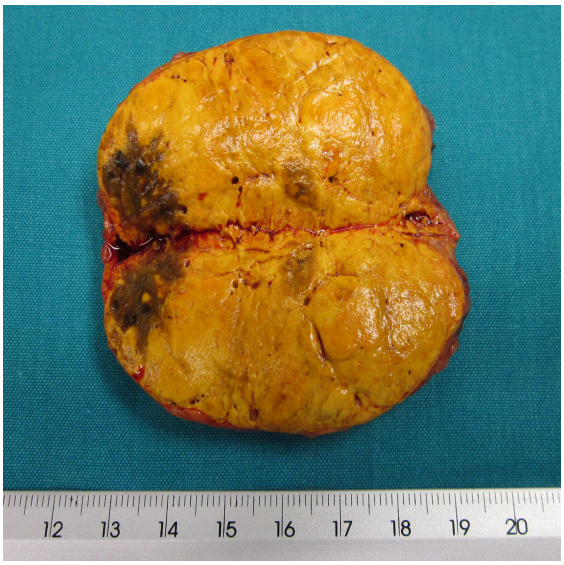

Figure 1: Adenoma in CS

ACTH-independent macronodular adrenal hyperplasia (AIMAH) is a rare distinctive subtype of Cushing's syndrome (CS), with different clinical manifestations according to the level of serum cortisol. Its main clinical features are: (a) male dominant; (b) usually a higher mean age; (c) autonomous cortisol production accompanied by a low ACTH concentration and no suppression by dexamethasone; (d) no abnormality in the pituitary region; and (e) marked enlargement of the adrenal glands and increased isotope uptake on adrenal scintigraphy (12,13)

In primary AIMAH, the disease eventually affects both adrenals, although it may present initially as an asymmetric unilateral nodule. Recent reports demonstrate an inherited mutation in the armadillo repeat-containing 5 (ARMC5) gene in patients with AIMAH and family members with unsuspected AIMAH (14,15).

The surgical treatment of choice is bilateral adrenalectomy, generally via the laparoscopic route, although some Authors advocate for selective removal of the larger adrenal in older patients in whom nonfunctional tumors are a possibility, especially if there is only a single nodule on each side (16).

Subclinical hypercortisolism or Subclinical Cushing Syndrome (SCS) is defined as a condition with excessive biochemical cortisol levels without classical signs or symptoms of overt hypercortisolism, for example purple striae, easy bruising, proximal muscle weakness and plethora. Although emerging evidence suggests that SCS should be corrected to prevent chronic sequelae, there is no consensus regarding the biochemical criteria for diagnosing SCS. It is estimated to be present in 5–30% of patients with adrenal masses serendipitously found by imaging for unrelated diseases (AI). Because AI are thought to be present in up to 4–7% of adults, the prevalence of SCS in this population may be estimated to be between 0.2 and 2.0% (17).

Actually, diagnosis of SCS relies on altered biochemical parameters related to the hypothalamic–pituitary–adrenal (HPA) axis with different cut-off levels (18). For example: (a) lack of cortisol suppression after a 1-mg overnight dexamethasone suppression test (1-mg DST); (b) elevated 24-h urinary-free cortisol (UFC) levels; (c) loss of cortisol diurnal rhythm; (d) low ACTH levels; and/or (e) low dehydroepiandrosterone–sulphate (DHEA-S) levels . Previously, only one study has evaluated the diagnostic criteria of SCS using postsurgical hypocortisolism occurrence (19).

1.3.2 Hyperaldosteronism

Primary aldosteronism (PA) is the most common cause of secondary hypertension (20), accounting for 10 % of hypertensives and 20 % of those with drug-resistant hypertension. In the Primary Aldosteronism Prevalence in Italy (PAPY) study (21), a prospective survey of 1180 consecutive newly diagnosed hypertensive patients referred to specialized hypertension centers, aldosterone-

producing adenoma and idiopathic hyperaldosteronism were found in 4.8% and 6.4% of all patients, respectively, thus leading to an overall prevalence of PA of 11%.

The diagnosis of PA is critical not only to prevent and correctly treat the complications related to hypertension, but also to prevent the non-epithelial effects related to hyperaldosteronism. Aldosterone excess is associated with the development of adverse cardiovascular, renal and metabolic effects that are partly independent of its effect on blood pressure (22,23).

PA has in fact been associated with tissue fibrosis, vascular remodeling, left ventricular hypertrophy, diastolic dysfunction and higher incidence of cardiovascular complications, including atrial fibrillation and renal damage (24).

Lateralized forms of PA, resulting from aldosterone producing adenoma (APA) (Figure 1) or unilateral adrenal hyperplasia (UAH), were shown to be surgically curable while non-lateralized disease, mainly due to bilateral adrenal hyperplasia, is usually managed by medical treatment including mineralocorticoid receptor antagonists (25).

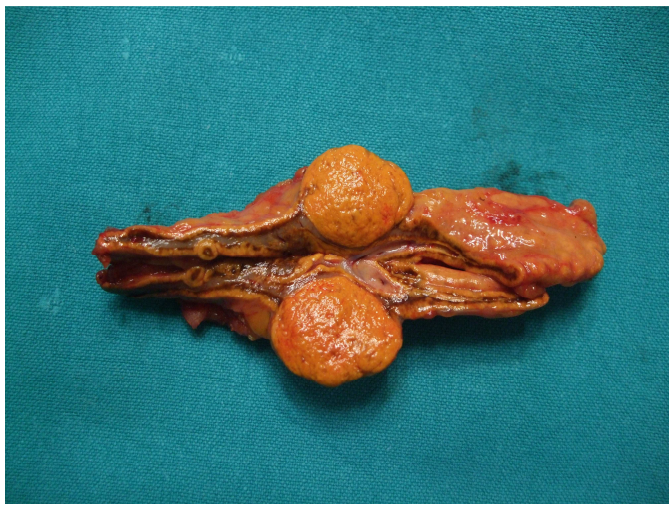

Figure 2: aldosterone producing adenoma (APA)

In recent years, Familial hyperaldosteronism (FH) has been well documented. To date, four forms of FH have been identified and are attributed to a chimeric CYP11B1/CYP11B2 gene (FH-I), a change in chromosomal region 7p22 (FH-II), KCNJ5 mutation (FH-III), and CACNA1H mutation (FH-IV), respectively (26).

1.3.3 Pheochromocytoma and paraganglioma

Pheochromocytomas (PHEOs) and paragangliomas (PPGLs) are rare neuroendocrine tumors. Standard treatment is surgical resection. Following complete resection of the primary tumor, patients with PPGL are at risk of developing new tumoral events (27). Initial biochemical testing for PPGLs should include measurements of plasma free or urinary fractionated metanephrines. Consideration should be given to preanalytical factors leading to false-positive or false-negative results. All positive results require follow-up. CT is suggested for initial imaging, but magnetic resonance image (MRI) is a better option in patients with metastatic disease or when radiation exposure must be limited. (123)I-metaiodobenzylguanidine scintigraphy is a useful imaging modality for metastatic PPGLs. We recommend consideration of genetic testing in all patients, with testing by accredited laboratories (27).

Nine genes play an important role in the pathogenesis of PHEOs (28). These genes include: Rearranged during Transfection (*RET*) proto-oncogene, von Hippel-Lindau disease tumor suppressor gene *(VHL)*, neurofibromatosis type 1 tumor suppressor gene *(NF 1)*, genes encoding four succinate dehydrogenase complex (SDH) subunits (*SDHx; i.e. SDHA*, *SDHB*, *SDHC*, and *SDHD* genes), gene encoding the enzyme responsible for flavination of the SDHA subunit

(*SDHAF2* or *SDH5* gene, for its yeast ortholog), and newly described tumor suppressor *TMEM127* gene.

Furthermore, although previously about 24% of sporadic PHEOs presented genetic mutations (29), nowadays this number is about 30% or more. Finally, there are new data linking specific genotype of these tumors to the specific localization, typical biochemical phenotype or future clinical behavior (*e.g.* *SDHB* gene mutations are associated with extra-adrenal localization, overproduction of norepinephrine and of dopamine, and a high risk of malignancy) PHEOs are associated with the following familial syndromes: multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau disease (VHL), von Recklinghausen's neurofibromatosis type 1 (NF 1) and familial paragangliomas (PGLs). Hereditary forms of PHEOs/PGLs can differ in age of diagnosis, localization, malignant potential and catecholamine phenotype (28).

All patients with functional PPGLs should undergo preoperative blockade to prevent perioperative complications (30).

Preparation should include a high-sodium diet and fluid intake to prevent postoperative hypotension. We recommend minimally invasive adrenalectomy for most pheochromocytomas with open resection for most paragangliomas. Partial adrenalectomy is an option for selected patients. Lifelong follow-up is suggested to detect recurrent or metastatic disease. Guidelines suggest personalized management with evaluation and treatment by multidisciplinary teams with appropriate expertise to ensure favorable outcomes (30).

