# The Treatment of Cushing's Disease

Rosario Pivonello, Monica De Leo, Alessia Cozzolino, and Annamaria Colao

Dipartimento Di Medicina Clinica E Chirurgia, Sezione Di Endocrinologia, Universita' Federico II di Napoli, 80131 Naples, Italy

Cushing's disease (CD), or pituitary-dependent Cushing's syndrome, is a severe endocrine disease caused by a corticotroph pituitary tumor and associated with increased morbidity and mortality. The first-line treatment for CD is pituitary surgery, which is followed by disease remission in around 78% and relapse in around 13% of patients during the 10-year period after surgery, so that nearly one third of patients experience in the long-term a failure of surgery and require an additional second-line treatment. Patients with persistent or recurrent CD require additional treatments, including pituitary radiotherapy, adrenal surgery, and/or medical therapy. Pituitary radiotherapy is effective in controlling cortisol excess in a large percentage of patients, but it is associated with a considerable risk of hypopituitarism. Adrenal surgery is followed by a rapid and definitive control of cortisol excess in nearly all patients, but it induces adrenal insufficiency. Medical therapy has recently acquired a more important role compared to the past, due to the recent employment of novel compounds able to control cortisol secretion or action. Currently, medical therapy is used as a presurgical treatment, particularly for severe disease; or as postsurgical treatment, in cases of failure or incomplete surgical tumor resection; or as bridging therapy before, during, and after radiotherapy while waiting for disease control; or, in selected cases, as primary therapy, mainly when surgery is not an option. The adrenal-directed drug ketoconazole is the most commonly used drug, mainly because of its rapid action, whereas the glucocorticoid receptor antagonist, mifepristone, is highly effective in controlling clinical comorbidities, mainly glucose intolerance, thus being a useful treatment for CD when it is associated with diabetes mellitus. Pituitary-directed drugs have the advantage of acting at the site responsible for CD, the pituitary tumor. Among this group of drugs, the dopamine agonist cabergoline and the somatostatin analog pasireotide result in disease remission in a consistent subgroup of patients with CD. Recently, pasireotide has been approved for the treatment of CD when surgery has failed or when surgery is not an option, and mifepristone has been approved for the treatment of Cushing's syndrome when associated with impairment of glucose metabolism in case of the lack of a surgical indication. Recent experience suggests that the combination of different drugs may be able to control cortisol excess in a great majority of patients with CD. (***Endocrine Reviews*** **36: 385–486, 2015)**



ISSN Print 0163-769X ISSN Online 1945-7189
Printed in USA

Received May 2, 2013. Accepted May 13, 2015.
First Published Online June 11, 2015

## I. Introduction

Cushing's disease (CD), or pituitary-dependent Cushing's syndrome (CS), is the most common form of endogenous CS, accounting for around 70% of the forms of chronic endogenous hypercortisolism (1, 2). CD is a

Abbreviations: BMI, body mass index; CBG, cortisol-binding globulin; CD, Cushing's disease; CRT, conventional radiotherapy; CS, Cushing's syndrome; CSF, cerebrospinal fluid; DDAVP, desmopressin; DDD, dichloro-diphenyl-dichloroethane; DI, diabetes insipidus; D2R, dopamine 2 receptor; EGFR, epidermal growth factor receptor; GABA, γ-aminobutyric acid; GI, gastrointestinal; GK, Gamma Knife; HPA, hypothalamus-pituitary-adrenal; LBA, laparoscopic bilateral adrenalectomy; LDDST, low-dose dexamethasone suppression test; LINAC, linear accelerator; MLC, multileaf collimator; MRI, magnetic resonance imaging; NS, Nelson's syndrome; OBA, open bilateral adrenalectomy; OGTT, oral glucose tolerance test; PDI, permanent DI; POMC, proopiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PRL, prolactin; SCRT, stereotactic conformal radiotherapy; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SMR, standardized mortality ratio; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; SSTR, somatostatin receptor; TCS, transcranial surgery; TDI, transient DI; TSS, transsphenoidal surgery.

serious endocrine disease caused by excessive secretion of cortisol from the adrenal glands as a consequence of excessive ACTH secretion from a pituitary tumor (1, 2). The pituitary tumor responsible for CD is generally an adenoma, whereas a pituitary carcinoma is a very rare cause of the disease. The pituitary adenoma responsible for CD is a microadenoma in more than 90% of cases, and a macroadenoma in less than 10% of cases; microadenomas are not visible during radiological examination in up to 40% of cases, and macroadenomas may occasionally acquire an aggressive behavior, characterized by a rapid growth and invasiveness of surrounding structures (1, 2).

The prevalence of CD is estimated to be nearly 40 cases per million, whereas the incidence of CD ranges from 1.2 to 2.4 per million per year. CD is at least three times more prevalent in women than in men, and mainly occurs during the fourth to sixth decades of life (1–3).

CD is characterized by a disruption of the hypothalamus-pituitary-adrenal (HPA) axis with consequent increase in circulating serum and urinary cortisol levels and lack of cortisol circadian rhythm (1, 2). The clinical picture of CD mainly includes weight gain with central obesity, fatigue with proximal myopathy, skin thinning with purplish striae, and diffuse bruising. The clinical picture is commonly complicated by several comorbidities, mainly including systemic arterial hypertension, diabetes mellitus, dyslipidemia, osteoporosis, and depression, together with an impairment of sexual function in men; menstrual disorders, acne, and hirsutism in women; and infertility in both men and women (1, 2).

The diagnosis of CD is a real challenge because of the variability of the clinical presentation of the disease and, particularly, the lack of discriminatory symptoms and signs in patients with CD (1, 2). As a consequence, a series of hormonal tests are required for a definitive diagnosis; however, these tests have a variable sensitivity and specificity and fail to reach 100% accuracy (4–6). Therefore, efficient screening and confirmatory diagnosis are essential before considering therapy (7). Moreover, a prompt and effective treatment is crucial to prevent the development and/or worsening of the comorbidities and clinical complications responsible for the increased mortality associated with the disease (8).

The current review summarizes the available treatments for CD, describing efficacy, in terms of control on hormone secretion and tumor mass, and safety, associated with the different treatments, and detailing specific effects on the clinical picture as well as on comorbidities and clinical complications that are the most important causes of death for patients with CD. An introduction on the mortality and morbidity of CD is included to emphasize the severity of the disease and the need for a treatment. Future available treatments and experimental therapeutic approaches are also considered to offer the largest possible view on perspectives in the disease management. This review systematically evaluates the efficacy and safety of the different treatments, considering the available literature published until December 31, 2014.

## II. Mortality and Morbidity in Cushing's Disease

CD is associated with excessive mortality, which is mainly due to cardiovascular or infectious diseases, and their organic or systemic clinical complications. The excessive mortality is usually observed in patients who do not achieve initial surgical remission, whereas those patients who do achieve an immediate surgical cure generally have a mortality rate similar to that of the normal population (9).

### A. Mortality

The studies on mortality in CD have reported nonhomogeneous results. Mortality in patients with CD has been analyzed in a series of studies, which reported the standardized mortality ratio (SMR). In these studies, the SMR of the total population of patients with CD ranged from 0.98 to 9.3 (10–20), being significantly different from the normal population in six studies, where SMR ranged from 2.39 to 9.3 (10, 15–18, 20), and similar to the normal population in five studies, where SMR ranged from 0.98 to 2.67 (11–14, 19). Moreover, eight of these studies evaluated mortality in patients submitted to surgical treatment, considering separately those who had disease remission and those with persistent disease; the results of these studies demonstrated that patients with persistent disease consistently had the highest mortality (13–20), whereas the patients with disease remission after pituitary surgery had a mortality rate generally similar to that of the general population (13–15, 17, 19). This finding suggests the importance of surgical removal of the pituitary tumor and disease remission. However, in contrast with these previous studies, the persistence of an increased mortality rate in patients who achieved disease remission after pituitary surgery has been reported in three different retrospective studies conducted in the United Kingdom (16, 18, 20). In the first of these studies, the SMR of the total population of CD patients was 4.8, with patients achieving surgical cure maintaining a significantly increased mortality (SMR, 3.3). Interestingly, patients with persistent or recurrent disease displayed a dramatically increased mortality (SMR, 16) compared with the normal population (16). In a recent study, the SMR of the total population of CD patients was 3.17, with an increased mortality rate both in patients achieving surgical cure (SMR, 2.47) and in patients with persistence or recurrence of the disease

after surgery (SMR, 4.12), although these values were reported to be not significantly different from that of the normal population (18). Finally, another recent study has demonstrated a similar mortality rate between patients cured or not cured by surgery, displaying an SMR of around 10, compared with the normal population (20). It is worthwhile noting a study conducted in New Zealand that demonstrated a persistently increased mortality rate in patients harboring either a pituitary microadenoma or macroadenoma, despite long-term remission after pituitary surgery (17). In contrast to the discordant evidence of the mortality risk in patients cured by surgery, there is consistent evidence that patients with persistent disease after initial surgery have the highest mortality rate. This finding has been clearly reported in a Danish study in which patients not cured after initial surgery had a SMR of 5.06; interestingly, patients with possible CD whose disease etiology was unproven had an SMR of 11.5. The group with unproven CD included those without clear identification of a pituitary tumor, those who did not achieve remission after surgery, and those who died before a full investigation could be performed (13).

The major cause of death in patients with CD reported in the literature is represented by cardiovascular disease and consequent cardiovascular events, although infectious diseases and consequent sepsis seem to play an important role in determining or precipitating death, and suicide associated with psychiatric disorders is also described in patients with CD (8–20).

The predictive factors for mortality have not been clearly identified in patients with CD. Indeed, whereas age at disease diagnosis seems to have a clear negative role in determining premature death (10, 11, 17, 19, 20), the evidence regarding the role of gender is discordant because an increased mortality in females (10), a similar mortality in females and males (13), and an increased mortality in males (19) have each been reported. Moreover, the higher prevalence of deaths in patients during active disease, compared with patients after surgical remission in most studies suggests a pivotal role for the exposure to cortisol excess in mortality. The presence and duration of active disease have been clearly confirmed as an important predictive factor for mortality (13–16, 19). However, the role of exposure to cortisol excess, in terms of extent and duration, still needs to be clarified. The presence of comorbidities, including systemic arterial hypertension and diabetes mellitus, has been indicated as a predictive factor for mortality in different studies (10, 16, 17). Two recent studies in a large number of patients with CD have addressed the issue of the predictive factors for mortality. One study confirmed that cardiovascular disease represents the main cause of death in patients with CD, with male gender, age at diagnosis, disease duration, and clinical complications elevating the risk of cardiovascular disease (21). In particular, age at diagnosis, duration of exposure to cortisol excess, and preoperative plasma ACTH concentration elevated the risk of death in the total cohort of patients; on the other hand, male gender, age at the diagnosis, and depression were the main determinants for mortality in patients who achieved immediate remission after pituitary surgery or late remission after second-line treatments (21). In the second study, mortality associated with CS was demonstrated to be strongly dependent on the multisystem morbidity of CS, although mainly cardiovascular disease and infectious diseases (22).

Table 1 summarizes the results of the main studies on mortality, including the evaluation of the SMR, in CD.

It should be taken into account that geographic variability in the management of CD can induce differences in reported mortality rates. The recent MISSION (Mortality in Cushing's Syndrome: an International and Observational Study of the European Neuroendocrine Association) study collected information on nearly 5000 patients with CS from around the world and confirmed that patients with CD had an increased mortality (crude mortality rate, 4.25), mainly associated with disease activity (crude mortality rate of patients with active CD, 24.45) and mostly secondary to cardiovascular disease, often resulting in fatal cardiovascular events, and infectious diseases, especially when leading to generalized sepsis, since myocardial infarction or heart failure represents 17.5% and severe infection or sepsis represents 17.3% of the causes of death (23). A recent meta-analysis on mortality in patients with CS, including six studies that focused on patients with CD, confirmed that CD is associated with an increased mortality, documented by an estimated cumulative SMR of 1.84. Patients with persistent or recurrent disease after surgery had a strong association with an increased mortality, with an SMR of 3.73, whereas the SMR of patients with cured disease after surgery, with an SMR of 1.2, was not significantly different from that of the normal population (24). This meta-analysis, in accordance with most of the available studies, seems to suggest that surgical cure is fundamental for protecting patients with CD from a premature death. This conclusion should, however, be interpreted with caution. Although a meta-analysis has the strength of a systematic approach, with the inclusion of only those studies with a clear SMR calculated from available data, it also has the drawback of a limited number of studies that include a relatively small number of patients with a relatively short period of follow-up and few analyzable events.

In summary, the results of the studies on mortality in CD demonstrate that patients with active disease, mainly

**Table 1.** Results of the Main Studies on Mortality in CD

| First Author, Year (Ref.) | Country | Patient Type (n) | Sex Ratio (F/M), n | Duration of Follow-Up as Mean ± SE or Median (Range), y | Study Design | SMR Total Population (95% CI) | SMR Cured Disease (95% CI) | SMR Persistent/ Recurrent Disease (95% CI) | Predictive Factors | Main Causes of Death |
|---|---|---|---|---|---|---|---|---|---|---|
| Etxabe, 1994 (10) | Spain | CD (49) | 46/3 | 6.3 ± 0.8 | Population-based study | 3.8 (2.5–17.9)[a] | NA | NA | Age at diagnosis; female gender; persistence of hypertension and abnormalities of glucose metabolism | Cardiovascular disease; infectious diseases |
| Swearingen, 1999 (11) | United States | CD (161) | 129/32 | 8.7 (1–20) | Retrospective single-center study | 0.98 (0.44–2.2) | NA | NA | Age at diagnosis | Cardiovascular disease; stroke |
| Pikkarainen, 1999 (12) | Finland | CS (74), CD (43) | CS 64/10 CD 38/5 | 7.4 (0–15) | Retrospective single-center study | 2.67 (0.89–5.25) | NA | NA | NA | Coronary heart disease; mitral valve insufficiency and heart failure; acute myocardial infarction; pancreatitis |
| Lindholm, 2001 (13) | Denmark | CS (166), CD (73)[b] | CD 50/23[b] | 8.1 (3.1–14.0) | National registry study | 1.7 (0.68–3.5) | 0.31 (0.01–1.72) | 5.06 (1.86–11.0)[a] | Disease persistence | Stroke; malignancy; sepsis; rupture of aortic aneurysm[b] |
| Hammer, 2004 (14) | United States | CD (289) | 239/50 | 11.1 (0.6–24.1) | Retrospective single-center study | 1.42 (0.95–2.1) | 1.18 (0.7–1.9) | 2.8 (1.35–5.9)[a] | Disease persistence | Myocardial infarction and/or cardiac failure; cardiac arrest[c] |
| Dekkers, 2007 (15) | The Netherlands | CD (74) | 56/18 | 12.8 ± 7.3 | Retrospective single-center study | 2.39 (1.22–3.9)[a] | 1.8 (0.71–3.37) | 4.38 (1.38–9.07)[a] | Disease duration | Cardiovascular disease; malignancy; infectious diseases |
| Clayton, 2011 (16) | United Kingdom | CD (60) | 51/9 | 15 (0.5–41) | Retrospective single-center study | 4.8 (2.8–8.3)[a] | 3.3 (1.7–6.7)[a] | 16 (6.7–38.4)[a] | Disease persistence; hypertension; diabetes | Cardiovascular disease; cerebrovascular disease; malignancy; rupture of aortic aneurysm |
| Bolland, 2011 (17) | New Zealand | CS (253), CD (188) | CS 192/61 CD 142/46 | Macro, 6.9 (0–30); micro, 7.5 (0–46) | Nationwide retrospective survey | Macro, 3.5 (1.3–7.8)[a]; micro, 3.2 (2.0–4.8)[a] | Macro, 2.3 (0.4–7.5); micro, 3.1 (1.8–4.9)[a] | Macro, 5.7 (1.4–15.4)[a]; micro, 2.4 (0.4–7.8)[a] | Age at diagnosis; diabetes mellitus at last follow-up; treatment with pituitary surgery or bilateral adrenalectomy | Malignancy; ischemic heart disease; stroke; sepsis; pulmunary embolism[d] |
| Hassan-Smith, 2012 (18) | United Kingdom | CD (80) | 63/17 | 10.9 (4.9–15.6) | Retrospective single-center study | 3.17 (1.7–5.43)[a] | 2.47 (0.8–5.77)[a] | 4.12 (1.12–10.54) | NA | Cardiovascular disease; malignancy; infectious diseases |
| Yaneva, 2013 (19) | Bulgaria | CS (386), CD (240) | CS 324/62, CD 197/43 | 8.8 (0–41.2) | Retrospective single-center study | 1.88 (0.69–4.08) | 1.67 (0.61–3.62)[e] | 2.4 (0.87–8.19)[a,f] | Age at diagnosis; male gender; disease duration; disease activity | Cardiovascular disease; cerebrovascular disease; infectious diseases and sepsis |
| Ntali, 2013 (20) | United Kingdom | CS (209), CD (182) | CS 157/52, CD 137/45 | 12 (0.1–46) | Retrospective multicenter study | 9.3 (6.2–13.4)[a] | 8.3 (5.1–12.7)[a] | 9.9 (3.6–21.9)[a] | Age at diagnosis | Cardiovascular disease; infectious diseases and sepsis; malignancy |

This table includes studies including the calculation of SMR. Abbreviations: CI, confidence interval; F, female; M, male; NA, not available.

[a] The SMR is significantly different from the general population.

[b] The population of CD considered was that with proven pituitary etiology.

[c] The main causes of death described in this study are exclusively related to the short-term follow-up (within six months after surgery), whereas information on causes of death after long-term follow-up is not available.

[d] The main causes of death are related to the entire population of patients with CS.

[e] The SMR is related to the entire population of CS.

[f] The SMR is the related to the entire population of active CS.

those with persistent or recurrent disease after surgery, have a seriously increased mortality, whereas some discrepancies are evident regarding the data on patients who achieved surgical cure. It cannot be excluded that these discrepancies may partially depend on the definition of "cure" applied in the single studies, considering that a consensus has never been reached on this issue. Nonetheless, it is clear that the normalization of cortisol secretion improves mortality, most likely because of the positive effects on the clinical comorbidities associated with CD, including cardiovascular disease, metabolic syndrome, infectious diseases, and neuropsychiatric disorders, which affect quality of life and represent the important risk of death for patients with CD (8).

Figure 1 shows the main comorbidities and clinical complications associated with mortality in patients with CD.

### B. Cardiovascular disease

Cardiovascular disease represents the direst complication and the leading cause of death in patients with CD (8).

**Figure 1.**

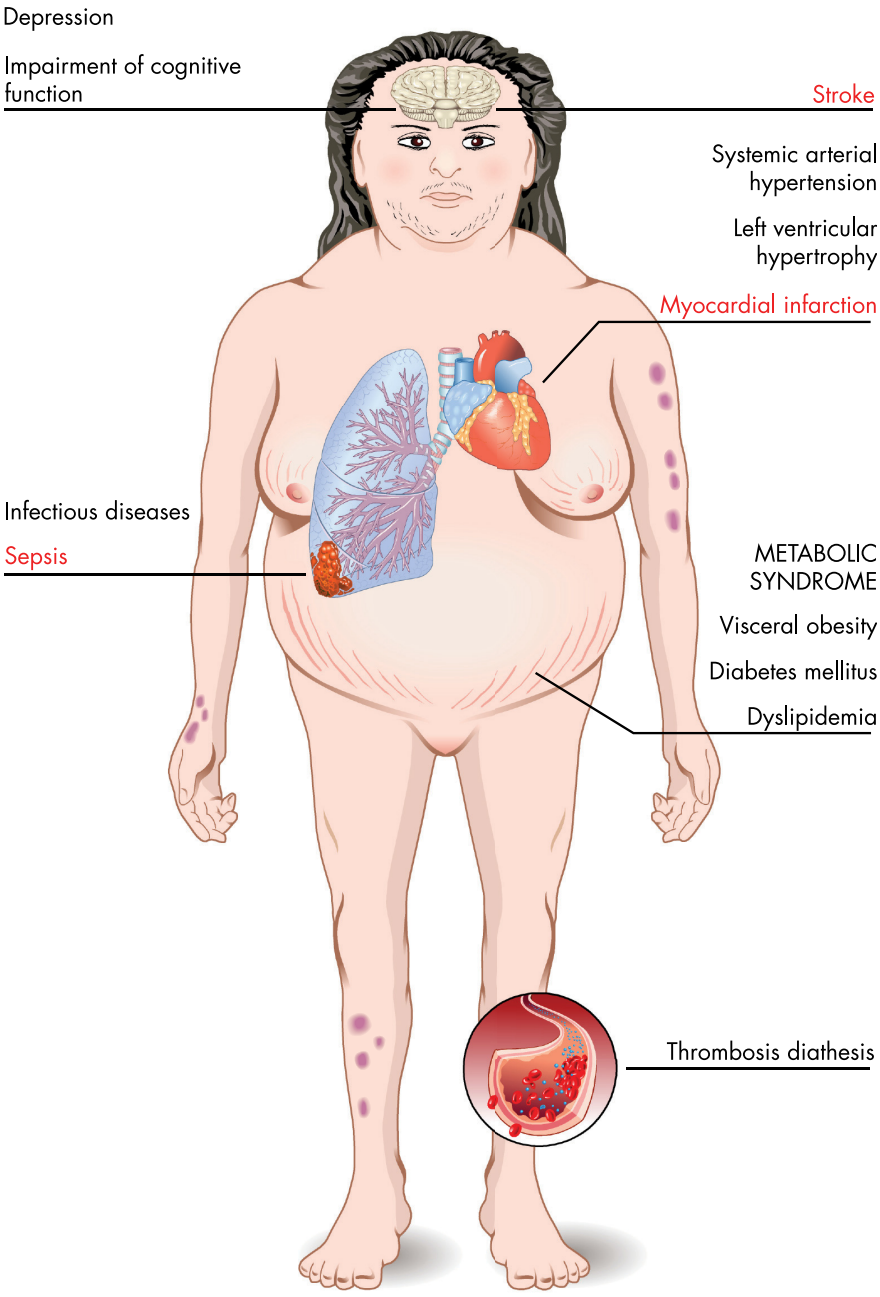


Figure 1. Comorbidities and clinical complications associated with excessive mortality in CD.

Cardiovascular risk is increased in CD because of the comorbidities associated with the disease and including visceral obesity, impairment of glucose tolerance or diabetes mellitus, dyslipidemia, and systemic arterial hypertension, which are constituent elements of metabolic syndrome, as well as thrombosis diathesis (25–27). Cardiovascular disease associated with CD includes both vascular and cardiac diseases.

#### *1. Vascular diseases*

Arterial atherosclerosis is the main vascular disease associated with CD. Indeed, carotid artery wall thickness, a strong predictor of systemic atherosclerosis, was found to be significantly increased and associated with the premature development of plaques in patients with CD during active disease, partially persisting after a short-term remission (28). Moreover, an increased prevalence of preatherosclerotic and atherosclerotic lesions was also found after long-term disease remission from CD (29). The carotid vascular damage was significantly and independently correlated with the degree of visceral obesity and insulin resistance, demonstrating that these two factors mainly contribute to the presence and persistence of vascular damage in patients with CD, both before and after disease remission (28, 29). In patients with CS, including both patients with CD and adrenal-dependent CS, an increased wall thickness and an increased prevalence of atherosclerotic plaques were described in multiple vascular locations (30), whereas in patients with CS, mainly represented by ectopic CS, an increased prevalence of atherosclerotic plaques was documented in the coronary artery system (31), confirming that hypercortisolism induces a premature arterial atherosclerosis in the entire vascular system with a consequent predisposition to coronary heart disease and myocardial infarction, as well as to cerebrovascular diseases and stroke. A functional alteration of the vascular system, evaluated by an endothelium-dependent flow-mediated vasodilation, was reported to be impaired in patients with CS compared with controls, contributing to the vascular damage associated with CS (32). The development of vascular disease is strictly dependent on two of the main cardiovascular clinical features of CS, including systemic arterial hypertension and thrombosis diathesis, the latter of which is due to coagulation disorders.

#### *2. Systemic arterial hypertension*

Hypertension is a common feature of CS, and it has been reported in 55–85% of patients with CD, where it represents an important factor for the development of both vascular and cardiac damage (8). The most important mechanism underlying the hypertension associated with CS lies in the activation of the mineralcorticoid receptor by the excessive cortisol levels (33–36). In addition, multiple factors including the activation of the renin-angiotensin system, together with increased reactivity of vasoconstrictor and decreased reactivity to the vasodilatory system, increased cardiac output and peripheral resistance, mainly the consequence of an increased sensitivity to catecholamines, may contribute to the development of hypertension in CS (33–36). The circadian blood pressure rhythm is generally altered in patients with CD, showing the typical nondipping pattern, which is related to greater end-organ damage and increased mortality (37). Hypertension associated with CS can be difficult to treat without the direct relief from hypercortisolism (36). However, besides the control of hypercortisolism, different antihypertensive drugs often need to be used to control hypertension in patients with CS during active disease; recently, a pathophysiology-oriented therapeutic algorithm has been developed, and it could serve as a first attempt to rationalize the treatment of hypertension in CS (36). Moreover, hypertension can persist even after remission; this is because of either a possible coexistence of essential hypertension or permanent damage incurred by cortisol excess in the cardiovascular system (33–37).

#### *3. Thrombosis diathesis*

Thrombosis diathesis is a dangerous feature associated with CD, where hemostasis abnormalities have been described in around 54% of patients and consequent vascular events in 10% of patients with CD (8). The increase in thrombosis risk associated with CD is not only a consequence of metabolic syndrome, but also a consequence of a specific coagulopathy, which represents another important factor contributing to the increase in cardiovascular risk in patients with CS, and particularly in patients with CD (38–40). Indeed, the cortisol excess stimulates the synthesis of several clotting factors, such as fibrinogen by the liver and von Willebrand factor by endothelial cells, and also induces the synthesis of plasminogen activator inhibitor, which is the main inhibitor of the fibrinolysis (38–40). The hypercoagulable state is considered a crucial factor predisposing patients with CS to thromboembolic events, mostly after surgery, suggesting the usefulness of an anticoagulant prophylaxis in patients with CS before being subjected to surgery in order to prevent postoperative thrombotic events (38–40). Moreover, the increased homocysteine and decreased taurine levels, which have been described in patients with CD, complicate the prothrombotic state and the cardiovascular risk associated with CD (41, 42).

#### *4. Cardiac diseases*

In contrast to the vascular system, cardiac morphology and performance have not been extensively studied in CD. An abnormal left ventricular geometry has been described to be associated with an increase in left ventricular mass in patients with CS (43, 44). These structural abnormalities were associated with diastolic dysfunction (43) or with normal diastolic function (44), and generally with a preserved systolic function (43, 44). Abnormalities in cardiac morphology and performance have been reported to be partially (44) or totally reversible (45) upon normalization of hypercortisolism and disease remission, independently on change in blood pressure. An alteration of the sympathovagal balance of heart rate variability has also been found to be associated with an increased risk of cardiac events, suggesting the possible occurrence of silent arrhythmias and/or myocardial ischemia in patients with CS (46). Indeed, an increased prevalence of coronary artery disease has been documented in patients with cured CS, so that patients, especially young and female patients, remained at risk of myocardial infarction even after long-term cure (47).

### C. Metabolic syndrome

The increased cardiovascular risk of patients with CD is associated with metabolic syndrome (26). Metabolic syndrome is a severe clinical condition affecting approximately 30–40% of the general population, being characterized by systemic arterial hypertension, together with visceral obesity, impairment of glucose metabolism, and dyslipidemia (48). Metabolic syndrome is common in developed countries, due to obesity and sedentary lifestyles, but whether it is a true syndrome or a chance association of unrelated phenotypes is controversial (49). However, there is general agreement that metabolic syndrome is associated with an increased risk to health; in particular, it is associated with a 5-fold risk of developing diabetes mellitus and a 2-fold risk of developing cardiovascular disease after 5–10 years (49). A considerable disagreement also exists regarding the diagnostic criteria for metabolic syndrome, which however are based on the following specific clinical and biochemical features: 1) visceral obesity, represented by an increased waist circumference; 2) dyslipidemia, represented by increased serum triglycerides or decreased high-density lipoprotein-cholesterol, or the presence of antidyslipidemic treatments; 3) impairment of glucose metabolism, represented by increased fasting plasma glucose levels, or the presence of antidiabetic treatments; and 4) hypertension, represented by increased blood pressure or the presence of antihypertensive treatment (49). These criteria are frequently met in CS, which appears as a severe form of metabolic syndrome, suggesting a crucial role of cortisol excess in the genesis of metabolic syndrome, probably through the development of visceral obesity and insulin resistance (49). The role of cortisol excess on the development of metabolic syndrome is confirmed by the evidence that metabolic syndrome is more severe in patients with CS who demonstrate a peculiar abdominal obesity and a severe insulin resistance, associated with dramatically elevated cortisol levels, as opposed to patients with obesity but without CS, usually characterized by a more generalized obesity and a variable insulin resistance associated with absent or slightly elevated cortisol levels. This confirms a role for visceral adiposity and the associated insulin resistance in the development and/or the worsening of metabolic syndrome, at least in CD (49).

The main components of metabolic syndrome in CD include visceral obesity, impairment of glucose metabolism, and dyslipidemia.

#### *1. Visceral obesity*

The prevalence of obesity, which is usually a central obesity and generally characterized by visceral adiposity with main abdominal localization or overweight, has been reported to range between 32 and 41%, and between 21 and 48%, respectively, in patients with CD and is reduced after normalization of cortisol secretion and disease remission (8). However, the reversibility of the alterations in body composition is limited, as demonstrated by the persistently increased fat mass and visceral obesity seen in patients whose hypercortisolism was controlled for an average of more than 10 years (8). In addition, patients with CD display an unfavorable adipocytokine profile with increased inflammatory markers, which persist after disease remission, are implicated in the increased risk of coronary heart disease, and are suggested to be the link between visceral adiposity and increased cardiovascular risk (8).

#### *2. Impairment of glucose metabolism*

The prevalence of impairment of glucose tolerance and diabetes mellitus has been reported to range between 21–64% and 20–47%, respectively, in patients with CD and is reduced after disease remission (8). However, it is very likely that the prevalence of both impairment of glucose tolerance and diabetes mellitus is underestimated either in patients with active disease or in cured patients because glucose tolerance tests are not systematically performed, although they are performed relatively more frequently compared to patients with exogenous CS (50). The disorder in glucose metabolism associated with CD has a multifactorial origin, being dependent on the stimulation of gluconeogenesis in the liver, the inhibition of insulin sensitivity mostly in the skeletal muscle, and the impairment

of β-cell function in the pancreas, induced by cortisol excess. The alteration in glucose production is also influenced by the effect of cortisol excess on adipose tissue structure and function, strongly contributing to the genesis of insulin resistance and metabolic syndrome (51). Diabetes mellitus associated with CD seems to be influenced by age as well as by genetic predisposition and lifestyle, in combination with the degree and duration of hypercortisolism (52). Moreover, the management of the diabetes associated with CD is often difficult and generally requires multiple therapeutic approaches, including glucose-lowering drugs especially directed at improving insulin sensitivity, but mainly cortisol-lowering treatments because cortisol normalization is crucial for the control of glucose metabolism (50).

#### *3. Dyslipidemia*

The prevalence of dyslipidemia has been reported to range from 38 to 71% in patients with CD, and it is markedly improved after normalization of cortisol secretion and disease remission (8). Dyslipidemia seems to be the least frequent metabolic comorbidity associated with CS, although it plays an important role in determining the global cardiovascular risk in patients with CS (53). It is mainly represented by hypercholesterolemia, with a constant increase in LDL-cholesterol and an inconstant decrease in HDL-cholesterol levels, and less frequently by hypertriglyceridemia (53). The pathogenic mechanism of dyslipidemia is multifactorial, including a direct and indirect action of cortisol excess on lipolysis, free fatty acid production and turnover, lipoprotein synthesis, and fat accumulation in the liver (53). The dyslipidemia associated with CD is significantly improved by disease remission and normalization of cortisol secretion (54). Nevertheless, it needs to be aggressively treated with antidyslipidemic agents in line with a strategy of reducing cardiovascular risk (54). It is important to consider that some adrenal-directed drugs used in the treatment of CD may negatively impact on lipid profile and/or interfere with the metabolism and action of lipid-lowering drugs and this negative effect may overcome the positive impact mediated by the drug-induced decrease or normalization of cortisol secretion (54).

#### *4. Insulin resistance*

Insulin resistance has been considered the main factor responsible for the development of metabolic syndrome, in particular the metabolic syndrome associated with CD (8, 26, 49). Indeed, insulin resistance, and the consequent hyperinsulinemia, is a common feature in patients with CD (8, 26, 49). The homeostatic model assessment confirmed the presence of a decrease in insulin sensitivity in patients with CD, independently on body mass index (BMI), suggesting that the impairment in insulin sensitivity is mainly secondary to the state of hypercortisolism (26). On the other hand, the direct correlation between visceral adiposity and hyperinsulinemia in patients with CD during active disease and after disease remission suggests the strict inter-relationship between visceral adiposity and insulin resistance in determining and maintaining the presence of metabolic syndrome in patients with CD during the different phases of the disease (26).

Insulin resistance and metabolic syndrome have been demonstrated to partially persist in patients after both short- and long-term disease remission (8, 26, 49). This is supported by the evidence that not only does hypertension persist in up to 40% of patients, but overweight or obesity also persist in up to 70%, glucose intolerance or diabetes mellitus in up to 60%, and dyslipidemia in up to 30% of patients with CD after disease remission (26), confirming that metabolic syndrome may represent an important factor that sustains an increase in cardiovascular risk even after disease cure (8, 26, 49).

### D. Infectious diseases

Infectious diseases are an important complication, and the frequent consequent sepsis is one of the most common and severe causes of death in CD (9). The susceptibility to infection, which characterizes CD, is a direct consequence of the immunosuppression induced by hypercortisolism. Indeed, CD is characterized by a state of transient immune deficiency (55). Glucocorticoids influence the traffic and regulate the function of leukocytes and immune accessory cells; as a result, glucocorticoid excess is associated with immunosuppression and a susceptibility to infections (55–57). Hypercortisolism has long been recognized to predispose patients to viral, bacterial, parasitic, and primarily fungal infections, which represent the typical opportunistic infections complicating CD (58–60).

The risk of a fungal infection strictly depends on the degree of cortisol excess (58–60). Indeed, fungal infections are more prevalent in ectopic CS, which is associated with extremely elevated cortisol levels, and less frequent in CD, which is associated with moderately elevated cortisol levels (58–60). In particular, opportunistic fungal infections have been reported in 9% of patients with CD (58). The fungal infections reported in patients with CS include superficial fungal infections, mainly cutaneous or mucosal candidiasis, and invasive fungal infections, whose risk of occurrence depends on the degree of cortisol excess (58–60). The invasive fungal infections are mainly located in the lung, with pneumonia the most common clinical manifestation, but cardiac, meningeal, cerebral, and disseminated infectious diseases have also been described (58–

60). The preponderant invasive fungal infections are cryptococcosis, aspergillosis, and pneumocystisosis, including pneumocystis carinii pneumonia. In addition, the type of infection also appears to be related to the degree of hypercortisolism, with criptococcosis associated with lower cortisol levels and pneumocystisosis with higher cortisol levels (58–60). It is noteworthy that in most previously described cases of pneumocystis carinii in CS, clinical pneumonia developed in association with decreasing cortisol levels after surgical or medical therapy (58–60). An explanation of this paradox probably lies in the fact that cortisol excess suppresses the inflammatory response to pneumocistis infection, thus delaying the clinical expression of the infection after the decrease or normalization of cortisol secretion. Correction of hypercortisolism, together with an aggressive antifungal treatment, often resolves the infections and greatly reduces the risk of recurrence. This holds true not only for serious systemic infectious diseases, but also for superficial cutaneous or mucosal fungal infections associated with CS. The opportunistic infections, especially invasive fungal infections, represent a dire complication of CS, including CD; they are often the cause of sepsis, which is undoubtedly associated with an increased risk of death (58–60).

Immunosuppression and the consequent susceptibility to infections for patients with CS appear to be reversible with disease treatment, suggesting that a prompt correction of hypercortisolism is mandatory to resolve or prevent infectious disease and to greatly reduce the risk of recurrence or the risk of degeneration in sepsis (55).

### E. Neuropsychiatric disorders

Neuropsychiatric disorders, which include psychiatric and neurocognitive disorders, represent a serious complication that frequently develops in patients with CD, are difficult to manage during the course of the disease, are also responsible for a significant impairment in the quality of life, and may result in suicide, an important cause of death in CD (61).

#### *1. Psychiatric disorders*

Psychiatric disorders represent significant contributors to the morbidity and mortality of patients with CD (8). In particular, major depression and generalized anxiety disorders have been diagnosed in 54–81% of patients with CD (8). Psychiatric disorders are more frequent in CD patients with higher urinary cortisol levels, absence of pituitary tumor, and longer disease duration, as well as in older and predominantly female patients (61–64). Suicidal ideations have also been described in patients suffering from CS and depression, but patients frequently try to minimize or conceal psychiatric disturbances, including suicide attempts (62, 65).

The most important and life-threatening psychiatric complication of CS is major depression, occurring in 50–80% of patients (62). In patients with CS, depression has been described to be intermittent, with episodes of exacerbation, which recur at irregular intervals (66, 67). Aside from patients who reach the threshold of a major depressive disorder, the remaining patients may report subclinical or subthreshold symptoms, which cause a functional impairment that compromises the quality of life and thus requires clinical attention (62). A high prevalence of atypical depression has also been reported in patients with CS, characterized by the presence of hypoactivation of the stress system, including severe fatigue, apathy, and excessive sleep (62, 68). Psychosis may even occur; manic and hypomanic episodes have been reported in 30% of patients with CS (69), with anxiety and panic disorders reported in 79% and 53% of patients with CD, respectively (70).

The differential diagnosis of depression secondary to CS and primary major depression with pseudo-Cushing's states may be arduous. However, the distinction between the two conditions might be helped by the following evidence: 1) CS is associated with clinical features, such as central obesity, facial plethora, proximal muscle weakness, bruising, and purplish striae, which are specific of the disease, although uncontrolled hypertension and unexplained osteoporosis are more predictive and more discriminative for CS; 2) primary major depression presents frequently with a positive familial history for mood disorders, whereas reports are contrasting about the rate of familial depression among CS patients; and 3) mood changes seem to be more labile, intermittent, and variable in patients with CS than in those affected by primary major depression and are frequently associated with irritability (5, 66, 71). The difficulties in the differential diagnosis of primary major depression with pseudo-Cushing's state and CS are further complicated by the presence of hypercortisolemia in primary major depression. Hypercortisolemia in pseudo-Cushing's states is often indistinguishable from the hypercortisolemia of CS because an overlap in most of the responses to hormonal tests has been described. In particular, urinary cortisol levels are often similar in CS and primary major depression, and these latter patients may present with a lack of cortisol suppression during the low-dose dexamethasone suppression test (LDDST) and/or the lack of a normal cortisol circadian rhythm, conditions that are not always present in patients with mild CS (5, 71). The hormonal test with the best discriminatory power between CD and primary major depression seems to be the CRH test, which usually induces an enhanced ACTH and cortisol response in patients with CD and a blunted/normal ACTH and cortisol response in

primary major depression; however, this test is useful in case of pituitary-dependent CS, but not in the case of adrenal-dependent or ectopic CS. These evidences make the differential diagnosis a complicated clinical procedure, and the diagnosis often needs to be based on the combination of clinical features and hormonal tests but it remains a challenge for endocrinologists (5, 66, 71).

Improvements in psychiatric disorders in CS after surgical or medical treatment have been described to be erratic, delayed, or incomplete (61–63, 67). Moreover, there is robust evidence indicating that anxiety, irritability, depression, and apathy can persist (62, 72). In particular, a slight increase in the frequency of suicidal ideation has been found after correction of hypercortisolism and disease remission (72). This most likely reflects a baseline tendency toward depression and suggests that there may be a persistent psychopathology even after the successful treatment of CD.

#### *2. Neurocognitive disorders*

Neurocognitive impairment may be associated with CD. This is especially related to memory domain, although impairments in visual and spatial information, reasoning, verbal learning, and language performance have also been reported (67). Morphological changes in the central nervous system have been reported in patients with CD as well as in CS, including decreased brain volume and hippocampal formation volume, when compared with healthy controls (73, 74). Structures involved in cognitive functioning are rich in glucocorticoid receptors and are therefore vulnerable to the cortisol excess of CD. Results of long-term studies have suggested that there are irreversible effects of previous cortisol excess on the central nervous system. Indeed, despite remission, many patients exhibit impairment in numerous domains of cognitive function, suggesting a global involvement of the brain function (75, 76).

#### *3. Impairment of quality of life*

CD is clearly characterized by an impairment of quality of life (8). The clinical syndrome and comorbidities of CS have been demonstrated to impact negatively on the health-related quality of life of these patients physically, mentally, and emotionally (77), and this impairment seems to persist even after a long-term successful cure (78, 79). The mechanism through which CS determines quality of life impairment is probably multifactorial, involving physical and psychological features (77–80). The evaluation of health-related quality of life in these patients is gaining importance, and several questionnaires and different criteria have been used. Moreover, during recent years two disease-specific questionnaires have been assessed: the Cushing QOL (77) and the Tuebingen CD QOL inventory (Tuebingen CD-25) questionnaire (81, 82). Both questionnaires are feasible, reliable and represent a valid instrument for measuring health-related quality of life in patients with CS.

It is important to point out that the impairment of quality of life together with most comorbidities associated with CS, as well as in CD, partially persists in patients not only after early remission but also after definitive cure, configuring a syndrome of the "cured CS patients," and clearly suggesting that patients with CD and, in general, patients with CS need to be monitored during their entire life, independently on the remission or cure from the condition of cortisol excess (83).

## III. The First-line Treatment of Cushing's Disease

The main objectives for the treatment of CD include: 1) normalization of cortisol secretion; 2) reversal of the clinical picture; 3) prevention or recovery of the concomitant comorbidities and clinical complications; and 4) long-term disease control without disease recurrence (1, 2, 7, 84–88). However, these ideal objectives are often difficult to achieve in clinical practice, where an improvement of clinical picture and comorbidities, sustained by the normalization or, at least, a consistent control, of cortisol secretion is more commonly achieved during or after a specific treatment. The achievement of these objectives, however, frequently requires a multimodal treatment approach (1, 2, 7, 84–88).

### A. Treatment algorithm

In general, the initial treatment of choice for CD is represented by pituitary surgery, usually consisting of the selective removal of the pituitary tumor (adenomectomy) and rarely by the removal of half (hemi-hypophysectomy) or nearly the entire (total hypophysectomy) pituitary gland; it is advisable that pituitary surgery is performed by a surgeon with documented experience in this type of surgery (1, 2, 7, 84–88). Transcranial surgery (TCS) has been used in the past, and it is occasionally used today, whereas transsphenoidal surgery (TSS) represents the main surgical approach to pituitary lesions in CD. The outcome of pituitary surgery may include the resolution or the persistence of hypercortisolism, depending on the complete or incomplete removal of the pituitary lesion. A complete and successful tumor resection usually leads to transient cortisol deficiency because the remaining normal corticotroph cells have been suppressed by long-standing hypercortisolism. This cortisol deficiency is managed with

physiological glucocorticoid replacement therapy until the recovery of the HPA axis. A permanent cortisol deficiency may occur in a group of patients after successful surgery, and it requires lifelong glucocorticoid replacement. In a selected group of patients, successful surgery may also be followed by normalization of cortisol levels, thus excluding the necessity for additional therapy (1, 2, 7, 84–88). An incomplete or unsuccessful tumor removal is associated with persistence of hypercortisolism. Moreover, initial postsurgical disease remission may be followed by disease recurrence, mainly during the following 10-year period (1, 2, 7, 84–88). Disease persistence or recurrence requires a second-line treatment; repeat pituitary surgery, pituitary radiotherapy, adrenal surgery, or medical therapy may be considered on the basis of patient characteristics or disease history (1, 2, 7, 84–88). Medical therapy, performed with different categories of drugs, has progressively acquired a growing role in different stages of the treatment schedule; nowadays medical therapy can be successfully used for chronic control of cortisol secretion, but it remains not a definitively curative treatment (1, 2, 7, 84–88). Repeat pituitary surgery may complete the tumoral removal of the initial pituitary surgery and induce disease remission without significant complications, but it is associated with a relevant percentage of failure, so that pituitary radiotherapy and adrenal surgery for a bilateral adrenalectomy, together with medical therapy, may also represent a third-line treatment (1, 2, 7, 84–88). Pituitary radiotherapy and adrenal surgery for bilateral adrenalectomy can also be considered in case of failure of medical therapy in safely controlled hypercortisolism during second-line or third-line treatment, especially when different medical treatments, alone or in combination, have been demonstrated to be ineffective or not tolerated (1, 2, 7, 84–88). The choice of the treatment as second-line and third-line approach needs to be based on patient's and disease characteristics, and to the balance between the efficacy and safety of the different available treatments.

Figure 2 shows the treatment algorithm currenty used in the management of CD.

### B. Criteria for remission and cure

The establishment of cure in CD represents a crucial but challenging point in the management of CD for various reasons. First, there is no clear agreement on the criteria that should be used to establish or predict cure, and this heterogeneity of criteria hinders a direct comparison of treatment outcome between different studies. Second, studies aimed at evaluating the different criteria for establishing or predicting cure are limited to the evaluation of the outcome of pituitary surgery, and the results of these studies cannot be completely adapted to the different therapeutic approaches. Third, there is evidence that an apparent cure after pituitary surgery may be followed by a recurrence even after many years, inducing the need to distinguish a temporary disease cure, more commonly defined as disease remission evaluated immediately after surgery, from a definitive disease cure, which can only be evaluated one or more decades after surgery (7, 83, 85, 88–90).

In studies evaluating the rate of remission or cure of CD after pituitary surgery, several methods have been used: 1) nonprovocative tests including measurement of morning serum cortisol and/or plasma ACTH levels and/or daily urinary cortisol levels within the postsurgical period; and 2) provocative tests including the overnight or 2-day LDDST, the CRH stimulation test, and the desmopressin (DDAVP) stimulation test during the 3-month period after surgery.

#### *1. Morning serum cortisol*

Postsurgical morning serum cortisol is the most important marker to evaluate disease activity after pituitary surgery (11, 14, 18, 21, 91–139). The ideal time for blood collection does not follow any standard pattern and presents a wide variation between different centers. Several investigators have recommended serial measurements of serum cortisol in the immediate postsurgical period (1–7 d after pituitary surgery) to identify patients with persistent disease (11, 14, 21, 94, 96, 100, 103, 105, 107, 108, 110, 113, 115–118, 120, 122, 123, 125–128, 130, 132, 133, 136, 138). Some investigators suggest that a late measurement of serum cortisol (1–6 mo after pituitary surgery) is a better parameter to establish disease remission (18, 95, 98, 99, 106, 112, 124, 129, 134, 137, 139). However, several clinical scenarios complicate the interpretation of these diagnostic tests in the postsurgical period. Circulating cortisol levels may not decrease immediately after successful resection of a corticotroph pituitary tumor, because long-standing ACTH excess could result in a marked adrenal hyperplasia and somewhat autonomous cortisol production by the adrenal glands (114, 116, 125, 131, 140, 141). Alternatively, a near-total resection of a corticotroph pituitary tumor may result in a marked decrease in ACTH hypersecretion and, in the setting of suppression of normal corticotroph pituitary cells, a temporary period of adrenal insufficiency (118, 120, 125, 126, 140, 142). The adrenal insufficiency ultimately resolves because ACTH secretion from the tumor gradually increases as a consequence of growth and progression of the residual tumor (118, 120, 125, 126, 140, 142). Moreover, the use of exogenous glucocorticoids to prevent adrenal insufficiency in the immediate postoperative period could interfere with endogenous cortisol secretion because it

**Figure 2.**

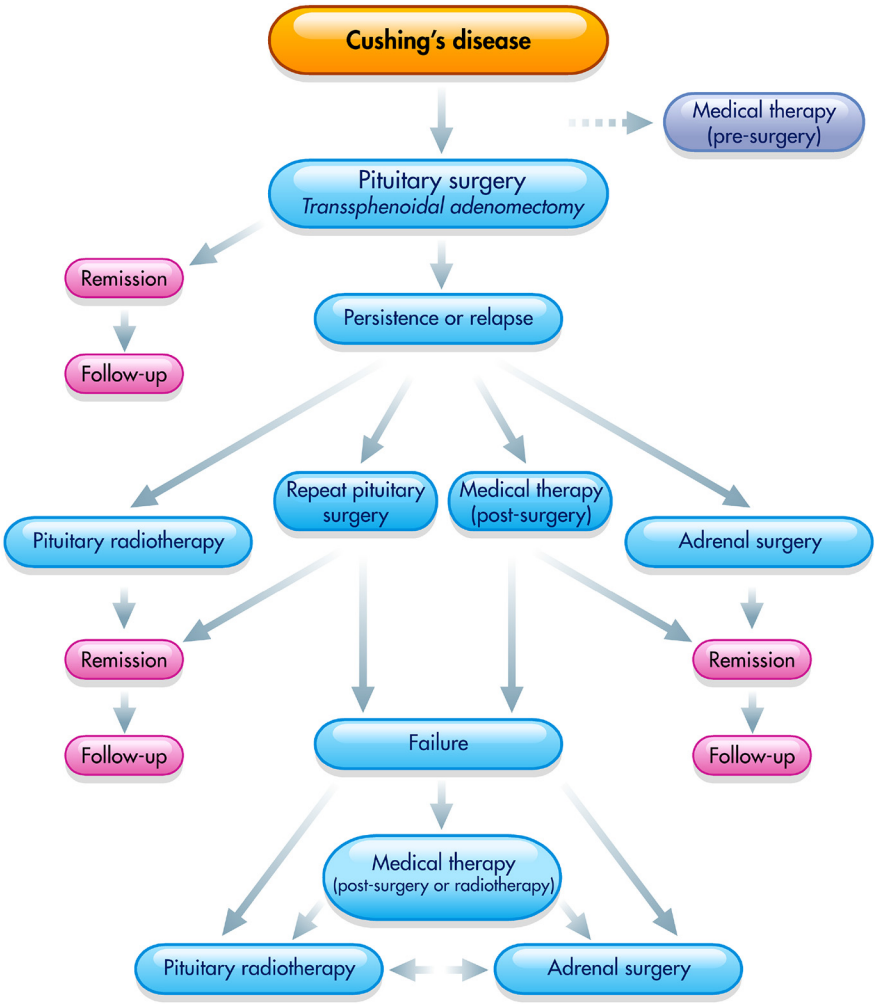


Figure 2. Schematic treatment algorithm for current management of CD. The dashed line means that the treatment option is presently considered an optional choice.

may suppress any remaining tumor tissue and mask the presence of persistent disease (89, 90, 143). Regarding the absolute cortisol cutoff for establishing disease remission, studies are conflicting. Indeed, differences in cortisol assay, which display variable sensitivities, may account for some of the differences in reported cutoff values. Many reports have established that low or undetectable postoperative cortisol levels are analogous with a "cure," being associated with sensitivity and specificity of 80–100% (11, 14, 18, 21, 95, 100, 103, 104, 107, 110–113, 115, 117–121, 123, 126–128, 130, 132–137, 139). In particular, some authors consider disease remission to be associated with cortisol levels lower than 5 μg/dL (138 nmol/L) (11, 14, 21, 111–113, 120, 121, 123, 126–128, 130, 132, 133, 136, 137, 139), whereas others consider a value such as 1.8 μg/dL (50 nmol/L) during the first week after surgery (18, 110, 117, 118, 134, 135). It is noteworthy that undetectable cortisol values in the immediate postoperative period are not consistently associated with long-term remission. In particular, undetectable postoperative cortisol values predict a more positive outcome, but do not eliminate the possibility of a recurrence (100, 102, 109, 110, 114, 117, 120, 123, 131, 135, 137, 139, 144). Indeed, Pereira et al (140) found that the optimal postoperative cortisol cutoff value predictive of cure was 5 μg/dL (138 nmol/L), measured 6–12 weeks after surgery with a sensitivity of 94% and a specificity of 79%. This was compared with a sensitivity of 67% and a specificity of 79% with a cutoff value of 1.8 μg/dL (50 nmol/L) measured 2 weeks after surgery, suggesting that the 6- to 12-week postsurgical evaluation has a better predictive value of disease persistence or cure than an earlier evaluation of morning cortisol, even considering as a cortisol cutoff a low rather than a completely undetectable cortisol value.

In addition, it has been demonstrated that a complete normalization of the HPA axis after pituitary surgery, including the rhythm and stress response, is also associated with a very low risk of recurrence (145). Conversely, a recent study suggested that the time to recovery of the HPA axis after surgery was the only significant predictor of a recurrence because all patients who recurred showed a recovery within 3 years of surgery. In particular, recovery within 6 months, 1 year, and 2 years had a positive predictive value of 64, 61, and 59%, respectively (135). Indeed, a relatively short duration of secondary adrenal insufficiency has been considered a risk factor for recurrence (146). A meta-analysis suggested that patients with subnormal morning cortisol levels, measured within 2 weeks after pituitary surgery, clearly have a reduced risk of long-term recurrence, compared with those with postoperative cortisol levels in the normal range (131). More specifically, based on the best existing published data, a subnormal immediate postoperative cortisol level has specificity for lasting disease freedom of approximately 88–94%. More importantly, a value in the normal range has a positive predictive value for a recurrence of only approximately 17–31% (131). It is notewothy that morning cortisol levels persistently below the normal range during the first months after surgery do not exclude the possibility of a late recurrence, thus necessitating continuous monitoring of patients for a long period of time after an apparently successful surgery (14, 100, 102, 109, 110, 114, 117, 118, 120, 123, 131, 135, 137, 139, 140, 144). On the other hand, morning cortisol levels persistently above the normal range may not always represent patients with residual tumor. Indeed, marked adrenal hyperplasia, as well as a somewhat autonomous cortisol production by the adrenal glands because of long-lasting ACTH excess, may temporarily produce increased morning cortisol levels (114, 116, 125, 131, 140, 141). This is particularly important in consideration of a repeat pituitary surgery after the real or apparent failure of the initial pituitary surgery because a repeat surgery could be performed soon after (within 60 d) the initial surgery (104, 135, 147–150). A consensus statement on the treatment of CD recommends an assessment of remission by measuring morning serum cortisol during the first postoperative week, either by withholding treatment with glucocorticoids or by using low doses of dexamethasone (below 1 mg). When morning serum cortisol levels are between 2 and 5 $\mu$g/dL (55–138 nmol/L), the patient can be considered in remission and can be observed without additional treatment for CD (7).

#### *2. Morning plasma ACTH*

The predictive value of postsurgical plasma ACTH levels for disease cure has not been evaluated extensively, and studies on this issue are not concordant. Recognizing that the half-life of ACTH is around 10 minutes, it would be reasonable to postulate that after a successful tumor removal, ACTH levels should drop dramatically 12 to 24 hours after surgery. Indeed, a study evaluating the dynamics of ACTH intraoperatively up to 1 hour after surgery has demonstrated that plasma ACTH levels decrease by 54% within 1 hour after surgery in patients who were subsequently considered cured and by 26% in patients who were subsequently considered not cured, with a cutoff of 40%, which discriminated between cured and not cured patients (151). However, in two other studies, the changes in plasma ACTH level failed to predict surgical success (152, 153). In a few studies, an early decline in ACTH levels was shown to differentiate subjects in surgical remission from those with persistent disease (103, 124, 149, 152–155). Furthermore, it has been reported that only 50% of patients with a clinical remission showed suppressed plasma ACTH levels (114). None of these studies examined the role of measuring plasma ACTH levels in the immediate postsurgical period for predicting future recurrences.

#### *3. Daily urinary cortisol*

Urinary cortisol excretion has been used as a measure of surgical success, but it is not usually considered the exclusive parameter for the assessment of disease remission (11, 92, 94, 96, 97, 102, 108, 109, 111, 112, 114, 115, 119, 122, 124, 126–130, 137, 138, 140, 145, 156–168). Moreover, there is no agreement on the cutoff of urinary cortisol levels for considering disease remission because either normal (92, 96, 97, 122, 127–129, 140, 156–160, 162, 163, 168) or lower-than-normal levels (11, 111, 112, 115, 119, 126, 130, 137, 158, 161) have been said to best determine disease cure. Actually, when considering the problems associated with the measurements of urinary cortisol levels, especially when patients are given exogenous glucocorticoids, combined with the difficulties encountered in obtaining an adequate collection, only a few centers currently use this parameter in the evaluation of disease remission. However, the evidence of several urinary cortisol levels below the normal range, in combination with different tests evaluating disease activity, can be considered a valuable method to confirm disease remission (5).

#### *4. Dexamethasone suppression test*

A LDDST performed days or weeks after surgery has been used to predict remission or cure of CD. However, no homogeneity in the type of LDDST, in terms of dexamethasone dose and time, was reported across different studies. Indeed, some authors performed a 1-mg overnight LDDST

(14, 120, 126, 134, 139, 140, 145, 165, 166, 169), whereas other authors performed a 2-mg overnight or 2-mg 2-day LDDST (102, 103, 109, 160, 161, 164, 167, 170, 171). However, only a few studies have used exclusively this parameter to evaluate disease remission (146, 169, 171). Additionally, there is no agreement on the serum cortisol cutoff to be used to define disease remission or cure. Boggan et al (98) and Mampalam et al (106) suggested that "normal serum cortisol levels," without a precise value in a LDDST, should be considered the criterion for cure. Conversely, different studies suggest that values of 1.8 μg/dL (50 nmol/L) (134), 3 μg/dL (83 nmol/L) (120, 126), 3.6 μg/dL (99 nmol/L) (140), 5 μg/dL (138 nmol/L) (14, 165, 166), or 8 μg/dL (220 nmol/L) (169) after a 1-mg overnight LDDST could perform better in identifying those patients with a disease remission. After a 2-mg overnight LDDST, a serum cortisol level <2 μg/dL (55 nmol/L) was considered a good predictor of cure (103, 164, 171). Conversely, after a 2-mg 2-day LDDST, different cutoffs have been used; in particular, a value of 2.2 μg/dL (60 nmol/L) (109), 3.6 μg/dL (99 nmol/L) (170), or 5 μg/dL (138 nmol/L) (160) identified patients with disease remission. Finally, in two series, after 2-mg 2-day LDDST a "normal cortisol level" has been considered the criterion of cure (102, 161). It is noteworthy that the predictivity value of this test is affected by the chance of false positive and false negative. Indeed, several drugs are able to influence the hepatic enzymatic clearance of dexamethasone, thereby reducing or increasing its plasma concentrations and resulting in false-positive or false-negative responses to a dexamethasone suppression test (5, 172). In particular, estrogens increase circulating cortisol-binding globulin (CBG) levels, inducing false-positive tests in about 50% of women on oral contraceptives when using radioimmunological assays, and therefore affecting positive predictive value (6). Finally, Castinetti et al (173) have demonstrated that a coupled dexamethasone-DDAVP test is an early predictor of a recurrence of CD, being positive in patients with a recurrence before other markers of hypercortisolism.

#### *5. CRH stimulation testing*

The rationale underlying the usefulness of CRH test in the postsurgical evaluation of CD patients is based on the evidence that CRH administration results in a disproportionate rise in ACTH and cortisol levels in patients with CD, which is supposed to be persistent in cases of failed surgery (4, 174, 175). Different studies have examined plasma ACTH and serum cortisol levels after CRH administration in the postsurgical period (107, 114, 146, 176, 177). The results are variable among these published studies, making it difficult to provide definitive criteria. It is not clear whether this approach offers any advantage over measurement of morning serum cortisol levels. Avgerinos et al (177) observed no relapse in 23 patients who showed a decreased response to CRH test in a follow-up period of 6–42 months after pituitary surgery. By contrast, three of six patients who responded normally to the test relapsed. Invitti et al (114) demonstrated that the risk of a relapse significantly correlated with an increase of more than 50% in plasma ACTH and serum cortisol after CRH administration. Several studies have shown similar results (146, 158, 176, 178–181), although a CRH test was not performed in the same period after surgery in the different studies.

#### *6. DDAVP stimulation test*

The rationale underlying the possible usefulness of the DDAVP test in the postsurgical evaluation of CD patients stands on the premise that ACTH and cortisol increments after DDAVP are secondary to the presence and up-regulation of the V3 receptor on tumor corticotroph cells (182, 183). Ideally, radical removal of tumor cells should lead to a disappearance of the ACTH and cortisol response to DDAVP. However, only 70–90% of patients with proven CD show an increment of ACTH and cortisol to DDAVP administration (5, 184–188). Clearly, the DDAVP test may be informative only in patients with a positive response before surgery. Another prerequisite for the DDAVP test should be its specificity to elicit the ACTH and cortisol response in patients with CD and not in normal subjects. The DDAVP test has been investigated as a predictor of long-term outcome after pituitary surgery in a small series of subjects (189). In particular, a persistent response of ACTH to DDAVP after surgery had a positive predictive value for disease recurrence of around 100% (188, 190–192). The role of the DDAVP test has also been investigated during long-term follow-up of apparently cured patients. Indeed, in patients who did not respond soon after surgery, a reappearance of a positive response to DDAVP during a long-term follow-up preceded the overt clinical and biochemical signs of hypercortisolism by 4–39 months (193, 194). Therefore, persistence of an ACTH response to DDAVP soon after surgery identifies a subgroup of patients with an increased risk of disease recurrence during follow-up. However, this test displays a low specificity and predictive value. Colombo et al (189), comparing the DDAVP test with a CRH test response in 34 patients before and after pituitary surgery, showed that patients considered to be in remission after a period of 1–36 months never responded to the DDAVP test, in contrast to a progressive recovery of ACTH and cortisol responses after CRH. Finally, in a recent paper, an ACTH response to a DDAVP+CRH test resulted in a positive

predictive value for recurrence of 100%, with no response to either test giving a negative predictive value for recurrence of 100% (192).

### C. Pituitary surgery

The first-line treatment of CD is mainly represented by the surgical removal of the pituitary tumor by TSS (1, 2, 7, 84–87). The progressive advances in neurosurgical techniques over the last several decades and the accumulated experience by pituitary surgeons have resulted in increasingly improved outcomes after pituitary surgery for patients with CD. However, because there is still no widespread agreement regarding the definition of remission or cure, the remission or cure rates after pituitary surgery vary according to the criteria used for each study.

#### *1. Types of pituitary surgery*

Pituitary surgery may be performed by a transcranial approach or a transphenoidal approach. Pituitary TCS is mainly a historical approach, which nowadays is only used in rare cases when the transphenoidal approach is not possible or a transcranial approach is necessary for the size, localization, and expansion of the pituitary tumor (1, 2, 7, 84–87). Pituitary TSS may be performed by two different techniques: microscopic and endoscopic (195, 196). Microscopic TSS is based on the standard microscopic transseptal approach popularized by Hardy (197). The key point of this procedure includes the submucosal transseptal approach, the use of nasal speculum to visualize the floor of the sphenoid sinus and opening of the sphenoid and sellar floor. The whole procedure is carried out under microscopic three-dimensional visualization, thus allowing operating in three-dimensional space (198–200). Endoscopic TSS has been advocated for the surgical treatment of pituitary tumors since the late 1990s on the basis of its panoramic visualization by the use of a rigid endoscope and the ability to easily visualize structures such as the optico-carotid recesses and to visually access suprasellar areas that are not in the direct line of vision during microscopic pituitary surgery (201–204). This improved visualization was felt to be theoretically associated with a greater extent of resection and improved safety, less invasiveness, and potentially better results compared to microscopic pituitary surgery. However, endoscopic pituitary surgery is bi-dimensional, and thus depth perception is missing, although maneuvers have been recommended to minimize this drawback (201–204). It is important for both TSS techniques to consider some important principles, such as the recognition that the pituitary gland is a midline and an extra-arachnoidal structure and, more importantly, that the normal anterior pituitary gland is distended by the pituitary tumors, especially the large tumors, into a thin layer of tissue surrounding the pathology, whose preservation maximizes postsurgical pituitary function. Therefore, TSS pituitary surgery needs to be extra-arachnoidal to respect the principle of midline and needs trying to identify and preserve normal pituitary tissue (205–207).

#### *2. Efficacy of pituitary surgery*

The efficacy and the consequent outcome of pituitary surgery in CD depend on two factors: the immediate remission rate and the late recurrence rate. The remission and recurrence rates reported in different studies on pituitary surgery display a wide variation. This evidence is not only related to the distinct remission and cure criteria, but also to the different times when hormone evaluations were undertaken and the different patient populations were considered in the different studies.

This review has considered 74 studies published between 1976 and 2014 involving a total of 6869 patients with CD, including a minimum of six patients and a maximum of 668, with a follow-up duration ranging from 1 to 444 months (mean, 64.3 mo; median, 55.2 mo) submitted to initial pituitary surgery, generally by TSS with selective adenomectomy or hemi/total hypophysectomy. However, because 737 patients are apparently included in two different studies, the real total number of different patients included in these studies is likely 6134. The overall initial remission rate ranged from 25 to 100% (11, 14, 18, 21, 91–115, 117–124, 126–130, 132–140, 145, 146, 154, 156–171, 208–211), with a mean remission rate of 77.8% and a median remission rate of 78.7%. The recurrence rate, when calculated as a percentage of the patients who obtained initial remission, ranged from 0 to 65.6%, with a mean recurrence of 13.2% and a median recurrence of 10.6%, whereas, when calculated as a percentage of the whole population of patients included in the study, it ranged from 0 to 51.2%, with mean and median recurrence rates of 9.6 and 7.5%, respectively. Comparing studies published before or after 2000, remission rates appear to be similar in studies published before 2000 (range, 41.7–100%; mean, 78.2%; median, 81.2%) (11, 91–114, 146, 156–159, 167, 168, 209, 210) than after 2000 (range, 25–96.5%; mean, 77.5%; median, 78.2%) (14, 18, 21, 115, 117–124, 126–130, 132–140, 145, 154, 160–166, 169–171, 208, 211). Conversely, recurrence rates appear to be lower in studies published before 2000 (range, 0–36.4%; mean, 9.8%; median, 7.7%) than after 2000 (range, 0–65.6%; mean, 15.9%; median, 12.2%). Taking into account only the 51 studies involving more than 30 patients with a minimum mean or median follow-up of 6 months, the mean and median remission rates were 78.2 and 78.7% (range, 41.7–96.5%), respectively.

Likewise, the mean and median recurrence rates were 13 and 10% (range, 0–65.6%), respectively (11, 14, 18, 21, 97, 98, 103, 104, 106, 108–110, 112, 115, 117, 118, 120, 121, 124, 126, 128–130, 132–137, 139, 140, 145, 146, 154, 156, 158–166, 168–171, 208, 210, 211). Among these 51 studies, remission rates are similar in studies published before 2000 (range, 41.7–87.7%; mean, 75.1%; median, 78%) and after 2000 (range, 65–96.5%; mean, 79.6%; median, 78.7%), whereas recurrence rates appear to be lower in studies published before 2000 (range, 0–20.6%; mean, 7.6%; median, 6.6%) than after 2000 (range, 2.4–65.6%; mean, 15.6%; median, 12.8%).

Tables 2, 3, and 4 summarize the results of the studies evaluating the outcome of pituitary surgery in CD. Table 2 includes the studies on the overall population of CD, Table 3 includes the studies clearly reporting results in patients with microadenoma, and Table 4 includes the studies clearly reporting results in the patients with macroadenoma.

The remission rates in patients with microadenomas ranged from 48.7 to 100% (mean, 82.1%; median, 85.7%) (11, 91–96, 98, 100, 101, 104, 106, 107, 109, 112, 113, 121, 124, 126–129, 132–136, 157, 159, 161, 162, 164–167, 169, 170, 209), whereas in those with macroadenomas it ranged from 30.8 to 100% (mean, 62.3%; median, 64.1%) (11, 98, 104, 106, 112, 113, 119, 122, 126, 127, 129, 132–136, 164–166, 169, 209). The recurrence rate in patients with microadenomas and macroadenomas was 0–36.4% (mean, 11.7%; median, 10.9%) (11, 91, 93, 95, 96, 98, 100, 101, 104, 106, 107, 109, 112, 121, 124, 127–129, 132–136, 157, 159, 161, 162, 164, 166, 167, 169, 170, 209) and 0–59% (mean, 18.8%; median, 13.9%) (11, 98, 104, 106, 112, 119, 122, 126, 127, 129, 132–136, 164–166, 209), respectively. Many of these studies have demonstrated that the remission and recurrence rates associated with macroadenomas are worse than those associated with microadenomas. The remission rate of invasive tumors ranged from 0 to 67% (mean, 41.1%; median, 43%), whereas the recurrence rate ranged from 15 to 36% (mean, 25.3%; median, 25%) (14, 97, 98, 102, 106, 112, 117, 119, 122, 134, 209), clearly reporting worse outcome for tumor invading cavernous sinuses or surrounding structures.

