Brain and Spine 2 (2022) 100917

Contents lists available at ScienceDirect

Brain and Spine

journal homepage: www.journals.elsevier.com/brain-and-spine

# Update in Cushing disease: What the neurosurgeon has to KNOW, on behalf of the EANS skull base section

Sayoa Eulate-Beramendi [a], Ainhoa Casajús [a], Lola Ollero [b], Lynnette K. Niemann [c], Juan Carlos Fernández-Miranda [d], Michaël Bruneau [e], Moncef Berhouma [f], Luigi Maria Cavallo [g], Jan Frederick Cornelius [h], Roy T. Daniel [i], Sebastien Froelich [j], Emmanuel Jouanneau [f], Ekkehard Kasper [k], Diego Mazzatenta [l], Torstein R. Meling [m], Mahmoud Messerer [i], Henry W.S. Schroeder [n], Marcos Tatagiba [o], Massimiliano Visocchi [p], Eduard H. Voormolen [q], Idoya Zazpe [a,*]

[a] Department of Neurosurgery, University Hospital of Navarre, Pamplona, Spain
[b] Department of Endocrinology, University Hospital of Navarre, Pamplona, Spain
[c] Department of Endocrinology, National Institute of Health, Bethesda, MD, USA
[d] Department of Neurosurgery, Stanford University Medical Center, USA
[e] Department of Neurosurgery, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium
[f] Neurosurgery Department, Hopital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, France
[g] Department of Neurosurgery, University of Naples Federico II, Naples, Italy
[h] Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany
[i] Department of Neurosurgery, Department of Neuroscience, Centre Hospitalier Universitaire Vaudois, University Hospital, Lausanne, Switzerland
[j] Department of Neurosurgery, Lariboisière Hospital, Université Paris Diderot, Paris, France
[k] Department of Neurosurgery, St Elizabeth's Medical Center, Brighton, Massachusetts, USA
[l] Department of Neurosurgery, Neurological Sciences Institut IRCCS, Bologna, Italy
[m] Department of Neurosurgery, University Hospital of Geneva, Geneva, Switzerland
[n] Department of Neurosurgery, University Medicine, Greifswald, Germany
[o] Department of Neurosurgery, University Hospital Tübingen, Tübingen, Germany
[p] Department of Neurosurgery, Institute of Neurosurgery Catholic University of Rome, Italy
[q] Department of Neurosurgery, University Medical Center, Utrecht, Netherlands

ARTICLE INFO

*Keywords:*
Pituitary adenoma
Transsphenoidal adenomectomy
Hypercortisolism
ACTH
Cushing disease

ABSTRACT

*Introduction:* Cushing's disease is a state of chronic and excessive cortisol levels caused by a pituitary adenoma
*Research question:* CD is a complex entity and often entails difficulties in its diagnosis and management. For that reason, there are still controversial points to that respect. The aim of this consensus paper of the skull base section of the EANS is to review the main aspects of the disease a neurosurgeon has to know and also to offer updated recommendations on the controversial aspects of its management.
*Material and methods:* PUBMED database was used to search the most pertinent articles published on the last 5 years related with the management of CD. A summary of literature evidence was proposed for discussion within the EANS skull base section and other international experts.
*Results:* This article represents the consensual opinion of the task force regarding optimal management and surgical strategy in CD
*Discussion and conclusion:* After discussion in the group several recommendations and suggestions were elaborated. Patients should be treated by an experienced multidisciplinary team. Accurate clinical, biochemical and radiological diagnosis is mandatory. The goal of treatment is the complete adenoma resection to achieve permanent remission. If this is not possible, the treatment aims to achieving eucortisolism. Radiation therapy is recommended to patients with CD when surgical options have been exhausted. All patients in remission should be tested all life-long.

* Corresponding author. C/ Irunlarrea 3, University Hospital of Navarre, CP, 31002, Pamplona, Navarra, Spain.
*E-mail address:* idoya.zazpe.cenoz@navarra.es (I. Zazpe).

https://doi.org/10.1016/j.bas.2022.100917
Received 1 June 2022; Received in revised form 27 June 2022; Accepted 19 July 2022
Available online 7 August 2022

Cushing's Disease (CD) is a complex pathology that requires multidisciplinary approach. For this reason, neurosurgeons should have a global knowledge of the pathology as a whole and the role of surgery in particular. The article tries one hand to summarize all the basic information a neurosurgeon may need about for the correct diagnosis of CD (clinical, biochemical, radiological…), the remission criteria, the prognosis and the alternative treatments in case of surgical failure. On the other hand, due to the existence of some points of controversy at this respect (difficulties in the diagnosis of CD microadenomas, indications for Inferior Petrosal Sinus Sampling (IPSS), surgical technique…) updated recommendations based on the literature and experts' opinion are also displayed in the article.

## 1. Introduction

### 1.1. Definition

Cushing syndrome (CS) is a serious disease caused by the chronic excessive levels of cortisol. CS caused by a pituitary adenoma secreting ACTH is known as Cushing disease (CD), whilst less frequently CS can be due to over-production of cortisol by adenomas or carcinomas of the adrenal gland (ACTH-independent CS) or by ectopic secretion of ACTH.

### 1.2. Epidemiology

CD has an approximate prevalence of 40 cases per million people and an incidence between 1 and 2.5 newly diagnosed cases per million people per year. The average age at diagnosis for adults is in their forties and females are more frequently affected than males (4:1) (Lonser et al., 2017; Valassi et al., 2011).

### 1.3. Prognosis

Hypercortisolism is associated with high mortality and morbidity, and poor quality of life (QOL). Untreated CD has an estimated standardized mortality ratio (SMR) (ratio of observed CD-related deaths to expected deaths in the general population) of up to 5.5. Successful complete resection of the ACTH-secreting pituitary adenoma produces immediate biochemical remission. Nevertheless, the physical symptoms and signs resolve gradually over a period ranging from 2 to 12 months approximately, with a long-term substantial reduction of morbidity and potential death (SMR 1.2) (Clayton et al., 2016).

## 2. Material and methods

The aim of this paper is to provide an overview of current modalities of the management of Cushing disease and an insight into the main controversies about its diagnosis and treatment.

The MedLine database was used to search the most pertinent articles published on the last 5 years related with the diagnosis and management of CD, with a special focus on surgical treatment. Research questions were formulated concerning practical management and decision making. The search was conducted using the terms "Cushing Disease" combined with "adenoma", "radiology," "biochemistry," "endocrinology", "surgery", "endoscopy," "microscopy," "resection," "radiation," "recurrence," "survival," and "outcome". Our search was limited to studies conducted in adults in English language. Three authors (SE, AC and IZ) independently reviewed the abstracts, full-text articles and citations to select pertinent studies. A summary of literature evidence was proposed for discussion within the EANS skull base section and other international experts. If unanimous responses were recorded, we used the terms: "we recommend", whereas if divergent opinions were obtained we used the terms: "we suggest" only after a consensus was reached among the group of experts. The literature supporting each assumption was detailed.

## 3. Diagnosis

Early diagnosis is a key step to decrease the morbidity and mortality. Because the diagnostic evaluation may be complex, multidisciplinary team including Endocrinologists, Neurosurgeons, Radiologists and Pathologists it is utmost importance. Patients should preferentially be referred to an experienced center for diagnosis and treatment (Casanueva et al., 2017).

Recommendation 1: We recommend CD patients to be diagnosed and treated by an experienced multidisciplinary team at high-volume pituitary centers.

### 3.1. Clinical diagnosis

Patients with endogenous hypercortisolism might develop multiple signs and symptoms that may not be synchronous and can increase in severity over time (Table 1). None of the symptoms or signs are pathognomonic, but some of them are more suggestive of hypercortisolism such us proximal muscle weakness, facial plethora, purplish striae, easy bruising and typical fat redistribution. Other symptoms, such as obesity, hypertension and glucose intolerance, are common in the general population (Lonser et al., 2017; Nieman et al., 2008).

It's important to take into account these two entities in the diagnosis of CD:

- Pseudo-Cushing syndrome: hypercortisolism caused by other non-neoplastic pathologies such us psychiatric disorders, alcohol abuse, polycystic ovary syndrome and obesity, that can present clinical features of CS (Fleseriu et al., 2021).
- Cyclic Cushing syndrome: CS where cortisol levels alternate between periods of hypercortisolism and spontaneous remission. The length of each period is variable, ranging from a few days to several months, sometimes with long disease-free intervals (Ironside et al., 2018a). The pathophysiology is not clear, although studies of isolated cases have suggested dopaminergic, serotoninergic and other hypothalamic influences (Estrada et al., 2001).

The fluctuations of cortisol levels make the diagnosis and differential diagnosis of CS extremely challenging, delaying a definitive treatment.