1.3.4 Adrenocortical cancer

Adrenocortical cancer (K) (Figure 3) is a rare and aggressive malignancy afflicting approximately two patients per million per year, accounting for 0.2 % of cancer-related mortality, with 5-year OS rates of 13–58 % following resection. K can occur at any age, with a peak incidence between 40 and 50 years, and women are more often affected (55–60%); the incidence in children is particularly high in southern Brazil due to the high prevalence (0.27%) of a specific TP53 germline mutation (R337H) (31). In most patients, the disease is locally advanced or metastatic at the presentation. In light of evidence demonstrating that chemotherapy and radiation in K are largely ineffective, a complete oncologic resection (R0) remains the most important component to achieve a curative intent (32). The current SAGES guidelines for the resection of K (33), dictate that the standard treatment should be open surgery. If malignancy is unknown preoperatively or if the minimally invasive approach is initiated for suspected early-stage disease, a low threshold for conversion is strongly recommended when there is evidence of invasion, adhesion, or enlarged lymph nodes. In fact, the ideal treatment includes en bloc resection of any involved structures and regional lymphadenectomy.

However, in the last years, many articles suggest minimally invasive approach. In patients undergoing curative intent resection for K, minimally invasive techniques offer comparable surgical and oncological outcomes to open surgery among highly selected patients with a preoperative tumor size less than or equal to 10.0 cm. There was no difference in overall survival or disease free survival based on the surgical approach. The choice of the surgical approach for K, must

be guided by the ability to achieve a complete and appropriate oncological resection (32).

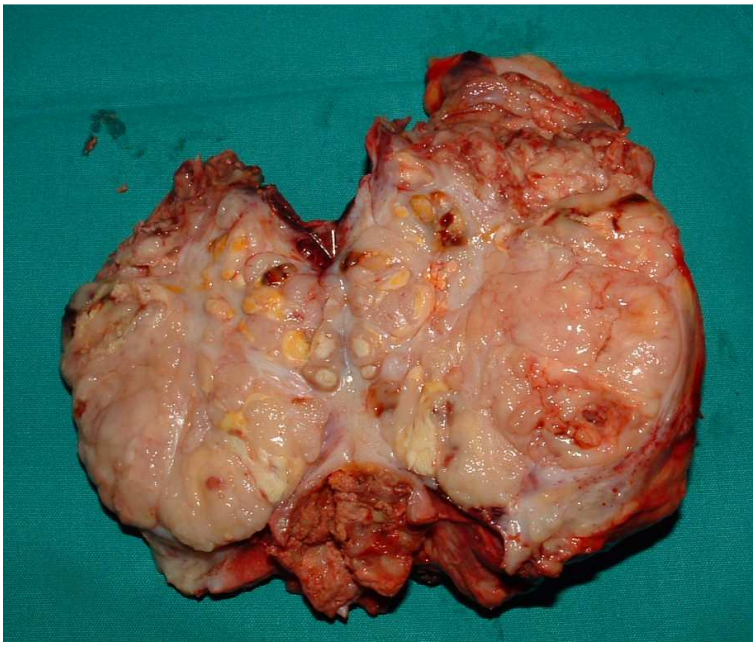

Figure 3: Adrenocortical cancer (K)

1.4 DIAGNOSIS

1.4.1 Clinical features

Patients with Cushing syndrome may complain of weight gain, especially in the face, supraclavicular region, upper back, and torso. Frequently, patients notice changes in their skin, including purple stretch marks, easy bruising, and other signs of skin thinning. Because of progressive proximal muscle weakness, patients may have difficulty climbing stairs, getting out of a low chair, and raising their arms. Menstrual irregularities, amenorrhea, infertility, and decreased libido may occur in women related to inhibition of pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which likely is due to interruption of luteinizing hormone-releasing hormone (LHRH) pulse

generation. In men, inhibition of LHRH and FSH/LH function may lead to decreased libido and impotence. Psychological problems such as depression, cognitive dysfunction, and emotional lability may develop. New-onset or worsening of hypertension and diabetes mellitus, difficulty with wound healing, increased infections, osteopenia, and osteoporotic fractures may occur.

PA is the most common cause of reversible hypertension, accounting for 10 % of hypertensives and 20 % of those with drug-resistant hypertension (20). Idiopathic hyperaldosteronism and aldosterone-producing adenomas account for more than 95% of PA and are characterized, respectively, by bilateral or unilateral involvement of the adrenal glands (34). According to different reviews and statistics, pheochromocytomas account for ~0.05–0.1% of patients with any degree of sustained hypertension. Pheochromocytoma occurs at any age, but most often in the fourth and fifth decade, and it occurs equally in men and women (29). At least 24% are familial and those tumors are often multi-focal and bilateral. In children, pheochromocytomas are more frequently familial (40%), extra-adrenal (8–43%), bilateral adrenal (7–53%), or multi-focal or bilateral if located in the adrenal gland (35). These tumors peak at 10–13 years, with a 2:1 male predominance before puberty. Previous studies suggested that less than 10% of pediatric pheochromocytomas are malignant with reported mean survival rates of 73% at 3 years and 40–50% at 5 years after diagnosis. There are currently new data suggesting that pheochromocytomas in children show much higher genetic incidence, are commonly associated with succinate dehydrogenase (SDH) subunit B (mainly in those patients with no family history of pheochromocytoma or paraganglioma) and often lead to metastatic disease even in very young children.

In case of K patients present evidence of adrenal steroid hormone excess in approximately 60% of cases (36). Rapidly progressing CS with or without virilization is the most frequent presentation. Androgen secreting K in women induces hirsutism and virilization with deepening of the voice, male pattern baldness, and oligoamenorrhea. Estrogen-secreting adrenal tumors in males lead to gynecomastia and testicular atrophy and are almost invariably malignant. Aldosterone-producing adrenocortical carcinomas present with hypertension and pronounced hypokalemia (mean serum potassium 2.3±0.08 mmol/liter). Hormonally inactive K usually presents with abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain caused by a mass effect of the large tumor.

1.4.2 Hormonal evaluation

All patients with an adrenal incidentaloma should be evaluated for autonomous cortisol secretion referred to as subclinical Cushing's syndrome (SCS), pheochromocytoma, and (if hypertensive) hyperaldosteronism (37). In most patients, a combination of 1-mg dexamethasone suppression test (DST), plasma metanephrines, along with aldosterone and plasma renin activity (PRA) measurements (if hypertensive) is a reasonable initial hormonal workup. Further hormonal evaluation is based on clinical and radiological findings. High concentration of dehydroepiandrosterone sulfate (DHEA-S) is another clue suggesting K, whereas decreased serum DHEA-S concentrations are suggestive of a benign adenoma (37).

1.4.3 Imaging

Computed Tomography (CT). With modern CT scanners, both adrenal glands are now easily recognized. On rare occasions, it is even possible to distinguish between cortex and medulla on CT scans (38,39). The three most important imaging criteria to distinguish between benign and malignant adrenal lesions are: 1) size of the lesion; 2) the CT attenuation value on an unenhanced CT scan; and 3) the pattern of enhancement and deenhancement (so-called “washout”).

Adrenal tumor size is an important determinant to help differentiate adrenal adenomas from nonadenomas; the majority of tumors less than 3 cm are benign, and the malignant adrenal lesions are generally more than 6 cm in size (38,39). Different cutoff values ranging from 4–6 cm have been proposed for surgical resection of adrenal masses . The risk of malignancy increases significantly with tumor size greater than 4 cm. the risk of malignancy in a 5-cm homogenous adrenal mass with noncontrast attenuation value of less than 10 Hounsfield units (HU) is close to 0%.

The noncontrast CT attenuation coefficient expressed in HU is superior to adrenal size in differentiating between benign and malignant adrenal tumors (40,41).

Pheochromocytomas are usually well circumscribed on CT scan and mostly inhomogeneous due to areas of cystic changes and hemorrhage. They exhibit increased vascularity with marked enhancement during contrast studies (38).

Magnetic Resonance Imaging (MRI). MRI is used to characterize adrenal lesions by characterizing the tissue signal. Several MRI techniques for characterizing adrenal lesions involve spin-echo imaging, contrastenhancement,

chemical shift imaging (CSI), diffusion weighted imaging (DWI) and MR spectroscopy (42). A normal adrenal gland has a low to intermediate signal on both T1- and T2-weighted sequences. On T2- spin-echo imaging, adenomas are generally isointense or hypointense compared with a normal adrenal gland. Sometimes, adenomas contain small foci of altered intensity that represent vascularity, cystic change or hemorrhage. Malignant lesions contain more fluid and generally have a higher T2 signal than adenomas and a higher T2 signal than a normal adrenal gland. Contrast enhancement with MRI has also been used to characterize adrenal lesions. After administration of gadolinium on dynamic imaging, the time to reach peak enhancement is the best indicator for differentiating adenomas from adrenal malignancies (43).

Positron Emission Tomography-Computed Tomography (PET-CT). Another modality widely used to characterize adrenal masses is PET-CT, which is a non-invasive whole-body imaging modality that uses the agent fluorine-18 fluorodeoxyglucose (18F-FDG) (44). Increased glucose metabolism is demonstrated in malignant tumors and secreting adrenal lesions. FDG-PET reveals information about the biochemical activity of the lesion of interest (in this case, the adrenal gland) that precedes macroscopic anatomic changes. FDG is relatively widely used for PET imaging, but there are other non-FDG radiopharmaceuticals that have limited roles. 18F-DA, 18F-DOPA and 68Ga-DOTA-peptide can be used to determine whether the lesion is of neuroendocrine origin.

