2 Indications for Adrenalectomy

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2.1 Introduction

The history of adrenal surgery dates back to 1914, when Perry Sargent performed the first planned adrenalectomy, followed by Charles Mayo in 1927 with the first flank approach to pheochromocytoma [1].

Laparoscopic adrenalectomy, described for the first time by Gagner, in 1992, rapidly became the gold standard for treating benign adrenal pathology [2]. As experience in this surgery increased, even some malignant diseases are amenable to laparoscopic resection without compromising the oncological outcome and having the benefits of the minimally invasive procedure [1].

In its current approach by Martin Walz, posterior retroperitoneoscopic adrenalectomy (PRA) was worldwide popularized as an effective alternative to laparoscopic adrenalectomy. This technique adds the advantages of the prior posterior approach with those of minimally invasive surgery, namely a more direct approach to the retroperitoneum and a simple access to the adrenal gland without the need to mobilize intra-abdominal organs [3]. Differently from transperitoneal laparoscopic adrenalectomy (TLAdr), where the working space is immediately obtained with gas insufflation, in PRA, the working space must be created [4]. All indications for laparoscopic adrenalectomy are nowadays also indications for the posterior retroperitoneoscopic approach [5]. Posterior approach has obvious advantages in patients with multiple prior abdominal surgeries since it provides an adhesion-free surgical field.

In general terms, there are two indications for the surgical removal of the adrenal glands: malignancy (or suspicion of malignancy) and hormonal overproduction caused by an adrenal tumor. Even though malignant adrenal tumors, especially adrenocortical tumors, are usually treated with open surgery, malignancy is not an absolute contraindication for minimally invasive surgery.

In this chapter, we describe the indications for adrenalectomy, emphasizing the advantages and disadvantages of PRA in contrast with the more common TLAdr.

2.2 Posterior Retroperitoneoscopic Adrenalectomy in Overproduction Adrenal Syndromes

Overproduction adrenal syndromes can affect any of the hormones produced by the adrenal glands: aldosterone, cortisol, catecholamines, or

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sexual hormones. Overproduction of sexual hormones is usually associated with malignancy so it will be described in that section.

2.2.1 Excessive Production of Aldosterone: Hyperaldosteronism

Aldosterone, the major mineralocorticoid steroid hormone, is secreted from zona glomerulosa of the adrenal cortex, and its primary effect is the uptake and retention of sodium and water, with potassium and hydrogen excretion acting in the distal convoluted tubules of kidney, gastrointestinal mucosa, salivary and sweat glands [6]. Hyperaldosteronism may be classified as primary or secondary, depending on the underlying causes (Table 2.1).

Primary aldosteronism (PA)—Conn's syndrome—represents the autonomous secretion of aldosterone from either one or both adrenal glands, independent of its primary regulators: angiotensin II, hyperkalemia, and adrenocorticotropic hormone (ACTH) [7]. The first description of the disease was written by Jerome W. Conn in 1955 [8].

PA is the most common cause of endocrine hypertension, with a prevalence of 6% in the general hypertensive population and 12% in severe cases of hypertension. It carries an increased risk of adverse health outcomes, which justifies screening of risky patients (Table 2.2), and an aggressive normalization of aldosterone [7]. Classic manifestations of PA include hypertension, hypokalemia, and metabolic alkalosis [9].

The most recommended screening test for PA is the Aldosterone/Renin Ratio (ARR) measured under standard conditions, with a value >30 ng/dl considered positive (with serum aldosterone level > 15 ng/dl) [7]. A positive screening test must be confirmed by one of the four confirmatory tests: oral sodium loading, saline infusion, fludrocortisone suppression, or captopril challenge [7].

PA may be caused by unilateral involvement, an aldosterone-producing adenoma (APA), which is considered a surgically curable disease, or bilateral involvement (idiopathic adrenal hyperplasia), considered non-amenable to surgical cure. Recent studies have reported new variants of surgically treatable PA, including diffuse or nodular unilateral hyperplasia [10].

Distinguishing between bilateral or unilateral hypersecretion is crucial since only the latter is amenable to surgical cure. For this purpose, several techniques can be used: adrenal venous sampling (AVS), magnetic resonance imaging (MRI), computed tomography (CT), and adrenocortical scintigraphy [7]. AVS is an invasive procedure, with a low risk of complications (0.6%) for

Table 2.1 Causes of hyperaldosteronism

Causes of primary hyperaldosteronism	
Aldosterone-producing adenoma	35%
Bilateral idiopathic adrenal hyperplasia	60%
Primary unilateral adrenal hyperplasia	2%
Pure aldosterone-producing adrenocortical carcinoma	<1%
Familiar aldosteronism Type 1—Glucocorticoid remediable Type 2—Familiar aldosteronism or hyperplasia	<1% <2%
Ectopic aldosterone-producing adenoma/carcinoma	<0.1%
Causes of secondary hyperaldosteronism	
Edema disorders 1. Cardiac failure 2. Liver failure / cirrhosis 3. Nephrotic syndrome	
States of reduced renal perfusion 1. Renal artery stenosis 2. Advanced atherosclerosis 3. Malignant hypertension	
Renin-producing tumors	
Pregnancy	

Table 2.2 Indications for screening for primary hyperaldosteronism

Early onset of hypertension (< 20 years)
Hypertension resistant to two or more antihypertensive drugs
Severe hypertension (systolic bp > 160 or diastolic bp > 100 mmHg)
Hypertension with spontaneous hypokalemia (or secondary to low-dose diuretic)
Adrenal incidentaloma
Evaluation for secondary causes of hypertension
Familiar history of hypertension and primary hyperaldosteronism

skilled radiologists, and a failure rate between 3 and 22%, yet superior to image-based techniques for surgical decision, namely identifying non-nodular unilateral hyperplasia [11].