**Table 1**
Signs and symptoms of hypercortisolism.

| Signs and symptoms of hypercortisolism | |
|---|---|
| **Metabolic, cardiovascular** | **Bone, musculoskeletal** |
| - **Progressive centripetal obesity, typical fat accumulation** (cheeks, dorsocervical area, supraclavicular fossae, retroorbital)[a] | - **Proximal muscle wasting and weakness** |
| - Glucose intolerance, diabetes | - Bone loss and fractures |
| - Sleep apnea | **Neuropsychologic and cognition** |
| - Hypertension | - Depression, anxiety, irritability |
| - Dyslipidemia | - Insomnia |
| - Thromboembolic events | - Learning, cognition and memory impairement |
| **Dermatologic** | - Mania, panic attacks |
| - **Easy bruisability** | **Reproductive** |
| - **Wide red-purple striae** | - Menstrual irregularities |
| - Skin atrophy | - Androgens excess (hirsutism, oily skin, acne …)[c] |
| - Hyperpigmentation[b] | **Impaired immune function** |
| - Cutaneous fungal infections | - Increase of infections |
| - Acanthosis nigricans | |

[a] Progressive obesity: the most common feature of patients with CS.
[b] Hyperpigmentation: induced by increased ACTH secretion (most often in ectopic ACTH syndrome, less often in Cushing disease).
[c] Induced by adrenal androgens excess in women (most common in adrenal carcinomas, usually mild in ACTH-dependent CS, not in adrenal adenomas).

Salivary cortisol is especially useful for patients suspected of having intermittent CS, as they can collect the samples at home, as soon as first symptoms of hypercortisolism appear. Tests for the differential diagnosis should be performed only after a period of active cortisol secretion to ensure that the normal corticotropes are suppressed.

### 3.2. Biochemical diagnosis

The biochemical diagnosis of CD can be complex and should be performed by an endocrinologist. It requires several steps (Fig. 1):

1. Diagnosis of hypercortisolism
2. Diagnosis of ACTH-dependent hypercortisolism
3. Diagnosis of pituitary ACTH-dependent hypercortisolism

Once exogenous glucocorticoid intake is excluded, three screening tests are recommended to confirm the presence of hypercortisolism. As none of these tests have 100% accuracy, the choice of tests should be individualized for each patient. The diagnosis of CD is established when at least two of the following different screening tests are unequivocally abnormal (Nieman et al., 2008):

→ Late night (bedtime) salivary cortisol: the physiological sleeping low level in cortisol secretion is not preserved in patients with CD. At least two samples should be collected just before bedtime. The cutoff depends on the assay-specific reference range.
→ 24-h urine free cortisol (UFC): values of UFC more than three times the upper limit of normal in at least two different measurements are needed to consider this test abnormal. The cutoff depends on the assay-specific reference range.
→ Low-dose dexamethasone suppression (1 mg overnight or 2 mg over 48 hours): consists of administration of 1 mg of dexamethasone at midnight and measurement of serum cortisol at 8 a.m. the next morning. Normal cortisol suppression is established at <1.8 mcg/dL.

After hypercortisolism is diagnosed, the next step is to determine whether the hypercortisolism is ACTH-dependent (pituitary adenoma or ectopic tumor) or ACTH-independent (adrenal cause) by measuring

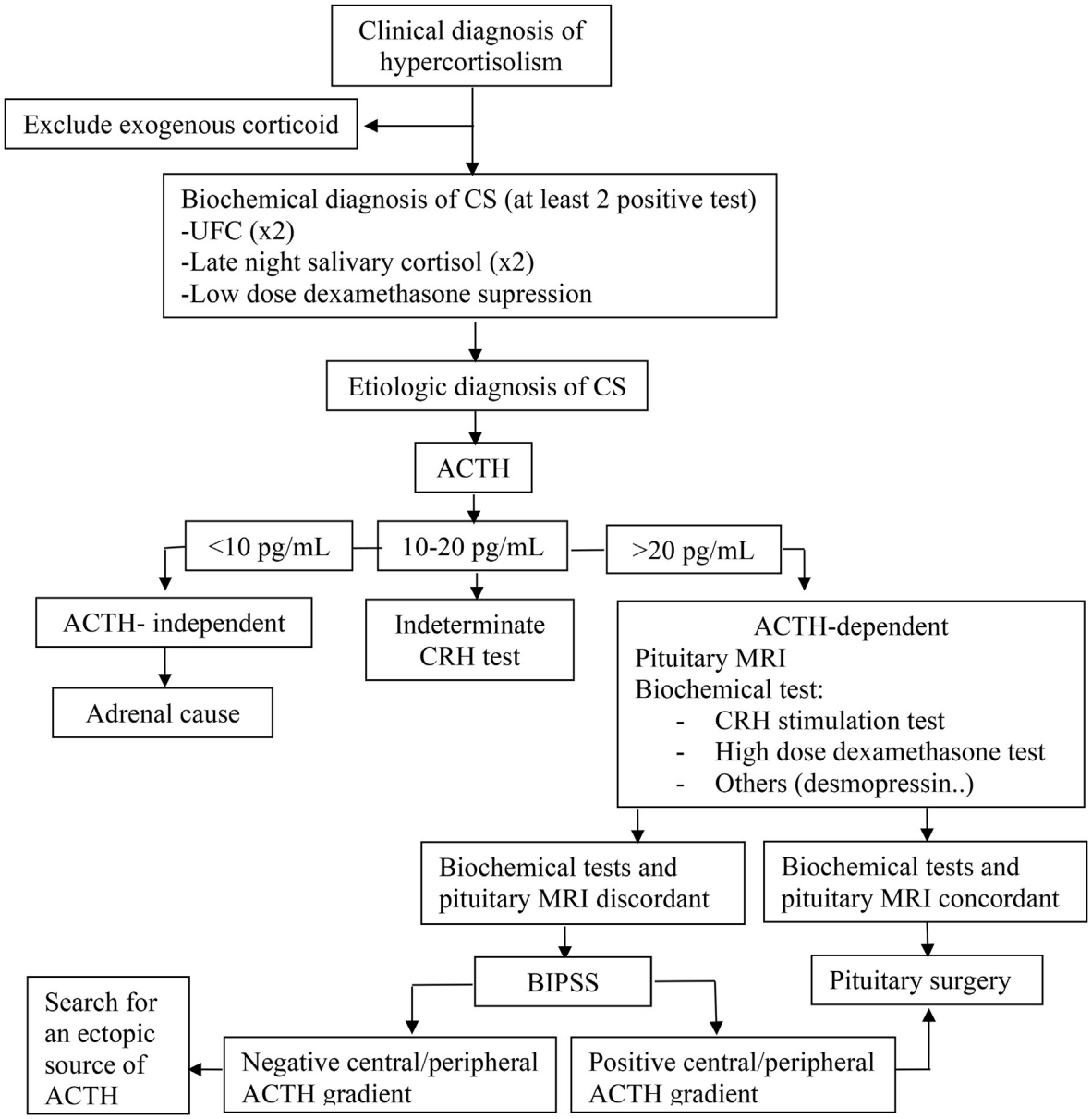


**Fig. 1.** Diagnostic algorithm.

plasma ACTH. A decreased plasma ACTH concentration (<10 pg/mL) suggests an adrenal origin and ACTH values above 20 pg/mL are consistent with an ACTH-dependent cause. Intermediate ACTH values are less definitive, but usually indicate that cortisol secretion is ACTH-dependent.

In cases of a diagnosed ACTH- dependent CS without definitive radiological findings on MRI (see below), the discrimination between an ectopic secretion and an ACTH secreting microadenoma is difficult. Several non-invasive tests are used to distinguish between pituitary or ectopic origin, however there is a significant overlap in responses of pituitary and ectopic tumors to these tests (Lonser et al., 2017). An extremely elevated urinary free cortisol (UFC) and plasma ACTH concentrations, hypokalemia and rapid onset of hypercortisolism are biochemical indicators in favor of ectopic ACTH secretion (Young et al., 2020). The most commonly used non-invasive tests to distinguish between pituitary or ectopic origin are:

→ High-dose dexamethasone suppression, where 8 mg of dexamethasone are given orally at midnight and a serum cortisol is measured at 8 a.m. on the day of dexamethasone and/or the next day. Many serum cortisol criteria have been proposed for the diagnosis of CD, including suppression <5 mcg/dL, or a 50% or more decrease in cortisol secretion (Lacroix et al., 2015).
→ Corticotropin-releasing hormone (CRH) stimulation: Pituitary adenomas should have receptors for CRH and respond to CRH stimulation, while ectopic ACTH-secreting tumors are derived from nonpituitary tissues, and generally do not respond to CRH. A positive response to CRH stimulation is set arbitrarily at a 50% or more increase in ACTH and 20% or more increase in cortisol (Lonser et al., 2017).

### 3.3. Radiological diagnosis

#### 3.3.1. Magnetic resonance imaging (MRI)

Most corticotropic adenomas (85%–90%) are microadenomas (<10mm in diameter) with a mean diameter of 6 mm at the time of diagnosis. Only 10–15% are macroadenomas (≥10mm in diameter). Up to 40% of microadenomas are not detectable by imaging, making tumor localization difficult and hindering tumor excision and biochemical remission (Lonser et al., 2017). In particular, picoadenomas, adenomas of less than 3mm, are less likely to be clearly identified by MRI. Tumor size does not necessarily correlate with hormonal activity and patients with large macroadenomas can present mild hypercortisolism (Fleseriu et al., 2021).

Most authors have found a correlation between visualization of an adenoma on preoperative MRI and a better clinical outcome (Prevedello et al., 2008). The presence of a visible adenoma on MRI provides valuable information for the selection of the pituitary site where exploration of the gland at surgery must begin. Care should be taken to evaluate the relationship of the adenoma with the medial wall of the cavernous sinus.