Radionuclide Imaging. 131I- and 123I-MIBG (metaiodobenzylguanidine) is the most common functional imaging technique used in the assessment of pheochromocytomas MIBG is a norepinephrine analogue whose uptake is proportional to the number of neurosecretory granules within the tumor (45). 123I-MIBG has a reported sensitivity of 77-90% and a specificity of 95-100%.

Adrenal Vein Sampling (AVS). AVS is recommended by current guidelines to identify surgically curable causes of hyperaldosteronism. Multiple studies have shown that the accuracy of imaging tests, such as adrenal CT and MRI, in localizing the source of aldosterone excess is poor because aldosterone-producing microadenomas and most bilateral lesions are CT- and MRI-undetectable. Therefore, in line with international experience that AVS helps to distinguish between unilateral and bilateral aldosterone excess, both the US Endocrine Society and the Japan Endocrine Society guidelines recommend that AVS be performed in all patients who have the diagnosis of PA and who want to pursue surgical management (46).

1.5 Treatment

The laparoscopic approach to adrenalectomy was first introduced in 1992 and has since been adopted as the preferred approach for resection of benign, functioning, and nonfunctioning adrenal masses (47).

Laparoscopic transperitoneal adrenalectomy, has now been proven to be a safe and effective treatment; laparoscopically treated patients have fewer postoperative complications when compared with patients treated with open adrenalectomy (48). Additional benefits of laparoscopy are smaller incisions, decreased

postoperative pain, and a shorter hospital stay. Complications of laparoscopic surgery may include conversion to open surgery (T), hematoma due to intraoperative vascular injury, thromboembolism, pneumothorax or hemothorax. Laparoscopic surgery using the transperitoneal (S) or retroperitoneal (S (RETRO)) approaches is currently the preferred strategy to treat patients with unilateral PA. In general, three recent meta-analyses compared the S and S (RETRO) adrenalectomy: two concluded that both techniques have equivalent outcomes whereas the other claimed the S (RETRO) approach to be superior in short-term outcomes (48). Figure 4.

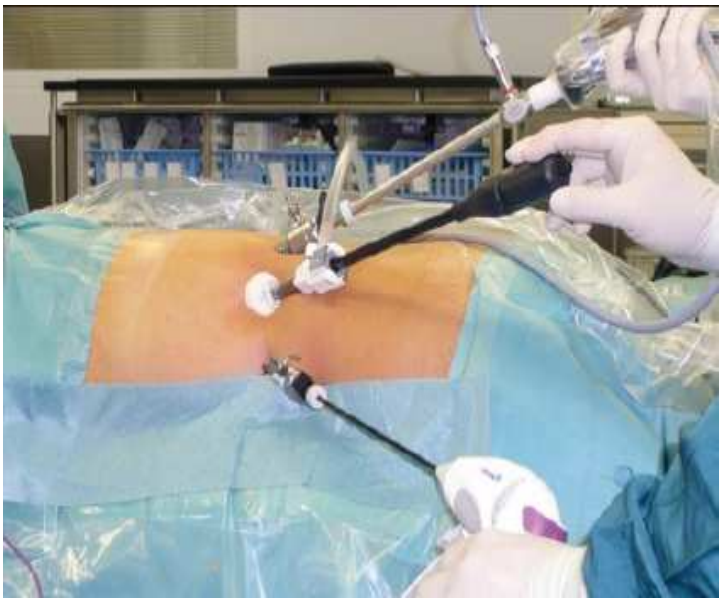

Figure 4. Retroperitoneal approach.

For a long time, unilateral total adrenal excision has been considered the technique of choice in patients with surgically correctable PA. However, the routine unilateral partial adrenalectomy has also been advocated in order to preserve the remnant adrenal function and avoid potential adrenal insufficiency (49).

This strategy may expose the patient to increased risk of failures because of incomplete excision with subsequent persistent and recurrent. If in familial

pheochromocythoma represents the treatment of choice, the indication to laparoscopic total or partial adrenalectomy in patients with unilateral PA remains controversial (48).

2. AIM OF THE STUDY

Aim of this study is to analyze the adrenal surgery experience in single high volume center to report the main characteristics of each disease and identify in each sub group of pathology rare forms that condition the surgical approach.

3. PATIENTS, MATERIALS AND METHODS

The study is a retrospective analysis of prospectively collected data from January 2012 to October 2016 at the Endocrine Surgery Unit of the University of Padua, Italy. The experience of the center is analyzed in term of diagnostic and surgical approach in relation to the different adrenal disease. Patients' records were reviewed to gather relevant demographics, personal and familial history, body mass index (BMI, defined as body weight (kg)/height (m^2), normal values 20 to 24.9), hormonal and biochemical parameters, number of antihypertensive drugs and lateralizing techniques used in case of PA, size of the nodule at preoperative imaging, postoperative morbidity, and histopathology findings. The general characteristics and some rare cases were reported for each group. All patients underwent lateralizing techniques including CT scan and/or MR, iodocholesterol or MIBG scintigraphy, FDG or DOPA PET-CT and/or AVS in case of PA.

AVS was performed with bilateral simultaneous catheterization, by using one catheter for each adrenal vein. Successful selective catheterization was usually confirmed when the ratio between cortisol concentration in each adrenal vein and the inferior vena cava was greater than 1.1; unilateral aldosterone hypersecretion

was usually confirmed when the ratio of adrenal vein aldosterone concentration to the ipsilateral cortisol concentration on the side with the higher ratio over the contralateral aldosterone to cortisol ratio (AVS ratio) was greater than 2. Each group of pathology were identify and treated separately. SCS was defined on the basis of the absence of clinical features specific for overt Cushing's syndrome (facial plethora, striae rubrae, easy bruising, and proximal muscle weakness, assessed on clinical basis, that best discriminate Cushing's syndrome) and the presence of laboratory abnormalities suggestive of ACTH-independent hypercortisolism (11,17): morning serum cortisol levels greater than 5 mg/dL after the administration of 1 mg of dexamethasone in the evening the day before; morning ACTH levels <10 pg/mL, and daily urinary-free cortisol (UFC) greater than 76 mg/day (168 nmol/24h).

The classification adrenocortical carcinoma stage defines: stage I, K ≤5 cm in the largest diameter and confined to the adrenal gland; stage II, K >5 cm without extra-adrenal invasion; stage III, presence of positive lymph nodes, infiltration to the surrounding tissue, or vascular tumor extension; stage IV, distant metastasis. Resection margins at surgery were defined as: R0, no evidence of tumor; R1, microscopically positive; R2, macroscopically positive; RX, unknown.

Statistical analysis was performed with SPSS program. Quantitative data are shown as mean ±SD, and numbers and percentages are provided for qualitative data. Percentages were compared using chi-squared tests, and Student's t-test was used for continuous variables. All tests were two-sided, and p values <0.05 were considered statistically significant.

4. RESULTS

Two hundred twelve patients underwent 224 surgical procedures for adrenal tumor and 221 adrenalectomies, at Endocrine Surgery Unit of Padua University. Three (1,3%) out of the 224 surgical procedures were performed for recurrent malignant disease. Ninety-four patients (38.7%) came from other regions than Veneto.

The mean age of the patients included in the study was 53.3 years (SD±13.58) (Figure 5), and the male/female ratio was 96/116 (45.3% vs. 54.7%).

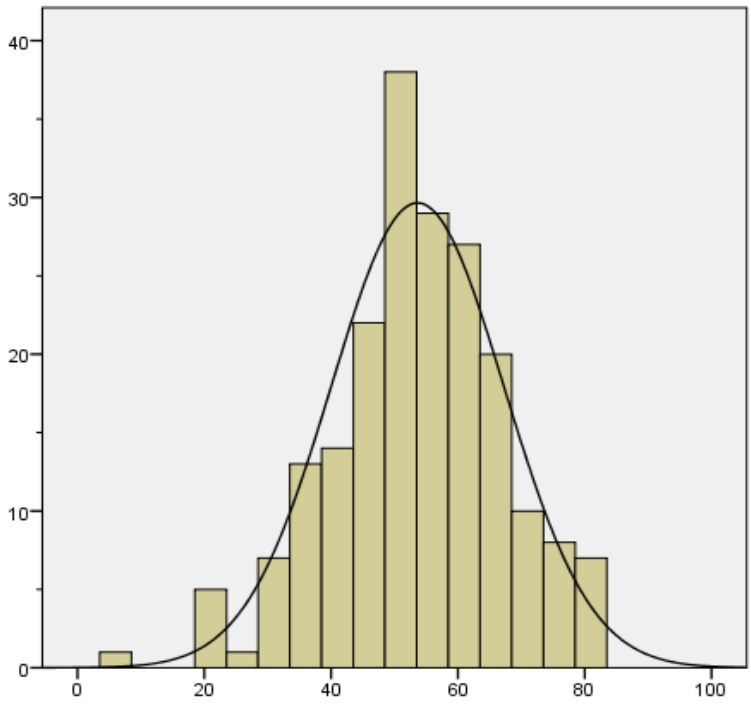

Figure 5: Age (Years)

All patients performed blood exams and CT scan and/or MRI, iodocholesterol or MIBG scintigraphy, FDG or DOPA PET-CT and/or AVS. CT was performed in

200 cases, MRI in 75 cases, PET-CT in 53 cases and scintigraphy in 21 cases. AVS was performed in 67 cases of PA.