Surgery is the treatment of choice in APA or other unilateral PA variants, since it provides the best blood pressure control, with an increase in patients' quality of life [7]. Minimally invasive surgery, either by transperitoneal (laparoscopic) or retroperitoneal approach, is, nowadays, the most popular strategy to treat patients with unilateral PA [7].

Hypokalemia is resolved in nearly all patients with APA after unilateral adrenalectomy. Hypertension is cured (no need for medication) in 30–35% of APA patients after unilateral adrenalectomy or subtotal resections, although hypertension improves in about 90% of them [12]. Some preoperative factors increase the likelihood of resolution of hypertension: fewer than three antihypertensive medications, younger age, female gender, shorter duration of hypertension, and lower body mass index (BMI) [12].

According to two meta-analyses comparing transperitoneal and retroperitoneal adrenalectomy, both techniques have similar outcomes, though a third meta-analysis claimed better short-term outcomes for the retroperitoneal approach (RA) [13]. Characteristics of patients and adenomas associated with Conn's syndrome make this disease particularly amenable to RA:

- patients are usually thin, without the amount of retroperitoneal fat associated with other adrenal diseases, which facilitates dissection.
- Conn's adenomas are generally small lesions, with dimensions that do not create the lack of space problems associated with bigger tumors.

As the most dissuasive arguments used against PRA are the absence of obvious anatomical landmarks in the retroperitoneal space, caused by the great amount of fat and the short working field, patients with PA are ideal for the PRA-initiating surgeon after proper training and mentoring. Some patients with APA are amenable to partial adrenalectomy, without compromising the outcome. Indications for partial adrenalectomy will be discussed in another section of this chapter.

2.2.2 Excessive Production of Glucocorticoids: Cushing's Syndrome

Since its first description by Harvey Cushing, in 1932, Cushing's syndrome or hypercortisolism has been a complex disease presenting diagnostic and therapeutic dilemmas [14]. Cushing's syndrome (endogenous hypercortisolism) is characterized by increased levels of circulating glucocorticoids and can be divided into two types [15]:

- ACTH dependent, caused by pituitary or ectopic ACTH secretion, representing the majority of patients
- ACTH independent, due to an autonomous adrenal excessive production of corticosteroids from zona fasciculata, which accounts for 20–30% of patients with endogenous hypercortisolism (10–15% adenomas, 5–10% carcinomas, 5% hyperplasia) [15]

Endogenous hypercortisolism is a rare condition (approximately 3.2 cases per million people/year), which usually occurs in adults and mainly in women [16]. The most common cause of endogenous hypercortisolism is a pituitary tumor secreting ACTH (Cushing's disease). Small-cell lung cancer is the most common source of ectopic ACTH secretion [17].

Cushing's syndrome is a debilitating disease, lethal if untreated (death rate is 51% at 5 years) [18]. Most common causes of death are infections, cerebrovascular accidents, pulmonary emboli, and myocardial infarction [18]. A complex mechanism controls glucocorticoid secretion involving the hypothalamus (secreting corticotropin releasing hormone), pituitary (secreting ACTH), and adrenal glands [14]. Clinical features of Cushing's syndrome include truncal obesity and limb muscle wasting, facial plethora, hirsutism, menstrual disorders, myopathy, striae, acne, psychological symptoms, congestive heart failure, hypertension, and secondary diabetes mellitus [19]. Mild autonomous hypercortisolism without clinical signs of cortisol excess, which is typically discovered in the context of an adrenal incidentaloma—subclinical

Cushing's syndrome—may be associated with hypertension and impaired glucose tolerance (see Sect. 2.4 of this chapter).

Upon clinical suspicion, biochemical investigations are necessary to confirm the diagnosis, after excluding excessive exogenous glucocorticoid exposure in a close collaboration with endocrinology [17]. Initial steps should include more than one of the screening tests:

- Late night salivary cortisol
- Urinary free cortisol
- Overnight dexamethasone suppression test (1 mg)

After confirming the overproduction of cortisol (and the loss of the normal circadian pattern of secretion), ACTH serum levels will indicate the etiology (pituitary or ectopic—ACTH dependent; adrenal—ACTH independent) [20].

For ACTH-dependent hypercortisolism, it is mandatory to distinguish between pituitary and ectopic origin. A high dose dexamethasone suppression test could be conducted, as well as an MRI of the pituitary gland and a chest CT scan [19]. An abdomen CT scan or MRI is necessary in all cases of ACTH-independent hypercortisolism.

The morbidity and mortality associated with Cushing's syndrome justifies that surgical treatment is indicated in the majority of patients, either pituitary (for pituitary adenomas—Cushing's disease) or adrenal [19]. Normalization of cortisol production is the most efficient way to improve and cure hypercortisolism-related comorbidities, despite the possibility that those complications persisting after Cushing's syndrome have been cured [21]. Indications for adrenalectomy in the context of Cushing's syndrome include unilateral adrenal diseases, bilateral macronodular hyperplasia, primary pigmented nodular adrenocortical disease (PPNAD), failure after pituitary surgery, and in some cases of irresectable or metastatic ACTH secreting tumors [22]. Adrenal adenoma is a benign tumor of cortical cells which usually does not exceed 5 cm. Larger lesions suggest carcinoma [14]. The possibility of malignancy must be always present, since adrenocortical carcinoma (ACC) may secrete cortisol, and features of malignancy (invasion, lymph node involvement, distant metastasis) may not be obvious. Malignancy is not an absolute contraindication for laparoscopic or retroperitoneoscopic surgery, but usually an open approach is the best option for those aggressive tumors [14, 22].

Surgical treatment of unilateral adrenal tumors is straightforward using minimally invasive surgery with cure rates of nearly 100%. After adrenalectomy, it is expectable that all patients develop adrenal insufficiency due to contralateral adrenal atrophy caused by the prolonged ACTH suppression. The hypothalamus-pituitary-adrenal axis usually recovers in 18–30 months. Meanwhile, hydrocortisone reposition is mandatory at an initial dose of 12–15 mg/m^2/day [17].

