Overview of the treatment of Cushing syndrome

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INTRODUCTION

The hypercortisolemia in Cushing syndrome is usually due to a corticotropin (ACTH)-producing pituitary tumor (Cushing disease), ectopic ACTH secretion by a nonpituitary tumor, or cortisol secretion by an adrenal adenoma or carcinoma. There are also very rare tumors that secrete corticotropin-releasing hormone (CRH) ectopically, and occasional cases are caused by cortisol secretion by ACTH-independent macronodular or micronodular hyperplasia of the adrenal cortex.

Treatment should be directed, whenever possible, at the primary cause of the syndrome. This topic provides an overview of the various therapeutic options available in the treatment of Cushing syndrome. A detailed review of therapy for Cushing disease and some of the primary adrenal causes of hypercortisolism is presented separately.

- (See "Primary therapy of Cushing disease: Transsphenoidal surgery and pituitary irradiation".)
- (See "Medical therapy of hypercortisolism (Cushing's syndrome)".)
- (See "Persistent or recurrent Cushing disease: Surgical adrenalectomy".)
- (See "Cushing's syndrome due to primary bilateral macronodular adrenal hyperplasia".)
- (See "Cushing syndrome due to primary pigmented nodular adrenocortical disease".)

- (See "Diagnosis and management of Cushing syndrome during pregnancy".)

GENERAL PRINCIPLES

Goals — Ideal therapy of Cushing syndrome would achieve the following goals [1,2]:

- Reverse the clinical manifestations by reducing cortisol secretion to normal
- Eradicate any tumor threatening the health of the patient
- Avoid permanent dependence upon medications
- Avoid permanent hormone deficiency

In individual patients, however, one or more of the last three goals may have to be sacrificed to achieve the essential first goal. The therapeutic protocols described below proceed from permanently curing the disorder by resecting or ablating its cause to merely controlling the hypercortisolism in patients in whom a cure cannot be achieved. Each stage in the treatment should provide maximum probability of cure with the least chance of permanent endocrine deficiency or other undesirable side effects.

Specific treatment may be delayed during diagnostic testing or while drug adjustments are made to achieve eucortisolism. During this time, treatment of comorbidities such as hypertension, osteoporosis, and diabetes should be instituted [3]. The use of medications to prevent thrombosis or bone loss should be considered. Treatment should be continued after remission and discontinued only if these comorbidities reverse. Our approach is largely consistent with the Endocrine Society Clinical Practice Guideline [4].

Exogenous Cushing syndrome — The treatment of Cushing syndrome due to exogenous therapy is to stop the glucocorticoid. Most patients who have taken enough glucocorticoid for a long enough time to cause Cushing syndrome will have a period of hypothalamic-pituitary adrenal insufficiency when therapy is discontinued. Thus, gradual withdrawal is necessary. (See "Glucocorticoid withdrawal", section on 'Hypothalamic-pituitary-adrenal axis suppression'.)

CUSHING DISEASE

The approach to the treatment of Cushing disease as outlined here is consistent with a 2015 consensus statement on the treatment of corticotropin (ACTH)-dependent Cushing syndrome [4].

Transsphenoidal surgery — The treatment of choice for Cushing disease (ACTH-producing pituitary tumor) is transsphenoidal microadenomectomy when a clearly circumscribed microadenoma can be identified at surgery (algorithm 1). In the remaining patients, subtotal (85 to 90 percent) resection of the anterior pituitary may be indicated if future fertility is not desired.

It is difficult to predict residual pituitary function after partial hypophysectomy; some patients have normal pituitary function even after subtotal hypophysectomy. However, the more extensive the resection, the greater the risk of loss of pituitary function. (See "Primary therapy of Cushing disease: Transsphenoidal surgery and pituitary irradiation".)

A practical approach to the uncertainty of surgical localization is to make a contract among the endocrinologist, the patient, and the neurosurgeon before surgery. Among expert pituitary neurosurgeons, the cure rate approximates 70 to 80 percent, but late recurrences reduce the permanent cure rate to approximately 60 to 70 percent. (See "Transsphenoidal surgery for pituitary adenomas and other sellar masses".)