Diagnosis and side of disease are described in Table 1.

Diagnosis	n. patients (%)	M/F	Right	Left	Bilateral
PA	69 (32.5)	40/29	32	37	0
PA+SCS	2 (0.9)	0/2	2	0	0
CS	16 (7.5)	2/14	11	5	0
AIMAH	9 (4.2)	3/6	4	3	2
SCS	6 (2.8)	0/6	2	4	0
CD	7 (3.3)	1/6	3	0	4
P	33 (15.6)	13/20	14	17	2
K	9 (4.2)	3/6	3	6	0
METASTASIS	19 (9)	14/5	10	8	1
NST	39 (18.4)	20/19	19	20	0
VT	1 (0.5)	0/1	1	0	0
Ectopic ACTH	1 (0.5)	0/1	0	0	1
Others	1 (1.5)	0/1	/	/	/
Total	212 (100)	96/116	101	100	10

Table 1: Diagnosis. PA: Primary Hyperaldosteronism; P: Pheochromocytoma; K: Carcinoma; CD: Cushing's Disease; CS: Cushing's Syndrome; SCS: Subclinical Cushing Syndrome; NST: Nonsecreting Tumors; VT: Virilizing Tumor; Ectopic ACTH: Ectopic ACTH secreting tumor; Others: surgery for recurrent disease.

The surgical approach is described in Table 2.

Surgery	n. patients	%
S	169	79.7
S (RETRO)	26	12.3
S SPARING	1	0.5
T	16	7.5
TOTAL	212	100.0

Table 2. Surgical approach. S: endoscopic transperitoneal; S (RETRO): retroperitoneoscopic; S SPARING: endoscopic transperitoneal with adrenal sparing; T: open transperitoneal.

The surgical approach in relation to the pathology is described in Table 3.

Diagnosis	S	S (RETRO)	T
PA	49	20	0
PA+SCS	1	0	1
CS	14	2	0
AIMAH	9	0	0
SCS	6	0	0
CD	5	1	1
P	29	1	4
K	2	1	6
METASTASIS	16	0	3
NST	37	1	1
VT	1	0	0
Ectopic ACTH	1	0	0
Others	0	0	1
Total	170	26	16

Table 3. The surgical approach in relation to the pathology. PA: Primary Hyperaldosteronism; P: Pheochromocytoma; K: Carcinoma; CD: Cushing's Disease; CS: Cushing's Syndrome; SCS: Subclinical Cushing Syndrome; NST: Nonsecreting Tumors; VT: Virilizing Tumor; Ectopic ACTH: Ectopic ACTH secreting tumor; Others: surgery for recurrent disease.

Only one patient, with adrenocortical cancer, experienced two different approach: S at the first operation and T for recurrence.

Two patients underwent reoperations for recurrent adrenal cancer and for recurrent malignant pheochromocytoma, respectively. In both cases an open approach was chosen.

Only in 2 cases final pathology described malignant features, in contrast with preoperative exams suggestive for benign disease. In both cases the disease didn't recur.

The size of nodules are described in Figure 6.

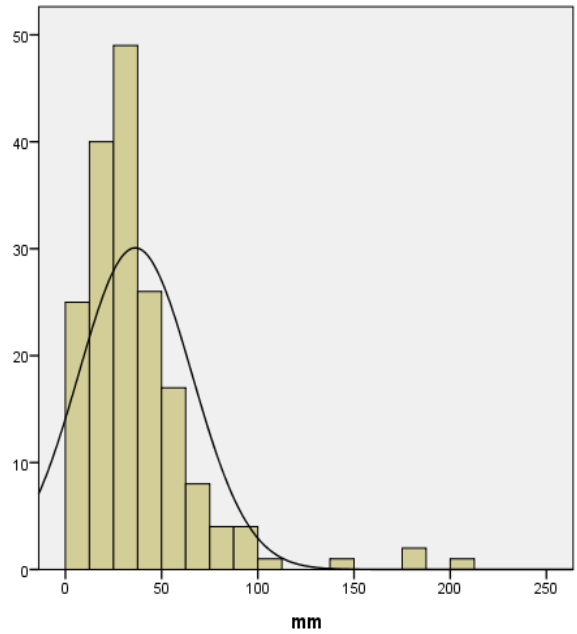

Figure 6. Size of nodules.

The comparison of the mean size of nodules between the groups is described in Table 4

Comparison	Mean Difference	P value
PA vs P	-27.9	P<0.001
PA vs CS	-18.3	P<0.01
PA vs K	-62.1	P<0.001
PA vs METASTASIS	-31.8	P<0.01
P vs CS	9.6	P>0.05
P vs K	-34.1	P<0.01
P vs METASTASIS	-3.8	P>0.05
CS vs K	-43.7	P<0.001
CS vs METASTASIS	-13.5	P>0.05
K vs METASTASIS	30.2	P>0.05

Table 4. The mean size of nodules between the groups. PA: Primary Hyperaldosteronism; P: Pheochromocytoma; K: Carcinoma; CS: Cushing's Syndrome; NST: Nonsecreting Tumors.

HYPERCORTISOLISM

Hypercortisolism occurred in 43 patients.

CS was diagnosed in 16 cases, CD in 7 cases and CS for ectopic ACTH secretion in one case. Male/Female ratio was 6/37. The mean age of patients was 50.72 years (SD ±15.2). In all cases were collected data about clinical findings, biochemical exams and imaging findings. The characteristics of different subgroups are reported in Table 5.

DIAGNOSIS	n. patients (%)	M/F	n. adrenalectomy (%)
CS	16 (37.3)	2/14	16 (32)
SCS	6 (13.9)	0/6	6 (12)
PA + SCS	2 (4.6)	0/2	2 (4)
AIMAH	9 (21)	3/6	11 (22)
K(CS)	2 (4.6)	0/2	2 (4)
CD	7 (16.3)	1/6	11 (22)
Ectopic ACTH	1 (2.3)	0/1	2 (4)
Total	43 (100)	6/37	50 (100)

Table 5. Characteristics of subgroups. CS: Cushing's Syndrome; K(CS): Carcinoma with Cushing's Sindrome; PA: Primary Hyperaldosteronism; SCS: Subclinical Cushing Syndrome; CD: Cushing's Disease; Ectopic ACTH: Ectopic ACTH secreting tumor.

The characteristics of patients are reported in Table 6.

	AGE years	SIZE mm	Cort 8 nmol/L	ACTH 8 ng/L	UFC nmol/24h
Mean (Std. deviation)	50.72 (±15.2)	38.8 (±14.8)	601.0 (±210.5)	5 (±2.6)	943.0 (±1277.5)
Median	51.5	35	578	5	412
Min	19	17	301	1	60
Max	82	85	1156	14	4959

Table 6. Characteristics: Cort 8: Cortisol h8; ACTH 8: adrenocorticotropin h8; UFC: Urinary Free Cortisol 24h.

Fifty adrenalectomy were performed. Transperitoneal laparoscopic adrenalectomy was performed in 36 cases and open adrenalectomy in 4 cases. Only in 3 cases a retroperitoneoscopic approach was performed. No postoperative complications occurred. The side of operation is described in Table 7.

Side	Patients n.	%
BILATERAL	7	16.3
RIGHT	23	53.5
LEFT	13	30.2
TOTAL	43	100.0

Table 7. Side of operation.

SCS was diagnosed in 6 patients. In others 2 SCS was associated to PA. In Table 8 are reported the characteristics of these patients.

	AGE years	SIZE mm	TIME min	K mmol/L	CORT 8 nmol/l	ACTH 8 ng/dl	Des 1mg nmol/L	DHEAS umol/l	CT mm	MRI mm
Mean (std.deviation)	58.8 (±13.9)	37.8 (±10.9)	66.6 (±6.5)	4.15 (±0.3)	469.5 (±192.8)	11.9 (±9.6)	286.8 (±156.1)	1.8 (±1.41)	35.2 (±9.3)	34.5 (±10.6)
Median	56.5	35	68.5	4.05	390.5	10.3	230	1.3	34	34.5
Min	42	27	58	3.9	301	2	140	0.70	27	27
Max	82	55	75	4.7	731	25	523	3.4	46	42

Table 8. K: kalemia mmol/L; CORT 8: cortisol h8; ACTH 8: adrenocorticotropin h8. Des 1mg: Nugent Test; CT: computed tomography; MRI: magnetic resonance imaging.

Patients with diagnosis of SCS underwent unilateral adrenalectomy. In 2 cases SCS was associated with PA.

No postoperative morbidity or mortality occurred in SCS group, and no conversion to laparotomy was needed. At 1 month of follow up not significant differences were reported from mean of 24-hour UFC, morning ACTH and morning Cortisol levels before and after surgery (Tab. 9).

	Before surgery	After surgery	p
24 h UFC (nmol/24h)	102 (±32.31)	79.6 (±48.74)	0.531
ACTH h8 (ng/L)	9.42 (±7.52)	57.2 (±77.39)	0.229
Cortisol h8 (nmol/L)	459.17 (±204.46)	365.8 (±116.24)	0.565

Table 9: UFC: Urinary Free cortisolo; ACTH h8: adrenocorticotropin h8. UFC: Urinary Free Cortisol 24h.