The risk of disease recurrence persists for at least 10 years after surgery, with a range of median times to recurrence from 13.6 to 66 months (11, 14, 18, 91, 95, 100, 107, 111, 114, 115, 118, 126, 129, 133, 135, 136, 140, 146, 154, 157, 159–163, 167–169). The time to recurrence ranges between 1 and 345 months (mean, 41.3 mo; median, 40.5 mo) (11, 14, 18, 21, 91, 95, 97, 98, 100, 102, 104, 106–108, 111, 112, 114, 115, 117–120, 124, 126, 128–130, 132–136, 139, 140, 146, 154, 156–164, 166–171, 209–211). The minimum reported mean time to recurrence was 2 months, and the maximum was 115 months (108, 114). A study carried out in a center experienced for pituitary surgery reported that the actuarial recurrence incidence increases with follow-ups, being 25 and 46%, respectively, in patients followed for shorter or longer than 5 years (162). The possibility of short-term but also long-term recurrence has been confirmed by further studies (11, 14, 21, 107, 112, 114, 115, 118–120, 124, 126, 128–130, 132–135, 139, 140, 146, 154, 158–163, 166, 168, 170, 210), thus suggesting a need for stringent and indefinite follow-up in patients with CD even after an apparent ongoing disease remission. Only one study has shown that the recurrence rate decreases over the years in some patients with a long follow-up period (171). Considering all patients with surgical failure, including those with disease persistence immediately after surgery and those with disease recurrence later after surgery, the long-term failure of pituitary surgery has been documented in 0–75% of cases (mean, 31.7%; median, 29.3%) (11, 14, 18, 21, 91–100, 102–115, 117–124, 126–130, 132–140, 145, 146, 154, 156–171, 208–211). Taking into account only the 51 studies involving more than 30 patients with a minimum mean or median follow-up of 6 months, the long-term failure of pituitary surgery ranged between 5.7 and 73.2% (mean, 32%; median, 29.4%) (11, 14, 18, 21, 97, 98, 103, 104, 106, 108–110, 112, 115, 117, 118, 120, 121, 124, 126, 128–130, 132–137, 139, 140, 145, 146, 154, 156, 158–166, 168–171, 208, 210, 211). Moreover, the long-term failure of pituitary surgery is evidently higher in patients with macroadenomas (range, 0–71.4; mean, 48.8; median, 52.2) than in patients with microadenomas (range, 0–55.5; mean, 25; median, 21.2). On the basis of this evidence, an average of approximately 32% of CD patients, and up to 75% of CD patients initially submitted to pituitary surgery, will require a second-line treatment during the disease course. In particular, around 25% of patients with CD bearing a microadenoma and around 50% of patients with CD bearing a macroadenoma experience an early, for persistence, or late, for recurrence, failure of pituitary surgery and require an additional treatment after initial surgery.

The remission rate after pituitary surgery in children and adolescent patients with CD ranged from 44 to 100%, with a mean remission rate of 77.3% and a median remission rate of 80%, whereas recurrence rates ranged from 0 to 42.8%, with mean and median recurrence rates of 11.9 and 6%, respectively (212–232). A study comparing the remission rate in pediatric and adult patients with CD showed similar results (233).

**Table 2.** Results of Studies Evaluating the Outcome of Initial Pituitary Surgery in Patients With CD

| First Author, Year (Ref.) | No. of Patients | Follow-up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Long-term Failure, % | Perioperative Mortality and Complications |
|---|---|---|---|---|---|---|---|
| Ludecke, 1976 (91)¶ | 15 | NA | 100 | 6.7 | 12 | 6.7 | Death:0.8%;[a] hypopituitarism:93.3%; TDI:93.3%; CSF: 4%[a] |
| Carmalt, 1977 (92) | 13 | R:1–180, M:78.5, m:84 | 100 | NA | NA | 0 | Death:0%; TDI:100%; hypothyroidism:53.8%; hypogonadism:46.1%; CSF:15.3%; DVT:15.3%; CNP:7.7%; meningitis:7.7%; nasal sepsis:7.7% |
| Salassa, 1978 (93) | 18 | R:1–36 | 88.9 | 0 | na | 11.1 | Death:0% |
| Tyrrell, 1978 (94) | 20 | R:6–42 | 85 | NA | NA | 15 | Death:0%; TDI:25%; panhypopituitarism:5% |
| Wajchenberg, 1979 (95)¶ | 6 | R:2–10 | 66.7 | 25 | 3 | 50 | Death:0%; TDI:33.3%; PDI:16.6% |
| Bigos, 1980 (209) | 24 | R:1–180, M:32.1, m:12.5 | 75 | 11.1 | M:20 | 33.3 | Death:4.1%; bleeding:16.6%; TDI:4.1% |
| Guthrie, 1981 (96) | 8 | R:12–48 | 87.5 | 0 | na | 12.5 | NA |
| Hardy, 1982 (97) | 75 | M:21 | 84 | 3.2 | M:20 | 18.7 | Death:1.3%; hypothyroidism:8%; TDI:6.7%; GHD: 4%; hypogonadism:2.7%; PDI:1.3%; subarachnoid hemorrhage:1.3% |
| Boggan, 1983 (98) | 96 | R:20–110, M:55.2 | 81.2 | 5.1 | R:19.2–48, M:26.4 | 22.9 | Death:1%; panhypopituitarism:12%; VD:3%; CSF: 2%; PDI:1%; myocardial infarction:1%; meningitis:1%; mycotic carotid pseudoaneurysm:1%; pseudotumor cerebri:1%; CNP:1% |
| Thomas, 1983 (99) | 16 | R:60–168, M:102, m:102 | 81.2 | 0 | na | 18.7 | Death:0%; hypothyroidism:68.8%; DI:12.5%; meningitis:12.5% |
| Burch, 1985 (100)¶ | 14 | R:24–60 | 64.3 | 11.1 | 24 | 42.9 | Death:7.1%; seizure:7.1%; TDI:7.1% |
| Brand, 1985 (101) | 14 | R:48–252, M:14.3, m:16.5 | 100 | 0 | na | 0 | Death:0%; hypothyroidism:45.5.%; hypogonadism: 18.1% |
| Tagliaferri, 1986 (102) | 23 | R:7–67, M:40.8, m:43 | 82.6 | 10.5 | M:30 | 26.1 | Death:4.3%; GHD:43.5%; PDI:8.7%; hypothyroidism:8.7%; hypogonadism:8.7% |
| Fahlbusch, 1986 (103) | 101 | M:38.4 | 70.3 | 7 | NA | 34.6 | Death:1.9%; TDI:28.3%; PE:3.8%; DVT:3.8%; meningitis:3.8%; CNP:1.9%; PDI:1.9%; pulmonary infection:1.9% |
| Nakane, 1987 (104) | 98 | M:38.4 | 87.7 | 9.3 | M:44 | 20.4 | Death:0% |
| Chandler, 1987 (105) | 34 | NA | 73.5 | NA | NA | 26.5 | Death:0%; PDI:2.9% |
| Guilhaume, 1988 (156) | 60 | R:3–84, m:24 | 70 | 14.3 | R:24–36, M:30 | 40 | Death:1.7%; TDI:48%; facial hematoma:45%; CSF: 8%; meningitis:1.7% |
| Mampalam, 1988 (106) | 216 | R:12–156, M:46.8 | 79.2 | 5.3 | M:45.6 | 25 | Death:0.9%; TDI:2.8%; CSF:1.9%; sinusitis:1.9%; meningitis:1.4%; VD:1.4%; myocardial infarction:0.9% |
| Pieters, 1989 (107) | 27 | R:18–90, m:54 | 59.3 | 25 | R:24–60, M:42, m:42 | 55.5 | Death:0%; hypopituitarism:18.5% |
| Arnott, 1990 (157) | 28 | R:3–56, M:22.3 | 85.7 | 12.5 | R:14–42, M:29.3, m:32 | 25 | Death:0%; CSF:17.8%; PDI:10.7%; hypopituitarism:14.3%; meningitis:3.6%; partial anosmia:3.6% |
| Tindall, 1990 (108) | 53 | R:2–130, M:60 | 84.9 | 2.2 | M:2 | 17 | Death:1.8%; meningitis:5.3%; DVT:3.6%; CSF: 1.8%; PE:1.8% |
| Burke, 1990 (158) | 54 | M:56, m:39 | 81.5 | 4.5 | R:19–64, M:41.5 | 22.2 | Death:0%; GHD:67.7%[b]; hypogonadism:48%[b]; TDI:34.9%[b]; hypothyroidism:28.3%[b]; PDI:25.4%[b]; CSF:15.8%[b]; bleeding:10.5%[b]; meningitis:5.3%[b]; PE:1.7%[b]; sinusitis:1.7%; hematoma:1.7%; |
| Tahir, 1992 (210) | 45 | R:12–180, M:69.6 | 75.5 | 20.6 | R:29–62, M:40 | 40 | NA |
| McCance, 1993 (109) | 41 | R:1–144, M:58.9 | 48.8 | 0 | na | 51.2 | Death:0%; TDI:17.5%; hypothyroidism:12.5%; meningitis:12.5%; CSF:10%; PDI:2.5%; hypogonadism:2.5%; PE:2.5%; benign intracranial hypertension:2.5%; local wound swelling:2.5%; maxillary abscess:2.5% |
| Trainer, 1993 (110) | 48 | R:15–70, m:40 | 41.7 | 0 | na | 58.3 | Death:0%; TDI:75%[c]; PDI:46% [c]; hypothyroidism: 39.6%[c]; hypogonadism:29.1%[c]; CSF:12.5%; meningitis:6.2%; idrocephalus:2%; stroke:2%; myocardial infarction:2% |
| Toms, 1993 (167) | 11 | NA | 100 | 36.4 | R: 2–52, M:20, m:13 | 36.4 | Death:0% |

(*Continued*)

**Table 2.** Continued

| First Author, Year (Ref.) | No. of Patients | Follow-up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Long-term Failure, % | Perioperative Mortality and Complications |
|---|---|---|---|---|---|---|---|
| Bochicchio, 1995 (146) | 668 | M:46 | 76.3 | 12.7 | R:6–104, M:39.3, m:33 | 33.4 | Death:1.9%; CSF:4.6%; TDI:3%; meningitis:2.8%; bleeding:1.3%; PE:0.6% |
| Bakiri, 1996 (168) | 50 | M:92 | 72 | 8.3 | R:12–60, M:40, m:48 | 34 | Death:0%; TDI:44%; GHD:12%; PDI:6%; meningitis:4% |
| Sonino, 1996 (159)§ | 103 | R:24–192, m:72 | 76.7 | 6.3/26 | R:24–216 M:24/120 m:120 | 28.1 | NA |
| Van Aken, 1997 (111) | 29 | R:8–118, m:35 | 58.6 | 17.6 | M:39.3, m:32 | 51.7 | NA |
| Blevins, 1998 (112) | 96 | R:12–264, M:62 | 85.4 | 15.8 | R:8–142 | 28.1 | Death:0%; TDI:45%; CSF:27%; hypogonadism: 14%; cardiovascular events:14%; hypothyroidism:14%; sinusitis:14%; PDI:9%; epistaxis:5%; infections:5% |
| Semple, 1999 (113) | 78 | NA | 75.2[c] | NA | NA | na | Death:0%; hyponatremia:4.8%; TDI:8.6%; DVT: 3.8%; nasal septal perforation:1.9%; CSF:0.9%; CNP:0.9%; VD:0.9%; pulmonary and urinary infection:0.9%; epistaxis:0.9% |
| Invitti, 1999 (114) | 236 | R:6–180 | 69.1 | 17 | R:6–120, M:115, m:27 | 42.6 | NA |
| Swearingen, 1999 (11) | 154 | R:12–240, M:104.4, m:96 | 87 | 7.5 | R:12–132, M:68.4, m:48 | 19.5 | Death:0%; hypothyroidism:23%[d]; hypogonadism: 14%[d]; sinus congestion:9%[d]; PDI:6%[d]; CSF: 2.6%[d]; meningitis:1.5%[d]; sinusitis:1%[d]; epistaxis:0.5%[d] |
| Barbetta, 2001 (115) | 68 | R:12–252, M:57.5 | 89.7 | 21.3 | R:8–84, M:36, m:24 | 29.4 | NA |
| Cavagnini, 2001 (208) | 300 | M:120 | 70 | 15.2 | NA | 40.7 | NA |
| Chee, 2001 (170) | 61 | R:7–211, M:83, m:88 | 78.7 | 14.6 | R:22–158, M:76.1 | 32.8 | Death:0%; TDI:21.3%; PDI:8.2%; hypopituitarism: 19.7%; hypothyroidism:19.7%; CSF:13.1%; epistaxis:1.6%; septal perforation:1.6% |
| Estrada, 2001 (145) | 109 | R:6–198, M:60.7 | 68.8 | 21.3 | R:12–110 | 45.9 | NA |
| Rees, 2002 (117) | 53 | R:6–252, m:72 | 77.4 | 4.9 | R:13–36, M:24.5 | 26.4 | Death:1.9%; hypopituitarism:52.8%; GHD:52.8%; hypothyroidism:30.2%; hypogonadism:1.9%; TDI:28%; CSF:12%; PDI:9%; DVT:6%; VD:4%; SIADH:2%, vascular injury:2%; left ventricular failure:2%; myocardial infarction:1.9% |
| Shimon, 2002 (160) | 74 | M:50.4 | 78.4 | 5.2 | R:24–60, M:44, m:48 | 25.7 | Death:0%; CSF:6.7%; DI:6.7%; hypopituitarism: 2.7%; SIADH:1.3% |
| Yap, 2002 (118) | 89 | R:6–348, M:92, m:38 | 68.5 | 11.5 | R:6–60, M:36.3, m:48 | 39.3 | Death:1%; hypogonadism:36.1%; hypothyroidism: 34.9%; TDI:34%; PDI:8.2%; CSF:8.2%; bleeding:6.2%; meningitis:2.1%; CNP III:2.1%; DVT:1%; myocardial infarction:1% |
| Chen, 2003 (169) | 174 | M:60 | 81.6 | 14.1 | R:6–48 m:27 | 29.9 | Death:0%; infections at graft donor site:1.7% |
| Flitsch, 2003 (154) | 147 | R:14–123, M:61 | 93.2 | 6.6 | R:19–100 M:43.9 m:34 | 12.9 | Death:0%; hypopituitarism:12.9%; PDI:3.4%; CSF: 2%; panhypopituitarism:1.4%; bleeding:0.7%; hematoma:0.7%; CNP:0.7% |
| Pereira, 2003 (140)§ | 78 | R:12–288, m:86 | 71.8 | 8.9/16.7 | R:24–240, M:84, m:48 | 34.6 | NA |
| Cannavò, 2003 (119) | 26 | R:25–190, M:78 | 65.4 | 53 | NA | 69.2 | Death:0% |
| Hammer, 2004 (14) | 289 | R:7.2–289, m:133 | 81.7 | 8.7 | R:13.2–133.2, m:58.8 | 25.4 | Death:1%; hypopituitarism:9.3%; hypogonadism: 8.7%; CSF:4.2%; PDI:3.1%; hypothyroidism: 3.1%; myocardial infarction:1%; meningitis: 0.7%; permanent vision loss:0.7%; hematoma/ hemorrhage:0.7%; transient vision loss:0.3% |
| Rollin, 2004 (120) | 40 | R:4–170, m:59 | 87.5 | 5.7 | R:54–66, M:60 | 17.5 | NA |
| Salenave, 2004 (121) | 54 | R:1–89, M:19.9 | 83.3 | 20 | R:1–35 | 33.3 | Death:0%; hypothyroidism:11.1%; hypogonadism: 7.4%; CSF:3.7%; PDI:3.7%; panhypopituitarism:3.7% |

(*Continued*)

**Table 2.** Continued

| First Author, Year (Ref.) | No. of Patients | Follow-up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Long-term Failure, % | Perioperative Mortality and Complications |
|---|---|---|---|---|---|---|---|
| Hoybye, 2004 (211) | 34 | M:72 | 91.2 | 6.4 | M:36 | 14.7 | Death:0%; hypogonadism:18%; GHD:12%; hypothyroidism:9%; DI:3% |
| Atkinson, 2005 (161) | 63 | R:12–252, M:115.2 | 71.4 | 22.2 | R:12–108, M:62.4, m:66 | 44.4 | Death:0%; DI:28.6%; PDI:6.3%; TDI:22.2%; hypothyroidism:20%; CSF:11.1%; meningitis: 7.9%; DVT:1.6%; hypogonadism:1.5%; myocardial infarction:1.6% |
| De Tommasi, 2005 (122) | 26 | R:1–108, M:37 | 53.8 | 35.7 | NA | 65.4 | Death:0%; CSF:45.7%[c]; DI:21.6%[c]; TDI:13.5%[c]; GHD:11.5%; PDI:11.5%; nasal septal perforation:10.8%[c]; SIADH:5.4%[c]; DVT:2.7%[c]; PE:2.7%[c]; CNP:2.7%[c]; vascular injury:2.7%[c] |
| Esposito, 2006 (123) | 28 | M:34 | 92.9 | 0 | na | 7.1 | Death:2.5%[c]; TDI:10%[c]; CSF:2.5%[c] |
| Acebes 2007 (124) | 44 | R:19–102, M:49 | 88.6 | 7.7 | R:30–84, M:54.6 | 18.2 | NA |
| Rollin, 2007 (126) | 103 | R:2–220, M:72 | 85.4 | 6.8 | R:24–66, M:51, m:57 | 20.4 | Death:1%; TDI:58.2%; hypopituitarism:31.1%; PDI: 1%; stroke:1% |
| Dehdashti, 2007 (127) | 22 | R:2–33, m:17 | 77.3 | 0 | na | 22.7 | Death:0%; hypothyroidism:12%[c]; hypogonadism: 8%[c]; CSF:4%[c]; TDI:4%[c] |
| Prevedello, 2008 (128) | 167 | R:6–157, M:39 | 88.6 | 12.8 | R:12–117, M:50 | 22.7 | Death:0%; panhypopituitarism:8.4%; hypopituitarism:13.1%; TDI:6%; PDI:4.8%; SIADH:3.6%; hypothyroidism:3.6%; CSF:1.8%; meningitis:0.6%; DVT:0.6%; hypogonadism: 0.6%; GHD:0.6% |
| Patil, 2008 (162)§ | 215 | R:6–166, M:45, m:33 | 85.6 | 17.4/46 | R:3–134, m:39/R:60–156 | 29.3 | NA |
| Hofmann, 2008 (171)§ | 426 | R:3–300, M:72.3, m:66.8 | 68.5 | 14.4/5.6 | M:7.3/ R:74–278, M:122 | 41.3 | Death:0.7%; DVT:1.6%; DI:0.9%; hypopituitarism: 0.9%; meningitis:0.9%; rhinorrhea:0.5%; CNP: 0.2%; acute respiratory distress syndrome:0.2%; mesenteric infarction:0.2%; hypovolemic shock: 0.2% |
| Fomekong, 2009 (129) | 40 | R:20–152 M:85.4 m:90.5 | 65 | 11.5 | R:18–96 M:54 m:48 | 42.5 | Death:0%; DI:32.5%; TDI:17.5%; PDI:15%; CSF: 10%; CNP:2.5%; SIADH:2.5%; DVT:2.5%; epistaxis:2.5% |
| Jagannathan, 2009 (130) | 261 | R:12–215 M:84 m:69 | 96.5;92[e] | 2.4;5.5[e] | R:5–129 M:56 | 5.7 | Death:0%; hyponatremia:11%; DI:6.1%;TDI:5.7%; CSF: 1.5%; maxillary numbness:1.5%; maxillary fracture: 1.5%; sinusitis:1.5%; meningitis:0.4%; epistaxis: 0.4%; PDI:0.4% |
| Ammini, 2011 (132) | 81 | R:18–132 M:40.8 | 66.7 | 18.5 | R:12–84 M:25.2 | 45.7 | Death:0% |
| Ciric, 2012 (133) | 121 | R:6–396 M:68.4 | 83.5 | 9.7 | R:12–176 M:81 m:108 | 24.6 | Death:0%; DI:12.5%; hypopituitarism:7.3%; CSF: 4.4%; epistaxis:3.6%; DVT:2.9%; PE:2.9%; SIADH:1.4%; sinusitis:2.2%; meningitis:0.7% |
| Kim, 2012 (163) | 54 | R:11.4–174.2 m:50.7 | 70.4 | 47.4 | R:13–148 m:57.2 | 63 | Death:0%; hypopituitarism:16.7%; meningitis:1.8% |
| Hassan-Smith, 2012 (18) | 72 | m:55.2 | 83.3 | 13.3 | m:25.2 | 27.8 | Death:0%; hypopituitarism:71%; TDI:35%; CSF: 11%; meningitis:4.2%; sinusitis:2.8%; septal perforation:1.4%; blocked lacrimal duct:1.4% |
| Honegger, 2012 (164) | 83 | R:3–156 M:38.2 | 84.3 | 7.1[c] | R:20–56 M:37 | na | Death:0%; TDI:19.7%; hypogonadism:8.3%; hypothyroidism:4.1%; GHD:4.1%; PE:3.6%; DVT:3.6% |
| Locatelli, 2013 (138) | 8 | R:24–180 M:66 | 25 | 0 | na | 75 | Death:0%; VD:44.1%; headache:11.6%; hydrocephalus:4.6% |
| Wagenmakers, 2013 (134) | 86 | R:5–164 M:71 | 72.1 | 16.1 | R:10–98 M:42 | 39.5 | Death:0%; hypopituitarism:35%; hypothyroidism: 22%; SIADH:11.6%; epistaxis:11.6%; GHD:6%; TDI:4.6%; CSF:4.6%; hypogonadism:3.5%; infection:3.4%; vascular injiury:1.2%; bleeding: 1.2%; PE:1.2% |
| Alexandraki, 2013 (135) | 131 | R:72–432 M:184 | 65.6 | 24.4 | m:65.1 | 50.4 | Death:0.8% |
| Berker, 2013 (136) | 69 | R:5–75 M:32 | 95.6 | 6.1 | R:20–35 M:24 m:20.5 | 10.1 | Death:0%; TDI:10.1%; CSF:3%; panhypopituitarism:3% ; PDI:1.5%; |
| Lambert, 2013 (21) | 346 | R:1–360 M:75.6 | 76 | 10.6 | R:14.4–345 M:69.6 | 32.1 | Death:0% |
| Starke, 2013 (137) | 61 | R:12–72 M:28 | 95.1 | 8.6 (10)[f] | NA | 13.1 | Death:0%; TDI:16.4%; hypopituitarism:13%; PDI: 4.9%; GHD:6.5% |

(*Continued*)

**Table 2.** Continued

| First Author, Year (Ref.) | No. of Patients | Follow-up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Long-term Failure, % | Perioperative Mortality and Complications |
|---|---|---|---|---|---|---|---|
| Alahmadi, 2013 (165) | 33 | R:3–102<br>M:33 | 75.8 | 7.1[c] | NA | na | Death:0%; TDI:19%; PDI:7.1%; CSF:4.8%; persistent nasal crusting and foul smell:4.8%; sinusitis:2.4% |
| Dimopoulou, 2014 (166) | 120 | M:79 | 70.8 | 34.1 | R:5–205<br>M:54 | 53.3 | Death:0%; hypopituitarism:68%; hypogonadism: 29%; hypothyroidism:22%; GHD:22%; DI:8% |
| Aranda, 2014 (139) | 41 | R:12–444<br>M:168<br>m:80.2 | 78 | 65.6 | R:6–60<br>M:28.8 | 73.2 | Death:0%; hypopituitarism:53.7%; hypothyroidism: 34.1%; GHD:34.1%; hypogonadism:29.3%; panhypopituitarism:29.3% |
| **Total** | **6869** | **R:1–444<br>M:64.3<br>m:55.2** | **R:25–100<br>M:77.8<br>m:78.7** | **R:0–65.6<br>M:13.2<br>m:10.6** | **R:1–345<br>M:41.3<br>m:40.5** | **R:0–75<br>M:31.7<br>m:29.3** | **Death:R:0–7.1, M:0.6, m:0; DI:R:0.9–32.5, M:12.3, m:8; PDI:R:0.4–16.6, M:5.9, m: 4.9; TDI:R:2.8–100, M:26.4, m:19.7; SIADH:R:1.3–11.6, M:3.7, m:2.2; CSF:R: 0.9–27, M:7.5, m:4.8; meningitis:R:0.4–12.5, M:2.7, m:2.8; CNP:R:0.2–7.7, M:2.3, m:2; visual disturbance:R:1.4–44.1, M: 13.1, m:3.5; sinusitis:R:1–14, M:4.1, m: 2.3; epistaxis:R:0–11.6, M:3.8, m:2.5; DVT:R:0.6–15.3, M:3.8, m:3.2; PE:R:0.6–3.8, M:3.5, m:2.5; hypopituitarism:R:0.9–93.3, M:29.6, m:17.6; hypothyroidism:R: 3.1–68.8, M:22.4, m:19.7; hypogonadism:R:0.6–46.1, M:13.9, m: 8.6; GHD:R:0.6–52.8, M:17.4, m:11.7; panhypopituitarism:R:1.4–29.3, M:9, m:5** |

Abbreviations: NA, not available; na, not applicable; TDI: transient diabetes insipidus; PDI: permanent diabetes insipidus; CSF: cerebrospinal fluid; DVT: deep venous thrombosis; PE: pulmonary embolism; VD: visual disturbance; CNP: cranial nerve palsy; GHD:GH deficit; THY: transient hyponatremia; DI: diabetes insipidus R: range; M: mean; m: median. This table lists the studies addressing the outcome of initial pituitary surgery published between 1976 and 2014, including those whose entire content was fully available for the authors. The underlined studies include at least 30 patients with a mean/median follow-up of at least 6 months. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD. In the studies where a recurrence rate was not described, the percentage of long-term failure corresponds to the percentage of patients not in remission after surgery, considering the percentage of recurrence to be zero. The column of the perioperative mortality and complications report the prevalence of death and the prevalence of the main complications, such as they are described in the single studies. The range, mean, and median percentage of the complications, including those of hypopituitarism and diabetes insipidus, were calculated considering the only studies were the specific complications were reported. In the studies marked with ¶ only 1 patient presented a recurrence, so that the time to recurrence is represented by a single time period, instead of a range, mean, or median. In the studies marked with § the values reported after the/describe the recurrence rate and the time to recurrence for a longer follow-up cohort, in line with the description included in the study; such values were not considered with regard to the total calculations.

[a] Results in 101 patients with pituitary tumors, including 80 with acromegaly, 15 with CD, and 6 with NS.

[b] Results in 58 patients including 4 patients with NS.

[c] Studies or results including repeat pituitary surgery.

[d] Results on 193 procedures.

[e] Patients with histological diagnosis of CD.

[f] In brackets the percentage of patients with recurrence considering the 50 patients treated for a long-term period.

### *3. Predictive factors for the outcome of pituitary surgery*

Several studies have investigated factors influencing the outcome of pituitary surgery associated with CD, so that different factors can be indicated as possible predictors of disease remission or recurrence after pituitary surgery.

The main predictive factors for the outcome of pituitary surgery involve patient and tumor features, presurgical imaging, surgical and pathological findings, and surgical features.

*a. Patient and tumor features.* Male gender has been associated with increased tumor aggressiveness, resulting in poorer surgical results (14, 132, 234). A worse prognosis has been associated with large macroadenomas because the presence of a tumor with a diameter of 2.0 cm or more has been demonstrated to be associated with an increased likelihood (odds ratio, 35) of residual disease after surgery (112). Tumor extension, especially to the suprasellar region and with the involvement of the pituitary intermediate lobe, is also associated with a worse prognosis (14, 98, 119, 209, 235, 236). Moreover, the evidence of a reduced success rate associated with invasive tumors indicated the presence of cavernous sinus invasion as a negative prognostic factor for disease cure (14, 97, 98, 102, 106, 112, 117, 119, 122, 134, 209), although in a single recent study, no significant difference was found in remission and recurrence rate between tumors with and without cavernous sinus invasion, probably because of the limited number of cases included in the study (166).

**Table 3.** Results of Studies Evaluating the Outcome of Initial Pituitary Surgery in Patients With CD Bearing a Microadenoma

| First Author, Year (Ref.) | No. of Patients | Follow-Up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Long-term Failure, % |
|---|---|---|---|---|---|---|
| Ludecke, 1976 (91)¶ | 15 | NA | 100 | 6.7 | 12 | 6.7 |
| Carmalt, 1977 (92) | 13 | R:1–180, M:78.5, m:84 | 100 | NA | NA | 0 |
| Salassa, 1978 (93) | 18 | R:1–36 | 88.9 | 0 | na | 11.1 |
| Tyrrell, 1978 (94) | 20 | R:6–42 | 85 | NA | NA | 15 |
| Wajchenberg, 1979 (95)¶ | 6 | R:2–10 | 66.7 | 25 | 3 | 50 |
| Bigos, 1980 (209) | 18 | m:12 | 72.2 | 15.4 | M:20 | 38.9 |
| Guthrie, 1981 (96) | 8 | R:12–48 | 87.5 | 0 | na | 12.5 |
| Boggan, 1983 (98) | 73 | R:20–110, M:55.2 | 87.7 | 1.6 | R:19.2–48, M:26.4 | 13.7 |
| Burch, 1985 (100)¶ | 14 | R:24–60 | 64.3 | 11.1 | 24 | 42.9 |
| Brand, 1985 (101) | 14 | R:48–252, M:14.3, m:16.5 | 100 | 0 | na | 0 |
| Nakane, 1987 (104) | 76 | M:38.4 | 86.8 | 10.6 | M:44.2 | 22.4 |
| Mampalam, 1988 (106) | 170 | R:12–156, M:46.8 | 84.7 | 3.5 | M:45.6 | 18.2 |
| Pieters, 1989 (107) | 27 | R:18–90, m:54 | 59.3 | 25 | R:24–60, M:42, m:42 | 55.5 |
| Arnott, 1990 (157) | 28 | R:3–56, M:22.3 | 85.7 | 12.5 | R:14–42, M:29.3, m:32 | 25 |
| McCance, 1993 (109) | 41 | R:1–144, M:58.9 | 48.8 | 0 | na | 51.2 |
| Toms, 1993 (167) | 11 | NA | 100 | 36.4 | R:2–52, M:20, m:13 | 36.4 |
| Sonino, 1996 (159)§ | 103 | R:24–192, m:72 | 76.7 | 6.3/26.0 | R:24–216; M:24/120; m:120 | 28.1 |
| Blevins, 1998 (112) | 75 | R:8–218, M:49 | 90.7 | 11.8 | R:8–142, M:49 | 20 |
| Semple, 1999 (113) | 72 | NA | 88.9 | NA | NA | 11.1 |
| Swearingen, 1999 (11) | 137 | R:12–240, M:96, m:104 | 89.8 | 5.7 | R:12–132, M:68.4, m:48 | 15.3 |
| Chee, 2001 (170) | 61 | R:7–211, M:83, m:88 | 78.7 | 14.6 | R:22–158, M:76.1 | 32.8 |
| Chen, 2003 (169) | 133 | M:60 | 96.2 | 3.1 | NA | 6.8 |
| Salenave, 2004 (121) | 54 | R:1–89, m:19.9 | 83.3 | 20 | R:1–35 | 33.3 |
| Atkinson, 2005 (161) | 63 | R:12–252, M:115.2 | 71.4 | 22.2 | R:12–108, M:62.4, m:66 | 44.4 |
| Acebes, 2007 (124) | 44 | R:19–102, M:49 | 88.6 | 7.7 | R:30–84, M:54.6 | 18.2 |
| Rollin, 2007 (126) | 59 | R:2–220, M:72 | 94.9 | NA | NA | 5.1 |
| Dehdashti, 2007 (127) | 16 | R:2–33, m:17 | 81.3 | 0 | na | 18.7 |
| Prevedello, 2008 (128) | 167 | R:6–157, M:39 | 88.6 | 12.8 | R:12–117, M:50 | 22.7 |
| Patil, 2008 (162)§ | 215 | R:6–166, M:45, m:33 | 85.6 | 17.4/46 | R:3–134, m:39, R:60–156 | 29.3 |
| Fomekong, 2009 (129) | 29 | R:20–152, M:92.5 | 72.4 | 14.3 | R:18–96, M:54, m:48 | 37.9 |
| Ammini, 2011 (132) | 68 | R:18–132, M:40.8 | 67.6 | 18.5[a] | R:12–84, M:25.2 | na |
| Ciric, 2012 (133) | 108 | R:6–396, M:68.4 | 89.8 | 9.7 | R:12–176, M:81, m:108 | 18.9 |
| Honegger, 2012 (164) | 72 | R:3–156, M:38.2 | 87.5 | 7.4[b] | R:20–56, m:37 | na |
| Wagenmakers, 2013 (134) | 55 | R:5–164, M:71 | 74.5 | 16.1[a] | R:10–98, M:42 | na |
| Alexandraki, 2013 (135) | 103 | R:72–348, M:180 | 72.8 | 22.7 | M:61.8 | 43.7 |
| Berker, 2013 (136) | 43 | R:5–75, m:32 | 93 | 10 | R:20–35, M:24, m:20.5 | 16.3 |
| Alahmadi, 2013 (165) | 27[b] | R:3–102, M:33 | 59.3[b] | 7.1[a,b] | NA | na |
| Dimopoulou, 2014 (166) | 88 | M:79 | 71.6 | 25.4 | R:5–205, M:54 | 46.6 |
| **Total** | **2344** | **R:1–396, M:63.6, m:48.4** | **R:48.7–100, M:82.1, m:85.7** | **R:0–36.4, M:11.7, m:10.9** | **R:1–216, M:43.5, m:44.9** | **R:0–55.5, M:25, m:21.2** |

Abbreviations: NA, not available; na, not applicable; R, range; M, mean; m, median. This table lists the studies addressing the outcome of initial pituitary surgery in microadenoma published between 1976 and 2014, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD and microadenoma. In some studies, recurrence rate were evaluated on a subgroup of patients used for the evaluation of remission rate, according the available follow-up. In the studies where a recurrence rate was not described, the percentage of long-term failure corresponds to the percentage of patients not in remission after surgery, considering the percentage of recurrence to be zero. The column of the perioperative mortality and complications report the prevalence of death and the prevalence of the main complications, such as they are described in the single studies. The range, mean, and median percentage of the complications, including those of hypopituitarism and diabetes insipidus, were calculated considering the only studies were the specific complications were reported. In the studies marked with ¶ only 1 patient presented a recurrence, so that the time to recurrence is represented by a single time period, instead of a range, mean, or median. In the studies marked with § the values reported after the/describe the recurrence rate and the time to recurrence for a longer follow-up cohort, in line with the description included in the study; such values were not considered with regard to the total calculations.

[a] Results on a population of patients including microadenomas and macroadenomas.

[b] Studies or results including repeat pituitary surgery.

*b. Presurgical imaging.* Contradictory data are available as to whether presurgical imaging detecting a pituitary tumor influences disease remission. Indeed, some studies have shown a direct correlation between preoperative tumor detection and disease remission (117, 126, 133, 134, 146, 170, 237), whereas others have shown the absence of such a correlation (18, 114, 118, 121, 128, 130, 135). In particular, a study demonstrated that an imaging technique positive for a pituitary tumor is associated not only with a greater chance of tumor localization at the time of surgery, but also a better prognosis for immediate postsurgical remission (133). The remission rate of patients with preoperative identification of tumor ranged from 52.6 to 100%, with mean and median remission rates of 79.5 and 80%, respectively. Instead, the remission rates of patients without preoperative identification of tumor ranged from

**Table 4.** Results of Studies Evaluating the Outcome of Initial Pituitary Surgery in Patients With CD Bearing a Macroadenoma

| First Author, Year (Ref.) | No. of Patients | Follow-Up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Long-Term Failure, % |
|---|---|---|---|---|---|---|
| Bigos, 1980 (209) | 6 | m:12 | 50 | 0 | na | 50 |
| Boggan, 1983 (98) | 23 | R:20–110, M:55.2 | 60.9 | 21.4 | M:19.2 | 52.2 |
| Nakane, 1987 (104)¶ | 17 | M:38.4 | 76.5 | 7.7 | 48 | 29.4 |
| Mampalam, 1988 (106) | 39 | R:12–156, M:46.8 | 64.1 | 16 | M:45.6, m:45.6 | 46.1 |
| Blevins, 1998 (112) | 21 | R:12–164, M:62 | 66.7 | 35.7 | R:8–142, M:16 | 57.1 |
| Swearingen, 1999 (11) | 17 | R:12–240, M:104.4 | 64.7 | 27.3 | R:12–132, M:68.4, m:48 | 52.9 |
| Semple, 1999 (113) | 6 | NA | 45.5[a] | NA | NA | na |
| Cannavò, 2003 (119) | 26 | R:25–190, M:78 | 65.4 | 52.9 | NA | 69.2 |
| Chen, 2003 (169) | 29 | M:60 | 34.5 | NA | NA | 65.5 |
| De Tommasi, 2005 (122) | 26 | R:1–108, M:37 | 53.8 | 35.7 | NA | 65.4 |
| Rollin, 2007 (126) | 23 | R:2–220, M:72 | 73.9 | 11.8 | R:36–66, M:51 | 34.8 |
| Dehdashti, 2007 (127) | 6 | R:2–33, m:17 | 50 | 0 | na | 50 |
| Fomekong, 2009 (129) | 12 | R:20–152, M:74 | 91.7 | 0 | na | 8.3 |
| Ammini, 2011 (132) | 14 | R:18–132, M:40.8 | 57.1 | 18.5[b] | R:12–84, M:25.2 | na |
| Ciric, 2012 (133) | 13 | R:6–396, M:67.2 | 30.8 | 0 | na | 69.2 |
| Honegger, 2012 (164) | 11 | R:3–156, M:38.2 | 63.6 | 0 | na | 36.4 |
| Wagenmakers, 2013 (134) | 31 | R:5–164, M:71 | 67.7 | 16.1[b] | R:10–98, M:42 | na |
| Alexandraki, 2013 (135) | 21/7[c] | R:72–434, M:184.8 | 42.9/28.6[c] | 33.3/50.0[c] | M:84/24[c] | 71.4/85.7[c] |
| Berker, 2013 (136) | 26 | R:5–75, M:32 | 100 | 0 | na | 0 |
| Alahmadi, 2013 (165) | 15[a,b] | R:3–102, M:33 | 66.7[a] | 7.1[a,b] | NA | na |
| Dimopoulou, 2014 (166) | 32 | M:79 | 68.7 | 59.1 | M:35 | 71.9 |
| **Total** | **414** | **Range:1–434, M:65.2, m:14.5** | **Range:30.8–100, M:62.3, m:64.1** | **Range:0–59, M:18.8, m:13.9** | **Range:2–142, M:43.4, m:47.2** | **R:0–71.9, M:48.8, m:52.2** |

Abbreviations: NA: not available; na: not applicable; R: range; M: mean; m: median. This table lists the studies addressing the outcome of initial pituitary surgery in macroadenoma published between 1976 and 2014, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD and macroadenoma. In the studies where a recurrence rate was not described, the percentage of long-term failure corresponds to the percentage of patients not in remission after surgery, considering the percentage of recurrence to be zero. The column of the perioperative mortality and complications report the prevalence of death and the prevalence of the main complications, such as they are described in the single studies. The range, mean, and median percentage of the complications, including those of hypopituitarism and diabetes insipidus, were calculated considering the only studies were the specific complications were reported. In the studies marked with ¶ only 1 patient presented a recurrence, so that the time to recurrence is represented by a single time period, instead of a range, mean, or median.

[a] Studies or results including repeat pituitary surgery.

[b] Results in a population of patients including microadenomas and macroadenomas.

[c] Results on pituitary surgery by transcranial approach.

50 to 95.2%, with mean and median remission rates of 68.2 and 68%, respectively (94, 114, 117, 118, 121, 123, 126, 130, 133–135, 139, 146, 160, 163, 166, 170, 171, 208, 209, 238). This evidence seems to reinforce the hypothesis that the absence of tumor identification at the preoperative imaging represents an unfavorable factor for surgical cure.

*c. Surgical and pathological findings.* The identification of the tumor during surgery has been proved in some studies to be a significant predictor of good prognosis (128, 130, 158, 164, 170, 208), although other authors are not in agreement (109, 168). Indeed, the remission rates of patients with intraoperative tumor identification ranged between 73 and 100% (mean, 87.7%; median, 89%), whereas the remission rates of patients without intraoperative tumor identification ranged between 33.3 and 83% (mean, 63.3%; median, 73.7%) (109, 128, 130, 158, 164, 168, 170, 208). Similarly, the absence of tumor identification at the pathological examination has been considered a factor for predicting poor prognosis. In particular, remission rates were remarkably lower in patients in whom a tumor could not be identified histologically (14, 98, 104–109, 117, 118, 121, 123, 124, 128, 129, 132, 135, 139, 146, 156–159, 162, 168, 170, 171, 209, 239), and the recurrence rate in these patients was higher than in those with evidence of a tumor at the pathological examination (98, 135, 157, 240). In particular, in patients without histological tumor confirmation, remission rates ranged from 0 to 85.7%, with mean and median remission rates of 48.5 and 52.6%, respectively. Conversely, remission rates in patients with histological tumor confirmation ranged from 40 to 97.1%, with mean and median remission rates of 81.5 and 82.1%, respectively (14, 21, 94, 98, 104–109, 117, 118, 123, 124, 128–130, 132, 134, 135, 139, 156–158, 160, 162, 163, 168, 170, 171, 209). Despite this evidence, different studies have reported indistinguishable remission rates between patients with and without pathological tumor confirmation (108, 117, 118, 121, 158, 241). It has been postulated that in many patients the small and fragile tissue specimens may have not

survived handling and processing during surgery, explaining a remission without a pathological diagnosis (98, 106, 121, 156, 157). A study has shown a correlation between pathological findings and the clinical behavior of the pituitary tumors (242). On this basis, specifically for CD, it is considered that the absence of peritumoral Crooke's cells could be a predictive factor for disease recurrence after successful surgery (243). Crooke's cells are nontumoral corticotroph cells that, in the setting of glucocorticoid excess, undergo massive accumulation of perinuclear cytokeratin filaments, giving their cytoplasm a distinct hyalinized appearance with hematoxylin and eosin staining. Crooke's cells are commonly seen in peritumoral tissue removed from patients with CD, where they are assumed to represent a response by non-neoplastic corticotrophs to cortisol excess and are thought to represent functionally suppressed corticotrophs (244–246). Therefore, the absence of peritumoral Crooke's cells has been postulated to be a predictive factor for disease recurrence (243). Interestingly, corticotroph tumors mostly composed of Crooke's cells are aggressive and have a higher recurrence rate than typical corticotroph tumors (247).

*d. Surgical features.* The type of surgical operation performed did not appear to have a dramatic impact on the long-term remission rate. Indeed, total hypophysectomy is associated with a remission rate ranging from 0 to 100%, with mean and median remission rates of 75.3 and 75%, respectively (14, 91, 92, 94, 95, 98, 99, 101, 106, 108, 109, 117, 128, 129, 133, 135, 146, 157, 158, 165, 171), whereas the hemihypophysectomy is associated with a remission rate ranging from 33.3 to 100%, with mean and median rates of 71.7 and 75.6%, respectively (14, 117, 128, 129, 135, 146, 157, 164, 165, 171). These data are not dramatically different from those associated with selective adenomectomy, which has a remission rate ranging from 59.3 to 100%, with mean and median remission rates of 81.6 and 80%, respectively (14, 93, 94, 98, 100, 102, 104, 106–108, 115, 117, 118, 128, 129, 133, 135, 146, 157, 158, 160, 163, 164, 167–171, 210). Conversely, the surgeon's experience is an important factor determining surgical success, independently of the tumor features (7, 100, 117). Registry studies have shown that the results of surgery on pituitary tumors differ widely in different countries and even in the same country, and the results achieved by the national health care system covering an entire population are worse than those published by specialized experts (248). Technical surgical procedures and available equipment that allow for better visualization of the tumor also play an important role in successful outcomes. Standard microscopic TSS is a well-established technique for the removal of the pituitary tumor, whereas the modern endoscopic TSS has progressively replaced the classical microscopic TSS in different specialized centers (127, 134, 136, 137, 150, 165, 201–204, 238, 249–252). Although several groups have presented excellent results using endoscope pituitary surgery (127, 134, 136, 137, 150, 165, 201–204, 238, 249–252), no randomized reports have compared the remission and/or recurrence rate of the modern endoscopic technique with that of the standard microscopic technique in patients with CD. Currently, five studies assessed the efficacy of a pure endoscopic approach for treatment of CD (127, 134, 136, 137, 165). These studies, published between 2007 and 2013, involve 258 patients (minimum, 17 patients; maximum, 86 patients) with a mean follow-up of 44.3 months (range, 2–164 mo). The overall remission rates ranged between 72.1 and 95.7%, with mean and median remission rates of 83.1 and 77.3%, repectively. The overall recurrence rate ranged between 0 and 16.1% (mean, 8.6%; median, 7.1%) (127, 134, 136, 137, 165). In patients with a microadenoma, the remission rate ranged between 74.5 and 95.7% (mean, 77.7%; median, 77.9%), whereas in patients with a macroadenoma, the remission rate ranged between 50 and 100% (mean, 71.1%; median, 67.2%) (127, 134, 136, 165). On the basis of 10 years of experience with the endoscopic transsphenoidal technique and at least 20 years with the transsphenoidal microsurgical technique for the treatment of CD, it would seem that, at least for the earlier results, the use of the endoscope is not superior to the use of the microscope in terms of results considering intrapituitary or small intrasuprasellar pituitary tumors (127, 134, 136, 137, 165). In fact, it has been argued that the optics of endoscopic surgery make it difficult to accurately differentiate tumor from normal gland, a factor particularly relevant in CD because tumors associated with CD are frequently small and are often not visible during imaging (252). On the other hand, the use of endoscopy, with a panoramic view, allows easier removal of a macroadenoma and lesions beyond the sellar area because it enables the use of different operating angles, which makes it possible to effectively reach suprasellar and parasellar portions of the lesion, including the cavernous sinus. This could explain the relatively high remission rate achieved in patients with a macroadenoma (127, 134, 136, 165). Recently, the endoscopic approach has given excellent results in the treatment of pediatric patients with CD (232). Finally, a surgical technique, which involves the histological pseudocapsule as a surgical capsule for the excision of the tumors, has been used. This technique allows for the accurate identification of the tumor during surgery and helps to guide its complete excision; this technique is also used in patients with negative imaging, and it results in a high rate of surgical remission (130).

Figure 3 shows the main possible factors unfavorably affecting the outcome of pituitary surgery in CD.

#### *4. Safety of pituitary surgery*

Pituitary surgery, performed by TSS, is a safe procedure in the hands of experienced neurosurgeons. Safety analysis usually includes the evaluation of the perioperative mortality and the complications secondary to surgical treatment. The complications of TSS include any event occurring during or in the month after surgery that requires an intervention.

*A. Mortality.* The perioperative mortality rate, considering the 61 studies on pituitary surgery in which safety analysis was clearly assessed, ranged between 0 and 7.1% (mean, 0.6%; median, 0%) (11, 14, 18, 21, 92–95, 97–110, 112, 113, 117–119, 121, 122, 126–130, 132–139, 146, 154, 156–158, 160, 161, 163–171, 209); however, generally it is not possible to differentiate the mortality rate among patients with microadenomas and macroadenomas. Deaths after pituitary surgery mostly arise as a result of myocardial infarction (14, 98, 106, 117, 118), pneumonia infection (103), or meningitis (156, 171), highlighting the importance of pre-, peri-, and postoperative assessment and treatment of cardiovascular risk factors, as well as immune function.

*B. Complications.* The postsurgical complications, considering the 61 studies on pituitary surgery in which safety analysis was clearly assessed, were reported in 90.6% of the study series. The complication rate after surgery for CD is higher than that for pituitary tumors in general, as might be expected from the increased cardiovascular risk, impairment of wound healing, and immune suppression associated with hypercortisolism (113, 198, 253, 254). The complications associated with pituitary surgery mainly comprise the impairment of fluid homeostasis and hypopituitarism, especially hypoadrenalism or adrenal insufficiency, together with different surgical or medical complications.

*a. Impairment of fluid homeostasis.* In the immediate postsurgical period, strictly according with the specific reports

**Figure 3.**

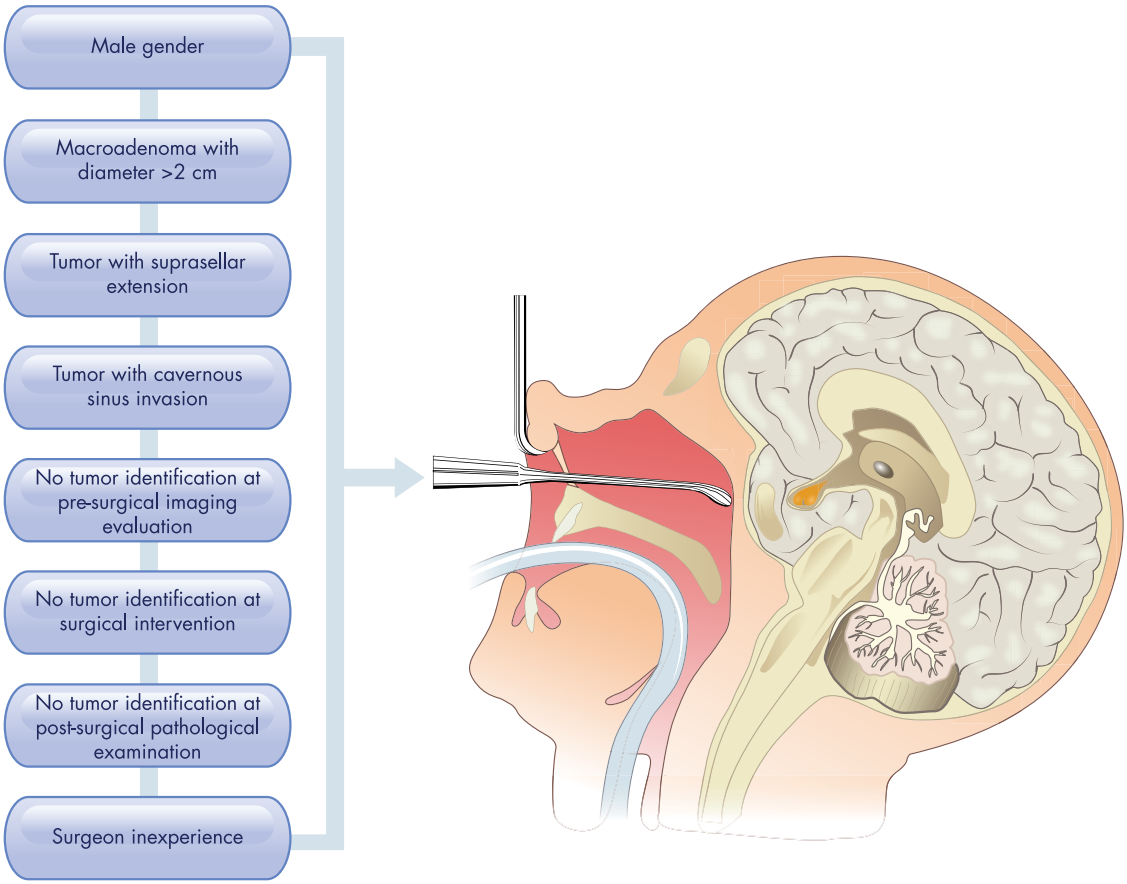


Figure 3. Main factors that can unfavorably affect the outcome of pituitary surgery in CD.

of the different studies, central diabetes insipidus (DI) was the most frequent complication (range, 0.9–32.5%; mean, 12.3%; median, 8%) in the 74 surgical series considered (99, 129, 130, 133, 160, 161, 166, 171, 211). However, some studies reported specifically the occurrence of a permanent or a transient DI. Permanent DI (PDI), which requires lifelong treatment, has a reported incidence of 0.4–16.6% (mean, 5.9%; median, 4.9%) (14, 95, 97, 98, 102, 103, 105, 109, 112, 117, 118, 121, 122, 126, 128–130, 136, 137, 154, 157, 161, 165, 168, 170), whereas transient DI (TDI), which begins with an abrupt onset of polyuria within 24–48 hours after surgery and gradually resolves over a 3- to 5-day period (255), occurs in 2.8–100% (mean, 26.4%; median, 19.7%) of cases (18, 91, 92, 94, 95, 97, 100, 103, 106, 109, 112, 113, 117, 118, 126, 128–130, 134, 136, 137, 146, 156,161, 164, 165, 168, 170, 209) and can be caused by temporary dysfunction of vasopressin-producing neurons as a result of surgical trauma. Taking into consideration the entire number of the studies on pituitary surgery, and presuming that the absence of any report means the absence of onset of DI, and considering any type of DI, this complication occurred in an avarage of 15.6% of patients, although it was represented by TDI in a great majority and by PDI a few number of patients. In particular, in the five purely endoscopic series including only patients with CD, TDI was the most frequent complication, occurring in 4.0–16.4% of patients (mean, 10.8%; median, 10.1%) (127, 134, 136, 137, 165), with PDI occurring in 1.5–7.1% of patients (mean, 4.5%; median, 4.7%) (136, 137, 165). Transient polyuria is frequently noted during the first postoperative day, and usually only 20% of the patients require treatment with DDAVP (113). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) (range, 1.3–11.6%; mean, 3.7%; median, 2.2%) occurs 5 to 7 days after surgery (117, 128, 129, 133, 134, 160). One of the explanations for this phenomenon is the release of stored vasopressin from the damaged posterior pituitary nerve terminals (256–258). The very early postoperative hyponatremia is probably a consequence of SIADH, but it is likely related to overhydration and hemodilution in the perioperative period or to relative adrenal insufficiency, which occurs if the patient is not receiving appropriate glucocorticoid replacement (113, 134). Moreover, patients with CD seem to have a higher risk of fluid and electrolyte abnormalities (12.5%) than patients with other pituitary tumors (259).

*b. Surgical complications.* A cerebrospinal fluid (CSF) leak, intra- or postoperatively, is another frequent complication with a mean reported incidence of 7.5% (range, 0.9–27%; median, 4.8%) (14, 18, 92, 98, 106, 108–110, 112, 113, 117, 118, 121, 128–130, 133, 134, 136, 146, 154, 156, 157, 160, 161, 165, 170). In the five purely endoscopic series including only patients with CD, CSF was reported in 3–4.8% of patients (mean, 4%; median, 4%) (127, 134, 136, 165). CSF entails the risk of meningitis that has a reported incidence of 0.4 to 12.5% (mean, 2.7%; median, 2.8%) (14, 18, 92, 98, 99, 103, 106, 108–110, 118, 128, 130, 133, 146, 156, 157, 161, 163, 168, 171). It is not always evident from studies whether the occurrence of meningitis is a direct consequence of CSF. On the other hand, meningitis has been reported to occur without evidence of a postoperative CSF leak in a mean of 4.6% of cases (range, 0.9–12.5%; median, 3.8%) (99, 103, 163, 168, 171). Prophylaxis with antibiotics is used by most surgeons in an attempt to prevent meningitis. Injuries to the cranial nerves usually occur as a result of exploration of the cavernous sinus, with the nerve most commonly injured being the third cranial nerve. The reported incidence of cranial nerve palsy ranges from 0.2 to 7.7% (mean, 2.3%; median, 2%) (92, 103, 113, 118, 129, 154, 171), and the injury may be temporary or permanent. Visual disturbances (range, 1.4–44.1%; mean, 13.1%; median, 3.5%) are dependent on several factors, including optic nerve contusion, vasospasm, hematoma, and devascularization of the optic nerve apparatus (98, 106, 117, 138). Injury to the cranial vascular system occurring during TSS is a rare, yet potentially fatal, complication and includes carotid artery rupture or vasospasm or cavernous fistulas, traumatic aneurysms, subarachnoid hemorrhage, and stroke (97, 98, 110, 117, 126, 134). Postoperative hemorrhage from the cavernous sinus, carotid arteries, or tumor bed can occur, albeit rarely, causing visual deterioration or hypothalamic injury. Injuries to the nasal structures represent common complications of TSS due to the nasal approach of the pituitary surgery. These complications mainly include sinusitis (range, 1–14%; mean, 4.1%; median, 2.3%) (18, 106, 112, 130, 133, 165) and epistaxis (range, 0–11.6%; mean, 3.8%; median, 2.5%) (112, 113, 129, 130, 133, 134, 170), which may produce significant discomfort and distress.

*c. Medical complications.* Deep vein thrombosis and pulmonary thromboembolism have been reported after pituitary surgery with an average frequency of 3.8% (range, 0.6–15.3%; median, 3.2%) (92, 103, 108, 113, 117, 118, 128, 129, 133, 161, 164, 171) and 3.5% (range, 0.6–3.8%; median, 2.5%) (103, 108, 109, 133, 134, 146, 164), respectively, and are distinct complications of surgery undertaken for CD. Indeed, immobilization, together with visceral obesity, vascular damage, and hypercoagulability, contributes to the thrombosis diathesis, and it is presently routine practice to give patients anticoagulation

treatment with low molecular weight heparin during the postoperative period, together with the advice to be mobile early and to use elastic stockings (40).

*d. Hypopituitarism.* Hypopituitarism is a common complication of pituitary surgery, although postsurgical pituitary deficiency is clearly correlated with the extent of surgery (1, 2, 7, 84–86, 260). In seven series including only patients who underwent selective adenomectomy, no case of new pituitary deficiency was described (93, 100, 123, 130, 132, 138, 168), but in all series that included only patients who had undergone total hypophysectomy, hypopituitarism was always reported (91, 92, 99, 101). Considering all the studies reporting the general rate of hypopituitarism, this rate ranges between 0.9 and 93.3% (mean, 29.6%; median, 17.6%) (14, 18, 91, 107, 117, 126, 128, 133, 134, 137, 139, 154, 157, 160, 163, 166, 170, 171). It is noteworthy that these values do not consider the studies that do not report the occurrence of hypopituitarism. Taking into account that these studies include some not evaluating hypopituitarism but also some others where hypopituitarism were presumably documented in none of the patients, the avarage prevalence of hypopituitarism could actually be lower than that calculated strictly considered the specific reports of the different studies. The evaluation of the entire number of studies, including those where hypopituitarism where presumably not occurring in the study patients, seem to suggest that the hypopituitarism develop in an avarage of 16% of patients with CD after pituitary surgery. It is clear that the loss of pituitary function is proportional to the aggressiveness of surgery, and the reported rate of hypopituitarism is associated with more extensive resection. Indeed, considering series including patients that had undergone adenomectomy, hemi-hyphysectomy, and total hypophysectomy, the mean rates of hypopituitarism were 6.6, 20.2, and 80.2%, respectively (94, 110, 117, 128, 157). The rate of postsurgical hypothyroidism ranges between 3.1 and 68.8% (mean, 22.4%; median, 19.7%) (14, 92, 97, 99, 101, 102, 109, 110, 112, 117, 118, 121, 128, 134, 139, 161, 164, 166, 170, 211), hypogonadism ranges between 0.6 and 46.1% (mean, 13.9%; median, 8.6%) (14, 92, 97, 101, 102, 109, 112, 117, 118, 121, 128, 134, 139, 161, 164, 166, 211), and GH deficiency ranges between 0.6 and 52.8% (mean, 17.4%; median, 11.7%) (97, 102, 117, 122, 128, 134, 137, 139, 164, 166, 168, 211), whereas panhypopituitarism ranges between 1.4 and 29.3% (mean, 9%; median, 5%) (94, 98, 121, 128, 136, 139, 154). Considering separately the five purely endoscopic series including only patients with CD, the occurrence of hypopituitarism or panhypopituitarism was reported in three out of these five studies (134, 136, 137). In particular, in these studies the rate of hypopituitarism was reported in two studies and ranges from 13% to 35% (mean and median, 24%) (134, 137); one study also reported the rate of hypothyroidism (22%) and hypogonadism (3.5%) (134), whereas another study reported the rate of GH deficiency (6.5%) (137), and one additional study reported a rate of panhypopituitarism (3%) (136). In the remaining two studies, hypopituitarism was not evaluated or not disclosed in any patient (127, 165). It is important to point out that the reported prevalence of pituitary deficiency, especially GH deficiency, might be underestimated because of the lack of a constant and appropriate evaluation of the entire pituitary function after surgery. Many patients have hypopituitarism induced by cortisol excess when their disease is active, and this often resolves after a successful surgical resection. The natural history of hypopituitarism recovery is highly variable. GH secretion often fails to normalize until 1 year or more after surgery (216, 261), in contrast to the thyroid and gonadal axes, which typically recover earlier (262). Differentiating true structural postsurgical hypopituitarism, however, from functional pituitary deficiency secondary to the effects of long-term hypercortisolism is often difficult. This is, nevertheless, an important distinction to make if patients can avoid periods of inadequate replacement therapy, or inappropriate and unnecessary replacement (7, 85).

*e. Hypoadrenalism or adrenal insufficiency.* Hypoadrenalism or adrenal insufficiency may have two different interpretations. First, hypoadrenalism may represent one of the components of the hypopituitarism, occurring in the postoperative period as a generally permanent complication of pituitary surgery. On the other hand, adrenal insufficiency may be transient and usually predictive of the disease remission after surgery (7). Indeed, patients with CD who are entering remission will probably experience adrenal insufficiency for some to several months after successful surgery as a result of suppression of the HPA axis. During this period, glucocorticoid replacement is needed to prevent symptomatic adrenal insufficiency (142). A very important part of the management of adrenal insufficiency is patient education; patients should understand the importance of replacement therapy, the need to increase the usual glucocorticoid dose during stress, and the need to notify medical staff in case of any surgical procedure. In addition, they must always have supplies of hydrocortisone for injection and should be taught how and when to administer it (263). Patients should be treated with hydrocortisone (or cortisone acetate if hydrocortisone is not available), and the recommended daily hydrocortisone dose is 10–20 mg/m$^2$; it can be given in two or three daily doses, with administration of one-half to two-thirds of the

total dose in the morning (7, 85). In the absence of objective variables of replacement therapy, the physician has to rely primarily on symptoms and signs that suggest underreplacement or over-replacement of glucocorticoids, to titrate the glucocorticoid replacement dose appropriately, and to prevent significant morbidity. Regardless of the approach taken with glucocorticoid replacements, once patients have been discharged, they should all receive a thorough assessment of the HPA axis, with dynamic testing 4–6 weeks after surgery. Some patients require further testing after 3–6 months. Dynamic tests should not be performed until at least 4 weeks after surgery because the presence of pituitary edema in the early postoperative period may interfere with pituitary function. In addition, testing earlier may underdiagnose ACTH deficiency, given that adrenal atrophy may not yet have occurred (263). An ACTH-stimulated cortisol level $< 18$ $\mu$g/dL (500 nmol/L) after a 1-$\mu$g ACTH-stimulating test confirms central adrenal insufficiency, but an ACTH-stimulated cortisol level $< 21.6$ $\mu$g/dL (600 nmol/L) does not exclude adrenal insufficiency (263).

#### *5. Summary and general considerations on pituitary surgery*

Pituitary surgery represents the first-line treatment for the great majority of patients with CD, but it is not advisable in patients with contraindications for surgery because of severe clinical conditions, or in patients without a clear-cut indication because of the absent or very limited chance of obtaining a beneficial result from surgery, such as patients with large extrasellar and/or invasive tumors, or with invisible tumors in case of the absence of an expert pituitary surgeon, prone to the exploratory pituitary surgery. Despite an avarage immediate success rate of 78%, pituitary surgery is associated with a long-term failure, including the immediate relapses and the late recurrences, in an average of approximately 32%, in particular in 25% of patients with a microadenoma and 50% of patients with a macroadenoma with no significant difference between microscopic and endoscopic approaches. On the other hand, pituitary surgery is associated with good safety, having a mortality rate that is very low and a morbidity rate mostly represented by DI and hypopituitarism, which mainly depends on the extent of surgery.

## IV. The Second-Line Treatment of Cushing's Disease

The persistence or recurrence of CD after surgery requires additional treatments to minimize the deleterious consequences of hypercortisolism. Persistent CD corresponds to a sustained elevation in postsurgical cortisol levels and/or a need for therapy within 6 months from the initial surgery, caused by a residual tumor hidden within the gland, in the cavernous sinus, the clivus, the dura, or less commonly, in an ectopic parasellar region (264). Recurrent CD is identified by the reappearance of clinical and hormonal features of hypercortisolism that occur more than 6 months after an initial posttreatment remission (264). The possible treatments for this group of patients might include repeat pituitary surgery, pituitary radiotherapy, adrenal surgery for bilateral or, less commonly, monolateral adrenalectomy, and/or medical therapy. A multimodal approach using a combination of these treatments may be an appropriate strategy in a relevant number of patients to achieve the best outcome (1, 7, 84–88, 264–270).

### A. Repeat pituitary surgery

Repeat pituitary surgery is the preferred treatment option for several expert endocrinologists in cases of persistent or recurrent CD, especially when associated with imaging evidence of a clear-cut residual tumor (7, 85, 88, 264–270). Indeed, despite the absence of specific studies demonstrating that the evidence at imaging of a clear-cut residual tumor is associated with a better outcome of repeat pituitary surgery compared with negative imaging, the visualization of the residual pituitary tumor is commoly considered a positive predictive factor for disease cure and/or a clear indication for repeat pituitary surgery (7, 265, 266, 269). However, several authors disagree with this concept and consider repeat pituitary surgery a good option or even a mandatory attempt in case of failure of the initial surgery, even in the case of an invisible tumor at the imaging examination, especially in the hands of an expert pituitary surgeon and a surgical and pathological confirmation of corticotroph pituitary tumor (85, 264, 267, 268, 270). The detection of the residual pituitary tumor may influence the surgical approach. In most cases of persistent or recurrent CD, tumor cells persist and/or recur locally, and therefore, a selective adenomectomy is a reliable option (7, 85, 88, 235, 264–270). However, some patients, in whom a pituitary tumor could not be detected after initial surgery, may require a more aggressive removal of the gland by hemi-hypophysectomy or even a total hypophysectomy (7, 85, 88, 264–270). In the studies considering persistent or recurrent disease, the timing between the first and second surgery is variable and ranges from 1 week to 38 months after the initial surgery (104, 123, 135, 147–150, 160, 166, 170, 171, 271–276).

Repeat TSS can be considered in the immediate postoperative period, particularly if a pituitary tumor is visualized at preoperative imaging before the initial pituitary

surgery and/or a tumor was found intraoperatively, and also if a corticotroph lesion was documented in the removed pituitary tissue after the initial pituitary surgery (88, 264–270). If no tumor is detected during initial surgery or findings on preoperative imaging are equivocal, an inferior petrosal sampling may help to establish the site of the tumor when considering a re-exploration (264–268). This method, however, is only 50% accurate in predicting tumor laterality during repeated TSS, because the venous drainage of the gland changes position during the initial surgery, causing false-positive results, or the drainage becomes impeded, causing false-negative results (264, 267).

Repeat pituitary surgery may be performed early after the initial surgery, generally within 2 months, or may be delayed. The strategy of early repeat TSS has several advantages. First, it allows a reapproach to the pituitary tumor with minimal additional trauma because it is undertaken before the formation of scar tissue and the modification of surgical anatomy (88, 264, 265, 269, 270). Second, the surgeon is often able to recall particular anatomical details of the earlier operation, which may be essential for reoperation (88, 264, 265, 269, 270). Finally, early repeat surgery has been suggested to have a relatively low morbidity, compared with delayed repeat surgery (260, 264, 265, 267), but this finding needs to be confirmed.