Coronal projections of high-resolution conventional MRI (CMRI) at 1.5 T with gadolinium (Gd) enhancement reveal microadenomas in approximately half of the patients. New MRI sequences have been developed to provide a higher sensitivity in visualizing a microadenoma (Bashari et al., 2019):

→ Dynamic contrast-enhanced MRI (DMRI) has a sensitivity of 70–75%.
→ High-resolution (1- to 1.5-mm slice thickness) Spoiled-gradient echo 3D T1 sequence (SGE) - also known as SPGR (spoiled gradient–recalled acquisition) and as VIBE (volumetric interpolated breath-hold examination) - enhances detection of microadenomas by 15–30% compared with conventional MRI imaging and reaches a sensitivity of 70–90% (Grober et al., 2018).

This increase in sensitivity is associated with a loss of specificity and a high detection rate of incidental pituitary lesions. Up to 10% of healthy adults have pituitary lesions <6 mm that are visible on an MRI (Hall et al., 1994). According to this data, there is a similar percentage of abnormal pituitary MRI scans in patients with ectopic ACTH syndrome (Ilias et al., 2005) and also a similar rate of false localization by MRI in patients with surgically proven CD (Wind et al., 2013).

For patients with suspected microadenomas but with equivocal or 'negative' 1.5T images, a 3T study should be considered, as it has a sensitivity of up to 72% (54/75) of microadenomas in one large series (Fukuhara et al., 2019). There are few data regarding the utility of 7T MRI; one study of eight patients showed that the sensitivity varied up to 100% depending on the pulse sequence used, so that this should be considered in addition to magnet strength (Patel et al., 2020).

Differentiating between ectopic and pituitary ACTH source is extremely challenging and localization of the tumor can be very difficult, especially when the adenoma is not visible by imaging. Ectopic ACTH tumors have a variety of locations, histological types and prognoses. Most are neuroendocrine tumors (NETs), but other tumor types are rarely associated with ACTH secretion. The most prevalent are pulmonary, pancreatic and thymic NETs, small cell lung carcinomas, medullary carcinomas of the thyroid, and pheochromocytomas. Occult tumors are highly represented in all the series and constitute the most challenging cases (Lacroix et al., 2015). Based on the high probability of locating a lesion in the chest cavity, when biochemical data suggest an ectopic source of ACTH, imaging studies looking for an ectopic ACTH-secreting tumor should be performed, using 1mm thin-slice thoracic CT-scan as the first option. A negative CRH and desmopressin stimulation test plus a positive CT scan had a negative predictive value 100% for CD (Young et al., 2020; Ikeda et al., 2010; Boyle et al., 2019). 68 Ga-DOTATE also proved useful in combination with TC/PET for the detection of ACTH-secreting ectopic tumors (Asa et al., 2017).

Recommendation 2: MRI should be performed preoperatively to try to locate the pituitary tumor. 3D T1 sequences with gadolinium and new MRI sequences such us DMRI or SGE/VIBE should be part of the standard MRI protocol for patients with Cushing's disease. In case of non-conclusive 1.5T scans, a 3T MRI is recommended.

### 3.4. Discrepancies between biochemical and radiological findings

#### 3.4.1. Bilateral Inferior Petrosal Sinus Sampling (BIPPS)

BIPSS is the most accurate biochemical test for discriminating CD from ectopic ACTH syndrome. It has a sensitivity and specificity of ca 95% at institutions with experienced radiologists (Lonser et al., 2017). Nevertheless, it is an invasive and expensive test and should only performed when other non-invasive tests result inconclusive.

It is very important to ensure that the patient is under hypercortisolic conditions at the time of the test. In case the patient is being medically treated to reduce the cortisol levels, medication should be ceased on time before the test is performed. Catheters are usually inserted via the femoral veins into both inferior petrosal sinuses, preferably in its vertical portion to avoid venous contamination coming from the jugular vein. ACTH levels are measured from samples obtained from each petrosal sinus and a peripheral vein. CRH (or desmopressin) stimulation is required to enhance central-to-peripheral gradients. ACTH is measured in all sites before and at multiple timepoints up to 15 minutes after administration of CRH. A central-to-peripheral plasma ACTH gradient of ≥2.0 before CRH administration, or ≥3.0 after CRH, is considered indicative of pituitary source of ACTH secretion.

*3.4.1.1. False negatives.* The main causes of absent ACTH gradient in patients with a pituitary ACTH-secreting adenoma are anatomical variants in the petrosal venous system, mispositioning of catheter, and/or a cyclical/periodic corticotrope secretory pattern (Pecori Giraldi et al., 2015). The presence of high basal serum cortisol on the day should be confirmed prior to the BIPSS (Albani et al., 2019; Perlman et al., 2021). Prolactin-adjusted ACTH gradients are also helpful to improve the

accuracy of the test.

*3.4.1.2. False positives.* A small portion of patients bearing an extra-pituitary ACTH-secreting tumor can present a central-to-peripheral ACTH gradient. This could be explained by incomplete suppression of pituitary ACTH secretion, tumors secreting both ACTH and CRH or tumors next to the pituitary (Pecori Giraldi et al., 2015).

*3.4.1.3. Tumor localization.* Although BIPSS is excellent for the differential diagnosis of CD, it is less reliable in terms of capability of localizing an adenoma, secondary to the anatomical/functional variations in the caliber/flow of the IPSs. Highest accuracy (70%–80%) is obtained when catheters are precisely located in the vertical portion of the IPS just at the exit of the pituitary in types I and II, because bilateral vein anastomosis below this point decreases specificity. A gradient $\geq$1.4 between the ACTH concentrations in the two sinuses predicted the side of the tumor in two-thirds of patients (Pecori Giraldi et al., 2015; Nieman and Ilias, 2005; Sharma et al., 2011).

*3.4.1.4. Complications.* The incidence of serious complications, such as a cerebrovascular accident, when performed by an experienced radiologist is extremely low. Transient cranial nerve palsy, hemiparesis, pulmonary embolism, deep venous thrombosis and inguinal hematomas have been reported with variable frequencies.

*3.4.1.5. Indications.* BIPSS is used to confirm a pituitary origin of ACTH secretion in patients with ACTH-dependent CS, who reported inconclusive MRI images (usually in lesions less than 6mm).

Recommendation 3: BIPPS is recommended to confirm the diagnosis of CD in patients with ACTH-dependent hypercortisolism and inconclusive pituitary MRI.

### *3.4.2. Positron emission tomography (PET)*

To date, functional imaging had limited use in the diagnostic protocol of pituitary adenomas, although several groups have explored various modalities including 11C-methionine (11C-Met)-PET. C-methionine uptake by corticotrophin adenomas is typically lower as compared to other adenomas. Success rates for localizing corticotrope tumors are ~70% (Koulouri et al., 2015).

An important limitation of (11C-Met)-PET is the lack of anatomical detail provided by CT as compared to MRI. For these reasons co-registration of 11C-methionine PET–CT with spoiled gradient recalled (SPGR) acquisition 3T MRI (Met-PET/MRI) has been reported to offer greater accuracy (Koulouri et al., 2015; Ikeda et al., 2010) pending to be confirmed with more recent studies.

FDG-PET after CRH pre-treatment may offer improved detection of CD compared to MRI, but has been tested in relatively few patients (Boyle et al., 2019).

## *3.5. Pathological diagnosis*

ACTH secreting tumors were originally described as basophilic adenomas. They account for around 15% of all pituitary adenomas. Immunohistochemistry of CD adenomas shows diffuse ACTH-positive tumor cells with loss of the typical pituitary architecture on reticulin immunohistochemistry. ACTH-positive staining of the normal pituitary gland corticotrope cells can occasionally lead to an incorrect diagnosis of corticotrope hyperplasia or adenoma (Lonser et al., 2017).

The new terminology "Pituitary neuroendocrine tumors" (PitNet) was proposed in 2017 to replace the classical term of "pituitary adenomas" (Asa et al., 2017). The last 2021 WHO classification divides pituitary adenomas by their adenohypophyseal cell lineage according to combined immunohistochemical expression of pituitary hormones and transcription factors and also includes the term Pituitary neuroendocrine tumor (PitNET). Corticotrophin adenoma is defined as an adenoma that expresses ACTH and other proopiomelanocortin-derived peptides and arises from adenohypophyseal cells of Tpit lineage.

Histologically, corticotrophin adenomas are classified into three subtypes, namely densely granulated corticotropic adenomas (DGCA), sparsely granulated corticotropic adenomas (SGCA), and Crooke cell adenomas. DGCA is the most common histological subtype and tends to present frequently as a microadenoma. Non-functional corticotropic tumors are termed as silent corticotropic adenomas. Both silent corticotropic adenomas and Crooke cell adenomas have been linked to more clinically aggressive tumor behavior (Asa et al., 2017).

# 4. Treatment

## *4.1. Treatment goals and remission criteria*

### *4.1.1. Treatment goals*

The goal is to eliminate its primary cause (ACTH-secreting pituitary adenoma) and achieve remission. The normalization of cortisol levels leads to the recover symptoms and comorbidities and thus to an improvement of the QOL and SMR. Suppression of the hypothalamic-pituitary axis usually resolves within 6–18 months in most of the patients.