In all cases pathology described a main single nodule with surrounding micronodules of the cortex. In three cases fasciculata zona cells were prevalent and in two cases, both type of cells (from fasciculata and reticularis) were present.

AIMAH was diagnosed in 9 patients. The largest adrenal gland was removed. At preoperative imaging, the mean size of the removed adrenal gland was 44.6 mm (SD ±17.3); the mean size of the other side was 24.4 mm (SD ±8.3) (p= 0.009).

Seven unilateral adrenalectomy was performed and in 2 cases the completion of contralateral adrenalectomy was needed because of persistent hypercortisolism. The reoperations were performed after 17 month and 5 month, respectively.

The characteristics of these two patients were reported in Tab 10.

SEX	Preoperative				Postoperative			
	AGE (year)	Cort 8 nmol/L	ACHT 8 ng/dl	UFC	AGE (year)	Cort 8 nmol/L	ACHT 8 ng/dl	UFC
M	44	761	30	800 mcg/24h	44	746	30	797 mcg/24h
F	62	395	<5	308 nmol/24h	63	433	<5	92 nmol/24h

Table 10. Characteristics of two patients underwent reoperation. CORT 8: cortisol h8; ACTH 8: adrenocorticotropin h8; UFC: Urinary Free Cortisol 24h.

At mean follow up of 20 months (range 44-3) the other 7 patients didn't received the indication for contralateral adrenalectomy. In all 9 cases pathology confirmed diffuse hyperplasia.

Genetic analysis described a mutation of ARMC5 gene in 2 patients. In another case the presence of illicit expression of membrane receptors in the adrenal cortex was observed, which may be responsible for the adrenal overgrowth and subsequent cortisol hypersecretion. The stimulation of receptors for Gonadotropin Releasing Hormone (GnRH) + Thyrotropin Releasing Hormone (TRH) resulted positive and there was a cortisol reduction after somatostatin analog drug. No others mutations or illicit receptors were reported in the remaining patients.

Seven patients underwent adrenalectomy for refractory CD. In 4 cases a synchronous bilateral resection was performed while in 3 cases the choice was a unilateral procedure. This second solution was determined in two cases by the refuse of bilateral adrenalectomy and in one case because of the normal appearance of the contralateral gland at CT scan.

One patient presented hypercortisolism in presence of ectopic ACTH secretion. CT scan described increased dimension in both glands, without prevalence. A bilateral laparoscopic adrenalectomy was performed. Final pathology was hyperplasia.

After discharge, all patients with hypercortisolism received cortisol supplementation. At a 1 month supplementation therapy was discontinued in all patients that underwent unilateral adrenalectomy. All bilateral adrenalectomy received cortisol and mineralocorticoid supplementation.

PRIMARY ALDOSTERONISM

PA was diagnosed in 71 patients, but 2 patients had also SCS. Demographics are described in Table 11. Sixty seven patients performed AVS and 4 patients refused the procedure. All patient were hypertensive. Features of surgery are described in Tables 12-13 and Figure 7.

	AGE years	SIZE mm	TIME min	DRUGS PRE	DRUGS POST
Mean (std. deviation)	51.96 (±11.3)	17.25 (±10.8)	82.61 (±37.8)	3 (±1.2)	1 (±1.1)
Median	50.0	15.0	70	3	1
Min	30	2	35	1	0
Max	82	65	235	6	4

Table 11. Demographics. AGE: age of patients, SIZE: size of nodule; TIME: time of surgery; DRUGS PRE: preoperative therapy; DRUGS POST: postoperative therapy.

The mean number of drugs was significantly reduced after treatment ($p<0.0001$).

SURGERY	n.	%
S	49	70.4
S (RETRO)	20	28.2
T	1	1.4
Total	69	100.0

Table 12. Surgical approach. S: endoscopic transperitoneal; S (RETRO): retroperitoneoscopic; T: open transperitoneal.

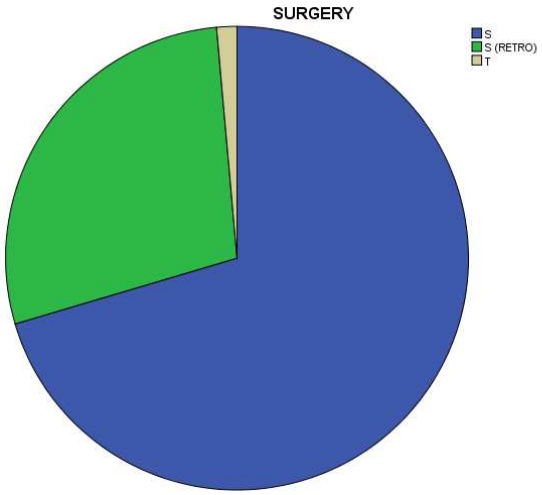

Figure 7. Surgical approach.

	S	S (RETRO)	P
Mean OPERATIVE TIME (Std deviation)	73.33 (±19.6)	112 (±55.4)	0.0004
Mean Age (Std deviation)	51.9 (±11.9)	52 (±10.2)	0.9
Mean size (Std deviation)	17 (±1.64)	14.9 (±1.09)	0.4
Mean BMI (Std deviation)	27.4 (±15)	24.8 (±2.8)	0.5

Table 13. Comparison between S and S (RETRO) groups. S: endoscopic transperitoneal; S (RETRO): retroperitoneoscopic.

Only the mean operative time of S and S (RETRO) was significantly different (p 0.0004).

An inferior caval vein injury was reported in a patient who underwent adrenalectomy with S (RETRO) approach; however, no conversion to open surgery was needed to control the bleeding. A retroperitoneal hematoma occurred after a laparoscopic procedure, that needed evacuation. In 2 patients a renal cyst evacuation was performed during laparoscopic operation. No conversion from laparoscopic to open approach was needed and no cortical sparing procedure was perfomed. In all cases pathology revealed a benign disease.

PHEOCHROMOCYTHOMA

Thirty-four patients underwent adrenalectomy for pheochromocythoma. The main characteristics of these patients are described in Table 14.

	AGE years	SIZE mm	U Metan umol/24h	U Normetan umol/24h	U Adren ug/24h	U Noradren ug/24h	U Dopamin nmol/24h	CT mm	MR mm
Mean (std. deviation)	55.6 (± 15.9)	42.1 (± 30.3)	167.4 (±707.1)	327.9 (±987.6)	540.1 (±1183.9)	1714.6 (±1349.5)	1741.5 (±1202.7)	40.2 (±29.2)	41.5 (±29.3
Median	58	35	1.31	3.57	159	1879	1200	30	34
Min	6	13	0.16	0.27	6.4	108.6	132	16	18
Max	82	180	3087	3662	5352	4682	3811	150	140

Table 14. Characteristics of patients underwent adrenalectomy for pheochromocythoma. U Metan: Urinary metanephrine; U Normetan: Urinary Normetanephrine; U Adren: Urinary Adrenaline; U Noradren: Urinary Noradrenaline; U Dopamin: Urinary Dopamine; CT: computed tomography; MRI: magnetic resonance imaging.

Surgical approach is described in Table 15.

SURGERY	Patient n.	%
S	29	87.9
S (RETRO)	1	3
T	3	9.1
Total	33	100.0

Table 15. Surgical approach. S: endoscopic transperitoneal; S (RETRO): retroperitoneoscopic; T: open transperitoneal.

Malignant pheochromocytoma was diagnosed in 3 cases and one of this patients had recurrent disease. In one case pathology described a typical pheochromocythoma without necrosis or nuclear atypia but with a local vascular invasion. No recurrent disease was reported after 46 mouth.

All cases underwent to genetic tests to identify mutations responsible of familial forms. RET, VHL, SDHA, SDHD, SDHB, SDHC, NF1, SDHAF2, TMEM127, MAX were analyzed. Mutations for VHL, SDHD, RET, and NF1 were identified.

One patient with VHL mutation underwent to cortical sparing bilateral adrenalectomy (Figure 8). He was a 6 years old boy. His mother and his sister had the same operation: the mother with open approach 13 years before and the sister with laparoscopic approach 1 year before. This patient and his mother had recurrence of disease in retrocaval paraganglioma after 6 month and 13 years respectively. Laparoscopic transperitoneal approach was performed without complications. In all cases cortical sparing approach avoided steroid hormone replacement.