This review has considered 17 studies published between 1987 and 2014, including 393 patients with persistent or recurrent CD. According to these studies, the remission rate after repeat TSS is 30–87.5%, with mean and median remission rates of 58 and 61.1%, respectively, in a mean follow-up period of 59.8 months (range:4–432 mo). Moreover, repeat pituitary surgery is affected by a recurrence rate ranging from 0 to 60% (mean, 16.1%; median, 9.1%) with time to recurrence ranging an average of 25 months (104, 123, 135, 147–150, 160, 166, 170, 171, 271–276).

Table 5 summarizes the results of the studies evaluating the outcome of repeat pituitary surgery for persistent or recurrent CD, considering only studies for which at least remission and recurrence rates were available.

An early reoperation within 60 days from the initial surgery results in a sustained remission in 66.7–87.5% of patients, with mean and median remission rates of 72.3 and 73.3%, respectively (104, 135, 136, 147–149). However, a delayed remission can occur in about 5% of patients after the initial operation. Serial testing over a period of 1–2 months might be advised, before considering additional therapy in patients who improve but are not in a clear-cut remission immediately after the initial surgery (141). A delayed reoperation, which is performed at least 60 days after the initial surgery, is associated with remission rate ranging between 30 and 71.4%, with mean and median remission rates of 51.5 and 46.2%, respectively (123, 160, 166, 170, 171, 271–276). The remission rate associated with a second operation is lower than that obtained after the first operation and may vary on the basis of tumor features, including the size and location of the residual pituitary tumor (264–268, 274). The extension in the extrasellar region and/or the location of residual tumor within the cavernous sinus or skull base bone is a factor clearly reducing the likelihood of achieving remission (85, 264, 265, 268). For these reasons, patients with large and/or invasive tumors might not benefit from a second surgical procedure. One strategy for these patients is removal of the sellar portion of residual tumor at the second surgery, followed by radiosurgery to the cavernous sinus (277).

The clinical variables that may predict the outcome of repeat pituitary TSS are debatable. Surgical and pathological identification of a tumor during first and second surgeries and the limited extent of the initial surgery seem to be positive predictive factors for a good outcome (147, 271), but in most series, no significant correlation has been found among presurgical, surgical, and pathological tumor identification and disease remission (149, 272, 274–276).

Repeat pituitary surgery is associated with a higher risk of hypopituitarism compared with initial pituitary surgery, in relation to the extent of removed pituitary tissue (264–269). The rate of hypopituitarism described in studies on repeat pituitary surgery, which report the general rate of hypopituitarism, varies between 9.1 and 78.6% (mean, 38%; median, 37%) (123, 147, 271, 275, 276). Different studies, however, reported the rate of the various pituitary deficiencies after repeat TSS; on the basis of these data, hypothyroidism ranges between 11.8 and 57.1% (mean, 30%; median, 21%) (147, 275, 276), hypogonadism ranges between 11.8 and 21.4% (mean, 16.4%; median, 16%) (147, 275, 276), and GH deficiency ranges between 21 and 28.6% (mean and median, 24.8%) (275, 276), whereas panhypopituitarism ranges between 5.2 and 83.3% (mean, 31.3%; median, 5.5%) (148, 274, 276). Importantly, the risk of hypopituitarism after repeat pituitary surgery appears to be lower than that reported to occur several years after radiotherapy (264, 265). Postoperative CSF leak has been reported to be more frequent after repeat TSS than after the initial TSS (range, 3.2–83.3%; mean, 28.7%; median, 15.9%) (147, 148, 170, 271, 275, 276). The rate of PDI ranges between 3.2 and 83.3% (mean, 24.7%; median, 11.1%) (123, 147, 148, 271, 274), whereas the rate of TDI ranges between 5.5 and 42.8% (mean, 23.1%; median, 22.1%) (271, 274–276). Finally, the rate of meningitis ranges between 3.8 and 8.3% (mean, 6.8%; median, 8.2%) (148, 271, 276).

In summary, repeat pituitary surgery is considered an optional second-line treatment after the failure of initial

**Table 5.** Results of Studies Evaluating the Outcome of Repeat Pituitary Surgery for Persistent or Recurrent CD

| First Author, Year (Ref.) | No. of Patients | Follow-Up, mo | Remission Rate, % | Recurrence Rate, % | Time to Recurrence, mo | Perioperative Mortality and Complications |
|---|---|---|---|---|---|---|
| Nakane, 1987 (104) | 8 | NA | 87.5 | NA | NA | NA |
| Friedman, 1989 (271)§ | 31 | M:10.1 | 71 | 13.6/9.7 | R:10–47<br>M:22.3<br>m:10 | Death:3.2%; TDI:9.7%; hypopituitarism:24.2%; meningitis: 8.2%; PDI:3.2%; CSF:3.2% |
| Ram, 1994 (147) | 17 | R:4–84<br>M:34 | 70.6 | 25 | M:13.7<br>m:12 | Death:0%; hypopituitarism:41.2%; hypothyroidism:11.8%; hypogonadism:11.8%; PDI:17.6%; CSF:17.6% |
| Chee, 2001 (170) | 13 | NA | 38.5 | 60 | NA | Death:0%; CSF:46.2% |
| Shimon, 2002 (160) | 13 | M:50.4 | 61.5 | 0 | na | NA |
| Benveniste, 2005 (272) | 44 | NA | 54.5 | 25 | M:31 | Death:0%; hypopituitarism:66%;[a] panhypopituitarim:65%;[a] PDI:28%;[a] TDI:19%;[a] sinusitis:5%;[a] CSF:1%;[a] epistaxis:1%;[a] CNP:1%[a] |
| Locatelli, 2005 (148) | 12 | R:4–76<br>M:27 | 66.7 | 0 | na | Death:0%; CSF:83.3%; panhypopituitarism:83.3%; PDI: 83.3%; meningitis:8.3%; PE: 8.3%; DVT:8.3% |
| Hofmann, 2006 (273) | 16 | M:23 | 43.7 | 0 | na | Death:0% |
| Esposito, 2006 (123)¶ | 11 | M:20 | 45 | 9.1 | 21 | Death:0%; PDI:9.1%; carotid artery injury:9.1%; hypopituitarism:9.1% |
| Hofmann, 2008 (171) | 59 | M:122<br>m:24 | 30.5 | 15.4 | NA | NA |
| Patil, 2008 (274)§ | 36 | M:34<br>m:24 | 61.1 | 9.1/5.5 | R:6–11<br>M:8.5 | Death:0%; PDI:11.1%; panhypopituitarism:5.5%; TDI:5.5% |
| Wagenmakers, 2009 (275) | 14 | M:21.9 | 70 | 0 | na | Death:0%; DI:30% |
| Hameed, 2013 (149) | 10 | R:72–432<br>M:185 | 50 | 4.5 | M:48 | NA |
| Alexandraki, 2013 (135) | 22 | R:5–75<br>M:32 | 76 | 6.7 | 12 | Death:0%;[b] TDI:7.8%;[b] meningitis: 2.2%;[b] panhypopituitarism:2.2%;[b] CSF:2.2%[b] |
| Berker, 2013 (136)¶ | 25 | M:62 | 41.7 | 40 | M:42 | NA |
| Dimopoulou, 2014 (166) | 36 | R:62–184<br>M:139 | 46.1 | 50 | M:13 | Death:0%; hypopituitarism:37%; TDI: 34.6%; hypothyroidism:21%; GHD: 21%; hypogonadism:16%; CSF:7.7%; panhypopituitarism:5.2%; meningitis:3.8% |
| Valderrabano, 2014 (276) | 26 | | | | | |
| **Total** | **393** | **R:4–432<br>M:59.8** | **R:30–87.5<br>M:58<br>m:61.1** | **R:0–60<br>M:16.1<br>m:9.1** | **M:25.5** | **Death:R:0–3.2, M:0.3, m:0; PDI:R: 3.2–83.3, M:24.7, m:11.1; TDI: R:5.5–42.8, M:23.1, m:22.1; CSF:R:3.2–83.3, M:28.7, m:15.9; meningitis:R:3.8–8.3, M:6.8, m:8.2; hypopituitarism: R:9.1–78.6, M:38, m:37; hypothyroidism:R:11.8–57.1, M:30, m:21; hypogonadism:R: 11.8–21.4, M:16.4, m:16; GHD: R:21–28.6, M:24.8, m:24.8; panhypopituitarism:R:5.2–83.3, M:31.3, m:5.5** |

Abbreviations: DI: diabetesinsipidus; TDI: transient diabetes insipidus; PDI: permanent diabetes insipidus; CSF: cerebrospinal fluid; DVT: deep venous thrombosis; PE: pulmonary embolism; CNP: cranial nerve palsy; GHD: GH deficiency; NA, not available; na, not applicable; R, range; M, mean; m, median. This table lists the studies addressing the outcome of repeat pituitary surgery published between 1987 and 2014, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD and to the only repeat surgery. The range, mean and median percentage of the adverse effects, including hypopituitarism and diabetes insipidus, were calculated considering the only studies were the specific side effect was reported. In the studies marked with ¶ only 1 patient presented a recurrence, so that the time to recurrence is represented by a single time period, instead of a range, mean, or median. In the studies marked with § the values reported after the/describe the recurrence rate and the time to recurrence for a longer follow-up cohort, in line with the description included in the study; such values were not considered with regard to the total calculations.

[a] Results in 96 patients. [b] Results including patients with initial surgery.

surgery, especially in case of well-defined, small, and non-invasive residual tumors and/or surgical and pathological tumor identification at the time of the first attempt of a selective adenomectomy. However, repeat surgery is associated with a lower success rate, due to a lower immediate remission rate with a similar recurrence rate, and a higher prevalence of hypopituitarism compared with the initial surgery, especially when a more aggressive surgical approach is preferred to the selective adenomectomy.

### B. Pituitary radiotherapy

From 1940 to the early 1980s, pituitary radiotherapy was widely used as a first-line treatment for CD, but nowadays it is typically used as a second-line or third-line treatment in CD patients after failure of initial or repeat pituitary surgery, especially in cases of aggressive and/or invasive tumors (1, 2, 7, 84–88, 264–270, 278–280). The recent development of novel medical therapies may limit the use of radiotherapy to patients who are unresponsive to or intolerant of medical treatment, or it may result in the deferral of radiotherapy until after a period of control of cortisol secretion by medical therapy. However, radiotherapy can be considered rarely as a first-line treatment in patients without indication or with contraindications to surgery or in patients who refuse surgery, especially for aggressive and/or invasive pituitary tumors (279, 280).

#### *1. Type of pituitary radiotherapy*

Different modalities have been developed and employed to irradiate pituitary tumors, including: 1) conventional radiotherapy (CRT), a technique delivering ionizing radiation to the target tumor in small, daily doses over a period of 25–30 days; and 2) stereotactic radiotherapy (SRT), a technique delivering ionizing radiation to the target tumor by stereotactic methods, which gives the precise identification of the tumor position with three spatial coordinates. SRT allows the delivery of a high dose of radiation to the tumor while preserving the surrounding tissues and organs. SRT can be delivered as: 1) a single treatment (stereotactic radiosurgery [SRS]); or 2) a fractionated treatment (stereotactic conformal radiotherapy [SCRT]). SRS can be performed with different techniques, including a multiheaded cobalt unit (Gamma Knife [GK]), a linear accelerator (LINAC) system [LINAC SRS], or a proton-beam system [Proton-beam SRS] (279–290).

CRT is historically the first radiation treatment for CD, although presently it has been replaced by SRT. The mechanism of action of CRT is based on the delivery of ionizing radiation to the pituitary gland in order to control hormone hypersecretion and tumor growth (279–290). The treatments are spread out over time to provide nontumor cells time to reoxygenate, repair, redistribute, and recover between doses. CRT is delivered in multiple sessions and is given with photons generated by a LINAC. Photon beams are shaped using a multileaf collimator (MLC) to conform to the shape of the tumor and to shield normal structures. The target tumor is reached using three different fixed radiation fields, in particular an anterior oblique field aiming at the pituitary through the forehead and two lateral fields traversing the temporal regions. Radiation doses generally range from 45 to 50 Gy, although studies that used lower and higher doses are available, divided in 25–30 daily fractions, with a total dose of 1.8 to 2 Gy per fraction (279–290).

SRT is presently the most common radiation treatment for CD, and has replaced CRT as the main radiation method for persistent and recurrent CD (279–290). The mechanism of action of SRT is based on the delivery of ionizing radiation directly to the pituitary tumor in order to control hormone hypersecretion and tumor growth. SRT focuses on a high dose of radiation to the pituitary tumor, while sparing the surrounding structures from significant irradiation (279–290). GK and LINAC SRS delivers focused radiation in a single treatment. GK is given via photons generated by radioactive isotope cobalt-60 housed within the machine, with the capacity of aiming multiple isocenters of varying photon beams to achieve a dose plan that conforms to the irregular three-dimensional volume of the tumor (279–290). LINAC SRS uses multiple radiation arcs cross-firing photon beams at the target. Photon beams are shaped using collimators with diameters ranging from 2 to 30 mm, to provide an optimal adaptation of the field size to the lesion size (279–290). Proton-beam SRS, currently available in very specialized centers worldwide, uses accelerated proton particles to deliver radiation to the target in a single treatment (279–290). Due to the physical properties of protons (Bragg-peak phenomenon), proton beams spare normal surrounding tissue from exposure more than photon beam technologies (291–293). SRS (GK, LINAC, and proton-beam SRS) is given as a single dose of 18–24 Gy (279–290). The optic apparatus can tolerate a maximal radiation dose of 8–12 Gy; consequently, SRS is limited to tumors smaller than 10 mm and 3–5 mm away from the optic apparatus (280–282, 290, 294–297). SCRT is given with photons generated by a LINAC system. Photon beams are shaped with a narrow-leaf MLC of 3 mm (micro-MLC) or 5 mm (mini-MLC), using four to six fixed radiation fields to reach the target tumor. Similarly to CRT, SCRT is given at a dose of 45–50 Gy in 25–30 daily treatments at daily doses $\leq$2 Gy per fraction. For SCRT, there is no size restriction of pituitary tumors because the delivered total doses are within the tolerance of optic apparatus (280, 294–297).

### 2. Efficacy of pituitary radiotherapy

The efficacy and the consequent outcome of radiotherapy in CD are based on two factors: 1) the control of hormone secretion; and 2) the control of tumor growth. Most studies have evaluated the effect of radiotherapy on the normalization or reduction of hormone levels, including urinary cortisol and/or plasma ACTH and/or serum cortisol levels, whereas a selection of studies also evaluated the effect on tumor size. The results of radiotherapy can be distinguished on the basis of the type of radiotherapy; indeed, a solid experience has been historically documented with the CRT, and a large experience has been more recently accumulated with the modern SRT, especially SRS.

*a. Conventional radiotherapy.* This review has considered 15 studies published between 1971 and 2007, including 341 patients with CD treated with CRT. Because 20 patients appear to be included in two different studies, the real total number of different patients included in the studies on CRT is likely 321 (159, 298–311).

Table 6 summarizes the results of the studies evaluating the outcome of CRT for CD.

The outcome of CRT was analyzed in seven studies as a primary treatment, in four studies as a secondary treatment after surgery, and in four additional studies either as a first-line or second-line treatment. Most studies included more than 10 patients with a follow-up longer than 5

**Table 6.** Results of Studies Evaluating the Outcome of Pituitary CRT in Patients With CD

| First Author, Year (Ref.) | No. of Patients | Follow-Up, mo | Dose, Gy | Remission Rate, % | Time to Remission, mo | Recurrence Rate, % | Time to Recurrence, mo | Tumor Control Rate, % | Hypopituitarism, % | Optic Nerve Damage, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Orth, 1971 (298)* | 51 | R:12–168<br>M:108 | 45 | 19.6 | NA | NA | NA | NA | 0 | 0 |
| Edmonds, 1972 (299)* | 15 | R:48–120 | R:35–50 | 60 | R:1–6 | 11.1 | M:18 | NA | NA | NA |
| Ross, 1979 (300)* | 13 | M:48 | 46 | 61.5 | NA | 62.5 | NA | NA | NA | NA |
| Ahmed, 1984 (301)* | 19 | R:12–96<br>M:43.2 | 20 | 36.8 | R:6–12 | 0 | na | NA | 0 | NA |
| Sharpe, 1985 (302)* | 8 | R:60–144<br>M:108 | 43 | 100 | NA | 12.5 | M:120 | NA | 100 | NA |
| Howlett, 1989 (303) | 30 (21,* 9) | R:69.6–186<br>M:123.6,*<br>m:114*<br>M:52.2<br>m:36.2 | 45 | 57.1,* 55.6 | NA | 0 | na | 100,* 100 | 28.6,* NA | 0 |
| Littley, 1990 (304)* | 24 | R:13–171<br>M:99.4<br>m:93 | 20 | 45.8 | R:4–36<br>M:15.9<br>m:16 | 45.4 | R:18–63<br>M:50.7<br>m:50.6 | NA | 66.7 | 0 |
| Vicente, 1991 (305) | 10 | R:18–42<br>M:29.1<br>m:27 | 50 | 80 | R:12–36 | 0 | na | NA | 30 | NA |
| Tran 1991 (306) | 3 (2,* 1) | R:30–250<br>M:84 | 49 | 100 | NA | NA | NA | NA | 77.7** | 0 |
| Murayama, 1992 (307)* | 20 | R:24–300<br>M:148.8<br>m:114 | 54 | 80 | R:2–28<br>M:10.2<br>m:6.5 | 25 | R:60–84<br>M:5.7<br>m:5.5 | 100 | 30 | 0 |
| Zierhut, 1995 (308) | 7 | R:12–216<br>M:84 | 45 | 57.1 | R:16–104 | 5.3** | R:9–98**<br>M:34.8** | 94.1** | 58.5** | 1.4** |
| Sonino, 1996 (159) | 42 (19,* 23) | R:24–216<br>m:120 | R:45–50 | 73.7,* 39.1 | NA | 50,* 0 | NA | NA | NA | NA |
| Tsang, 1996 (309) | 29 (8,* 3, 18***) | R:1–223<br>m:87.6 | R:40–52 | 55.2 | NA | NA | NA | 96*** | 13.9–31.1** | 0 |
| Estrada, 1997 (310) | 30 | R:18–114<br>M:55<br>m:42 | 50 | 83.3 | M:18 | 0 | na | 100 | 23.3 | 0 |
| Minniti, 2007 (311) | 40 | R:24–180<br>m:108 | 44 | 80 | M:24 | 0 | na | 92.5 | 74.9 | 0 |
| **Total** | **341** | **R:1–300<br>M:81.9<br>m:86.2** | **R:20–54<br>M:43.5<br>m:45** | **R:19.6–100<br>M:63.8<br>m:60** | **R:1–104<br>M:17.4<br>m:6.5** | **R:0–62.5<br>M:15.9<br>m:0** | **R:18–84<br>M:48.6<br>m:28.1** | **R:53–100<br>M:98.5<br>m:100** | **R:0–100<br>M:39.3<br>m:30** | **0** |

Abbreviations: NA, not available; na, not applicable; R, range, M, mean; m, median. This table lists the studies addressing the outcome of pituitary CRT that were published between 1971 and 2007, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD.

* Primary therapy without surgery.

** These data are related to a population including all types of pituitary tumors.

*** Radiation therapy as part of a salvage therapy.

years. In particular, all but three series included more than 10 patients (159, 298–301, 303–305, 307, 309–311), whereas all but five had a mean and median follow-up period longer than 5 years (159, 298, 302–304, 306–309, 311). The mean and median total radiotherapy doses were 43.5 and 45 Gy, respectively, with a range of 20–54 Gy (one patient included in a single study [307] received a total dose of 66 Gy), and according to the information included in 11 studies containing details of dose fractioning, the mean and median fraction dose was 1.9 Gy (range, 1.8–2.0 Gy) in a mean of 20 fractions (299, 302–311). The overall remission rate of CRT, based on hormone control, generally normalization of cortisol secretion, ranged from 19.6 to 100%, with mean and median rates of remission of 63.8 and 60%, respectively, during a follow-up of 1–300 months (mean, 81.9 mo; median, 86.2 mo) (159, 298–308, 310, 311). The time to remission is nonhomogeneously expressed in the different studies, being reported as a range (1–104 mo) in six studies (299, 301, 304, 305, 307, 308) and as a mean (10.2–24 mo) in four studies (304, 307, 310, 311); two of these latter studies also reported a median time to remission of 6.5–16.6 months (304, 307). Specifically, when CRT was the exclusive therapy, the mean and median remission rates were 63.5 and 60.8%, respectively (159, 298–304, 306, 307); when used after pituitary surgery, the mean and median remission rates were 70.7 and 80%, respectively (159, 303, 305, 306, 308, 310, 311). The overall recurrence rate after CRT, whose definition was based on the evidence of a re-increase in hormone levels after previous normalization ranged from 0 to 62.5% (mean, 15.9%; median, 0%) (159, 299–305, 307, 310, 311). The mean and median times to recurrence were 48.6 and 28.1 months, respectively, in four series where this was described (range, 18–84 mo) (299, 302, 304, 307). Considering only the studies where CRT was the primary therapy, the mean and median recurrence rates were 25.8 and 18.8%, respectively (159, 299–304, 307). When CRT was used after pituitary surgery, the mean and median recurrence rate was 0% (159, 303, 305, 310, 311). According to this data, CRT appears to be less effective when used as an exclusive treatment for CD, leading not only to a lower rate of disease remission, but also to a higher risk of disease recurrence. Moreover, CRT appears to be less effective when given at doses <40 Gy; in particular, two studies in which patients were treated with a mean dose of 20 Gy reported a lower remission rate and higher recurrence rate (301, 304). A selected number of studies have evaluated the effect of CRT on tumor mass (303, 307, 310, 311). According to the studies, which included only patients with CD, tumor control, which was defined as an unchanged or decreased tumor mass on posttreatment imaging in a follow-up period of 1–300 months (mean, 108.9 mo; median, 93.1 mo), ranged between 53 and 100% (mean, 98.5%; median, 100%) (303, 307, 310, 311). The variability in the success rate observed in 15 studies may be attributed to different selection criteria of patients who underwent radiotherapy, as well as the variable criteria used to define remission and the possible use of concomitant medical therapies.

In small studies, CRT has been demonstrated to be an effective treatment for pediatric CD, where the cure rates were reported to be between 80 and 100% (mean, 91.8%; median, 93.7%) (312–317).

*b. Stereotactic radiotherapy.* This review has considered 36 studies published between 1986 and 2014, including 850 patients with CD who underwent SRT as a first-line treatment or secondary to an unsuccessful pituitary surgery. Since 93 patients appeared to be included in two different studies, the real total number of different patients included in the evaluation of SRT outcome is likely 757.

Table 7 summarizes the results of the studies evaluating the outcome of SRT for CD.

Twenty-seven studies described results of GK, five studies of LINAC SRS, and three studies of proton-beam SRS; only one study described the results of SCRT (291–293, 318–349). The mean radiosurgical margin dose (dose to the margin of the tumor) for these series ranged from 14.7 to 45 Gy, with an avarage radiosurgical margin dose of 23.6 Gy. The overall remission rate of SRT, considered as hormone normalization, ranged from 10 to 100% (mean, 60.8%; median, 57.2%) during a follow-up of 2–264 months (mean, 48.6 mo; median, 47.2 mo). Disease remission after SRT occurs after 1–166 months, where the mean and median times to hormone normalization were 16 and 24.5 months, respectively (291–293, 318, 319, 322, 323, 327–329, 331, 332, 334–338, 341–344, 346–349). A selected number of studies have evaluated the recurrence rate, which ranged from 0 to 100%, with mean and median recurrence rates of 12.3 and 0%, respectively (291–293, 318, 320, 323, 326, 328, 329, 332–336, 338, 339, 342–348).

Most studies have focused on the outcome of SRS, mainly GK. Considering the studies on GK, in a follow-up period of 2–264 months (mean, 48.9 mo; median, 46.1 mo), the remission rate was 10–100% (mean, 58.7%; median, 55.6%) (318–321, 323–334, 336, 337, 339–347). The time to remission is nonhomogeneously expressed in the different studies, being reported as a range (1–166 mo) in 10 studies (318, 327–329, 331, 334, 342–344, 346), as a mean (3–58.3 mo) in 11 studies (323, 327–329, 332, 336, 337, 342–344, 347) and as a median (14–45 mo) in five studies (329, 334, 341, 342, 346). In these series, the recurrence rate was 0–100%, with mean and median re-

**Table 7.** Results of Studies Evaluating the Outcome of Pituitary SRT in Patients With CD

| First Author, Year (Ref.) | No. of Patients | Radiosurgery Unit | Follow-Up, mo | Mean Margin Dose, Gy | Remission Rate, % | Time to Remission, mo | Recurrence Rate, % | Time to Relapse, mo | Tumor Control Rate, % | Hypopituitarism, % | Optic Nerve Damage, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Degerblad, 1986 (318) | 29 | GK | R:36–108<br>m:72 | NA | 48.3 | R:12–36 | 0 | na | NA | 41.1 | 0 |
| Levy, 1991 (291) | 64 | PB | NA | NA | 92.2 | M:12 | 15.2 | NA | NA | 0 | 0 |
| Ganz, 1993 (319) | 4 | GK | m:18 | 25 | 50 | NA | NA | NA | 100 | NA | NA |
| Martinez, 1998 (320) | 3 | GK | R:26–45<br>m:36 | 24 | 100 | NA | 0 | na | 33.3 | 33.3 | 0 |
| Lim, 1998 (321) | 4 | GK | R:3–54<br>M:25.5 | 25.4 | 25 | NA | NA | NA | NA | 1.5* | 1.5* |
| Mitsumori, 1998 (322) | 5 | LINAC | m:36 | 15 | 40 | M:8.5 | NA | NA | 100* | 77.1* | 0 |
| Morange-Ramos, 1998 (323) | 6 | GK | R:6–36<br>m:20 | 28 | 66.7 | M:6 | 0 | na | 100 | 16.7* | 0 |
| Hayashy, 1999 (324) | 10 | GK | M:14.9 | 23.9 | 10 | NA | NA | NA | 100 | 0 | 0 |
| Inoue, 1999 (325) | 3 | GK | M:24<br>m:24.3 | 20 | 100 | NA | NA | NA | 100 | 0 | 0 |
| Mokry, 1999 (326) | 5 | GK | R:7.1–71<br>M:56.3 | 17 | 20 | NA | 0 | na | 98* | 40 | 0 |
| Laws, 1999 (327) | 50 | GK | M:12 | 18 | 58.9 | R:3–48<br>M:13.7 | NA | NA | NA | NA | 2.5* |
| Sheehan, 2000 (328) | 43 | GK | R:18–113<br>M:39.1<br>m:44 | 20 | 62.8 | R:3–48<br>M:12.1 | 11 | R:19–38<br>M:31.3<br>m:37 | 100 | 16.3 | 2.3 |
| Shin, 2000 (329) | 6 | GK | R:9–112<br>M:88.2 | 32.3 | 50 | R:34–96<br>M:58.3<br>m:45 | 33.3 | 36 | 100 | 0 | 0 |
| Izawa, 2000 (330) | 12 | GK | M:26.4<br>m:10 | 24.2 | 16.7 | NA | NA | NA | 83.3 | 0 | 0 |
| Zhang, 2000 (331) | 18 | GK | R:12–46<br>m:32.1 | 32.4 | 83.3 | R:6–12 | NA | NA | 83.3 | NA | NA |
| Hoybye, 2001 (332) | 18 | GK | R:144–264<br>M:204<br>m:198 | NA | 83 | M:3 | 0 | na | NA | 66 | 0 |
| Kobayashi, 2002 (333) | 20 | GK | M:64.1<br>m:60 | 28.7 | 35 | NA | 0 | na | 100 | NA | NA |
| Pollock, 2002 (334) | 9 | GK | R:12–115<br>M:42.4<br>m:36 | 20 | 77.8 | R:2–44<br>m:14 | 0 | na | 100* | 16.3* | 11.1 |
| Wong, 2003 (335) | 5 | LINAC | R:27–49<br>M:38 | 17 | 100 | R:6–18<br>M:8.4 | 20 | 12 | NA | 0 | 0 |
| Petrovich, 2003 (336) | 4 | GK | M:41<br>m:36 | 15 | 50 | M:22 | 100 | M:30 | 50 | 3.8* | 3.8* |
| Choi, 2003 (337) | 9 | GK | R:6–98<br>M:42.5<br>m:43 | 28.5 | 55.6 | M:21.1 | NA | NA | 100 | 0 | 0 |
| Devin, 2004 (338) | 35 | LINAC | R:2–137<br>M:42<br>m:23 | 14.7 | 48.6 | R:1–33<br>M:7.5 | 23.5 | R:17–64<br>M:35.5 | 90.9 | 40 | 0 |
| Colin, 2005 (339) | 10 | LINAC | m:80 | NA | 100 | NA | 0 | na | 98* | 36.7* | 0 |
| Colin, 2005 (339) | 40 | GK | m:54.7 | 29.5 | 42.5 | NA | 0 | na | NA | 35.1* | 0 |
| Kajiwara, 2005 (340) | 2 | GK | R:18–59<br>M:44<br>m:50 | 17.5 | 50 | NA | NA | NA | 50 | 50 | 0 |
| Kong, 2007 (341) | 7 | GK | M:36.8<br>m:35 | NA | 100 | m:26 | NA | NA | 100 | 11.5* | 0 |
| Jagannathan, 2007 (342) | 90 | GK | R:12–132<br>M:41.3<br>m:45 | 23 | 54.4 | R:2–67<br>M:13<br>m:16 | 20.4 | R:7–60<br>M:27<br>m:25 | 95.5 | 22.2 | 5.6 |
| Castinetti, 2007 (343) | 40 | GK | R:12–120<br>M:54.7<br>m:48 | 29.5 | 42.5 | R:12–48<br>M:22 | 0 | na | 100 | 15 | 5 |
| Petit, 2008 (292) | 33 | PB | R:20–108<br>M:58.5<br>m:58 | 20 | 51.5 | R:5–49<br>M:14 | 0 | na | 93.9 | 51.5 | 0 |
| Wein, 2012 (344) | 17 | GK | R:12–59<br>m:23 | 18 | 58.8 | R:15–31<br>M:23 | 10 | 14 | 50 | 5.8 | 0 |
| Zeiler, 2013 (345) | 8 | GK | R:2–79<br>M:32.8<br>m:35 | 23.6 | 100 | NA | 0 | na | 100 | 12.8* | 2.5* |
| Sheehan, 2013 (346) | 96 | GK | R:12–209<br>m:48 | 22 | 69.8 | R:1–166<br>m:16.6 | 22.4 | R:5–120<br>m:38 | 97.9 | 36.4 | 5.2 |

(*Continued*)

**Table 7.** Continued

| First Author, Year (Ref.) | No. of Patients | Radiosurgery Unit | Follow-Up, mo | Mean Margin Dose, Gy | Remission Rate, % | Time to Remission, mo | Recurrence Rate, % | Time to Relapse, mo | Tumor Control Rate, % | Hypopituitarism, % | Optic Nerve Damage, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Grant, 2013 (347) | 15 | GK | R:12–96 M:40.2 | 35 | 73.3 | M:11.7 | 36.4 | R:9–24 M:14.2 | 100 | 40 | 3.2* |
| Budyal, 2014 (348) | 20 | SCRT | R:12–144 m:37.5 | 45 | 75 | R:5–84 m:20 | 0 | na | 95 | 40 | 0 |
| Wilson, 2014 (349) | 36 | LINAC | R:2–183.6 m:66 | 20 | 22.2 | m:27.7 | NA | NA | 83.3 | 11.1 | NA |
| Wattson, 2014 (293) | 74 | PB | R:6–247 m:52 | 20 | 75.7 | m:31 | 1.8 | 84 | 98.5 | 62* | 1.4* |
| **Total** | **850** | | **R:2–264 M:48.6 m:47.2** | **R:14.7–45 M:23.6** | **R:10–100 M:60.8 m:57.2** | **R:1–166 M:16 m:24.5** | **R:0–100 M:12.3 m:0** | **R:0–120 M:27.6 m:33.5** | **R:50–100 M:90.9 m:100** | **R:0–66 M:23.1 m:19.3** | **R:0–11.1 M:1.1 m:0** |

Abbreviations: PB, proton beam radiotherapy; NA, not available; na, not applicable; R, range; M, mean; m, median. This table lists the studies addressing the outcome of pituitary SRT and published between 1986 and 2014, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD.

* These data are related to a population including all types of pituitary tumors.

currence rates of 13.7 and 0%, respectively (318, 320, 323, 326, 328, 329, 332–334, 336, 339, 342–347); the time to relapse was reported as a range (5–120 mo) in four studies (328, 342, 346, 347), as a mean (14.2–35.5 mo) in four studies (328, 336, 342, 347), and as a median (25.5–37 mo) in three studies (328, 342, 346). Furthermore, considering the studies that used GK as primary or secondary therapy after unsuccessful surgery, the remission rate after primary GK ranged between 10 and 83.3% (mean, 53.6%; median, 50%) (318, 319, 324, 331, 332, 343, 347), whereas the remission rate after secondary GK ranged between 16.7 and 100% (mean, 59.8%; median, 57.2%) (320, 321, 323, 325–330, 333, 334, 336, 337, 339–346).

LINAC SRS was associated with a remission rate of 22.2–100%, with mean and median remission rates of 62.2 and 48.6%, respectively (322, 335, 338, 339, 349). The time to remission is reported as a range (1–33 mo) in two studies (335, 338) and as a mean (7.5–8.5 mo) in three studies (322, 335, 338), whereas one study reported a median time to remission of 27.7 months (349). The recurrence rate is reported in only three studies, with a range of 0 to 23.5% (mean, 14.5%; median, 20%) and a time to recurrence of 12–64 months (335, 338, 339).

Finally, three studies have reported their results of proton-beam SRS, showing mean and median remission rates of 73.1 and 75.7%, respectively, and a recurrence rate of 0–15.3% (mean, 5.7%; median, 1.9%) (291–293).

Considering these results, the treatment response to SRS, in terms of hormone normalization, appears to be equivalent across the different modalities (GK, LINAC, or proton beam SRS), despite variability in the criteria for the definition of disease remission, as well as possible inclusion of patients receiving concomitant medical therapies.

Tumor control after SRT, defined as a reduction or stability of tumor volume on postradiosurgical imaging, ranged from 50 to 100% in the different series. This included only patients with CD, having a mean tumor control rate of 90.9% and median tumor control rate of 100%, after a mean and median follow-up of 43.2 and 38.4 months, respectively (range 2–247 mo) (292, 293, 319, 320, 323–325, 328–331, 333, 336–338, 340–349). It is noteworthy that most pituitary tumors associated with CD are slow-growing lesions. Therefore, it is important to perform long-term imaging follow-up. This will help to differentiate between the natural history of a corticotroph pituitary tumor and the true effect of radiotherapy.

No data are currently available on the outcome of SRT in children with CD.

### *3. Predictive factors for the outcome of radiotherapy*

The variables of CRT and SRT treatment affecting the rate of hormone remission remain debatable. For CRT, no study has found a correlation between the outcome of radiotherapy and cortisol levels before irradiation, the interval between surgery and radiotherapy, tumor size or the radiation dose. For SRT, although margin radiation dose seems not to affect the remission rate (310, 342, 350), a correlation has been described between remission and maximal radiation dose (319, 334). It is noteworthy that whereas the radiation dose may positively influence the disease remission, it may negatively affect the safety of SRT, being the maximal and margin dose crucial for the protection of optic apparatus as well as the other neural and vascular structrures surrounding the tumor by an irradiation-dependent damage. Therefore, the tumor features, mainly including postsurgical tumor remnant

> 10 mm, and tumors with distance from the optic chiasm <5 mm, which would require a radiation dose superior to those tolerated by the optic apparatus or the other structures, are potentially undertreated; this is the reason why these tumor features are indirectly associated with a worse prognosis, and it is often indicated as a factor unfavorably affecting the outcome of SRT (280, 281, 284, 290, 294–297). However, no study has definitely demonstrated a clear correlation between these conditions and a worse outcome of SRT. No correlation between change in tumor volume and hormone response to GK has been described (282, 351). The absence of hormone-suppressive medication at the start of GK seems to be associated with a higher likelihood of and earlier remission (328, 334, 342, 343, 346). This evidence supports the concept that pituitary hormone-suppressive medications may act as radioprotective agents (352, 353).

Figure 4 shows the main possible factors unfavorably affecting the outcome of SRT in CD.

#### *4. Safety of radiotherapy*

The complications of pituitary radiotherapy include hypopituitarism, associated with neurocognitive, cerebrovascular, and neoplastic complications (84).

*a. Hypopituitarism.* The main hormonal consequence of pituitary radiotherapy is hypopituitarism (one or more hormone deficiencies), which seems to be mediated by hypothalamic-pituitary damage in the case of CRT, and by direct damage to the pituitary gland and/or pituitary stalk in the case of SRT (282, 351, 354, 355). Actually, the incidence of hypopituitarism attributable to pituitary radiotherapy is difficult to ascertain because persistent hypercortisolism, pituitary mass effects, and prior pituitary surgery beyond radiation therapy may lead to a deficiency of pituitary function (1, 2, 7, 84–88, 264–270, 279–290). An accurate assessment of the incidence of hypopituitarism requires many years of follow-up, but most published reports include an average follow-up period of < 10 years. Indeed, pituitary hormone deficiency secondary to pituitary radiation is time-dependent, with both increased incidence and severity of hormonal deficiency observed with longer postirradiation follow-up intervals (279–290, 351, 354–356).

Regarding CRT, radiation-induced insufficiencies are attributed to high radiation doses and unintended irradiation of the hypothalamic-pituitary region caused by limited precision in outlining the target volume (351, 354–356). In particular, Littley et al (357), in a study of 227 patients with a pituitary tumor, described cases where a dose of fractionated radiation ≤12 Gy did not incur detectable adrenal insufficiency, whereas doses ≥20 Gy did result in a detectable deficiency in thyroid and gonadal function. In the series including only patients with CD, the reported rate of new-onset hypopituitarism ranged between 0 and 100% (mean, 39.3%; median, 30%) in a follow-up period that ranged between 1 and 300 months (298, 301–305, 307, 310, 311). Considering only the series of CD patients with a follow-up of at least 5 years, the mean and median rates of hypopituitarism rose to 50 and 48.3%, respectively (range, 0–100%) (298, 302–304, 307, 311).

Regarding SRT, total dose and margin dose are the major factors determining the risk and onset of radiation-induced hypopituitarism (358–360). For GK, new-onset hypopituitarism has been reported in 0–66% of patients (mean, 22.9%; median, 19.3%) in the series including

**Figure 4.**

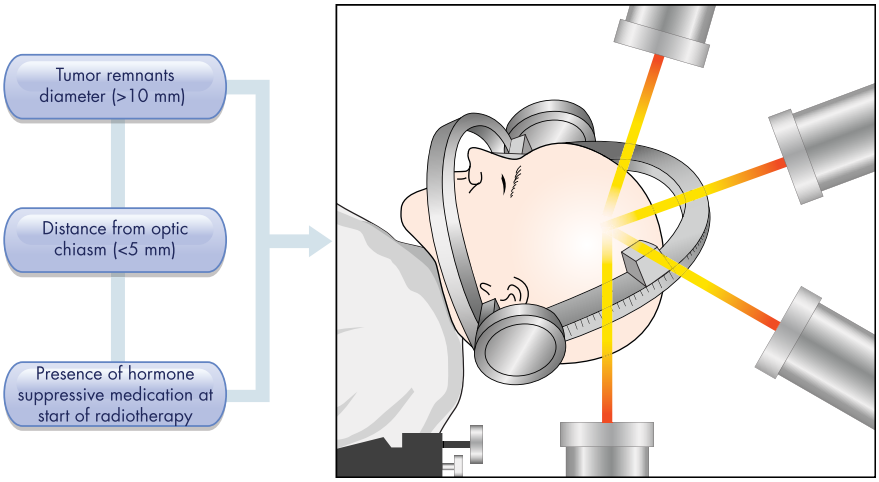


Figure 4. Main factors that can unfavorably affect the outcome of SRT in CD.

only those with CD (318, 320, 324–326, 328–330, 332, 337, 340, 342–344, 346, 347). It is noteworthy that no case of hypopituitarism was reported in three series with a mean follow-up <3.5 years (324, 325, 330), whereas the study with a mean follow-up of 17 years demonstrated a greater incidence (66%) of new pituitary hormone deficiency (332). However, many patients in this study had received higher doses than those currently used in radiosurgery and were targeted using outdated imaging modalities (332). Therefore, considering only the studies with a mean or median follow-up of at least 5 years, the mean and median rates of hypopituitarism were 49.1 and 41.3%, respectively (318, 326, 332). In LINAC SRS, considering three studies including only patients with CD, the hypopituitarism rate ranged between 0 and 40% (mean, 17.1%; median, 11.1%), during a follow-up period of 2–137 months (mean and median, 40 mo) (335, 338, 349). In three studies of proton-beam SRS, considering only patients with CD, hypopituitarism was reported in 0–52% of patients (mean and median, 26%) during a follow-up period of 20–108 months (291, 292). In the SCRT study, the rate of hypopituitarism was 40% after a median follow-up period of 37.5 months (348).

In general, for radiotherapy, sensitivity of individual hormonal axes to CRT and SRT varies among patients, with the exception of the GH-IGF-1 axis, which is consistently the most sensitive, particularly with regard to the time to deficiency (261, 357–361). With the high rate of pituitary dysfunction after radiotherapy, all patients should be counseled on the importance of a neuroendocrine evaluation and surveillance.

*b. Neurocognitive complications.* Multiple cranial nerves, including II (optic), III (oculomotor), IV (trochlear), V (trigeminal), and VI (abducens), by virtue of their location in the parasellar and suprasellar regions, are at risk of injury from inadvertent irradiation (279–290). The mechanism of radiation injury to the cranial nerves is among the critical determinants of the feasibility of pituitary radiotherapy. Most of this damage is thought to be secondary to the damage of small vessels and protective Schwann cells or oligodendroglia. There is a difference in the tolerance of the different cranial nerves, with the optic nerve, being a sensory nerve, tolerating the least amount of radiation, and the nerves in the parasellar region, the facial nerves and the lower cranial nerves, tolerating higher doses of radiation (279–290). This may be due to the fact that the optic nerve is actually comprised of fiber tracts of the central nervous system. Clinical experience suggests that these specialized sensory nerves do not show a great capacity to recover from injury (290). Optic neuropathy is the most frequent alteration, arising from the irradiation of the optic chiasm or optic nerves, and has been reported after radiotherapy for all types of pituitary tumor (281, 284, 290). The dysfunction of the optic apparatus caused by radiotherapy varies from quadrantopsia to complete visual loss. Early pathological lesions of optic neuropathy are characterized by inflammation, can be asymptomatic, and are generally reversible. By contrast, late pathological lesions occurring months to years after the completion of treatment are characterized by necrosis and vasculitis and are usually irreversible (281, 284, 290). The incidence of optic neuropathy depends on various aspects of the treatment, including the number and size of fractions and the total dose (279–290). After CRT and SRT, in the series including only patients with CD, the incidence of optic neuropathy was consistently 0% (298, 303, 304, 306, 307, 309–311) and 0–11.1% (mean, 1.1%; median, 0%) (291, 292, 318, 320, 322–326, 328–330, 332, 334, 335, 337–344, 346, 348), respectively. For fractionated radiotherapy, CRT, and SCRT, if the total dose delivered is between 45 and 50 Gy, the risk of a deterioration in vision is below 1% (362–364), with an estimated incidence of 0.8–1.3% at 10 years and 1.5% at 20 years, based on data from two large studies including 796 patients (365, 366). For SRS, the maximal radiation dose tolerated by the optic apparatus is controversial, with some studies suggesting a dose tolerance as high as 12–14 Gy (297, 367–369), whereas others limit the dose to 8–10 Gy (296, 370, 371). In particular, Stafford et al (368) have estimated that the incidence of optic neuropathy after GK is 1.7% if the dose to the optic chiasm is < 8 Gy, 1.8% if it is between 8 and 10 Gy, and 6.9% if > 12 Gy. Other risk factors for the development of optic neuropathy include previous radiation therapy, pretherapy visual loss, a tumor size > 10 mm, and a tumor target within 5 mm of the visual pathways (321, 367, 372–374). Improvement in visual acuity and fields has been noted after GK in some patients with pituitary tumors and may be a result of tumor shrinkage and optic nerve decompression (324, 330, 367, 375). The cranial nerves in the cavernous sinus appear to be more resistant to radiation than the optic nerve, but reports of cranial neuropathy including oculomotor, trochlear, and abducens nerves, particularly after repeat SRS, are well-documented. Many of these neuropathies were transient (296, 342, 343, 368, 370). Repeat GK for CD may pose a higher than normal risk of cranial neuropathy (342). The incidence of temporal lobe necrosis after CRT and SRT for pituitary tumors is difficult to determine from the literature. This is a rare complication of pituitary radiotherapy, with a long-term risk of 0.2% in all types of pituitary tumor (284). Temporal lobe necrosis is described in two studies including patients with CD. A study reported that a patient developed normal brain tissue necrosis, but only

after receiving a very high and unusual dose of 66 Gy (307), whereas another study identified two patients with necrosis previously treated with a combination of SRS and CRT (334).

The exposure of large areas of normal brain to radiation, particularly in children, is associated with cognitive impairment (376–379). The effect of small volume irradiation on cognitive function in adults is not clear, given that the current literature on this issue consists mostly of uncontrolled studies, with small patient numbers and heterogeneous patient groups. In addition, only a few trials have used validated batteries of cognitive tests exploring the main domains of cognitive function. Furthermore, the analysis of cognitive decline can be confounded by the effects of other therapeutic interventions, the tumor itself, and the hypopituitarism (380, 381). Therefore, long-term, controlled, prospective studies are required to determine the relative contribution of current radiotherapy techniques on cognitive functions.

*c. Cerebrovascular complications.* In 1999, Brada et al (382) reported that a cohort of patients with pituitary tumors treated with surgery and adjuvant radiotherapy developed a cerebrovascular accident with an actuarial incidence of 4% at 5 years, 11% after 10 years, and 21% after 20 years. The relative risk of developing a cerebrovascular accident in comparison to the general population was 4.1 and was higher in patients undergoing a debulking surgery (382). Seven patients with CD were enrolled in this study, but it was not possible to extrapolate the data from other types of pituitary tumors.

*d. Neoplastic complications.* An increased risk of secondary intracranial tumors has been described in patients with pituitary tumors treated with radiotherapy after surgery (383). In a rigorous discussion regarding the induction of secondary neoplasms in normal tissues within the irradiated field, an appropriate definition is required. Radiation-induced neoplasms must meet the following criteria: 1) the tumor must be within the previous field of irradiation; 2) a sufficient interval must be registered between the irradiation and the development of the new tumor (typically 3 y); 3) the histological characteristics of the new tumor must differ from that of the original lesion; and 4) the patient must not have a disease associated with the development of new tumors, such as neurofibromatosis, Li-Fraumeni syndrome, or tuberous sclerosis (281, 384–386). Actually, the main limitation of many studies evaluating the development of secondary brain tumors after radiotherapy is the lack of a control group that did not receive radiotherapy and a comparison with the general population. Nevertheless, it seems that a strong relationship exists between radiation dose and the development of secondary brain tumors because the risk of a second tumor would seem to be associated with higher radiation doses (287, 387–389). Despite this, there is no threshold dose of radiation at which tumor development is expected to occur (287, 387), and the minimum carcinogenic dose for brain tissue is not known (388, 389). Recently, Ecemis et al (390) considered a cohort of 3664 patients with pituitary tumors included in 16 studies from 1990 to 2012 who had undergone CRT at a median dose of 42.5 Gy. Of these patients, 52 (1.42%) developed secondary brain tumors, among which 51.9% were meningiomas, 15.5% gliomas, 15.3% astrocytomas, and 17.3% other tumors (glioblastoma multiforme, cerebral lymphoma, meningeal sarcoma, pineal tumor, and primitive neuroectodermal tumor). The mean latency period between CRT and secondary tumor development was 19.6 years for meningioma, 11 years for glioma, and 9 years for astrocytoma. In these patients there was a slight but significant 1.3–2.7% increase in actuarial risk of secondary brain tumor (390). The incidence and the actuarial risk of secondary brain tumors are not clear in patients with CD. However, one case of fibroblastic meningioma that developed 25 years after CRT has been described, as well as one case of opticochiasmatic glioblastoma multiforme that developed 6 years after CRT (391, 392). The risk of SRS-associated secondary brain tumors is estimated to be lower than the risk with CRT for the following reasons: 1) high-dose radiation administrated via SRS is cytotoxic rather than mutagenic; and 2) radiation volume in SRS is much smaller than the volume irradiated in CRT (393, 394). A minimum carcinogenic radiation dose for the brain could not be determined precisely. Therefore, it is difficult to predict the relative risk of SRS-associated secondary tumors (388). Two cases of radiation-induced neoplasms have been reported after SRS for pituitary tumors, both in patients with acromegaly; a meningioma developed in one patient, and a vestibular schwannoma in the other, with latency periods of 16 and 19 years, respectively (389). To date, no case of secondary brain tumor after SRT has been reported in a patient with CD. No study has estimated the risk of a secondary brain tumor after SCRT.

### *5. Summary and general considerations on radiotherapy*

Pituitary radiotherapy mainly represents a second-line treatment for patients with CD unsuccessfully treated by surgery. The results of the studies on radiotherapy demonstrated that it is associated with disease control in an average of 64% of patients by using CRT and 61% by using the different types of SRT, and it is associated with disease recurrence in an average of around 16% and 12% of patients, for CRT and SRT, respectively.

The studies on the use of radiotherapy in CD indicate that radiotherapy can be an effective second-line treatment for patients with CD who have undergone unsuccessful surgery, especially in invasive and/or aggressive tumors. However, radiotherapy is nowadays generally used as a third-line treatment after unsuccessful surgery and the lack of effectiveness of, or presence of intolerance to, medical therapy, which is presently often considered before radiotherapy. Moreover, given the better efficacy and safety profile of pituitary surgery, radiation therapy might be considered as an optional first-line therapy only in selected patients without a clear indication for pituitary surgery—mainly those who have tumors in a surgically inaccessible location such as the cavernous sinus, or in patients with uncontrolled disease and severe comorbidities, with evident contraindications for surgery. The use of radiotherapy as first-line therapy has become an even rarer event with the incremental number of choices of medical treatments, which are able to control at least a subset of patients, while acting at the tumor level, or which are able to control clinical syndrome in a great majority of patients while acting at the adrenal or peripheral level. However, in any of these clinical situations, considering the time elapsed between the administration of radiotherapy and the onset of effect, radiotherapy can be considered a reasonable treatment option when performed in conjunction with medical therapy, or even adrenalectomy, to achieve a relatively rapid lowering of cortisol levels.

SRS is the most common type of radiotherapy used for persistent or recurrent CD, and it represents the best choice in case of small postsurgical remnants with a good target definition and sufficient distance from the optic chiasm to minimize unintentional irradiation to local neural and vascular structures, especially to optic apparatus. It is noteworthy that tolerable distance is a function of the degree to which a dose plan can be designed to deliver a suitable radiation dose to the tumor yet spare the optic apparatus. Although most studies suggested 5 mm as an acceptable distance, on the basis of the planned maximal radiation dose for the target and the reached margin dose, a distance of 3 mm, or even 1–2 mm, could be considered plausible in specific cases. Without achievement of a suitable SRS dose plan, an alternative treatment modality, such as fractionated radiation therapy, should be chosen. Indeed, SCRT may represent an alternative choice in cases with large tumors close to the optic chiasm or different neural and vascular surrounding structures. No study is available on the utility of SRT in the treatment of patients with occult tumors, namely those patients in whom no abnormality appears on pituitary imaging.

Despite the initial enthusiasm for SRT, in particular for GK, SRT does not appear to be more efficacious than CRT in CD, with no clear difference in the time of decline of cortisol levels compared to CRT. Moreover, longer-term follow-up studies are necessary to determine the durability of the initial remission and the possibility of recurrence after SRT, although it remains a good modality of radiotherapy for adjunctive therapy in CD. No prospective studies comparing the outcome of the different radiation delivery methods used in SRT with regard to the overall efficacy are presently available.

The main limitations and drawbacks of pituitary radiotherapy, considering the historical CRT but also the modern SRT, are the time elapsing between the administration and complete efficacy of the treatment, and the complications, the most common of which is the hypopituitarism that occurs in a great majority of patients and develops a long time after radiotherapy.

### C. Adrenal surgery

Adrenal surgery represents an alternative secondary approach for patients with CD unsuccessfully treated by pituitary surgery, especially for those refractory to a number of previous treatments, or those who require an immediate reversal of hypercortisolism because of the presence of prolonged and severe disease (1, 2, 7, 84–88, 264–270, 279–290). Adrenal surgery is generally considered as a bilateral adrenalectomy, which consists of the removal of both adrenal glands aiming at inducing an immediate suppression of cortisol production and rapid improvement of the clinical picture. However, unilateral adrenalectomy, which aims at removing only one adrenal gland to preserve an endogenous cortisol production, followed by CRT, has also been performed, and it has been considered an alternative to bilateral adrenalectomy in a select group of patients with CD (395–398).

#### *1. Bilateral adrenalectomy*

In the past, bilateral adrenalectomy was widely used as a primary therapy in CD, before the technical improvements of pituitary surgery. Currently, bilateral adrenalectomy has a secondary role, and it is reserved only for patients with unsuccessful pituitary surgery, being used as an alternative or adjuvant treatment of pituitary radiotherapy, especially if patients are refractory or intolerant to medical therapy. In addition, bilateral adrenalectomy has an important role in patients with prolonged severe disease, but without clinical contraindications for surgery, who are likely to benefit from a rapid and definitive control of hypercortisolism, as well as in patients who might wish to avoid the risk of hypopituitarism that is associated with radiation therapy, including those at a reproductive age wishing to preserve their fertility, which can be invalidated either by pituitary surgery or radiotherapy. Two

different techniques have been used to remove the adrenal glands. The laparoscopic technique is the most recent and the most commonly used approach nowadays, and it is considered the standard approach to adrenal surgery. The laparotomic technique represents the original approach to adrenal surgery, but it is currently used only in cases of contraindication for laparoscopic surgery (399–401).

Twenty-eight studies, published between 1972 and 2014, describe the results of 713 CD patients treated by bilateral adrenalectomy, with a mean follow-up period of 71.8 months (range, 0.8–612 mo; median, 85.7 mo) (402–429). However, considering that 12 patents appear to be included in two different studies, the real number of different patients included in these studies is likely 701.

Table 8 summarizes the results of the studies evaluating the outcome, in terms of efficacy and/or safety, of bilateral adrenalectomy in CD.

Twelve studies include patients treated by laparoscopic adrenalectomy (412, 414–418, 420, 423, 424, 426, 428, 429), 11 studies include patients treated by open adrenalectomy (402–411, 419), whereas five studies include patients treated by both a laparoscopic and an open adrenalectomy (413, 421, 422, 425, 427). Overall, in the studies involving only patients with CD, bilateral adrenalectomy is effective in controlling hormone excess and clinical syndrome in 78.9–100% of patients (mean, 96.8%; median, 100%) (402–410, 412, 414–425, 428, 429); disease persistence or recurrence was observed in 0–12% of cases (mean, 1.7%; median, 0%) (402–410, 412, 414–425, 428, 429), although <1% of these patients had clinical symptoms or signs of hypercortisolism (418, 423). The relapse of hypercortisolism is generally due to the presence of adrenal rests that have escaped the surgeon's knife and that have been attributed to technical difficulties such as intraoperative bleeding and poor visualization due to scar tissue (399–401, 430). Alternatively, it might be the consequence of adrenal accessory glands or adrenal rest tumors located in retroperitoneal tissue, kidney, mediastinum, or genital organs that have regrown under the stimulatory action of chronically and highly elevated ACTH levels after bilateral adrenalectomy (87, 430). Bilateral adrenalectomy, in the studies involving only patients with CD, was associated with a mortality rate ranging between 0 and 11.1% (mean, 1.8%; median, 0%) (402–406, 408–429), with a rate of perioperative complications ranging between 0 and 44.4% (mean, 11.9%; median, 9.1%) (402–406, 409, 410, 412, 415, 417, 419, 420, 424–426). Presumably as a result of the removal of negative feedback inhibition after adrenalectomy, the prevalence of Nelson's syndrome (NS), recently renamed as corticotroph tumor progression and defined as the growth of the pituitary corticotroph tumor, ranged from 0 to 34.6% (mean, 18.6%; median, 22.2%) in 16 studies in which this complication was described (402–407, 409–412, 418, 419, 424–426, 428).

*a. Laparoscopic bilateral adrenalectomy (LBA).* LBA has become the standard approach to bilateral adrenalectomy, and in specialized centers there has been a gradual shift from open to laparoscopic adrenalectomy (399–401). The advantages with LBA compared to the open approach include reduced recovery time, hospitalization time, and perioperative complications (especially wound-related). Contraindications to a laparoscopic approach include the patient's physical characteristics, primarily obesity, and scarring due to previous surgery. Indeed, marked visceral adiposity and adhesions from previous abdominal operations can hinder the identification of the anatomy and make the dissection more difficult during a laparoscopic surgery (399–401). In 11 out of 12 studies, which included only patients who underwent laparoscopic adrenalectomy, and in four out of five that included patients who underwent an open or laparoscopic adrenalectomy, the remission rate was 100% over a mean follow-up period of 32.7 months (412–418, 420–425, 428, 429). The mortality rate ranged from 0 to 5.9% (mean, 1.3%; median, 0%) and was correlated with cardiovascular events, mainly myocardial infarction (418, 423). Laparoscopic adrenalectomy has been associated with a rate of perioperative complications ranging from 0 to 44.4% (mean, 15.4%; median, 11.5%) mainly due to injury of the peritoneal and retroperitoneal organs, including injury to the liver, spleen, pancreas, and colon (412, 415, 417, 420, 424, 426). Conversion to open adrenalectomy is reported in 5.8–33.3% of cases (mean, 17.4%; median, 18.2%) and is mainly induced by vascular injury and uncontrollable bleeding from smaller vessels, followed by organ injuries, intra-abdominal adhesions, and obesity (415, 418, 420, 421, 423). Late complications, rarely reported by one or more studies, included deep vein thrombosis (2.9–40%) (422, 423), port-site incisional hernia (6.6–11.1%) (424, 426), and wound hematomas (1.5%) (423). The mean hospitalization time in the laparoscopic studies was 5.3 days (range, 2.7–9.9 d) (412–414, 416, 417, 420–422, 427, 429). No studies on LBA in a series of children with CD are currently available.

*b. Open bilateral adrenalectomy (OBA).* OBA represents the first approach to bilateral adrenalectomy, but it is now used in cases of contraindications for LBA or in cases of an absence of a surgical expert. In 11 studies, which included only patients who underwent laparotomic adrenalectomy, and in four studies that included patients who underwent open or laparoscopic adrenalectomy, the remission rate ranged from 78.9 to 100% (mean, 94.2%; median,

**Table 8.** Results of the Studies Evaluating the Outcome of Bilateral Adrenalectomy in Patients With CD

| First Author, Year (Ref.) | No. of Patients | Follow-Up, mo | Approach | Remission Rate, % | Recurrence Rate | Time to Recurrence, mo | Perioperative Mortality, % | Postoperative Hospitalization, d | Complications, % | Corticotroph Tumor Progression, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Ernest, 1972 (402) | 44 | R:24–180<br>M:102 | OA | 95.4 | 9.5 | M:20.5 | 6.8 | NA | 9.1 | 9.1 |
| Scott, 1977 (403) | 28 | R:1–240<br>M:102<br>m:90 | OA | 89.3 | 0 | NA | 3.4 | NA | 38 | 3.6 |
| Tomita, 1981 (404) | 19 | NA | OA | 78.9 | 0 | na | 10.5 | NA | NA | 5.3 |
| Urbanic, 1981 (405) | 27 | M:94.5 | OA | 92.6 | 12 | M:49.3 | 0 | NA | 0 | 22.2 |
| Kelly, 1983 (406) | 43 | R:12–240<br>m:120 | OA | 88.4 | 5.3 | M:24 | 4.7 | NA | 7 | 25.6 |
| Pelkonen, 1983 (407) | 27 | R:48–348<br>M:144 | OA | 88.9 | 4.2 | 36 | 5.7* | NA | 11.4 | 22.2 |
| Welbourn, 1985 (408) | 79 | M:135 | OA | 94.9 | 1.3 | NA | 2.5 | NA | NA | NA |
| McCance, 1993 (409) | 26 | R:7.2–229<br>m:63 | OA | 100 | 0 | na | 0 | NA | 15.4 | 34.6 |
| O'Riordain, 1994 (410) | 25 | R:47–90<br>m:62 | OA | 100 | 0 | na | 0 | NA | 0 | 15 |
| Jenkins, 1995 (411) | 37 | m:120 | OA | NA | NA | NA | 0 | NA | 32.6* | 28.9 |
| Bax, 1996 (412) | 4 | M:10 | LA | 100 | 0 | na | 0 | R:1–18<br>M:6.5<br>m:3.5 | 25 | 0 |
| MacGillivray, 1996 (413) | 8 | NA | 4OA 4LA | NA | NA | NA | 0 | M:7.9OA*<br>M:3LA* | 55.6OA*<br>21.4LA* | NA |
| Fernandez- Cruz, 1996 (414) | 6 | M:9.19 | LA | 100 | 0 | na | 0 | R:2–9<br>M:6.33 | 13.3* | NA |
| Chapuis, 1997 (415) | 10 | NA | LA | 100 | 0 | na | 0 | R:4–8, m:6 | 10 | NA |
| Ferrer, 1997 (416) | 1 | NA | LA | 100 | 0 | na | 0 | R:3–8<br>M:5.75 | 25* | NA |
| Lanzi, 1998 (417) | 4 | R:6–23<br>M:13.8<br>m:13 | LA | 100 | 0 | na | 0 | R:4–5<br>M:4.75<br>m:5 | 0 | NA |
| Acosta, 1999 (418) | 21 | NA | LA | 100 | 0 | na | 4.8 | R:3–17<br>m:6 | 20.7* | 4.8 |
| Negesser, 2000 (419) | 44 | R:12–478<br>M:228 | OA | 95.5 | 4.8 | NA | 0 | NA | 0 | 9.1 |
| Vella, 2001 (420) | 12 | R:14.4–58.8<br>M:33.6 | LA | 100 | 0 | na | 0 | R:2–5, M:2.7 | 0 | NA |
| Porpiglia, 2004 (421) | 16 | NA | 5OA 11LA | 100 | 0 | na | 0 | M:14.5OA*<br>M:5.7LA* | 25 | NA |
| Mikhail, 2006 (422) | 12 | M:31.2 | 7OA 5LA | 100 | 0 | na | 0 | M:11OA*<br>M:3LA* | 71OA*<br>60LA* | NA |
| Chow, 2008 (423) | 42 | NA | LA | 100 | 4.8 | NA | 0 | R.3–29<br>M:5.5 | 20.6* | NA |
| Smith, 2009 (424) | 40 | R:2.4–122<br>M:60 | LA | 100 | 0 | na | 0 | R:3–54<br>m:6 | 17.5 | 32.5 |
| Ding, 2010 (425) | 43 | R:14–92<br>M:48.5 | 11OA<br>32LA | 100 | 0 | na | 0 | R:3–27<br>m:9OA<br>m:4LA | 11.6 | 27.3 |
| Tiyadatah, 2012 (426) | 9 | R:6–73<br>M:32.6 | LA | NA | NA | NA | 11.1 | NA | 44.4 | 33.3 |
| Bulus, 2013 (427) | 35 | NA | 18OA<br>17LA | NA | NA | NA | 0 | R:4.4–12<br>M:7.1OA*<br>M:5.1* | NA | NA |
| Osswald, 2014 (428) | 34 | R:0.8–612<br>m:132 | LA | 100 | 0 | na | 5.9 | NA | 6* | 24.1 |
| Raffaelli, 2014 (429) | 17 | R:2–98<br>M:33 | LA | 100 | 0 | na | 0 | R:2–22, M:9.9 | 25.6* | NA |
| **Total** | **713** | **R:0.8–612<br>M:71.8<br>m:85.7** | | **R:78.9–100<br>M:96.8<br>m:100** | **R:0–12<br>M:1.7<br>m:0** | **M:32.4<br>m:30** | **R:0–11.1<br>M:1.8<br>m:0** | **M:10.1 OA*<br>M:5.3 LA** | **R:0–44.4<br>M:12.7<br>m:9.6** | **R:0–34.6<br>M:18.6<br>m:22.2** |

Abbreviations: OA, open adrenalectomy; LA, laparoscopic adrenalectomy; NA, not available; na, not applicable; R, range; M, mean; m, median. This table lists the studies addressing the outcome of bilateral adrenalectomy and published between 1972 and 2014, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD.

* Results including patients with adrenal adenoma, and/or aldosteronoma, and/or pheocromocitoma, and/or CS.

95.5%) over a mean follow-up period of 111.1 months (402–410, 419, 422, 425). Disease recurrence was reported in 0–12% of cases (mean, 2.9%; median, 0%) (402–410, 419, 422, 425); mean time of recurrence was reported in only four studies with an average recurrence time of 36.4 months (402, 405–407). The mortality rate ranged from 0 to 10.5% (mean, 2.2%; median, 0%) and was generally correlated with cardiovascular events,

mainly secondary to postoperative hemorrhage (402–406, 408–411, 413, 419, 422, 425, 427). However, it is difficult to attribute the complications to the technical procedure or to the perioperative care, which significantly improved during decades. The percentage of patients experiencing perioperative complications ranged from 0 to 38% (mean, 9.9%; median, 7%), including primarily abdominal bleeding due to vascular injury from adrenal veins (402, 403, 405, 406, 409, 410, 419). Severe perioperative complications include pancreatic fistula and subphrenic abscess (406, 409). The most frequent late complication reported was wound infection (mean, 9.9%; median, 4.5%, range, 3.8–21.4%) (402, 403, 409). Four studies reported the mean time of hospitalization for open adrenalectomy, which was 10.1 days (mean 7.1–14.5 d). These four studies included either patients undergoing open adrenalectomy or patients undergoing laparoscopic adrenalectomy although also including patients not having a diagnosis of CD; the time of hospitalization of the first group (range, 3–5.7 d; mean, 4.2 d) was lower than that of the second group (range, 7.1–14.5 d; mean, 10.1 d) (413, 421, 422, 427). No studies on OBA in a series of children with CD are currently available.

#### *2. Unilateral adrenalectomy*

Unilateral adrenalectomy followed by CRT has been proposed by some endocrinologists, and it is performed in some centers as an alternative to either bilateral adrenalectomy or pituitary radiotherapy as single treatments. The concept behind this approach is to correct hypercortisolism while avoiding an acute adrenal insufficiency and especially corticotroph tumor progression, the main consequences of bilateral adrenalectomy (395–398). Experience with this type of combination therapy is very limited. On the basis of the few studies reported in literature, unilateral adrenalectomy together with pituitary radiotherapy has shown average remission and recurrence rates of 64 and 20%, respectively (395–398), with a low incidence of corticotroph tumor progression and pituitary dysfunction (395–398). These data do not seem to present a real advantage when compared to bilateral adrenalectomy. Presently, this approach is not used as a routine cinical practice.

#### *3. General considerations on adrenal surgery*

Adrenal surgery is generally used with the purpose of performing a bilateral adrenalectomy. This therapeutic approach represents a second- or third-line treatment, after failure of surgery and/or radiotherapy, especially in case of ineffectiveness of, or intolerance to, medical therapy. Bilateral adrenalectomy is associated with definitive disease cure in the vast majority of patients with CD, corresponding to an average of around 97% of cases, and with a disease recurrence in a negligible percentage of patients, corresponding to an average of 2%, despite some sporadic evidence of recurrence in up to 12% of cases. On the other hand, it is associated with the consistent presence of perioperative complications and mortality. Regarding the two different surgical approaches, LBA is associated with reduced recovery time, hospitalization time, and perioperative complications compared to OBA.

The major advantage of bilateral adrenalectomy is the rapid and definitive control of the clinical syndrome together with the rapid improvement or reversal of the comorbidities and prevention of clinical complications associated with the mortality of the disease. The major shortcoming of bilateral adrenalectomy is the development of permanent adrenal insufficiency, which leads to a lifelong requirement of glucocorticoid and mineralocorticoid replacement therapy to prevent a life-threatening adrenal crisis, and which is also associated with an increased morbidity and mortality. Bilateral adrenalectomy is also associated with a risk of corticoptroph tumor progression.