In those cases where cure cannot be achieved, the treatment goal focuses on control of cortisol levels as persistent hypercortisolism is associated with higher mortality and morbidity.

While hypercortisolism is corrected, secondary comorbidities, such as hypertension, diabetes, and osteoporosis should be adequately monitored and treated. Prophylaxis for venous thromboembolism and appropriate age-vaccination should also be addressed.

Recommendation 4: The goal of treatment is the complete adenoma resection to achieve permanent remission. If this is not possible, the treatment aims to achieving eucortisolism while containing secondary side effects.

### *4.1.2. Remission criteria*

There is no consensus in regard to the criteria of CD remission after surgery.

It is advisable to consider patients defined as "cured" in remission: a strict follow-up is recommended as 10–20% of cases may relapse in the long term.

Successful pituitary adenoma resection usually leads to corticosteroid deficiency because normal corticotroph cells have been suppressed by longstanding hypercortisolism; therefore, very low or undetectable early postoperative cortisol levels have been pointed out as prognostic factor for surgical success (Fleseriu et al., 2021; Stroud et al., 2020)

Perioperative glucocorticoid replacement strategies also vary among centers and mostly depend on the clinical condition and biochemical evidences at postoperative period. It has been shown that postoperative steroid deprivation up to 72 hours is safe and allows for early adjudication of remission (Asuzu et al., 2017).

Several tests can be used to assess for remission in CD:

- Serum cortisol level: Remission is generally defined as morning serum cortisol values < 2–5μg/dL during the first postoperative week (Nieman and Ilias, 2005; Stroud et al., 2020).
  Serum cortisol should be measured first in the morning at 8 am at least 24 hours after the last dose of glucocorticoid. An undetectable serum cortisol concentration is said to be a predictor of long-lasting remission (Stroud et al., 2020; Mehta and Lonser, 2017).
- Rate of cortisol drop: Not only the levels of postoperative cortisol, but also the rate of cortisol drop after surgery predicts outcome. Hypocortisolemia $\leq$2 μg/dL prior than 21 hours after surgery accurately predicts a durable remission in the intermediate term (Ironside et al., 2018a).
- 24-h Urinary Free Cortisol (UFC) values below 20 mcg/24 h (55 nmol/24 h) suggest remission (Nieman et al., 2008).

- Salivary cortisol: measurement of salivary cortisol at midnight is likely to be abnormal with persistent disease. Lack of cortisol suppression by the overnight 1 mg dexamethasone suppression test may support the suspicion of a persistent disease.
- Normalization of adrenocortical function: Patients with complete normalization of adrenocortical functions at immediate postoperative period had much lower recurrence rates (3.4%) than those with hypocortisolism (50–65%) (Estrada et al., 2001).

### 4.2. Surgical treatment

Surgery is first line treatment being the transsphenoidal selective adenomectomy the treatment of choice for CD. Patients who achieved remission of CD after surgery have shown better results in terms of SMR (0.95) as compared to patients being in remission after other treatment modalities (SMR 2.53) (Clayton et al., 2016). Complete selective adenomectomy can provide an immediate cure with minimum side-effects and preservation of normal pituitary functions: recent surgical series showed remission rates between 80% and 90% for microadenomas and lower than 65% for macroadenomas, with recurrence rates of 10–35% (Lonser et al., 2017; Stroud et al., 2020; Guaraldi et al., 2020; Cebula et al., 2017). It should be highlighted however that these rate variations are affected by the cure criteria used and the time of follow-up.

#### 4.2.1. Microscopic vs endoscopic surgery

Transsphenoidal adenomectomy is the most common surgical approach. A transcranial approach is only rarely run (Buchfelder and Schlaffer, 2010).

Several cohort studies have compared the microscopic and endoscopic surgical techniques at the same center, showing no clear differences (Alahmadi et al., 2013; Atkinson et al., 2008; Cheng et al., 2011; Broersen et al., 2019; Wang et al., 2019). A Japanese multicentric retrospective study found that endoscopic surgery granted a significant reduction of hospital stay and costs in multivariable analysis (Hattori et al., 2020). One larger study found no significative differences over time (Qiao, 2018) whilst another showed similar results for microadenomas, but better results of the endoscopic approach in macroadenomas with higher remission rates (76.3 vs. 59.9%) and lower recurrence rates (1.5 vs. 17.0%) (Broersen et al., 2018a). These results are probably related to the visualization provided by the endoscope, especially in those cases extending laterally into the cavernous sinus.

Recommendation 5: Selective surgical transsphenoidal adenomectomy is the treatment of choice in CD. Both the endoscopic and microscopic techniques have proved to be effective in the surgical management of CD. Nevertheless, the endoscopic technique present advantages in some selected cases.

According to preoperative MRI findings two subsets of patients could be distinguished and though different surgical attitudes can be identified us:

→ Visible adenoma: surgery is targeted to the area of the lesion

→ Non visible or non-conclusive MRI images: careful exploration of the anterior, inferior and lateral aspects of the pituitary gland is recommended, taking great care at the level of anterior and posterior hypophysis junction and areas adjacent to the medial wall of the cavernous sinus. Whether no tumor is found, vertical incisions at the pituitary gland tissue, starting at the side where the higher ACTH gradient on BIPSS was detected, are run to explore eventual pathological tissue. In case of adenoma successfully detected (upon intraoperative pathology confirmation) and removed, more than 90% of patients report biochemical remission (Lonser et al., 2017). If an adenoma is not discovered after complete exploration of the gland, a partial/subtotal hypophysectomy could be performed. A two thirds (2/3) removal of the anterior pituitary gland (ventromedial and lateral parts with preservation of the superior third attached to the stalk) is preferable than complete hypophysectomy: similar rates of biochemical remission (60%–80%) with only 15% of hypopituitarism, are reported (Lonser et al., 2017; Carr et al., 2018).

Recommendation 6: Once other causes of hypercortisolemia have been ruled out and a pituitary origin has been established, pituitary surgical exploration starting at the side where the higher ACTH gradient on BIPSS was obtained is suggested, even if a tumor is not visualized.

In cases where the adenoma cannot be identified intraoperatively, a subtotal hypophysectomy is favored rather than a complete hypophysectomy.

#### 4.2.2. Prognostic factors

There are many factors that influence surgical results:

1. Preoperative visualization on MRI: Surgical remission rates for CD are in the range of 80–90% when a tumor is detected on MRI but decrease to 50–70% when MRI fails to detect a lesion (Stroud et al., 2020; Yamada et al., 2012).
2. Adenoma size: Most adenomas are microadenomas and non-invasive. Macroadenomas are more often associated with dural and cavernous sinus invasion which could preclude complete resection and is associated with lower cure rates (Lonser et al., 2017). Remission rates in microadenoma surgery are significantly higher than in macroadenoma surgery (83% vs 63%) (Stroud et al., 2020; Shin et al., 2017).
3. Anatomical factors:
   a. A group of authors have described the presence of a tumoral pseudocapsule when adenomas reach a diameter of approximately 3 mm. This psedocapsule is considered to be a rim of compressed gland tissue adjacent to the edge of the adenoma. The dissection of the adenoma following the plane of this pseudocapsule (pseudocapsular dissection) was described by Oldfield and Vortmeyer (2006) who found it to improve cure rates (Jagannathan et al., 2009). According to this group, it facilitates complete resection while preserving the rest of the healthy gland (Monteith et al., 2012). Nevertheless, most authors in this paper underline the importance of ensuring a complete resection whenever possible, even supramarginal in case of intraoperative suspicion of infiltration of adjacent tissue.
   b. Dural and cavernous sinus invasion. Remission rates after surgery in adenomas invading the cavernous sinuses are reported to be significantly lower (30% vs 80%) (Stroud et al., 2020). This feature is usually not well detected on MRI imaging (Lonser et al., 2012) but should be suspected when tumors are adjacent to the medial wall of the cavernous sinus. Most relapses are due to microscopic dural invasion at the adenoma margin or along the wall of the cavernous sinus (Lonser et al., 2012; Dickerman and Oldfield, 2002). Resection of dural invasion, including medial cavernous sinus wall, is essential to achieve surgical cure (Oldfield, 2017) but should only be performed by very experienced surgeons. Oldfield first described the steps for the microscopic “en bloc” removal of adenomas invading the medial wall of the cavernous sinus by opening first the anterior wall of the cavernous sinus at its inferior margin (Oldfield, 2017). Later studies described the parasellar ligaments that anchor the medial wall to the cavernous ICA (Fernandez-Miranda et al., 2018; Cohen-Cohen et al., 2018) and successfully reported endoscopic medial wall cavernous sinus resection.
4. Surgeon's expertise. The lower complications rates and better results are achieved by surgeons who have experience in pituitary pathology and works within centers with adequate caseload (Casanueva et al., 2017; Mortini et al., 2020; Honegger and Grimm, 2018; McLaughlin et al., 2012).
5. Reintervention

The chance of remission is lower in revision surgery rather than in

primary surgery (50% vs 80%) (Stroud et al., 2020) and the risk of hypopituitarism is higher in reinterventions. (Casanueva et al., 2017).

In summary, the highest probability of cure (more than 95% biochemical remission) occurs in CD patients with microadenomas that are large enough to be visible on the MRI, but that do not invade the dura mater or cavernous sinus wall.