Primary bilateral macronodular hyperplasia (PBMH) is a rare condition that is more common in children. Bilateral adrenalectomy is the standard treatment for PBMH, with a significant advantage over pharmacological therapies, despite the resulting definitive adrenal insufficiency. Since the intrinsic steroidogenic capacity of adenomatous cells in PBMH is limited, unilateral adrenalectomy may be also effective in controlling cortisol rates. In this case, a straight follow-up is mandatory to check for recurrences [17].

For PPNAD, bilateral adrenalectomy is the treatment of choice in bilateral glandular disease. However, selected patients with mild phenotype may benefit from unilateral adrenalectomy or even partial adrenalectomy, as reported by Walz et al. and Iacoboni et al. [23, 24].

Bilateral adrenalectomy is a second-line treatment of Cushing's disease, in patients not suitable for pituitary surgery or after failure of the surgical treatment. As previously mentioned, bilateral adrenalectomy has the advantage of a rapid cortisol reduction, which must be balanced with the need of permanent glucocorticoid and mineralocorticoid reposition [17].

Surgical resection of ACTH secreting tumors may not be possible in all cases because of local invasion or metastatic disease. In that scenario, bilateral adrenalectomy may be necessary for hypercortisolism control [17].

Bilateral adrenalectomy performed to control hypercortisolism in ACTH-dependent Cushing's syndrome achieves clinical remission in more than 95% of cases, and an improvement of health-

related quality of life in 82 to 89% of patients. Surgical morbidity and mortality are 18% and 3%, respectively [22]. In Nelson's syndrome, a condition characterized by corticotropic tumor growth that may develop in patients with Cushing's disease after bilateral adrenalectomy, doctors must actively seek and control both a gradually increasing serum ACTH and skin pigmentation [22].

In 1990, the surgical treatment of Cushing's patients was historically associated with non-neglectable rates of morbidity and mortality of 7–13% and 2.3%, respectively [25]. Those rates decreased dramatically with the advent of minimally invasive surgery, which is a safe procedure, either performed by laparoscopy or by retroperitoneoscopy [25]. In a study of 170 patients submitted to retroperitoneoscopic adrenalectomy (13 bilateral) for Cushing's syndrome, Alesina, a member of the Essen pioneer group headed by Martin Walz, reported no mortality or major morbidity, and an incidence of minor complications of 5.3%. Mean operative time was 53 ± 36 minutes and 99.4% of patients were cured. Only 10% of the patients needed Intensive Care Unit (ICU) support in postoperative period. Operative time and morbidity compare favorably with laparoscopic approach [25]. Retroperitoneoscopic adrenalectomy has another important advantage over laparoscopic surgery—the possibility of simultaneous bilateral surgery, with two surgical teams working at the same time, without patient mobilization, thus reducing operative time [25].

As the laparoscopic approach has made adrenalectomy for Cushing's syndrome a safer therapeutic option, the new possibilities provided by PRA may represent a further improvement in the treatment of this pathology.

2.2.3 Excessive Production of Catecholamines: Pheochromocytoma and Paraganglioma

A pheochromocytoma is a tumor arising from adrenomedullary chromaffin cells that commonly produce one or more catecholamines: epinephrine, norepinephrine, and dopamine. These tumors are rarely biochemically silent [26]. A paraganglioma is a tumor derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. Paragangliomas can also arise from parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull [26]. About 80–85% of chromaffin-cell tumors are pheochromocytomas, whereas 15–20% are paragangliomas [26].

The pheochromocytoma was first described in 1886 by Felix Frankel and owes its name to Ludwig Pick in view of its staining with chromium salt: dusky (phaios) color (chroma) [27, 28]. Pheochromocytoma and paraganglioma (PPGL) are rare tumors, with annual incidence of 1–300,000 habitants in the United States, representing 0.2 to 0.6% of the adults with hypertension and 1.7% of hypertensive children, there not being a difference in terms of gender, and a mean age at diagnosis of 55 years in sporadic cases. Hereditary pheochromocytomas are usually diagnosed earlier in life [29]. Pheochromocytomas represent 5% of the incidentally discovered adrenal masses [29]. Pheochromocytomas may occur sporadically or as part of hereditary syndrome. According to the latest studies among patients with non-syndromic pheochromocytoma, up to 24% of tumors may be hereditary, which challenges the ancient 10% rule of pheochromocytoma (10% malignant, 10% bilateral, and 10% extra-adrenal) [30].

Hereditary pheochromocytoma is associated with multiple endocrine neoplasia type 2 (MEN-2A or MEN-2B), neurofibromatosis type 1 (NF-1), von Hippel-Lindau (VHL) syndrome, and familial paragangliomas and pheochromocytomas due to germline mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD). In general, the traits are inherited in an autosomal dominant pattern [30]. Hereditary pheochromocytomas and paragangliomas have major probability of being bilateral, multifocal, extra-adrenal, or malignant [26]. Malignancy is defined by local invasion or distant metastasis. Tumor size larger than 5 cm, lymphovascular or capsular invasion, and increased Ki67 proliferation index are associated with an increased risk of malignancy [26].

Excessive secretion of catecholamines has noxious effects on the organism leading to an important increase in morbidity and mortality in non-treated patients [26]. PPGL patients can be symptomatic or asymptomatic. Main signs and symptoms of catecholamine excess include hypertension (sustained or episodic), which occurs in more than 90% of the cases, palpitations, headache, sweating, and pallor. Presentation depends on the predominant catecholamine secreted: tumors secreting noradrenaline tend to cause sustained hypertension, whereas tumors secreting adrenaline and noradrenaline often cause episodic hypertension. Only rarely do dopamine secreting tumors cause hypotension [30]. Less common signs and symptoms include fatigue, nausea, weight loss, constipation, flushing, and fever [30]. According to the degree of catecholamine excess, patients may suffer myocardial infarction, arrhythmia, stroke, or other vascular presentations (e.g., any organ ischemia). Similar signs and symptoms are produced by numerous other clinical conditions and, therefore, pheochromocytoma is often referred to as the "great mimic" [30].