Medical therapy — Although the hypercortisolism of Cushing disease is optimally treated surgically, medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Adrenal enzyme inhibitors are the most commonly used drugs, but adrenolytic agents, drugs that target the pituitary, and glucocorticoid-receptor antagonists also have been used. Medical therapy targeting the corticotroph tumor such as cabergoline or pasireotide can result in normalization of 24-hour urinary free cortisol in 20 to 40 percent of them, especially if they have only mild hypercortisolism. The glucocorticoid (as well as progestin) antagonist mifepristone is approved in the United States for treatment of glucose intolerance in patients with Cushing syndrome who are not surgical candidates [5]. This topic is reviewed in detail separately. (See "Medical therapy of hypercortisolism (Cushing's syndrome)".)

Aggressive corticotroph tumors — While up to one-third of pituitary tumors, mostly macroadenomas, are locally invasive, a few are more aggressive and 0.1 to 0.2 percent are carcinomas that metastasize in the central nervous system or systemically. These aggressive tumors are resistant to treatment and result in death, usually within several months, or occasionally after several years [6]. Chemotherapy may offer temporary remission in a minority of patients. In a review of 20 patients with aggressive tumors refractory to conventional treatment, the alkylating agent temozolomide resulted in a partial response in approximately two-thirds of patients [7]. The use of immunohistochemical demonstration of low expression of the DNA-repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) appeared to predict responsiveness to the agent. While preliminary, these reports offer a new approach to patients with aggressive or metastatic tumors.

Pituitary irradiation — For patients in whom fertility is an important concern and in whom a tumor is not found or who are not cured by transsphenoidal resection of a tumor, pituitary irradiation is one of the next treatment options; it may also be considered as primary therapy for children under age 18 years. Conventional megavoltage linear accelerator after transsphenoidal surgery will correct the hypercortisolism in up to 85 percent of adults when used after debulking surgery and in 85 percent of children when used as monotherapy [4,8,9].

Maximum benefit is usually achieved within 6 to 12 months, but may require two to three years, and during this time period hypercortisolism should be controlled with one or several adrenal enzyme inhibitors. Pituitary irradiation may also decrease the occurrence of Nelson syndrome in patients not cured by irradiation for whom adrenalectomy becomes necessary, but this has not been tested in a prospective randomized trial.

Stereotactic radiosurgery (SRS) is the delivery of a single high dose of radiation therapy using a high-precision localization system to treat a small target. SRS is more convenient (a single treatment) than fractionated radiation therapy (many treatments) and provides less irradiation to neuronal tissues It may also provide more rapid biochemical control of cortisol excess than conventional radiation, but this is not well established.

However, adenomas that are too close, 3 to 5 mm, to radiation-sensitive tissues, such as the optic chiasm or other parts of the optic pathway, are more safely treated with fractionated radiation therapy since a large, single dose of radiation to these tissues can cause blindness. In addition, large adenomas should be treated with conventional radiotherapy.

In a retrospective study of 278 patients who underwent SRS for Cushing disease, with a mean follow-up of 5.6 years, cumulative control of hypercortisolism at 10 years was 80 percent (mean time to normalization 14.5 months) [10]. However, 18 percent of patients experienced a recurrence after cortisol normalized. This study suggests that a similar percent of patients undergoing SRS or conventional RT eventually have normal cortisols. However, SRS is more convenient, and time to cure may be faster.

Adrenalectomy — Bilateral total adrenalectomy with lifelong daily glucocorticoid and mineralocorticoid replacement therapy is the final definitive cure, and may be preferred by some patients instead of radiation therapy. In one series, laparoscopic adrenalectomy was successful in 42 patients with Cushing disease who had not been cured by previous pituitary surgery, radiotherapy and/or medical therapy [11]. (See "Persistent or recurrent Cushing disease: Surgical adrenalectomy".)