Recommendation 7: In cases of dural or cavernous sinus invasion, maximal safe resection should be performed. Resection of the medial cavernous sinus wall, when invaded, can be a valuable adjuntive maneuver to achieve surgical cure, but it should only be attempted exclusively by experienced surgeons, as per the higher risks of injuries its neurovascular contents.

#### 4.2.3. Complications

The complication rates in CD surgery (10% morbidity and less than 1% mortality) can vary upon the patient and the extent of tumor. There is a greater risk of loss of pituitary function's worsening, when a more extensive pituitary exploration is needed. The most common complications are: hypopituitarism (10%), diabetes insipidus (20%) – transient in most of the cases (Nemergut et al., 2005), CSF leak, venous thrombosis (<5%) and infection (Fleseriu et al., 2021; Broersen et al., 2018a). The administration of subcutaneous heparin is recommended in the perioperative period as per the higher incidence of venous thromboembolic events in CD (Stuijver et al., 2011) and this latter can persists in the first months despite cortisol normalization (Wagner et al., 2018); although there is not yet concrete evidence thromboprophylaxis (Fleseriu et al., 2021) can be extended in selected cases up to 30 days after surgery (Barbot et al., 2015).

#### 4.2.4. Early surgical failure and indications for repeat surgery

When an invasive adenoma is identified during surgery and/or a subtotal hypophysectomy has been completed in case of misidentified lesion, the chances of achieving remission by reoperation are remote and adjuvant second line therapies should be considered.

Repeat surgery might be indicated under two different circumstances:

→ Early re-intervention in persistent disease within 3–4 weeks
→ Delayed reintervention in cases of recurrent disease

Remission rates of revision surgery are higher in recurrent disease (64%–80%) than in persistent disease (54%) (Stroud et al., 2020; Braun et al., 2020). On the other hand, also complication rates (panhypopituitarism, CSF leak) are higher in reinterventions as more aggressive maneuvers might be needed (Carr et al., 2018; Braun et al., 2020; Rubinstein et al., 2019).

Current practice guidelines recommend a first postoperative MRI at ≥3 months after transsphenoidal surgery; some authors advocate to perform an early MRI (<48h) in all cases (Alhilali et al., 2020) or no later than 72h after surgery in cases of lack remission upon intraoperative evidence of lesion gross-total removal. In these clatter circumstances, peer review of the tissue samples is mandatory. Success of an early reintervention varies from 7 to 71% of patients (Benveniste et al., 2005).

The choice of an early reoperation when first surgical attempt fails and its eventual success can depend on the following (Lonser et al., 2017; Ram et al., 1994):

→ If MRI reveals a residual resectable adenoma, early surgery (within three weeks) is advised because the probability of remission is high (Friedman et al., 1989).
→ If no adenoma is apparent at postoperative MRI and a pathology report was consistent with ACTH adenoma, a reoperation or further treatment modalities should be considered depending on patient condition. In case a reoperation is considered it should be directed to the site of previous adenoma resection because residual tumor will be located in the same region or the adjacent dura or cavernous sinus wall (Dickerman and Oldfield, 2002).
→ In cases of postoperative MRI without any evidence of residual tumor and pathology report was inconsistent, a subtotal hypophysectomy or further treatment modalities should be considered depending on patient condition.

Recommendation 8: Early reoperation is advised when a biological remission is not obtained after surgery and a residual resectable adenoma is visible on postoperative MRI.

In cases of lack of remission and no tumor visible at postoperative MRI, reoperation or further treatment modalities should be considered depending on patient condition and individualized circumstances.

#### 4.2.5. Long-term follow-up and delayed recurrence after initial remission

The long-term cure rates are not exactly known because of the various criteria used to define cure and the short duration of follow-up of too many patients. Recurrence rates vary between 5% and 35% (Fleseriu et al., 2021), with almost 50% of the relapses occurring within five years after surgery (Braun et al., 2020).

Patients should be lifelong under surveillance (Fleseriu et al., 2021) being tested annually for recurrence, or sooner if clinical symptoms develop. Increased late-night serum/salivary cortisol is one of the earliest biochemically detectable signs of recurrence and almost always precedes the raise of urine cortisol.

Delayed recurrence after initial remission of CD usually entails the presence of residual tumor at the site or adjacent to the initial adenoma resection site. Again, re-do surgery should be run upon the most appropriate indication.

Recommendation 9: All patients in remission from CD should be tested all life-long: eventual reintervention and its outcomes should be carefully measured.

### 4.3. Second line treatments

Recommendation 10: Adjuvant treatment should be considered in patients who cannot receive surgery or if case remission is not achieved (or to be achieved) after successful surgery.

#### 4.3.1. Radiotherapy (RT)

Radiotherapy is mainly used in patients with persistent or recurrent disease, particularly in aggressive or invasive adenomas. The goals of RT are the long-term control of both ACTH secretion and tumor growth. Normalization of cortisol occurs in 50–80% of patients (Mehta et al., 2017) and tumor growth control in around 90% of patients with all RT modalities (Jagannathan et al., 2007).

There are two main types of radiation to be used in CD:

Stereotactic radiosurgery (SRS): is the delivery of a single (or a few) high dose(s) of radiation therapy to the lesion (or the entire *sella* when the location of the tumor is misidentified). It is considered the first choice if the adenoma is at least 3–5mm away from the optic apparatus (Mehta et al., 2017) with at an optimal dose of 20–23 Gy (Gy) - no more than 8–10 Gy to the optic pathway-. The results of different SRS modalities seem to be similar in CD with rate of remission of 43–58% (Starke et al., 2010) and earlier control of cortisol levels as compared to conventional radiotherapy (Mehta et al., 2017).

In cases of recurrent and persistent CD, a second TSS could be more challenging due to scar tissue formation and SRS could be an alternative. An international meta-analysis showed that patients treated with SRS had a higher remission rate (74%) than TSS (59%), however, these differences were not statistically different. Patients with cavernous sinus invasion, asymmetric extension of the adenoma or negative pre-operative MRI might be good candidates for SRS (Perez-Vega et al., 2022).

Conventional fractionated radiation: 45–54 Gy administered to the whole pituitary with 1,8-2 Gy per fraction over 5 weeks (Jagannathan et al., 2007; Starke et al., 2010).

The maximal benefit of RT occurs at a median of 15–24 months, with a range of up to 10–12 years (Ironside et al., 2018b). During this time,

hypercortisolism should be controlled with medical treatment. Thus, before pituitary RT is given, adequate biochemical control must be achieved by medical treatment and if medical treatment is not effective, a different treatment modality than radiotherapy should be considered. Cabergoline and Ketokonazole in all cases are to be suspended during radiotherapy due to radioprotective mechanisms (Mehta et al., 2017; Thakkar et al., 2020).

The major side effect of RT is the eventual loss of pituitary functions, which occurs in 20% of patients at 5 years, up to 30% at 10 years and increases afterwards (Lonser et al., 2017; Minniti and Brada, 2007).

#### 4.3.2. Medical treatment

Pharmacological treatment for CD is used after unsuccessful pituitary surgery, combined or not with RT, in patients who are not surgical candidates, or to ameliorate metabolic status at preoperative stage.

Medical therapy options include pituitary-acting agents (cabergoline, pasireotide), steroidogenesis inhibitors (ketoconazole, metyrapone, osilodrostat), and glucocorticoid receptor antagonists (mifepristone). There are no direct comparative studies between the different medications. The choice of medical therapy (alone or in combination) by the endocrinological team should be guided by effectiveness, individual patient factors, and cost. All agents require careful monitoring to ensure that treatment goals are being met and to detect associated toxicity (Tritos and Biller, 2020). Although medical therapy can lower cortisol levels, data regarding clinical improvement and quality of life are scarce (Broersen et al., 2018b). The choice of medical therapy should be guided by effectiveness above all in terms of QOL.

#### 4.3.3. Bilateral adrenalectomy

It produces biochemical remission in more than 95% of cases of CD (Lonser et al., 2017; Ferriere and Tabarin, 2020) and clinical improvement in more than 80% of patients (Oβwald et al., 2014). Although bilateral adrenalectomy has been used as an emergency option in severe uncontrolled hypercortisolism or as a last option when other treatments have failed (Wong et al., 2015), it requires life-long glucocorticoid and mineralocorticoid replacement therapy and is burdened by a median rate of 21% of Nelson's syndrome (Oβwald et al., 2014).

Recommendation 11: Second line treatments should be tailored in each case:

Radiation therapy is recommended to patients with CD when surgical options have been exhausted. Hypopituitarism is a concrete risk in all forms.

Medical therapy for CD is recommended after unsuccessful pituitary surgery, combined or not with RT or to ameliorate metabolic status at preoperative stage.

Bilateral adrenalectomy is recommended when other treatments have failed or as a last option in severe uncontrolled hypercortisolism. Nelson syndrome can occur.

## 5. Conclusion

Although most recommendations in this article are based in previous published articles and guidelines, the main highlight of this paper is this group of experts' consensus opinion on controversial points.