Diagnosis of PPGL relies on biochemical evidence of catecholamine production by the tumor. Biochemical testing should be performed in symptomatic patients, patients with an adrenal incidentaloma, and those with a hereditary risk of developing a pheochromocytoma or paraganglioma [30]. Catecholamines are metabolized within chromaffin cells to metanephrines (norepinephrine to normetanephrine and epinephrine to metanephrine, respectively) [26]. Measurements of fractionated metanephrines in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines [26]. Values four times higher than the upper limit of normal are diagnostic of a functioning pheochromocytoma or paraganglioma. False positive results due to medications, clinical conditions, or inadequate sampling conditions must be excluded. In patients with plasma metanephrine above the upper reference limit but less than four times above that limit, a clonidine suppression test combined with measurements of plasma catecholamines and normetanephrine may prove useful [26].

A positive test must be followed by abdominal imaging since the abdomen is the most probable localization. Both CT and MRI have excellent sensitivity (90–100%) in detecting catecholamine producing tumors with a good specificity (70–80%), especially for tumors >1 cm [26, 30]. Extra-adrenal lesions may occur anywhere along the sympathetic chain and may need investigation with cervical ultrasound, chest-abdomen-pelvis CT, or MRI [26, 30]. Functional imaging uses different methods of nuclear medicine and is indicated for incidental lesions highly suspicious for PPGL with inconclusive biochemical testing, young patients, assessment of regional extension or multifocality, exclusion of metastases and in syndromic disease (MEN 2 A/B, VHL, NF1, SDH-mutation) [26]. These include metaiodobenzylguanidine (MIBG) scan/scintigraphy, positron emission tomography (PET) with 18-fluorodihydroxyphenylalanine (FDOPA), 18-fluorodopamine (FDA), 18-fluorodeoxyglucose (FDG), and PET with radiolabeled dodecane tetraacetic acid (DOTA) peptides [26]. Unequivocal biochemical evidence with typical adrenal imaging does not require functional imaging [26].

In proven evidence of pheochromocytoma and/or paraganglioma, surgical indication is generally given to all patients fit for surgery, due to the cardiovascular morbidity and mortality of uncontrolled catecholamine secretion, as well as to local tumor growth and malignant potential. In metastasized PPGL, surgery aims to prevent local complications, reduce hormone production, and improve successive therapeutic measures [31]. In some metastatic tumors, even debulking of the lesion can help control the symptoms [31]. Due to the high incidence of bilateral adrenal disease in hereditary pheochromocytoma, partial adrenalectomies are advocated in these patients, thereby avoiding morbidity associated with medical adrenal replacement. It remains controversial whether partial adrenalectomies should be considered in patients with a sporadic unilateral pheochromocytoma. However, open surgical approaches could still be necessary in selected

patients with locally invasive or malignant disease [30, 31]. The first adrenalectomies for pheochromocytoma were performed in 1926 by Roux, in Lausanne, and by Charles Mayo, in Rochester [32].

Even after the widespread dissemination of laparoscopic adrenalectomy, minimally invasive surgery for pheochromocytoma was met with some reservation due to concerns of adverse hemodynamic sequelae resulting from pneumoperitoneum and gland manipulation, as well as due to the technical challenges involved in removing these highly vascular and generally large tumors [33]. However, after several studies, minimally invasive approach for pheochromocytoma was deemed safe, effective, and resulting in decreased postoperative pain and shorter hospital stays when compared with open adrenalectomy [33]. Open surgical approaches could still be necessary in selected patients with locally invasive or malignant disease. Most position statements also recommended an open approach for tumors >6 cm, ensuring complete tumor resection, preventing tumor rupture, and avoiding local recurrence [31]. As abdominal paragangliomas have more propensity to be malignant, most authors recommend the open approach, but a minimally invasive approach can be performed for small, noninvasive paragangliomas in surgically favorable locations [31].

Current recommendations for patients undergoing surgery for PPGL suggest preoperative α-blockage to prevent perioperative hypertensive crisis. In selective cases with no hypertension or cardiovascular risk factors, preoperative blockage may be omitted [31]. Phenoxybenzamine (α-adrenoceptor blocker) is commonly used for preoperative control of blood pressure (10–20 mg twice daily for 10–14 days). Alternatives to phenoxybenzamine for preoperative blockade include calcium channel blockers and selective competitive α1-adrenoceptor blocking agents, such as terazosin and doxazosin, which have shorter half-lives and lower the risk for postoperative hypotension. A β-adrenoceptor blocker may be used for preoperative control of tachyarrhythmias or angina. However, loss of β-adrenoceptor-mediated vasodilatation in a patient with unopposed catecholamine-induced vasoconstriction can result in dangerous increases in blood pressure. Therefore, β-adrenoceptor blockers should never be employed without first blocking α-adrenoceptor-mediated vasoconstriction [26]. Volume contraction associated with chronic vasoconstriction may occur in patients with PPGL. Recent works by Groeben et al., from the Essen group, suggest that preoperative blockage may not be necessary and can even be associated with an increased rate of complications [34, 35]. Saline infusion or increased water intake is recommended to expand volume and reduce postoperative hypotension [26].

There are no data regarding any difference in recurrence rate after open vs minimally invasive adrenalectomy. Mortality rate is about 1%, and the conversion rate and transfusion rate are about 5% (rate of conversion to open is influenced by tumor size and surgeon experience). Because pheochromocytomas are rare, a prospective randomized study comparing open with minimally invasive surgery is unlikely [26].