#### *4. Nelson syndrome or corticotroph tumor progression*

NS, or corticotroph tumor progression, represents the most important complication after bilateral adrenalectomy. NS is historically and classically defined as the association of expanding pituitary mass and high circulating ACTH concentrations after bilateral adrenalectomy in patients with CD (431). As a consequence, patients may present clinical and hormonal profiles, which relate to an expanding pituitary mass and/or the effects of the ACTH hypersecretion, mainly skin hyperpigmentation. Mass effects include compression of the optic apparatus and visual field defects, headache, external ophthalmoplegias, and hypopituitarism (431). The prevalence of NS ranges from 0 to 34.6% (mean, 18.6%; median, 22.2%) in the studies, which clearly report this complication of bilateral adrenalectomy (402–407, 409–412, 418, 419, 424–426, 428), with a time interval between the bilateral adrenalectomy and a diagnosis of NS of 0.5–24 years. Studies that have evaluated the incidence of NS are, however, generally characterized by several major limitations: 1) the pituitary tumor was often diagnosed, especially in older series, by sellar x-ray or on the basis of visual defects, or it was not even considered; 2) the ACTH hypersecretion definition is often based on an assessment of skin pigmentation or on various arbitrary cutoff points for plasma ACTH level; and 3) the cohorts of patients often received different treatments, some of which may have directly interfered with pituitary tumor growth. Alternatively, during the inclusion period for these studies, major technical advances occurred, such as pituitary magnetic resonance imaging

(MRI), together with the common employment of TSS instead of TCS. Consequently, data from these studies are difficult to interpret and compare (432).

Recently, the definition of NS has been revisited, using more sensitive diagnostic tools, in particular pituitary MRI, to assess the natural history of the development or the enlargement of the pituitary tumor after bilateral adrenalectomy, a phenomenon that has been named corticotroph tumor progression (432). Corticotroph tumor progression has been defined as the occurrence of a tumor or the growth of a pre-existing tumor documented with a pituitary MRI after a bilateral adrenalectomy. Corticotroph tumor progression has been evaluated in a homogeneous series of 53 patients subjected to bilateral adrenalectomy for CD and followed in a single center. All had pituitary MRI before adrenal surgery, and all were closely followed with annual pituitary MRI and measurements of plasma ACTH levels. The median follow-up after adrenalectomy was 7.1 years (range, 1.1–11). The prevalence of corticotroph tumor progression reached 38% at 3 years, 47% at 7 years, and plateaued thereafter. Factors that were found to be significantly associated with a higher risk of developing corticotroph tumor progression included the duration of CD, the baseline plasma ACTH levels in the year after the bilateral adrenalectomy, and the rate of increase in plasma ACTH levels after surgery (432). The evidence raised from the evaluation of corticotroph tumor progression and the history of NS suggest that the crucial point in the prevention of this complication is a close clinical and radiological follow-up, with recommendations to perform a pituitary MRI 3–6 months after a bilateral adrenalectomy and then yearly (432, 433).

The management of NS or corticotroh tumor progression is still under debate. When there is evidence of limited tumor progression without an anatomical damage, observation and repeated imaging are an acceptable strategy (433–435). Pituitary surgery should be the first-line treatment, particularly in case of compression of the optic apparatus (436–438), with success rates ranging from 10 to 70% (122, 436–440). Overall mortality after surgical management of NS or corticotroph tumor progression is around 5%, with significant morbidity rates including hypopituitarism occurring in up to 69%, cranial nerve palsy in 5%, CSF leak in 15%, and meningitis in 8% of patients (122, 436–439). Radiotherapy may be required in the event of significant tumor progression, despite surgical intervention. CRT has been demonstrated to decrease plasma ACTH levels and induce shrinkage of the pituitary tumor in 93.3% of patients with NS (303). The data on the use of GK, the only type of radiosurgery reported in the management of corticotroph tumor progression, are conflicting, and the remission rate represented by tumor growth arrest and/or decline in circulating ACTH levels, ranges from 14 to 100% (319, 441–445). Although one study showed tumor growth arrest and no tumor regrowth in 100% of patients at 7 years after GK therapy (444), another study showed remission rate after GK to be only 14% (445). GK seems to be more effective in the treatment of corticotroph tumor progression when administered soon after bilateral adrenalectomy and when the anatomical target is clear and discrete (319, 443, 444). There is currently no consensus on the use of neoadjuvant pituitary radiotherapy after bilateral adrenalectomy in patients with CD. Some studies suggest that a lack of prophylactic pituitary radiotherapy is not a risk factor for the subsequent development of corticotroph tumor progression (159, 442, 446, 447). Conversely, a study on 39 patients followed over a period of 15 years after bilateral adrenalectomy demonstrated that none of the patients who received neoadjuvant radiotherapy developed corticotroph tumor progression, compared with 50% of those who did not receive neoadjuvant radiotherapy (448). Similarly, in another study of 56 patients, 25% of the patients receiving prophylactic pituitary radiotherapy developed corticotroph tumor progression, compared with 50% of those who did not receive the therapy (411). Although neoadjuvant pituitary radiotherapy may reduce the occurrence of corticotroph tumor progression in those patients with residual pituitary tumor, the potential benefits of this procedure need to be weighed carefully against the high probability of the development of adverse consequences after the administration of pituitary radiotherapy.

No medical therapy has been shown to achieve control of plasma ACTH levels and tumor growth in patients with NS or corticotroph tumor progression. However, some anecdotal responses were described with dopamine agonists, in particular with cabergoline (449–451). The multireceptor-targeted somatostatin analog pasireotide has shown promising results in an experimental setting (452), and recently, a case with a significant clinical and biochemical response to long-acting release formulation of pasireotide has been reported (453). The peroxisome proliferator-activated receptor (PPAR)-γ agonist rosiglitazone used at a maximum dose was demonstrated to be not effective in controlling corticotroph tumor progression in different patients (454–456). Conversely, temozolomide, an alkylating chemotherapeutic agent that has been used for the treatment of aggressive, as far as for malignant pituitary tumors, has also been reported to be an effective option for the treatment of NS (457–459).

## V. The Medical Therapy of Cushing's Disease

Historically, medical therapy has played a secondary role in the management of CD. Until recently, no available

medical treatment was licensed for CD, although several drugs had demonstrated efficacy in lowering cortisol excess in selected patients with CD. However, the development of novel compounds and the successful use of drugs for different clinical conditions in CD over the last 10 years, as well as the achievement of regulatory approval for specific drugs for the treatment of groups of patients with CD, have significantly increased the role of medical therapy in the management of CD. Medical therapy is presently considered in the following situations: 1) before surgery, as preoperative treatment, especially in patients with severe disease, in order to control cortisol excess and improve the clinical picture before surgical intervention; 2) after surgery as adjuvant treatment in patients with surgical failure or partial success, due to incomplete removal of the pituitary tumor, while awaiting for the decision of a definitive therapeutic approach, including repeat pituitary surgery, pituitary radiotherapy, or adrenal surgery; 3) before, during, and after pituitary radiotherapy as a bridging treatment, while waiting for the complete effectiveness of radiotherapy; and 4) as first-line treatment, mainly in patients without a clear indication for surgery, due to a pituitary tumor that is nonvisible or with an extrasellar expansion or an unfavorable location, or that is invasive of the surrounding tissue, in case of the lack of availability of an expert pituitary surgeon, in addition to patients who display contraindications for surgery or refuse surgery (172, 460–470).

### A. Classification of medical therapy

Medical therapy for CD includes three categories of drugs: 1) adrenal-directed drugs, which block cortisol production through the inhibition of enzymes involved in steroidogenesis; 2) pituitary-directed drugs, which inhibit tumoral ACTH secretion and, secondarily, cortisol production; and 3) glucocorticoid receptor-directed drugs, which peripherally block the activation of the glucocorticoid receptor, without influencing pituitary and adrenal hormone production. Pituitary-directed drugs theoretically represent the most physiological approach to the disease since it is caused by a pituitary tumor; however, adrenal-directed drugs have been the most commonly used drugs in clinical practice.

Figure 5 shows the three categories of drugs and the single agents currently and routinely used in the clinical practice for the treatment of CD.

A recent systematic review on medical therapy in CD graded the quality of supporting data for each type of treatment (468). This analysis showed that most medical agents currently used in the treatment of CD are supported by a low level of evidence. In particular, studies of adrenal-directed drugs are single-center retrospective studies and case series, whereas cabergoline studies are multicenter retrospective or single-center open-label prospective studies including a limited number of patients with CD, and mifepristone studies include a multicenter open-label prospective study on a consistent number of patients that lacks randomization or a control group. Studies of pasireotide include a large multicenter, double-blind, prospective study and, therefore, are associated with a moderate level of evidence, without reaching a high level of evidence because of the lack of a control group (468). Taking into account that retrospective studies or case series are generally not based on predefined temporal end-points and predefined treatment schedules but generally allow patients to continue treatment or to adjust the drug dose until response or withdrawal, these studies may be affected by selection or publication bias. Therefore, it is important that the higher response rates reported in the lower quality studies are considered in the light of these drawbacks (468). On the other hand, the lower response rates reported in the higher quality studies might be influenced by the design of the studies, which include strict criteria for efficacy analysis, such as in double-blind randomized phase III studies (468). Similarly, differences in the accuracy of documenting adverse effects in retrospective studies compared with prospective studies might result in an apparently better safety profile for drugs evaluated in the former, compared with the latter type of study (468). Therefore, this information must be taken into consideration when evaluating the efficacy and safety of the different categories of drugs used in the management of CD.

### B. Adrenal-directed therapy

Adrenal-directed therapy is represented by adrenostatic drugs, or steroidogenesis inhibitors, which inhibit one or more enzymes responsible for the adrenal steroidogenesis, and adrenolytic drugs, which, beyond the effect on steroidogenesis inhibition, induce cell death at the level of the adrenal gland (84, 172, 460–466, 468–475). Adrenal-directed drugs may be highly effective in controlling cortisol excess, but they do not treat the underlying corticotroph pituitary tumor or restore normal HPA axis function. These drugs are effective in most patients in a dose-dependent manner, although a progressive increase of the drug dose may be necessary because of an "escape" phenomenon that may occur, particularly for specific drugs (84, 172, 460–466, 468–475). The use of adrenal-directed drugs is generally temporary, although experience with chronic treatment has been described. Their uses include the preoperative preparation of patients who need to rapidly correct severe complications of the disease, the control of cortisol excess during the period between irradiation and the complete response to pituitary radiother-

**Figure 5.**

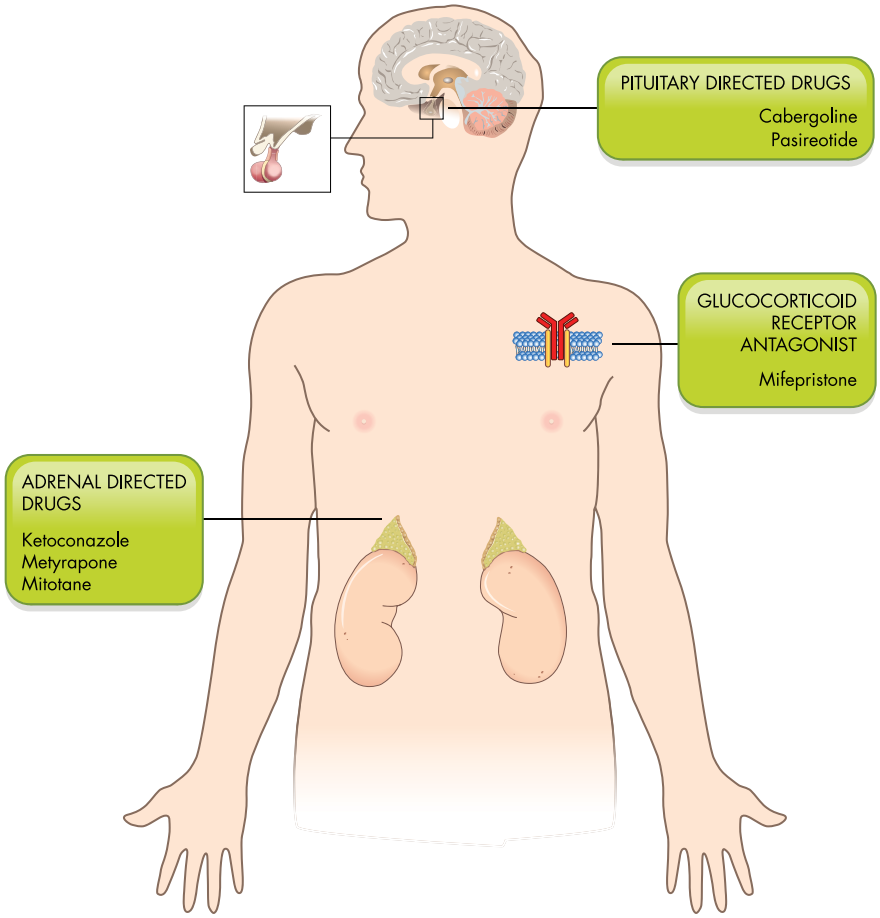


Figure 5. Mechanisms of action and targets for drugs currently used in the treatment of CD.

apy, and whenever a rapid control of the clinical syndrome is required (84, 172, 460–466, 468–475). Despite this, adrenal-directed therapy has not been officially approved for the treatment of CD and has been used as an off-label therapy worldwide, but the European Union (EU) recently approved two agents of this category of drugs, ketoconazole and metyrapone, in the treatment of CS.

**Figure 6** shows the mechanisms of action of the adrenal-directed drugs used in the treatment of CS.

The intrinsic property of these drugs to act at the adrenal level makes them useful not only for CD but also for any type of CS; this is the reason that most clinical studies available in literature concerning these drugs include patients with different types of CS. In the current review on the efficacy and safety of adrenal-directed drugs for CD, wherever possible, data and results from CD patients only have been extrapolated from single studies, whereas data and results from the overall population of patients with CS have been considered when the distinction between CD and the other forms of CS was not feasible. It is noteworthy that treatment with adrenal-directed drugs has been widely used in patients previously treated with radiotherapy as a bridging therapy between irradiation and definitive control of hypercortisolism; therefore, the results of studies where adrenal-directed drugs have been administered with this modality need to be interpreted with caution because it is difficult to exclude a possible effect of radiotherapy.

The most commonly used adrenal-directed drugs are ketoconazole and metyrapone, but aminoglutethimide, trilostane, etomidate, and mitotane have been used or are currently used for specific conditions.

### *1. Ketoconazole*

Ketoconazole is an imidazole derivative used as an antifungal agent and has been shown to have a potent inhibitory effect on steroidogenesis at the level of the adrenal, and also at the levels of gonads, with a negative impact mainly on testicular function (476–478). This action is secondary to the inhibition of cytochrome P450 enzymes, including the cholesterol side-chain cleavage complex,

**Figure 6.**

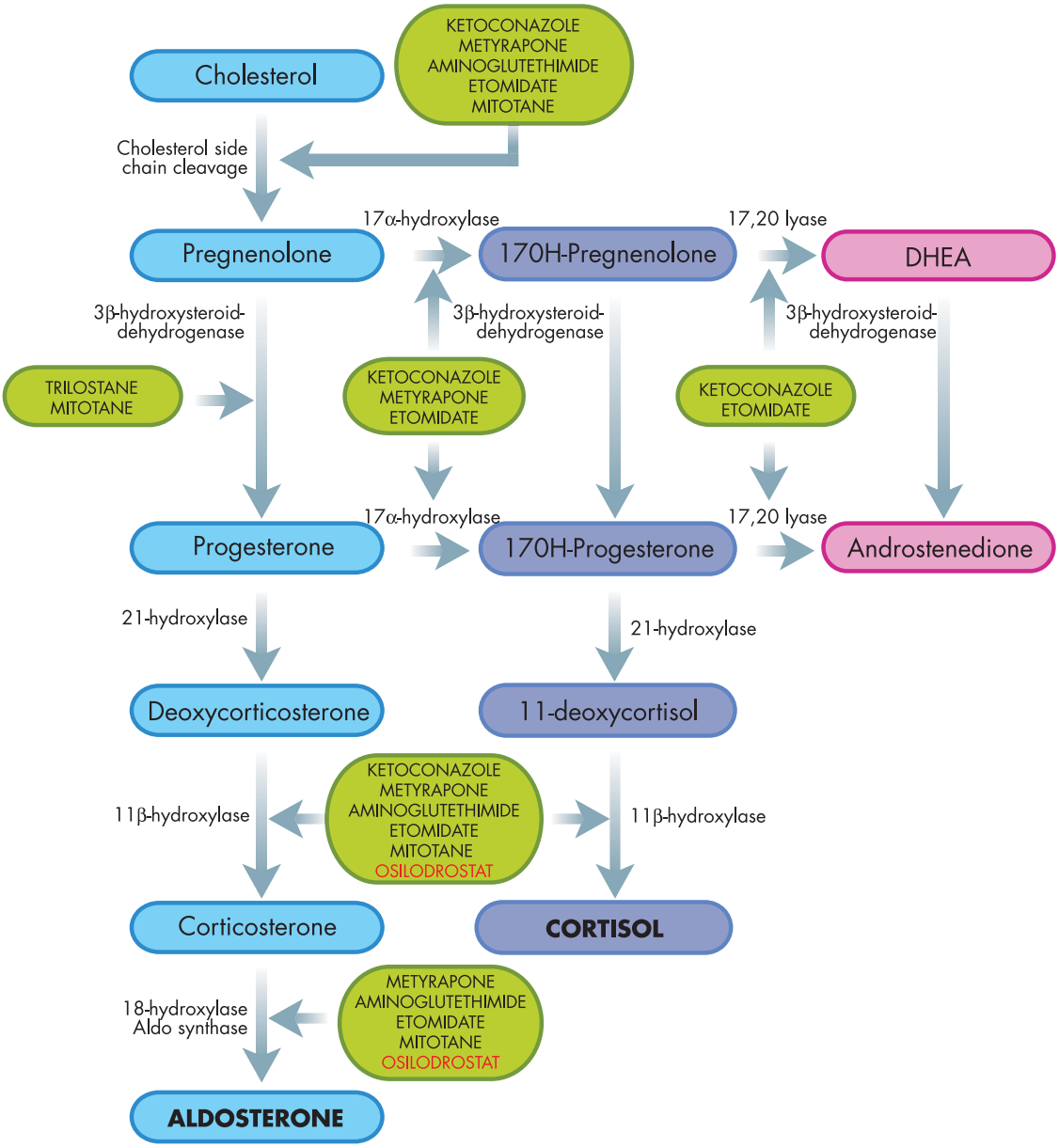


Figure 6. Summary of the site of action of adrenal-directed drugs.

17,20-lyase, 11β-hydroxylase, and 17α-hydroxylase (477, 479, 480). Moreover, a possible but debated direct effect of ketoconazole on pituitary corticotroph tumor cells has been hypothesized. In fact, experimental studies have demonstrated that ketoconazole inhibits ACTH release from rat anterior pituitary cells (481), as well as from a mouse corticotroph pituitary tumor cell line and human corticotroph tumor cell culture (474, 482). In addition, ketoconazole seems to inhibit pituitary corticotropic tumor cell growth, in part inducing apoptosis (474). However, in different studies evaluating basal or CRH-stimulated ACTH secretion in CD patients treated with ketoconazole, no clear blunting of ACTH secretion was found when compared to baseline evaluations (483, 484). In clinical practice, ketoconazole is administered orally at dosages ranging from 200 to 1200 mg/d; it has a rapid action, but its relatively short half-life (mean half-life ~3.3 h) requires a twice/thrice daily dosing during treatment.

The studies of ketoconazole in patients with CD vary significantly for drug efficacy, dose, and duration (485–508). Considering the entire number of studies with CD patients available in the literature, with the exclusion of case reports, ketoconazole has been administered at a dosage ranging from 200 to 1200 mg/d (mean, 683.1 mg/d;

median, 652.9 mg/d), with a follow-up ranging from 0.03 to 156 months (mean, 12.4 mo; median, 10.9 mo) (485–503, 506–508). However, normalization of cortisol was most commonly observed between ketoconazole dosages of 600–800 mg/d (84, 485–508).

Five studies have evaluated the efficacy and safety of ketoconazole treatment in a relatively large number of patients, specifically, more than 10 patients, for a sufficiently long period of follow-up, specifically a mean and/or median follow-up of at least 6 months (494, 501, 502, 507, 508). These studies included a total number of 310 patients with CD; however, the real total number of different patients is likely 272, since 38 of these patients were apparently included in two different studies. Considering these five major studies, ketoconazole has been administered at dosages ranging from 200 to 1200 mg/d (mean, 673.9 mg/d; median, 620 mg/d), with a follow-up ranging from 0.03 to 156 months (mean, 12.6 mo; median, 7.5 mo). According to the results of these studies, ketoconazole treatment controlled cortisol secretion in 44.7% to 92.9% of patients, with mean and median response rates of 64.3% and 50%, respectively (494, 501, 502, 507, 508).

Table 9 summarizes the results of the main studies evaluating the outcome of ketoconazole therapy in CD.

In the first study, Sonino et al (494) considered 34 patients with CS, including 28 patients with CD, with a follow-up ranging from 4 days to 3 years (mean, 8.1 mo; median, 5 mo) and ketoconazole dosages ranging from 400 to 800 mg/d (mean, 564.3 mg/d; median, 600 mg/d), divided in two daily doses. Among these CD patients, 12 were followed for a period equal to or longer than 6 months; nine of them received pituitary radiotherapy during the treatment period. Considering the CD patients, 26 of 28 (92.9%) displayed normalization of urinary cortisol levels; however, for one of the responsive patients (3.6%), ketoconazole was withdrawn after 4 days because of the development of skin rash. An escape from response to ketoconazole treatment, defined as the increase to above normal limits after previous normalization of urinary cortisol levels, was seen in two patients (7.1% of the total and initially responsive population), corresponding to the two patients finally considered not responsive after 12 months of treatment. Adverse effects were observed in 28.6% of patients and were mainly represented by a transient increase in liver enzymes (10.7%), gastrointestinal (GI) disturbances (10.7%), skin rash (3.6%), and worsening of pre-existing gynecomastia (25% of men included in the study) (494).

In the second study, Moncet et al (501) considered 54 patients with CS and evaluated the drug efficacy in 52 patients with CS, with a follow-up ranging from 15 days to 13 years (mean, 9.6 mo) and ketoconazole dosage ranging from 200 to 1200 mg/d (median, 600 mg/d). Sixteen patients had been pretreated with surgery or radiotherapy. This study included 37 patients with CD; however, because they were not distinguished from CS patients, the outcome of ketoconazole treatment in this study is described for the entire population. Normal or subnormal urinary cortisol levels were reached in 44 of 52 (84.6%) patients, whereas a significant decrease in urinary cortisol levels was registered in the remaining eight (15.4%) patients, ranging from 52 to 88% of their initial levels. An escape from the response was observed in six patients (11.5% of the total population and 12.8% of the initially responsive population), including five CD patients and one with undetermined CS; escape occurred after 4–11 months of treatment, although urinary cortisol levels renormalized in three patients after increasing the daily dosage of ketoconazole. Adverse effects were evaluated in the whole cohort of 54 CS patients, were observed in 33% of patients, and included adrenal insufficiency (18.5%), hepatotoxicity (11.1%), skin rash (5.5%), and digestive intolerance (3.7%) (501).

In the third study, Castinetti et al (502) described the results of ketoconazole treatment in 38 patients with CD, among whom 17 underwent unsuccessful pituitary surgery and four were awaiting the effects of radiosurgery, with a follow-up ranging from 0.25 to 72 months (mean, 15.2 mo; median, 12 mo) and ketoconazole dosage ranging from 200 to 1200 mg/d (mean, 636.8 mg/d; median, 600 mg/d). In this study, ketoconazole induced a normalization of urinary cortisol levels in 17 of 38 (44.7%) patients; this percentage rose to 51.5% when five patients were excluded because of drug discontinuation due to intolerance during the first week, and only the patients with long-term follow-up were considered (502). It is noteworthy that during treatment in five patients, a tumor became visible at pituitary MRI, allowing these patients to undergo pituitary surgery 12–30 months after initiation of ketoconazole. An escape from response, defined as an increase in urinary cortisol levels after an initial control, was observed in five of the 38 patients (13.2% of the total population and 22.7% of the initially responsive population) treated for a long-term period. Adverse effects were observed in 29% of patients; these mainly included GI disturbances (18.4%) and increased γ-glutamyl-transferase (10.5%) and transaminase (2.6%) levels (502).

In the fourth study, van den Bosch et al (507) evaluated the efficacy of ketoconazole in 10 patients with CD receiving the drug as presurgical treatment, with a follow-up ranging from 2.4 to 40.5 months (mean, 9.5 mo; median, 5.5 mo) and ketoconazole dosage ranging from 400 to 1000 mg/d (mean, 720 mg/d; median, 700 mg/d). An adequate pretreatment, consisting of the normalization of urinary cortisol levels, was reached in five (50%) of 10 patients (507). The escape phenomenon was not considered in this

**Table 9.** Results of the Main Studies Evaluating the Outcome of Ketoconazole and Metyrapone in CD

| First Author, Year (Ref.) | Study Drug | No. of Patients | Drug Dose, mg/d | Follow-up, mo | Remission Rate, %* | Escape (% of the Total Population)* | Escape (% of Initially Responsive Population) * | Adverse Effects, % |
|---|---|---|---|---|---|---|---|---|
| Sonino, 1991 (494) | Ketoconazole | 28 (9 RT) | R:400–800; M: 564.3; m:600 | R:0.13–36; M: 8.1; m:5 | 92.9 | 7.1 | 7.1 | Transient increase in liver enzymes:10.7; GI disturbances:10.7; Skin rash:3.6; worsening of gynecomastia:25 (of men) |
| Moncet, 2007 (501) | Ketoconazole | 52 (CS), 37 CD (16 S/RT) | R:200–1200; m:600** | R:0.5–156; M: 9.6** | 84.6** | 11.5** | 12.8** | Adrenal insufficiency:18.5**; hepatotoxicity:11.1**; skin rash:5.5**; digestive intolerance:3.7** |
| Castinetti, 2008 (502) | Ketoconazole | 38 (17 PS, 4 RT) | R:200–1200; M:636.8; m: 600 | R:0.25–72; M: 15.2; m:12 | 44.7 | 13.2 | 22.7 | Gastrointestinal disturbances:18.4; increase in gamma-glutamyl-transpherase:10.5; increase in liver enzymes:2.6 |
| Van den Bosch, 2014 (507) | Ketoconazole | 10 | R:400–1000; M:720; m: 700 | R:2.4–40.5; M: 9.5; m:5.5 | 50 | NA | NA | Hepatotoxicity:18.7#; GI disturbances:18.7#; fatigue and malaise:12.5#; exanthema:6.2#; headache:6.2# |
| Castinetti, 2014 (508) (global population) | Ketoconazole | 197 (93 PS, 35 RT) | R:200–1200; M:774.6; m: 600 | R:0.03–135; M: 20.6 | 49.2* | na | na | Increase in liver enzymes:18.4§; gastrointestinal disturbances:13.1§ adrenal insufficiency:5.3§; pruritus:3.7§ |
| *Castinetti, 2014 (508) (long-term population)* | *Ketoconazole* | *51* | | *R:24.1–135; M: 108* | *64.7* | *11.8** | *15.4** | |
| **Total** | **Ketoconazole** | **310** | **R:200–1200; M:673.9; m:620** | **R:0.03–156; M:12.6; m: 7.5** | **R:44.7–92.9; M:64.3; m: 50** | **R:7.1–13.2; M:10.9; m: 11.6** | **R:7.1–22.7; M:14.5; m: 14.1** | **Hepatotoxicity:R:10.7–18.7; M:14.5; m: 13.6; GI disturbances:R:3.7–18.7; M: 12.9; m:13.1; skin rash:R:3.6–6.2; M: 5.1; m:5.5; adrenal insufficiency:R: 5.3–18.5; M:11.9; m:11.9** |
| Jeffcoat, 1977 (524) | Metyrapone | 13 (9 RT) | R:500–4000 | R:2–66; M:18.2; m:11 | 100 | 0 | 0 | Worsening of hirsutism and/or acne:71.4 (of the women); feeling lightheaded:30.8 |
| Thorén, 1985 (528) | Metyrapone | 9 (8 RT, 1 BA) | R:1000–3000; M:1777.8; m:1500 | R:0.6–6.5; M: 1.9; m:1.2 | 77.8 | NA | NA | Dizziness:44.4; increase in facial hair and acne: 12.5 (of the women) |
| Verhelst, 1991 (529) (short-term study) | Metyrapone | 53 | R:500–6000 | R:0.25–4 | 75.5* | na | na | Dizziness:16**; adrenal insufficiency:13.3**; worsening of edema:8**; hypokalaemia: 6.7**; nausea:5.3**; skin rash:4**; hirsutism: 56.2 (of the women treated long-term)** |
| *Verhelst, 1991 (529) (long-term study)* | *Metyrapone* | *24 (24 RT)* | *R:750–4000; m:750* | *R:3–140; m:27* | *83.3* | *4.2** | *4.8** | |
| Valassi, 2012 (506) | Metyrapone | 23 (CS) | R:750–1000 (initial dose) | R:1–30.7; m:4 | 56.5 | 13 | 18.7 | Hypertension:48.4$; edema:20$; severe tiredness:13; hirsutism:11.1 (of the women)£; arthralgia:8.7; headache:4.8$ |
| van den Bosch, 2014 (507) | Metyrapone | 22 | R:1000–6000; M:2477.2; m:2000 | R:1.7–11.6; M: 5.9; m:5.8 | 45.4 | NA | NA | Arthralgia and myalgia:18.2; hypokalaemia:13.6; fatigue and malaise:13.6; nausea and vomiting:13.6; hirsutism:4.5 of the women |
| **Total** | **Metyrapone** | **120** | **R:500–6000; M:2127.5; m:1750** | **R:0.25–66; M: 8.7; m:5.5** | **R:45.4–100; M:71; m: 75.5** | **R:0–13; M:5.7; m:4.2** | **R:0–18.7; M: 7.8; m:4.8** | **Hirsutism:R:4.5–71.4; M:36.1; m:34.3; hypokalemia:R:6.7–13.6; M:10.1; m:10.1; nausea:R:5.3–13.6; M:9.4; m:9.4; fatigue:R:13–13.6; M:13.3; m:13.3; dizziness:R:16–44.4; M: 30.4; m:30.8; arthralgia:R:8.7–18.2; M:13.4; m:13.4** |

Abbreviations: S, previous surgery; PS, previous pituitary surgery; RT, previous or concomitant radiotherapy; BA, previous bilateral adrenalectomy; R, range; M, mean; m, median; NA, not available; na, not applicable. Gastrointestinal disturbances include: nausea, vomiting, diarrhea, and anorexia; Hepatotoxicity includes: increase in transaminase and/or gamma-glutamyl-transpherase.

This table lists the studies addressing the outcome of ketoconazole and metyrapone therapy, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD, with the exception of the study of Valassi on metyrapone, where the entire CS population was considered for the analysis and included in the total calculations. The escape has been reported only for the studies that clearly described the occurrence of this phenomenon.

* For studies, including analysis of global and long-term population of patients with CD, remission rate of the global population and escape rate of the long-term population have been considered for the calculation of total range, mean, and median.

** Results in overall population of patients with CS.

# Results in 16 patients according to the original manuscript.

§ Results in 190 patients.

$ Results in the entire population of patients treated with ketoconazole and metyrapone either as monotherapy or in combination.

£ Results in the entire female population.

study (507). Adverse effects were evaluated in 16 patients, according to the original study, and were reported in 43.7% of patients; they included hepatotoxicity (18.7%), nausea, vomiting and anorexia (18.7%), fatigue and malaise (12.5%), exanthema (6.2%), and headache (6.2%).

In the fifth and most recent study, Castinetti et al (508) described the results of the largest retrospective multicenter study, which reviewed data from 200 patients followed in 14 French centers, namely the French Retrospective Study on Ketoconazole Outcome (FReSKO). In this study, the efficacy analysis was performed in 197 patients who had available urinary cortisol levels during the study. Forty patients received ketoconazole as a presurgical treatment, 32 received ketoconazole as a primary treatment, and 128 received ketoconazole as a secondary treatment (after unsuccessful surgery or radiotherapy), with a follow-up ranging from 0.03 to 135 months (mean, 20.6 mo) and ketoconazole dosage ranging from 200 to 1200 mg/d (mean, 774.6 mg/d; median, 600 mg/d). At the last follow-up, 97 of 197 (49.2%) patients had normal urinary cortisol levels, 51 (25.9%) had at least a 50% decrease, and 49 (24.9%) had unchanged levels.

Figure 7 shows the changes in urinary cortisol levels after ketoconazole treatment in the 197 patients included in the FReSKO study and with available urinary cortisol levels.

The FReSKO study also evaluated the efficacy of long-term treatment in a subgroup of patients with CD. Fifty-one patients were treated with ketoconazole for more than 24 months (range, 24.1–135 mo; mean, 108 mo), and

**Figure 7.**

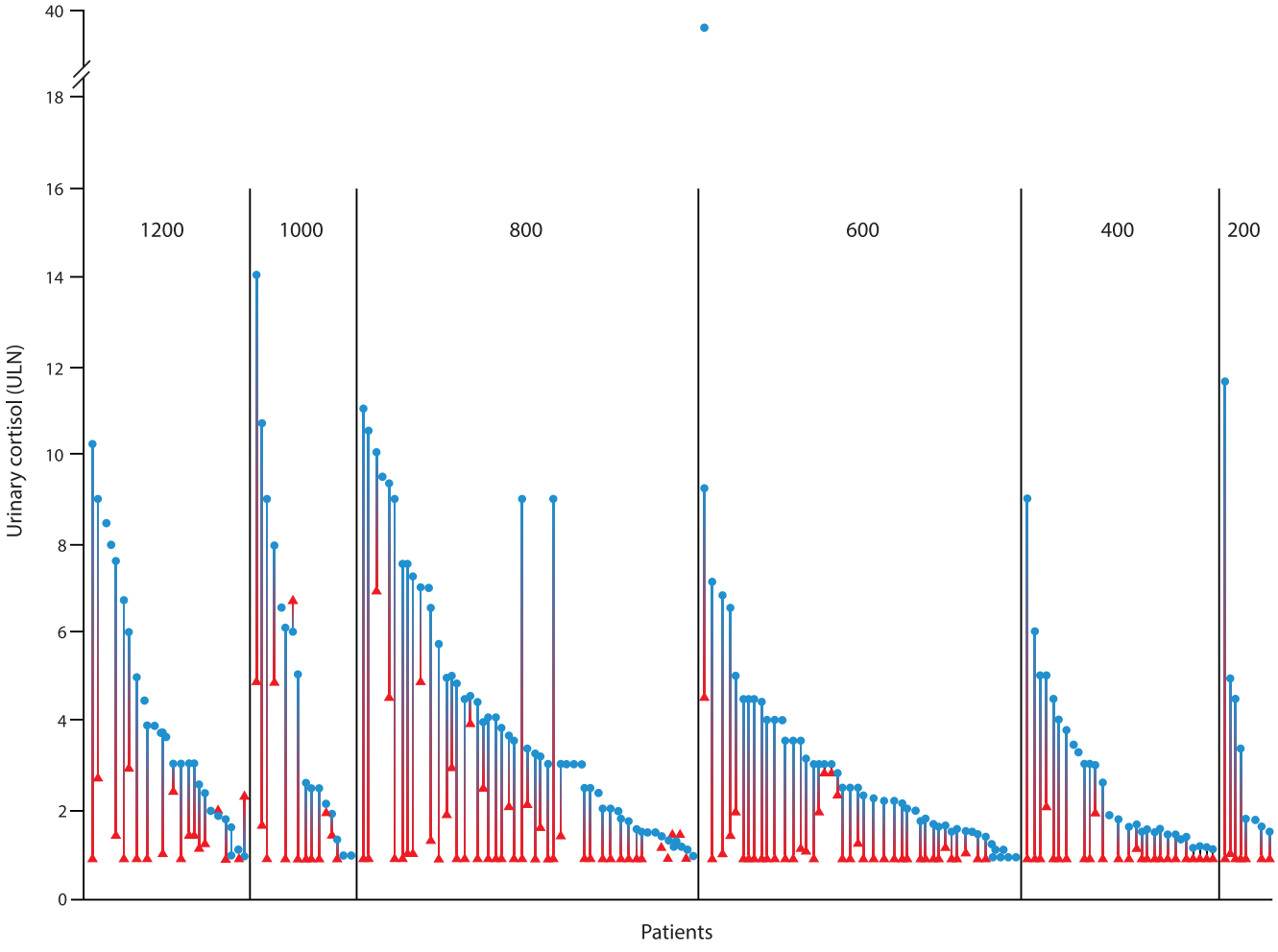


Figure 7. Results of a multicenter retrospective study on ketoconazole (FReSKO study) performed in French centers on 197 patients with CD. The graph shows the daily urinary cortisol (fold upper limit normal [ULN] level) before (circles) and after (triangles) treatment period. Patients were divided on the basis of final dose of ketoconazole (represented by the numbers above urinary cortisol levels in $\mu$g/d) and ordered on the basis of the initial urinary cortisol levels. [Modified from F. Castinetti et al: Ketoconazole in Cushing's disease: is it worth a try? *J Clin Endocrinol Metab.* 2014;99(5):1623–1630 (508), with permission. © The Endocrine Society.].

among these, 33 (64.7%) achieved normal urinary cortisol levels at last follow-up. In this study, six of 51 patients (11.8% of the total population and 15.4% of the initially responsive population) treated for a long period of time had a final increase in urinary cortisol levels despite an initial control, thus experiencing an escape from response. Safety data were available for 190 patients (508). Forty-one patients (21.5%) stopped treatment because of intolerance. Adverse effects were observed with a frequency of 0.6–18.4%. In particular, an increase in liver enzymes was observed in 35 of 190 patients (18.4%), among whom the increase was up to 5-fold the normal values in 30 patients (85.7%), 5- to 10-fold in 4 patients (11.4%), and 40-fold higher than normal values in 1 patient (2.9%). The elevation of liver enzyme levels generally normalized within 1–3 months after ketoconazole withdrawal and occurred at the beginning of treatment or after a dose change, suggesting that a strict follow-up of liver function for 1 month after a dose change could avoid the risk of hepatotoxicity. No fatal hepatitis was observed. The other most frequent adverse effects were GI complaints (13.1%), adrenal insufficiency (5.3%), and pruritus (3.7%) (508).

Generally, in the studies reporting ketoconazole treatment in CS, as well as in CD, control of cortisol secretion was almost always associated with improvement of the clinical picture. In particular, an improvement in the control of blood pressure and glucose tolerance was described in most of the clinical studies (494, 501, 502, 508). In some studies, a decrease in body weight was also found (501, 502). Moreover, reappearance or improvement of menstrual cycles was reported in women of a fertile age with menstrual disorders (494, 501), in some cases accompanied by an improvement of hirsutism (494). Some studies have reported improvement of hypokalemia (494, 508), as well as of myopathy and muscle weakness (494, 501). In addition, one study showed an improvement of bone status in three patients who presented with osteoporosis at diagnosis and with osteopenia or normal bone mass after 36 months of treatment (502). Moreover, one study showed improvement of psychiatric symptoms (494).

The major adverse effect of ketoconazole is hepatotoxicity (84, 472–475, 509). Fatal hepatitis has been reported in a few patients treated with ketoconazole as an antifungal agent (84, 510–512), as well as in one adolescent patient treated for CS (513). In July 2013, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) gave strong warnings about the use of ketoconazole as an antifungal agent, due to its potential for hepatotoxicity. Although fatal hepatitis is a very rare event during ketoconazole treatment for CS, an increase in liver enzymes is frequently observed, ranging from 2.6 to 18.7% of cases in the major studies (494, 501, 502, 507, 508). Generally, this increase occurred at the beginning of treatment and normalized a few months after withdrawal. The other limitation of ketoconazole is the impairment of its intestinal absorption when administered concomitantly with proton-pump inhibitors, which reduce the gastric acidity that is crucial for the dissolution and intestinal absorption of the drug. Therefore, the use of proton-pump inhibitors needs to be considered when choosing the dose of ketoconazole during treatment of CD (514). It is noteworthy that ketoconazole may affect testosterone synthesis at the gonadal level and induce hypogonadism in men, and consequently gynecomastia. This is the reason that ketoconazole is a second-line medical treatment in men with CS (494, 515).

Considering the five studies that have included the largest series of patients with CD and with the longest follow-up, escape from response occurred in 7.1–13.2% (mean, 10.9%; median, 11.6%) of the total population of patients after a period ranging from 3 months to 3 years. These percentages rose to 7.1–22.7% (mean, 14.5%; median, 14.1%) when considering the population of patients initially responsive to treatment (494, 501, 502, 507, 508).

Ketoconazole has been used in a number of pregnant women with good maternal and fetal outcomes (516–518). However, it has also been implicated as a teratogen drug, but a recent population-based case-control study found no association between the use of ketoconazole and congenital anomalies, although only a small number of exposed cases are described (519).

Ketoconazole has also been used successfully in children (316) and in the elderly (498), but conclusions on the safety of ketoconazole treatment in these populations require studies on a larger number of patients.

In summary, ketoconazole induced normalization of cortisol secretion at the end of the treatment period in an average of 64% of patients, with a consequent improvement in the clinical picture, although ketoconazole treatment is associated with an escape from the response in up to 23% patients with initial response to treatment. Therefore, it can be a good temporary option for controlling cortisol excess, but it might be considered a valuable alternative as a chronic treatment for selected patients with CD and, in general, for CS. Ketoconazole is a well-tolerated medication, although attention needs to be paid to liver function, which must be strictly monitored mainly during the first months of treatment. It is preferable for women rather than men because of the occurrence of hypogonadism and its clinical consequences, especially in men. One of the advantages of ketoconazole is its rapid action, whereas disadvantages are the multiple daily dosing and different drug-drug interactions. It is noteworthy that information related to the use of ketoconazole in CD

is supported mainly by noncontrolled retrospective studies, which might have overestimated the efficacy and underestimated the safety of the drug. In November 2014, ketoconazole received authorization from the EMA in the EU with the indication for treatment of endogenous CS.

#### *2. Metyrapone*

Metyrapone is a pyridine derivative with the ability to inhibit 11$\beta$-hydroxylase, the enzyme responsible for the final step of cortisol synthesis, therefore blocking cortisol production (520–522). This compound can also interfere with cortisol formation by inhibiting the cholesterol side chain cleavage complex (522) and, to a lesser extent, 17$\alpha$-hydroxylase and 18-hydroxylase activity (523). In clinical practice, metyrapone is administered orally at a dosage ranging from 500 to 6000 mg/d; it has a rapid action, but the short half-life (1.9 $\pm$ 0.7 h) means multiple daily dosing, generally four times, and up to six times a day (524).

Treatment with metyrapone in CD has been documented in case reports (525–527) and in five main studies including a total of 120 patients with CD (506, 507, 524, 528, 529). In these studies, the dosage of metyrapone ranged from 500 to 6000 mg/d (mean, 2127.5 mg/d; median, 1750 mg/d), with a follow-up ranging from 0.25 to 66 months (mean, 8.7 mo; median, 5.5 mo). According to the results of these five main studies, metyrapone has a remission rate ranging from 45.4 to 100%, with mean and median remission rates of 71 and 75.5%, respectively (506, 507, 524, 528, 529).

Table 9 summarizes the results of the main studies evaluating the outcome of metyrapone therapy in CD.

Jeffcoat et al (524) evaluated the effectiveness of metyrapone treatment in 13 patients with CD, with a follow-up ranging from 2 to 66 months (mean, 18.2 mo; median, 11 mo) and metyrapone dosage ranging from 500 to 4000 mg/d. It is noteworthy that 9 of the 13 patients also received pituitary irradiation. During treatment, all 13 (100%) patients achieved disease control, with mean plasma cortisol levels between 300 and 400 nmol/L (11–14.4 $\mu$g/dL), together with rapid improvement of the clinical picture. Plasma ACTH levels rose after the start of treatment, but in none of the patients was this rise sufficient to cause a loss of disease control (524). The only documented adverse effect was the worsening of hirsutism and/or acne in five of the seven (71.4%) women who were treated for at least 6 months; in one case, this phenomenon was severe enough to lead to treatment discontinuation. Curiously, four (30.8%) patients felt light-headed for several minutes after ingesting each dose (524).

Thorén et al (528) described the results of treatment with metyrapone and/or aminoglutethimide in 15 CS patients, among whom nine patients with CD were treated with metyrapone monotherapy, with a follow-up ranging from 0.6 to 6.5 months (mean, 1.9 mo; median, 1.2 mo) and metyrapone dosage ranging from 1000 to 3000 mg/d (mean, 1777.8 mg/d; median, 1500 mg/d). Eight of the nine patients also received pituitary irradiation, either concomitantly with the medical therapy or more than 6 months before. During treatment, seven of the nine (77.8%) patients achieved a significant reduction in urinary cortisol levels during a generally short period of time (0.6–2.6 mo), with normalization in one (11.1%) patient after a longer period (6.5 mo), together with significant clinical improvement (528). It is noteworthy that the endpoint of this study was not clearly described as the normalization of urinary cortisol levels, but, more generically, a significant reduction of urinary cortisol levels together with the improvement of clinical picture were the criteria considered for defining the responsiveness to the treatment. The escape phenomenon was not considered in this study. Adverse effects included an increase in facial hair and acne (12.5% of the female population) and dizziness (44.4%) (528).

Verhelst et al (529) described the results of treatment with metyrapone in the largest cohort of patients with CD; the study included 91 patients with CS, of whom there were 53 with CD. A short-term study was described in the cohort of 53 patients with CD, whereas a long-term study was described in 24 of these 53 patients with CD, treated for a long period of time waiting for the complete response of radiotherapy. In the short-term study, follow-up ranged from 0.25 to 4 months, and metyrapone dosage ranged from 500 to 6000 mg/d; in particular, metyrapone was given at dosages ranging from 250 mg twice daily to 1500 mg four times daily. During treatment, the individual daily mean serum cortisol levels were reduced to values below 400 nmol/L (14.5 $\mu$g/dL), with a target range of 300–400 nmol/L (10.9–14.5 $\mu$g/dL), in 40 of the 53 (75.5%) patients with CD (529). In the long-term study, 24 patients underwent pituitary irradiation while receiving metyrapone for a long duration of time (range, 3–140 mo; median, 27 mo), at a dose ranging from 750 to 4000 mg/d (median, 750 mg/d), with a subsequent control of cortisol levels in 20 of the 24 (83.3%) patients (529). An improvement of the clinical picture was observed in most patients. Among patients treated long-term, one (4.2% of the total population and 4.8% of the responsive population) had escape from response after 6 years, and therefore treatment was changed to a combination of metyrapone and mitotane (529). It is noteworthy that plasma ACTH levels significantly increased during treatment in 76% of the overall population of patients, and no difference was seen between controlled and uncontrolled patients (529). Adverse effects, which were assessed in 82.4% of CS patients,

included dizziness (16%), adrenal insufficiency (13%), worsening of edema (8%), hypokalemia (6.7%), nausea (5.3%), skin rash during the first week of treatment (4%), whereas hirsutism and/or acne were described in 9 of 16 (56.2%) women treated long-term, although these symptoms were already present in 6 of these women before starting treatment (529).

Valassi et al (506) evaluated the outcome of presurgical therapy with ketoconazole and metyrapone alone or in combination in 62 patients with CS, including 52 with CD. Twenty-three CS patients were treated with metyrapone monotherapy, with a follow-up ranging from 1 to 30.7 months (median, 4 mo), and metyrapone initial doses ranging from 750 to 1000 mg/d. At the end of treatment, 13 of 23 (56.5%) patients had control of cortisol secretion. Considering the whole CS population, an escape from response was observed in three of 23 patients (13% of the total population and 18.7% of the responsive population), corresponding to three patients with CD, treated with metyrapone monotherapy (506). The main adverse effects, evaluated in the entire population of patients treated with ketoconazole and metyrapone as either monotherapy or in combination, were hypertension (48.4%), edema (20%), and headache (4.8%) (506). In addition, specific adverse effects, which were clearly reported for the group of patients treated with metyrapone monotherapy, included severe tiredness (13%), hirsutism (11.1% of the entire female population), and arthralgia (8.7%).

A recent paper by van den Bosch et al (507) evaluated the efficacy of metyrapone as presurgical treatment in 22 patients with CD, with a follow-up ranging from 1.7 to 11.6 months (mean, 5.9 mo; median, 5.8 mo) and metyrapone dosage ranging from 1000 to 6000 mg/d (mean, 2477.2 mg/d; median, 2000 mg/d). An adequate pretreatment, defined as normalization of urinary cortisol levels or a decrease in the mean serum cortisol level below 300 nmol/L (10.9 $\mu$g/dL), was reached in 10 of 22 (45.4%) patients. The escape phenomenon was not considered in this study. Adverse effects included arthralgia and myalgia (18.2%), hypokalemia (13.6%), fatigue and malaise (13.6%), nausea and vomiting (13.6%), and hirsutism (4.5% of the women) (507).

Generally, in the studies reporting metyrapone treatment in CS as well as in CD, control of cortisol secretion was almost always associated with improvement of the clinical picture. In particular, an improvement in glucose tolerance and blood pressure was described in most of the clinical studies (506, 524, 529). Cushingoid features, such as facial plethora and round face, were often found to be improved (506, 524, 529). Moreover, some studies also found improvement in muscle weakness and psychiatric symptoms (524, 529).

The analysis of the studies on metyrapone efficacy in patients with CD shows a frequent increase in ACTH levels, suggesting that ACTH secretion may override blockade of steroidogenesis, at least in some patients, and drive androgen and mineralcorticoid precursor overproduction (474, 475, 506, 524, 529). However, when considering only the five larger studies, an escape from response has been described in 0–13% (mean, 5.7%; median, 4.2%) of the total population of patients. These percentages rose to 0–18.7% (mean, 7.8%; median, 4.8%) when considering the population of patients initially responsive to treatment. On the other hand, hyperandrogenism, a consequence of the ACTH increase, together with its clinical manifestations, represents the reason that metyrapone is generally considered second-line medical therapy in females (474, 475). Mineralcorticoid precursor overproduction is responsible for mineralcorticoid adverse effects observed during metyrapone therapy, namely hypertension, hypokalaemia, and edema that could limit long-term treatment (474, 475).

Metyrapone has been the most commonly used medical therapy in pregnant women with CS. The relationship between metyrapone administration and the incidence of pre-eclampsia, strictly related to the persistence or worsening of hypertension, has been largely debated. However, the coadministration of metyrapone with an antihypertensive drug is recommended to guarantee a safer outcome during pregnancy (518, 530, 531).

Metyrapone has also been used safely in children who await the efficacy of radiotherapy (316). Moreover, a case report described successful control of disease in an elderly woman with CD after long-term treatment with metyrapone (525).

In summary, metyrapone induces normalization of cortisol secretion at the end of the treatment period in an average of 71% of patients, with a consequent rapid improvement in the clinical picture, but it is affected by an escape from the response in up to 19% of patients with initial response to treatment. Therefore, metyrapone can be considered an effective drug in the medical management of CD; it is mainly advised for short-term treatment but is occasionally used for chronic treatment. Although a treatment escape is not frequently observed, adverse effects, especially those secondary to hyperandrogenism, can limit prolonged treatment, especially in female patients, and attention needs to be paid to the possible occurrence of hypokalemia. One of the advantages of metyrapone is its rapid action, but the main disadvantage is the multiple daily dosing. No prospective studies are available for the use of metyrapone in the treatment of CD, so

the results on efficacy and safety of this agent need to be considered with caution. Metyrapone was approved in 15 European countries through a mutual recognition procedure, which ended in April 2014 and was followed by national procedures for the granting of national approvals, with indications for the treatment of CS.

#### *3. Aminoglutethimide and trilostane*

Aminoglutethimide is phenylpiperidine with the ability to block cholesterol side-chain cleavage and the steroidogenic enzymes 11$\beta$-hydroxylase and 18-hydroxylase (474, 475). It was first introduced as an anticonvulsivant and was subsequently employed in the treatment of CS for a limited period. In clinical practice, before its disuse, aminoglutethimide was administered orally. In the studies evaluating the efficacy of aminoglutethimide in patients with CD, the drug dosage ranged from 0.75 to 2 g/d, with a follow-up ranging from 0.1 to 8 months. In these studies, the remission rate ranged from 42.4 to 100% (mean, 69.6%; median, 66.6%) (532–534). In particular, Misbin et al (533) evaluated the efficacy and safety of aminoglutethimide in 66 patients with CS, of whom 33 had CD. This is the biggest series of CD patients treated with aminoglutethimide, and it shows a complete hormone remission in 14 of 33 (42.4%) patients. Adverse effects were reported in 57.6% of all patients with CS included in the study, and mainly comprised adverse effects on the central nervous system, including lethargy, sedation, dizziness, blurred vision, and depression, in 30%, together with skin rash in 21%, gastrointestinal disturbances, including nausea, vomiting, and anorexia, in 12%, myalgia in 6%, and headache in 5% of patients (533). The incidence of adverse effects, particularly those associated with the central nervous system, was generally mild and transient at a usual dose of 1 g/day (533). It is noteworthy that an escape phenomenon has been sporadically described (532–534). Aminoglutethimide is no longer used in the treatment of CD because of an unfavorable adverse event profile (474).

Trilostane is an androstene-carbonitrile derivative agent with the ability to competitively inhibit 3$\beta$-hydroxysteroid dehydrogenase/$\Delta$5-$\Delta$4-isomerase, the enzyme that blocks an early stage of steroidogenesis, with a consequent block of the biosynthesis of entire classes of adrenal hormones (475). A preliminary study suggested that trilostane might be effective in the treatment of CD (535), but these enthusiastic results were not confirmed by a further study (536). In the studies evaluating the efficacy of trilostane in patients with CD, the drug dosage ranged from 120 to 1440 mg/d, with a follow-up ranging from 0.2 to 7.2 months (535, 536). The results of the two studies are completely discordant because a significant decrease of urinary cortisol secretion was found in patients included in the first study (535), whereas no change in cortisol secretion was registered in patients included in the second study (536). Adverse effects were reported, including diarrhea, asthenia, abdominal discomfort, paresthesias, and increased salivation, similar to different steroidogenesis inhibitors (475, 535). An escape phenomenon was not described, but it was considered possible because of an increase in ACTH levels (475). Trilostane is no longer used in the treatment of CD because of its limited efficacy in controlling hypercortisolism compared with different steroidogenesis inhibitors.

#### *4. Etomidate*

Etomidate is an imidazole derivative agent generally used as an anesthetic for the induction of general anesthesia, but it has been occasionally used in the treatment of CD, and in general of CS, for its properties of a steroidogenesis inhibitor (472–475). It has the ability to inhibit the cholesterol side-chain cleavage complex and the enzymes 17-hydroxylase, 11$\beta$-hydroxylase, and 17–20 lyase (475, 537–543). Studies in adrenal cell cultures demonstrated that etomidate is the most potent adrenostatic agent (544). More recent studies showed that etomidate also blocks aldosterone synthase and appears to have antiproliferative effects on adrenal cortical cells (545, 546). Moreover, a low dose of the drug was shown to block cortisol biosynthesis without inducing anesthesia (547). Because the activation of $\gamma$-aminobutyric acid (GABA) type A receptor is thought to be the reason for its anesthetic effects in the central nervous system, the production of novel synthetic compounds similar to etomidate, with high potency in steroidogenesis inhibition and with weak interactions to the GABA type A receptors, is warranted to improve the therapeutic use of etomidate in patients with CS and to minimize its anesthetic effects (548). Etomidate is the only drug used for CS with parenteral administration. It has a very rapid onset of action, leading to significant suppression of cortisol within 6 hours and maximal suppression within 12 hours, whereas its half-life ranges between 3 and 5 hours. Therefore, after a bolus of a nonhypnotic dose, a constant infusion is required for the following 24 hours, when replacement treatment with hydrocortisone starts to be required (475). Because of these peculiar pharmacokinetic properties, etomidate can be particularly useful in patients with acute and/or life-threatening complications of CS, such as serious psychosis and severe hypertension (549–553). Generally, patients with such a severe disease have an ectopic source of CS, but patients with CD treated with etomidate have also been reported (549, 552–556). Etomidate has been shown to rapidly normalize cortisol levels in almost all patients with CD (549, 552–556).

Schulte et al (555) demonstrated that an iv infusion of etomidate at dosages between 0.01 and 0.1 mg/kg/h might be sufficient to inhibit adrenal steroidogenesis within a wide margin of safety. In several subsequent studies, etomidate has been administered as iv infusion at dosages ranging from 0.02 to 0.08 mg/kg/h, occasionally preceded by an etomidate bolus of 0.03 mg/kg (549, 552, 553, 556). Preda et al (549) have recommended low-dose etomidate iv infusion rates of 0.04–0.05 mg/kg/h, with a dose titration dependent on circulating cortisol levels when a partial blockade is required; indeed, in specific cases, the dosage of etomidate might be 0.5–1 mg/h, when a complete blockade is required; in this latter case, iv hydrocortisone is required to prevent or treat adrenal insufficiency induced by the block of etomidate ("block and replace"). Dosages of etomidate need to be individualized on the basis of the clinical picture. Frequent monitoring of circulating cortisol levels is necessary to obtain either complete or partial blockade and to avoid adrenal insufficiency (549). Recently, Soh et al (550) described a protocol for etomidate infusion for the emergency management of hypercortisolism, suggesting a starting dosage of 2.5 mg/h, regardless of the patient's weight, with dose titration up to a maximum of 4 mg/h according to circulating cortisol levels, which can be measured 4 hours after starting etomidate infusion and/or after each dose titration.

Etomidate is unstable in water at physiological pH, so it is available as a preparation in propylene glycol or in lipid emulsion (557). As an anesthetic drug, adverse effects due to etomidate treatment include myoclonus, nausea, vomiting, and dystonic reactions in up to one-third of patients (558). Compared with the lipid formulation, the propylene glycol preparation is more frequently associated with thrombophlebitis and pain on injection, and also with additional adverse effects, such as hemolysis, renal tubular injury, and lactic acidosis at high dosages (559–562). The World Health Organization recommends a maximum daily dose of 25 mg/kg of propylene glycol to reduce the incidence of adverse effects (563). The lipid formulation should be the preferred choice, in order to avoid the adverse effects of propylene glycol vehicle. In elderly and very ill patients, the dose should be reduced because of the decrease in protein binding and renal clearance (548).

In summary, etomidate might be considered an effective drug that is able to rapidly control hypercortisolism; therefore, it is indicated as an emergency drug for the acute control of severe hypercortisolism and its associated severe clinical conditions. It is also indicated in critically ill patients, although careful monitoring of both cortisol levels and electrolyte balance to detect adrenal insufficieny and documentation of the level of sedation are highly recommended during treatment.

### *5. Mitotane*

Mitotane, which is best known by its trivial name o,p'DDD, is a diphenylmethane derivative agent generally used as a chemotherapic drug, but it has been occasionally used in the treatment of CD, and in general of CS, for its adrenostatic and adrenolytic properties (474, 475). Because it is mainly considered an adrenolytic agent, it is mostly used in the treatment of adrenal carcinoma, for which the drug has the official indication. The hypothesis that this drug had cytotoxic effects on the adrenal gland was made in 1949 by Nelson and Woodard (564), who found that dogs treated with dichloro-diphenyl-dichloroethane (DDD) developed adrenal cortex atrophy. This finding led to the development of the derivative of DDD, namely o,p'DDD, in the late 1950s (565, 566). Mitotane has the advantage of having both adrenolytic and adrenostatic activity (567, 568). The adrenolytic activity of mitotane has been documented mainly with animal studies. Indeed, mitotane induces lipid accumulation and atrophy of the adrenal cortex (566), which was found to be more pronounced in the fasciculate and reticularis than in the glomerulosa zone (569). The cytotoxic effect is mediated by the rapid disruption of the mitochondrial cristae followed by mitochondrial swelling, lysis, and cell death (570). The adrenostatic activity of mitotane is based on the inhibition of the cholesterol side-chain cleavage complex, 11$\beta$-hydroxylase, 18-hydroxylase, and 3$\beta$-hydroxysteroid-dehydrogenase, reducing cortisol production (571). Aside from the effect on cortisol production, mitotane induces an increase in cortisol-binding globulin (CBG) levels, so that urinary cortisol levels are the most reliable index of the cortisol secretion rate in assessing the effects of mitotane on cortisol metabolism in CS (572). In clinical practice, mitotane is administered orally at dosages generally ranging from 1 to 12 g/d, but it is associated with delayed efficacy due to its slow onset of action because therapeutic levels are reached in up to 3 months, whereas its long half-life (18–159 d) implies the persistence of significant circulating drug levels and effects for a long time after drug discontinuation, where monitoring of efficacy and safety remain mandatory (573).

Mitotane was used for the first time in the treatment of CD in 1961 by Southren et al (574). In 1969, Temple et al (575) reported that low dosages of mitotane, corresponding to approximately 3 g/d, were able to lower cortisol secretion and the cortisol response to administration of ACTH in patients with CD with a good safety.

The efficacy of mitotane has been reported in several studies (298, 572, 574–582), including, beyond case reports, four main studies (298, 577, 578, 582). These main studies included 173 patients with CD; the drug dose ranged from 0.9 to 12 g, with follow-up ranging from 0.3 to 114.9 months (mean, 15.1 mo)

(298, 577, 578, 582). According to the results of these studies, mitotane has a remission rate ranging from 71.6 to 100% (mean, 86.9%; median, 82.6%).

Table 10 summarizes the results of the main studies evaluating the outcome of mitotane therapy in CD.

Orth and Liddle (298) treated eight CD patients with mitotane, with a follow-up ranging from 12 to 60 months (mean, 36 mo) and dosages ranging from 3 to 6 g/d, given in divided daily doses, generally three doses per day. All eight patients (100%) were considered cured by the treatment. The only adverse effect described was the occurrence of nausea in four (50%) patients (298).

Luton et al (577) evaluated the effectiveness of mitotane in a cohort of 62 patients with CD. These patients were divided into two groups: one including 46 patients treated with mitotane alone, with a follow-up ranging from 3 to 34 months (mean, 8 mo); and one including 16 patients treated with both mitotane and pituitary irradiation (cobalt radiotherapy, 40 to 50 Gy for 45 days), starting either before or during mitotane treatment, with follow-up ranging from 5 to 15 months (mean, 8.3 mo) and for both, a mitotane dosage ranging from 4 to 12 g/d. After a mean follow-up of 8 months, 38 of the 46 (82.6%) patients in the first group achieved remission, whereas all (100%) patients in the second group were in remission. At long-term follow-up, lasting for more than 2 years after the end of the treatment period and mitotane withdrawal, of the 38 patients who were in remission in the first group, 14 (36.8%) remained controlled after 6 to 80 months from treatment discontinuation, 20 (52.6%) patients relapsed, one (2.6%) died, and no examination was performed in three patients. In the second group, 11 (68.7%) patients remained controlled, four (25%) had relapsed, and no examination was performed in one patient (577). A significant increase in plasma ACTH levels was observed in these patients, and the radiological enlargement of both adrenal glands was remarkably reduced in most patients (577). No correlation was found between mitotane dosage and effectiveness (577). Adverse effects were registered for 67 patients and included GI disturbances, such as anorexia (38.8%), nausea (34.3%), and vomiting (10.4%), together with hypersialorrhea in two (3.2%) patients, skin rash in one (1.6%) patient, and chloasma in one (2%) of the 50 female patients. Neurological adverse effects occurred in four patients, including cerebral atrophy in one and cerebral thrombosis in three patients. A significant increase in both serum cholesterol and alkaline phosphatase levels was also found during the study (577).

Schteingart et al (578) studied 36 CD patients treated with both pituitary irradiation (cobalt radiotherapy) and mitotane at an initial dosage of 4 g/d, reaching a maintenance level of 1.5 to 2 g/d during the first 3 to 4 months of therapy. In seven patients, cobalt therapy was started 10 to 12 months before medical treatment; three had under-

**Table 10.** Results of the Main Studies Evaluating the Outcome of Mitotane in CD

| First Author, Year (Ref.) | No. of Patients | Drug Dose, g/d | Follow-Up, mo | Remission Rate, % | Adverse Effects, % |
|---|---|---|---|---|---|
| Orth, 1971 (298) | 8 | R:3–6 | R:12–60; M:36 | 100 | Nausea:50 |
| Luton, 1979 (577) | 46/16 (16 RT)* | R:4–12 | R:3–34/5–15*; M:8/8.3* | 82.6/100* | GI disturbances:10–39; hypersialorrhea:3.2; skin rash:1.6; neurological disturbances:6.4; chloasma:2 (of women) |
| Schteingart, 1980 (578) | 36 (36 RT, 3 BA) | R:1.5–2 | NA | 80.5 | GI disturbances:88.9; impairment of memory:50; increase in cholesterol and triglycerides:55.5; hypouricemia and low serum $T_4$ levels:100; leukopenia:8.3; increase in alkaline phosphatase:5.5; gynecomastia:50 (of men) |
| Baudry, 2012 (582) | 40/27 (27 PS)* | R:1.1–4.3/0.9–6.1*#; M:2.5/2.4*# | R:0.3–114.9/0.8–68.9*#; M:6.9/16.4*# | 71.6 | GI disturbances:47.4/6.6**,#; increase in transaminase:17.1/1.3**,#; increase in γ-glutamyl-transpherase:47.4#; neurological signs:30.3/7.9**,#; lipid disorders:71#; neutropenia:6.6#; skin rash:3.9/6.6**,#; gynecomastia: 17.6 (of men)# |
| **Total** | **173** | **R:0.9–12** | **R:0.3–114.9; M:15.1** | **R:71.6–100; M:86.9; m: 82.6** | **GI disturbances:R:10–88.9; M:46.3; m:43.2; skin rash:R:1.6–3.9; M:2.75; m:2.75; neurological signs:R:6.4–50; M:29.9; m:30.3; lipid disorders:R: 55.5–71; M:63.3; m:63.3; leukopenia:R:6.6–8.3; M:7.4; m:7.4** |

Abbreviations: PS, previous pituitary surgery; RT, previous or concomitant radiotherapy; BA, previous bilateral adrenalectomy; R, range; M, mean; m, median; NA, not available. This table lists the studies addressing the outcome of therapy with mitotane, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD.

* The double sets of data refer to the two different groups of patients included in the study (Luton study: group 1, mitotane alone; group 2, mitotane with pituitary irradiation; Baudry study: group 1, mitotane as first-line treatment; group 2, mitotane as second-line treatment). Remission rates of the two different groups were considered separately for calculation of the total remission rate.

** The double sets of data refer to degree (mild/serious).

# These data refer to the entire population of patients included in the study, comprising not only the 67 patients treated long-term and used for the efficacy analysis but also the 9 patients who receive mitotane only transiently, and therefore excluded from the efficacy analysis, so they are calculated on an overall population of 76 patients.

gone unsuccessful bilateral adrenalectomy, whereas in the remaining 26 patients, cobalt radiotherapy was started concomitantly (total dose of 40 Gy). Among the 36 patients, 29 (80.5%) achieved a clinical and biochemical remission, two (5.5%) had a partial response after 16 months, and four (11.1%) were considered not responsive. One patient (2.7%) died because of an invasive corticotroph pituitary tumor, discovered before starting treatment. It is noteworthy that one of the patients classified as failure achieved clinical and biochemical remission after 17 months of treatment. Among the responsive patients, 17 (47.2% of the total population, and 58.6% of the responsive population) had an early response witin 4 months and maintained remission even 2 years after drug discontinuation, whereas the remaining 12 (33.3% of the total population, and 41.4% of the responsive population) had late responses ranging from 13 to 16 months. Adverse effects included GI disturbances such as anorexia and nausea, which occurred in 88.9% of patients, and impairment of memory, which occurred in 50% of patients. Moreover, six of 12 (50%) males included in the study experienced gynecomastia, associated with increased estrogen production. The elevation of both serum cholesterol and triglyceride levels was observed in 55.5%, whereas hypouricemia and low serum $T_4$ levels occurred in all (100%) patients, suggesting that dose adjustment may be necessary in patients on thyroid replacement therapy. Three (8.3%) patients showed leukopenia, and two (5.5%) patients had elevation of alkaline phosphatase (578).