### 5.1. Summary of recommendations

1. We recommend CD patients to be diagnosed and treated by an experienced multidisciplinary team at high-volume pituitary centers.
2. MRI with gadolinium and sequences such us DMRI or SGE/VIBE should be part of the standard MRI protocol for patients with Cushing's disease. In case of non-conclusive 1.5T scans, a 3T MRI is recommended.
3. BIPPS is recommended to confirm the diagnosis of CD in patients with ACTH-dependent CS with doubtful MRI.
4. The goal of treatment is complete adenoma resection to achieve remission. In cases where this is not possible, maximal safe resection is recommended aiming to obtain eucortisolism while containing the secondary side effects.
5. Selective transsphenoidal surgical adenomectomy is the treatment of choice in CD. Both the endoscopic and microscopic techniques have proved to be effective in the treatment of CD.
6. In cases of inconclusive MRI where ACTH dependent hypersortisolism of pituitary origin has been established, pituitary surgical exploration starting at the side where the higher ACTH gradient on BIPSS was obtained is suggested. In cases where the adenoma cannot be identified intraoperatively, a subtotal hypophysectomy is favored rather than a complete hypophysectomy
7. In cases of dural or cavernous sinus invasion, maximal safe resection should be performed. Resection of the medial cavernous sinus wall can be a valuable maneuver in the attempt of increasing the extent of tumor removal, but it should be reserved exclusively to experienced surgeons.
8. Early reoperation is advised when a biological remission is not obtained after surgery and a residual resectable adenoma is visible on postoperative MRI.
9. All patients in remission from CD should be tested all life-long: eventual reintervention and its outcomes should be carefully measured
10. Adjuvant treatment should be considered in patients who cannot receive surgery or if case remission is not achieved (or to be achieved) after successful surgery.
11. Second line treatments should be tailored in each case:
    - ➢ Radiation therapy is recommended to patients with CD when surgical options have been exhausted. Hypopituitarism is a concrete risk in all forms.
    - ➢ Medical therapy for CD is recommended after unsuccessful pituitary surgery, combined or not with RT or to ameliorate metabolic status at preoperative stage.
    - ➢ Bilateral adrenalectomy is recommended when other treatments have failed or as a last option in severe uncontrolled hypercortisolism. Nelson syndrome can occur.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

Alahmadi, H., Cusimano, M.D., Woo, K., Mohammed, A.A., Goguen, J., Smyth, H.S., Macdonald, R.L., Muller, P.J., Horvath, E., Kovacs, K., 2013. Impact of technique on cushing disease outcome using strict remission criteria. Can. J. Neurol. Sci. J. Can. Sci. Neurol. 40, 334–341. https://doi.org/10.1017/s031716710001427x.

Albani, A., Berr, C.M., Beuschlein, F., Treitl, M., Hallfeldt, K., Honegger, J., Schnauder, G., Reincke, M., 2019. A pitfall of bilateral inferior petrosal sinus sampling in cyclic Cushing's syndrome. BMC Endocr. Disord. 19, 105. https://doi.org/10.1186/s12902-019-0433-9.

Alhilali, L.M., Little, A.S., Yuen, K.C.J., Lee, J., Ho, T.K., Fakhran, S., White, W.L., 2020. Early postoperative MRI and detection of residual adenoma after transsphenoidal pituitary surgery. J. Neurosurg. 134, 761–770. https://doi.org/10.3171/2019.11.JNS191845.

Asa, S.L., Casar-Borota, O., Chanson, P., Delgrange, E., Earls, P., Ezzat, S., Grossman, A., Ikeda, H., Inoshita, N., Karavitaki, N., et al., 2017. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an international pituitary pathology club proposal. Endocr. Relat. Cancer 24, C5–C8. https://doi.org/10.1530/ERC-17-0004.

Asuzu, D., Chatain, G.P., Hayes, C., Benzo, S., McGlotten, R., Keil, M., Beri, A., Sharma, S.T., Nieman, L., Lodish, M., et al., 2017. Normalized early postoperative cortisol and ACTH values predict nonremission after surgery for cushing disease. J. Clin. Endocrinol. Metab. 102, 2179–2187. https://doi.org/10.1210/jc.2016-3908.

Atkinson, J.L.D., Young, W.F.J., Meyer, F.B., Davis, D.H., Nippoldt, T.B., Erickson, D., Vella, A., Natt, N., Abboud, C.F., Carpenter, P.C., 2008. Sublabial transseptal vs transnasal combined endoscopic microsurgery in patients with cushing disease and MRI-depicted microadenomas. Mayo Clin. Proc. 83, 550–553. https://doi.org/10.4065/83.5.550.

Barbot, M., Daidone, V., Zilio, M., Albiger, N., Mazzai, L., Sartori, M.T., Frigo, A.C., Scanarini, M., Denaro, L., Boscaro, M., et al., 2015. Perioperative thromboprophylaxis in Cushing's disease: what we did and what we are doing? Pituitary 18, 487–493. https://doi.org/10.1007/s11102-014-0600-y.

Bashari, W.A., Senanayake, R., Fernández-Pombo, A., Gillett, D., Koulouri, O., Powlson, A.S., Matys, T., Scoffings, D., Cheow, H., Mendichovszky, I., et al., 2019. Modern imaging of pituitary adenomas. Best Pract. Res. Clin. Endocrinol. Metabol. 33, 101278. https://doi.org/10.1016/j.beem.2019.05.002.

Benveniste, R.J., King, W.A., Walsh, J., Lee, J.S., Delman, B.N., Post, K.D., 2005. Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. J. Neurosurg. 102, 1004–1012. https://doi.org/10.3171/jns.2005.102.6.1004.

Boyle, J., Patronas, N.J., Smirniotopoulos, J., Herscovitch, P., Dieckman, W., Millo, C., Maric, D., Chatain, G.P., Hayes, C.P., Benzo, S., et al., 2019. CRH stimulation improves (18)F-FDG-PET detection of pituitary adenomas in Cushing's disease. Endocrine 65, 155–165. https://doi.org/10.1007/s12020-019-01944-7.

Braun, L.T., Rubinstein, G., Zopp, S., Vogel, F., Schmid-Tannwald, C., Escudero, M.P., Honegger, J., Ladurner, R., Reincke, M., 2020. Recurrence after pituitary surgery in adult Cushing's disease: a systematic review on diagnosis and treatment. Endocrine 70, 218–231. https://doi.org/10.1007/s12020-020-02432-z.

Broersen, L.H.A., Biermasz, N.R., van Furth, W.R., de Vries, F., Verstegen, M.J.T., Dekkers, O.M., Pereira, A.M., 2018a. Endoscopic vs. Microscopic transsphenoidal surgery for Cushing's disease: a systematic review and meta-analysis. Pituitary 21, 524–534. https://doi.org/10.1007/s11102-018-0893-3.

Broersen, L.H.A., Jha, M., Biermasz, N.R., Pereira, A.M., Dekkers, O.M., 2018b. Effectiveness of medical treatment for Cushing's syndrome: a systematic review and meta-analysis. Pituitary 21, 631–641. https://doi.org/10.1007/s11102-018-0897-z.

Broersen, L.H.A., van Haalen, F.M., Biermasz, N.R., Lobatto, D.J., Verstegen, M.J.T., van Furth, W.R., Dekkers, O.M., Pereira, A.M., 2019. Microscopic versus endoscopic transsphenoidal surgery in the leiden cohort treated for Cushing's disease: surgical outcome, mortality, and complications. Orphanet J. Rare Dis. 14, 64. https://doi.org/10.1186/s13023-019-1038-0.

Buchfelder, M., Schlaffer, S., 2010. Pituitary surgery for Cushing's disease. Neuroendocrinology 92 (Suppl. 1), 102–106. https://doi.org/10.1159/000314223.

Carr, S.B., Kleinschmidt-DeMasters, B.K., Kerr, J.M., Kiseljak-Vassiliades, K., Wierman, M.E., Lillehei, K.O., 2018. Negative surgical exploration in patients with Cushing's disease: benefit of two-thirds gland resection on remission rate and a review of the literature. J. Neurosurg. 129, 1260–1267. https://doi.org/10.3171/2017.5.JNS162901.

Casanueva, F.F., Barkan, A.L., Buchfelder, M., Klibanski, A., Laws, E.R., Loeffler, J.S., Melmed, S., Mortini, P., Wass, J., Giustina, A., 2017. Criteria for the definition of pituitary tumor centers of excellence (ptcoe): a pituitary society statement. Pituitary 20, 489–498. https://doi.org/10.1007/s11102-017-0838-2.

Cebula, H., Baussart, B., Villa, C., Assié, G., Boulin, A., Foubert, L., Aldea, S., Bennis, S., Bernier, M., Proust, F., et al., 2017. Efficacy of endoscopic endonasal transsphenoidal surgery for Cushing's disease in 230 patients with positive and negative MRI. Acta Neurochir. (Wien) 159, 1227–1236. https://doi.org/10.1007/s00701-017-3140-1.

Cheng, R.-X., Tian, H.-L., Gao, W.-W., Li, Z.-Q., 2011. A comparison between endoscopic trans-sphenoidal surgery and traditional trans-sphenoidal microsurgery for functioning pituitary adenomas. J. Int. Med. Res. 39, 1985–1993. https://doi.org/10.1177/147323001103900545.