When performing a partial adrenalectomy, it is necessary to preserve 1/3 of the gland to maintain sufficient cortical function. Adrenal vein preservation is not necessary if this amount of normal adrenal is kept [27]. Alesina et al., in a series of 66 patients with bilateral pheochromocytomas treated by retroperitoneoscopic cortical-sparing adrenalectomy (32 synchronous surgeries), reported a cortisol-free postoperative course in 60 patients (91%), with one persistence disease needing reoperation, and no recurrences or mortality. Those results confirm the efficacy of retroperitoneoscopic adrenalectomy in the treatment of this disease [27].

A potential advantage of the retroperitoneoscopic approach (RA) over the transperitoneal laparoscopic approach (TLA) in bilateral adrenalectomy is the possibility of resecting both left and right glands simultaneously, as there is no need to change the patient's positioning, which shortens operative time. Studies comparing TLAdr with PRA for pheochromocytoma have concluded that both are safe and effective approaches. However, PRA results in decreased

operative times, less blood loss, and lower postoperative length of stay [36]. RA is also suitable for children and adolescents with pheochromocytomas or retroperitoneal paraganglioma, as reported by Walz et al. in a series of 42 patients [36].

2.3 Posterior Retroperitoneoscopic Adrenalectomy in Adrenal Malignancies

2.3.1 Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare tumor affecting 1 to 2 patients per million inhabitants, representing 0.2% of all cancer deaths in the United States [37, 38]. In Southern Brazil, the incidence during childhood is 2.9 to 4.2 per million per year, compared with an estimated incidence of 0.2 to 0.3 per million children per year worldwide, which can be mainly attributed to the high prevalence of the p.R337H low-penetrance allele of *TP53* [37]. There are two peaks of increased incidence: in childhood and at 50–55 years, with a slight prevalence in females (ratio female/male ranges from 1.5–2.5:1) [37].

In 2% to 10% of ACC patients, a contralateral tumor is present, either representing a synchronous or a metachronous ACC, making it difficult to determine whether the contralateral tumor is an independent primary tumor or a metastasis to the contralateral gland [37].

Some data suggest a genetic predisposition [37]. Germline *TP53* mutations are the underlying genetic cause of ACC in 50% to 80% of children with ACC [37]. Childhood ACC is a core malignancy of Li–Fraumeni Syndrome (LFS). Other core cancers are choroid plexus tumors, sarcomas, early-onset breast cancers, brain cancers, and leukemias [38]. Because of the impact of a diagnosis of LFS for the patient and at-risk relatives, *TP53* germline testing should be considered in all ACC patients [37]. ACC patients usually present one of three scenarios [37]:

- symptoms and signs of hormone excess (40–60%)
- nonspecific symptoms due to local tumor growth, such as abdominal or flank pain, abdominal fullness, or early satiety (30%)
- incidental finding (20–30%)

Hypercortisolism is the most common presentation in patients with hormone excess (50%–80% of hormone-secreting ACCs), causing the classic signs and symptoms of plethora, muscle weakness/atrophy, diabetes mellitus, and osteoporosis. It is also common that high cortisol levels in ACC saturate the renal HSD11B2 system, resulting in glucocorticoid-mediated mineralocorticoid receptor activation. Therefore, hypokalemia and hypertension are commonly observed in ACC patients with hypercortisolism. When combined with pronounced muscle weakness, these symptoms of rapidly progressive Cushing's syndrome are generally indicative of a malignant adrenal tumor [37]. The second most produced hormones in patients with ACC are adrenal androgens (40–60% of hormone-secreting ACCs), causing rapid-onset male pattern baldness, hirsutism, virilization, and menstrual irregularities in women. Concurrent androgen and cortisol production is frequent (half of hormone-secreting ACC) [37]. Estrogen production occurs in 1–3% of male ACC patients, causing gynecomastia and testicular atrophy (through suppression of the gonadal axis) [37]. Autonomous aldosterone secretion is rare in ACC [37]. At the time of presentation, ACCs are frequently large tumors, measuring on average 10 to 13 cm. Only a minority of tumors are <6 cm (9–14%), with only 3% presenting as lesions <4 cm [37].

The European Network for the Study of Adrenal Tumors (ENSAT) defined a staging system for ACC that became widely adopted [39]. The ENSAT staging system defines 4 stages. Stage 1 (≤5 cm) and stage 2 (>5 cm) tumors are confined to the adrenal gland. Stage 3 tumors extend into surrounding tissue (para-adrenal adipose tissue or adjacent organs) or involve locoregional lymph nodes. Stage 4 is reserved for patients with distant metastasis [39]. Data from

more than 400 patients collected by the Michigan Endocrine Oncology Repository reported the following mean stage at diagnosis: stage 1, 14%; stage 2, 45%; stage 3, 27%; and stage 4, 24%. The most common metastatic sites are lung (40–80%), liver (40–90%), and bone (5–20%) [37].

Initial evaluation upon diagnosis must include a physical examination and patient clinical history with particular emphasis on symptoms and signs of hormone excess. A focus on family history is important to identify possible hereditary contributions [37, 40]. A basic biochemical evaluation, which includes creatinine, liver function tests, and a complete blood count should also be performed, as these values may guide further therapy and disease management [31]. The initial hormonal evaluation is essential and must include a dexamethasone suppression test, cortisol levels, 24-hour urine free cortisol, ACTH, dehydroepiandrosterone sulfate (DHEAS), testosterone, aldosterone, renin, metanephrine, and normetanephrine [31, 37]. Patients who have lesions with features suspected of malignancy, as well as patients with signs and symptoms suggestive of sex hormone excess, should have estradiol, DHEAS, and testosterone levels measured [31, 37]. Staging should also include a CT or an MRI of the abdomen and pelvis, and a chest CT scan. Other imaging should be guided by clinical suspicion (e.g., bone scan for skeletal metastasis) [31, 37].