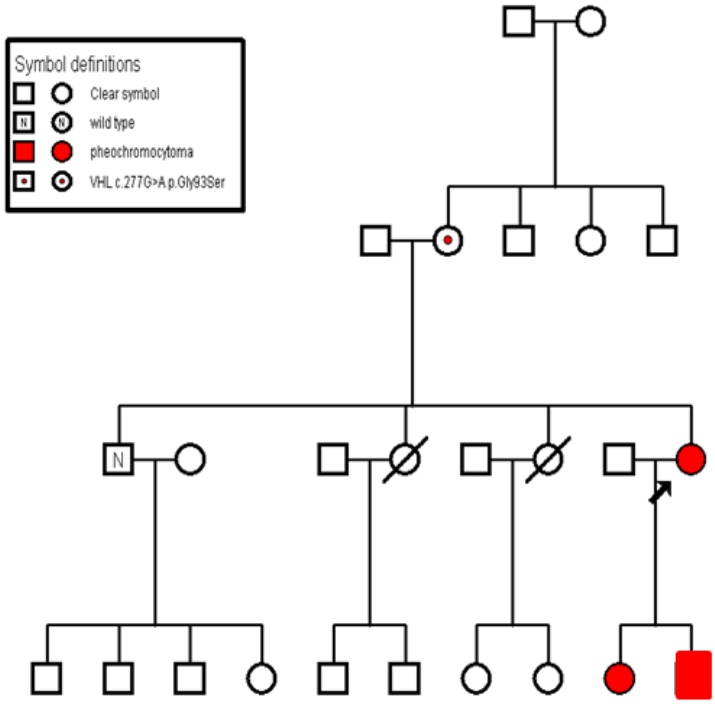

Figure 8. Genealogic tree of familial pheochromocyatomas. Arrow represents the mother of patient described.

Another patient with bilateral disease presented a mutation in the RET proto-oncogene. A bilateral open adrenalectomy was performed.

In the others cases, patients carrier of genetic mutation, underwent unilateral adrenalectomy. No recurrences of disease occurred at follow up of patient with NF1 mutation (4 month) and SDHD mutation (30 month).

NON SECRETING TUMORS (NST)

NST is heterogeneous group of adrenal disease characterized by absence of hormones hyperproduction. The summary of epidemiologic, bioumoral and radiological findings are reported in Tables 16-18.

	AGE	SIZE mm	TC mm	MRI mm
Mean (std. deviation)	56.08 (±12.38)	45.41 (±35.16)	37.41 (±18.27)	34.65 (±15.5)
Median	57	39	40	38.5
Min	20	3	2.5	3
Max	82	200	150	170

Table 16. Epidemiologic features. Age of patients, SIZE of nodules; Size at CT scan and MRI. CT: computed tomography; MRI: magnetic resonance imaging.

	Na mmol/L	K mmol/L	Aldosterone pmol/L	PRA ug/L/h	Cort h8 nmol/L	ACTH h8 ng/L	DES 1mg nmol/L	UFC nmol/24h
Mean (std. deviation)	140.3 (±2.2)	4.1 (±0.3)	306.4 (±180.1)	1.3 (±1.1)	412.4 (±152.1)	17.2 (±8.4)	35.5 (±12.8)	171.9 (±197.3)
Median	140.5	4.1	261.5	0.9	411	16.5	37	96
Min	135	3.4	52.8	0.3	26	9	19	40
Max	144	4.7	750	3.48	666.3	43	62	649.6

Table 17. Blood and urinary exams. Na: sodium; K: potassium; PRA: plasma Renin Activity; Cort h8: Cortisol h8; DES: Dehydroepiandrosterone sulphate, UFC: Urinary Free Cortisolo.

	U Metan umol/24h	U Normetan umol/24h	U Adren ug/24h	U Noradren ug/24h	U Dopamin nmol/24h
Mean (std. deviation)	15.1 (±44.2)	65.6 (±182.6)	21.8 (±14.1)	235.9 (±173.2)	1607.2 (±435.3)
Median	0.14	0.28	19	209.5	1578.5
Min	0.06	0.11	2.9	53.7	1125
Max	164	630	44	605	2147

Table 18. Urinary exams. U Metan: Urinary metanephrine; U Normetan: Urinary Normetanephrine; U Adren: Urinary Adrenaline; U Noradren: Urinary Noradrenaline; U Dopamin: Urinary Dopamine

Pathology is described in table 19 and Figure 9.

Pathology	n.	%
Adenoma	25	64.1
Adrenalitis	1	2.56
Angioma	1	2.56
Cyst	1	2.56
Ganglioneuroma	1	2.56
Liposarcoma	1	2.56
Lymphoma	1	2.56
Myelolipoma	7	17.98
Neurofibromas	1	2.56
Total	39	100.0

Table 19. Pathology.

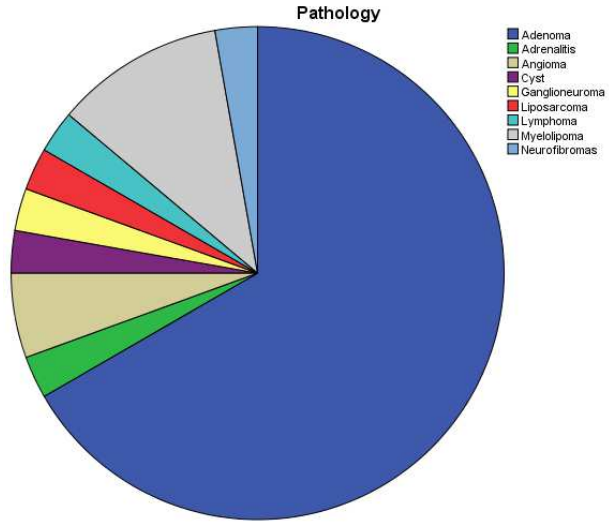

Figure 9. Pathology

ADRENOCORTICAL CANCER

Ten patients underwent surgery for K; 9 adrenalectomies for initial diagnosis and one reoperation were performed. The characteristics of these patients are described in Tables 18-22.

STAGE	n.	%
1	3	33.3
2	2	22.2
3	3	33.3
4	1	11.2
Total	9	100

Table 20. Stage at diagnosis

SEX	n.	%
F	7	70
M	3	30
Total	10	100

Table 21. Sex distribution.

SIDE	n.	%
Right	3	30
Left	7	70
Total	10	100

Table 22. Side of the disease.

	AGE years	SIZE mm
Mean (std. deviation)	53.1 (±13)	96.7 (±64.8)
Median	55	90
Min	26	25
Max	74	220

Table 20. Age of patients and size of cancer.

DIAGNOSIS	n.	%
K	4	40
K and caval thrombosis	1	10
K(CS)	1	10
K(CS) and caval thrombosis	1	10
K(TV)	2	20
Kr(TV)	1	10
Total	10	100

Table 21. Pathology. K: adrenal cancer; K(CS): adrenal cancer with Cushing syndrome; K(TV) adrenal cancer and virilizing syndrome; Kr(TV): recurrent adrenal cancer and virilizing syndrome.

SURGERY	n.	%
S	2	20
S (RETRO)	1	10
T	7	70
Total	10	100.0

Table 22. Surgical approach. S: endoscopic transperitoneal; S (RETRO): retroperitoneoscopic; T: open transperitoneal

	STAGE			
SURGERY	1	2	3	4
S	2	0	0	0
S (RETRO)	1	0	0	0
T	0	2	3	1
Total	3	2	3	1

Table 23. Surgical approach and stage. S: endoscopic transperitoneal ; S (RETRO): retroperitoneoscopic; T: open transperitoneal

In 3 cases, a nephrectomy, nephrectomy and liver resection, and splenectomy and nephrectomy were also performed.

Recurrent disease occurred in 3 cases. In one case, a 53 years old woman, 22 month after left adrenalectomy for adrenal cancer secreting virilizing hormones, had local and omental recurrence. Thus, this patient underwent to 2 operations (R1).

In another case, a 50 years old female, 6 month after right adrenalectomy for cortisol hypersecreting adrenal cancer, had local and lymph node recurrence. Surgical resection was performed with open approach (R1).

Moreover, a 62 years old female, 17 month after right adrenalecomy for adrenal cancer presented local recurrence: a laparotomy was performed to remove a mass between caval and portal vein, but it was not possible remove completely the tumor because of vascular infiltration (R2).

Three patients died 10, 13 and 18 months after surgical treatment, respectively. Others four patients are alive after e mean follow up of 23.2 month (range 6-40).

The survival of patients with K is reported n Figure 10 and 11.

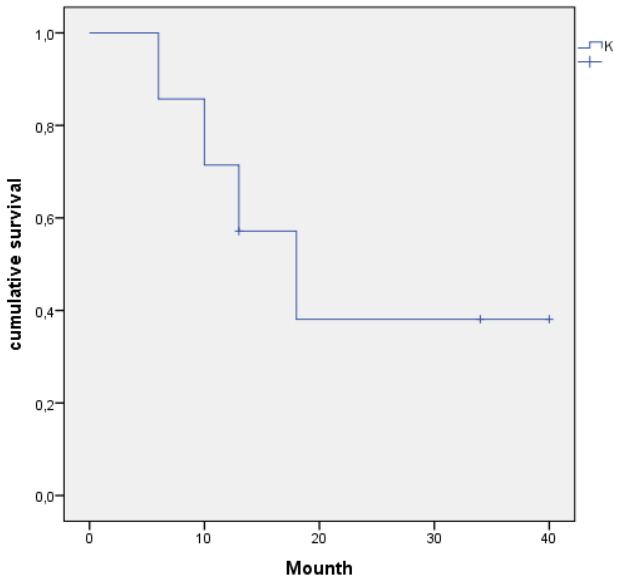

Figure 10. Kaplan-Meier curve: overall survival in K patients.