Clayton, R.N., Jones, P.W., Reulen, R.C., Stewart, P.M., Hassan-Smith, Z.K., Ntali, G., Karavitaki, N., Dekkers, O.M., Pereira, A.M., Bolland, M., et al., 2016. Mortality in patients with Cushing's disease more than 10 Years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol. 4, 569–576. https://doi.org/10.1016/S2213-8587(16)30005-5.

Cohen-Cohen, S., Gardner, P.A., Alves-Belo, J.T., Truong, H.Q., Snyderman, C.H., Wang, E.W., Fernandez-Miranda, J.C., 2018. The medial wall of the cavernous sinus. Part 2: selective medial wall resection in 50 pituitary adenoma patients. J. Neurosurg. 131, 131–140. https://doi.org/10.3171/2018.5.JNS18595.

Dickerman, R.D., Oldfield, E.H., 2002. Basis of persistent and recurrent cushing disease: an analysis of findings at repeated pituitary surgery. J. Neurosurg. 97, 1343–1349. https://doi.org/10.3171/jns.2002.97.6.1343.

Estrada, J., García-Uría, J., Lamas, C., Alfaro, J., Lucas, T., Diez, S., Salto, L., Barceló, B., 2001. The complete normalization of the adrenocortical function as the criterion of cure after transsphenoidal surgery for Cushing's disease. J. Clin. Endocrinol. Metab. 86, 5695–5699. https://doi.org/10.1210/jcem.86.12.8069.

Fernandez-Miranda, J.C., Zwagerman, N.T., Abhinav, K., Lieber, S., Wang, E.W., Snyderman, C.H., Gardner, P.A., 2018. Cavernous sinus compartments from the endoscopic endonasal approach: anatomical considerations and surgical relevance to adenoma surgery. J. Neurosurg. 129, 430–441. https://doi.org/10.3171/2017.2.JNS162214.

Ferriere, A., Tabarin, A., 2020. Cushing's syndrome: treatment and new therapeutic approaches. Best Pract. Res. Clin. Endocrinol. Metabol. 34, 101381. https://doi.org/10.1016/j.beem.2020.101381.

Fleseriu, M., Auchus, R., Bancos, I., Ben-Shlomo, A., Bertherat, J., Biermasz, N.R., Boguszewski, C.L., Bronstein, M.D., Buchfelder, M., Carmichael, J.D., et al., 2021. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 9, 847–875. https://doi.org/10.1016/S2213-8587(21)00235-7.

Friedman, R.B., Oldfield, E.H., Nieman, L.K., Chrousos, G.P., Doppman, J.L., Cutler, G.B.J., Loriaux, D.L., 1989. Repeat transsphenoidal surgery for Cushing's disease. J. Neurosurg. 71, 520–527. https://doi.org/10.3171/jns.1989.71.4.0520.

Fukuhara, N., Inoshita, N., Yamaguchi-Okada, M., Tatsushima, K., Takeshita, A., Ito, J., Takeuchi, Y., Yamada, S., Nishioka, H., 2019. Outcomes of three-tesla magnetic resonance imaging for the identification of pituitary adenoma in patients with Cushing's disease. Endocr. J. 66, 259–264. https://doi.org/10.1507/endocrj.EJ18-0458.

Grober, Y., Grober, H., Wintermark, M., Jane, J.A., Oldfield, E.H., 2018. Comparison of MRI techniques for detecting microadenomas in Cushing's disease. J. Neurosurg. 128, 1051–1057. https://doi.org/10.3171/2017.3.JNS163122.

Guaraldi, F., Zoli, M., Asioli, S., Corona, G., Gori, D., Friso, F., Pasquini, E., Bacci, A., Sforza, A., Mazzatenta, D., 2020. Results and predictors of outcome of endoscopic endonasal surgery in Cushing's disease: 20-year experience of an Italian referral pituitary center. J. Endocrinol. Invest. 43, 1463–1471. https://doi.org/10.1007/s40618-020-01225-5.

Hall, W.A., Luciano, M.G., Doppman, J.L., Patronas, N.J., Oldfield, E.H., 1994. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann. Intern. Med. 120, 817–820. https://doi.org/10.7326/0003-4819-120-10-199405150-00001.

Hattori, Y., Tahara, S., Aso, S., Matsui, H., Fushimi, K., Yasunaga, H., Morita, A., 2020. Pituitary surgery's epidemiology using a national inpatient database in Japan. Acta Neurochir. (Wien) 162, 1317–1323. https://doi.org/10.1007/s00701-020-04270-4.

Honegger, J., Grimm, F., 2018. The experience with transsphenoidal surgery and its importance to outcomes. Pituitary 21, 545–555. https://doi.org/10.1007/s11102-018-0904-4.

Ikeda, H., Abe, T., Watanabe, K., 2010. Usefulness of composite methionine-positron emission tomography/3.0-tesla magnetic resonance imaging to detect the localization and extent of early-stage cushing adenoma. J. Neurosurg. 112, 750–755. https://doi.org/10.3171/2009.7.JNS09285.

Ilias, I., Torpy, D.J., Pacak, K., Mullen, N., Wesley, R.A., Nieman, L.K., 2005. Cushing's syndrome due to ectopic Corticotropin secretion: twenty years' experience at the national institutes of health. J. Clin. Endocrinol. Metab. 90, 4955–4962. https://doi.org/10.1210/jc.2004-2527.

Ironside, N., Chatain, G., Asuzu, D., Benzo, S., Lodish, M., Sharma, S., Nieman, L., Stratakis, C.A., Lonser, R.R., Chittiboina, P., 2018a. Earlier post-operative hypocortisolemia may predict durable remission from Cushing's disease. Eur. J. Endocrinol. 178, 255–263. https://doi.org/10.1530/EJE-17-0873.

Ironside, N., Chen, C.-J., Lee, C.-C., Trifiletti, D.M., Vance, M.L., Sheehan, J.P., 2018b. Outcomes of pituitary radiation for Cushing's disease. Endocrinol Metab. Clin. N. Am. 47, 349–365. https://doi.org/10.1016/j.ecl.2018.01.002.

Jagannathan, J., Sheehan, J.P., Pouratian, N., Laws, E.R., Steiner, L., Vance, M.L., 2007. Gamma knife surgery for Cushing's disease. J. Neurosurg. 106, 980–987. https://doi.org/10.3171/jns.2007.106.6.980.

Jagannathan, J., Smith, R., DeVroom, H.L., Vortmeyer, A.O., Stratakis, C.A., Nieman, L.K., Oldfield, E.H., 2009. Outcome of using the histological pseudocapsule as a surgical capsule in cushing disease. J. Neurosurg. 111, 531–539. https://doi.org/10.3171/2008.8.JNS08339.

Koulouri, O., Steuwe, A., Gillett, D., Hoole, A.C., Powlson, A.S., Donnelly, N.A., Burnet, N.G., Antoun, N.M., Cheow, H., Mannion, R.J., et al., 2015. A role for 11C-methionine PET imaging in ACTH-dependent Cushing's syndrome. Eur. J. Endocrinol. 173, M107–M120. https://doi.org/10.1530/EJE-15-0616.

Lacroix, A., Feelders, R.A., Stratakis, C.A., Nieman, L.K., 2015. Cushing's syndrome. Lancet Lond. Engl. 386, 913–927. https://doi.org/10.1016/S0140-6736(14)61375-1.

Lonser, R.R., Ksendzovsky, A., Wind, J.J., Vortmeyer, A.O., Oldfield, E.H., 2012. Prospective evaluation of the characteristics and incidence of adenoma-associated dural invasion in cushing disease. J. Neurosurg. 116, 272–279. https://doi.org/10.3171/2011.8.JNS11456.

Lonser, R.R., Nieman, L., Oldfield, E.H., 2017. Cushing's disease: pathobiology, diagnosis, and management. J. Neurosurg. 126, 404–417. https://doi.org/10.3171/2016.1.JNS152119.

McLaughlin, N., Laws, E.R., Oyesiku, N.M., Katznelson, L., Kelly, D.F., 2012. Pituitary centers of excellence. Neurosurgery 71, 916–926. https://doi.org/10.1227/NEU.0b013e31826d5d06.

Mehta, G.U., Lonser, R.R., 2017. Management of hormone-secreting pituitary adenomas. Neuro Oncol. 19, 762–773. https://doi.org/10.1093/neuonc/now130.

Mehta, G.U., Ding, D., Patibandla, M.R., Kano, H., Sisterson, N., Su, Y.-H., Krsek, M., Nabeel, A.M., El-Shehaby, A., Kareem, K.A., et al., 2017. Stereotactic radiosurgery for cushing disease: results of an international, multicenter study. J. Clin. Endocrinol. Metab. 102, 4284–4291. https://doi.org/10.1210/jc.2017-01385.

Minniti, G., Brada, M., 2007. Radiotherapy and radiosurgery for Cushing's disease. Arq. Bras. Endocrinol. Metabol. 51, 1373–1380. https://doi.org/10.1590/S0004-27302007000800024.

Monteith, S.J., Starke, R.M., Jane, J.A.J., Oldfield, E.H., 2012. Use of the histological pseudocapsule in surgery for cushing disease: rapid postoperative cortisol decline predicting complete tumor resection. J. Neurosurg. 116, 721–727. https://doi.org/10.3171/2011.12.JNS11886.