A more recent study from Baudry et al (582) evaluated the effectiveness and safety of mitotane treatment in 76 patients with CD, although the evaluation of efficacy was performed in 67 patients because nine patients received mitotane transiently, in preparation for pituitary surgery. Among the entire population of 76 patients, 49 were treated with mitotane as the first-line treatment, with a follow-up ranging from 0.3 to 114.9 months (mean, 6.9 mo) and a dosage of mitotane ranging from 1.1 to 4.3 g/d (mean, 2.5 g/d), whereas 27 patients were treated with mitotane as a second-line treatment after TSS, with a follow-up ranging from 0.8 to 68.9 months (mean, 16.4 mo) and a dosage ranging from 0.9 to 6.1 g/d (mean, 2.4 g/d). Disease remission was obtained in 48 of the 67 (71.6%) patients treated for a long period, after a median time of 6.7 months. Of the 19 patients not achieving remission, treatment was withdrawn because of the lack of efficacy in 10 (14.9%) (after a median period of 7.9 mo) or intolerance in nine (13.4%) patients (after a median period of 2.2 mo) (582). Mean plasma ACTH levels were significantly increased during the study. Significant improvement was found in all metabolic parameters after 6 months of treatment, except in systolic blood pressure and the lipid profile (582). The persistence or recurrence of hypercortisolism has also been evaluated during the study. Treatment was discontinued in 44 patients. In particular, 18 patients discontinued mitotane but immediately received an alternative treatment; these patients discontinued mitotane because a pituitary tumor became visible at imaging evaluation (8 patients) and, therefore, underwent pituitary surgery, or because of a relapse of hypercortisolism under mitotane treatment, due to a dose reduction for intolerance (5 patients) or because of patients' choice (5 patients), and were submitted to different treatments. The remaining 26 patients discontinued mitotane without an alternatve treatment because of controlled disease (13 patients), serious intolerance (9 patients), and pregnancy wish (4 patients); among these patients, 24 were followed for a long period after mitotane discontinuation. The follow-up duration after treatment discontinuation ranged from 29 to 126 months (median, 71 mo; range, 29–126 mo). During this follow-up, 17 of 24 (71%) patients showed disease recurrence, with a median time to recurrence after discontinuation of 13.2 months (range, 5–67.9 mo) (582). In 12 patients, a pituitary tumor became apparent on MRI during, or at the end of, mitotane treatment. Adverse effects were divided into two groups: serious events that led to treatment discontinuation, and mild events that allowed for the continuation of treatment. The first group included lipid disorders in 71%, GI disturbances in 47.4%, increase in liver γ-glutamil-transferase and transaminase in 47.4 and 17.1%, respectively, neurological disorders in 30.3%, mild neutropenia in 6.6%, skin rash in 3.9% of patients, and in 17.6% of males, gynecomastia. The second group included neurological disorders in 7.9%, GI disturbances in 6.6%, skin rash in 6.6%, and increased transaminase in 1.3% (582).

Because of its slow onset of action and associated adverse effects, mitotane therapy requires a careful monitoring of drug levels (474, 475). Indeed, a monitoring of plasma levels of mitotane has been demonstrated to be a very useful tool in the optimization of therapy (580). An optimal dose of mitotane for CD has not been established, but it is likely less than that reported for adrenal carcinoma treatment (580, 582). Indeed, a goal in CD patients is a mitotane plasma concentration between 8.5 mg/L and 18 mg/L (582). Because of its adrenolytic effect, mitotane is generally coadministered with exogenous corticosteroids, mainly hydrocortisone, to avoid adrenal insufficiency according to a "block and replace" strategy (577, 582). Because mitotane induces an increase in CBG levels as well as the activation of CYP3A4, the liver enzyme involved in the glucocorticoid metabolism, it is necessary to increase the dosage of hydrocortisone during the mitotane treatment. The escape phenomenon has not been described in

patients treated with mitotane because its mechanism of action prevents the risk of an escape in response attributable to a rise in ACTH that generally occurs in CD as a consequence of cortisol suppression (298, 577, 578, 582).

The use of mitotane has been described in children, in combination with metyrapone and as a bridging therapy while awaiting the complete response to radiotherapy after unsuccessful TSS (315). Its use has also been described in the elderly (579). However, the use of mitotane is absolutely contraindicated during pregnancy and in women desiring pregnancy because it has been demonstrated to be a teratogenic agent (583).

In summary, mitotane is an effective treatment in a great majority, corresponding to 87% of patients with CD, but its use is generally limited because of its significant adverse effects, mainly neurological toxicity. The main advantage of the drug is its adrenolytic action, which might be useful in patients with very severe CD, but the disadvantages include the delayed efficacy, the necessity of a strict monitoring of drug levels, the contemporary need of hydrocortisone replacement, together with the teratogenic action, which precludes its use in women desiring pregnancy.

Mitotane is currently authorized for the treatment adrenal carcinoma by the EMA in the EU and by the FDA in the United States, although in some countries it is authorized for the use of severe CS independently of any association with an adrenal carcinoma.

### C. Pituitary-directed therapy

Pituitary-directed medical therapy targets the source of the disease, the pituitary tumor. Therefore, pituitary-directed drugs represent, at least theoretically, the ideal category of drugs for the management of CD. Presently, however, no pituitary-directed drugs investigated in patients with CD have demonstrated complete efficacy in a large population of patients, and/or an optimal safety profile to be routinely used in clinical practice, and with the exception of pasireotide, no drug has actually been licensed for the treatment of CD (84, 172, 460–469, 471).

Pituitary-directed medical therapy can be divided in two main categories of drugs. The first category is neuromodulatory drugs, which directly influence the HPA axis and include some historical agents, such as serotonin antagonists and GABA receptor agonists, as well as modern agents such as dopamine agonists, mainly represented by cabergoline, and somatostatin analogs, mainly represented by pasireotide. The second category is nuclear receptor ligands, which indirectly influence the HPA axis, because they target different nuclear receptors involved in the regulation of the HPA axis, such as the PPAR-γ agonists and retinoic acid receptor agonists (84, 172, 460–469, 471).

#### *1. Neuromodulatory drugs*

Neuromodulatory drugs include serotonin antagonists and GABA agonists, as well as dopamine agonists and somatostatin analogs. Serotonin antagonists and GABA agonists have been evaluated in the past, but they did not demonstrate sufficiently positive results, so their use was abandoned and they are currently not used in clinical practice. Conversely, the dopamine agonist cabergoline and the somatostatin analog pasireotide have been tested in the last decade and have demonstrated a good performance in disease control, so they are currently used in clinical practice. However, cabergoline, for which efficacy has been demonstrated by single center or multicenter prospective studies in a small population of patients with CD, is currently used as off-label treatment for CD, whereas pasireotide, for which efficacy has been demonstrated by a worldwide, multicenter, randomized, double-blind phase III study, has been approved by the EMA in the EU and by the FDA in the United States for the treatment of patients with CD when surgery has failed or is not an option, and it is currently used as an on-label treatment for CD.

*a. Serotonin antagonists.* Serotonin antagonists, which are mainly indicated for psychosis, hypertension, and allergy, have been proposed for the treatment of CD. Several compounds belonging to the category of serotonin antagonists have been investigated in CD in case reports and limited clinical trials in the past with little evidence of a clinical benefit (84, 461–463, 466, 470). Cyproheptadine, an agent with antiserotonergic, antihistaminic, and anticholinergic properties, and the more selective antiserotonergic agent metergoline have been studied in CD since 1975 (84). More recent evidence refers to different serotoninergic agents, such as ketanserine and ritanserine (84, 462, 470). The potential efficacy of these compounds is based on the assumption that they have a direct serotoninergic control of the central nervous system on the hypothalamic factors that promote ACTH secretion (584), or that they may exert a direct inhibitory effect on CRH and AVP secretion from the hypothalamus (585). Studies in normal subjects have revealed that cyproheptadine treatment induces a decrease in basal ACTH values (586), whereas metergoline treatment induces a decrease in the ACTH response to metyrapone (587). Krieger et al have reported several cases of remission of CD using chronic cyproheptadine therapy (588, 589), with a reported response rate of 30–50% in unpublished cases (590). Three prospective studies with cyproheptadine or metergoline, however, have shown a normalization of cortisol in one of 11 (9%)

patients with CD (591–593). Numerous case reports have documented a remission of CD after cyproheptadine treatment (594–601), whereas others have not confirmed the efficacy of this drug in inducing the normalization of cortisol secretion in CD (602–606). In summary, clinical studies performed in CD patients have demonstrated that the response rate in patients treated with cyproheptadine or metergoline is not higher than 20% in the series of patients published in literature (467). Similar results have been reported in studies with the more selective serotonin antagonists ritanserine and ketanserine, which demonstrated a success rate of around 30% (607, 608). Cyproheptadine, however, has been proposed to be more effective in cases of CD with a presumed hypothalamic origin (404). The main adverse effects were sedation and an increase in appetite (84, 462, 463). The variable efficacy and the occurrence of serious adverse effects have limited the use of serotonin antagonists in the treatment of CD.

*b. GABA agonists.* Valproic acid, which is indicated for epilepsy, is the only GABA agonist that has been proposed as a possible treatment for CD (84, 461–463, 470). Indeed, in the middle of the 1970s, neuropharmacological studies suggested an inhibitory role for GABA in ACTH release (609, 610). After its introduction as an antiepileptic medication, valproic acid was found to lower ACTH levels in patients under chronic treatment (611). It was, therefore, presumed that valproic acid was able to inhibit ACTH secretion by enhancing GABA inhibition of hypothalamic CRH release. In the early 1980s, several reports described patients with CD responsive to treatment with valproic acid (594, 604, 612–614). Despite these, placebo-controlled studies of the acute effects of valproic acid infusion did not demonstrate ACTH-lowering effects in 17 patients with CD (615–617). Longer periods of treatment similarly failed to show a clinical or hormonal improvement in the near totality of patients patients with CD after 3 weeks to 3 months of treatment (618, 619). The lack of efficacy of valproic acid was also demonstrated in a more recent study in which valproic acid was administered at the dosage of 600 mg/d for 3 months in 19 patients with CD, before or after unsuccessful pituitary surgery; no patients normalized their urinary cortisol levels during the period of treatment (620). Specific experience seems to suggest that valproic acid may be effective under particular conditions. Indeed, long-term remission with valproic acid, when used as a monotherapy, has been documented in a patient with cyclical CD after surgical failure (621). Successful treatment has also been described in patients with CD, where valproic acid was coadministered with the steroidogenic inhibitor metyrapone (622). It is possible that valproic acid may alter cortisol metabolism, thereby only indirectly affecting ACTH release. The main adverse effects were sedation, nausea, and hepatotoxicity (84, 462, 463). The scant efficacy and serious adverse effects have limited the use of valproic acid, which does not seem to be of value as a therapy in CD.

*c. Dopamine agonists.* Dopamine is the predominant catecholamine neurotransmitter in the human central nervous system, but it also plays multiple roles in the periphery as a modulator of cardiovascular and renal functions and GI motility and is an important modulator of the endocrine system, specifically the HPA axis (623). Dopamine exerts its functions through its binding to dopamine receptors, including five different subtypes, D1–D5, variably distributed in the different cells, tissues, and organs (623).

The D2 receptor (D2R) is the most important dopamine receptor in the endocrine system, as well as in the pituitary, where it is expressed in the anterior and intermediate lobe of the gland (624, 625). Indeed, D2R is expressed mainly in lactotroph cells (626), but there is evidence of its expression in more than 75% of cells of the anterior pituitary, indicating a broader spectrum of expression extending beyond lactotroph cells and including the corticotroph cell population (627). The expression of D2R has been confirmed in both the corticotroph cells of the anterior pituitary and the melanotroph cells, a peculiar population of corticotroph cells located in the area between the anterior and posterior lobes, corresponding to the residual intermediate lobe of the pituitary gland (628). Moreover, D2R has a variable and heterogeneous expression in nearly 90% of all types of pituitary tumors, but mainly in lactotroph and clinically nonfunctioning pituitary tumors, where D2R expression represents a prerequisite for medical treatment with dopamine agonists (629–634).

D2R expression has been detected more recently in 70–75% of silent or functioning corticotroph pituitary tumors (623, 635). Despite this, no specific signal of the radiolabeled dopamine agonist spiperone has been demonstrated in a series of corticotroph pituitary tumor tissues in receptor-binding studies (636), and no specific signal for D2R has been demonstrated by single-photon emission computed tomography imaging using the radiolabeled dopamine antagonist $^{123}$I-epidepride in the pituitary of patients with CD or NS (637). On the other hand, the presence of a functional D2R has been confirmed by the correlation of the inhibitory effect of dopamine agonists on ACTH secretion and the expression of the receptor, evaluated by molecular techniques, in cells derived from corticotroph pituitary tumors (635).

The dopamine agonists used in the treatment of CD included bromocriptine and cabergoline.

*d. Bromocriptine.* Bromocriptine was one of the first dopamine agonists used in the treatment of pituitary tumors, and it was the most commonly used dopamine agonist until it was almost completely replaced by cabergoline.

Bromocriptine is administered orally either once or multiple times a day, and in patients with CD it has been administered at high dosages ranging from 3.75 to 30 mg/d.

Bromocriptine was found to suppress ACTH secretion from cultured human pituitary tumor cells (638), and to induce cell apoptosis in murine corticotroph tumor cell line AtT-20 cells (639). Dopaminergic modulation of ACTH secretion has been suggested to occur through the regulation of the hypothalamic CRH release in addition to a direct inhibition of ACTH secretion by the corticotroph cells (640).

In clinical practice, bromocriptine treatment has shown variable results in the management of patients with CD, although presently it is not considered an effective therapeutic approach in patients with CD (84, 461, 463, 464, 466, 470, 641). The efficacy of bromocriptine in different studies varied between 0 and 50%, with normalization of urinary and/or plasma cortisol in up to 40% of patients in various case reports and small study series after short-term treatment (642–644). The normalization of cortisol secretion was rarely maintained during long-term treatment (644). Tumor shrinkage was only sporadically detected during treatment with bromocriptine (645). This evidence suggests that only a subset of patients with CD is able to respond to chronic treatment with bromocriptine. Bromocriptine has also been considered in cases of cyclical CD, where its beneficial effect has been suggested to characterize this peculiar disorder (646). Notably, it has previously been speculated that a subset of corticotroph pituitary tumors in CD were presumably originated from the intermediate lobe and were associated with hyperprolactinemia and relative insensitivity to dexamethasone suppression. This subset of tumors could be characterized by bromocriptine responsiveness because they were thought to be under hypothalamic dopaminergic control, being mainly characterized by a corticotroph hyperplasia rather than a real tumor (236). This hypothesis, however, was not confirmed by subsequent studies, which did not find evidence of an intermediate lobe origin of corticotroph tumors (647) and which showed that the response to bromocriptine was associated with both corticotroph hyperplasia and a normal anterior pituitary gland (648). Despite this evidence, the concept of the origin of a subset of corticotroph pituitary tumors by the residual intermediate area of the pituitary gland and their possible sensitivity to dopamine agonists is still a matter of debate.

Bromocriptine has been associated with adverse effects, including nausea, dry mouth, nasal congestion, and postural hypotension, which could induce discontinuation of the treatment. Acute adrenal insufficiency has also been described occasionally (84).

The variability in responsiveness, and the lack of control during long-term treatment, together with the occurrence of adverse effects limited the use of bromocritpine in the management of CD.

*e. Cabergoline.* Cabergoline is a more recently developed, and presently a more commonly used, dopamine agonist in the treatment of pituitary tumors. Indeed, it has been shown to be more potent than bromocriptine in the treatment of prolactin (PRL)-secreting pituitary tumors, as well as nonfunctioning pituitary tumors, and it has also been investigated in CD (631, 632).

Cabergoline is administered orally from once a week to twice a day, and it has been administered in patients with CD at dosages ranging from 0.5 to 7 mg/wk.

Several case reports and small study series demonstrated that cabergoline induced the normalization of ACTH and/or cortisol secretion and/or significant tumor shrinkage in patients with corticotroph tumor progression after adrenalectomy (449, 450) and in patients with silent or functional ACTH-secreting macroadenomas and microadenomas, whether administered alone (649–651) or in combination with ketoconazole (652), as well as in aberrant ACTH-secreting macroadenoma (653) and mixed ACTH and PRL-secreting macroadenomas (654, 655).

Cabergoline treatment has been more extensively evaluated in five different studies performed in a limited but relevant series of patients with CD. These studies included a total of 88 patients with CD, followed for a period ranging from 3 to 60 months, although long-term treatment was performed in a subset of patients for a period ranging from 6 to 60 months (mean, 16.5 mo; median, 12 mo); cabergoline was used at a dosage ranging from 0.5 to 7 mg/wk (mean, 3.1 mg/wk; median, 3.2 mg/wk).

Table 11 summarizes the results of the main studies evaluating the outcome of cabergoline therapy in CD.

In the first open-label prospective study, by Pivonello et al (656), cabergoline was administered to 20 patients with persistent disease after unsuccessful pituitary surgery at the initial dosage of 1 mg/wk. The dosage was increased monthly on the basis of urinary cortisol levels until normalization or until the achievement of the maximal dosage of 7 mg/wk (656). After 3 months of treatment (short-term treatment) with cabergoline at a dosage of 1–3 mg/wk (mean, 2.4 mg/wk; median, 3 mg/wk), responsiveness, in terms of normalization (full response) or significant (≥25%) inhibition (partial response) of urinary cortisol levels, was demonstrated in 15 (75%) patients; among

**Table 11.** Results of the Main Studies Evaluating the Outcome of the Pituitary-Directed Drugs in CD

| First Author, Year (Ref.) | Study Drug | No. of Patients | Drug Dose | Follow-Up, mo | Remission Rate, % | Escape (% of Total Population) | Escape (% of Initially Responsive Population) | Adverse Effects,% |
|---|---|---|---|---|---|---|---|---|
| Pivonello, 2009 (656) | Cabergoline | 20 (PS) | R:1–7; M:4.1; m:3.5 mg/wk# | R:12–24; M:21.6; m: 24# | 40 | 25 | 33.3 | Hypotension and severe asthenia:10; transient moderate asthenia:20; transient mild dizziness and nausea:5 |
| Godbout, 2010 (658) | Cabergoline | 30 (27 PS) | R:0.5–6; M:2.1 mg/wk# | R:12–60; M:37# | 30 | 6.7 | 18.2 | Dizziness and nausea:10 |
| Vilar, 2010 (659) | Cabergoline | 12 (PS) | R:2–3; M:2.8; m:3 mg/wk | M:6; m:6 | 25 | NA | NA | Dizziness and nausea:25 |
| Barbot, 2014 (660) | Cabergoline | 6 (5 PS) | R:0.5–3 mg/wk | M:6; m:6 | 33.3 | NA | NA | None |
| Lila, 2010 (661) | Cabergoline | 20 (20 PS, 5 RT) | R:2–5; M:3.6 mg/wk# | M:12; m:12# | 27.8§ | NA | NA | None |
| **Total** | **Cabergoline** | **88** | **R:0.5–7; M: 3.1; m:3.2 mg/wk** | **R:6–60; M: 16.5; m:12** | **R:25–40; M: 31.2; m:30** | **R:6.7–25; M: 15.8; m: 15.8** | **R:18.2–33.3; M:25.7; m: 25.7** | **Dizziness and nausea:R:5–25; M:13.3; m:10 moderate to severe asthenia: R:10–20; M: 15, m:15;** |
| Colao, 2012 (698) | Pasireotide | 162 (128 PS, 7 RT) | R:300–1200 $\mu$g (600-$\mu$g group); M: 1353 $\mu$g (6 mo), 1569 $\mu$g (12 mo) (900-$\mu$g group); M:1875 $\mu$g (6 mo), 1813 $\mu$g (12 mo) | R:0.03–37.8; M:10.8 | 6 mo:14.6 (600 $\mu$g ), 26.2 (900 $\mu$g); 12 mo:13.4 (600 $\mu$g), 25.0 (900 $\mu$g) | NA | NA | Hyperglycemia:72.8; diarrhea:58; nausea:51.8; cholelithiasis:30.2; elevation in liver enzymes:29; abdominal pain:24.1; upper abdominal pain:9.9; hypocortisolism:8; prolongation of QT interval:1.8 |
| Ambrosi, 2004 (727) | Rosiglitazone | 14 (7 PS) | R:8–16; M:9.1; m:8 mg/d | R:1–7; M:2.6; m:2 | 42.9 | 7.1 | 16.7 | Hypercholesterolemia:7.1 |
| Pecori Giraldi, 2006 (728) | Rosiglitazone | 10 (6 PS) | R:4–16; M:9; m:8 mg/d | R:1.3–8; M:3.7; m:3 | 40 | NA | NA | Weight gain:50; edema:50; worsening of bruisability:20; somnolence:10; hypertensive crisis and precordial pain:10; hirsutism: 12.5 (of the women) |
| Morcos, 2007 (729) | Rosiglitazone | 14 (PS/RT) | R:4–24 mg/d | R:4–12; M:6.8; m:7 | 71.4 | 71.4 | 100 | Elevation in liver enzymes:14.3 |
| **Total** | **Rosiglitazone** | **38** | **R:4–24; M:9; m:8 mg/d** | **R:1–12; M:4.4; m:4** | **R:40–71.4; M: 51.4; m: 42.9** | **R:7.1–71.4; M:39.2, m: 39.2** | **R:16.7–100; M:58.3, m: 58.3** | |
| Pecori Giraldi, 2012 (740) | Retinoic acid | 7 (3 PS) | R:10–80 mg/d | R:6–12; M:10.3; m:12 | 71.4 | 28.6 | 40 | Arthralgia:42.8; dryness of the mouth and conjunctiva:42.8; diarrhea and abdominal discomfort:28.6; worsening of leucocytosis:28.6; headache:14.3 |

Abbreviations: PS, previous pituitary surgery; RT, previous or concomitant radiotherapy; R, range; M, mean; m, median; NA, not available. This table lists the studies addressing the outcome of therapy with pituitary-directed drugs, including those whose entire content was fully available for the authors. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies, considering exclusively those where these parameters were available and were clearly attributable to the only patients with CD. The escape has been reported only for the studies that clearly described the occurrence of this phenomenon.

# Range, mean, and median calculations considered the data on patients in long-term follow-up in these studies.

§ The remission rate was calculated on 18 of the 20 initial patients, excluding the two patients for whom efficacy was attributed to previous radiotherapy.

these, a full response was found in seven (35%) and a partial response in eight (40%) patients. Treatment was continued in the responsive patients for an additional period of 12–24 months (long-term treatment). Among the patients with an initial response, five (25% of the total population, 33.3% of the initially responsive population) had a treatment escape, defined as progressive reinrease in urinary cortisol levels towards their baseline levels, after their previous normalization, whereas two (10%) patients experienced drug intolerance and discontinued cabergoline after 12–18 months of treatment. Therefore, eight of the 15 (53.3%) patients with a short-term response continued to safely respond to cabergoline for a long-term period. It is noteworthy that although five (25%) patients were completely resistant and seven (35%) patients withdrew cabergoline because of treatment escape or intolerance, six of eight patients partially responsive to short-term treatment became fully responsive after increasing the cabergoline dose, and three of them showed a persistent normalization of cortisol secretion during long-term

treatment, suggesting that the cabergoline dose and the period of treatment necessary to normalize cortisol secretion were extremely variable for each patient with CD. The results of the study demonstrated that a cabergoline dosage of 1–7 mg/wk (mean, 4.1 mg/wk; median, 3.5 mg/wk) was able to safely control cortisol secretion in 50% of patients after 12 months of treatment and in 40% of patients at the last evaluation, corresponding to a follow-up of 12–24 months (mean: 21.6 mo; median: 24 mo).

Figure 8 shows the changes in urinary cortisol levels during the 12–24 months of treatment and the differential response of urinary cortisol levels after short-term and long-term treatment in the 20 patients included in Naples cabergoline study.

Treatment with cabergoline improved the clinical picture of the patients, as well as the comorbidities, mainly hypertension and glucose intolerance, and induced tumor shrinkage in four of the eight (50%) patients with a measurable tumor (656). Cabergoline was well tolerated, with the exception of the occurrence of hypotension associated with severe asthenia in two (10%) patients after a prolonged period of treatment at the maximal dose of cabergoline, transient moderate asthenia in four (20%) patients, and transient mild dizziness and nausea in one (5%) patient (656). A subsequent evaluation of the clinical impact of cabergoline treatment in patients with persistent CD after unsuccessful surgery included in this study, and in additional patients with newly diagnosed CD, confirmed the effectiveness of cabergoline in improving the clinical syndrome and comorbidities, mainly hypertension and glucose intolerance (657).

In a second retrospective study, by Godbout et al (658), cabergoline was administered in 30 patients with CD, of whom 27 had persistent disease after surgery and three had newly diagnosed disease. The initial dosage was 0.5–1 mg/wk, which was progressively increased by 0.5 or 1 mg/wk at 1- or 2-month intervals until there was a complete and sustained normalization of urinary cortisol levels (658). After short-term treatment, responsiveness, in terms of normalization (complete response) or a decrease to < 125% of the

**Figure 8.**

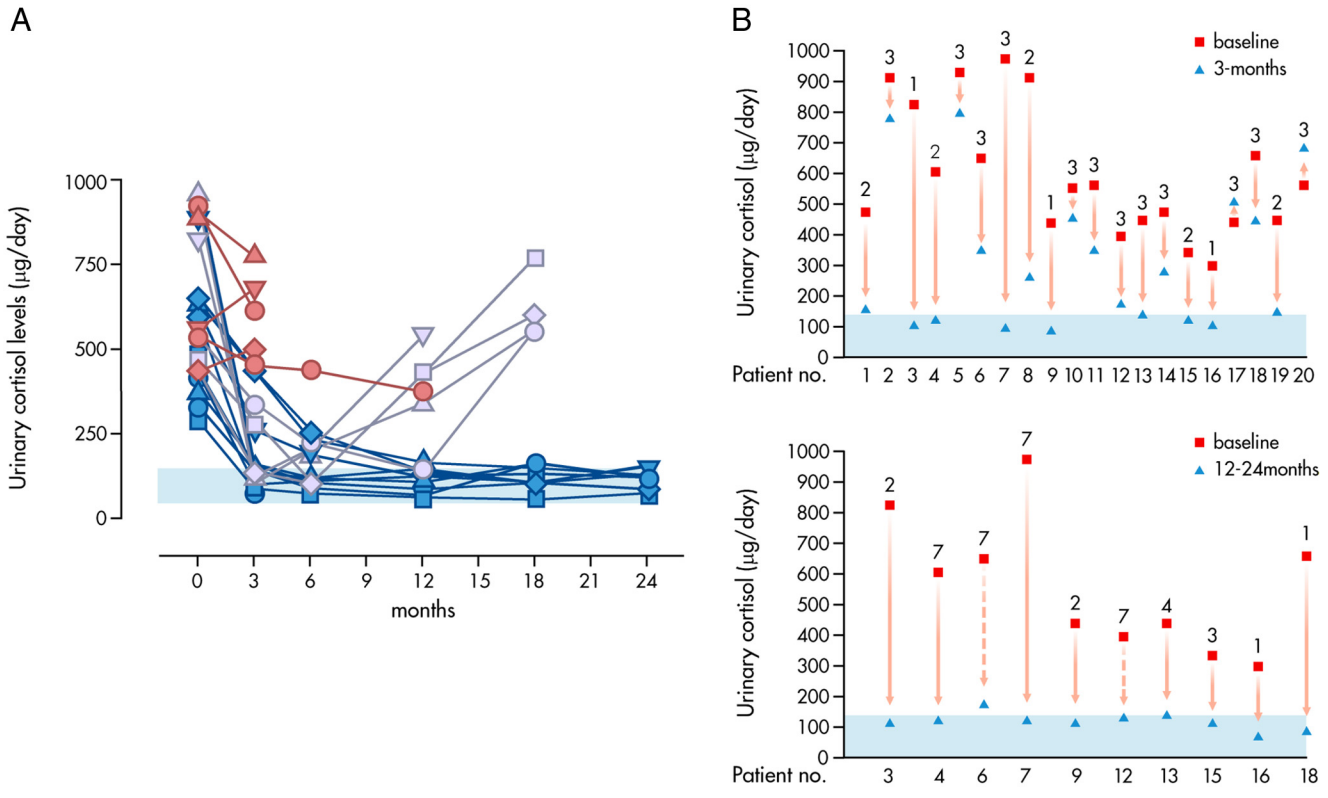


Figure 8. Results of single center prospective open lable study on cabergoline performed in Naples Center on 20 patients with CD. A, Changes in urinary cortisol levels (in $\mu$g/d) during the entire period of the study in the individual patients. B, Response of urinary cortisol levels (in $\mu$g/d) to short-term (upper graph) and long-term (lower graph) treatment in the individual patients. Squares represent the baseline urinary cortisol levels, whereas triangles represent urinary cortisol levels at the end of follow-up. [Modified from R. Pivonello et al: The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. *J Clin Endocrinol Metab*. 2009:94(1):223–230, 2009 (656), with permission. © The Endocrine Society.]

upper limit of normal range (partial response) of urinary cortisol levels, was found in 15 (50%) patients; among these, a complete response was found in 11 (36.7%) and a partial response in four (13.3%). A long-term follow-up of cabergoline treatment at a dosage ranging from 0.5 to 6 mg/wk (mean, 2.1 mg/wk) during a period ranging from 12 to 60 months (mean, 37 mo) showed a persistent efficacy of cabergoline in nine (30%) patients, associated with a progressive regression of clinical symptoms and signs in these responsive patients. An escape from response was only observed in two patients (6.7% of the total population, 18.2% of the initially responsive population) after 2.5 and 5 years of treatment. Cabergoline was well tolerated, with the exception of the occurrence of dizziness and nausea in 3 (10%) patients (658).

These two relevant studies have collectively demonstrated that cabergoline treatment persistently normalizes cortisol secretion without significant adverse effects for a long time period in 30–40% of patients, although further studies are mandatory to evaluate the impact of this treatment on the clinical syndrome and clinical burden of CD. These studies have indicated, however, that cabergoline can be considered a therapeutic option in a subset of patients with CD, especially for those without remission after pituitary surgery.

Two additional studies evaluated the effectiveness of cabergoline treatment in a small series of patients with CD (659, 660). In the study by Vilar et al (659), cabergoline was given at dosages ranging from 0.5 to 3 mg/wk, with final doses ranging from 2 to 3 mg/wk (mean, 2.8 mg/wk; median, 3 mg/wk) for 6 months in 12 CD patients with persistent disease after unsuccessful surgery. Normalization of urinary cortisol levels was observed in three (25%) patients, whereas reductions ranging from 15 to nearly 50% without normalization were observed in the remaining 75% of patients (659). The modest complete response rate in the patients from this study may result from the maximal cabergoline dosage of 3 mg/wk, which is lower than that used in the previous studies, or from the maximal period of treatment, which was no longer than 6 months. The only adverse effect recorded was the occurrence of dizziness and nausea in 3 (25%) patients. Similarly, in the study of Bardot et al (660), cabergoline was given at dosages ranging from 0.5 to 3 mg/wk for 6 months in six patients with CD. Normalization of urinary cortisol levels was observed in two (33.3%) patients, whereas three other patients had a 21–30% decrease of urinary cortisol levels; the remaining patient was completely unresponsive to treatment. No adverse effect occurred during cabergoline treatment. These patients were subsequently treated with ketoconazole (660).

Finally, the most recent study by Lila et al (661), which evaluated cabergoline treatment in CD, did not use urinary cortisol levels, but instead used serum midnight cortisol levels and cortisol after low-dose dexamethasone for monitoring the efficacy of treatment. In this study, cabergoline was given at the initial dosage of 1 mg/wk and a maximal dosage of 5 mg/wk, with the effective dosage ranging from 2 to 5 mg/wk (mean, 3.6 mg/wk), to 20 patients with persistent or recurrent CD for a period of 1 year. Five patients received radiotherapy from 1 to 77 months before enrollment. This treatment induced the normalization of midnight or postdexamethasone cortisol levels in seven of the 20 patients; however, among these seven patients, five had received radiotherapy, which was considered responsible for the cortisol response in two patients maintaining cortisol normalization after 2 months from the drug discontinuation. Therefore, with the exclusion of these two cases, five of 18 (27.8%) patients were considered responsive to cabergoline treatment, confirming that a subset of CD patients might benefit from treatment with cabergoline. No adverse effects have been reported (661).

Considering that cabergoline is effective in controlling cortisol secretion in a subset of patients with CD, it would be important to be able to predict responsiveness. No study has definitely addressed this issue. The acute administration of 1 mg cabergoline with evaluation of 6-hour plasma cortisol has been proposed as an acute test, but although it has been found to predict cortisol response after a short-term treatment, it only seems able to exclude a response to long-term treatment in patients with CD (662). On the other hand, there is some preliminary evidence that seems to support the hypothesis that the origin of corticotroph tumors from the corticotroph cells of the intermediate area of the pituitary gland and/or the expression of the short isoform of the D2 receptor or D4 receptors in the corticotroph tumors seem to be the best predictors of the responsiveness to short-term and long-term treatment with cabergoline, respectively (663, 664). The response of a corticotroph tumor associated with CD to cabergoline could be difficult to evaluate, considering that cabergoline might act not only at the level of the pituitary tumor but also at different levels of the HPA axis. Indeed, dopamine receptors are expressed in the cells of the adrenal gland, including cortisol-secreting cells (665). A decrease in cortisol levels may, therefore, reflect an adrenal response rather than a responsiveness of the pituitary tumor to cabergoline. However, further studies supporting this hypothesis are mandatory in order to draw definitive conclusions.

Recently, cabergoline has been under strict analysis as a potential cause of cardiac valve disease. Two large studies have suggested that cabergoline used at high doses as a treatment for patients with Parkinson's disease is associated with a risk for cardiac valve disease (666, 667). The doses of cabergoline used in the different CD studies were

relatively high (maximal dosage ranging from 3 to 7 mg/wk, compared with 2 mg/wk generally used for the treatment of PRL-secreting pituitary tumors), raising concerns about long-term safety. None of the main studies investigating the use of cabergoline in CD have documented any significant change in the cardiac valves of patients during treatment (657–661). In particular, in a study where patients' cardiac valves were carefully monitored by periodical echocardiography, no development of cardiac valve insufficiency or worsening of previously diagnosed valve insufficiency was documented, except in one patient who had a mild tricuspid regurgitation at baseline and a moderate tricuspid regurgitation with normal pulmonary pressure after 2 years of treatment (656). Although cabergoline treatment seems to be a safe treatment with respect to cardiac valve disease at doses used in CD, serial echocardiographic monitoring might be advisable in CD patients on long-term cabergoline therapy.

Cabergoline has been shown to safely control hypercortisolism during pregnancy in a patient with CD (668), suggesting that cabergoline may be the best choice of treatment for pregnant women with CD.

In summary, cabergoline can be considered an effective pituitary-directed drug, although the currently available studies, which include retrospective and open-label prospective studies in a limited population of patients, report a safe control of the disease at the end of the treatment period in an average of 31% of patients, but cabergoline treatment is associated with an escape from the response in up to 33% of patients initially responsive to the treatment, suggesting that cabergoline is able to control a subset of patients with CD. The advantages of cabergoline are the oral administration and the very good tolerance, whereas the disadvantages are the variable time necessary to reach disease control and the occurrence of escape during long-term treatment. Cabergoline is not approved for the treatment of CD, so it presently represents an off-label treatment.

*f. Somatostatin analogs.* Somatostatin is a peptide hormone with an important role in the regulation of the endocrine system, mainly in the control of pituitary GH secretion and pancreatic insulin secretion (669, 670). Somatostatin exerts its effects through five different somatostatin receptors (SSTR1–5), which are G protein-coupled transmembrane receptors that are widely expressed throughout the body with a variable cell, tissue, and organ distribution (669). Endocrine tumors often express one or more receptor subtypes with different densities (669). The different SSTR subtypes have differential functions and are able to activate various intracellular pathways. Indeed, SSTR1, -2, -4, and -5 are associated with the inhibition of cell proliferation through a phosphotyrosine-phosphatase-dependent MAPK pathway, as well as the serine-threonine phosphatase pathway, whereas SSTR3 activation results in cell death or apoptosis through a phosphotyrosine-phosphatase-dependent mechanism (669, 670). Although the heterogeneity of the studies performed and the differences in methodology have resulted in some contradictory findings, human corticotroph tumors express multiple SSTR subtypes, with SSTR5, -2, and -1 being the most frequently expressed, with the predominant receptor being SSTR5 (671–673).

Somatostatin analogs include the synthetic compounds octreotide and lanreotide, which have been widely used in endocrinology and oncology clinical practice, and the novel synthetic compound pasireotide, which has been recently approved for the treatment of CD, as a second-line treatment in case of failure of pituitary surgery or when surgery is not an option.

The classical somatostatin analogs octreotide and lanreotide are commonly used in the treatment of GH-secreting pituitary as well as gastroenteropancreatic neuroendocrine tumors (674), which frequently express functional SSTRs; they are also proposed for the treatment of nonfunctioning pituitary and neuroendocrine tumors (675). Moreover, somatostatin and octreotide have been shown to inhibit basal and stimulated ACTH secretion in experimental settings in either murine or human corticotroph tumor cells (452, 673, 676–678). Somatostatin analogs have also been tested as a possible treatment in patients with CD, although most of the available data are for octreotide, which is predominantly an SSTR2-selective ligand, having only moderate affinity for SSTR5. Despite this, however, octreotide has been shown to be virtually ineffective in the great majority of patients with CD (679–682).

*g. Pasireotide.* Pasireotide is a new multireceptor-targeted somatostatin analog with a high binding affinity for SSTR5, but also for the SSTR1, -2, and -3 subtypes (683–686). Experimental studies and animal models have implicated both SSTR2 and -5 in the regulation of ACTH release (687–690). Pasireotide inhibits basal and stimulated ACTH release from human corticotroph pituitary tumors and the murine corticotroph tumor cell line AtT-20, but it does not inhibit AtT-20 cell proliferation, nor does it induce apoptosis or inhibit proopiomelanocortin (POMC) synthesis in experimental settings, suggesting a possible blockade of ACTH release or an increased breakdown of ACTH (452, 672, 673). The functional activity of pasireotide compared with octreotide has been found to be 30-, 11-, and 158-fold higher for SSTR1, -3, and -5, respectively, and approximately 7-fold lower for SSTR2 (683). In experimental studies in both human ACTH-secreting tumor cells and the AtT-20 tumor cell line, pasir-

eotide suppressed ACTH secretion and CRH-induced ACTH release to a greater extent than octreotide (452, 673). This finding may be attributed to the relatively low levels of SSTR2 in corticotroph tumors (452). Furthermore, preincubation with dexamethasone did not affect the ability of pasireotide to inhibit CRH-induced ACTH release, whereas the suppressive action of octreotide was virtually lost (452, 673). SSTR2, but not SSTR5, messenger levels were also significantly suppressed after 24 and 48 hours of dexamethasone treatment (673). These findings suggest that glucocorticoids differentially affect SSTR expression, with SSTR2 being down-regulated and SSTR5 being resistant to corticosteroid modulation (452, 673). It can be hypothesized that the sensitivity to somatostatin inhibition of ACTH secretion is observed only when the physiological feedback regulation of ACTH release by glucocorticoids fails, as supported by the absence of any effect on ACTH levels after experimental infusions of natural somatostatin or octreotide in normal individuals (689, 690), as well as by their suppression in patients with adrenal insufficiency or those who underwent adrenalectomy (691–693). A direct effect on transcription or on messenger stability might also be implicated (462). The regulation of the gene promoter sequence of SSTR2 by glucocorticoids has been experimentally demonstrated in the mouse (694). Moreover, in rats, pasireotide inhibited both CRH-induced ACTH secretion and corticosterone release, but octreotide inhibited only ACTH release, and to a lesser extent than pasireotide (695). Recently, pasireotide was shown to suppress cell proliferation (in the range of 10–70%) as well as ACTH secretion (in the range of 23–56%) in human corticotroph tumors (672), but possibly via independent mechanisms because no correlation was found between these effects. Another mechanism for its action might be an indirect influence of decreasing the secretion of pituitary hormones and/or growth factors (696).

Pasireotide is currently administered sc twice a day, and it has been administered in patients with CD at dosages ranging from 300 to 1200 $\mu$g/d.

The use of pasireotide in the treatment of CD was first investigated in a phase II, open-label, single-arm, multicenter pilot study (697). Self-administered sc pasireotide was given to 29 patients at the dosage of 600 $\mu$g twice a day for 15 days. The results demonstrated a reduction in urinary cortisol levels in 75.9% of the patients, of whom 37.9% displayed a $>$ 50% decrease and 17.2% achieved a complete normalization of urinary cortisol levels; a similar reduction was observed in serum cortisol and plasma ACTH levels during this short-term treatment period. In this phase II trial, safety analysis was assessed in 39 patients and 87% of them reported adverse events considered to be drug related, but these adverse events were mild in most cases. The most common adverse events were diarrhea (43.6%), hyperglycemia (35.9%), nausea (23.1%), abdominal pain (17.9%), headache (17.9%), asthenia (12.8%), hypotension (12.8%), and fatigue (10.3%). Discontinuation was registered in 1 patient (2.6%) for hyperglycemia (697).

A worldwide phase III, randomized, double-blind, 12-month clinical trial (Study Protocol no. CSOM230B2305; ClinicalTrials.gov no. NCT00434148) has evaluated the efficacy and safety of pasireotide in a large population of patients with CD for a long period of time (698).

Table 11 summarizes the results of the phase III study evaluating the outcome of pasireotide therapy in CD.

The study included 162 patients with CD and evaluated the efficacy of pasireotide at the dosage of 600 or 900 $\mu$g administered sc twice daily. The study included 135 patients with persistent or recurrent CD (128 patients after pituitary surgery, seven patients with previous pituitary radiotherapy performed more than 10 y before enrollment), and 27 naive patients who could also be enrolled if they were not candidates for surgery; 78 patients also had previous medical treatment, discontinuated before enrollment after an appropriate washout. The study randomized patients to pasireotide 600 or 900 $\mu$g twice daily in a double-blind manner for 3 months. At the 3-month follow-up, patients with urinary cortisol levels not exceeding two times the upper limit of the normal range and less than the baseline continued receiving double-blind randomized doses until the sixth month of treatment; conversely, patients with urinary cortisol levels exceeding twice the upper limit of normal range were unblinded, and their dosage was escalated by 300 $\mu$g to 900 or 1200 $\mu$g twice daily; these patients were considered nonresponsive. At the 6-month follow-up, patients were unblinded, and open-label treatment continued for an additional 6 months. The primary end-point, represented by the normalization of urinary cortisol levels, defined as urinary cortisol levels at or below the upper limit of normal, at the 6-month follow-up without up-titration of the pasireotide dose during the previous period of treatment, was achieved in 33 of 162 (20.4%) patients, particularly in 12 of 82 (14.6%) receiving the 600-$\mu$g dose and in 21 of 80 (26.2%) receiving the 900-$\mu$g dose. A rapid decrease in urinary cortisol levels was observed, with a median 50% reduction in both dose groups in the first 1–3 months, which remained stable for up to 12 months of treatment. In most of the 103 patients evaluable at the 6-month follow-up, a decrease in urinary cortisol levels was observed from baseline to the sixth month, and almost half (49%) achieved a substantial ($>$50%) reduction or a normalization in urinary cortisol levels.

Figure 9 shows the change in urinary cortisol levels after 6 months of treatment with pasireotide in the 103 patients with available urinary cortisol levels in the phase III study.

**Figure 9.**

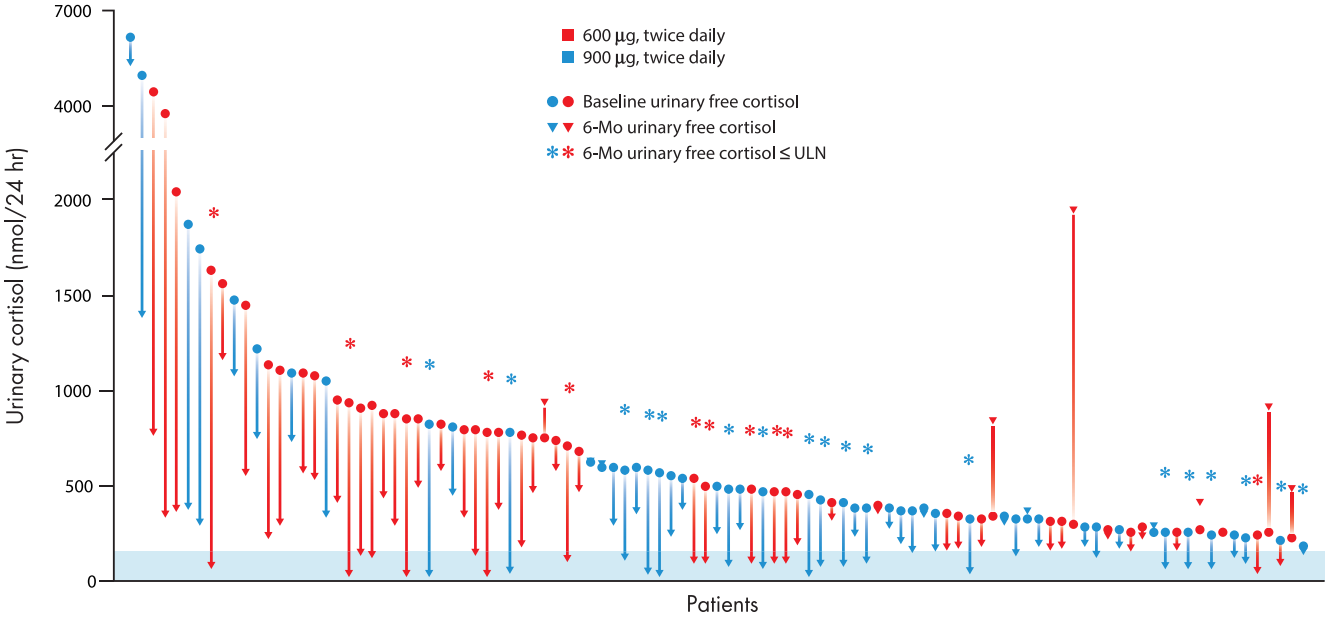


Figure 9. Results of a multicenter, prospective, randomized, double-blind, phase III study on pasireotide performed in several international centers on 103 patients with CD and with available urinary cortisol levels included in the study. The graph shows the absolute change of urinary cortisol levels (in nmol/d) before and after 6 months of treatment in individual patients belonging to the group randomized to 600 μg (red) or 900 μg (blue) twice of day. Patients were ordered on the basis of initial urinary cortisol levels. [Modified from A. Colao et al: A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med.* 2012;366(10):914–924 (698), with permission. © Massachusetts Medical Society.]

It is important to note that the population enrolled in this study was predominantly (77.8%) composed of patients with moderate to very severe hypercortisolism, displaying mean baseline urinary cortisol levels of 6.5 and maximal urinary cortisol levels of more than 10 times the upper limit of normal. Moreover, patients randomized to receive 900 μg of pasireotide twice daily had lower baseline urinary cortisol levels than those randomized to 600 μg twice daily; this selection bias could have influenced the percentage of patients responsive to the two different doses of pasireotide. Indeed, the population of patients with severe hypercortisolism at baseline had a lower urinary cortisol normalization rate, whereas the population of patients with mild hypercortisolism at baseline had a higher normalization rate of urinary cortisol levels, which reached 50% in the group randomized to 900 μg twice a day (698). At the 12-month follow-up, 31 of 162 (19.1%) patients, including 11 of 82 (13.4%) in the 600-μg group and 20 of 80 (25%) in the 900-μg group, were considered fully responsive to the treatment, with urinary cortisol levels still in the normal range, demonstrating that control of the disease was maintained during 1 year of treatment (698). It is noteworthy that an analysis of the results during the different time points of the study demonstrated that among the 72 patients with uncontrolled hypercortisolism, namely those displaying a <50% decrease of urinary cortisol during the first and second months, the vast majority remained uncontrolled after 6 months (91.7%) and 12 months (88.9%), suggesting that the lack of normalization of urinary cortisol levels over the long term might be predicted during the first 2 months of treatment with pasireotide (698).

Discontinuation during the 12 months of treatment occurred in 84 (51.9%) patients (43 [52.4%] in the 600-μg group and 41 [51.2%] in the 900-μg group). In particular, discontinuation for adverse events was observed in 16% of patients (12 [14.6%] in the 600-μg group and 14 [17.5%] in the 900-μg group), whereas discontinuation for lack of efficacy was observed in 22.8% of patients (16 [19.5%] in the 600-μg group and 21 [26.3%] in the 900-μg group) and for consent withdrawal or protocol deviation in 13% of patients (698).

A significant improvement in the clinical picture of CD was also observed; the beneficial effects included reductions in body weight and systolic and diastolic blood pressure and improvement of lipid profile and health-related quality of life. An effect of pasireotide treatment was also observed at the tumor level; indeed, in 75 (46.3%) patients who had a measurable pituitary tumor on MRI, a reduction of tumor volume at the 12-month follow-up was observed in 9.1% of patients in the 600-μg group and 46.3% in the 900-μg group (698).

The safety profile of pasireotide was similar to that of conventional somatostatin analogs with respect to adverse

events such as GI disturbances and cholelithiasis, except for an increased frequency and degree of hyperglycemia with pasireotide. Most drug-related adverse events were grade 1 or 2 and resolved without dose modification, whereas the most frequently reported grade 3 or 4 adverse events were hyperglycemia (13%) and diabetes mellitus (6.8%), which induced treatment discontinuation in 5.6% of patients. The most common adverse events included hyperglycemia-related adverse events (72.8%), GI disturbances (diarrhea, 58%; nausea, 51.8%; abdominal pain, 24%; and upper abdominal pain, 9.9%), cholelithiasis (30.2%), and mostly mild and transient elevations of liver enzymes (29%). Hypocortisolism-related adverse events were reported in 8% of patients; hypocortisolism resolved in the great majority of these patients with a reduction of pasireotide dose or temporary interruption of the treatment. Three (1.8%) patients experienced a QT prolongation; this event was generally sporadic and did not require medical intervention or treatment interruption (698).

Importantly, compared with conventional somatostatin analogs used in different studies for different patients, pasireotide was associated with a higher rate of hyperglycemia-related adverse events. Glucose and glycated hemoglobin levels increased soon after the start of pasireotide treatment, necessitating the administration of glucose-lowering medications in almost half (45.6%) of the patients (698). Recent studies with healthy volunteers indicate that hyperglycemia associated with pasireotide is related to a decrease in insulin and incretin secretion, with no changes in insulin sensitivity (699–702), and that the incretin-based antidiabetic agents liraglutide and vildagliptin significantly reduced pasireotide-induced hyperglycemia (699–701). Therefore, glucose status should be assessed and glucose regulation optimized before starting with pasireotide therapy. It is advisable to monitor patients strictly for hyperglycemia throughout treatment, and to start or adjust appropriate antidiabetic treatment promptly on evidence of hyperglycemia, following established treatment guidelines for diabetes mellitus. An expert panel has recently proposed an algorithm for the monitoring and intervention of patients with CD before and during treatment with pasireotide (700, 701). Treatment with pasireotide, however, might not be considered the best first option in the case of severe and uncontrollable diabetes. Moreover, evidence of a possible effect on liver function suggests that liver function monitoring should be recommended during pasireotide treatment. Pasireotide was found to increase the QT interval in normal subjects, and it can decrease heart rate in patients with CD; careful monitoring of electrocardiogram is therefore recommended before and during its use, and combinations with drugs, which can also increase the QT interval, should be avoided (698).

A report of Pivonello et al focused attention on the impact of pasireotide treatment on the clinical syndrome and comorbidities of patients with CD who participated in the phase III clinical trial (703). This study demonstrated that improvement in clinical symptoms and signs was observed in most patients, regardless of the normalization of urinary cortisol levels (703). In particular, reductions in blood pressure were observed even without full control of urinary cortisol levels and were greatest in patients who did not receive antihypertensive medications during the study. Significant reductions in total cholesterol and LDL-cholesterol levels were observed in patients who achieved full disease control. Reductions in BMI, weight, and waist circumference occurred during the study even without full disease control (703). This evidence suggests that clinical benefit may be obtained in patients who did not normalize, but who experienced a significant reduction in cortisol secretion. Pasireotide treatment could be protracted in a subgroup of patients despite the lack of a complete normalization of urinary cortisol levels if a significant clinical improvement is observed during the first months of treatment.

On the other hand, the evidence that normalization of urinary cortisol is achieved by 50% of only those patients with mild hypercortisolemia, whereas a lower response rate is observed in patients with severe disease, does not suggest prolonging treatment with pasireotide in patients with severe disease when nonresponsiveness, either in terms of hormone control or improvement of the clinical syndrome, is persistently documented, especially in patients with elevated risk of developing adverse effects such as hyperglycemia. In line with the evidence that urinary cortisol levels after the first 2 months of treatment have a high negative predictive value on the long-term control, a short-term trial (1–3 mo) might be employed in the selected group of patients with severe hypercortisolism and a high risk for adverse effects to test the efficacy and safety of the treatment before deciding on a long-term therapy.

A report of Simeoli et al focused attention on the impact of pasireotide on tumor mass in a group of eight patients treated for a long period with pasireotide at the dosage of 600–1200 $\mu$g twice a day at a single center participating in the phase III study. A significant (>25%) reduction in tumor volume was found in 100% of the 7 patients reaching 12 months of treatment; in particular, tumor shrinkage was slight in 42.9%, moderate in 14.2%, and marked in 42.9% of patients, and two (25%) displayed impressive tumor shrinkage, with tumor disappearance in one (12.5%) patient (704). Additional case reports have recently demonstrated tumor shrinkage in patients with CD under pasireotide treatment (705, 706). The evidence of significant tumor shrinkage induced by pasireotide treat-

ment suggests that the presence of a large tumor with extrasellar expansion or an unfavorable location, which is unlikely to be completely removed by pituitary surgery, and particularly by a repeat surgery, may be considered a specific target for pasireotide, especially in case of the lack of availability of a neurosurgeon who is an expert in pituitary tumors.

More recently, Schopohl et al (707) reported the results of the extension phase of the phase III study on pasireotide, evaluating the efficacy and safety of pasireotide during a long-term period of treatment up to 50 months from the start of the core to the end of the extension phase. In particular, among the 78 patients (48% of the initial population of 162 patients) who entered the core study and completed the 12 months of treatment, 58 entered the optional extension phase and continued the pasireotide dose of the end of core phase (26 patients from the 600-$\mu$g group and 32 from the 900-$\mu$g group) (707). The duration of treatment in patients who entered the extension phase was 12–50 months (mean, 27 mo); 40 completed 24 months of treatment, and 10 were treated for more than 36 months. In the 600- and 900-$\mu$g groups, the dosages of pasireotide were 1509 and 1766 $\mu$g/d for the period from 12–18 months and 1500 and 1620 $\mu$g/d from 18–24 months, respectively (707). Among the 58 patients participating at the core and at the optional extension study, full disease control (normalization of urinary cortisol levels) was reached by 29 (50%) patients after 12 months (end of the core and start of the extension phase), and by 20 (34.5%) patients after 24 months of treatment. Partial control of the disease ($\geq$50% decrease without normalization of urinary cortisol levels) was obtained in 12 (20.7%) and 26 (44.8%) patients, whereas uncontrolled disease was documented in 17 (29.3%) and 12 (20.7%) patients, after 12 and 24 months, respectively (707). The mean percentage decrease of urinary cortisol levels from core baseline during the first 12 months of treatment (57.3%) in patents who entered the extension phase was maintained throughout the 24-month study (24 mo, 62.1%) (707). It is noteworthy that of the 29 patents, who were fully controlled at the 12-month follow-up, 14 (48.3%) were fully controlled and three (10.3%) were partially controlled at the 24-month follow-up, whereas of the 12 patients who were partially controlled at the 12-month follow-up, two (16.7%) remained partially controlled and three (25%) became fully controlled at the 24-month follow-up. Finally, of the 17 patients who were uncontrolled at the 12-month follow-up, three (17.6%) reached control at the 24-month follow-up (707). An overall decrease in the proportion of patients with fully controlled urinary cortisol levels was observed at 24 months compared with the 12-month follow-up. This could be partially attributed to patients who discontinued or who were without available urinary cortisol levels and were considered to be uncontrolled. Although escape from the response has not been described, it is possible that a loss of pasireotide efficacy in a small number of patients may have contributed to the reduction in the number of responders during the extension study (707). Significant improvement in clinical symptoms and signs was observed in these patients during the first 12 months of the core study, with further improvement during the second year of the extension study; the clinical benefit was mainly related to systolic and diastolic blood pressure, weight, and BMI, but improvement was also observed in lipid profile. The safety profile was similar to that observed in the global phase III study. In summary, the results of this extension phase of the phase III study on pasireotide have demonstrated that pasireotide is able to maintain the reduction in mean urinary cortisol levels and induce further improvement in the clinical picture over 24 months of treatment, confirming the usefulness of pasireotide in responsive patients with CD over a prolonged period of time (707).

On the basis of data reported in literature and results of the phase III clinical trial, pasireotide became the first drug to gain approval for treatment of CD from the EMA in the EU in April 2012 and from the FDA in the United States in December 2012, being indicated for patients who fail pituitary surgery or for whom surgery is not considered an option (708).

Unlike the results from studies of other drug therapies in CD, results of the phase III study on the efficacy and safety of pasireotide are influenced by the strict criteria of the study design and outcome analysis, which might have underestimated the responsiveness and overestimated the adverse effects of pasireotide in CD. Therefore, a real-world-evidence multicenter study has been performed on a series of patients with CD treated with pasireotide at the dosage of 600–900 $\mu$g twice a day for at least 6 months according to routine clinical practice (709). Most of these patients had unsuccessful pituitary surgery and/or radiotherapy and had a residual, very mild to moderate disease with urinary cortisol levels between one and three times the upper limit of normal. The preliminary results of this study on 27 patients with CD, among whom 24 reached 6 months of follow-up, have demonstrated that pasireotide treatment at a median dosage of 600 $\mu$g twice a day was able to normalize urinary cortisol levels in more than 65% of patients. The normalization of cortisol secretion was accompanied by improvement of the clinical picture, although associated with a deterioration of glucose metabolism (709). These preliminary data seem to confirm that the use of pasireotide in clinical practice might control CD in a relevant number of patients, at least the ones without severe disease, although further experience with a large population of patients is required to draw more definitive conclusions on the efficacy and safety of pasireotide in the

**Figure 10.**

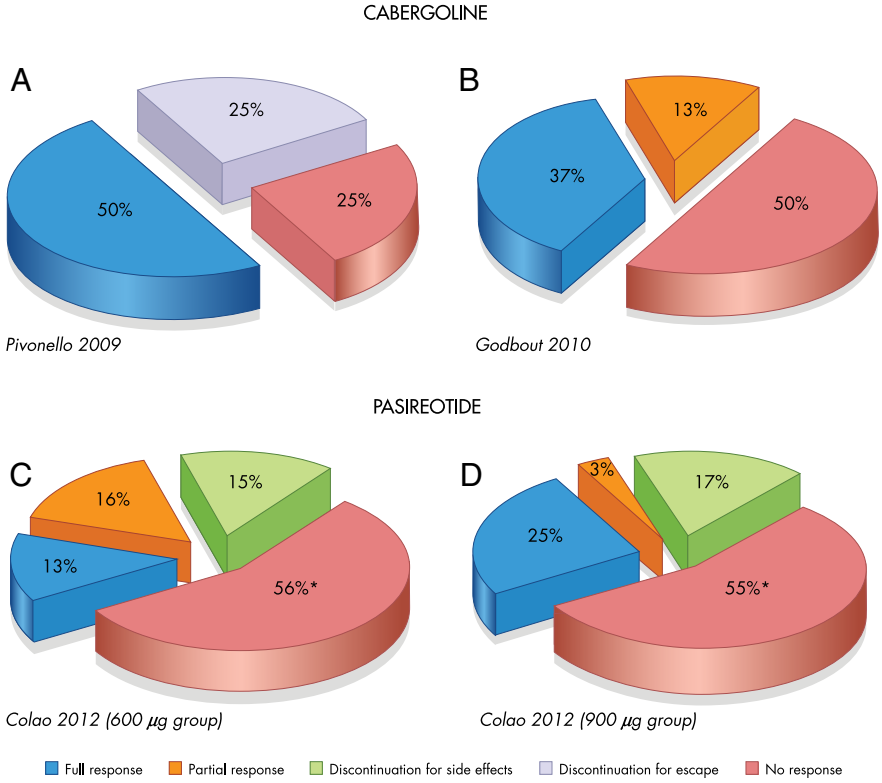


Figure 10. Comparison of the results of the studies investigating the effectiveness of cabergoline in two main studies (A and B) and the effectiveness of pasireotide in the large phase III study, at 12-month follow-up (C and D). A, Pivonello et al (656): prospective nonrandomized study, 20 patients; full response, urinary cortisol levels in the normal range. B, Godbout et al (658): retrospective nonrandomized study, 30 patients; full response, urinary cortisol levels in the normal range; partial response, urinary cortisol level decrease < 125% of upper limit of normal. C, Colao et al (698): prospective, randomized, double-blind phase III study, 162 patients, pasireotide 600 μg; full response: urinary cortisol levels in the normal range; partial response: urinary cortisol level decrease ≥ 50%. D, Colao et al (698): prospective, randomized, double-blind phase III study, 162 patients, pasireotide 900 μg; full response, urinary cortisol levels in the normal range; partial response, urinary cortisol level decrease ≥ 50%. *, This group includes nonresponsive patients at 12-month follow-up and patients who discontinued for: 1) unsatisfactory therapeutic effect; 2) consent withdrawal; and 3) study protocol deviation.

real-world setting. An additional series of case reports or small case series have recently confirmed that pasireotide treatment may maintain disease control for a period of up to 7 years, while inducing generally tolerable and controllable adverse effects together with improving the clinical syndrome (705, 706, 710–713).

A long-acting release formulation of pasireotide (pasireotide LAR), which has the advantage of being administered monthly by the im route and presumably has better patient compliance, is under evaluation for the treatment of CD. However, pasireotide LAR has already been reported to dramatically reduce ACTH secretion, improve skin hyperpigmentation, and decrease tumor mass in a patient with corticotroph tumor progression (453).

In summary, pasireotide can be considered an effective pituitary-directed drug, based on the evidence that a prospective, randomized, double-blind, phase III study in a large population of patients with mainly moderate to very severe disease reported disease control after long-term treatment in up to 25% of patients, and that a preliminary, real-world-evidence, prospective, open-label study seems to suggest a possible efficacy in disease control in around 65% of patients with very mild to moderate disease. The advantages of pasireotide are the relatively rapid action in controlling cortisol secretion and the positive impact on either the clinical picture or tumor mass; the disadvantages of pasireotide are the sc multiple daily injection of the current formulation and the safety profile, which includes hyperglycemia, requiring additional medical intervention for control of glucose metabolism. Pasireotide is approved for the treatment of CD, so it presently represents an on-label treatment for CD when surgery has failed or is not considered an option.

Figure 10 shows the outcome of the pivotal studies describing the effect of treatments with the main pituitary-directed drugs, namely cabergoline and pasireotide, in CD.

### 2. Nuclear receptor ligands

The nuclear receptor ligands include the PPAR-γ agonists and the retinoic acid receptor agonists; this group of drugs has been evaluated in few studies in a limited number of patients with CD, but both categories of agents are not used in the current clinical practice.

*a. PPAR-γ agonists.* PPAR-γ is a member of the nuclear receptor superfamily and functions as a transcription factor mediating ligand-dependent transcriptional regulation (714, 715). PPAR-γ mediates different functions related to metabolism and cell growth. Indeed, its activation is responsible for the regulation of glucose metabolism, differentiation of adipocytes, inhibition of monocyte and macrophage activation, and inhibition of angiogenesis (715–718). Moreover, PPAR-γ is widely expressed in several normal tissues, including breast, prostate, and colon epithelium, as well as in the corresponding tumor cells, where it mediates the inhibition of tumor growth (715–718). In addition, it is expressed to a small degree in autopsy-derived normal human pituitary tissue, where its expression was predominantly localized in corticotroph cells (719). By contrast, PPAR-γ is abundantly expressed in different pituitary tumors, including a series of corticotroph pituitary tumors, compared to minimal expression in normal pituitary gland (718, 719). PPAR-γ ligands include the insulin-sensitizing thiazolidinedione compounds troglitazone, rosiglitazone, and pioglitazone. It is noteworthy that troglitazone has been early withdrawn from the medical market because of associated hepatotoxicity in some countries where it had been approved, and it was never approved in other countries. Moreover, rosiglitazone has been withdrawn from the medical market because of associated cardiotoxicity in Europe after an EMA alert in July 2000. Conversely, the FDA disagreed, and rosiglitazone remained available in United States; from November 2011 to November 2012, its prescription was allowed with restrictions, but in November 2013, the FDA lifted its earlier restrictions after reviewing the results of the 2009 RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) clinical trial, a 6-year, randomized, open-label clinical trial that failed to demonstrate increased cardiovascular risk associated with the drug (720, 721).

PPAR-γ agonists have been suggested as promising agents that specifically target pituitary tumors based on in vitro and in vivo studies of rodent models. However, different clinical trials performed in a limited number of patients with CD did not confirm expectations and did not support their use in routine clinical practice. Indeed, thiazolidinediones were shown to be effective in controlling hormone secretion and cell proliferation in models of corticotroph pituitary tumors. In experimental studies on the murine AtT-20 corticotroph tumor cell line and/or primary cultures of human corticotroph tumor cells, rosiglitazone treatment induced cell cycle arrest and apoptosis as well as inhibition of POMC messenger expression (719, 722). High-dose rosiglitazone treatment inhibited circulating ACTH and corticosterone levels and tumor growth in athymic nude mice harboring sc pituitary corticotroph tumors (719, 722). These findings supported a potential role for rosiglitazone in the management of CD. The acute effect of thiazolinediones on ACTH and cortisol secretion has been tested in patients with CD. The administration of a single dose of 8 mg rosiglitazone did not decrease plasma ACTH and serum cortisol levels or blunt their response after CRH administration in 10 patients with active CD, suggesting the absence of an acute effect of thiazolidinediones on cortisol secretion in patients with CD (723).

The clinical experience with thiazolidinediones in CD is presently limited to a few short-term studies, suggesting that a subset of patients with CD exhibit reductions in plasma ACTH and/or serum cortisol levels during treatment (724–729).

The first three reports were related to small groups of patients or single clinical cases (724–726). In one study by Alevizaki et al (724), five patients with CD who remained uncured despite prior pituitary surgery, and who had previously been treated with ketoconazole, were treated with rosiglitazone at the dosage of 8 mg/d for 16 weeks. In four of the five (80%) patients, a decline in serum cortisol levels was evident starting from the second week, and after 16 weeks of rosiglitazone treatment, the morning and evening serum cortisol levels were lowered by 5–36% in comparison to baseline values. The treatment was well tolerated, with the exception of the occurrence of a mild edema. The patients considered treatment with rosiglitazone better than that with ketoconazole (724). In a second study by Hull et al (725), two patients were treated with rosiglitazone at the dosage of 8 mg/d for 33 and 20 days, respectively, before scheduled pituitary surgery. Morning urinary cortisol-to-creatinine ratios were reduced across the treatment period, although this reduction only reached statistical significance in one of the two patients; normalization of morning urinary cortisol-to-creatinine ratios and improvement in the clinical picture were not demonstrated in either patient. Additionally, it is noteworthy that the patient who displayed a significant reduction in urinary cortisol levels was cotreated with metyrapone, and the possibility that the two compounds acted in a synergistic fashion to reduce cortisol levels cannot be excluded (725). Similarly, cotreatment of a patient with ketoconazole and rosiglitazone 8 mg/d resulted in normalization of urinary cortisol levels that had not been achieved during

the previous 12 months treatment with ketoconazole alone (726). Clearly, because both metyrapone and ketoconazole act at the level of the adrenal to inhibit cortisol synthesis and secretion, the possibility of synergy or indeed prolongation of the half-life of either drug is highly likely. Nonetheless, if combination drug therapy with rosiglitazone could offer a drug sparing of ketoconazole and/or metyrapone, thereby lessening the adverse effects of either drug alone, this would open up new perspectives on currently available medical therapies.