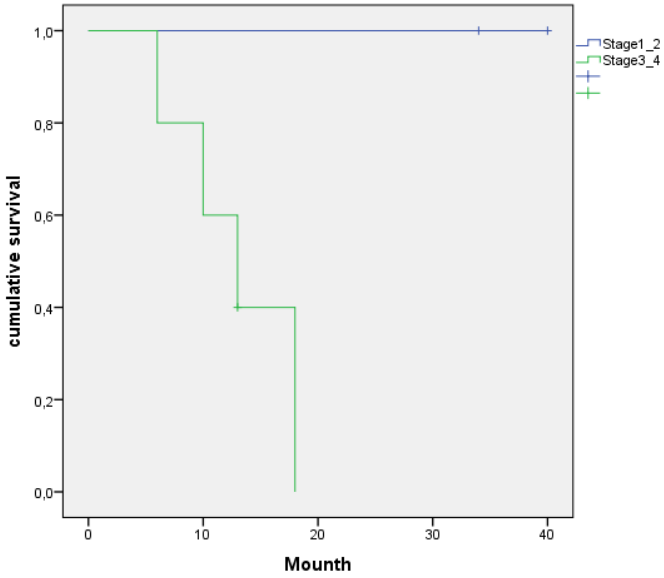

Figure 11. Kaplan-Meier curve: overall survival in K patients per Stage (early 1-2 and advanced 3-4).

METASTASIS

Adrenal gland is frequently side of metastasis. Tables 23-25 and Figure 12 describe the characteristics of the patients.

	AGE years	SIZE mm
Mean (std. deviation)	62.3 (±15.7)	47.2 (±24.5)
Median	64	39
Min	21	24
Max	82	95

Table 23. Age of patients. Size of nodules.

SURGERY	n.	%
S	16	84.2
S (RETRO)	0	0
T	3	15.8
Total	19	100.0

Table 24. SURGERY. S: endoscopic transperitoneal; S(RETRO): retroperitoneoscopic; T: open transperitoneal

SIDE	Patient n.	%
Bilateral	1	5.3
Right	10	52.6
Left	8	42.1
Total	19	100

Table 25. Side of nodules

	Frequenza	%
COLON METHASTASIS	3	15.8
LUNG METHASTASIS	12	63.2
PANCREATIC METHASTASIS	1	5.3
RENAL METHASTASIS	2	10.5
THYMUS METHASTASIS	1	5.3
Total	19	100.0

Table 26. Pathology.

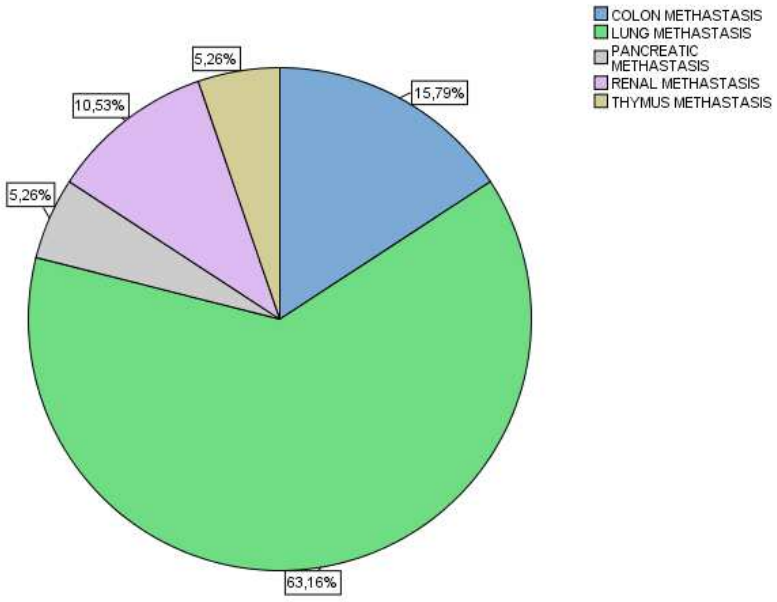

Figure 12. Pathology

5. DISCUSSION

Epidemiology and diagnosis

Adrenal neoplasms are rare diseases that account for less than 0.5% of all clinically significant tumors. At Endocrine Surgery Unit of Padua, patients from Veneto (61.3%) and from all over Italy (38.7%) were treated. It is crucial to be a reference center for rare pathologies: it guarantees a specific experience and thorough knowledge of these disease and allows to have a multidisciplinary team that is necessary, in particular in rare conditions. In fact, it is possible to achieve board decisions about diagnosis, treatment and follow up of the patients and design a precise profile of patients with a rare disease.

Nowadays, the evolution of knowledge in adrenal disease open new perspectives for understanding the pathophysiology.

Until few years ago, the classifications described only few groups of adrenal disease, based on clinical findings, hormonal hypersecretion and benign or malignant behavior. At the present, many subgroups are described.

Imaging, genetic and tailored surgical techniques permit to define new categories and offer the better treatment.

In our experience, blood and urinary exams permit to define two main groups of diagnosis: hypersecreting (69.3%) and non-secreting tumors (30.7%).

The optimal diagnostic approach to a patient who incidentally discover an adrenal mass has not been completely established. However, it is reasonable to start by taking history and performing a physical examination, focusing on the signs and symptoms suggestive of adrenal hyperfunction or malignant disease and hormonal testing.

The use of ultrasound (US) depends on operator skill; obesity and overlying gas are common obstacles for visualization of the adrenal glands. Thus, US does not detect adrenal masses with the same sensitivity as CT or MRI (50)

According to the literature, in our experience the initial clinical work up was usually performed using enhanced CT scan, the more used exam, followed by MRI. Some patients performed both exams before surgery, at different times.

Functional radiological exams are useful in presence of features that suggest pheochromocythoma or malignant disease. In our experience, 18F-fluorodeoxyglucose (FDG) PET-CT and 18F-dihydroxyphenylalanine (DOPA) PET-CT and 123I-metaiodobenzylguanidine (MIBG) scintigraphy were usually performed.

The size of the nodules affects the surgical approach, because big mass are often malignant. In our experience, K and PA compared with other groups presented the biggest and the smaller size, respectively. The features of contralateral gland was carefully analyzed in patients with bilateral hyperplasia or metastasis.

AVS is recommended by current guidelines to identify surgically curable causes of hyperaldosteronism. It was performed in the majority of our patients with PA; only 4 patients refused the procedure.

Hypercortisolism

Hypercortisolism represented in this experience one of the most common diagnosis. In the past CS and CD were recognized as the causes of hypercortisolism, but nowadays many etiologies could be identified: CS represents the most frequent disease, but there are also AIMAH, CD, SCS and more rare conditions like ectopic ACTH and K(CS).

In the present study, CS represented 37.3% of cases of hypercortisolism and was more frequent in female patients. Unilateral adrenalectomy was always performed and there have been no recurrences of disease. After surgery, all patients received a temporary glucocorticoid replacement to avoid adrenal insufficiency, with a progressive reduction and discontinuation of therapy within one month.

The group of patients with SCS represented 18.5% of our patients with hypercortisolism. The interest for this condition is due to its high prevalence. The diagnosis and treatment of SCS have recently become a topic of growing interest and are currently under debate. There is no consensus regarding the biochemical criteria for diagnosing and treatment, mainly due to a lack of large-scale prospective studies regarding its long-term sequelae (51).

Moreover the role of surgical therapy is not completely accepted. In this context, a recommendation for adrenalectomy in patients with SCS largely depends on expert opinion. In our experience all patients underwent unilateral adrenalectomy. No complication occurred. Final pathology was benign in all cases. We didn't found significant differences in 24hours UFC, Cortisol h8 and ACTH h8 before and after surgery but this result could be explained by the limited number of patients. No patient underwent contralateral adrenalectomy for worsening of the disease. In contrast, many papers reported a worsening in conservatively treated patients. (52-55)

In SCS specimen, our pathologists always described different cells type in the main tumor surrounded by micronodules of the cortex. These characteristics are not described in literature and could be an unknown representation of different etiology of disease.

AIMAH is a rare cause of CS in which massive bilateral enlargement of adrenal glands is observed. Excess of cortisol secretion produces ACTH suppression to an undetectable level in the plasma. Bilateral adrenalectomy and steroid hormone replacement represented in many cases the cure for these patients. The advantage of bilateral adrenalectomy is the swift and definitive control of hypercortisolism; its disadvantages include the need for lifelong glucocorticoid and mineralocorticoid replacement therapy. In our experience, at the beginning all patients underwent unilateral adrenalectomy and the gland was chosen according to the largest size at preoperative imaging. In fact, AIMAH steroid hormone synthesis is inefficient as a result of altered steroidogenic enzymatic pathways (56) and a significant but incomplete removal of adrenal tissue may be enough to reduce cortisol secretion to the normal range (57-59).

At mean follow up of 20 months 7 patients didn't received the indication for contralateral adrenalectomy. Only 2 patients that underwent unilateral adrenalectomy required contralateral adrenalectomy for persistent hypercortisolism. New therapeutic alternatives to surgery specifically directed toward ectopic aberrant receptors (octreotide, propanolol, long-acting GnRH agonist) have been proposed, although the effectiveness of these treatments needs further investigations (60).

In one patient the research of illicit receptor explained in part the cause of hormonal hypersecretion and permits to have pharmacological partial cortisol reduction.

Recently, the mutation of ARMC5 was identified as a frequent cause of sporadic or familial AIMAH (61). In 2 patients genetic analyses revealed mutations of this gene.