Though ACC prognosis is poor, there is a marked individual variation in disease progression, recurrence, and overall survival. Even in patients with stage 4 disease, survival ranges from a few months to several years [31, 37, 38]. Nowadays, the only curative therapeutic for ACC is complete tumor resection. Adjuvant therapies aim only to decrease the chance of recurrence and all therapy of unresectable or metastatic ACC must be considered palliative [31, 38].

Appropriate preoperative evaluation, operative planning, and a surgical team experienced in adrenal resections are essential to achieve the best outcomes [37]. Unfortunately, most patients with ACC are operated outside reference centers and global results may reflect this lack of expertise [37]. After a thorough medical evaluation, nearly 25% of stage 3 tumors were preoperatively underestimated as stage 2 [37]. Surgery for stage 4 should be individually decided [31, 37].

Patients with distant metastatic disease in multiple organs, and patients with non-resectable multiple metastatic deposits in one organ, should not be submitted to adrenalectomy [31, 38]. Other options must be considered, such as external beam radiation for palliation, with other adjuncts to improve local symptoms, and better control hormone excess. A tumor thrombus within the vena cava is not a contraindication for surgery if the tumor is otherwise technically resectable [38–40]. Debulking for control of hormone excess in the setting of known metastatic disease can also be performed in some situations, after balancing risks and benefits of an aggressive procedure in a usually debilitated patient [37]. The extension and role of lymph node dissection in ACC remain controversial [31, 37, 38]. In one retrospective study, locoregional lymph node dissection improved tumor staging ability and led to a more favorable oncological outcome in patients with otherwise localized ACC [37]. In adrenal tumors, the main lymphatic areas that should be removed as part of the *en bloc* resection include the renal hilum and the origin of the celiac and mesenteric artery. A balance between the risk caused by the extended surgery and the benefit of radical lymph node dissection must be carefully evaluated on an individual basis. Large prospective studies on this topic are still lacking [31, 37].

The possibility of removing ACC by laparoscopic or retroperitoneoscopic approach is largely debatable (see Chap. 5), and most guidelines recommend an open access [31, 38]. The advantages of a minimally invasive adrenal surgery (lower morbidity, less pain, shorter hospital stays, and decreased overall time to recovery) lose relevance when treating an aggressive tumor like ACC, in which case the initial surgery has strong impact on prognosis. The higher propensity for shedding of malignant cells caused by the laparoscopic instruments, the lack of tactile sensation, and the need for a big incision for removing ACC tumors (usually large) are arguments against minimally invasive surgery in this context [38]. Published data comparing the efficacy of

the laparoscopic approach (LA) vs. the open approach (OA) for ACC are limited. All large series are retrospective, include fewer than 200 patients (most reports including fewer than 10 patients), provide limited or no follow-up, and evidence several biases [37, 38]. Considering the available data, the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons advocate OA by an experienced surgeon as the procedure of choice, raising the important question of defining what an "experienced" surgeon is [41]. The European Society of Endocrine Surgeons and European Society for Medical Oncology have a more liberal position, suggesting that LA could be performed for stage 1 and 2 ACC tumors less than 8 or 10 cm if an R0 resection is performed and the surrounding periadrenal tissue is removed [37, 40, 42, 43]. More studies are needed to evaluate the possibility and results of lymph node dissection by a minimally invasive approach to treat an ACC.

2.3.2 Malignant Pheochromocytoma and Paraganglioma

Approximately 10% of pheochromocytomas and 15% to 35% of paragangliomas are malignant, with malignancy being defined as the presence of distant metastasis. There are no reliable histological features allowing a distinction between a benign tumor and a malignant primary tumor. Despite local tissue invasion, blood vessel invasion, tumor size larger than 5 cm, and DNA ploidy suggest malignancy, these characteristics do not distinguish between benign and malignant tumors with certainty [44–46]. Efforts are ongoing to identify predictors of malignancy, but only the presence of distant metastases, including locoregional lymph nodes, is widely accepted as a malignant criterion. Metastasis is defined as the appearance of chromaffin tissue in non-chromaffin sites distant from the primary tumor [45]. Metastases occur most frequently in lymph nodes, bone (50%), liver (50%), and lungs (30%) and can appear as many as 20 years after initial presentation. Liver involvement may be the result of direct continuous spread of the primary tumor [44, 45]. Clinically, there is no significant difference between benign and malignant disease [46].

There is no curative treatment for metastatic pheochromocytoma. Although data suggesting improved survival after surgical debulking is scarce, surgical intervention is favored for palliation of local complications due to metastatic disease and reduction of chromaffin tissue and hormonal activity. Surgical debulking may also be used to increase the efficacy of other therapeutic modalities, but there is no evidence that this therapeutic approach prolongs survival of patients with metastatic disease [44, 45]. The prognosis of malignant pheochromocytoma is poor. Though long-term survival is possible, the overall 5-year survival is less than 50%. Medical control of the catecholamine excess is mandatory. Surgery, radiation therapy or chemotherapy, and new targeted therapies may provide palliative benefit [44–46]. In contrast to benign pheochromocytomas, in which minimally invasive surgery is gold standard, malignant pheochromocytomas often feature large tumors or extra-adrenal tumors in locations difficult to be removed by laparoscopy or retroperitoneoscopy. Therefore, in cases of proven or suspected malignancy, open surgery is recommended. Minimally invasive approaches can eventually be indicated on an individual basis and in centers with large expertise [31].

2.3.3 Metastases to the Adrenal Glands

Metastases to the adrenal glands are the second most common type of adrenal masses after adenomas. Data from the autopsy of patients with malignancies revealed metastases to the adrenal glands in 10–27% of cases. This incidence may be explained by the rich sinusoidal blood flow and the multiple pathways of arterial blood supply to the adrenal glands [47]. Isolated adrenal metastases are rare, most of which are found in patients with disseminated cancer [47].