Three relevant studies have investigated the efficacy and safety of rosiglitazone in patients with CD (727–729). These three studies included 38 patients with CD, followed for a period of treatment ranging from 1 to 12 months (mean, 4.4 mo; median, 4 mo) at a dosage of rosiglitazone ranging from 4 to 24 mg/d (mean, 9 mg/d; median, 8 mg/d). The results of these three studies show a remission rate ranging from 40 to 71.4% (mean, 51.4%; median, 42.9%); however, it is noteworthy that in the studies using urinary cortisol levels as a marker, the remission rate was around 40%, whereas the study with a remission rate higher than 70% had used serum cortisol as the main marker to monitor the effectiveness of treatment, and it registered a dramatic number of patients experiencing an escape from response over the long-term treatment.

Table 11 summarizes the results of the main studies evaluating the outcome of rosiglitazone therapy in CD.

In the first study, Ambrosi et al (727) treated 14 patients with CD (seven with newly diagnosed disease and seven with postsurgical disease) with rosiglitazone at the initial dosage of 8 mg/d for 1–7 months (mean, 2.6 mo; median, 2 mo). This dosage was increased to 16 mg/d in two patients over the treatment period, so that the final dosage ranged from 8–16 mg/d (mean, 9.1 mg/d; median, 8 mg/d). Six of the 14 (42.9%) patients were considered responsive because normalization of urinary cortisol excretion was observed during treatment, and the changes in urinary cortisol, but not those of plasma ACTH and serum cortisol levels, reached statistical significance. The normalization of cortisol secretion was generally evident after 30–60 days of treatment. A mild improvement in clinical features was observed in two of the six (33.3%) responsive patients who were followed for 7 months. In one of these patients, although urinary cortisol levels normalized after 30 days of treatment, cortisol levels rose again by 4 months, prompting an increase in rosiglitazone dosage to 16 mg daily, which again led to normalization of urinary cortisol levels. The remaining eight patients were considered nonresponsive because no normalization of urinary cortisol and no sustained plasma ACTH and serum cortisol level reductions were observed. One patient (7.1% of the total population, 16.7% of the initially responsive population) exhibited an initial striking decrease in urinary cortisol levels, which rose again thereafter although the rosiglitazone dosage was increased to 16 mg/d. It is noteworthy that rosiglitazone treatment improved insulin sensitivity in two responsive patients, induced the reduction of insulin requirement in a third, and improved control of the glucose profile in a fourth responsive patient, whereas no change in insulin sensitivity or control of glucose profile was seen in the remaining two responsive patients or in the eight nonresponsive patients (727). With the exception of one patient (7.1%) who developed hypercholesterolemia, leading to drug discontinuation, none of the patients showed drug toxicity.

In another study, Pecori Giraldi et al (728) treated 10 CD patients (four with newly diagnosed disease and six with postsurgical disease persistence or relapse) with rosiglitazone at the dosage of 4–16 mg/d (mean, 9 mg/d; median, 8 mg/d) for a period of 1.3–8 months (mean, 3.7 mo; median, 3 mo). Four of the 10 (40%) patients were responsive to the treatment, reaching normalization (three patients), or near normalization and with marked decrease of urinary cortisol levels (one patient), after 1–3 months of treatment. The decrease from baseline in urinary cortisol levels in these patients ranged from 24 to 78%. The remaining six (60%) patients were considered nonresponsive because, despite a maximal decrease from baseline ranging from 15 to 70%, urinary cortisol levels oscillated and occasionally normalized or never normalized during treatment. It is noteworthy that neither plasma ACTH nor serum cortisol was manifestly reduced by treatment with rosiglitazone. No clear escape was documented during the treatment period. Three (30%) patients (one responsive and two nonresponsive) reported a subjective clinical amelioration, whereas menses regularized in all three patients with menstrual disturbances, despite the absent normalization of urinary cortisol levels. Insulin sensitivity improved in four of five (80%) patients with impairment of glucose tolerance, independently from the changes in cortisol secretion, whereas glucose control remained unchanged in the five patients with diabetes mellitus. Rosiglitazone was not well tolerated in the remaining seven (70%) patients because of weight gain (50%), edema (50%), and somnolence (10%). Two patients (20%) complained of an increase in bruisability, whereas one patient (10%) developed a hypertensive crisis and precordial pain. Finally, one of the women (12.5%) developed hirsutism (728).

The results of these two studies (727, 728) suggest that treatment with rosiglitazone performed for a short period of time is effective in normalizing urinary cortisol levels in a subset of patients with CD. However, there was no con-

comitant significant improvement of the clinical picture, except for a certain improvement in insulin sensitivity, probably independent from the changes in cortisol secretion. The main drawbacks of these studies are represented by the use of a standard dose of rosiglitazione, similar to those used in the treatment of diabetes, and the short treatment period.

Finally, a recent study by Morcos et al (729) evaluated the long-term effectiveness of high-dose rosiglitazone treatment in 14 patients with persistent disease after unsuccessful surgery and radiotherapy. The patients were treated with a rosiglitazone dosage starting at 4 mg/d and reaching 24 mg/d for a period ranging between 4 and 12 months (mean, 6.8 mo; median, 7 mo). Morning plasma ACTH and serum cortisol levels, but not urinary cortisol, were monitored during the study together with the pituitary tumor mass, evaluated by MRI. During rosiglitazone treatment, both plasma ACTH and serum cortisol levels significantly dropped after 12 weeks and remained persistently controlled for as long as 24 weeks. Plasma ACTH normalized in seven (50%) patients, whereas serum cortisol levels normalized in 10 (71.4%) of the 14 patients. However, either ACTH or cortisol rose again after 24 weeks despite continuous treatment and dose increase up to the maximal dosage, demonstrating the occurrence of treatment escape (71.4% of the total population, 100% of the initially responsive population). The changes in cortisol secretion were accompanied by improvement of the clinical picture, which started to worsen with the increase of cortisol levels during treatment. Moreover, no significant change was found in the tumor mass during treatment and the main adverse effect was represented by the elevation in liver enzymes, which occurred in 2 (14.3%) patients (729). As compared with other studies, this study has the advantage that the effect of rosiglitazone was investigated at higher doses and for a longer period of time. However, the results need to be interpreted with caution because morning circulating ACTH and cortisol levels are frequently normal in patients with CD, especially in the postsurgical period, and cannot be considered an ideal marker to monitor the efficacy of medical treatment. Nevertheless, the results of this study seem to suggest that rosiglitazone is not an option for long-term treatment in patients with persistent CD after unsuccessful pituitary surgery and radiotherapy.

In addition to the clinical trials on rosiglitazone, some studies have evaluated the efficacy of pioglitazone in the treatment of CD. In one study, five patients with CD were treated with 45 mg/d pioglitazone for 30 days, but showed no significant change in daily urinary cortisol levels, or daily ACTH and cortisol profile, or responses to CRH challenge, suggesting that pioglitazone is completely ineffective in controlling cortisol secretion in patients with CD (730). However, the description of a patient with CD who experienced a normalization of urinary cortisol levels after 8 months of treatment with pioglitazone may suggest that a long period of treatment is needed to obtain a significant effect of pioglitazone on cortisol secretion in patients with CD (731).

The reason for the apparent difference in action of rosiglitazone and pioglitazone in CD is not known, but several factors require consideration. First, the duration of treatment in the single study exploring the effectiveness of pioglitazone in a series of patients was comparatively short, although rosiglitazone has been observed to induce a decrease of cortisol secretion after periods as short as 4 weeks. Second, although these compounds have a similar binding affinity for PPAR-$\gamma$, pioglitazone, but not rosiglitazone, also has significant affinity for PPAR-$\alpha$, whose effect on ACTH and cortisol secretion is unknown. Third, the putative actions of rosiglitazone on corticotroph pituitary tumors might be partially independent of PPAR-$\gamma$, and rosiglitazone and pioglitazone may exert variable potency on the alternative mechanisms (716, 717).

It is important to mention that three studies have evaluated the effectiveness of rosiglitazone in the treatment of corticotroph tumor progression (454–456). In the first study, rosiglitazone was administered at the dosage of 8 mg/d for 12 weeks in seven patients (454), whereas in the second study it was administered at the dosage of 12 mg/d for 14 weeks in six patients (455), and in the third study it was administered at the dosage of 4–16 mg/d for 5 months in three patients with corticotroph tumor progression (456). All three studies did not demonstrate any effect of rosiglitazone treatment on plasma ACTH secretion or the clinical syndrome over the treatment period, suggesting that rosiglitazone is not an option in the treatment of corticotroph tumor progression (454–456).

In summary, PPAR-$\gamma$ agonists, in particular the most commonly experimented rosiglitazone, are able to control cortisol secretion in an average of 51% of patients during a short-term period, but disease control seems to be transient and associated with a negligible improvement in clinical picture, and a treatment escape in around 58% of patients initially responsive to the treatment and up to 100% of patients, making this category of drugs inadequate in the long-term treatment of CD. The advantage of this category of drugs is represented by the beneficial effect on glucose metabolism. The possible use of these compounds in combination with other drugs cannot be completely ruled out, and it is even hypothesized in patients with diabetes mellitus.

*b. Retinoic acid receptor agonists.* Retinoic acid has been proposed as a possibly effective drug for CD, after the demonstration of its ability to reduce hormone levels and tu-

mor size in animal models of CD (732, 733). Indeed, in rodent models, retinoic acid decreased hormone secretion and inhibited cell proliferation in corticotroph tumor in vitro, and induced hormone control and tumor shrinkage in vivo (732); moreover, in canine models of CD, it induced improvement of the clinical picture and a prolongation of survival, as well as pituitary tumor shrinkage, without significant adverse effects (733). The effect of retinoic acid on corticotroph pituitary tumor secretion and proliferation seems to be mediated by the ability of the drug to antagonize the effect of transcription factors, such as activator protein-1 (AP-1) and Nur77/Nurr1, positive regulators of the ACTH gene, in corticotroph pituitary tumors, but not in normal pituitary corticotroph cells (734–736), suggesting that retinoic acid does not play a role in the physiological control of ACTH synthesis. However, genes that are differentially expressed in pituitary tumors might also be involved in the differential action of retinoic acid (735, 737, 738). Notably, retinoic acid reduces adrenal hyperplasia by direct inhibition of adrenal cell proliferation (739).

At present, only one clinical trial has evaluated the efficacy of retinoic acid as a treatment for patients with CD (740).

In this prospective proof-of-concept study performed in seven patients with CD, the efficacy and safety of escalating dosages of retinoic acid (10–80 mg/d orally) was evaluated over a period of 6–12 months (mean, 10.3 mo; median, 12 mo). Five patients (71.4%) had a $\geq$ 50% decrease or normalization of urinary cortisol levels after 6 months; three (42.9%) patients had full disease control, whereas the remaing two (28.6%) had partial disease control. Among the five responsive patients, three (42.9%) had a marked and prolonged decrease or normalization in urinary cortisol levels, whereas 2 patients (28.6% of the total population and 40% of the initially responsive population) had treatment escape after the 6-month follow-up. The changes in circulating ACTH levels were variable but generally less pronounced than those of urinary cortisol levels. The treatment was generally well tolerated, except for mild and mostly transitory mouth and conjuctival dryness (42.8%), arthralgias (42.8%), diarrhea and abdominal discomfort (28.6%), headache (14.3%), and worsening of leukocytosis (28.6%) (740). Table 11 summarizes the results of the study evaluating the outcome of retinoic acid therapy in CD. Further studies on a larger number of patients treated for a long-term period are necessary to evaluate the real potential of retinoic acid in the control of CD.

### D. Glucocorticoid receptor-directed drugs

Glucocorticoid receptor-directed drugs, or glucocorticoid antagonists, represent an alternative treatment for a group of patients with CD. Glucocorticoid antagonism is rapidly effective in controlling hypercortisolism, so it can play a role in the management of CD, especially when the presence of severe disease or concomitant conditions requires a rapid control of cortisol excess. Mifepristone is the first and only glucocorticoid receptor antagonist available, and it was approved by the FDA in the United States in February 2012 for the treatment of hyperglycemia in patients with endogenous CS associated with diabetes mellitus or glucose intolerance who are not candidates for surgery or who have not responded to prior surgery (741–746). Experimental data are only presently available regarding different potential drugs belonging to this category.

#### *1. Mifepristone*

Mifepristone is a high-affinity nonselective antagonist of the glucocorticoid receptor type II, with an affinity for the glucocorticoid receptor more than three times higher than that of dexamethasone and more than 10 times higher than that of cortisol (747, 748). The blocking effect of mifepristone on cortisol action acts both at a peripheral and a central level, also affecting its negative feedback to inhibit CRH and ACTH secretion (743, 748). Mifepristone was initially considered as the "abortion pill" because of its antiprogestin activity; its affinity for the progesterone receptor is more than twice that of progesterone. Mifepristone also has weak antiandrogen activity, although its affinity for the androgen receptor is less than one-third that of testostrone (741, 742, 749, 750). These effects on progestin and androgen receptors are responsible for specific adverse effects on female and male reproductive and/or sexual function (742, 744). The antiglucocorticoid effect is dose-dependent and requires higher doses than that required for its antiprogestin activity (751). Mifepristone is administered orally, and it has a rapid onset of action (1–4 h) and a long half-life (24–90 h), which permits once daily administration at dosages ranging from 300 to 1200 mg/d (752). Because the blockade of glucocorticoid receptors leads to increased ACTH and cortisol levels, these parameters cannot be considered in the evaluation of drug efficacy or to monitor disease control, which needs to be based on the evaluation of clinical parameters (746). In addition, the cortisol excess, which is further enhanced by glucocorticoid receptor blockade, might activate the mineralocorticoid receptor (753), potentially resulting in an increase in blood pressure, hypokalemia, edema, and alkalosis, which requires

the use of high-dose antialdosterone treatment for prevention and/or control (741).

Mifepristone was used for the first time in the treatment of CS in 1985 (754); since then, it has been used as an off-label medication for years, but in only a small number of patients with CD, obtaining improvement of the clinical picture in most patients (741–746, 755–760). Excluding case reports, two main studies have evaluated the efficacy and safety of mifepristone, including a total of 47 patients with CD (757, 758). In these two studies, mifepristone has been administered at a dosage ranging from 300 to 1200 mg/d (mean, 766 mg/d), with a follow-up ranging from 0.5 to 24 months (mean, 7.9 mo; median, 6.7 mo), and was considered effective in 38.1 to 75% of patients (mean, 57.7%; median, 60%) (757, 758).

Castinetti et al (757) described the results of a retrospective single center study of mifepristone in 20 patients with CS, including four with CD, treated in seven European centers. Focusing on CD patients, the mifepristone dosage ranged from 600 to 1200 mg/d (mean, 800 mg/d; median, 700 mg/d), and the follow-up ranged from 0.5 to 24 months (mean, 9.9 mo; median, 7.5 mo). Clinical symptoms and signs of hypercortisolism improved rapidly in three (75%) patients. One (25%) patient developed hypertension and hypokalemia, whereas another (25%) developed adrenal insufficiency during mifepristone treatment (757).

An important study from Fleseriu et al (758) described the largest prospective multicenter trial of mifepristone in the treatment of CS (Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's Syndrome [SEISMIC]) and demonstrated its effectiveness in treating clinical and metabolic features related to hypercortisolism. Fifty patients with CS, including 43 patients with CD, entered the study and received mifepristone treatment for 24 weeks, with a starting dosage of 300 mg/d, a maximum dosage of 1200 mg/d, and a final mean dosage of 732 mg/d. It is not possible to distinguish results for patients with CD from those of the entire population of patients with CS. The patients were divided into two groups: the first group included patients with diabetes mellitus or impaired glucose tolerance, whereas the second group included patients with hypertension. The primary end-point for CS patients with type 2 diabetes mellitus or impaired glucose tolerance was a change in the area under the curve for glucose on an oral glucose tolerance test (OGTT) of at least 25%, whereas the primary end-point for patients with CS and hypertension was a change in diastolic blood pressure of at least 5 mm Hg from baseline to week 24. The secondary end-points included clinical response graded by an independent data review board. The two primary end-points were met in 15 of 25 (60%) and in 8 of 21 (38.1%) patients in the first and second groups, respectively. Considering the secondary end-points, clinically significant improvement was observed in 87% of patients; body weight, waist circumference, and body fat decreased significantly, whereas insulin sensitivity increased. During mifepristone treatment, 31 of 43 (72%) patients with CD had at least a 2-fold increase in ACTH and cortisol levels (758). Pituitary MRI images showed no change in tumor volume during the study in all CD patients but one, who had an aggressive pituitary tumor that increased in size after 10 weeks. Adverse events occurred in 88% of patients and included nausea (48%), fatigue (48%), headache (44%), hypokalemia (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), hypertension (24%), dizziness (22%), and decreased appetite (20%) (758). Endometrial thickening occurred in 10 of the of 26 (38.5%) female patients who underwent baseline and end-of-trial transvaginal ultrasound, and was likely due to the antiprogestin effects of mifepristone that induce modification of endometrial structure associated with cystically dilated endometrial glands (741–746, 758, 761). An abnormal vaginal bleeding occurred in 5 (14.3%) of the women. Reversible decreases in high-density lipoprotein cholesterol and decreases in TSH levels were observed. Adrenal insufficiency was reported in two (4%) patients (758).

Another more recent paper from Fleseriu et al (762) described changes in plasma ACTH levels and corticotroph tumor size in CD patients after long-term follow-up in the SEISMIC study. Among the 43 patients with CD enrolled, 27 continued into the long-term extension of the study after a 6-week off-drug safety evaluation period, with a starting dose equal to the final dose in the core study and treatment duration of the extension phase ranging from 0.5 to 42 months (762). ACTH and pituitary MRI were assessed at baseline and at regular intervals during treatment. A $\geq$ 2-fold increase in ACTH was observed in 72.1% of patients treated for a median duration of 11.3 months, and mean ACTH levels remained stable during the extension study. The ACTH increase directly correlated with the mifepristone dose, and ACTH levels returned nearly to baseline after drug discontinuation. The tumor regressed in two (4.7%) patients, whereas tumor progression was observed in four (9.3%) patients; three had a macroadenoma that increased in size, whereas one patient with a previous tumor-negative MRI developed a microadenoma (762).

Katznelson et al (759) reported an additional analysis on the clinical response data of the SEISMIC study. The authors assessed the global clinical response in patients with CS treated with mifepristone. The assessment has

been made by three independent reviewers using a three-point ordinal scale based on eight broad clinical categories including: glucose control, lipids, blood pressure, body composition, clinical appearance, strength, psychiatric/cognitive symptoms, and quality of life over a period of 24 weeks. This study demonstrated a progressive clinical benefit of mifepristone, with 88% of patients having improved after 24 weeks of treatment. Four significant predictors of global clinical response have been found: change in baseline body weight, change in diastolic blood pressure, change in 120-minute glucose on an OGTT, and change in Cushingoid appearance (759).

Wallia et al (760) also reported an analysis in a subgroup of patients treated with mifepristone in the SEISMIC study. The authors assessed insulin sensitivity in 19 patients, using OGTT data from the study. The results of the analysis demonstrated that the Matsuda index improved in the total population, with the greatest improvement occurring between baseline and the sixth week; conversely, weight and waist circumference declined linearly over the 24 weeks of treatment (760). Patients with hypertension experienced declines in insulinogenic index$_{0-30}$, insulinogenic index$_{0-120}$, and homeostasis model of assessment-$\beta$ index by week 24, whereas these parameters showed an upward trend in diabetic patients. Adiponectin levels increased from baseline to week 24 in hypertensive patients in a temporal pattern that followed changes in weight and waist circumference. These data suggested that rapid improvements in insulin sensitivity occurred because of the direct effects of glucocorticoid blockade, and longer-term improvements resulted from weight loss. Patients with impaired glucose tolerance or diabetes present a defect in $\beta$-cell secretory responsiveness at baseline, which is partially retrievable along with improvement in insulin sensitivity during mifepristone therapy (760).

On the basis of the results of the SEISMIC study, which demonstrated an important impact of mifepristone treatment on the glucose profile of patients with CS complicated by glucose intolerance and/or type 2 diabetes (758), mifepristone received FDA approval in the United States for the treatment of adult patients with endogenous CS who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

The use of mifepristone in a child with CS has been described in the literature (763) with a dramatic improvement in the patient's health; this evidence on one patient needs confirmation in a larger cohort of pediatric patients.

The lack of available biological parameters for monitoing during follow-up represents a limitation for the use of mifepristone. Therefore, the efficacy of the treatment should be evaluated on any improvement in the clinical picture and comorbidities, such as visceral obesity, hypertension, diabetes, and dyslipidemia, together with depression and quality of life. Similarly, the eventual occurrence of adrenal insufficiency should be suspected in case of suggestive symptoms and/or signs, which mainly include weakness, fatigue, nausea, vomiting, and episodes of hypoglycemia (764). Based on the long half-life of mifepristone and its high affinity for the glucocorticoid receptor relative to endogenous cortisol, adrenal insufficiency is best treated with supraphysiological dexamethasone for at least 48 hours after mifepristone withdrawal (764).

It is notable that drug-drug interactions are important during mifepristone treatment. Mifepristone inhibits CYP3A and CYP2C8/2C9 and is mainly metabolized via CYP3A; therefore, drugs that are major CYP3A substrates are contraindicated when using mifepristone (745). Ketoconazole and other CYP3A inhibitors could increase mifepristone levels in the blood, so discontinuing ketoconazole 14 days before starting mifepristone is advisable. Moreover, the administration of drugs whose metabolism is largely mediated by CYP2C8/2C9, including warfarin, should be strictly monitored in patients receiving mifepristone (745). Caution is also needed in the administration of drugs that prolong the QT interval in patients on mifepristone treatment because it can prolong QT interval in dose-related manner (745).

On the basis of the frequent occurrence of hypokalemia, it would be appropriate to correct any pre-existing hypokalemia before initiation of mifepristone treatment to prevent the risk of worsening hypokalemia and the consequences of severe hypokalemia (745). The institution of a mineralocorticoid antagonist, such as spironolactone, before starting mifepristone treatment should be suggested for patients who have already experienced hypokalemia and need potassium supplementation. Eprenolone should be preferred in men to prevent sexual dysfunction and gynecomastia associated with spironolactone (745). Due to its effect on endometrial proliferation, mifepristone is also contraindicated in women with unexplained vaginal bleeding or women with endometrial hyperplasia, atypia, or endometrial carcinoma. Unexpected vaginal bleeding on mifepristone would warrant additional evaluation (741–746).

In summary, mifepristone should be considered as a novel alternative approach to control the clinical manifestations of CS, including CD, especially for patients who require rapid control of the clinical syndrome associated with the disease because it is able to improve the majority of clinical manifestation in up to 75% of patients, and in particular, to improve glucose tolerance in 60% of patients and blood pressure in almost 40% of patients. The main advantage of mifepristone is the rapid improvement of the clinical picture, especially the glucose profile and

**Table 12.** Results of the Main Studies Evaluating the Outcome of Mifepristone in CD

| First Author, Year (Ref.) | No. of patients | Drug Dose, mg/d | Follow-up, mo | Remission Rate, % | Adverse Effects, % |
|---|---|---|---|---|---|
| Castinetti, 2009 (757) | 4 | R:600–1200; M:800; m: 700 | R:0.5–24; M:9.9; m:7.5 | 75 | Hypertension and hypokalemia:25; adrenal insufficiency:25 |
| Fleseriu, 2012 (758) | 50 CS, 43 CD | R:300–1200; M:732 | M:6; m:6 | 60/38.1[a] | Nausea:48; fatigue:48; headache:44; hypokalemia:34; arthralgia:30; vomiting:26; peripheral edema:26; hypertension:24; dizziness:22; decreased appetite:20; adrenal insufficiency:4; endometrial thickening:38.5% (of the women) |
| **Total** | **47** | **R:300–1200; M:766** | **R:0.5–24; M: 7.9; m:6.7** | **R:38.1–75; M: 57.7; m:60** | **Hypokalemia:R:25–34; M:29.5; m:29.5; hypertension:R:24–25; M:24.5; m:24.5; adrenal insufficiency:R:4–25; M:14.5; m:14.5** |

Abbreviations: R, range; M, mean; m, median. This table lists the two main studies addressing the outcome of therapy with mifepristone. The last line (total) includes the general range and the "average" mean and median values of the different parameters included in the studies.

[a] The two sets of data refer to the two different groups of CS patients included in the study (group 1, patients with diabetes mellitus or impaired glucose tolerance; group 2, patients with hypertension).

insulin sensitivity. However, its main disadvantage is the lack of any possible hormonal marker used to evaluate the efficacy of the drug and the control of the disease during the follow-up, as well as to evaluate the occurrence of an important adverse effect, which is adrenal insufficiency. Moreover, several clinical parameters need to be strictly monitored for the double purpose of evaluating the efficacy of the drug in controlling the disease as well as the development and the course of specific adverse effects, mainly adrenal insufficiency, and consequently treated promptly and appropriately. In addition, it is important to consider possible drug-drug interaction when mifepristone is administered. The long-term efficacy and safety profiles of mifepristone remain to be determined. Mifepristone is approved by FDA for the treatment of hyperglycemia secondary to CS, and therefore, in the United States it is an on-label treatment limited to patients with CS and impairment of glucose tolerance and diabetes, and who have failed surgery or are not candidates for surgery.

Table 12 summarizes the results of the main studies evaluating the outcome of mifepristone therapy in CD.

Safety represents a crucial issue for most drugs currently used in the management of CD. The most important adverse effects of the most commonly used drugs for the treatment of CD are summarized in Table 13.

### E. Combination therapy

The treatment of CD with the combination of different drugs has a two-fold purpose: to increase disease control compared with monotherapy, especially if they act at different levels, and to reduce adverse effects, especially if the agents are administered at a lower dose compared to that classically used as monotherapy.

In CD, combination therapies have been tested using agents of the same or different categories of drugs.

This first combination treatment group described in literature is represented by the combination of different adrenal-directed drugs.

Combined therapy with low-dose aminoglutethimide and metyrapone, performed in a limited number of patients for a limited period of time, demonstrated normalization of cortisol levels in a high percentage of patients

**Table 13.** The Most Common Adverse Effects of the Main Drugs Currently Used in CD

| Drug | Adverse Effects, % |
|---|---|
| Ketoconazole | Hepatotoxicity: R:10.7–18.7; M:14.5; m:13.6; GI disturbances: R:3.7–18.7; M:12.9; m:13.1; skin rash: R:3.6–6.2; M:5.1; m:5.5; adrenal insufficiency: R:5.3–18.5; M:11.9; m:11.9 |
| Metyrapone | Hirsutism: R:4.5–71.4; M:36.1; m:34.3; hypokalemia: R:6.7–13.6; M:10.1; m:10.1; nausea: R:5.3–13.6; M:9.4; m:9.4; fatigue: R:13–13.6; M:13.3; m:13.3; dizziness: R:16–44.4; M:30.4; m:30.8; arthralgia: R:8.7–18.2; M:13.4; m:13.4 |
| Mitotane | GI disturbances: R:10–88.9; M:46.3; m:43.2; skin rash: R:1.6–3.9; M:2.75; m:2.75; neurological signs: R:6.4–50; M:29.9; m:30.3; lipid disorders: R:55.5–71; M:63.3; m:63.3; leukopenia: R:6.6–8.3; M: 7.4; m:7.4 |
| Cabergoline | Dizziness and nausea: R:5–25; M:13.3; m:10; moderate to severe asthenia: R:10–20, M.15; m:15, |
| Pasireotide | Hyperglycemia:72.8; diarrhea:58; nausea:51.8; cholelithiasis:30.2; elevation in liver enzymes:29; abdominal pain: 24.1; upper abdominal pain: 9.9; hypocortisolism:8; prolongation of QT interval:1.8 |
| Mifepristone | Hypokalemia: R:25–34; M:29.5; m:29.5; hypertension: R:24–25; M:24.5; m:24.5; adrenal insufficiency: R:4–25; M:14.5; m:14.5 |

This table includes the adverse effects of the most commonly used pharmaceutical agents reported at least twice among the different studies, expect for the drug where only one male study is available. Abbreviations: R, range; M, mean; m, median.

with CD. These studies evaluating the effectiveness of this combination therapy in patients with CD suggested that it might be preferable to monotherapy when dosages higher than 1 g/d of aminoglutethimide are needed. At the doses used when the drugs have been administered together, the adverse effects were mild and reversible (528, 765).

Three different steroidogenesis inhibitors, such as mitotane, metyrapone, and ketoconazole, were administered to 11 patients with severe ACTH-dependent CS, of whom four had CD, for a median follow-up of 14 months (766). In particular, the 4 CD patients were followed for a period ranging from 14 to 42 months (mean: 23.7; median: 19.3), although the period of real triple combination therapy was 2–3.5 months; this period was followed by a period of mitotane monotherapy. In the totality of patients with ACTH-dependent CS, the starting dosages were metyrapone 2.25 g/d, ketoconazole 800 mg/d, and mitotane 3 g/d, but they were adjusted according to clinical severity, urinary cortisol excretion, and drug tolerance, reaching a final dose of metyrapone of 4.5 g/d, ketoconazole 1200 mg/d, and mitotane 5 g/d. The median dose of the three drugs used during the study were metyrapone 3 g/d, ketoconazole 800 mg/d, and mitotane 3 g/d. This combination treatment induced a rapid decrease of urinary cortisol excretion in all patients and also a rapid clinical improvement. However, adverse effects, including hypokalemia (100%), nausea and vomiting (63.7%), acute adrenal insufficiency (36.4%), dizziness and confusion (9.1%), and increases in liver enzymes (18.2–81.8%), were reported in a significant percentage of patients. The results of the study suggested that combination therapy with mitotane, metyrapone, and ketoconazole could be an effective alternative to bilateral adrenalectomy when immediate etiological treatment of severe CS is not feasible, but caution should be paid to adverse effects (766).

Preoperative therapy with ketoconazole and/or metyrapone has been performed in 62 patients with CS, among whom 52 had CD (506). The initial dosage of ketoconazole was 200–600 mg/d, and the metyrapone starting dosage was 750–1000 mg/d; the median duration of treatment was 4 months. Normalization of urinary cortisol levels was observed in 10 of 22 (45.4%) patients treated with combined ketoconazole and metyrapone therapy, of whom five (50%) had an improved clinical picture.

The second combination treatment group described in literature is represented by the combination with drugs acting at different levels of the HPA axis, in particular at pituitary and adrenal levels.

Vilar et al (659) demonstrated the usefulness of combination treatment with cabergoline and ketoconazole in 12 patients with CD. In this study, cabergoline monotherapy induced normalization of cortisol secretion in 25% of patients, whereas a partial decrease was observed in the remaining patients. In these latter patients, the addition of ketoconazole at the dosage of 200–400 mg/d induced normalization of urinary cortisol levels in an additional 66.7% of patients, demonstrating the effectiveness of combined cabergoline and ketoconazole treatment in 75% of patients (659).

Barbot et al (660) demonstrated that either the addition of ketoconazole, at the dosage of 200–600 mg/d, to an initial treatment with cabergoline or the addition of cabergoline, at the dosage of 1–3 mg/wk, to an initial treatment with ketoconazole was similarly effective in normalizing urinary cortisol levels, which was controlled in 79% of patients with good tolerability.

These studies demonstrated that the combination of cabergoline and low-dose ketoconazole might induce biochemical remission in a majority of patients with CD (659, 660). These data were also confirmed by similar data collected in a recent study by the authors of the current review (767).

An important study has evaluated the efficacy of a stepwise combination of pasireotide, cabergoline, and ketoconazole in 17 patients with CD. The initial treatment with pasireotide at the dosage of 300–750 mg/d induced normalization of urinary cortisol levels in 29% of patients; the addition of cabergoline at the dosage of 0.5–1.5 mg every other day in the remaining patients led to normalization of cortisol secretion in an additional 24% of patients; the final addition of ketoconazole at the dosage of 600 mg/d permitted the achievement of a complete response in an additional 35% of patients, with a final complete response in 88% of patients after 6 months of combined treatment (768). The results of this study clearly suggest that a combined treatment with different drugs might induce hormone normalization in a great percentage of patients with CD.

In summary, the combination of different drugs belonging to the same or to different categories of compounds seems to be able to enlarge the population of patients responsive to medical treatment in terms of the control of cortisol secretion. Further studies on larger populations of patients are required to balance the clinical advantages of this approach, in terms of the clinical impact of the drug benefits and adverse effects and the compliance of patients who have to increase the number of drugs taken during the course of the treatment.

### F. Experimental therapy

Different categories of drugs with potential for use in the management of CD or CS are under investigation,

either in phase II studies in patients with CD or in experimental settings.

A novel adrenal-directed drug, osilodrostat (LCI699), has been developed recently for potential use in the treatment of CD. Osilodrostat is a potent inhibitor of 11β-hydroxylase, the enzyme that catalyzes the last step of cortisol synthesis (769), but it also inhibits aldosterone synthase and is able to reduce blood pressure in patients with essential hypertension and primary hyperaldosteronism (770, 771). Osilodrostat and metyrapone have a similar mechanism of action; however, osilodrostat has a 3-fold higher affinity for its targeted sterodogenic enzyme, and it has a more than 2-fold longer half-life. These characteristics make osilodrostat more potent than metyrapone and allow for oral administration twice daily instead of four to six times daily (772, 773). Due to its effect in suppressing cortisol levels, osilodrostat is under investigation as a potential new treatment for CS. An open-label, proof-of-concept, single-arm study has been conducted to assess the safety and tolerability of osilodrostat in patients with CD after 10 weeks of treatment (772, 773). In this study, 12 CD patients received osilodrostat orally for 10 weeks. The drug was given at the starting dosage of 2 mg twice a day and was progressively increased on the basis of the urinary cortisol levels until their normalization or a maximum dosage of 50 mg twice a day was achieved. After 10 weeks of treatment, all 12 patients normalized urinary cortisol levels or achieved a $> 50\%$ reduction in urinary cortisol levels. Normalization of urinary cortisol levels was obtained at least once during the study in all 12 (100%) patients, and 11 (91.7%) patients had urinary cortisol levels within the normal range at the end of the 10 weeks of treatment (772, 773). The reduction of urinary cortisol levels was accompanied by a trend toward a decrease in blood pressure. The decrease in urinary cortisol levels resulted in a compensatory increase in ACTH levels, as well as in cortisol and aldosterone precursors and androgen levels. Osilodrostat was generally well tolerated, with the most frequently reported adverse events being fatigue (58.3%), nausea (41.7%), diarrhea (25%), headache (25%), hypokalemia (25%), muscle spasms (25%), and vomiting (25%) (772, 773). Four patients experienced a drug-related mild hypokalemia (minimum potassium levels, 3.1) and promptly recovered after potassium supplementation during the study. Recently, an amended extension of the phase II study has been performed with the overall purpose of evaluating the efficacy and safety of osilodrostat for a longer period of time (774, 775). The study included 19 patients, belonging to two different groups: the follow-up cohort ($n = 4$), comprised of patients enrolled in the previous study; and the expansion cohort ($n = 15$), comprised of newly enrolled patients. The main efficacy end-point was the proportion of response (defined as normalization or $\geq 50\%$ decrease from baseline in urinary cortisol levels) at weeks 10 and 22. After 10 weeks of treatment, all four patients (100%) in the follow-up cohort and 13 patients (86.7%) in the expansion cohort were considered responsive to treatment, with an overall success rate of 89.5%; after 22 weeks, three patients (75%) in the follow-up cohort and 12 patents (80%) in the expansion cohort remained controlled, resulting in a final response rate of 78.9%. The decrease in urinary cortisol levels was associated with improvements in the glucose and lipid profiles. Adverse events during this extension of the study included GI disturbances (nausea and diarrhea, 31.6%), asthenia (31.6%), and adrenal insufficiency (31.6%), together with an increase in ACTH, cortisol, and aldosterone precursors and an increase in testosterone, which was associated in some women with onset or worsening of acne and hirustism (774, 775). Therefore, osilodrostat seems to be a promising drug for the treatment of CD, with a satisfactory safety and tolerability profile. Despite these promising results, a phase III study on a larger number of patients followed for a longer period of time is mandatory to evaluate the real potential efficacy and safety of this novel adrenal-directed drug, as well as to determine whether patients will experience a late escape from response.

Additional novel compounds have been investigated in experimental settings and are considered to be promising agents for CD treatment.

The epidermal growth factor receptor (EGFR) blockers represent a category of these experimental compounds of potential utility in the management of CD. Indeed, EGFR was found to be expressed in pituitary tumors, mainly corticotroph tumors, where EGFR is also associated with reduced levels of p27/kip1; the down-regulation of p27/kip1 plays an important role in corticotroph tumorigenesis, suggesting a role for EGFR in the unbalanced growth of corticotroph tumor cells (776). More recently, gefitinib, an EGFR tyrosine kinase inhibitor, has been shown to attenuate hormone secretion, inhibit cell proliferation, and induce apoptosis in mouse corticotroph EGFR transfectants (777). Moreover, in athymic nude mice, EGFR overexpression enhanced the growth of explanted corticotroph tumors and glucocorticoid hormone secretion, whereas gefitinib treatment decreased both hormone secretion and tumor size in association with an improvement of the clinical syndrome (777).

The cyclin-dependent kinase (CDK) inhibitors might represent an interesting and potential class of compounds for the treatment of CD. Recently, a germline transgenic zebrafish was generated; this was characterized by the overexpression of pituitary tumor transforming gene

(PTTG/securin) targeted to the adenohypophyseal POMC lineage, which recapitulated early features pathognomonic of corticotroph tumors, including corticotroph expansion and partial glucocorticoid resistance (779). Adult transgenic zebrafish develop neoplastic corticotrophs and pituitary cyclin E up-regulation, as well as metabolic disturbances mimicking hypercortisolism caused by CD. A pharmacological CDK2/cyclin E inhibitor, R-roscovitine, which specifically reversed corticotroph expansion in live transgenic embryos, was found to suppress ACTH and corticosterone levels and also restrained tumor growth in a mouse model of ACTH-secreting pituitary tumors (778). Molecular analyses either in vitro or in vivo showed that R-roscovitine suppresses ACTH expression; induces corticotroph tumor cell senescence and cell cycle exit by up-regulating p27, p21, and p57; and down-regulates cyclin E expression. The results of this study suggested that the use of selective CDK inhibitors could effectively target corticotroph tumor growth and hormone secretion (778).

Finally, somatostatin-dopamine chimeric molecules may also represent a theoretically promising category of compounds useful for the management of CD. Indeed, somatostatin and dopamine receptors have been suggested to work synergistically, and both types of receptors are expressed in corticotroph pituitary tumors (779). Based on these observations, chimeric molecules, which bind with high affinity to both somatostatin and dopamine receptor subtypes, might have more enhanced potency than two separate dopamine agonist or somatostatin analogs in controlling hormone secretion and tumor growth in corticotroph pituitary tumors (779). With chronic administration, however, the chimeric compound mostly evaluated in in vivo studies, BIM-23A760, was found to produce a metabolite with dopaminergic activity that gradually accumulates and interferes with the activity of the parent compound. Consequently, efforts are currently under way to produce a second-generation chimeric compound for treatment of neuroendocrine disease (780).

It is important to emphasize that CD caused by an aggressive or malignant pituitary tumor may require a different therapeutic approach, represented by multiple pituitary surgery and one or more cycles of radiotherapy, more frequently than for benign pituitary tumor (781). Medical treatment in this specific category of patients may include chemotherapy, of which temozolamide, an orally administered second-generation alkylating chemoterapic agent, has been experimented in a group of patients with CD associated with aggressive pituitary adenoma and pituitary carcinoma, and it was described to be effective in obtaining disease control, although this is only based on limited experience (781).

## VI. Summary

CD is a severe disease associated with increased mortality, mainly related to cardiovascular and infectious diseases, and a serious burden, mostly due to metabolic complications and psychiatric disorders that significantly impair the health-related quality of life. Because the mortality of patients with CD is significantly associated with the time of exposure to cortisol excess, prompt normalization of cortisol secretion is mandatory to reverse the comorbities and prevent clinical complications associated with premature death. The goals of the treatment for CD include not only normalization of cortisol secretion with minimal damage and the consequent improvement of clinical picture and quality of life, but also removal of the tumor mass or control of tumor growth, with preservation of pituitary function and long-term control of the disease without recurrences. The management of CD requires a multidisciplinary and individualized approach. The first-line treatment for CD is presently pituitary surgery by the transsphenoidal approach, aiming at removal of the pituitary tumor. However, aside from the possibility of hypopituitarism, nearly one third of patients will experience an immediate failure or subsequent relapse during the 10 years after surgery. Therefore, a significant percentage of patients will require a second-line treatment approach. Second-line treatment may be represented by a repeat surgery, which is however associated with a lower chance of success and higher chance of hypopituitarism compared with the initial surgery, or more radical treatments such as pituitary radiotherapy and bilateral adrenalectomy. Pituitary radiotherapy successfully controls cortisol secretion in more than half of patients and has the advantage of being directed at the pituitary tumor, but the disadvantages are the latency between treatment and disease control, which may last several years, and the high risk of the occurrence of hypopituitarism. On the other hand, bilateral adrenalectomy is followed by immediately successful disease control in nearly the totality of patients. However, the main disadvantage of this therapeutic approach is the consequent adrenal insufficiency, requiring lifelong glucocorticoid and mineralocorticoid replacement. Moreover, this treatment is not directed at the pituitary tumor, which can subsequently keep increasing in size with the possible development of corticotroph tumor progression; prevention of this condition requires periodic monitoring of tumor mass. In the past, medical treatment played a secondary role in the management of CD because no agent had displayed sufficient efficacy and acceptable safety profile to be used routinely in clinical practice. However, in recent years, development and/or employment of novel compounds have significantly increased the role of phar-

macotherapy in the treatment strategies of CD. Medical treatment is presently used in different situations, including: presurgical treatment aimed at improving the clinical picture of patients before surgery; postsurgical treatment in case of unsuccessful pituitary surgery, which is aimed at controlling cortisol excess before a definitive therapy; bridging treatment before, during, and after the administration of radiotherapy, while awaiting its definitive effects; and primary treatment in case of severe disease, lack of indications, for instance due to a negligible curative chance, or contraindications, for instance due to a severe deterioration of the clinical condition, as well as in case of refusal, of surgery and/or radiotherapy. Different categories of drugs may be used in the treatment of CD. Among these, the adrenal-directed drugs do not act at the level of the pituitary tumor, so that they are generally used in the short term for controlling cortisol excess and the clinical picture before choosing a more definitive approach. The most commonly used drug is ketoconazole, which is effective in a significant number of patients but is associated with treatment escape and hepatotoxicity. On the other hand, the pituitary-directed drugs currently include two main agents: the dopamine agonist cabergoline, which has been shown to be effective in a subset of patients in studies on a limited number of patients and to have a good tolerability profile, with hypotension as a possible adverse effect, and the association of possible treatment escape; and the somatostatin analog pasireotide, which has been shown in a study on a large number of patients to be effective in a similar subset of patients with CD, with hyperglycemia and GI discomfort as common adverse events. Cabergoline and pasireotide have the advantage of acting at the level of the pituitary tumor, with potential effectiveness in inducing tumor shrinkage. However, whereas cabergoline is used as an off-label therapy, pasireotide is the only pituitary-directed agent to have obtained official approval by EMA and FDA, with the indication for treatment of patients with CD who are not candidates for surgery or who have not responded to surgery. The last category of drugs is represented by the glucocorticoid receptor antagonist mifepristone, which peripherally blocks cortisol action with a rapid improvement of the clinical syndrome. However, because of its action on blocking not only glucocorticoid but also different steroid hormone receptors, and because of the increased circulating cortisol levels, which activate the mineralocorticoid receptor, mifepristone is associated with adverse effects that include hypokalemia and adrenal insufficiency. Its main disadvantage is the lack of a biomarker to monitor the efficacy of the drug and to adjust its dosage in order to balance the best therapeutical effect with the minimal impact on adverse effects. Mifepristone has been approved by the FDA for the treatment of hyperglycemia in adult patients with endogenous CS who have type 2 diabetes mellitus or glucose intolerance and who failed surgery or are not candidates for surgery. Presently, the availability of different agents able to control cortisol secretion has raised the possibility of combination medical therapy with the purpose of normalizing cortisol secretion in a larger number of patients with potentially improved safety. Experience with the combined use of cabergoline and ketoconazole or pasireotide and cabergoline and ketoconazole demonstrated a control of cortisol excess in up to 90% of patients with CD, and it is suggested as an interesting possible treatment strategy, especially for patients who experienced a failure of pituitary surgery or patients who are not candidates for surgery. However, any chronic or even lifelong medical treatment for CD, as monotherapy or combined therapy, needs an accurate evaluation of the ratio between costs and benefits of the specific treatment strategy. In summary, the modern view of the medical treatment of CD is based on the concept of the tailoring of treatment, which should be chosen in order to be adapted to the single patient on the basis of the patient's features (gender and desire of conception), disease characteristics (disease severity and duration, and presence and comorbidites, and concomitant medications), and tumor features (microadenoma or macroadenoma, invisible tumor, or aggressive tumor), besides the consideration of the ratio between costs and benefits of the specific treatment. Independent of the type of treatment, the goal of the management of CD is to rapidly control cortisol excess to reverse the clinical syndrome and the systemic complications, which are associated with increased mortality of patients with CD.

## Acknowledgments

We are greatly indebted to Keri Wellington, PhD, and Dr Gillian Walker, PhD, for English language assistance. We are grateful to the "Cushing's team" of the Department of Clinical Medicine and Surgery, Federico II University of Naples, including, besides the authors of the current review, Maria Cristina De Martino, Chiara Simeoli, Francesco Carlomagno, and Rosario Ferrigno, who significantly contributed to the revision of the review, as well as Davide Iacuaniello, who contributed to the management of patients with Cushing's disease, and Renata Simona Auriemma, Claudia Pivonello, Donatella Paola Provvisiero, Roberta Patalano, Maria Rosaria Negri, Cristina De Angelis, Gaia Cuomo, Giacomo Galdiero, Gilda Di Gennaro, belonging to the Pituitary and Laboratory team, for their help in revising the proof of this review. We are grateful to the entire pituitary network of the Naples Center, including the neurosurgical team, particularly Paolo Cappabianca, Luigi Maria Cavallo, and Domenico Solari; the radiological team, particularly Francesco Briganti, Sossio Cirillo, Fabio Tortora, Ferdinando Caranci, and Andrea Elefante; and the pathological team, particularly Maria Laura Del Basso De Caro and Elia Guadagno, for the routine management of patients with Cushing's disease.

Address all correspondence and requests for reprints to: Rosario Pivonello, Dipartimento di medicina clinica e chirurgia, Università Federico II di Napoli, Via Sergio Pansini, 5, 80131 Naples, Italy. E-mail: rosario.pivonello@unina.it.

Disclosure Summary: R.P. has been Principal Investigator of Research Studies for Novartis; received research grants from Novartis, Pfizer, HRA Pharma, and Viropharma; has been an occasional consultant for Novartis, Ipsen, Pfizer, Viropharma, Ferring, and Italfarmaco; and has received fees and honoraria for presentations from Novartis. M.D.L. has nothing to disclose. A.Coz. received a fee for a presentation from Novartis. A.Col. has been Principal Investigator of Research Studies for Novartis, Ipsen, and Pfizer; received research grants from Novartis, Ipsen, Pfizer, Ferring, Lilly, Novo Nordisk, HRA Pharma, and Italfarmaco; has been an occasional consultant for Novartis, Ipsen, Pfizer, and Italfarmaco; and has received fees and honoraria for presentations from Novartis and Ipsen.

## References


1. **Pivonello R, De Martino MC, De Leo M, Lombardi G, Colao A.** Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2008;37(1):135–149; ix.
2. **Newell-Price J, Bertagna X, Grossman AB, Nieman LK.** Cushing's syndrome. *Lancet*. 2006;367(9522):1605–1617.
3. **Steffensen C, Bak AM, Rubeck KZ, Jørgensen JO.** Epidemiology of Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):1–5.
4. **Arnaldi G, Angeli A, Atkinson AB, et al.** Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2003;88(12):5593–5602.
5. **Newell-Price J, Trainer P, Besser M, Grossman A.** The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev*. 1998;19(5):647–672.
6. **Nieman LK, Biller BM, Findling JW, et al.** The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526–1540.
7. **Biller BM, Grossman AB, Stewart PM, et al.** Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2008;93(7):2454–2462.
8. **Feelders RA, Pulgar SJ, Kempel A, Pereira AM.** The burden of Cushing's disease: clinical and health-related quality of life aspects. *Eur J Endocrinol*. 2012;167(3):311–326.
9. **Clayton RN.** Mortality in Cushing's disease. *Neuroendocrinology*. 2010;92(suppl 1):71–76.
10. **Etxabe J, Vazquez JA.** Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clin Endocrinol (Oxf)*. 1994;40(4):479–484.
11. **Swearingen B, Biller BM, Barker FG 2nd, et al.** Long-term mortality after transsphenoidal surgery for Cushing disease. *Ann Intern Med*. 1999;130(10):821–824.
12. **Pikkarainen L, Sane T, Reunanen A.** The survival and well-being of patients treated for Cushing's syndrome. *J Intern Med*. 1999;245(5):463–468.
13. **Lindholm J, Juul S, Jørgensen JO, et al.** Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin Endocrinol Metab*. 2001;86(1):117–123.
14. **Hammer GD, Tyrrell JB, Lamborn KR, et al.** Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *J Clin Endocrinol Metab*. 2004;89(12):6348–6357.
15. **Dekkers OM, Biermasz NR, Pereira AM, et al.** Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab*. 2007;92(3):976–981.
16. **Clayton RN, Raskauskiene D, Reulen RC, Jones PW.** Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metab*. 2011;96(3):632–642.
17. **Bolland MJ, Holdaway IM, Berkeley JE, et al.** Mortality and morbidity in Cushing's syndrome in New Zealand. *Clin Endocrinol (Oxf)*. 2011;75(4):436–442.
18. **Hassan-Smith ZK, Sherlock M, Reulen RC, et al.** Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. *J Clin Endocrinol Metab*. 2012;97(4):1194–1201.
19. **Yaneva M, Kalinov K, Zacharieva S.** Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. *Eur J Endocrinol*. 2013;169(5):621–627.
20. **Ntali G, Asimakopoulou A, Siamatras T, et al.** Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. *Eur J Endocrinol*. 2013;169(5):715–723.
21. **Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD, Geer EB.** Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. *J Clin Endocrinol Metab*. 2013;98(3):1022–1030.
22. **Dekkers OM, Horváth-Puhó E, Jørgensen** JO, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metab*. 2013;98(6):2277–2284.
23. **Pivonello R, Melnichenko G, Zacharieva S, et al.** Mission study: an international observational study on the mortality in Cushing's syndrome. In: Proceedings from the European Congress of Endocrinology; April 30-May 4, 2011; Rotterdam, The Netherlands.
24. **Graversen D, Vestergaard P, Stochholm K, Gravholt CH, Jørgensen JO.** Mortality in Cushing's syndrome: a systematic review and meta-analysis. *Eur J Intern Med*. 2012;23(3):278–282.
25. **Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G.** High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. *Clin Endocrinol (Oxf)*. 2004;61(6):768–777.
26. **Pivonello R, Faggiano A, Lombardi G, Colao A.** The metabolic syndrome and cardiovascular risk in Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2005;34(2):327–339, viii.
27. **De Leo M, Pivonello R, Auriemma RS, et al.** Cardiovascular disease in Cushing's syndrome: heart versus vasculature. *Neuroendocrinology*. 2010;92(suppl 1):50–54.
28. **Faggiano A, Pivonello R, Spiezia S, et al.** Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. *J Clin Endocrinol Metab*. 2003;88(6):2527–2533.
29. **Colao A, Pivonello R, Spiezia S, et al.** Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *J Clin Endocrinol Metab*. 1999;84(8):2664–2672.

30. **Albiger N, Testa RM, Almoto B, et al.** Patients with Cushing's syndrome have increased intimal media thickness at different vascular levels: comparison with a population matched for similar cardiovascular risk factors. *Horm Metab Res*. 2006;38:405–410.
31. **Neary NM, Booker OJ, Abel BS, et al.** Hypercortisolism is associated with increased coronary arterial atherosclerosis: analysis of noninvasive coronary angiography using multidetector computerized tomography. *J Clin Endocrinol Metab*. 2013;98(5):2045–2052.
32. **Baykan M, Erem C, Gedikli O, et al.** Impairment of flow-mediated vasodilatation of brachial artery in patients with Cushing's syndrome. *Endocrine*. 2007;31(3):300–304.
33. **Magiakou MA, Smyrnaki P, Chrousos GP.** Hypertension in Cushing's syndrome. *Best Pract Res Clin Endocrinol Metab*. 2006;20(3):467–482.
34. **Cicala MV, Mantero F.** Hypertension in Cushing's syndrome: from pathogenesis to treatment. *Neuroendocrinology*. 2010;92(suppl 1):44–49.
35. **van der Pas R, van Esch JH, de Bruin C, et al.** Cushing's disease and hypertension: in vivo and in vitro study of the role of the renin-angiotensin-aldosterone system and effects of medical therapy. *Eur J Endocrinol*. 2014;170(2):181–191.
36. **Isidori AM, Graziadio C, Paragliola RM, et al.** The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications. *J Hypertens*. 2015;33(1):44–60.
37. **Pecori Giraldi F, Toja PM, De Martin M, et al.** Circadian blood pressure profile in patients with active Cushing's disease and after long-term cure. *Horm Metab Res*. 2007;39:908–914.
38. **Trementino L, Arnaldi G, Appolloni G, et al.** Coagulopathy in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):55–59.
39. **van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA.** Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol (Oxf)*. 2013;78(4):481–488.
40. **Boscaro M, Sonino N, Scarda A, et al.** Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. *J Clin Endocrinol Metab*. 2002;87(8):3662–3666.
41. **Terzolo M, Allasino B, Bosio S, et al.** Hyperhomocysteinemia in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2004;89(8):3745–3751.
42. **Faggiano A, Melis D, Alfieri R, et al.** Sulfur amino acids in Cushing's disease: insight in homocysteine and taurine levels in patients with active and cured disease. *J Clin Endocrinol Metab*. 2005;90(12):6616–6622.
43. **Muiesan ML, Lupia M, Salvetti M, et al.** Left ventricular structural and functional characteristics in Cushing's syndrome. *J Am Coll Cardiol*. 2003;41(12):2275–2279.
44. **Pereira AM, Delgado V, Romijn JA, Smit JW, Bax JJ, Feelders RA.** Cardiac dysfunction is reversed upon successful treatment of Cushing's syndrome. *Eur J Endocrinol*. 2010;162(2):331–340.
45. **Toja PM, Branzi G, Ciambellotti F, et al.** Clinical relevance of cardiac structure and function abnormalities in patients with Cushing's syndrome before and after cure. *Clin Endocrinol (Oxf)*. 2012;76(3):332–338.
46. **Fallo F, Maffei P, Dalla Pozza A, et al.** Cardiovascular autonomic function in Cushing's syndrome. *J Endocrinol Invest*. 2009;32(1):41–45.
47. **Barahona MJ, Resmini E, Viladés D, et al.** Coronary artery disease detected by multislice computed tomography in patients after long-term cure of Cushing's syndrome. *J Clin Endocrinol Metab*. 2013;98(3):1093–1099.
48. **Kassi E, Pervanidou P, Kaltsas G, Chrousos G.** Metabolic syndrome: definitions and controversies. *BMC Med*. 2011;9:48.
49. **Chanson P, Salenave S.** Metabolic syndrome in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):96–101.
50. **Munir A, Newell-Price J.** Management of diabetes mellitus in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):82–85.
51. **Pivonello R, De Leo M, Vitale P, et al.** Pathophysiology of diabetes mellitus in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):77–81.
52. **Giordano C, Guarnotta V, Pivonello R, et al.** Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? *Eur J Endocrinol*. 2014;170(2):311–319.
53. **Arnaldi G, Scandali VM, Trementino L, Cardinaletti M, Appolloni G, Boscaro M.** Pathophysiology of dyslipidemia in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):86–90.
54. **Greenman Y.** Management of dyslipidemia in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):91–95.
55. **Würzburger MI, Prelević GM, Brkiæ SD, Vuckoviæ S, Pendiæ B.** Cushing's syndrome–transitory immune deficiency state? *Postgrad Med J*. 1986;62:657–659.
56. **Chrousos GP.** The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332:1351–1362.
57. **Silverman MN, Sternberg EM.** Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann NY Acad Sci*. 2012;1261:55–63.
58. **Graham BS, Tucker WS Jr.** Opportunistic infections in endogenous Cushing's syndrome. *Ann Intern Med*. 1984;101(3):334–338.
59. **Bakker RC, Gallas PR, Romijn JA, Wiersinga WM.** Cushing's syndrome complicated by multiple opportunistic infections. *J Endocrinol Invest*. 1998;21(5):329–333.
60. **Lionakis MS, Kontoyiannis DP.** Glucocorticoids and invasive fungal infections. *Lancet*. 2003;362(9398):1828–1838.
61. **Pereira AM, Tiemensma J, Romijn JA.** Neuropsychiatric disorders in Cushing's syndrome. *Neuroendocrinology*. 2010;92(suppl 1):65–70.
62. **Sonino N, Fava GA.** Psychiatric disorders associated with Cushing's syndrome. Epidemiology, pathophysiology and treatment. *CNS Drugs*. 2001;15(5):361–373.
63. **Sonino N, Fallo F, Fava GA.** Psychosomatic aspects of Cushing's syndrome. *Rev Endocr Metab Disord*. 2010;11(2):95–104.
64. **Sonino N, Fava GA, Raffi AR, Boscaro M, Fallo F.** Clinical correlates of major depression in Cushing's disease. *Psychopathology*. 1998;31(6):302–306.
65. **Haskett RF.** Diagnostic categorization of psychiatric disturbance in Cushing's syndrome. *Am J Psychiatry*. 1985;142(8):911–916.
66. **Starkman MN, Schteingart DE, Schork MA.** Depressed

mood and other psychiatric manifestations of Cushing's syndrome: relationship to hormone levels. *Psychosom Med*. 1981;43(1):3–18.
67. **Starkman MN.** Neuropsychiatric findings in Cushing syndrome and exogenous glucocorticoid administration. *Endocrinol Metab Clin North Am*. 2013;42(3):477–488.
68. **Dorn LD, Burgess ES, Dubbert B, et al.** Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. *Clin Endocrinol (Oxf)*. 1995; 43(4):433–442.
69. **Hudson JI, Hudson MS, Griffing GT, Melby JC, Pope HG Jr.** Phenomenology and family history of affective disorder in Cushing's disease. *Am J Psychiatry*. 1987;144(7):951–953.
70. **Loosen PT, Chambliss B, DeBold CR, Shelton R, Orth DN.** Psychiatric phenomenology in Cushing's disease. *Pharmacopsychiatry*. 1992;25(4):192–198.
71. **Boscaro M, Barzon L, Sonino N.** The diagnosis of Cushing's syndrome: atypical presentations and laboratory shortcomings. *Arch Intern Med*. 2000;160(20):3045–3053.
72. **Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW, Chrousos GP.** The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *J Clin Endocrinol Metab*. 1997;82(3):912–919.
73. **Simmons NE, Do HM, Lipper MH, Laws ER Jr.** Cerebral atrophy in Cushing's disease. *Surg Neurol*. 2000;53(1):72–76.
74. **Bourdeau I, Bard C, Noël B, et al.** Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. *J Clin Endocrinol Metab*. 2002;87(5):1949–1954.
75. **Tiemensma J, Kokshoorn NE, Biermasz NR, et al.** Subtle cognitive impairments in patients with long-term cure of Cushing's disease. *J Clin Endocrinol Metab*. 2010;95(6): 2699–2714.
76. **Ragnarsson O, Berglund P, Eder DN, Johannsson G.** Long-term cognitive impairments and attentional deficits in patients with Cushing's disease and cortisol-producing adrenal adenoma in remission. *J Clin Endocrinol Metab*. 2012; 97(9):E1640–E1648.
77. **Webb SM, Badia X, Barahona MJ, et al.** Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. *Eur J Endocrinol*. 2008; 158(5):623–630.
78. **van Aken MO, Pereira AM, Biermasz NR, et al.** Quality of life in patients after long-term biochemical cure of Cushing's disease. *J Clin Endocrinol Metab*. 2005;90(6):3279–3286.
79. **Wagenmakers MA, Netea-Maier RT, Prins JB, Dekkers T, den Heijer M, Hermus AR.** Impaired quality of life in patients in long-term remission of Cushing's syndrome of both adrenal and pituitary origin: a remaining effect of long-standing hypercortisolism? *Eur J Endocrinol*. 2012; 167(5):687–695.
80. **Colao A, Cozzolino A, Pivonello R.** Quality of life in patients with Cushing's disease: a modern approach. *Clin Endocrinol (Oxf)*. 2012;76(6):776–777.
81. **Milian M, Teufel P, Honegger J, Gallwitz B, Schnauder G, Psaras T.** The development of the Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25). Part I: construction and psychometric properties. *Clin Endocrinol (Oxf)*. 2012;76(6):851–860.
82. **Milian M, Teufel P, Honegger J, Gallwitz B, Schnauder G, Psaras T.** The development of the Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25). Part II: normative data from 1784 healthy people. *Clin Endocrinol (Oxf)*. 2012;76(6):861–867.
83. **Pivonello R, De Martino MC, De Leo M, et al.** Cushing's syndrome: aftermath of the cure. *Arq Bras Endocrinol Metabol*. 2007;51(8):1381–1391.
84. **Miller JW, Crapo L.** The medical treatment of Cushing's syndrome. *Endocr Rev*. 1993;14(4):443–458.
85. **Tritos NA, Biller BM, Swearingen B.** Management of Cushing disease. *Nat Rev Endocrinol*. 2011;7(5):279–289.
86. **Juszczak A, Ertorer ME, Grossman A.** The therapy of Cushing's disease in adults and children: an update. *Horm Metab Res*. 2013;45(2):109–117.
87. **Bertagna X, Guignat L, Groussin L, Bertherat J.** Cushing's disease. *Best Pract Res Clin Endocrinol Metab*. 2009; 23(5):607–623.
88. **Beauregard C, Dickstein G, Lacroix A.** Classic and recent etiologies of Cushing's syndrome: diagnosis and therapy. *Treat Endocrinol*. 2002;1(2):79–94.
89. **Czepielewski MA, Rollin GA, Casagrande A, Ferreira NP.** Criteria of cure and remission in Cushing's disease: an update. *Arq Bras Endocrinol Metabol*. 2007;51(8):1362–1372.
90. **Ayala A, Manzano AJ.** Detection of recurrent Cushing's disease: proposal for standardized patient monitoring following transsphenoidal surgery. *J Neurooncol*. 2014; 119(2):235–242.
91. **Lüdecke D, Kautzky R, Saeger W, Schrader D.** Selective removal of hypersecreting pituitary adenomas? An analysis of endocrine function, operative and microscopical findings in 101 cases. *Acta Neurochir (Wien)*. 1976;35:27–42.
92. **Carmalt MH, Dalton GA, Fletcher RF, Smith WT.** The treatment of Cushing's disease by trans-sphenoidal hypophysectomy. *Q J Med*. 1977;46(181):119–134.
93. **Salassa RM, Laws ER Jr, Carpenter PC, Northcutt RC.** Transsphenoidal removal of pituitary microadenoma in Cushing's disease. *Mayo Clin Proc*. 1978;53(1):24–28.
94. **Tyrrell JB, Brooks RM, Fitzgerald PA, Cofoid PB, Forsham PH, Wilson CB.** Cushing's disease. Selective transsphenoidal resection of pituitary microadenomas. *N Engl J Med*. 1978;298(14):753–758.
95. **Wajchenberg BL, Silveira AA, Goldman J, Cesar FP, Marino R Jr, Lima SS.** Evaluation of resection of pituitary microadenoma for the treatment of Cushing's disease in patients with radiologically normal sella turcica. *Clin Endocrinol (Oxf)*. 1979;11(3):323–331.
96. **Guthrie FW Jr, Ciric I, Hayashida S, Kerr WD Jr, Murphy ED.** Pituitary Cushing's syndrome and Nelson's syndrome: diagnostic criteria, surgical therapy, and results. *Surg Neurol*. 1981;16(5):316–323.
97. **Hardy J.** Presidential address: XVII Canadian Congress of Neurological Sciences. Cushing's disease: 50 years later. *Can J Neurol Sci*. 1982;9(4):375–380.
98. **Boggan JE, Tyrrell JB, Wilson CB.** Transsphenoidal microsurgical management of Cushing's disease. Report of 100 cases. *J Neurosurg*. 1983;59(2):195–200.