Mortini, P., Nocera, G., Roncelli, F., Losa, M., Formenti, A.M., Giustina, A., 2020. The optimal numerosity of the referral population of pituitary tumors centers of excellence (ptcoe): a surgical perspective. Rev. Endocr. Metab. Disord. 21, 527–536. https://doi.org/10.1007/s11154-020-09564-7.

Nemergut, E.C., Zuo, Z., Jane, J.A.J., Laws, E.R.J., 2005. Predictors of diabetes insipidus after transsphenoidal surgery: a review of 881 patients. J. Neurosurg. 103, 448–454. https://doi.org/10.3171/jns.2005.103.3.0448.

Nieman, L.K., Ilias, I., 2005. Evaluation and treatment of Cushing's syndrome. Am. J. Med. 118, 1340–1346. https://doi.org/10.1016/j.amjmed.2005.01.059.

Nieman, L.K., Biller, B.M.K., Findling, J.W., Newell-Price, J., Savage, M.O., Stewart, P.M., Montori, V.M., 2008. The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 93, 1526–1540. https://doi.org/10.1210/jc.2008-0125.

Oldfield, E.H., 2017. Cushing's disease: lessons learned from 1500 cases. Neurosurgery 64, 27–36. https://doi.org/10.1093/neuros/nyx378.

Oldfield, E.H., Vortmeyer, A.O., 2006. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. J. Neurosurg. 104, 7–19. https://doi.org/10.3171/jns.2006.104.1.7.

Oßwald, A., Plomer, E., Dimopoulou, C., Milian, M., Blaser, R., Ritzel, K., Mickisch, A., Knerr, F., Stanojevic, M., Hallfeldt, K., et al., 2014. Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. Eur. J. Endocrinol. 171, 209–215. https://doi.org/10.1530/EJE-14-0214.

Patel, V., Liu, C.-S.J., Shiroishi, M.S., Hurth, K., Carmichael, J.D., Zada, G., Toga, A.W., 2020. Ultra-high field magnetic resonance imaging for localization of corticotropin-secreting pituitary adenomas. Neuroradiology 62, 1051–1054. https://doi.org/10.1007/s00234-020-02431-x.

Pecori Giraldi, F., Cavallo, L.M., Tortora, F., Pivonello, R., Colao, A., Cappabianca, P., Mantero, F., 2015. The role of inferior petrosal sinus sampling in ACTH-dependent Cushing's syndrome: review and joint opinion statement by members of the Italian society for endocrinology, italian society for neurosurgery, and italian society for neuroradiology. Neurosurg. Focus 38, E5. https://doi.org/10.3171/2014.11.FOCUS14766.

Perez-Vega, C., Ramos-Fresnedo, A., Tripathi, S., Domingo, R.A., Ravindran, K., Almeida, J.P., Peterson, J., Trifiletti, D.M., Chaichana, K.L., Quinones-Hinojosa, A., et al., 2022. Treatment of recurrent and persistent Cushing's disease after first transsphenoidal surgery: lessons learned from an international meta-analysis. Pituitary. https://doi.org/10.1007/s11102-022-01215-1.

Perlman, J.E., Johnston, P.C., Hui, F., Mulligan, G., Weil, R.J., Recinos, P.F., Yogi-Morren, D., Salvatori, R., Mukherjee, D., Gallia, G., et al., 2021. Pitfalls in performing and interpreting inferior petrosal sinus sampling: personal experience and literature review. J. Clin. Endocrinol. Metab. 106, e1953–e1967. https://doi.org/10.1210/clinem/dgab012.

Prevedello, D.M., Pouratian, N., Sherman, J., Jane, J.A.J., Vance, M.L., Lopes, M.B., Laws, E.R.J., 2008. Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. J. Neurosurg. 109, 751–759. https://doi.org/10.3171/JNS/2008/109/10/0751.

Qiao, N., 2018. Outcome of endoscopic vs microsurgical transsphenoidal resection for Cushing's disease. Endocr. Connect. 7, R26–R37. https://doi.org/10.1530/EC-17-0312.

Ram, Z., Nieman, L.K., Cutler, G.B., Chrousos, G.P., Doppman, J.L., Oldfield, E.H., 1994. Early repeat surgery for persistent Cushing's disease. J. Neurosurg. 80, 37–45. https://doi.org/10.3171/jns.1994.80.1.0037.

Rubinstein, G., Osswald, A., Zopp, S., Ritzel, K., Theodoropoulou, M., Beuschlein, F., Reincke, M., 2019. Therapeutic options after surgical failure in Cushing's disease: a critical review. Best Pract. Res. Clin. Endocrinol. Metabol. 33, 101270. https://doi.org/10.1016/j.beem.2019.04.004.

Sharma, S.T., Raff, H., Nieman, L.K., 2011. Prolactin as a marker of successful catheterization during IPSS in patients with ACTH-dependent Cushing's syndrome. J. Clin. Endocrinol. Metab. 96, 3687–3694. https://doi.org/10.1210/jc.2011-2149.

Shin, S.S., Gardner, P.A., Ng, J., Faraji, A.H., Agarwal, N., Chivukula, S., Fernandez-Miranda, J.C., Snyderman, C.H., Challinor, S.M., 2017. Endoscopic endonasal approach for adrenocorticotropic hormone-secreting pituitary adenomas: outcomes and analysis of remission rates and tumor biochemical activity with respect to tumor invasiveness. World Neurosurg 102, 651–658. https://doi.org/10.1016/j.wneu.2015.07.065 e1.

Starke, R.M., Williams, B.J., Vance, M.L., Sheehan, J.P., 2010. Radiation therapy and stereotactic radiosurgery for the treatment of Cushing's disease: an evidence-based review. Curr. Opin. Endocrinol. Diabetes Obes. 17, 356–364. https://doi.org/10.1097/MED.0b013e32833ab069.

Stroud, A., Dhaliwal, P., Alvarado, R., Winder, M.J., Jonker, B.P., Grayson, J.W., Hamizan, A., Harvey, R.J., McCormack, A., 2020. Outcomes of pituitary surgery for Cushing's disease: a systematic review and meta-analysis. Pituitary 23, 595–609. https://doi.org/10.1007/s11102-020-01066-8.

Stuijver, D.J.F., van Zaane, B., Feelders, R.A., Debeij, J., Cannegieter, S.C., Hermus, A.R., van den Berg, G., Pereira, A.M., de Herder, W.W., Wagenmakers, M.A.E.M., et al., 2011. Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. J. Clin. Endocrinol. Metab. 96, 3525–3532. https://doi.org/10.1210/jc.2011-1661.

Thakkar, K., Lila, A., Sarathi, V., Ramteke-Jadhav, S., Goroshi, M., Memon, S.S., Krishnatry, R., Gupta, T., Jalali, R., Goel, A., et al., 2020. Cabergoline may act as a radioprotective agent in Cushing's disease. Clin. Endocrinol. (Oxf.) 92, 55–62. https://doi.org/10.1111/cen.14123.

Tritos, N.A., Biller, B.M.K., 2020. Advances in the medical treatment of cushing disease. Endocrinol Metab. Clin. N. Am. 49, 401–412. https://doi.org/10.1016/j.ecl.2020.05.003.

Valassi, E., Santos, A., Yaneva, M., Tóth, M., Strasburger, C.J., Chanson, P., Wass, J.A.H., Chabre, O., Pfeifer, M., Feelders, R.A., et al., 2011. The European registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. Eur. J. Endocrinol. 165, 383–392. https://doi.org/10.1530/EJE-11-0272.

Wagner, J., Langlois, F., Lim, D.S.T., McCartney, S., Fleseriu, M., 2018. Hypercoagulability and risk of venous thromboembolic events in endogenous Cushing's syndrome: a systematic meta-analysis. Front. Endocrinol. 9, 805. https://doi.org/10.3389/fendo.2018.00805.

Wang, E.W., Zanation, A.M., Gardner, P.A., Schwartz, T.H., Eloy, J.A., Adappa, N.D., Bettag, M., Bleier, B.S., Cappabianca, P., Carrau, R.L., et al., 2019. ICAR: endoscopic skull-base surgery. Int. Forum Allergy Rhinol. 9, S145–S365. https://doi.org/10.1002/alr.22326.

Wind, J.J., Lonser, R.R., Nieman, L.K., DeVroom, H.L., Chang, R., Oldfield, E.H., 2013. The lateralization accuracy of inferior petrosal sinus sampling in 501 patients with Cushing's disease. J. Clin. Endocrinol. Metab. 98, 2285–2293. https://doi.org/10.1210/jc.2012-3943.

Wong, A., Eloy, J.A., Liu, J.K., 2015. The role of bilateral adrenalectomy in the treatment of refractory Cushing's disease. Neurosurg. Focus 38, E9. https://doi.org/10.3171/2014.10.FOCUS14684.

Yamada, S., Fukuhara, N., Nishioka, H., Takeshita, A., Inoshita, N., Ito, J., Takeuchi, Y., 2012. Surgical management and outcomes in patients with cushing disease with negative pituitary magnetic resonance imaging. World Neurosurg 77, 525–532. https://doi.org/10.1016/j.wneu.2011.06.033.

Young, J., Haissaguerre, M., Viera-Pinto, O., Chabre, O., Baudin, E., Tabarin, A., 2020. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. Eur. J. Endocrinol. 182, R29–R58. https://doi.org/10.1530/EJE-19-0877.