The increasing survival of cancer patients and the growing use of imaging technology has led to an increment in the number of adrenal metastases found [48]. Lung (39%) and breast (35%) cancers account for most adrenal metastases, but metastases from melanoma, renal cancer, hepatocarcinoma, and colorectal cancer are also frequent [31, 47]. Relative prevalence varies according to geographic region [47].

Isolated adrenal metastasis can be synchronous (discovered at the time of the primary cancer or within 6 months after identification of the primary tumor) or metachronous (found after a disease-free interval [DFI] of more than 6 months). Bilateral adrenal metastases are common [47].

Most patients (95%) with adrenal metastases are asymptomatic at the time of diagnosis [47]. In cases of bilateral metastases to the adrenal glands, symptomatic hormonal insufficiency may develop and should be treated with substitution doses of glucocorticoids before and after adrenalectomy [47]. In case of suspicion of adrenal metastases, it is paramount to rule out gland dysfunction, as up to 48% of adrenal masses in patients with a known malignancy may be true incidentalomas. Ruling out pheochromocytoma is mandatory, as stated in a previous section, but also exclusion of hypercortisolism and hyperaldosteronism must be performed [31].

Imaging investigation must include not only CT or MRI, exams that frequently provide the initial suspicion, but also a PET scan (usually PET/CT) to access further metastatic disease [47, 48]. The suspicion of adrenal metastases is one of the few indications for biopsy of the gland, judiciously reserved for cases in which the doubt persists after noninvasive imaging techniques [38, 48].

Even though the existence of adrenal metastases represents advanced disease with a generally poor prognosis, surgical resection may increase survival, and even cure some patients with a 5-year survival rate of 20–45% [47]. Indications for surgical resection of the adrenal must fulfill the following conditions [47]:

- Control of extra-adrenal disease can be accomplished.
- Metastatic disease only to the adrenal gland(s).
- Adrenal imaging is highly suggestive of metastasis, or the patient has a biopsy-proven adrenal malignancy.
- Metastasis is confined to the adrenal gland as assessed by a recent imaging study.
- The patient's performance status warrants an aggressive approach.

Traditionally, open adrenalectomy was the preferred option for patients with adrenal metastasis, but enhanced experience in minimally invasive techniques has changed this. Solitary adrenal metastases from an extra-adrenal primary neoplasm are generally small and confined to the adrenal gland, making the laparoscopic or retroperitoneoscopic approaches amenable for these cases [31, 47]. The main concern is whether laparoscopic or retroperitoneoscopic adrenalectomy can be considered equivalent to open adrenalectomy from an oncological point of view (recurrence rates and survival time). The proper patient selection remains key in deciding the best treatment. Ensuring wide surgical margins with *en bloc* excision of periadrenal fat is an absolute requirement [47]. There are few studies (only case series) comparing open with minimally invasive adrenalectomy for adrenal metastases. In those studies, no superiority could be attributed to one approach. Additionally, they supported the known advantages of laparoscopy/retroperitoneoscopy in terms of lower blood loss, operative time, hospital stay, and complication rates [47]. The majority of authors report no port-site metastases or locoregional recurrences after minimally invasive adrenalectomy for metastatic tumors, even after a long-term follow-up [47]. Open surgery is perhaps more indicated when preoperative imaging suggests local invasion, large metastases (>9 cm), vena cava thrombus, or significant lymphadenopathies [31].

Studies comparing TLAdr with PRA for adrenal metastases are lacking. Significant adhesions from prior surgery could preclude the TLA. The RA has the advantage of not being affected by prior surgery adhesions, since there is no incursion into the peritoneal cavity. Relative contraindications for the minimally invasive approach include morbid obesity, coag-

ulopathy, and severe cardiopulmonary disease which precludes the hypercapnia associated with pneumoperitoneum/pneumoretroperitoneum [47].

2.4 Adrenal Incidentaloma

The growing utilization of imaging exams allied with the continuous enhancement in image definition has led to the increased discovery of unexpected pathological findings, with variable clinical implications. One of the most common unexpected findings revealed by CT, MRI, or ultrasonography is an incidental adrenal mass or incidentaloma. It is defined as a clinically unapparent adrenal mass > 1 cm in diameter detected during imaging performed for reasons other than for suspected adrenal disease [49, 50]. The overall incidence of adrenal incidentalomas is 4% of the general population, increasing to 7% in patients over 70 years old [50]. Many adrenal incidentalomas, while picked up incidentally, may have clinical symptoms or associated signs on closer questioning and clinical examination, namely those associated with obesity, diabetes mellitus, and hypertension [49]. The finding of an adrenal incidentaloma must be followed by a diagnosis workup directed at answering some pertinent questions [31]:

- Is the mass hormonally active?
- Does the tumor exhibit radiological features of malignancy?
- Does the patient have a personal or familial history of cancer?

Investigation for excessive hormone production, as stated in previous sections, must include a dexamethasone suppression test to exclude adrenal Cushing's syndrome, determination of free metanephrines in plasma and urine to exclude a pheochromocytoma and, in hypertensive patients, the determination of the aldosterone–renin ratio to exclude Conn's syndrome. If the imaging reveals any suspicion of ACC, DHEAS, 17-OH-progesteron, and estradiol should be determined in serum [31].

Although most adrenal incidentalomas are unilateral, bilateral incidentalomas are found in 10–15% of the cases. The most common causes of bilateral adrenal incidentalomas are metastases, PBMH, and bilateral cortical adenomas. Other causes of bilateral incidentalomas include bilateral pheochromocytomas, congenital adrenal hyperplasia, Cushing's disease, or ectopic ACTH secretion with secondary bilateral adrenal hyperplasia [50]. Up to 15% of patients with an adrenal incidentaloma will have a hormonally active tumor [31, 50].