99. **Thomas JP, Richards SH.** Long term results of radical hypophysectomy for Cushing's disease. *Clin Endocrinol (Oxf)*. 1983;19(5):629–636.
100. **Burch WM.** Cushing's disease. A review. *Arch Intern Med*. 1985;145(6):1106–1111.
101. **Brand IR, Dalton GA, Fletcher RF.** Long-term follow up of trans-sphenoidal hypophysectomy for Cushing's disease. *J R Soc Med*. 1985;78(4):291–293.
102. **Tagliaferri M, Berselli ME, Loli P.** Transsphenoidal microsurgery for Cushing's disease. *Acta Endocrinol (Copenh)*. 1986;113(1):5–11.
103. **Fahlbusch R, Buchfelder M, Müller OA.** Transsphenoidal surgery for Cushing's disease. *J R Soc Med*. 1986;79(5):262–269.
104. **Nakane T, Kuwayama A, Watanabe M, et al.** Long term results of transsphenoidal adenomectomy in patients with Cushing's disease. *Neurosurgery*. 1987;21(2):218–222.
105. **Chandler WF, Schteingart DE, Lloyd RV, McKeever PE, Ibarra-Perez G.** Surgical treatment of Cushing's disease. *J Neurosurg*. 1987;66(2):204–212.
106. **Mampalam TJ, Tyrrell JB, Wilson CB.** Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. *Ann Intern Med*. 1988;109(6):487–493.
107. **Pieters GF, Hermus AR, Meijer E, Smals AG, Kloppenborg PW.** Predictive factors for initial cure and relapse rate after pituitary surgery for Cushing's disease. *J Clin Endocrinol Metab*. 1989;69(6):1122–1126.
108. **Tindall GT, Herring CJ, Clark RV, Adams DA, Watts NB.** Cushing's disease: results of transsphenoidal microsurgery with emphasis on surgical failures. *J Neurosurg*. 1990;72(3):363–369.
109. **McCance DR, Gordon DS, Fannin TF, et al.** Assessment of endocrine function after transsphenoidal surgery for Cushing's disease. *Clin Endocrinol (Oxf)*. 1993;38(1):79–86.
110. **Trainer PJ, Lawrie HS, Verhelst J, et al.** Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. *Clin Endocrinol (Oxf)*. 1993;38(1):73–78.
111. **van Aken MO, de Herder WW, van der Lely AJ, de Jong FH, Lamberts SW.** Postoperative metyrapone test in the early assessment of outcome of pituitary surgery for Cushing's disease. *Clin Endocrinol (Oxf)*. 1997;47(2):145–149.
112. **Blevins LS Jr, Christy JH, Khajavi M, Tindall GT.** Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. *J Clin Endocrinol Metab*. 1998;83(1):63–67.
113. **Semple PL, Laws ER Jr.** Complications in a contemporary series of patients who underwent transsphenoidal surgery for Cushing's disease. *J Neurosurg*. 1999;91(2):175–179.
114. **Invitti C, Pecori Giraldi F, de Martin M, Cavagnini F.** Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. *J Clin Endocrinol Metab*. 1999;84(2):440–448.
115. **Barbetta L, Dall'Asta C, Tomei G, Locatelli M, Giovanelli M, Ambrosi B.** Assessment of cure and recurrence after pituitary surgery for Cushing's disease. *Acta Neurochir (Wien)*. 2001;143(5):477–481; discussion 481–472.
116. **Simmons NE, Alden TD, Thorner MO, Laws ER Jr.** Serum cortisol response to transsphenoidal surgery for Cushing disease. *J Neurosurg*. 2001;95(1):1–8.
117. **Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF.** Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. *Clin Endocrinol (Oxf)*. 2002;56(4):541–551.
118. **Yap LB, Turner HE, Adams CB, Wass JA.** Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. *Clin Endocrinol (Oxf)*. 2002;56(1):25–31.
119. **Cannavò S, Almoto B, Dall'Asta C, et al.** Long-term results of treatment in patients with ACTH-secreting pituitary macroadenomas. *Eur J Endocrinol*. 2003;149(3):195–200.
120. **Rollin GA, Ferreira NP, Junges M, Gross JL, Czepielewski MA.** Dynamics of serum cortisol levels after transsphenoidal surgery in a cohort of patients with Cushing's disease. *J Clin Endocrinol Metab*. 2004;89(3):1131–1139.
121. **Salenave S, Gatta B, Pecheur S, et al.** Pituitary magnetic resonance imaging findings do not influence surgical outcome in adrenocorticotropin-secreting microadenomas. *J Clin Endocrinol Metab*. 2004;89(7):3371–3376.
122. **De Tommasi C, Vance ML, Okonkwo DO, Diallo A, Laws ER Jr.** Surgical management of adrenocorticotropic hormone-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndrome. *J Neurosurg*. 2005;103(5):825–830.
123. **Esposito F, Dusick JR, Cohan P, et al.** Clinical review: early morning cortisol levels as a predictor of remission after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab*. 2006;91(1):7–13.
124. **Acebes JJ, Martino J, Masuet C, Montanya E, Soler J.** Early post-operative ACTH and cortisol as predictors of remission in Cushing's disease. *Acta Neurochir (Wien)*. 2007;149:471–477; discussion 477–9.
125. **Krikorian A, Abdelmannan D, Selman WR, Arafah BM.** Cushing disease: use of perioperative serum cortisol measurements in early determination of success following pituitary surgery. *Neurosurg Focus*. 2007;23(3):E6.
126. **Rollin G, Ferreira NP, Czepielewski MA.** Prospective evaluation of transsphenoidal pituitary surgery in 108 patients with Cushing's disease. *Arq Bras Endocrinol Metabol*. 2007;51(8):1355–1361.
127. **Dehdashti AR, Gentili F.** Current state of the art in the diagnosis and surgical treatment of Cushing disease: early experience with a purely endoscopic endonasal technique. *Neurosurg Focus*. 2007;23(3):E9.
128. **Prevedello DM, Pouratian N, Sherman J, et al.** Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. *J Neurosurg*. 2008;109(4):751–759.
129. **Fomekong E, Maiter D, Grandin C, Raftopoulos C.** Outcome of transsphenoidal surgery for Cushing's disease: a high remission rate in ACTH-secreting macroadenomas. *Clin Neurol Neurosurg*. 2009;111(5):442–449.
130. **Jagannathan J, Smith R, DeVroom HL, et al.** Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease. *J Neurosurg*. 2009;111:531–539.
131. **Sughrue ME, Shah JK, Devin JK, Kunwar S, Blevins LS Jr.** Utility of the immediate postoperative cortisol concentra-

tions in patients with Cushing's disease. *Neurosurgery*. 2010;67(3):688–695; discussion 695.
132. **Ammini AC, Bhattacharya S, Sahoo JP, et al.** Cushing's disease: results of treatment and factors affecting outcome. *Hormones (Athens)*. 2011;10(3):222–229.
133. **Ciric I, Zhao JC, Du H, et al.** Transsphenoidal surgery for Cushing disease: experience with 136 patients. *Neurosurgery*. 2012;70(1):70–80; discussion 80–81.
134. **Wagenmakers MA, Boogaarts HD, Roerink SH, et al.** Endoscopic transsphenoidal pituitary surgery: a good and safe primary treatment option for Cushing's disease, even in case of macroadenomas or invasive adenomas. *Eur J Endocrinol*. 2013;169(3):329–337.
135. **Alexandraki KI, Kaltsas GA, Isidori AM, et al.** Long-term remission and recurrence rates in Cushing's disease: predictive factors in a single-centre study. *Eur J Endocrinol*. 2013;168(4):639–648.
136. **Berker M, Işikay I, Berker D, Bayraktar M, Gürlek A.** Early promising results for the endoscopic surgical treatment of Cushing's disease. *Neurosurg Rev*. 2014;37:105–114.
137. **Starke RM, Reames DL, Chen CJ, Laws ER, Jane JA Jr.** Endoscopic transsphenoidal surgery for Cushing disease: techniques, outcomes, and predictors of remission. *Neurosurgery*. 2013;72(2):240–247; discussion 247.
138. **Locatelli M, Bertani G, Carrabba G, et al.** The trans-sphenoidal resection of pituitary adenomas in elderly patients and surgical risk. *Pituitary*. 2013;16(2):146–151.
139. **Aranda G, Enseñat J, Mora M, et al.** Long-term remission and recurrence rate in a cohort of Cushing's disease: the need for long-term follow-up. *Pituitary*. 2015;18:142–149.
140. **Pereira AM, van Aken MO, van Dulken H, et al.** Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. *J Clin Endocrinol Metab*. 2003;88(12):5858–5864.
141. **Valassi E, Biller BM, Swearingen B, et al.** Delayed remission after transsphenoidal surgery in patients with Cushing's disease. *J Clin Endocrinol Metab*. 2010;95(2):601–610.
142. **Fitzgerald PA, Aron DC, Findling JW, et al.** Cushing's disease: transient secondary adrenal insufficiency after selective removal of pituitary microadenomas; evidence for a pituitary origin. *J Clin Endocrinol Metab*. 1982;54(2):413–422.
143. **AbdelMannan D, Selman WR, Arafah BM.** Peri-operative management of Cushing's disease. *Rev Endocr Metab Disord*. 2010;11(2):127–134.
144. **Lindsay JR, Oldfield EH, Stratakis CA, Nieman LK.** The postoperative basal cortisol and CRH tests for prediction of long-term remission from Cushing's disease after transsphenoidal surgery. *J Clin Endocrinol Metab*. 2011;96(7):2057–2064.
145. **Estrada J, García-Uría J, Lamas C, et al.** The complete normalization of the adrenocortical function as the criterion of cure after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab*. 2001;86(12):5695–5699.
146. **Bochicchio D, Losa M, Buchfelder M.** Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. *J Clin Endocrinol Metab*. 1995;80(11):3114–3120.
147. **Ram Z, Nieman LK, Cutler GB Jr, Chrousos GP, Doppman JL, Oldfield EH.** Early repeat surgery for persistent Cushing's disease. *J Neurosurg*. 1994;80(1):37–45.
148. **Locatelli M, Vance ML, Laws ER.** Clinical review: the strategy of immediate reoperation for transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab*. 2005;90(9):5478–5482.
149. **Hameed N, Yedinak CG, Brzana J, et al.** Remission rate after transsphenoidal surgery in patients with pathologically confirmed Cushing's disease, the role of cortisol, ACTH assessment and immediate reoperation: a large single center experience. *Pituitary*. 2013;16(4):452–458.
150. **Berker M, Hazer DB, Yücel T, et al.** Complications of endoscopic surgery of the pituitary adenomas: analysis of 570 patients and review of the literature. *Pituitary*. 2012;15(3):288–300.
151. **Graham KE, Samuels MH, Raff H, Barnwell SL, Cook DM.** Intraoperative adrenocorticotropin levels during transsphenoidal surgery for Cushing's disease do not predict cure. *J Clin Endocrinol Metab*. 1997;82(6):1776–1779.
152. **Pimentel-Filho FR, Cukiert A, Miyashita F, et al.** Adrenocorticotropin levels do not change during early recovery of transsphenoidal surgery for ACTH-secreting pituitary tumors. *J Endocrinol Invest*. 2001;24(2):83–87.
153. **Czirják S, Bezzegh A, Gál A, Rácz K.** Intra- and postoperative plasma ACTH concentrations in patients with Cushing's disease cured by transsphenoidal pituitary surgery. *Acta Neurochir (Wien)*. 2002;144(10):971–977; discussion 977.
154. **Flitsch J, Knappe UJ, Lüdecke DK.** The use of postoperative ACTH levels as a marker for successful transsphenoidal microsurgery in Cushing's disease. *Zentralbl Neurochir*. 2003;64(1):6–11.
155. **Srinivasan L, Laws ER, Dodd RL, et al.** The dynamics of post-operative plasma ACTH values following transsphenoidal surgery for Cushing's disease. *Pituitary*. 2011;14(4):312–317.
156. **Guilhaume B, Bertagna X, Thomsen M, et al.** Transsphenoidal pituitary surgery for the treatment of Cushing's disease: results in 64 patients and long term follow-up studies. *J Clin Endocrinol Metab*. 1988;66(5):1056–1064.
157. **Arnott RD, Pestell RG, McKelvie PA, Henderson JK, McNeill PM, Alford FP.** A critical evaluation of transsphenoidal pituitary surgery in the treatment of Cushing's disease: prediction of outcome. *Acta Endocrinol (Copenh)*. 1990;123(4):423–430.
158. **Burke CW, Adams CB, Esiri MM, Morris C, Bevan JS.** Transsphenoidal surgery for Cushing's disease: does what is removed determine the endocrine outcome? *Clin Endocrinol (Oxf)*. 1990;33(4):525–537.
159. **Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M.** Risk factors and long-term outcome in pituitary-dependent Cushing's disease. *J Clin Endocrinol Metab*. 1996;81(7):2647–2652.
160. **Shimon I, Ram Z, Cohen ZR, Hadani M.** Transsphenoidal surgery for Cushing's disease: endocrinological follow-up monitoring of 82 patients. *Neurosurgery*. 2002;51(1):57–61; discussion 61–52.

161. **Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B.** Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. *Clin Endocrinol (Oxf)*. 2005;63(5):549–559.
162. **Patil CG, Prevedello DM, Lad SP, et al.** Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *J Clin Endocrinol Metab*. 2008;93(2):358–362.
163. **Kim JH, Shin CS, Paek SH, Jung HW, Kim SW, Kim SY.** Recurrence of Cushing's disease after primary transsphenoidal surgery in a university hospital in Korea. *Endocr J*. 2012;59(10):881–888.
164. **Honegger J, Schmalisch K, Beuschlein F, et al.** Contemporary microsurgical concept for the treatment of Cushing's disease: endocrine outcome in 83 consecutive patients. *Clin Endocrinol (Oxf)*. 2012;76(4):560–567.
165. **Alahmadi H, Cusimano MD, Woo K, et al.** Impact of technique on Cushing disease outcome using strict remission criteria. *Can J Neurol Sci*. 2013;40:334–341.
166. **Dimopoulou C, Schopohl J, Rachinger W, et al.** Long-term remission and recurrence rates after first and second transsphenoidal surgery for Cushing's disease: care reality in the Munich Metropolitan Region. *Eur J Endocrinol*. 2014;170(2):283–292.
167. **Toms GC, McCarthy MI, Niven MJ, Orteu CH, King TT, Monson JP.** Predicting relapse after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab*. 1993;76(2):291–294.
168. **Bakiri F, Tatai S, Aouali R, et al.** Treatment of Cushing's disease by transsphenoidal, pituitary microsurgery: prognosis factors and long-term follow-up. *J Endocrinol Invest*. 1996;19(9):572–580.
169. **Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH.** Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. *J Neurosurg*. 2003;98(5):967–973.
170. **Chee GH, Mathias DB, James RA, Kendall-Taylor P.** Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? *Clin Endocrinol (Oxf)*. 2001;54(5):617–626.
171. **Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Müller OA, Fahlbusch R.** Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. *J Neurosurg*. 2008;108(1):9–18.
172. **Findling JW, Raff H.** Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab*. 2006;91(10):3746–3753.
173. **Castinetti F, Martinie M, Morange I, et al.** A combined dexamethasone desmopressin test as an early marker of postsurgical recurrence in Cushing's disease. *J Clin Endocrinol Metab*. 2009;94(6):1897–1903.
174. **Newell-Price J, Morris DG, Drake WM, et al.** Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 2002;87(4):1640–1645.
175. **Reimondo G, Paccotti P, Minetto M, et al.** The corticotrophin-releasing hormone test is the most reliable noninvasive method to differentiate pituitary from ectopic ACTH secretion in Cushing's syndrome. *Clin Endocrinol (Oxf)*. 2003;58(6):718–724.
176. **Vignati F, Berselli ME, Loi P.** Early postoperative evaluation in patients with Cushing's disease: usefulness of ovine corticotropin-releasing hormone test in the prediction of recurrence of disease. *Eur J Endocrinol*. 1994;130(3):235–241.
177. **Avgerinos PC, Chrousos GP, Nieman LK, Oldfield EH, Loriaux DL, Cutler GB Jr.** The corticotropin-releasing hormone test in the postoperative evaluation of patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 1987;65(5):906–913.
178. **Nishizawa S, Oki Y, Ohta S, Yokota N, Yokoyama T, Uemura K.** What can predict postoperative "endocrinological cure" in Cushing's disease? *Neurosurgery*. 1999;45(2):239–244.
179. **Newell-Price J.** Transsphenoidal surgery for Cushing's disease: defining cure and following outcome. *Clin Endocrinol (Oxf)*. 2002;56(1):19–21.
180. **Schrell U, Fahlbusch R, Buchfelder M, Riedl S, Stalla GK, Müller OA.** Corticotropin-releasing hormone stimulation test before and after transsphenoidal selective microadenomectomy in 30 patients with Cushing's disease. *J Clin Endocrinol Metab*. 1987;64(6):1150–1159.
181. **Alwani RA, de Herder WW, van Aken MO, et al.** Biochemical predictors of outcome of pituitary surgery for Cushing's disease. *Neuroendocrinology*. 2010;91:169–178.
182. **Dahia PL, Ahmed-Shuaib A, Jacobs RA, et al.** Vasopressin receptor expression and mutation analysis in corticotropin-secreting tumors. *J Clin Endocrinol Metab*. 1996;81(5):1768–1771.
183. **de Keyzer Y, René P, Beldjord C, Lenne F, Bertagna X.** Overexpression of vasopressin (V3) and corticotrophin-releasing hormone receptor genes in corticotroph tumours. *Clin Endocrinol (Oxf)*. 1998;49(4):475–482.
184. **Malerbi DA, Mendonça BB, Liberman B, et al.** The desmopressin stimulation test in the differential diagnosis of Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1993;38(5):463–472.
185. **Colombo P, Passini E, Re T, Faglia G, Ambrosi B.** Effect of desmopressin on ACTH and cortisol secretion in states of ACTH excess. *Clin Endocrinol (Oxf)*. 1997;46(6):661–668.
186. **Tsagarakis S, Vasiliou V, Kokkoris P, Stavropoulos G, Thalassinos N.** Assessment of cortisol and ACTH responses to the desmopressin test in patients with Cushing's syndrome and simple obesity. *Clin Endocrinol (Oxf)*. 1999;51(4):473–477.
187. **Losa M, Mortini P, Dylgjeri S, et al.** Desmopressin stimulation test before and after pituitary surgery in patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 2001;55(1):61–68.
188. **Losa M, Bianchi R, Barzaghi R, Giovanelli M, Mortini P.** Persistent adrenocorticotropin response to desmopressin in the early postoperative period predicts recurrence of Cushing's disease. *J Clin Endocrinol Metab*. 2009;94(9):3322–3328.
189. **Colombo P, Dall'Asta C, Barbetta L, et al.** Usefulness of the desmopressin test in the postoperative evaluation of patients with Cushing's disease. *Eur J Endocrinol*. 2000;143(2):227–234.
190. **Valéro R, Vallette-Kasic S, Conte-Devolx B, Jaquet P, Brue T.** The desmopressin test as a predictive factor of outcome

after pituitary surgery for Cushing's disease. *Eur J Endocrinol*. 2004;151(6):727–733.
191. **Romanholi DJ, Machado MC, Pereira CC, et al.** Role for postoperative cortisol response to desmopressin in predicting the risk for recurrent Cushing's disease. *Clin Endocrinol (Oxf)*. 2008;69(1):117–122.
192. **Barbot M, Albiger N, Koutroumpi S, et al.** Predicting late recurrence in surgically treated patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 2013;79(3):394–401.
193. **Dall'asta C, Barbetta L, Bonavina L, Beck-Peccoz P, Ambrosi B.** Recurrence of Cushing's disease preceded by the reappearance of ACTH and cortisol responses to desmopressin test. *Pituitary*. 2004;7(3):183–188.
194. **Ambrosi B, Malavazos AE, Passeri E, Dall'Asta C.** Desmopressin test may predict the risk of recurrence in Cushing's disease. *Clin Endocrinol (Oxf)*. 2009;70(5):811.
195. **Powell M.** Microscope and endoscopic pituitary surgery. *Acta Neurochirurgica*. 2009;151(7):723–728.
196. **Swearingen B.** Update on pituitary surgery. *J Clin Endocrinol Metab*. 2012;97(4):1073–1081.
197. **Hardy J.** Transphenoidal microsurgery of the normal and pathological pituitary. *Clin Neurosurg*. 1969;16:185–217.
198. **Ciric I, Ragin A, Baumgartner C, Pierce D.** Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. *Neurosurgery*. 1997;40(2):225–236; discussion 236–227.
199. **Ciric I, Rosenblatt S, Zhao JC.** Transsphenoidal microsurgery. *Neurosurgery*. 2002;51(1):161–169.
200. **Ciric IS, Zhao J.** Transsphenoidal microsurgery: past, present and future. *Expert Rev Anticancer Ther*. 2006;6(suppl 9):S75–S78.
201. **Cappabianca P, Alfieri A, de Divitiis E.** Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPS). *Minim Invasive Neurosurg*. 1998;41(2):66–73.
202. **Cappabianca P, Cavallo LM, Colao A, et al.** Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. *Minim Invasive Neurosurg*. 2002;45(4):193–200.
203. **Cappabianca P, Cavallo LM, de Divitiis E.** Endoscopic endonasal transsphenoidal surgery. *Neurosurgery*. 2004; 55:933–940; discussion 940–941.
204. **Frank G, Pasquini E, Farneti G, et al.** The endoscopic versus the traditional approach in pituitary surgery. *Neuroendocrinology*. 2006;83:240–248.
205. **Strychowsky J, Nayan S, Reddy K, Farrokhyar F, Sommer D.** Purely endoscopic transsphenoidal surgery versus traditional microsurgery for resection of pituitary adenomas: systematic review. *J Otolaryngol Head Neck Surg*. 2011; 40(2):175–185.
206. **Ammirati M, Wei L, Ciric I.** Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2013;84(8):843–849.
207. **Laws ER Jr, Barkhoudarian G.** The transition from microscopic to endoscopic transsphenoidal surgery: the experience at Brigham and Women's Hospital. *World Neurosurg*. 2014;82(6 suppl):S152–S154.
208. **Cavagnini F, Pecori Giraldi F.** Epidemiology and follow-up of Cushing's disease. *Ann Endocrinol (Paris)*. 2001;62(2): 168–172.
209. **Bigos ST, Somma M, Rasio E, et al.** Cushing's disease: management by transsphenoidal pituitary microsurgery. *J Clin Endocrinol Metab*. 1980;50(2):348–354.
210. **Tahir AH, Sheeler LR.** Recurrent Cushing's disease after transsphenoidal surgery. *Arch Intern Med*. 1992;152(5): 977–981.
211. **Hoybye C, Grenback E, Thoren M, et al.** Transsphenoidal surgery in Cushing disease: 10 years of experience in 34 consecutive cases. *J Neurosurg*. 2004;100(4):634–638.
212. **Styne DM, Grumbach MM, Kaplan SL, Wilson CB, Conte FA.** Treatment of Cushing's disease in childhood and adolescence by transsphenoidal microadenomectomy. *N Engl J Med*. 1984;310(14):889–893.
213. **Buchfelder M, Fahlbusch R.** Neurosurgical treatment of Cushing's disease in children and adolescents. *Acta Neurochir Suppl (Wien)*. 1985;35:101–105.
214. **Haddad SF, VanGilder JC, Menezes AH.** Pediatric pituitary tumors. *Neurosurgery*. 1991;29(4):509–514.
215. **Partington MD, Davis DH, Laws ER Jr, Scheithauer BW.** Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery. *J Neurosurg*. 1994;80(2):209–216.
216. **Magiakou MA, Mastorakos G, Oldfield EH, et al.** Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N Engl J Med*. 1994;331(10):629–636.
217. **Dyer EH, Civit T, Visot A, Delalande O, Derome P.** Transsphenoidal surgery for pituitary adenomas in children. *Neurosurgery*. 1994;34(2):207–212; discussion 212.
218. **Weber A, Trainer PJ, Grossman AB, et al.** Investigation, management and therapeutic outcome in 12 cases of childhood and adolescent Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1995;43(1):19–28.
219. **Leinung MC, Kane LA, Scheithauer BW, Carpenter PC, Laws ER Jr, Zimmerman D.** Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. *J Clin Endocrinol Metab*. 1995;80(8):2475–2479.
220. **Devoe DJ, Miller WL, Conte FA, et al.** Long-term outcome in children and adolescents after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab*. 1997; 82(10):3196–3202.
221. **Massoud AF, Powell M, Williams RA, Hindmarsh PC, Brook CG.** Transsphenoidal surgery for pituitary tumours. *Arch Dis Child*. 1997;76(5):398–404.
222. **Savage MO, Lienhardt A, Lebrethon MC, et al.** Cushing's disease in childhood: presentation, investigation, treatment and long-term outcome. *Horm Res*. 2001;55(suppl 1):24–30.
223. **Joshi SM, Hewitt RJ, Storr HL, et al.** Cushing's disease in children and adolescents: 20 years of experience in a single neurosurgical center. *Neurosurgery*. 2005;57(2):281–285; discussion 281–285.
224. **Kanter AS, Diallo AO, Jane JA Jr, et al.** Single-center experience with pediatric Cushing's disease. *J Neurosurg*. 2005;103(5 suppl):413–420.
225. **Storr HL, Afshar F, Matson M, et al.** Factors influencing cure by transsphenoidal selective adenomectomy in pae-

diatric Cushing's disease. *Eur J Endocrinol*. 2005;152(6):825–833.
226. **Mehrazin M.** Pituitary tumors in children: clinical analysis of 21 cases. *Childs Nerv Syst*. 2007;23(4):391–398.
227. **Das NK, Lyngdoh BT, Bhakri BK, et al.** Surgical management of pediatric Cushing's disease. *Surg Neurol*. 2007;67(3):251–257; discussion 257.
228. **Dias RP, Kumaran A, Chan LF, et al.** Diagnosis, management and therapeutic outcome in prepubertal Cushing's disease. *Eur J Endocrinol*. 2010;162(3):603–609.
229. **Oliveira RS, Castro Md, Antonini SR, Martinelli CE Jr, Moreira AC, Machado HR.** Surgical management of pediatric Cushing's disease: an analysis of 15 consecutive cases at a specialized neurosurgical center. *Arq Bras Endocrinol Metabol*. 2010;54(1):17–23.
230. **Shah NS, George J, Acharya SV, et al.** Cushing disease in children and adolescents: twenty years' experience in a tertiary care center in India. *Endocr Pract*. 2011;17(3):369–376.
231. **Lonser RR, Wind JJ, Nieman LK, Weil RJ, DeVroom HL, Oldfield EH.** Outcome of surgical treatment of 200 children with Cushing's disease. *J Clin Endocrinol Metab*. 2013;98(3):892–901.
232. **Storr HL, Drake WM, Evanson J, et al.** Endonasal endoscopic transsphenoidal pituitary surgery: early experience and outcome in paediatric Cushing's disease. *Clin Endocrinol (Oxf)*. 2014;80(2):270–276.
233. **Storr HL, Alexandraki KI, Martin L, et al.** Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's disease. *Eur J Endocrinol*. 2011;164(5):667–674.
234. **Pecori Giraldi F, Moro M, Cavagnini F, Study Group on the Hypothalamo-Pituitary-Adrenal Axis of the Italian Society of Endocrinology.** Gender-related differences in the presentation and course of Cushing's disease. *J Clin Endocrinol Metab*. 2003;88(4):1554–1558.
235. **Dickerman RD, Oldfield EH.** Basis of persistent and recurrent Cushing disease: an analysis of findings at repeated pituitary surgery. *J Neurosurg*. 2002;97(6):1343–1349.
236. **Lamberts SW, de Lange SA, Stefanko SZ.** Adrenocorticotropin-secreting pituitary adenomas originate from the anterior or the intermediate lobe in Cushing's disease: differences in the regulation of hormone secretion. *J Clin Endocrinol Metab*. 1982;54(2):286–291.
237. **Yamada S, Fukuhara N, Nishioka H, et al.** Surgical management and outcomes in patients with Cushing disease with negative pituitary magnetic resonance imaging. *World Neurosurg*. 2012;77:525–532.
238. **Dehdashti AR, Ganna A, Karabatsou K, Gentili F.** Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. *Neurosurgery*. 2008;62(5):1006–1015; discussion 1015–1007.
239. **Hofmann BM, Fahlbusch R.** Treatment of Cushing's disease: a retrospective clinical study of the latest 100 cases. *Front Horm Res*. 2006;34:158–184.
240. **Pouratian N, Prevedello DM, Jagannathan J, Lopes MB, Vance ML, Laws ER Jr.** Outcomes and management of patients with Cushing's disease without pathological confirmation of tumor resection after transsphenoidal surgery. *J Clin Endocrinol Metab*. 2007;92(9):3383–3388.
241. **Sheehan JM, Lopes MB, Sheehan JP, Ellegala D, Webb KM, Laws ER Jr.** Results of transsphenoidal surgery for Cushing's disease in patients with no histologically confirmed tumor. *Neurosurgery*. 2000;47(1):33–36; discussion 37–39.
242. **Scheithauer BW, Gaffey TA, Lloyd RV, et al.** Pathobiology of pituitary adenomas and carcinomas. *Neurosurgery*. 2006;59(2):341–353; discussion 341–353.
243. **Hague K, Post KD, Morgello S.** Absence of peritumoral Crooke's change is associated with recurrence in surgically treated Cushing's disease. *Surg Neurol*. 2000;53(1):77–81.
244. **Doniach I.** Histopathology of the anterior pituitary. *Clin Endocrinol Metab*. 1977;6(1):21–52.
245. **Kovács GL, Góth M, Rotondo F, et al.** ACTH-secreting Crooke cell carcinoma of the pituitary. *Eur J Clin Invest*. 2013;43(1):20–26.
246. **Felix IA, Horvath E, Kovacs K.** Massive Crooke's hyalinization in corticotroph cell adenomas of the human pituitary. A histological, immunocytological, and electron microscopic study of three cases. *Acta Neurochir (Wien)*. 1981;58:235–243.
247. **George DH, Scheithauer BW, Kovacs K, et al.** Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. *Am J Surg Pathol*. 2003;27(10):1330–1336.
248. **Barker FG 2nd, Klibanski A, Swearingen B.** Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab*. 2003;88(10):4709–4719.
249. **Jho HD, Carrau RL.** Endoscopy assisted transsphenoidal surgery for pituitary adenoma. Technical note. *Acta Neurochir (Wien)*. 1996;138:1416–1425.
250. **Jho HD.** Endoscopic transsphenoidal surgery. *J Neurooncol*. 2001;54(2):187–195.
251. **Cappabianca P, Cavallo LM, Colao A, de Divitiis E.** Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. *J Neurosurg*. 2002;97(2):293–298.
252. **Netea-Maier RT, van Lindert EJ, den Heijer M, et al.** Transsphenoidal pituitary surgery via the endoscopic technique: results in 35 consecutive patients with Cushing's disease. *Eur J Endocrinol*. 2006;154(5):675–684.
253. **Laws ER Jr.** Pituitary surgery. *Endocrinol Metab Clin North Am*. 1987;16(3):647–665.
254. **Zada G, Governale LS, Laws ER Jr.** Intraoperative conversion from endoscopic to microscopic approach for the management of sellar pathology: incidence and rationale in a contemporary series. *World Neurosurg*. 2010;73(4):334–337.
255. **Schreckinger M, Walker B, Knepper J, et al.** Post-operative diabetes insipidus after endoscopic transsphenoidal surgery. *Pituitary*. 2013;16(4):445–451.
256. **Kelly DF, Laws ER Jr, Fossett D.** Delayed hyponatremia after transsphenoidal surgery for pituitary adenoma. Report of nine cases. *J Neurosurg*. 1995;83(2):363–367.
257. **Murty GE, Lamballe P, Welch AR.** Early inappropriate secretion of antidiuretic hormone after trans-sphenoidal

pituitary adenomectomy. *J Laryngol Otol*. 1990;104(11):894–895.
258. **Ultmann MC, Hoffman GE, Nelson PB, Robinson AG.** Transient hyponatremia after damage to the neurohypophyseal tracts. *Neuroendocrinology*. 1992;56(6):803–811.
259. **Patil CG, Lad SP, Harsh GR, Laws ER Jr, Boakye M.** National trends, complications, and outcomes following transsphenoidal surgery for Cushing's disease from 1993 to 2002. *Neurosurg Focus*. 2007;23(3):E7.
260. **Devin JK.** Hypopituitarism and central diabetes insipidus: perioperative diagnosis and management. *Neurosurg Clin N Am*. 2012;23(4):679–689.
261. **Hughes NR, Lissett CA, Shalet SM.** Growth hormone status following treatment for Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1999;51(1):61–66.
262. **Stratakis CA, Mastorakos G, Magiakou MA, Papavasiliou E, Oldfield EH, Chrousos GP.** Thyroid function in children with Cushing's disease before and after transsphenoidal surgery. *J Pediatr*. 1997;131(6):905–909.
263. **Charmandari E, Nicolaides NC, Chrousos GP.** Adrenal insufficiency. *Lancet*. 2014;383(9935):2152–2167.
264. **McLaughlin N, Kassam AB, Prevedello DM, Kelly DF.** Management of Cushing's disease after failed surgery–a review. *Can J Neurol Sci*. 2011;38(1):12–21.
265. **Liu JK, Fleseriu M, Delashaw JB Jr, Ciric IS, Couldwell WT.** Treatment options for Cushing disease after unsuccessful transsphenoidal surgery. *Neurosurg Focus*. 2007;23(3):E8.
266. **Kelly DF.** Transsphenoidal surgery for Cushing's disease: a review of success rates, remission predictors, management of failed surgery, and Nelson's syndrome. *Neurosurg Focus*. 2007;23(3):E5.
267. **Aghi MK.** Management of recurrent and refractory Cushing disease. *Nat Clin Pract Endocrinol Metab*. 2008;4(10):560–568.
268. **Blevins LS Jr, Sanai N, Kunwar S, Devin JK.** An approach to the management of patients with residual Cushing's disease. *J Neurooncol*. 2009;94(3):313–319.
269. **Liubinas SV, Porto LD, Kaye AH.** Management of recurrent Cushing's disease. *J Clin Neurosci*. 2011;18(1):7–12.
270. **Bertagna X, Guignat L.** Approach to Cushing's disease patients with persistent/recurrent hypercortisolism after pituitary surgery. *J Clin Endocrinol Metab*. 2013;98(4):1307–1318.
271. **Friedman RB, Oldfield EH, Nieman LK, Chrousos GP, Doppman JL, Cutler GB Jr, Loriaux DL.** Repeat transsphenoidal surgery for Cushing's disease. *J Neurosurg*. 1989;71(4):520–527.
272. **Benveniste RJ, King WA, Walsh J, Lee JS, Delman BN, Post KD.** Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *J Neurosurg*. 2005;102(6):1004–1012.
273. **Hofmann BM, Hlavac M, Kreutzer J, Grabenbauer G, Fahlbusch R.** Surgical treatment of recurrent Cushing's disease. *Neurosurgery*. 2006;58(6):1108–1118; discussion 1108–1118
274. **Patil CG, Veeravagu A, Prevedello DM, Katznelson L, Vance ML, Laws ER Jr.** Outcomes after repeat transsphenoidal surgery for recurrent Cushing's disease. *Neurosurgery*. 2008;63:266–270; discussion 270–271.
275. **Wagenmakers MA, Netea-Maier RT, van Lindert EJ, Timmers HJ, Grotenhuis JA, Hermus AR.** Repeated transsphenoidal pituitary surgery (TS) via the endoscopic technique: a good therapeutic option for recurrent or persistent Cushing's disease (CD). *Clin Endocrinol (Oxf)*. 2009;70(2):274–280.
276. **Valderrábano P, Aller J, García-Valdecasas L, et al.** Results of repeated transsphenoidal surgery in Cushing's disease. Long-term follow-up. *Endocrinol Nutr*. 2014;61(4):176–183.
277. **Liu JK, Schmidt MH, MacDonald JD, Jensen RL, Couldwell WT.** Hypophysial transposition (hypophysopexy) for radiosurgical treatment of pituitary tumors involving the cavernous sinus. Technical note. *Neurosurg Focus*. 2003;14(5):e11.
278. **Tritos NA, Biller BM.** Update on radiation therapy in patients with Cushing's disease. *Pituitary*. 2015;18(2):263–268.
279. **Mahmoud-Ahmed AS, Suh JH.** Radiation therapy for Cushing's disease: a review. *Pituitary*. 2002;5(3):175–180.
280. **Vance ML.** Cushing's disease: radiation therapy. *Pituitary*. 2009;12(1):11–14.
281. **Hentshel S, McCutcheon IE.** Stereotactic radiosurgery for Cushing's disease. *Neurosurg Focus*. 2004;16:E5.
282. **Minniti G, Brada M.** Radiotherapy and radiosurgery for Cushing's disease. *Arq Bras Endocrinol Metabol*. 2007;51(8):1373–1380.
283. **Brada M, Jankowska P.** Radiotherapy for pituitary adenomas. *Endocrinol Metab Clin North Am*. 2008;37(1):263–275, xi.
284. **Minniti G, Gilbert DC, Brada M.** Modern techniques for pituitary radiotherapy. *Rev Endocr Metab Disord*. 2009;10(2):135–144.
285. **Sheehan JP, Niranjan A, Sheehan JM, et al.** Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. *J Neurosurg*. 2005;102(4):678–691.
286. **Starke RM, Williams BJ, Vance ML, Sheehan JP.** Radiation therapy and stereotactic radiosurgery for the treatment of Cushing's disease: an evidence-based review. *Curr Opin Endocrinol Diabetes Obes*. 2010;17(4):356–364.
287. **Loeffler JS, Shih HA.** Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab*. 2011;96(7):1992–2003.
288. **Ding D, Starke RM, Sheehan JP.** Treatment paradigms for pituitary adenomas: defining the roles of radiosurgery and radiation therapy. *J Neurooncol*. 2014;117(3):445–457.
289. **Oyesiku NM.** Stereotactic radiosurgery for Cushing disease: a review. *Neurosurg Focus*. 2007;23(6):E14.
290. **Jagannathan J, Yen CP, Pouratian N, Laws ER, Sheehan JP.** Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the gamma knife. *J Neurooncol*. 2009;92(3):345–356.
291. **Levy RP, Fabrikant JI, Frankel KA, et al.** Heavy-charged-particle radiosurgery of the pituitary gland: clinical results of 840 patients. *Stereotact Funct Neurosurg*. 1991;57:22–35.
292. **Petit JH, Biller BM, Yock TI, et al.** Proton stereotactic radiotherapy for persistent adrenocorticotropin-produc-

ing adenomas. *J Clin Endocrinol Metab*. 2008;93(2):393–399.
293. **Wattson DA, Tanguturi SK, Spiegel DY, et al.** Outcomes of proton therapy for patients with functional pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 2014;90(3):532–539.
294. **Flickinger JC, Lunsford LD, Wu A, Maitz AH, Kalend AM.** Treatment planning for gamma knife radiosurgery with multiple isocenters. *Int J Radiat Oncol Biol Phys*. 1990; 18:1495–1501.
295. **Stephanian E, Lunsford LD, Coffey RJ, Bissonette DJ, Flickinger JC.** Gamma knife surgery for sellar and suprasellar tumors. *Neurosurg Clin N Am*. 1992;3(1):207–218.
296. **Tishler RB, Loeffler JS, Lunsford LD, et al.** Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys*. 1993;27(2):215–221.
297. **Leber KA, Berglöff J, Pendl G.** Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *J Neurosurg*. 1998; 88(1):43–50.
298. **Orth DN, Liddle GW.** Results of treatment in 108 patients with Cushing's syndrome. *N Engl J Med*. 1971;285(5): 243–247.
299. **Edmonds MW, Simpson WJ, Meakin JW.** External irradiation of the hypophysis for Cushing's disease. *Can Med Assoc J*. 1972;107(9):860–862.
300. **Ross WM, Evered DC, Hunter P, Benaim M, Cook D, Hall R.** Treatment of Cushing's disease with adrenal blocking drugs and megavoltage therapy to the pituitary. *Clin Radiol*. 1979;30(2):149–153.
301. **Ahmed SR, Shalet SM, Beardwell CG, Sutton ML.** Treatment of Cushing's disease with low dose radiation therapy. *Br Med J Clin Res Ed*. 1984;289(6446):643–646.
302. **Sharpe GF, Kendall-Taylor P, Prescott RW, et al.** Pituitary function following megavoltage therapy for Cushing's disease: long term follow up. *Clin Endocrinol (Oxf)*. 1985; 22(2):169–177.
303. **Howlett TA, Plowman PN, Wass JA, Rees LH, Jones AE, Besser GM.** Megavoltage pituitary irradiation in the management of Cushing's disease and Nelson's syndrome: long-term follow-up. *Clin Endocrinol (Oxf)*. 1989;31(3): 309–323.
304. **Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Sutton ML.** Long-term follow-up of low-dose external pituitary irradiation for Cushing's disease. *Clin Endocrinol (Oxf)*. 1990;33(4):445–455.
305. **Vicente A, Estrada J, de la Cuerda C, et al.** Results of external pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *Acta Endocrinol (Copenh)*. 1991;125(5):470–474.
306. **Tran LM, Blount L, Horton D, Sadeghi A, Parker RG.** Radiation therapy of pituitary tumors: results in 95 cases. *Am J Clin Oncol*. 1991;14(1):25–29.
307. **Murayama M, Yasuda K, Minamori Y, Mercado-Asis LB, Yamakita N, Miura K.** Long term follow-up of Cushing's disease treated with reserpine and pituitary irradiation. *J Clin Endocrinol Metab*. 1992;75(3):935–942.
308. **Zierhut D, Flentje M, Adolph J, Erdmann J, Raue F, Wannenmacher M.** External radiotherapy of pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 1995;33(2):307–314.
309. **Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ.** Role of radiation therapy in clinical hormonally-active pituitary adenomas. *Radiother Oncol*. 1996;41(1):45–53.
310. **Estrada J, Boronat M, Mielgo M, et al.** The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med*. 1997;336(3):172–177.
311. **Minniti G, Osti M, Jaffrain-Rea ML, Esposito V, Cantore G, Maurizi Enrici R.** Long-term follow-up results of postoperative radiation therapy for Cushing's disease. *J Neurooncol*. 2007;84(1):79–84.
312. **Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ.** Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. *Int J Radiat Oncol Biol Phys*. 1994;30(3):557–565.
313. **Jennings AS, Liddle GW, Orth DN.** Results of treating childhood Cushing's disease with pituitary irradiation. *N Engl J Med*. 1977;297(18):957–962.
314. **Thoren M, Rahn T, Hallengren B, et al.** Treatment of Cushing's disease in childhood and adolescence by stereotactic pituitary irradiation. *Acta Paediatr Scand*. 1986; 75(3):388–395.
315. **Grigsby PW, Thomas PR, Simpson JR, Fineberg BB.** Long-term results of radiotherapy in the treatment of pituitary adenomas in children and adolescents. *Am J Clin Oncol*. 1988;11(6):607–611.
316. **Storr HL, Plowman PN, Carroll PV, et al.** Clinical and endocrine responses to pituitary radiotherapy in pediatric Cushing's disease: an effective second-line treatment. *J Clin Endocrinol Metab*. 2003;88(1):34–37.
317. **Pandey P, Ojha BK, Mahapatra AK.** Pediatric pituitary adenoma: a series of 42 patients. *J Clin Neurosci*. 2005; 12(2):124–127.
318. **Degerblad M,Rahn RT, Bergstrand G, Thoren M.** Long-term results of stereotactic radiosurgery to the pituitary gland in Cushing's disease. *Acta Endocrinol (Copenh)*. 1986;112(3):310–314.
319. **Ganz JC, Backlund EO, Thorsen FA.** The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies. Stereotact *Funct Neurosurg*. 1993;61(suppl 1):30–37.
320. **Martinez R, Bravo G, Burzaco J, Rey G.** Pituitary tumors and gamma knife surgery. Clinical experience with more than two years of follow-up. *Stereotact Funct Neurosurg*. 1998;70(suppl 1):110–118.
321. **Lim YL, Leem W, Kim TS, Rhee BA, Kim GK.** Four years' experiences in the treatment of pituitary adenomas with gamma knife radiosurgery. *Stereotact Funct Neurosurg*. 1998;70(suppl 1):95–109.
322. **Mitsumori M, Shrieve DC, Alexander E 3rd, et al.** Initial clinical results of LINAC-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 1998;42(3):573–580.
323. **Morange-Ramos I, Regis J, Dufour H, et al.** Gamma-knife surgery for secreting pituitary adenomas. *Acta Neurochir (Wien)*. 1998;140(5):437–443.
324. **Hayashi M, Izawa M, Hiyama H, et al.** Gamma Knife radiosurgery for pituitary adenomas. *Stereotact Funct Neurosurg*. 1999;72(suppl 1):111–118.
325. **Inoue HK, Kohga H, Hirato M, et al.** Pituitary adenomas treated by microsurgery with or without Gamma Knife

surgery: experience in 122 cases. *Stereotact Funct Neurosurg*. 1999;72(suppl 1):125–131.
326. **Mokry M, Ramschak-Schwarzer S, Simbrunner J, Ganz JC, Pendl G.** A six year experience with the postoperative radiosurgical management of pituitary adenomas. *Stereotact Funct Neurosurg*. 1999;72(suppl 1):88–100.
327. **Laws ER Jr, Vance ML.** Radiosurgery for pituitary tumors and craniopharyngiomas. *Neurosurg Clin N Am*. 1999; 10(2):327–336.
328. **Sheehan JM, Vance ML, Sheehan JP, Ellegala DB, Laws ER, Jr.** Radiosurgery for Cushing's disease after failed transsphenoidal surgery. *J Neurosurg*. 2000;93(5):738–742.
329. **Shin M, Kurita H, Sasaki T, et al.** Stereotactic radiosurgery for pituitary adenoma invading the cavernous sinus. *J Neurosurg*. 2000;93(suppl 3):2–5.
330. **Izawa M, Hayashi M, Nakaya K, et al.** Gamma knife radiosurgery for pituitary adenomas. *J Neurosurg*. 2000;93 (suppl 3):19–22.
331. **Zhang N, Pan L, Dai J, et al.** Gamma Knife radiosurgery as a primary surgical treatment for hypersecreting pituitary adenomas. *Stereotact Funct Neurosurg*. 2000;75(2–3): 123–128.
332. **Hoybye C, Grenback E, Rahn T, Degerblad M, Thoren M, Hulting AL.** Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. *Neurosurgery*. 2001;49(2): 284–291; discussion 291–282.
333. **Kobayashi T, Kida Y, Mori Y.** Gamma knife radiosurgery in the treatment of Cushing disease: long-term results. *J Neurosurg*. 2002;97(suppl 5):422–428.
334. **Pollock BE, Nippoldt TB, Stafford SL, Foote RL, Abboud CF.** Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. *J Neurosurg*. 2002; 97(3):525–530.
335. **Wong GK, Leung CH, Chiu KW, et al.** LINAC radiosurgery in recurrent Cushing's disease after transsphenoidal surgery: a series of 5 cases. *Minim Invasive Neurosurg*. 2003;46(6):327–330.
336. **Petrovich Z, Yu C, Giannotta SL, Zee CS, Apuzzo ML.** Gamma knife radiosurgery for pituitary adenoma: early results. *Neurosurgery*. 2003;53(1):51–59; discussion 59–61.
337. **Choi JY, Chang JH, Chang JW, Ha Y, Park YG, Chung SS.** Radiological and hormonal responses of functioning pituitary adenomas after gamma knife radiosurgery. *Yonsei Med J*. 2003;44(4):602–607.
338. **Devin JK, Allen GS, Cmelak AJ, Duggan DM, Blevins LS.** The efficacy of linear accelerator radiosurgery in the management of patients with Cushing's disease. *Stereotact Funct Neurosurg*. 2004;82(5–6):254–262.
339. **Colin P, Jovenin N, Delemer B, et al.** Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. *Int J Radiat Oncol Biol Phys*. 2005;62(2):333–341.
340. **Kajiwara K, Saito K, Yoshikawa K, et al.** Image-guided stereotactic radiosurgery with the CyberKnife for pituitary adenomas. *Minim Invasive Neurosurg*. 2005;48(2):91–96.
341. **Kong DS, Lee JI, Lim do H, et al.** The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas: long-term results of 125 consecutive patients treated in a single institution. *Cancer*. 2007;110(4): 854–860.
342. **Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML.** Gamma Knife surgery for Cushing's disease. *J Neurosurg*. 2007;106(6):980–987.
343. **Castinetti F, Nagai M, Dufour H, et al.** Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease. *Eur J Endocrinol*. 2007;156(1):91–98.
344. **Wein L, Dally M, Bach LA.** Stereotactic radiosurgery for treatment of Cushing disease: an Australian experience. *Intern Med J*. 2012;42(10):1153–1156.
345. **Zeiler FA, Bigder M, Kaufmann A, et al.** Gamma knife in the treatment of pituitary adenomas: results of a single center. *Can J Neurol Sci*. 2013;40(4):546–552.
346. **Sheehan JP, Xu Z, Salvetti DJ, Schmitt PJ, Vance ML.** Results of gamma knife surgery for Cushing's disease. *J Neurosurg*. 2013;119(6):1486–1492.
347. **Grant RA, Whicker M, Lleva R, Knisely JP, Inzucchi SE, Chiang VL.** Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report. *World Neurosurg*. 2014;82(1–2):195–201.
348. **Budyal S, Lila AR, Jalali R, et al.** Encouraging efficacy of modern conformal fractionated radiotherapy in patients with uncured Cushing's disease. *Pituitary*. 2014;17(1):60–67.
349. **Wilson PJ, Williams JR, Smee RI.** Cushing's disease: a single centre's experience using the linear accelerator (LINAC) for stereotactic radiosurgery and fractionated stereotactic radiotherapy. *J Clin Neurosci*. 2014;21(1): 100–106.
350. **Kim MS, Lee SI, Sim JH.** Gamma Knife radiosurgery for functioning pituitary microadenoma. *Stereotact Funct Neurosurg*. 1999;72(suppl 1):119–124.
351. **Feigl GC, Bonelli CM, Berghold A, Mokry M.** Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function. *J Neurosurg*. 2002;97(5 suppl):415–421.
352. **Landolt AM, Haller D, Lomax N, et al.** Octreotide may act as a radioprotective agent in acromegaly. *J Clin Endocrinol Metab*. 2000;85(3):1287–1289.
353. **Landolt AM, Lomax N.** Gamma knife radiosurgery for prolactinomas. *J Neurosurg*. 2000;93(suppl 3):14–18.
354. **Darzy KH, Shalet SM.** Hypopituitarism as a consequence of brain tumours and radiotherapy. *Pituitary*. 2005;8: 203–211.
355. **Feigl GC, Pistracher K, Berghold A, Mokry M.** Pituitary insufficiency as a side effect after radiosurgery for pituitary adenomas: the role of the hypothalamus. *J Neurosurg*. 2010;113(suppl):153–159.
356. **Kokubo M, Sasai K, Shibamoto Y, et al.** Long-term results of radiation therapy for pituitary adenoma. *J Neurooncol*. 2000;47(1):79–84.
357. **Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML.** Radiation-induced hypopituitarism is dose-dependent. *Clin Endocrinol (Oxf)*. 1989;31(3):363–373.
358. **Pai HH, Thornton A, Katznelson L, et al.** Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys*. 2001;49(4):1079–1092.
359. **Leenstra JL, Tanaka S, Kline RW, et al.** Factors associated

with endocrine deficits after stereotactic radiosurgery of pituitary adenomas. *Neurosurgery*. 2010;67(1):27–32; discussion 32–33.
360. **Xu Z, Lee Vance M, Schlesinger D, Sheehan JP.** Hypopituitarism after stereotactic radiosurgery for pituitary adenomas. *Neurosurgery*. 2013;72(4):630–637; 636–637.
361. **Degerblad M, Brismar K, Rahn T, Thoren M.** The hypothalamus-pituitary function after pituitary stereotactic radiosurgery: evaluation of growth hormone deficiency. *J Intern Med*. 2003;253(4):454–462.
362. **Harris JR, Levene MB.** Visual complications following irradiation for pituitary adenomas and craniopharyngiomas. *Radiology*. 1976;120(1):167–171.
363. **Aristizabal S, Caldwell WL, Avila J, Mayer EG.** Relationship of time dose factors to tumor control and complications in the treatment of Cushing's disease by irradiation. *Int J Radiat Oncol Biol Phys*. 1977;2(1–2):47–54.
364. **Kline LB, Kim JY, Ceballos R.** Radiation optic neuropathy. *Ophthalmology*. 1985;92(8):1118–1126.
365. **Brada M, Rajan B, Traish D, et al.** The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol (Oxf)*. 1993;38(6):571–578.
366. **Erridge SC, Conkey DS, Stockton D, et al.** Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. *Radiother Oncol*. 2009;93(3):597–601.
367. **Chen JC, Giannotta SL, Yu C, Petrovich Z, Levy ML, Apuzzo ML.** Radiosurgical management of benign cavernous sinus tumors: dose profiles and acute complications. *Neurosurgery*. 2001;48(5):1022–1030; discussion 1030–1022.
368. **Stafford SL, Pollock BE, Leavitt JA, et al.** A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1177–1181.
369. **Ove R, Kelman S, Amin PP, Chin LS.** Preservation of visual fields after peri-sellar gamma-knife radiosurgery. *Int J Cancer*. 2000;90(6):343–350.
370. **Girkin CA, Comey CH, Lunsford LD, Goodman ML, Kline LB.** Radiation optic neuropathy after stereotactic radiosurgery. *Ophthalmology*. 1997;104(10):1634–1643.
371. **Mehta MP, Kinsella TJ.** Cavernous sinus cranial neuropathies: is there a dose-response relationship following radiosurgery? *Int J Radiat Oncol Biol Phys*. 1993;27(2):477–480.
372. **Liu AL, Wang C, Sun S, Wang M, Liu P.** Gamma knife radiosurgery for tumors involving the cavernous sinus. *Stereotact Funct Neurosurg*. 2005;83(1):45–51.
373. **Kuo JS, Chen JC, Yu C, et al.** Gamma knife radiosurgery for benign cavernous sinus tumors: quantitative analysis of treatment outcomes. *Neurosurgery*. 2004;54(6):1385–1393; discussion 1393–1384.
374. **Lundström M, Frisén L.** Atrophy of optic nerve fibres in compression of the chiasm. Degree and distribution of ophthalmoscopic changes. *Acta Ophthalmol (Copenh)*. 1976;54(5):623–640.
375. **Abe T, Yamamoto M, Taniyama M, Tanioka D, Izumiyama H, Matsumoto K.** Early palliation of oculomotor nerve palsy following gamma knife radiosurgery for pituitary adenoma. *Eur Neurol*. 2002;47(1):61–63.
376. **Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ.** Change in neurocognitive functioning after treatment with cranial radiation in childhood. *J Clin Oncol*. 2004;22(4):706–713.
377. **Packer RJ, Sutton LN, Atkins TE, et al.** A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results. *J Neurosurg*. 1989;70(5):707–713.
378. **Packer RJ.** Radiation-induced neurocognitive decline: the risks and benefits of reducing the amount of whole-brain irradiation. *Curr Neurol Neurosci Rep*. 2002;2(2):131–133.
379. **Keime-Guibert F, Napolitano M, Delattre JY.** Neurological complications of radiotherapy and chemotherapy. *J Neurol*. 1998;245(11):695–708.
380. **Guinan EM, Lowy C, Stanhope N, Lewis PD, Kopelman MD.** Cognitive effects of pituitary tumours and their treatments: two case studies and an investigation of 90 patients. *J Neurol Neurosurg Psychiatry*. 1998;65(6):870–876.
381. **Peace KA, Orme SM, Padayatty SJ, Godfrey HP, Belchetz PE.** Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. *Clin Endocrinol (Oxf)*. 1998;49(3):391–396.
382. **Brada M, Burchell L, Ashley S, Traish D.** The incidence of cerebrovascular accidents in patients with pituitary adenoma. *Int J Radiat Oncol Biol Phys*. 1999;45(3):693–698.
383. **Minniti G, Traish D, Ashley S, Gonsalves A, Brada M.** Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab*. 2005;90(2):800–804.
384. **Cahan WG, Woodard HQ, et al.** Sarcoma arising in irradiated bone; report of 11 cases. *Cancer*. 1948;1(1):3–29.
385. **Niranjan A, Kondziolka D, Lunsford LD.** Neoplastic transformation after radiosurgery or radiotherapy: risk and realities. *Otolaryngol Clin North Am*. 2009;42(4):717–729.
386. **Jones A.** Radiation oncogenesis in relation to the treatment of pituitary tumours. *Clin Endocrinol (Oxf)*. 1991;35(5):379–397.
387. **Wu-Chen WY, Jacobs DA, Volpe NJ, Dalmau JO, Moster ML.** Intracranial malignancies occurring more than 20 years after radiation therapy for pituitary adenoma. *J Neuroophthalmol*. 2009;29(4):289–295.
388. **Balasubramaniam A, Shannon P, Hodaie M, Laperriere N, Michaels H, Guha A.** Glioblastoma multiforme after stereotactic radiotherapy for acoustic neuroma: case report and review of the literature. *Neuro Oncol*. 2007;9(4):447–453.
389. **Loeffler JS, Niemierko A, Chapman PH.** Second tumors after radiosurgery: tip of the iceberg or a bump in the road? *Neurosurgery*. 2003;52(6):1436–1440; discussion 1440–1442.
390. **Ecemis GC, Atmaca A, Meydan D.** Radiation-associated secondary brain tumors after conventional radiotherapy and radiosurgery. *Expert Rev Neurother*. 2013;13(5):557–565.
391. **Tsukamoto H, Yoshinari M, Okamura K, Ishitsuka T, Fujishima M.** Meningioma developed 25 years after radi-

ation therapy for Cushing's disease. *Intern Med*. 1992; 31(5):629–632.
392. **Sarkar S, Rajaratnam S, Backianathan S, Chacko G, Chacko AG.** Radiation-induced opticochiasmatic glioblastoma multiforme following conventional radiotherapy for Cushing's disease. *Br J Neurosurg*. 2014;28(4):510–512.
393. **Larson DA, Flickinger JC, Loeffler JS.** The radiobiology of radiosurgery. *Int J Radiat Oncol Biol Phys*. 1993;25(3): 557–561.
394. **Nishioka H, Hirano A, Haraoka J, Nakajima N.** Histological changes in the pituitary gland and adenomas following radiotherapy. *Neuropathology*. 2002;22(1):19–25.
395. **Croughs RJ, Docter R.** Immediate effect of unilateral adrenalectomy followed by external pituitary irradiation on cortisol secretion rate in subjects suffering from pituitary dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 1971;33(6):912–916.
396. **Lamberts SW, de Jong FH, Birkenhäger JC.** Evaluation of a therapeutic regimen in Cushing's disease. The predictability of the result of unilateral adrenalectomy followed by external pituitary irradiation. *Acta Endocrinol (Copenh)*. 1977;86(1):146–155.
397. **Landau B, Leiba S, Kaufman H, Servadio C, Wainrach B.** Unilateral adrenalectomy and pituitary irradiation in the treatment of ACTH-dependent Cushing's disease in children and adolescents. *Clin Endocrinol (Oxf)*. 1978;9(3): 221–226.
398. **Nagesser SK, van Seters AP, Kievit J, et al.** Treatment of pituitary-dependent Cushing's syndrome: long-term results of unilateral adrenalectomy followed by external pituitary irradiation compared to transsphenoidal pituitary surgery. *Clin Endocrinol (Oxf)*. 2000;52(4):427–435.
399. **Assalia A, Gagner M.** Laparoscopic adrenalectomy. *Br J Surg*. 2004;91(10):1259–1274.
400. **Young WF Jr, Thompson GB.** Role for laparoscopic adrenalectomy in patients with Cushing's syndrome. *Arq Bras Endocrinol Metabol*. 2007;51(8):1349–1354.
401. **Gumbs AA, Gagner M.** Laparoscopic adrenalectomy. *Best Pract Res Clin Endocrinol Metab*. 2006;20(3):483–499.
402. **Ernest I, Ekman H.** Adrenalectomy in Cushing's disease. A long-term follow-up. *Acta Endocrinol Suppl (Copenh)*. 1972;160:3–41.
403. **Scott HW Jr, Liddle GW, Mulherin JL Jr, Mckenna TJ, Stroup SL, Rhamy RK.** Surgical experience with Cushing's disease. *Ann Surg*. 1977;185(5):524–534.
404. **Tomita A, Suzuki S, Hara I, et al.** Follow-up study on treatment in 27 patients with Cushing's disease: adrenalectomy, transsphenoidal adenomectomy and medical treatment. *Endocrinol Jpn*. 1981;28(2):197–205.
405. **Urbanic RC, George JM.** Cushing's disease–18 years' experience. *Medicine (Baltimore)*. 1981;60(1):14–24.
406. **Kelly WF, MacFarlane IA, Longson D, Davies D, Sutcliffe H.** Cushing's disease treated by total adrenalectomy: long-term observations of 43 patients. *Q J Med*. 1983;52(206): 224–231.
407. **Pelkonen R, Eistola P, Grahne B, et al.** Treatment of pituitary Cushing's disease: results of adrenal and pituitary surgery. *Acta Endocrinol Suppl (Copenh)*. 1983;251:38–46.
408. **Welbourn RB.** Survival and causes of death after adrenalectomy for Cushing's disease. *Surgery*. 1985;97(1):16–20.
409. **McCance DR, Russell CF, Kennedy TL, Hadden DR, Kennedy L, Atkinson AB.** Bilateral adrenalectomy: low mortality and morbidity in Cushing's disease. *Clin Endocrinol (Oxf)*. 1993;39(3):315–321.
410. **O'Riordain DS, Farley DR, Young WF Jr, Grant CS, van Heerden JA.** Long-term outcome of bilateral adrenalectomy in patients with Cushing's syndrome. *Surgery*. 1994; 116(6):1088–1093; discussion 1093–1084.
411. **Jenkins PJ, Trainer PJ, Plowman PN, et al.** The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 1995;80(1):165–171.
412. **Bax TW, Marcus DR, Galloway GQ, Swanstrom LL, Sheppard BC.** Laparoscopic bilateral adrenalectomy following failed hypophysectomy. *Surg Endosc*. 1996; 10(12):1150–1153.
413. **MacGillivray DC, Shichman SJ, Ferrer FA, Malchoff CD.** A comparison of open vs laparoscopic adrenalectomy. *Surg Endosc*. 1996;10(10):987–990.
414. **Fernández-Cruz L, Saenz A, Benarroch G, Astudillo E, Taura P, Sabater L.** Laparoscopic unilateral and bilateral adrenalectomy for Cushing's syndrome. Transperitoneal and retroperitoneal approaches. *Ann Surg*. 1996;224(6): 727–734; discussion 734–736.
415. **Chapuis Y, Chastanet S, Dousset B, Luton JP.** Bilateral laparoscopic adrenalectomy for Cushing's disease. *Br J Surg*. 1997;84(7):1009.
416. **Ferrer FA, MacGillivray DC, Malchoff CD, Albala DM, Shichman SJ.** Bilateral laparoscopic adrenalectomy for adrenocorticotropic dependent Cushing's syndrome. *J Urol*. 1997;157(1):16–18.
417. **Lanzi R, Montorsi F, Losa M, et al.** Laparoscopic bilateral adrenalectomy for persistent Cushing's disease after transsphenoidal surgery. *Surgery*. 1998;123(2):144–150.
418. **Acosta E, Pantoja JP, Gamino R, Rull JA, Herrera MF.** Laparoscopic versus open adrenalectomy in Cushing's syndrome and disease. *Surgery*. 1999;126(6):1111–1116.
419. **Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ.** Long-term results of total adrenalectomy for Cushing's disease. *World J Surg*. 2000;24(1): 108–113.
420. **Vella A, Thompson GB, Grant CS, van Heerden JA, Farley DR, Young WF Jr.** Laparoscopic adrenalectomy for adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 2001;86(4):1596–1599.
421. **Porpiglia F, Fiori C, Bovio S, et al.** Bilateral adrenalectomy for Cushing's syndrome: a comparison between laparoscopy and open surgery. *J Endocrinol Invest*. 2004;27(7): 654–658.
422. **Mikhail AA, Tolhurst SR, Orvieto MA, et al.** Open versus laparoscopic simultaneous bilateral adrenalectomy. *Urology*. 2006;67(4):693–696.
423. **Chow JT, Thompson GB, Grant CS, Farley DR, Richards ML, Young WF Jr.** Bilateral laparoscopic adrenalectomy for corticotrophin-dependent Cushing's syndrome: a review of the Mayo Clinic experience. *Clin Endocrinol (Oxf)*. 2008;68(4):513–519.
424. **Smith PW, Turza KC, Carter CO, Vance ML, Laws ER, Hanks JB.** Bilateral adrenalectomy for refractory Cushing

disease: a safe and definitive therapy. *J Am Coll Surg*. 2009; 208(6):1059–1064.
425. **Ding XF, Li HZ, Yan WG, Gao Y, Li XQ.** Role of adrenalectomy in recurrent Cushing's disease. *Chin Med J (Engl)*. 2010;123(13):1658–1662.
426. **Tiyadatah BN, Kalavampara SV, Sukumar S, et al.** Bilateral simultaneous laparoscopic adrenalectomy in Cushing's syndrome: safe, effective, and curative. *J Endourol*. 2012;26(2):157–163.
427. **Bulus H, Uslu HY, Karakoyun R, Koçak S.** Comparison of laparoscopic and open adrenalectomy. *Acta Chir Belg*. 2013;113(3):203–207.
428. **Osswald A, Plomer E, Dimopoulou C, et al.** Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. *Eur J Endocrinol*. 2014;171(2):209–215.
429. **Raffaelli M, Brunaud L, De Crea C, et al.** Synchronous bilateral adrenalectomy for Cushing's syndrome: laparoscopic versus posterior retroperitoneoscopic versus robotic approach. *World J Surg*. 2014;38(3):709–715.
430. **Ritzel K, Beuschlein F, Mickisch A, et al.** Clinical review: outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. *J Clin Endocrinol Metab*. 2013;98(10):3939–3948.
431. **Assié G, Bahurel H, Coste J, et al.** Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome. *J Clin Endocrinol Metab*. 2007;92(1):172–179.
432. **Assié G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X.** The Nelson's syndrome… revisited. *Pituitary*. 2004;7(4):209–215.
433. **Munir A, Newell-Price J.** Nelson's syndrome. *Arq Bras Endocrinol Metabol*. 2007;51(8):1392–1396.
434. **Banasiak MJ, Malek AR.** Nelson syndrome: comprehensive review of pathophysiology, diagnosis, and management. *Neurosurg Focus*. 2007;23(3):E13.
435. **Barber TM, Adams E, Ansorge O, Byrne JV, Karavitaki N, Wass JA.** Nelson's syndrome. *Eur J Endocrinol*. 2010; 163(4):495–507.
436. **Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ.** Neurosurgical treatment of Nelson's syndrome. *J Clin Endocrinol Metab*. 2002;87(12):5465–5469.
437. **Kasperlik-Załuska AA, Bonicki W, Jeske W, Janik J, Zgliczyński W, Czernicki Z.** Nelson's syndrome – 46 years later: clinical experience with 37 patients. *Zentralbl Neurochir*. 2006;67(1):14–20.
438. **Xing B, Ren Z, Su C, Wang R, Yang Y, Hu Y.** Microsurgical treatment of Nelson's syndrome. *Chin Med J Engl*. 2002;115(8):1150–1152.
439. **Kemink SA, Grotenhuis JA, De Vries J, Pieters GF, Hermus AR, Smals AG.** Management of Nelson's syndrome: observations in fifteen patients. *Clin Endocrinol (Oxf)*. 2001; 54(1):45–52.
440. **Grua JR, Nelson DH.** ACTH-producing pituitary tumors. *Endocrinol Metab Clin N Am*. 1991;20(2):319–362.
441. **Wolffenbuttel BH, Kitz K, Beuls EM.** Beneficial gamma-knife radiosurgery in a patient with Nelson's syndrome. *Clin Neurol Neurosurg*. 1998;100(1):60–63.
442. **Moore TJ, Dluhy RG, Williams GH, Cain JP.** Nelson's syndrome: frequency, prognosis, and effect of prior pituitary irradiation. *Ann Intern Med*. 1976;85(6):731–734.
443. **Mauermann WJ, Sheehan JP, Chernavvsky DR, Laws ER, Steiner L, Vance ML.** Gamma knife surgery for adrenocorticotropic hormone-producing pituitary adenomas after bilateral adrenalectomy. *J Neurosurg*. 2007;106(6): 988–993.
444. **Vik-Mo EO, Øksnes M, Pedersen PH, et al.** Gamma knife stereotactic radiosurgery of Nelson syndrome. *Eur J Endocrinol*. 2009;160(2):143–148.
445. **Jane JA Jr, Vance ML, Woodburn CJ, Laws ER Jr.** Stereotactic radiosurgery for hypersecreting pituitary tumors: part of a multimodality approach. *Neurosurg Focus*. 2003; 14(5):e12.
446. **Manolas KJ, Farmer HM, Wilson HK, et al.** The pituitary before and after adrenalectomy for Cushing's syndrome. *World J Surg*. 1984;8(3):374–387.
447. **Mehta GU, Sheehan JP, Vance ML.** Effect of stereotactic radiosurgery before bilateral adrenalectomy for Cushing's disease on the incidence of Nelson's syndrome. *J Neurosurg*. 2013;119(6):1493–1497.
448. **Gil-Cárdenas A, Herrera MF, Díaz-Polanco A, Rios JM, Pantoja JP.** Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. *Surgery*. 2007;141(2):147–151; discussion 151–152.
449. **Pivonello R, Faggiano A, Di Salle F, Filippella M, Lombardi G, Colao A.** Complete remission of Nelson's syndrome after 1-year treatment with cabergoline. *J Endocrinol Invest*. 1999;22(11):860–865.
450. **Casulari LA, Naves LA, Mello PA, Pereira Neto A, Papadia C.** Nelson's syndrome: complete remission with cabergoline but not with bromocriptine or cyproheptadine treatment. *Horm Res*. 2004;62(6):300–305.
451. **Shraga-Slutzky I, Shimon I, Weinshtein R.** Clinical and biochemical stabilization of Nelson's syndrome with long-term low-dose cabergoline treatment. *Pituitary*. 2006; 9(2):151–154.
452. **Hofland LJ, van der Hoek J, Feelders R, et al.** The multiligand somatostatin analogue SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. *Eur J Endocrinol*. 2005; 152(4):645–654.
453. **Katznelson L.** Sustained improvements in plasma ACTH and clinical status in a patient with Nelson's syndrome treated with pasireotide LAR, a multireceptor somatostatin analog. *J Clin Endocrinol Metab*. 2013;98(5):1803–1807.
454. **Mullan KR, Leslie H, McCance DR, Sheridan B, Atkinson AB.** The PPAR-γ activator rosiglitazone fails to lower plasma ACTH levels in patients with Nelson's syndrome. *Clin Endocrinol (Oxf)*. 2006;64(5):519–522.
455. **Munir A, Song F, Ince P, Walters SJ, Ross R, Newell-Price J.** Ineffectiveness of rosiglitazone therapy in Nelson's syndrome. *J Clin Endocrinol Metab*. 2007;92(5):1758–1763.
456. **Kreutzer J, Jeske I, Hofmann B, et al.** No effect of the PPAR-γ agonist rosiglitazone on ACTH or cortisol secretion in Nelson's syndrome and Cushing's disease in vitro and in vivo. *Clin Neuropathol*. 2009;28:430–439.
457. **Kovacs K, Horvath E, Syro LV, et al.** Temozolomide therapy in a man with an aggressive prolactin-secreting pituitary neoplasm: morphological findings. *Hum Pathol*. 2007;38(1):185–189.
458. **Fadul CE, Kominsky AL, Meyer LP, et al.** Long-term re-