Conn and Pheochromocytoma: different surgical approach

The most common adrenal tumor in our experience is responsible of aldosterone hypersecretion (32.5%). All patients underwent unilateral adrenalectomy and no malignant disease was described at final pathology (APA: adenoma with PA). A significant reduction in postoperative antihypertensive drugs was observed. In literature some authors, in the presence of APA, suggest to perform a cortical sparing approach in order to preserve the remnant adrenal function and to avoid potential adrenal insufficiency. Walz et al.(62) suggested that adenoma in primary aldosteronism could be an ideal indication for partial adrenalectomy, because these tumors are almost always benign, small, and often lie eccentrically. Instead, Ishidoya et al. (63) highlight that primary hyperaldosteronism is highly associated with multiple adrenal space occupying lesions. In this experience, about 55% of cases, presented at final pathology many micro nodules in the cortex. This evidence could explain the persistence or recurrence of disease after an adrenal sparing procedure.

Laparoscopic surgery using the S or S (RETRO) approach is currently the preferred strategy in treating patients with unilateral nodules.

In this experience 26 operations were performed by the S (RETRO) approach: 20 APA, 2 CD, 2 CS, 1 PHEO, 1 K. Only one complication was reported: the damage of inferior vena cava, during adrenal dissection. It was sufficient to increase the CO2 pressure to stop bleeding and to repair the wall with stitches. Conversion to open surgery or blood transfusions were not required.

In this experience, S (RETRO) approach has been used mainly in patients with PA. Comparing the operative time in patients with PA that underwent S and S

(RETRO) approach, it was longer in S (RETRO) procedures. This result might be explained by the learning curve required for a new approach. No cortical sparing adrenalectomies were performed in S (RETRO) approach.

Bilateral cortical sparing adrenalectomy was performed in a young six years old boy with familial Pheochromocythomas (with VHL mutation), using S approach.

This is in agreement with guidelines that suggest partial adrenalectomy as the gold standard for selected patients, such as those with hereditary pheochromocytoma, with small tumors who have already undergone a contralateral complete adrenalectomy to spare the adrenal cortex and prevent permanent hypocortisolism. However, this young patient had the recurrence of the disease, caused by a retrocaval paraganglioma.

Recurrent pheochromocytomas and paragangliomas in some families suggest a genetic predisposition. Until 2000 adrenal medullary and paraganglioma tumor were mainly considered a sporadic disease. After 2002 more papers described the presence of unsuspected germline mutations in more than 24% (until 51.7%) of patients with clinical findings suggestive of sporadic tumors. Since the effective prevalence of hereditary disease is difficult to assess, routine genetic screening should be considered.

In our experience all patients were studied to research mutations in RET, VHL, SDHA, SDHD, SDHB, SDHC, NF1, SDHAF2, TMEM1, MAX. Mutations for VHL, SDHD, RET and NF1 were identified. In one case, the above mentioned young patient, we found VHL mutation. Two patients (with NF1 and SDHD mutations) underwent unilateral adrenalectomy because the tumor position didn't permit adrenal cortex preservation. Another patient with a RET mutation in

MEN2A, underwent bilateral adrenalectomy for multiple nodules (four on each side). In all cases, no recurrent disease occurred in the side of operation.

Adrenal Incidentaloma and Non secreting tumors.

Non secreting tumors is a common disease and represent 39% of all adrenal neoplasia that underwent surgery. They are not symptomatic.

In many cases they and are incidentally discovered during radiologic exams performed for others reasons. Size and radiological features are crucial to decide for observation or surgery. Adenoma is the more frequent diagnosis but there is a large heterogeneous group of pathologies.

The role of adrenal biopsy is debate. It is not accurate in differentiating benign from malignant primary adrenal tumors and may be useful in selected cases only, in patients with a history of an underlying extra-adrenal malignancy and inconclusive results of imaging tests, or if there is suspicion of a rare tumor (50). It is contraindicated if adrenal carcinoma or pheochromocytoma is strongly suspected. In the first case for the risk of diffusion of disease, in the second for the hypertensive crisis. In this experience we never performed biopsy of adrenal mass.

Malignant disease primitive or metastatic.

Adrenocortical carcinoma (K) is a rare disease with an incidence of one to two cases per 1 million inhabitants. The prognosis is stage dependent with overall 5-year survival ranging from 84% for stage 1 disease to 15% for stage 4 disease (64).

Aggressive surgery is the treatment of choice, since radical resection is the only chance of cure. The diagnosis at first stage is not frequent. Pooled data from multiple institutions demonstrates that the majority of patients will present with regional or distant spread: 18% present with Stage III disease and 61% present with Stage IV disease. Only 21% present with either Stage I or II disease (65).

In this experience, only 55.5% of patients at diagnosis were in stage 1 and 2. Most experts agree that laparoscopic adrenalectomy is the criterion standard treatment for small to medium sized (6 cm) benign adrenal tumors, both functioning and nonfunctioning, the role of laparoscopic adrenalectomy in patients with adrenal malignancies is still controversial. It is relevant to consider that the diagnosis of adrenocortical carcinoma is frequently made in up to 10% of patients underwent surgery for adrenal incidentaloma (66).

Lombardi et al. (67) demonstrated that no significant differences were found between the laparoscopic and open approach in terms of 5-year overall survival and disease free survival rates in patients with localized adrenocortical carcinoma, if the principles of surgical oncology are respected.

In this study, 2 S approach were performed in patients with K. This approach was effective and safe, without postoperative complication. In one patients with K, a S (RETRO) adrenalectomy was performed, without complication. One of the two patients that underwent S approach for K, had a inter aorta-caval recurrence and 5 month after surgery and a new operation with open was performed. No recurrence occurred in the others two patients after 51 and 44 months, respectively. This findings are not sufficient to conclude that laparoscopic adrenalectomy for cancer in early stages could be the best approach but it suggests the opportunity of more experience.

Unfortunately in many cases K is diagnosed too late, in stage 3 and 4, because it is asymptomatic and without clinical findings. In this experience 44.5% of patients were in stage 3 (33.3%) and 4 (11.2%). Often, at the diagnosis K has already local invasion (in particular vascular thrombosis) or metastases.

In literature local and locoregional recurrence is frequent and it is the most common site of recurrence in some series (up to 65%) (68,69). Neoplasms that infiltrate surrounding tissue or invade adjacent organs have a similar prognosis 30% to 40% 5-year survival rate (64). These observations support an aggressive operative approach with en bloc, multiorgan resection when complete resection can be accomplished.

In our series, 3 patients underwent en bloc resection of the adrenal, kidney and regional lymph nodes for local invasion with open approach. In one case also splenectomy and wedge hepatic resection were performed. Surgery remains the only potentially curative treatment, and complete resection is crucial. A large resection may be necessary especially in patients with hormone hypersecretion, because debulking can alleviate symptoms. For the same reason another patient underwent two reoperation for omental and peritoneal debulking.

K with extension to the adrenal, renal vein, or inferior caval vein has been noted to be as frequent as 25% (70,71) and was more frequent on the right side because of the shorter length of the adrenal vein. This condition can be a life-threatening complication because of the risk of pulmonary tumor embolism and is associated with a poorer prognosis.

Thrombosis interest inferior caval vein on the right and renal vein and/or inferior caval vein on the left. If tumor extraction is not feasible, the infrarenal inferior caval vein can generally be resected without replacement. For tumor involving the

suprahepatic inferior caval vein, right atrium, or superior vena cava, cardiopulmonary bypass or hypothermic circulatory arrest via a thoracoabdominal approach with median sternotomy may be necessary. It is critical to understand the superior extent of the caval tumor burden preoperatively as attempts at extraction or caval clamping can result in massive tumor embolus, resulting in hemodynamic instability or tumor vascularization and growth. In this experience thrombectomy was performed according to the level of the thrombus and cavotomy was closed by direct suture.

Overall survival depends on the stage. Our experience confirm that early stages, with localized disease, have a better prognosis compared advanced stages.

The adrenal gland is a site of metastatic spread for many tumors. Metastatic tumor is the most common lesion in the adrenal gland at postmortem. The common occurrence of this adrenal lesion is related to its rich sinusoidal blood supply. Common primary tumors that metastasize to the adrenal glands include lung, cancer colorectal carcinoma, breast cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma and malignant melanoma. In the current study, adrenal metastases were most commonly from lung, colon and kidney. Adenocarcinoma is the most common histological subtype described in the adrenal metastases from lung.

In literature, many cases of metastatic lesions are bilateral. Conversely, in this study we found only one bilateral adrenalectomy for bilateral adrenal metastasis, with S approach. No complications have been reported. In some cases the operation were performed immediately after lung resection. In patients with adrenal metastasis the hormonal function was always assessed before surgery to exclude other hyperfunctioning adrenal tumors.

6. CONCLUSIONS

Until few years ago adrenal tumors were classified in a few well-defined groups. Today, following the availability of more accurate diagnostic and genetics methods, the classification is enriched by numerous subgroups with peculiar epidemiological and diagnostic features. The treatment is the final answer to a clinical, endocrinological, radiological and surgical evaluation.

The complexity of the cases reported is in itself an indication at multidisciplinary approach of adrenal diseases in high-volume centers, in order to determine the most appropriate treatment.

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