A tumor >6 cm has a malignancy risk of 25%. Additionally, vascular invasion, lack of well-demarcated margins, and presence of suspicious lymph nodes are also radiological features suggestive of malignancy [31, 49, 50]. A CT with adrenal protocol and measurement of the Hounsfield Units (HU) is useful to distinguish between benign and malignant tumors. A threshold value of 10 HU has a sensitivity of 71% and a specificity of 91% for benignity. Incidentalomas with >10 HU attenuation require more detailed evaluation [31, 50]. Familial or personal history of cancer must raise the suspicion of adrenal metastases. In a patient without a past medical history of malignancy, the probability of an adrenal nodule being malignant is very low. On the contrary, for a patient with known cancer, this probability is considerably higher, with metastases occurring in 32–72% of these cases [47]. For surgical treatment of adrenal metastases, see Chap. 5 and previous section of current chapter (2.3.3 Metastases to the Adrenal Glands).

Surgery for adrenal incidentalomas is indicated in functioning nodules, or in nodules ≥6 cm, excluding myelolipoma, which usually does not indicate resection [31, 39, 40]. Nonfunctioning adrenal tumors <4 cm, which carry a low risk of malignancy (< 2%), do not usually indicate resection [31, 39]. There is no consensus for adrenal tumors between 4 and 6 cm without radiological features of malignancy. A tailored approach, either surveillance or minimally invasive adrenalectomy, must be discussed with the patient [31, 39]. For tumors <6 cm without suspicion of malignancy, a minimally invasive approach is recommended [49]. Larger

tumors can also be amenable to transperitoneal laparoscopic or retroperitoneoscopic resection, depending on the surgeon's expertise [31].

In many cases of adrenal incidentalomas with documented autonomous cortisol hypersecretion (ACS), cortisol secretion rates may not be significantly elevated. As a result, the patient may be asymptomatic, has no clinical features, and has few comorbidities that may be ascribed to cortisol hypersecretion. ACS is defined as an alteration of the hypothalamic-pituitary-adrenal axis, characterized by ACTH-independent cortisol excess, often without clinical signs and symptoms of overt Cushing's syndrome [31]. In the past, terms as "subclinical Cushing's syndrome," "subclinical hypercortisolism," and "preclinical Cushing's syndrome" have all been used to describe this condition [31]. Despite the absence of signs and symptoms, ACS has been associated with hypertension, insulin resistance, type 2 diabetes mellitus, obesity, metabolic syndrome, and increased mortality. ACS is the commonest functional abnormality in patients with adrenal incidentalomas, with a prevalence of up to 20% [50]. Indication for surgery must be tailored to the patient with ACS, taking into consideration that metabolic improvement after adrenalectomy, including weight loss, blood pressure-lowering, glucose tolerance, lower lipids, and beneficial effects on bone have been reported [50]. A recent systematic review addressed the cardiovascular benefit of surgery in ACS patients. The adrenalectomy improves cardiovascular outcomes and mortality in these patients [50]. This decision must also balance the severity of clinical features against the risks of surgery in an aged population, whose comorbidities could be coincidentally age-related and without causative relation to a false positive ACS diagnosis, leading to unnecessary surgery [50].

Follow-up of non-operated adrenal incidentalomas is not consensual. The American Association of Clinical Endocrinologists recommends repeating the imaging for up to 5 years for benign tumors, whereas the European Guidelines do not recommend further imaging for benign, nonfunctioning lesions with less than 4 cm. Patients with adrenal lesions over 4 cm or indeterminate lesions who have not undergone surgery are recommended to repeat imaging in 6 to 12 months. The optimal timing depends on the index of suspicion [39, 41, 50]. Surgical resection is recommended if there is a 20% increase in size, in addition to at least a 5 mm increase in diameter over the same period. Both adrenocortical cancers and metastases usually demonstrate rapid growth over months, in contrast to a benign adenoma. Further imaging should be undertaken once again at 6–12 months [39, 41, 50].

Repeating hormonal testing is not advised in patients without evidence of hormone oversecretion on their initial assessment. It should only be considered if patients develop new clinical signs and symptoms of adrenal hormone hypersecretion or in case of worsening of comorbidities, including diabetes, hypertension, or osteoporosis [50].

Patients with ACS have a low risk of progressing to overt Cushing's syndrome, but since ACS is associated with numerous comorbidities, patients not initially operated on must be reassessed annually for cortisol hypersecretion and potential worsening of comorbidities. If there is clinical or biochemical progression, then patients can be re-evaluated for surgery [50].

2.5 Partial Adrenalectomy

Partial (or subtotal) adrenalectomy or cortex preserving adrenalectomy was first proposed by Irvin et al., in 1983, for the treatment of hereditary bilateral pheochromocytoma aiming at preserving the adrenocortical function and avoiding lifelong steroid replacement therapy [50]. In 1995, Walz et al. presented the first cases of retroperitoneoscopic partial adrenalectomies [51].

Nowadays, indications for partial adrenalectomy include not only bilateral adrenal masses, but also solitary masses in context of hereditary diseases with increased risk of developing multiple adrenal tumors [27, 32, 36]. Usually, nonfunctional adrenal tumors have no indication for partial adrenalectomy, since their formal surgical indication is the suspicion of malignancy, which makes total adrenalectomy mandatory [31].

There is a trend towards the use of partial adrenalectomy in the treatment of small adrenal masses. In the future, minimally invasive partial adrenalectomy may become the standard treatment of small benign and functioning adrenal tumors [50].

There is no need to preserve the adrenal vein to warrant adrenal cortical function if a minimum of 1/3 of the gland is kept in place and there is no excessive and unnecessary dissection. This allows for an adequate vascular supply and blood drainage of the adrenal remnant by the diaphragmatic and retroperitoneal collateral arteries and veins, respectively [27]. In the pheochromocytoma, the adrenal vein should be divided to prevent hypertensive crisis due to the discharge of catecholamines secreted by the medulla into the venous system [36]. The use of intraoperative ultrasound can be helpful in tumor localization to preclude unnecessary dissection [36, 50].

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