sponse of pituitary carcinoma to temozolomide. Report of two cases. *J Neurosurg*. 2006;105(4):621–626.
459. **Moyes VJ, Alusi G, Sabin HI, et al.** Treatment of Nelson's syndrome with temozolomide. *Eur J Endocrinol*. 2009; 160(1):115–119.
460. **Gross BA, Mindea SA, Pick AJ, Chandler JP, Batjer HH.** Medical management of Cushing disease. *Neurosurg Focus*. 2007;23(3):E10.
461. **Schteingart DE.** Drugs in the medical treatment of Cushing's syndrome. *Expert Opin Emerg Drugs*. 2009;14(4): 661–671.
462. **Alexandraki KI, Grossman AB.** Medical therapy of Cushing's disease: where are we now? *Front Horm Res*. 2010; 38:165–173.
463. **Fleseriu M.** Medical management of persistent and recurrent Cushing disease. *Neurosurg Clin N Am*. 2012;23(4): 653–668.
464. **Fleseriu M, Petersenn S.** Medical management of Cushing's disease: what is the future? *Pituitary*. 2012;15(3): 330–341.
465. **van der Pas R, de Herder WW, Hofland LJ, Feelders RA.** New developments in the medical treatment of Cushing's syndrome. *Endocr Relat Cancer*. 2012;19(6):R205–R223.
466. **Feelders RA, Hofland LJ.** Medical treatment of Cushing's disease. *J Clin Endocrinol Metab*. 2013;98(2):425–438.
467. **Nieman LK.** Update in the medical therapy of Cushing's disease. *Curr Opin Endocrinol Diabetes Obes*. 2013; 20(4):330–334.
468. **Gadelha MR, Vieira Neto L.** Efficacy of medical treatment in Cushing's disease: a systematic review. *Clin Endocrinol (Oxf)*. 2014;80(1):1–12.
469. **Tritos NA, Biller BM.** Medical management of Cushing's disease. *J Neurooncol*. 2014;117(3):407–414.
470. **Cuevas-Ramos D, Fleseriu M.** Treatment of Cushing's disease: a mechanistic update. *J Endocrinol*. 2014;223(2): R19–R39.
471. **Fleseriu M.** Recent advances in the medical treatment of Cushing's disease. *F1000Prime Rep*. 2014;6:18.
472. **Engelhardt D.** Steroid biosynthesis inhibitors in Cushing's syndrome. *Clin Investig*. 1994;72(7):481–488.
473. **Engelhardt D, Weber MM.** Therapy of Cushing's syndrome with steroid biosynthesis inhibitors. *J Steroid Biochem Mol Biol*. 1994;49:261–267.
474. **Feelders RA, Hofland LJ, de Herder WW.** Medical treatment of Cushing's syndrome: adrenal-blocking drugs and ketaconazole. *Neuroendocrinology*. 2010;92(suppl 1): 111–115.
475. **Igaz P, Tömböl Z, Szabó PM, Likó I, Rácz K.** Steroid biosynthesis inhibitors in the therapy of hypercortisolism: theory and practice. *Curr Med Chem*. 2008;15(26):2734–2747.
476. **Pont A, Williams PL, Loose DS, et al.** Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med*. 1982;97(3): 370–372.
477. **Loose DS, Kan PB, Hirst MA, Marcus RA, Feldman D.** Ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome P450-dependent enzymes. *J Clin Invest*. 1983; 71(5):1495–1499.
478. **Pont A, Williams PL, Azhar S, et al.** Ketoconazole blocks testosterone synthesis. *Arch Intern Med*. 1982;142(12): 2137–2140.
479. **Feldman D.** Ketoconazole and other imidazole derivatives as inhibitors of steroidogenesis. *Endocr Rev*. 1986;7(4): 409–420.
480. **Sonino N.** The use of ketoconazole as an inhibitor of steroid production. *N Engl J Med*. 1987;317(13):812–818.
481. **Stalla GK, Stalla J, Huber M, et al.** Ketoconazole inhibits corticotropic cell function in vitro. *Endocrinology*. 1988; 122(2):618–623.
482. **Jimenez Reina L, Leal-Cerro A, Garcia J, Garcia-Luna PP, Astorga R, Bernal G.** In vitro effects of ketoconazole on corticotrope cell morphology and ACTH secretion of two pituitary adenomas removed from patients with Nelson's syndrome. *Acta Endocrinol (Copenh)*. 1989;121(2):185–190.
483. **Berselli ME, Tagliaferri M, Vignati F, Loli P.** Effect of ketoconazole on CRH-induced ACTH and cortisol release in patients with Cushing's disease. *Horm Metab Res Suppl*. 1987;16:58–59.
484. **Boscaro M, Sonino N, Rampazzo A, Mantero F.** Response of pituitary-adrenal axis to corticotrophin releasing hormone in patients with Cushing's disease before and after ketoconazole treatment. *Clin Endocrinol (Oxf)*. 1987; 27(4):461–467.
485. **Sonino N, Boscaro M, Merola G, Mantero F.** Prolonged treatment of Cushing's disease by ketoconazole. *J Clin Endocrinol Metab*. 1985;61(4):718–722.
486. **Angeli A, Frairia R.** Ketoconazole therapy in Cushing's disease. *Lancet*. 1985;1(8432):821.
487. **Loli P, Berselli ME, Tagliaferri M.** Use of ketoconazole in the treatment of Cushing's syndrome. *J Clin Endocrinol Metab*. 1986;63(6):1365–1371.
488. **McCance DR, Hadden DR, Kennedy L, Sheridan B, Atkinson AB.** Clinical experience with ketoconazole as a therapy for patients with Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1987;27(5):593–599.
489. **Terzolo M, Panarelli M, Piovesan A, Torta M, Paccotti P, Angeli A.** Ketoconazole treatment in Cushing's disease. Effect on the circadian profile of plasma ACTH and cortisol. *J Endocrinol Invest*. 1988;11(10):717–721.
490. **Diop SN, Warnet A, Duet M, Firmin C, Mosse A, Lubetzki J.** Long-term treatment of Cushing's disease using ketoconazole. Possibility of therapeutic escape [in French]. *Presse Med*. 1989;18(27):1325–1328.
491. **Cerdas S, Billaud L, Guilhaume B, Laudat MH, Bertagna X, Luton JP.** Short term effects of ketoconazole in Cushing's syndrome [in French]. *Ann Endocrinol (Paris)*. 1989; 50(6):489–496.
492. **Engelhardt D, Jacob K, Doerr HG.** Different therapeutic efficacy of ketoconazole in patients with Cushing's syndrome. *Klin Wochenschr*. 1989;67(4):241–247.
493. **Tabarin A, Navarranne A, Corcuff B, Guerin J, Kern AM, Roger P.** Efficacy and long-term tolerance of ketoconazole in the treatment of Cushing's disease [in French]. *Ann Endocrinol (Paris)*. 1990;51(1):27–32.
494. **Sonino N, Boscaro M, Paoletta A, Mantero F, Ziliotto D.** Ketoconazole treatment in Cushing's syndrome: experience in 34 patients. *Clin Endocrinol (Oxf)*. 1991;35(4): 347–352.
495. **Tabarin A, Navarranne A, Guérin J, Corcuff JB, Parneix M, Roger P.** Use of ketoconazole in the treatment of Cush-

ing's disease and ectopic ACTH syndrome. *Clin Endocrinol (Oxf)*. 1991;34(1):63–69.
496. **Mortimer RH, Cannell GR, Thew CM, Galligan JP.** Ketoconazole and plasma and urine steroid levels in Cushing's disease. *Clin Exp Pharmacol Physiol*. 1991;18(8):563–569.
497. **Li KL, Tung SC, Wang PW.** The effect of ketoconazole in pre-operative treatment in Cushing's syndrome: three cases report. *Changgeng Yi Xue Za Zhi*. 1996;19(4):358–363.
498. **Berwaerts JJ, Verhelst JA, Verhaert GC, Verhaegen AA, Abs RE.** Corticotropin-dependent Cushing's syndrome in older people: presentation of five cases and therapeutical use of ketoconazole. *J Am Geriatr Soc*. 1998;46(7):880–884.
499. **Chou SC, Lin JD.** Long-term effects of ketoconazole in the treatment of residual or recurrent Cushing's disease. *Endocr J*. 2000;47(4):401–406.
500. **Manavela MP, Goodall CM, Katz SB, Moncet D, Bruno OD.** The association of Cushing's disease and primary empty sella turcica. *Pituitary*. 2001;4(3):145–151.
501. **Moncet D, Morando DJ, Pitoia F, Katz SB, Rossi MA, Bruno OD.** Ketoconazole therapy: an efficacious alternative to achieve eucortisolism in patients with Cushing's syndrome. *Medicina (B Aires)*. 2007;67(1):26–31.
502. **Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T.** Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. *Eur J Endocrinol*. 2008;158(1):91–99.
503. **Correa-Silva SR, Nascif SO, Molica P, Sá LB, Vieira JG, Lengyel AM.** Adrenocorticotrophic hormone (ACTH) responsiveness to ghrelin increases after 6 months of ketoconazole use in patients with Cushing's disease: comparison with GH-releasing peptide-6 (GHRP-6). *Clin Endocrinol (Oxf)*. 2010;72(1):70–75.
504. **Mert M, Kocabay G.** Effectiveness of chronic treatment with ketoconazole in a patient with diabetic Cushing's disease resistant to surgery. *Endokrynol Pol*. 2011;62(3):271–274.
505. **Costenaro F, Rodrigues TC, Ferreira NP, et al.** Pseudotumor cerebri during Cushing's disease treatment with ketoconazole. *Arq Bras Endocrinol Metabol*. 2011;55(4):284–287.
506. **Valassi E, Crespo I, Gich I, Rodríguez J, Webb SM.** A reappraisal of the medical therapy with steroidogenesis inhibitors in Cushing's syndrome. *Clin Endocrinol (Oxf)*. 2012;77(5):735–742.
507. **van den Bosch OF, Stades AM, Zelissen PM.** Increased long-term remission after adequate medical cortisol suppression therapy as presurgical treatment in Cushing's disease. *Clin Endocrinol (Oxf)*. 2014;80(2):184–190.
508. **Castinetti F, Guignat L, Giraud P, et al.** Ketoconazole in Cushing's disease: is it worth a try? *J Clin Endocrinol Metab*. 2014;99(5):1623–1630.
509. **Sugar AM, Alsip SG, Galgiani JN, et al.** Pharmacology and toxicity of high-dose ketoconazole. *Antimicrob Agents Chemother*. 1987;31(12):1874–1878.
510. **Lewis JH, Zimmerman HJ, Benson GD, Ishak KG.** Hepatic injury associated with ketoconazole therapy. Analysis of 33 cases. *Gastroenterology*. 1984;86(3):503–513.
511. **Duarte PA, Chow CC, Simmons F, Ruskin J.** Fatal hepatitis associated with ketoconazole therapy. *Arch Intern Med*. 1984;144(5):1069–1070.
512. **Lake-Bakaar G, Scheuer PJ, Sherlock S.** Hepatic reactions associated with ketoconazole in the United Kingdom. *Br Med J (Clin Res Ed)*. 1987;294:419–422.
513. **Zöllner E, Delport S, Bonnici F.** Fatal liver failure due to ketoconazole treatment of a girl with Cushing's syndrome. *J Pediatr Endocrinol Metab*. 2001;14(3):335–338.
514. **Ogawa R, Echizen H.** Drug-drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet*. 2010;49(8):509–533.
515. **Usmani KA, Tang J.** Human cytochrome P450: metabolism of testosterone by CYP3A4 and inhibition by ketoconazole. *Curr Protoc Toxicol*. 2004; Chapter 4: Unit 4.13.
516. **Berwaerts J, Verhelst J, Mahler C, Abs R.** Cushing's syndrome in pregnancy treated by ketoconazole: case report and review of the literature. *Gynecol Endocrinol*. 1999;13(3):175–182.
517. **Boronat M, Marrero D, López-Plasencia Y, Barber M, Schamann Y, Nóvoa FJ.** Successful outcome of pregnancy in a patient with Cushing's disease under treatment with ketoconazole during the first trimester of gestation. *Gynecol Endocrinol*. 2011;27(9):675–677.
518. **Lim WH, Torpy DJ, Jeffries WS.** The medical management of Cushing's syndrome during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2013;168(1):1–6.
519. **Kazy Z, Puhó E, Czeizel AE.** Population-based case-control study of oral ketoconazole treatment for birth outcomes. *Congenit Anom (Kyoto)*. 2005;45(1):5–8.
520. **Chart JJ, Sheppard H, Allen MJ, Bencze WL, Gaunt R.** New amphenone analogs as adrenocortical inhibitors. *Experientia*. 1958;14(4):151–152.
521. **Liddle GW, Island D, Lance EM, Harris AP.** Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of 11 $\beta$-hydroxylation. *J Clin Endocrinol Metab*. 1958;18(8):906–912.
522. **Carballeira A, Fishman LM, Jacobi JD.** Dual sites of inhibition by metyrapone of human adrenal steroidogenesis: correlation of in vivo and in vitro studies. *J Clin Endocrinol Metab*. 1976;42(4):687–695.
523. **Gower DB.** Modifiers of steroid-hormone metabolism: a review of their chemistry, biochemistry and clinical applications. *J Steroid Biochem*. 1974;5:501–523.
524. **Jeffcoate WJ, Rees LH, Tomlin S, Jones AE, Edwards CR, Besser GM.** Metyrapone in long-term management of Cushing's disease. *Br Med J*. 1977;2(6081):215–217.
525. **Donckier J, Burrin JM, Ramsay ID, Joplin GF.** Successful control of Cushing's disease in the elderly with long term metyrapone. *Postgrad Med J*. 1986;62(730):727–730.
526. **Dickstein G, Lahav M, Shen-Orr Z, Edoute Y, Barzilai D.** Primary therapy for Cushing's disease with metyrapone. *JAMA*. 1986;255(9):1167–1169.
527. **Traina AN, Farr A, Malik R, Bingham RJ.** Metyrapone for long-term medical management of Cushing's syndrome. *Case Rep Endocrinol*. 2013;2013:782068.
528. **Thorén M, Adamson U, Sjöberg HE.** Aminoglutethimide and metyrapone in the management of Cushing's syndrome. *Acta Endocrinol (Copenh)*. 1985;109(4):451–457.
529. **Verhelst JA, Trainer PJ, Howlett TA, et al.** Short and long-

term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1991;35(2):169–178.
530. **Cabezón C, Bruno OD, Cohen M, García S, Gutman RA.** Twin pregnancy in a patient with Cushing's disease. *Fertil Steril*. 1999;72(2):371–372.
531. **Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK.** Cushing's syndrome during pregnancy: personal experience and review of the literature. *J Clin Endocrinol Metab*. 2005; 90(5):3077–3083.
532. **Fishman LM, Liddle GW, Island DP, Fleischer N, Küchel O.** Effects of amino-glutethimide on adrenal function in man. *J Clin Endocrinol Metab*. 1967;27(4):481–490.
533. **Misbin RI, Canary J, Willard D.** Aminoglutethimide in the treatment of Cushing's syndrome. *J Clin Pharmacol*. 1976; 16:645–651.
534. **Zachmann M, Gitzelmann RP, Zagalak M, Prader A.** Effect of aminoglutethimide on urinary cortisol and cortisol metabolites in adolescents with Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1977;7(1):63–71.
535. **Komanicky P, Spark RF, Melby JC.** Treatment of Cushing's syndrome with trilostane (WIN 24,540), an inhibitor of adrenal steroid biosynthesis. *J Clin Endocrinol Metab*. 1978;47(5):1042–1051.
536. **Dewis P, Anderson DC, Bu'lock DE, Earnshaw R, Kelly WF.** Experience with trilostane in the treatment of Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1983;18(6):533–540.
537. **Allolio B, Stuttmann R, Leonhard U, Fischer H, Winkelmann W.** Adrenocortical suppression by a single induction dose of etomidate. *Klin Wochenschr*. 1984;62(21):1014–1017.
538. **Fry DE, Griffiths H.** The inhibition by etomidate of the 11 $\beta$-hydroxylation of cortisol. *Clin Endocrinol (Oxf)*. 1984; 20(5):625–629.
539. **Kenyon CJ, Young J, Gray CE, Fraser R.** Inhibition by etomidate of steroidogenesis in isolated bovine adrenal cells. *J Clin Endocrinol Metab*. 1984;58(5):947–949.
540. **Vanden Bossche H, Willemsens G, Cools W, Bellens D.** Effects of etomidate on steroid biosynthesis in subcellular fractions of bovine adrenals. *Biochem Pharmacol*. 1984; 33(23):3861–3868.
541. **Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D.** Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med*. 1984;310(22):1415–1421.
542. **Allolio B, Dörr H, Stuttmann R, Knorr D, Engelhardt D, Winkelmann W.** Effect of a single bolus of etomidate upon eight major corticosteroid hormones and plasma ACTH. *Clin Endocrinol (Oxf)*. 1985;22(3):281–286.
543. **Lamberts SW, Bons EG, Bruining HA, de Jong FH.** Differential effects of the imidazole derivatives etomidate, ketoconazole and miconazole and of metyrapone on the secretion of cortisol and its precursors by human adrenocortical cells. *J Pharmacol Exp Ther*. 1987;240(1): 259–264.
544. **Lambert A, Mitchell R, Frost J, Ratcliffe JG, Robertson WR.** Direct in vitro inhibition of adrenal steroidogenesis by etomidate. *Lancet*. 1983;2(8358):1085–1086.
545. **Fassnacht M, Hahner S, Beuschlein F, Klink A, Reincke M, Allolio B.** New mechanisms of adrenostatic compounds in a human adrenocortical cancer cell line. *Eur J Clin Invest*. 2000;30(suppl 3):76–82.
546. **Hahner S, Stürmer A, Fassnacht M, et al.** Etomidate unmasks intraadrenal regulation of steroidogenesis and proliferation in adrenal cortical cell lines. *Horm Metab Res*. 2010;42(7):528–534.
547. **Engelhardt D, Suttmann H, Jacob K, Dörr HG.** Influence of low-dose etomidate on adrenal and gonadal steroid hormone secretion in normal men. *Acta Endocrinologica*. 1986;113(suppl 1):S21–S22.
548. **Forman SA.** Clinical and molecular pharmacology of etomidate. *Anesthesiology*. 2011;114(3):695–707.
549. **Preda VA, Sen J, Karavitaki N, Grossman AB.** Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review. *Eur J Endocrinol*. 2012;167(2):137–143.
550. **Soh LM, Gunganah K, Akker SA, et al.** Etomidate in the emergency management of hypercortisolemia. *Eur J Endocrinol*. 2012;167(5):727–728; author reply 729.
551. **Drake WM, Perry LA, Hinds CJ, Lowe DG, Reznek RH, Besser GM.** Emergency and prolonged use of intravenous etomidate to control hypercortisolemia in a patient with Cushing's syndrome and peritonitis. *J Clin Endocrinol Metab*. 1998;83(10):3542–3544.
552. **Greening JE, Brain CE, Perry LA, et al.** Efficient short-term control of hypercortisolaemia by low-dose etomidate in severe paediatric Cushing's disease. *Horm Res*. 2005; 64(3):140–143.
553. **Chan LF, Vaidya M, Westphal B, et al.** Use of intravenous etomidate to control acute psychosis induced by the hypercortisolaemia in severe paediatric Cushing's disease. *Horm Res Paediatr*. 2011;75(6):441–446.
554. **Allolio B, Schulte HM, Kaulen D, Reincke M, Jaursch-Hancke C, Winkelmann W.** Nonhypnotic low-dose etomidate for rapid correction of hypercortisolaemia in Cushing's syndrome. *Klin Wochenschr*. 1988;66(8):361–364.
555. **Schulte HM, Benker G, Reinwein D, Sippell WG, Allolio B.** Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. *J Clin Endocrinol Metab*. 1990;70(5):1426–1430.
556. **Mettauer N, Brierley J.** A novel use of etomidate for intentional adrenal suppression to control severe hypercortisolemia in childhood. *Pediatr Crit Care Med*. 2009;10(3): e37–e40.
557. **Doenicke A, Roizen MF, Nebauer AE, Kugler A, Hoernecke R, Beger-Hintzen H.** A comparison of two formulations for etomidate, 2-hydroxypropyl-$\beta$-cyclodextrin (HPCD) and propylene glycol. *Anesth Analg*. 1994;79(5): 933–939.
558. **Morris C, McAllister C.** Etomidate for emergency anaesthesia; mad, bad and dangerous to know? *Anaesthesia*. 2005;60(8):737–740.
559. **Zacharias M, Clarke RS, Dundee JW, Johnston SB.** Venous sequelae following etomidate. *Br J Anaesth*. 1979; 51(8):779–783.
560. **Nyman Y, Von Hofsten K, Palm C, Eksborg S, Lönnqvist PA.** Etomidate-Lipuro is associated with considerably less injection pain in children compared with propofol with added lidocaine. *Br J Anaesth*. 2006;97(4):536–539.
561. **Doenicke A, Roizen MF, Hoernecke R, Mayer M, Ostwald**

**P, Foss J.** Haemolysis after etomidate: comparison of propylene glycol and lipid formulations. *Br J Anaesth*. 1997; 79(3):386–388.
562. **Yorgin PD, Theodorou AA, Al-Uzri A, Davenport K, Boyer-Hassen LV, Johnson MI.** Propylene glycol-induced proximal renal tubular cell injury. *Am J Kidney Dis*. 1997; 30(1):134–139.
563. **Krakoff J, Koch CA, Calis KA, Alexander RH, Nieman LK.** Use of a parenteral propylene glycol-containing etomidate preparation for the long-term management of ectopic Cushing's syndrome. *J Clin Endocrinol Metab*. 2001; 86(9):4104–4108.
564. **Nelson AA, Woodard G.** Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)-1,1-dichloroethane (DDD or TDE). *Arch Pathol (Chic)*. 1949;48(5):387–394.
565. **Cueto C, Brown JH, Richardson AP Jr.** Biological studies on an adrenocorticolytic agent and the isolation of the active components. *Endocrinology*. 1958;62(3):334–339.
566. **Vilar O, Tullner WW.** Effects of o,p' DDD on histology and 17-hydroxycorticosteroid output of the dog adrenal cortex. *Endocrinology*. 1959;65(1):80–86.
567. **Hart MM, Straw JA.** Studies on the site of action of o,p'-DDD in the dog adrenal cortex. 1. Inhibition of ACTH-mediated pregnenolone synthesis. *Steroids*. 1971;17(5): 559–574.
568. **Hart MM, Swackhamer ES, Straw JA.** Studies on the site of action of o,p'-DDD in the dog adrenal cortex. II. TPNH- and corticosteroid precursor-stimulation of o,p'-DDD inhibited steroidogenesis. *Steroids*. 1971;17(5):575–586.
569. **Kaminsky N, Luse S, Hartroft P.** Ultrastructure of adrenal cortex of the dog during treatment with DDD. *J Natl Cancer Inst*. 1962;29:127–159.
570. **Hart MM, Reagan RL, Adamson RH.** The effect of isomers of DDD on the ACTH-induced steroid output, histology and ultrastructure of the dog adrenal cortex. *Toxicol Appl Pharmacol*. 1973;24(1):101–113.
571. **Young RB, Bryson MJ, Sweat ML, Street JC.** Complexing of DDT and o,p'DDD with adrenal cytochrome P-450 hydroxylating systems. *J Steroid Biochem*. 1973;4(6):585–591.
572. **Koide Y, Inoue S, Murayama H, Kawai K, Yamashita K.** Effect of o,p'-DDD on cortisol metabolism in Cushing's syndrome of various etiology. *Endocrinol Jpn*. 1985; 32(5):615–624.
573. **van Erp NP, Guchelaar HJ, Ploeger BA, Romijn JA, Hartigh Jd, Gelderblom H.** Mitotane has a strong and a durable inducing effect on CYP3A4 activity. *Eur J Endocrinol*. 2011;164(4):621–626.
574. **Southren AL, Weisenfeld S, Laufer A, Goldner MG.** Effect of o,p'DDD in a patient with Cushing's syndrome. *J Clin Endocrinol Metab*. 1961;21:201–208.
575. **Temple TE Jr, Jones DJ Jr, Liddle GW, Dexter RN.** Treatment of Cushing's disease. Correction of hypercortisolism by o,p'DDD without induction of aldosterone deficiency. *N Engl J Med*. 1969;281(15):801–805.
576. **Dickerman Z, Kaufman H, Laron Z.** Successful treatment of Cushing's disease with o,p'-DDD followed by pituitary irradiation in a 19-year-old male patient. *Isr J Med Sci*. 1979;15(5):455–459.
577. **Luton JP, Mahoudeau JA, Bouchard P, et al.** Treatment of Cushing's disease by O,p'DDD. Survey of 62 cases. *N Engl J Med*. 1979;300(9):459–464.
578. **Schteingart DE, Tsao HS, Taylor CI, McKenzie A, Victoria R, Therrien BA.** Sustained remission of Cushing's disease with mitotane and pituitary irradiation. *Ann Intern Med*. 1980;92(5):613–619.
579. **Takamatsu J, Kitazawa A, Nakata K, Furukawa K, Nakai Y.** Does mitotane reduce endogenous ACTH secretion? *N Engl J Med*. 1981;305(16):957.
580. **Benecke R, Keller E, Vetter B, de Zeeuw RA.** Plasma level monitoring of mitotane (o,p'-DDD) and its metabolite (o,p'-DDE) during long-term treatment of Cushing's disease with low doses. *Eur J Clin Pharmacol*. 1991;41(3): 259–261.
581. **Kawai S, Ichikawa Y, Kaburaki J, Yoshida T.** 18 Years mitotane therapy for intractable Cushing's disease. *Lancet*. 1999;354(9182):951.
582. **Baudry C, Coste J, Bou Khalil R, et al.** Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. *Eur J Endocrinol*. 2012;167(4):473–481.
583. **Leiba S, Weinstein R, Shindel B, et al.** The protracted effect of o,p'-DDD in Cushing's disease and its impact on adrenal morphogenesis of young human embryo. *Ann Endocrinol (Paris)*. 1989;50(1):49–53.
584. **Suda T, Tozawa F, Mouri T, et al.** Effects of cyproheptadine, reserpine, and synthetic corticotropin-releasing factor on pituitary glands from patients with Cushing's disease. *J Clin Endocrinol Metab*. 1983;56(6):1094–1099.
585. **van Waveren Hogervorst CO, Koppeschaar HP, Zelissen PM, Lips CJ, Garcia BM.** Cortisol secretory patterns in Cushing's disease and response to cyproheptadine treatment. *J Clin Endocrinol Metab*. 1996;81(2):652–655.
586. **Plonk J, Feldman J.** Modification of adrenal function by the anti-serotonin agent cyproheptadine. *J Clin Endocrinol Metab*. 1976;42(2):291–295.
587. **Cavagnini F, Panerai AE, Valentini F, Bulgheroni P, Peracchi M, Pinto M.** Inhibition of ACTH response to oral and intravenous metyrapone by antiserotoninergic treatment in man. *J Clin Endocrinol Metab*. 1975;41(1):143–148.
588. **Krieger DT, Amorosa L, Linick F.** Cyproheptadine-induced remission of Cushing's disease. *N Engl J Med*. 1975; 293(18):893–896.
589. **Kriegert T.** Letter: cyproheptadine for pituitary disorders. *N Engl J Med*. 1976;295:394–395.
590. **Krieger DT.** Physiopathology of Cushing's disease. *Endocr Rev*. 1983;4(1):22–43.
591. **Ambrosi B, Gaggini M, Secchi F, Faglia G.** Lack of effect of antiserotoninergic and/or dopaminergic treatment in patients with pituitary-dependent Cushing's syndrome. *Horm Metab Res*. 1979;11(4):318–319.
592. **Tyrrell JB, Brooks RM, Forsham PH.** More on cyproheptadine. *N Engl J Med*. 1976;295(20):1137–1138.
593. **Copinschi G, Goldstein J, Virasoro E, Frackson JM.** Lack of effect of cyproheptadine in Cushing's disease and in Nelson's syndrome. *Acta Endocrinol (Copenh)*. 1977; 312(suppl 130).
594. **Koppeschaar HP, Croughs RJ, Thijssen JH, Schwarz F.** Sodium valproate and cyproheptadine may independently induce a remission in the same patient with Cushing's disease. *Acta Endocrinol (Copenh)*. 1983;104:160–163.
595. **Tucci JR, Nowakowski KJ, Jackson IM.** Cyproheptadine

may act at the pituitary in Cushing's disease: evidence from CRF stimulation. *J Endocrinol Invest*. 1989;12(3):197–200.
596. **Hsu TH, Gann DS, Tsan KW, Russell RP.** Cyproheptadine in the control of Cushing's disease. *Johns Hopkins Med J*. 1981;149(2):77–83.
597. **Barnes P, Shaw K, Ross E.** Cushing's disease: successful treatment with cyproheptadine. *Lancet*. 1977;1(8022):1148–1149.
598. **Ooi TC, Twum-Barima Y.** Rebound elevation of cortisol following cyproheptadine withdrawal in Cushing's disease from a pituitary macroadenoma. *J Endocrinol Invest*. 1987;10(2):107–109.
599. **Middler SA.** Letter: cyproheptadine for pituitary disorders. *N Engl J Med*. 1976;295:394–395.
600. **Ferrari C, Bertazzoni A, Ghezzi M.** More on cyproheptadine in Cushing's disease. *N Engl J Med*. 1977;296:576–577.
601. **Grant DB, Atherden SM.** Cushing's disease presenting with growth failure: clinical remission during cyproheptadine therapy. *Arch Dis Child*. 1979;54(6):466–468.
602. **Schteingart DE, McKenzie AK.** Twelve-hour cycles of adrenocorticotropin and cortisol secretion in Cushing's disease. *J Clin Endocrinol Metab*. 1980;51(5):1195–1198.
603. **Pearce CJ, Isaacs AJ, Gomez J.** Treatment of Cushing's disease with cyproheptadine. *Lancet*. 1977;1:1368–1369.
604. **Glaser B, Kahana L, Elias V, Sheinfeld M.** Sodium valproate and metyrapone for pituitary-dependent Cushing's disease. *Lancet*. 1984;2(8403):640.
605. **Allgrove J, Husband P, Brook CG.** Cushing's disease: failure of treatment with cyproheptadine. *Br Med J*. 1977;1(6062):686–687.
606. **D'Ercole AJ, Morris MA, Underwood LE, Van Wyk JJ, Feldman JM.** Treatment of Cushing disease in childhood with cyproheptadine. *J Pediatr*. 1977;90(5):834–835.
607. **Sonino N, Boscaro M, Fallo F, Fava GA.** Potential therapeutic effects of ritanserin in Cushing's disease. *JAMA*. 1992;267(8):1073.
608. **Sonino N, Fava GA, Fallo F, Franceschetto A, Belluardo P, Boscaro M.** Effect of the serotonin antagonists ritanserin and ketanserin in Cushing's disease. *Pituitary*. 2000;3(2):55–59.
609. **Makara GB, Stark E.** Effects of γ-aminobutyric acid (GABA) and GABA antagonist drugs on ACTH release. *Neuroendocrinology*. 1974;16:178–190.
610. **Jones MT, Hillhouse EW.** Neurotransmitter regulation of corticotropin-releasing factor in vitro. *Ann N Y Acad Sci*. 1977;297:536–560.
611. **Kritzler RK, Vining EP, Plotnick LP.** Sodium valproate and corticotropin suppression in the child treated for seizures. *J Pediatr*. 1983;102(1):142–143.
612. **Koppeschaar HP, Croughs RJ, Thijssen JH, Schwarz F.** Sodium valproate and heterogeneity of pituitary dependent Cushing's syndrome. *Lancet*. 1982;1:1253.
613. **Koppeschaar HP, Croughs RJ, van't Verlaat JW, et al.** Successful treatment with sodium valproate of a patient with Cushing's disease and gross enlargement of the pituitary. *Acta Endocrinol (Copenh)*. 1984;107(4):471–475.
614. **Cavagnini F, Invitti C, Polli EE.** Sodium valproate in Cushing's disease. *Lancet*. 1984;2(8395):162–163.
615. **Ambrosi B, Bochicchio D, Riva E, Faglia G.** Effects of sodium-valproate administration on plasma ACTH levels in patients with ACTH hypersecretion. *J Endocrinol Invest*. 1983;6(4):305–306.
616. **Reincke M, Allolio B, Kaulen D, Jaursch-Hancke C, Winkelmann W.** The effect of sodium valproate in Cushing's disease, Nelson's syndrome and Addison's disease. *Klin Wochenschr*. 1988;66(15):686–689.
617. **Loli P, Berselli ME, Frascatani F, Muratori F, Tagliaferri M.** Lack of ACTH lowering effect of sodium valproate in patients with ACTH hypersecretion. *J Endocrinol Invest*. 1984;7(2):93–96.
618. **Allolio B, Winkelmann W, Kaulen D, Hipp FX, Mies R.** Valproate in Cushing's syndrome. *Lancet*. 1982;1(8264):171.
619. **Koppeschaar HP, Croughs RJ, Thijssen JH, Schwarz F.** Response to neurotransmitter modulating drugs in patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 1986;25:661–667.
620. **Colao A, Pivonello R, Tripodi FS, et al.** Failure of long-term therapy with sodium valproate in Cushing's disease. *J Endocrinol Invest*. 1997;20(7):387–392.
621. **Beckers A, Stevenaert A, Pirens G, Flandroy P, Sulon J, Hennen G.** Cyclical Cushing's disease and its successful control under sodium valproate. *J Endocrinol Invest*. 1990;13(11):923–929.
622. **Nussey SS, Price P, Jenkins JS, Altaher AR, Gillham B, Jones MT.** The combined use of sodium valproate and metyrapone in the treatment of Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1988;28(4):373–380.
623. **Pivonello R, Ferone D, Lombardi G, Colao A, Lamberts SW, Hofland LJ.** Novel insights in dopamine receptor physiology. *Eur J Endocrinol*. 2007;156(suppl 1):S13–S21.
624. **Caron MG, Beaulieu M, Raymond V, et al.** Dopaminergic receptors in the anterior pituitary gland. Correlation of [3H]dihydroergocryptine binding with the dopaminergic control of prolactin release. *J Biol Chem*. 1978;253(7):2244–2253.
625. **Munemura M, Cote TE, Tsuruta K, Eskay RL, Kebabian JW.** The dopamine receptor in the intermediate lobe of the rat pituitary gland: pharmacological characterization. *Endocrinology*. 1980;107(6):1676–1683.
626. **Lamberts SW, Macleod RM.** Regulation of prolactin secretion at the level of the lactotroph. *Physiol Rev*. 1990;70:279–318.
627. **Renner U, Arzberger T, Pagotto U, et al.** Heterogeneous dopamine D2 receptor subtype messenger ribonucleic acid expression in clinically nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab*. 1998;83(4):1368–1375.
628. **Pivonello R, Waaijers M, Kros JM, et al.** Dopamine D2 receptor expression in the corticotroph cells of the human normal pituitary gland. Paper presented at: 12th Annual Meeting of the European Neuroendocrine Association; October 21–24, 2006; Athens, Greece.
629. **Stefaneanu L, Kovacs K, Horvath E, Buchfelder M, Fahlbusch R, Lancranjan L.** Dopamine D2 receptor gene expression in human adenohypophysial adenomas. *Endocrine*. 2001;14(3):329–336.
630. **Ferone D, Pivonello R, Resmini E, et al.** Preclinical and clinical experiences with the role of dopamine receptors in

the treatment of pituitary adenomas. *Eur J Endocrinol*. 2007;156(suppl 1):S37–S43.
631. **Colao A, di Sarno A, Pivonello R, di Somma C, Lombardi G.** Dopamine receptor agonists for treating prolactinomas. *Expert Opin Investig Drugs*. 2002;11(6):787–800.
632. **Pivonello R, Matrone C, Filippella M, et al.** Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: comparison with the effectiveness of cabergoline treatment. *J Clin Endocrinol Metab*. 2004; 89(4):1674–1683.
633. **Nobels FR, de Herder WW, van den Brink WM, et al.** Long-term treatment with the dopamine agonist quinagolide of patients with clinically non-functioning pituitary adenoma. *Eur J Endocrinol*. 2000;143(5):615–621.
634. **Greenman Y, Tordjman K, Osher E, et al.** Postoperative treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists decreases tumour remnant growth. *Clin Endocrinol (Oxf)*. 2005;63(1):39–44.
635. **Pivonello R, Ferone D, de Herder WW, et al.** Dopamine receptor expression and function in corticotroph pituitary tumors. *J Clin Endocrinol Metab*. 2004;89(5):2452–2462.
636. **Cronin MJ, Cheung CY, Wilson CB, Jaffe RB, Weiner RI.** [3H]Spiperone binding to human anterior pituitaries and pituitary adenomas secreting prolactin, growth hormone, and adrenocorticotropic hormone. *J Clin Endocrinol Metab*. 1980;50(2):387–391.
637. **Pirker W, Riedl M, Luger A, et al.** Dopamine D2 receptor imaging in pituitary adenomas using iodine-123-epidepride and SPECT. *J Nucl Med*. 1996;37(12):1931–1937.
638. **Adams EF, Ashby MJ, Brown SM, White MC, Mashiter K.** Bromocriptine suppresses ACTH secretion from human pituitary tumour cells in culture by a dopaminergic mechanism. *Clin Endocrinol (Oxf)*. 1981;15(5):479–484.
639. **Yin D, Kondo S, Takeuchi J, Morimura T.** Induction of apoptosis in murine ACTH-secreting pituitary adenoma cells by bromocriptine. *FEBS Lett*. 1994;339:73–75.
640. **Lamberts SWJ, Klijn JG, de Quijada M.** The mechanism of suppressive action of bromocriptine on ACTH secretion in patients with Cushing's and Nelson syndrome. *J Clin Endocrinol Metab*. 1980;51:307–315.
641. **Petrossians P, Thonnard AS, Beckers A.** Medical treatment in Cushing's syndrome: dopamine agonists and cabergoline. *Neuroendocrinology*. 2010;92(suppl)1:116–119.
642. **Lamberts SWJ, Birkenhager JC.** Bromocriptine in Nelson's syndrome and Cushing's disease (Letter). *Lancet* 1976;2: 811.
643. **Lamberts SWJ, Timmermans HA, De Jong FH.** The role of dopaminergic depletion in the pathogenesis of Cushing's disease and the possible consequences for medical therapy. *Clin Endocrinol (Oxf)*. 1977;7:185–193.
644. **Invitti C, De Martin M, Danesi L, Cavagnini F.** Effect of injectable bromocriptine in patients with Cushing's disease. *Exp Clin Endocrinol Diabetes*. 1995;103(4):266–271.
645. **Bevan JS, Webster J, Burke CW, Scanlon MF.** Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev*. 1992; 13(2):220–240.
646. **Adachi M, Takayanagi R, Yanase T.** Cyclic Cushing's disease in long-term remission with a daily low dose of bromocriptine. *Intern Med*. 1996;35(3):207–211.
647. **McNicol AM, Teasdale GM, Beastall GH.** A study of corticotroph adenomas in Cushing's disease: no evidence of intermediate lobe origin. *Clin Endocrinol (Oxf)*. 1986; 24(6):715–722.
648. **Croughs RJ, Koppeschaar HP, van't Verlaat JW, McNicol AM.** Bromocriptine-responsive Cushing's disease associated with anterior pituitary corticotroph hyperplasia or normal pituitary gland. *J Clin Endocrinol Metab*. 1989; 68(2):495–498.
649. **Petrossians P, Ronci N, Valdés Socin H, et al.** ACTH silent adenoma shrinking under cabergoline. *Eur J Endocrinol*. 2001;144(1):51–57.
650. **Manavela MP, Danilowicz K, Bruno OD.** Macrocorticotropinoma shrinkage and control of hypercortisolism under long-term cabergoline therapy: case report. *Pituitary*. 2012;15(suppl 1):33–36.
651. **Elshafie O, Osman A, Aamer F, Al-Mamari A, Woodhouse N.** Cushing's disease: sustained remission in five cases induced by medical therapy with the dopamine agonist cabergoline. *Sultan Qaboos Univ Med J*. 2012;12(4):493–497.
652. **Ahmed A, Furqan S, Islam N.** Disappearance of pituitary macro adenoma with combination of ketoconazole and cabergoline treatment: an unusual case of Cushing's syndrome with interesting findings. *BMJ Case Rep*. 2012; 2012:pii:bcr0320126025.
653. **Miyoshi T, Otsuka F, Takeda M, et al.** Effect of cabergoline treatment on Cushing's disease caused by aberrant adrenocorticotropin-secreting macroadenoma. *J Endocrinol Invest*. 2004;27(11):1055–1059.
654. **T'Sjoen G, Defeyter I, Van De Saffele J, Rubens R, Vandeweghe M.** Macroprolactinoma associated with Cushing's disease, successfully treated with cabergoline. *J Endocrinol Invest*. 2002;25(2):172–175.
655. **Meij BP, Lopes MB, Vance ML, Thorner MO, Laws ER Jr.** Double pituitary lesions in three patients with Cushing's disease. *Pituitary*. 2000;3(3):159–168.
656. **Pivonello R, De Martino MC, Cappabianca P, et al.** The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. *J Clin Endocrinol Metab*. 2009;94(1):223–230.
657. **Cozzolino A, Vitale P, De Leo M, et al.** Impact of long-term cabergoline treatment on clinical, metabolic and hormonal features in patients with Cushing's syndrome. Paper presented at: 13th European Congress of Endocrinology; April 30 to May 4, 2011; Rotterdam, The Netherlands. Abstract P28.
658. **Godbout A, Manavela M, Danilowicz K, Beauregard H, Bruno OD, Lacroix A.** Cabergoline monotherapy in the long-term treatment of Cushing's disease. *Eur J Endocrinol*. 2010;163(5):709–716.
659. **Vilar L, Naves LA, Azevedo MF, et al.** Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. *Pituitary*. 2010;13(2):123–129.
660. **Barbot M, Albiger N, Ceccato F, et al.** Combination therapy for Cushing's disease: effectiveness of two schedules of treatment: should we start with cabergoline or ketoconazole? *Pituitary*. 2014;17(2):109–117.
661. **Lila AR, Gopal RA, Acharya SV, et al.** Efficacy of caber-

goline in uncured (persistent or recurrent) Cushing disease after pituitary surgical treatment with or without radiotherapy. *Endocr Pract*. 2010;16(6):968–976.
662. **Vitale P, Cozzolino A, De Leo M, et al.** Predictive value of acute cortisol response to cabergoline administration on the responsiveness of cortisol secretion to short and long term treatment with cabergoline. Paper presented at: 13th European Congress of Endocrinology; April 30 to May 4, 2011; Rotterdam, The Netherlands. Abstract P26.
663. **Pivonello R, Faggiano A, De Martino MC, et al.** Long-term effectiveness of cabergoline treatment in Cushing's disease: comparison with D2 dopamine receptor expression. Presented at: the 86th Annual Meeting of The Endocrine Society; June 16–19, 2004; New Orleans, LA. Abstract OR40-4.
664. **Pivonello R, de Herder WW, Ferone D, et al.** Dopamine receptor expression and dopamine agonist effectiveness in corticotroph pituitary tumors; comparison with clinical, biochemical, radiological and pathological features of patients with Cushing's disease. Paper presented at: The Endocrine Society's 90th Annual Meeting and Expo; June 15–18, 2008; San Francisco, CA. Abstract P395.
665. **Pivonello R, Ferone D, de Herder WW, et al.** Dopamine receptor expression and function in human normal adrenal gland and adrenal tumors. *J Clin Endocrinol Metab*. 2004; 89(9):4493–4502.
666. **Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E.** Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med*. 2007;356(1):29–38.
667. **Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G.** Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med*. 2007; 356(1):39–46.
668. **Woo I, Ehsanipoor RM.** Cabergoline therapy for Cushing disease throughout pregnancy. *Obstet Gynecol*. 2013; 122:485–487.
669. **Patel YC.** Somatostatin and its receptor family. *Front Neuroendocrinol*. 1999;20(3):157–198.
670. **Colao A, Auriemma RS, Lombardi G, Pivonello R.** Resistance to somatostatin analogs in acromegaly. *Endocr Rev*. 2011;32(2):247–271.
671. **Nielsen S, Mellemkjaer S, Rasmussen LM, et al.** Expression of somatostatin receptors on human pituitary adenomas in vivo and ex vivo. *J Endocrinol Invest*. 2001;24(6):430–437.
672. **Batista DL, Zhang X, Gejman R, et al.** The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas. *J Clin Endocrinol Metab*. 2006;91(11):4482–4488.
673. **van der Hoek J, Waaijers M, van Koetsveld PM, et al.** Distinct functional properties of native somatostatin receptor subtype 5 compared with subtype 2 in the regulation of ACTH release by corticotroph tumor cells. *Am J Physiol Endocrinol Metab*. 2005;289(2):E278–E287.
674. **Colao A, Faggiano A, Pivonello R.** Somatostatin analogues: treatment of pituitary and neuroendocrine tumors. *Prog Brain Res*. 2010;182:281–294.
675. **Pivonello R, Ferone D, Filippella M, et al.** Role of somatostatin analogs in the management of non-functioning neuroendocrine tumors. *J Endocrinol Invest*. 2003;26(8 suppl):82–88.
676. **Richardson UI, Schonbrunn A.** Inhibition of adrenocorticotropin secretion by somatostatin in pituitary cells in culture. *Endocrinology*. 1981;108(1):281–290.
677. **Heisler S, Reisine TD, Hook VY, Axelrod J.** Somatostatin inhibits multireceptor stimulation of cyclic AMP formation and corticotropin secretion in mouse pituitary tumor cells. *Proc Natl Acad Sci USA*. 1982;79(21):6502–6506.
678. **Strowski MZ, Dashkevicz MP, Parmar RM, et al.** Somatostatin receptor subtypes 2 and 5 inhibit corticotropin-releasing hormone-stimulated adrenocorticotropin secretion from AtT-20 cells. *Neuroendocrinology*. 2002;75(6): 339–346.
679. **Lamberts SW, Uitterlinden P, Klijn JM.** The effect of the long-acting somatostatin analogue SMS 201–995 on ACTH secretion in Nelson's syndrome and Cushing's disease. *Acta Endocrinol (Copenh)*. 1989;120(6):760–766.
680. **Invitti C, de Martin M, Brunani A, Piolini M, Cavagnini F.** Treatment of Cushing's syndrome with the long-acting somatostatin analogue SMS 201–995 (sandostatin). *Clin Endocrinol (Oxf)*. 1990;32(3):275–281.
681. **Ambrosi B, Bochicchio D, Fadin C, Colombo P, Faglia G.** Failure of somatostatin and octreotide to acutely affect the hypothalamic-pituitary-adrenal function in patients with corticotropin hypersecretion. *J Endocrinol Invest*. 1990; 13(3):257–261.
682. **Stalla GK, Brockmeier SJ, Renner U, et al.** Octreotide exerts different effects in vivo and in vitro in Cushing's disease. *Eur J Endocrinol*. 1994;130(2):125–131.
683. **Schmid HA, Schoeffter P.** Functional activity of the multiligand analog SOM230 at human recombinant somatostatin receptor subtypes supports its usefulness in neuroendocrine tumors. *Neuroendocrinology*. 2004;80(suppl 1):47–50.
684. **Pedroncelli AM.** Medical treatment of Cushing's disease: somatostatin analogues and pasireotide. *Neuroendocrinology*. 2010;92(suppl 1):120–124.
685. **Feelders RA, Yasothan U, Kirkpatrick P.** Pasireotide. *Nat Rev Drug Discov*. 2012;11(8):597–598.
686. **Arnaldi G, Boscaro M.** Pasireotide for the treatment of Cushing's disease. *Expert Opin Investig Drugs*. 2010; 19(7):889–898.
687. **Park S, Kamegai J, Kineman RD.** Role of glucocorticoids in the regulation of pituitary somatostatin receptor subtype (sst1-sst5) mRNA levels: evidence for direct and somatostatin-mediated effects. *Neuroendocrinology*. 2003; 78(3):163–175.
688. **Lamberts SW.** The role of somatostatin in the regulation of anterior pituitary hormone secretion and the use of its analogs in the treatment of human pituitary tumors. *Endocr Rev*. 1988;9(4):417–436.
689. **Invitti C, Pecori Giraldi F, Dubini A, Piolini M, Cavagnini F.** Effect of sandostatin on CRF-stimulated secretion of ACTH, β-lipotropin and β-endorphin. *Horm Metab Res*. 1991;23(5):233–235.
690. **Stafford PJ, Kopelman PG, Davidson K, et al.** The pituitary-adrenal response to CRF-41 is unaltered by intravenous somatostatin in normal subjects. *Clin Endocrinol (Oxf)*. 1989;30(6):661–666.
691. **Fehm HL, Voigt KH, Lang R, Beinert KE, Raptis S, Pfeiffer EF.** Somatostatin: a potent inhibitor of ACTH-hypersecre-

tion in adrenal insufficiency. *Klin Wochenschr*. 1976; 54(4):173–175.
692. **Julesz J, Laczi F, Janáky T, László F.** Effects of somatostatin and bromocryptine on the plasma ACTH level in bilaterally adrenalectomized patients with Cushing's disease. *Endokrinologie*. 1980;76(1):68–72.
693. **Kelestimur F, Utas C, Ozbakir O, Selçuklu A, Kandemir O, Ozcan N.** The effects of octreotide in a patient with Nelson's syndrome. *Postgrad Med J*. 1996;72(843):53–54.
694. **Kraus J, Wöltje M, Höllt V.** Regulation of mouse somatostatin receptor type 2 gene expression by glucocorticoids. *FEBS Lett*. 1999;459(2):200–204.
695. **Silva AP, Bethmann K, Raulf F, Schmid HA.** Regulation of ghrelin secretion by somatostatin analogs in rats. *Eur J Endocrinol*. 2005;152(6):887–894.
696. **Ruan W, Fahlbusch F, Clemmons DR, et al.** SOM230 inhibits insulin-like growth factor-I action in mammary gland development by pituitary independent mechanism: mediated through somatostatin subtype receptor 3? *Mol Endocrinol*. 2006;20(2):426–436.
697. **Boscaro M, Ludlam WH, Atkinson B, et al.** Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. *J Clin Endocrinol Metab*. 2009;94(1):115–122.
698. **Colao A, Petersenn S, Newell-Price J, et al.** A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 2012;366(10):914–924.
699. **Henry RR, Mudaliar S, Wetli-Hermosillo K, Ligueros-Saylan M, Chenji S, Golor G.** Mechanism and management of hyperglycemia associated with pasireotide: results from studies in healthy volunteers. Paper presented at: 93rd Annual Meeting of The Endocrine Society; June 4–7, 2011; Boston, MA. Abstract P260.
700. **Colao A, De Block C, Gaztambide MS, Kumar S, Seufert J, Casanueva FF.** Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. *Pituitary*. 2014;17(2):180–186.
701. **Reznik Y, Bertherat J, Borson-Chazot F, et al.** Management of hyperglycaemia in Cushing's disease: experts' proposals on the use of pasireotide. *Diabetes Metab*. 2013; 39(1):34–41.
702. **Breitschaft A, Hu K, Hermosillo Reséndiz K, Darstein C, Golor G.** Management of hyperglycemia associated with pasireotide (SOM230): healthy volunteer study. *Diabetes Res Clin Pract*. 2014;103(3):458–465.
703. **Pivonello R, Petersenn S, Newell-Price J, et al.** Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. *Clin Endocrinol (Oxf)*. 2014;81(3):408–417.
704. **Simeoli C, Auriemma RS, Tortora F, et al.** The treatment with pasireotide in Cushing's disease: effects of long-term treatment on tumor mass in the experience of a single center [published online March 6, 2015]. *Endocrine*. doi: 10.1007/s12020–015-0557–2.
705. **Shimon I, Rot L, Inbar E.** Pituitary-directed medical therapy with pasireotide for a corticotroph macroadenoma: pituitary volume reduction and literature review. *Pituitary*. 2012;15(4):608–613.
706. **Lu L, Duan L, Jin Z, Lu Z, Gu F.** Effective long-term treatment of Cushing's disease with pasireotide: a case report. *Endocr Pract*. 2013;19(4):e92–96.
707. **Schopohl J, Gu F, Rubens R, et al.** Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial [published online December 24, 2014]. *Pituitary*. doi: 10.1007/s11102-014-0618-1.
708. **Lacroix A, Pivonello R.** Medical treatment of Cushing's disease with pasireotide. *Eur J Endocrinol*. 2012;8:99–104.
709. **Pivonello R, Arnaldi G, Scaroni C, et al.** Effectiveness of pasireotide treatment in patients with Cushing's disease: a national experience based on clinical practice. Presented at: the 16th Congress of European Neuroendocrine Association; September 10–13, 2014; Sofia, Bulgaria. OC;ID: 467.
710. **Cukier K, Tewari R, Kurth F, Schmid HA, Lai C, Torpy DJ.** Significant response to pasireotide (SOM230) in the treatment of a patient with persistent, refractory Cushing's disease. *Clin Endocrinol (Oxf)*. 2009;71(2):305–307.
711. **MacKenzie Feder J, Bourdeau I, Vallette S, Beauregard H, Ste-Marie LG, Lacroix A.** Pasireotide monotherapy in Cushing's disease: a single-centre experience with 5-year extension of phase III Trial. *Pituitary*. 2014;17(6):519–529.
712. **Yedinak C, Brzana J, Fleseriu M.** Monitoring patient improvement parameters following pasireotide treatment in Cushing's disease. *Case Rep Endocrinol*. 2013;2013: 735489.
713. **Trementino L, Cardinaletti M, Concettoni C, Marcelli G, Boscaro M, Arnaldi G.** Up-to 5-year efficacy of pasireotide in a patient with Cushing's disease and pre-existing diabetes: literature review and clinical practice considerations. *Pituitary*. 2015;18(3):359–365.
714. **Issemann I, Green S.** Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*. 1990;347(6294):645–650.
715. **Lehrke M, Lazar MA.** The many faces of PPARγ. *Cell*. 2005;123(6):993–999.
716. **Heaney AP.** Novel pituitary ligands: peroxisome proliferator activating receptor-γ. *Pituitary*. 2003;6(3):153–159.
717. **Heaney AP.** PPAR-γ in Cushing's disease. *Pituitary*. 2004; 7(4):265–269.
718. **Mannelli M, Cantini G, Poli G, et al.** Role of the PPAR-γ system in normal and tumoral pituitary corticotropic cells and adrenal cells. *Neuroendocrinology*. 2010;92(suppl 1): 23–27.
719. **Heaney AP, Fernando M, Yong WH, Melmed S.** Functional PPAR-γ receptor is a novel therapeutic target for ACTH-secreting pituitary adenomas. *Nat Med*. 2002; 8(11):1281–1287.
720. **Sood V, Colleran K, Burge MR.** Thiazolidinediones: a comparative review of approved uses. *Diabetes Technol Ther*. 2000;2(3):429–440.
721. **Stone JC, Furuya-Kanamori L, Barendregt JJ, Doi SA.** Was there really any evidence that rosiglitazone increased the risk of myocardial infarction or death from cardiovascular causes? *Pharmacoepidemiol Drug Saf*. 2015;24(3):223–227.

722. **Heaney AP, Fernando M, Melmed S.** PPAR-γ receptor ligands: novel therapy for pituitary adenomas. *J Clin Invest*. 2003;111(9):1381–1388.
723. **Cannavò S, Ambrosi B, Chiodini I, et al.** Baseline and CRH-stimulated ACTH and cortisol levels after administration of the peroxisome proliferator-activated receptor-γ ligand, rosiglitazone, in Cushing's disease. *J Endocrinol Invest*. 2004;27(5):RC8–RC11.
724. **Alevizaki M, Philippou G, Zapanti L, Alevizaki CC, Anastasiou E, Mavrikakis M.** Significant improvement of recurrent pituitary-dependent Cushing's syndrome after administration of a PPAR-γ agonist. Paper presented at: 86th Annual Meeting of The Endocrine Society; June 16–19, 2004; New Orleans, LA. Abstract P2–453.
725. **Hull SS, Sheridan B, Atkinson AB.** Pre-operative medical therapy with rosiglitazone in two patients with newly diagnosed pituitary-dependent Cushing's syndrome. *Clin Endocrinol (Oxf)*. 2005;62:259–261.
726. **Heaney A, Drange MR, Melmed S.** Functional PPAR-γ receptor is a novel target for ACTH-secreting pituitary adenomas (Cushing's disease). Paper presented at: 85th Annual Meeting of The Endocrine Society; June 19–22, 2003; Philadelphia, PA.
727. **Ambrosi B, Dall'Asta C, Cannavo S, et al.** Effects of chronic administration of PPAR-γ ligand rosiglitazone in Cushing's disease. *Eur J Endocrinol*. 2004;151(2):173–178.
728. **Pecori Giraldi F, Scaroni C, Arvat E, et al.** Effect of protracted treatment with rosiglitazone, a PPARγ agonist, in patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 2006;64(2):219–224.
729. **Morcos M, Fohr B, Tafel J, et al.** Long-term treatment of central Cushing's syndrome with rosiglitazone. *Exp Clin Endocrinol Diabetes*. 2007;115(5):292–297.
730. **Suri D, Weiss RE.** Effect of pioglitazone on adrenocorticotropic hormone and cortisol secretion in Cushing's disease. *J Clin Endocrinol Metab*. 2005;90(3):1340–1346.
731. **Barbaro D, Lapi P, Orsini P, Pasquini C, Ciaccio S.** Pioglitazone treatment in Cushing's disease. *J Endocrinol Invest*. 2005;28:388–389.
732. **Páez-Pereda M, KovalovskyD, Hopfner U, et al.** Retinoic acid prevents experimental Cushing syndrome. *J Clin Invest*. 2001;108:1123–1131.
733. **Castillo V, Giacomini D, Páez-Pereda M, et al.** Retinoic acid as a novel medical therapy for Cushing's disease in dogs. *Endocrinology*. 2006;147:4438–4444.
734. **Philips A, Lesage S, Gingras R, et al.** Novel dimeric Nur77 signaling mechanism in endocrine and lymphoid cells. *Mol Cell Biol*. 1997;17:5946–5951.
735. **Tran P, Zhang XK, Salbert G, Hermann T, Lehmann JM, Pfahl M.** COUP orphan receptors are negative regulators of retinoic acid response pathways. *Mol Cell Biol*. 1992; 12(10):4666–4676.
736. **Boutillier AL, Monnier D, Lorang D, Lundblad JR, Roberts JL, Loeffler JP.** Corticotropin-releasing hormone stimulates proopiomelanocortin transcription by cFos-dependent and -independent pathways: characterization of an AP1 site in exon 1. *Mol Endocrinol*. 1995;9(6):745–755.
737. **Kliewer SA, Umesono K, Heyman RA, Mangelsdorf DJ, Dyck JA, Evans RM.** Retinoid X receptor-COUP-TF interactions modulate retinoic acid signaling. *Proc Natl Acad Sci USA*. 1992;89(4):1448–1452.
738. **Cooney AJ, Leng X, Tsai SY, O'Malley BW, Tsai MJ.** Multiple mechanisms of chicken ovalbumin upstream promoter transcription factor-dependent repression of transactivation by the vitamin D, thyroid hormone, and retinoic acid receptors. *J Biol Chem*. 1993;268(6):4152–4160.
739. **Schwartz E, Mezick JA, Gendimenico GJ, Kligman LH.** In vivo prevention of corticosteroid-induced skin atrophy by tretinoin in the hairless mouse is accompanied by modulation of collagen, glycosaminoglycans, and fibronectin. *J Invest Dermatol*. 1994;102(2):241–246.
740. **Pecori Giraldi F, Ambrogio AG, Andrioli M, et al.** Potential role for retinoic acid in patients with Cushing's disease. *J Clin Endocrinol Metab*. 2012;97(10):3577–3583.
741. **Castinetti F, Conte-Devolx B, Brue T.** Medical treatment of Cushing's syndrome: glucocorticoid receptor antagonists and mifepristone. *Neuroendocrinology*. 2010; 92(suppl 1):125–130.
742. **Castinetti F, Brue T, Conte-Devolx B.** The use of the glucocorticoid receptor antagonist mifepristone in Cushing's syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2012; 19(4):295–299.
743. **Johanssen S, Allolio B.** Mifepristone (RU 486) in Cushing's syndrome. *Eur J Endocrinol*. 2007;157(5):561–569.
744. **Carmichael JD, Fleseriu M.** Mifepristone: is there a place in the treatment of Cushing's disease? *Endocrine*. 2013; 44(1):20–32.
745. **Fleseriu M, Molitch ME, Gross C, Schteingart DE, Vaughan TB 3rd, Biller BM.** A new therapeutic approach in the medical treatment of Cushing's syndrome: glucocorticoid receptor blockade with mifepristone. *Endocr Pract*. 2013;19(2):313–326.
746. **Morgan FH, Laufgraben MJ.** Mifepristone for management of Cushing's syndrome. *Pharmacotherapy*. 2013; 33(3):319–329.
747. **Jung-Testas I, Baulieu EE.** Inhibition of glucocorticosteroid action in cultured L-929 mouse fibroblasts by RU 486, a new anti-glucocorticosteroid of high affinity for the glucocorticosteroid receptor. *Exp Cell Res*. 1983;147(1): 177–182.
748. **Bertagna X, Bertagna C, Luton JP, Husson JM, Girard F.** The new steroid analog RU 486 inhibits glucocorticoid action in man. *J Clin Endocrinol Metab*. 1984;59(1):25–28.
749. **Bourgeois S, Pfahl M, Baulieu EE.** DNA binding properties of glucocorticosteroid receptors bound to the steroid antagonist RU-486. *EMBO J*. 1984;3(4):751–755.
750. **Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T, Lähteenmäki P.** Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. *J Steroid Biochem*. 1987;26(2):279–284.
751. **Cadepond F, Ulmann A, Baulieu EE.** RU486 (mifepristone): mechanisms of action and clinical uses. *Annu Rev Med*. 1997;48:129–156.
752. **Sitruk-Ware R, Spitz IM.** Pharmacological properties of mifepristone: toxicology and safety in animal and human studies. *Contraception*. 2003;68(6):409–420.
753. **van Uum SH, Lenders JW, Hermus AR.** Cortisol, 11β-hydroxysteroid dehydrogenases, and hypertension. *Semin Vasc Med*. 2004;4(2):121–128.

754. **Nieman LK, Chrousos GP, Kellner C, et al.** Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab*. 1985;61(3):536–540.
755. **Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D.** Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *J Clin Endocrinol Metab*. 2001;86(8):3568–3573.
756. **Basina M, Liu H, Hoffman AR, Feldman D.** Successful long-term treatment of Cushing disease with mifepristone (RU486). *Endocr Pract*. 2012;18(5):e114–e120.
757. **Castinetti F, Fassnacht M, Johanssen S, et al.** Merits and pitfalls of mifepristone in Cushing's syndrome. *Eur J Endocrinol*. 2009;160(6):1003–1010.
758. **Fleseriu M, Biller BM, Findling JW, et al.** Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2012;97(6):2039–2049.
759. **Katznelson L, Loriaux DL, Feldman D, Braunstein GD, Schteingart DE, Gross C.** Global clinical response in Cushing's syndrome patients treated with mifepristone. *Clin Endocrinol (Oxf)*. 2014;80(4):562–569.
760. **Wallia A, Colleran K, Purnell JQ, Gross C, Molitch ME.** Improvement in insulin sensitivity during mifepristone treatment of Cushing syndrome: early and late effects. *Diabetes Care*. 2013;36(9):e147–e148.
761. **Mutter GL, Bergeron C, Deligdisch L, et al.** The spectrum of endometrial pathology induced by progesterone receptor modulators. *Mod Pathol*. 2008;21(5):591–598.
762. **Fleseriu M, Findling JW, Koch CA, Schlaffer SM, Buchfelder M, Gross C.** Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing's disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone. *J Clin Endocrinol Metab*. 2014;99(10):3718–3727.
763. **Beaufrère B, de Parscau L, Chatelain P, Morel Y, Aguercif M, François R.** RU 486 administration in a child with Cushing's syndrome. *Lancet*. 1987;2(8552):217.
764. **Raux-Demay MC, Pierret T, Bouvier d'Yvoire M, Bertagna X, Girard F.** Transient inhibition of RU 486 antiglucocorticoid action by dexamethasone. *J Clin Endocrinol Metab*. 1990;70(1):230–233.
765. **Child DF, Burke CW, Burley DM, Rees LH, Fraser TR.** Drug controlled of Cushing's syndrome. Combined aminoglutethimide and metyrapone therapy. *Acta Endocrinol (Copenh)*. 1976;82(2):330–341.
766. **Kamenický P, Droumaguet C, Salenave S, et al.** Mitotane, metyrapone, and ketoconazole combination therapy as an alternative to rescue adrenalectomy for severe ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 2011;96(9):2796–2804.
767. **Pivonello R, De Leo M, De Martino MC, et al.** Effectiveness and safety of combined therapy with low dose ketoconazole and cabergoline in patients with Cushing's disease partially responsive to monotherapy with cabergoline. Paper presented at: 11th European Congress of Endocrinology; April 25–29, 2009; Istanbul, Turkey. Abstract P193.
768. **Feelders RA, de Bruin C, Pereira AM, et al.** Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *N Engl J Med*. 2010;362(19):1846–1848.
769. **Menard J, Watson C, Rebello S, Zhang YM, Dole WP.** Hormonal and electrolyte responses to the aldosterone synthase inhibitor LCI699 in sodium depleted healthy subjects. *J Am Coll Cardiol*. 2010;55:A61.E583.
770. **Amar L, Azizi M, Menard J, Peyrard S, Watson C, Plouin PF.** Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. *Hypertension*. 2010;56(5):831–838.
771. **Calhoun DA, White WB, Krum H, et al.** Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. *Circulation*. 2011;124(18):1945–1955.
772. **Bertagna X, Pivonello R, Fleseriu M, et al.** LCI699, a potent 11$\beta$-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. *J Clin Endocrinol Metab*. 2014;99(4):1375–1383.
773. **Pivonello R, Fleseriu M, Guignat L, et al.** Patients with Cushing's disease achieve normal urinary cortisol with LCI699, a potent 11$\beta$-hydroxylase inhibitor: preliminary results from a multicenter, proof-of-concept study. Oral presentation at: The Endocrine Society's 94th Annual Meeting and Expo; June 23–26, 2012; Houston, TX. Abstract OR49-1.
774. **Pivonello R, Fleseriu M, Young J, et al.** LCI699, a potent 11$\beta$-hydroxylase Inhibitor, normalizes urinary free cortisol level in patients with Cushing's disease: 22-week, multicenter, open-label study. Oral presentation at: The Endocrine Society's 96th Annual Meeting and Expo; June 21–24, 2014; Chicago, IL. Abstract OR17–4.
775. **Pivonello R, Fleseriu M, Young J, et al.** Efficacy and safety of LCI699, a potent 11$\beta$-hydroxylase inhibitor, in patients with Cushing's disease: a 22 week, multicenter, open-label study. Oral presentation at: the 14th International Pituitary Congress; March 2–4, 2015; San Diego, CA.
776. **Theodoropoulou M, Arzberger T, Gruebler Y, et al.** Expression of epidermal growth factor receptor in neoplastic pituitary cells: evidence for a role in corticotropinoma cells. *J Endocrinol*. 2004;183(2):385–394.
777. **Fukuoka H, Cooper O, Ben-Shlomo A, et al.** EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas. *J Clin Invest*. 2011;121(12):4712–4721.
778. **Liu NA, Jiang H, Ben-Shlomo A, et al.** Targeting zebrafish and murine pituitary corticotroph tumors with a cyclin-dependent kinase (CDK) inhibitor. *Proc Natl Acad Sci USA*. 2011;108(20):8414–8419.
779. **de Bruin C, Feelders RA, Lamberts SW, Hofland LJ.** Somatostatin and dopamine receptors as targets for medical treatment of Cushing's Syndrome. *Rev Endocr Metab Disord*. 2009;10(2):91–102.
780. **Culler MD.** Somatostatin-dopamine chimeras: a novel approach to treatment of neuroendocrine tumors. *Horm Metab Res*. 2011;43(12):854–857.
781. **Colao A, Ochoa AS, Auriemma RS, Faggiano A, Pivonello R, Lombardi G.** Pituitary carcinomas. *Front Horm Res*. 2010;38:94–108.