ECTOPIC ACTH AND CRH SYNDROMES

Ectopic ACTH — The optimal therapy of the ectopic corticotropin (ACTH) syndrome (secretion of ACTH by a nonpituitary tumor) is **surgical excision** of the tumor, thereby removing the source of ACTH and curing the metabolic disorder. In several reports, remission occurred after removal of 28 of 34, 10 of 12, and 10 of 26 pulmonary carcinoid tumors and eight of nine localized neuroendocrine or other carcinoid tumors [12-14]. Metastatic tumors cannot be treated by surgical excision.

In patients with metastases limited to the liver, after resection of the primary tumor, resection or cryoablation of the metastases or even liver transplantation may result in cure [15]. In a study of 103 patients with neuroendocrine carcinomas metastatic to the liver, 60 percent of patients were alive two years after liver transplantation and 47 percent, half of whom were disease-free, were alive after five years [16]. Patients who were less than 50 years old, had primary lung or bowel tumors, and had pretransplant somatostatin treatment had the best prognosis. Depending on the tumor type, chemotherapy and/or radiotherapy may be helpful. (See "Diagnosis of carcinoid syndrome and tumor localization".)

Nonresectable tumors — For those patients with nonresectable tumors, the hypercortisolism can be controlled with adrenal enzyme inhibitors, such as ketoconazole, metyrapone, and etomidate. (See "Medical therapy of hypercortisolism (Cushing's syndrome)", section on 'Initial therapy'.)

- Therapy with an adrenal enzyme inhibitor can be continued for a prolonged period in patients in whom a tumor cannot be identified. Such patients should be reexamined periodically with 111-In-pentetreotide, computed tomography (CT), or magnetic resonance imaging (MRI) for several years, if necessary, until the tumor can be located and treated [13,14].

- Some patients have indolent tumors and a long life expectancy but cannot be cured surgically. These patients can be treated with mitotane to achieve a medical adrenalectomy. (See "Medical therapy of hypercortisolism (Cushing's syndrome)".)

Bilateral surgical adrenalectomy or long-term treatment with steroidogenesis inhibitors may be used as an alternative to mitotane (figure 1) [12-14].

Patients whose hypercortisolism is controlled by any means may occasionally develop rebound thymic hyperplasia. Recognition of this condition is important because it may be confused radiologically with tumor recurrence or metastasis in the anterior mediastinum [17].

Other potential treatment options that have been tried include mifepristone and octreotide:

- The glucocorticoid (as well as progestin) antagonist mifepristone has been used to control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing syndrome and type 2 diabetes or glucose intolerance who have failed surgery or are not candidates for surgery. (See "Medical therapy of hypercortisolism (Cushing's syndrome)", section on 'Glucocorticoid-receptor antagonists'.)

- Octreotide, a long-acting analogue of somatostatin, rapidly reduces ectopic ACTH secretion by some nonpituitary tumors, but does not usually reduce tumor size [18,19]. Uptake of 111-In-pentetreotide by the tumor also predicts a positive response to the drug [20]. The agent may be given either as a twice-daily or monthly injection and is expensive [21]. It therefore has limited value in treating patients with the ectopic ACTH syndrome.

Ectopic CRH secretion — Ectopic corticotropin-releasing hormone (CRH) secretion is a very rare disorder, having been proved in only a small number of cases, mostly with fairly well-differentiated pulmonary carcinoid tumors [22]. The treatment and prognosis of this condition is the same as for ectopic ACTH secretion. The Cushing syndrome can easily be controlled, but the ultimate prognosis depends upon the malignancy of the tumor and whether it can be completely resected.

PRIMARY ADRENAL DISEASES

Several different adrenal diseases can cause Cushing syndrome; the approach to such patients is generally directed at removal of the adrenal gland(s). Adrenal tumors should be removed with unilateral adrenalectomy while bilateral adrenalectomy is required for bilateral micronodular and most patients with macronodular adrenal hyperplasia. The management of adrenal carcinoma is reviewed separately. (See "Treatment of adrenocortical carcinoma".)

Adrenal adenomas — Some functional adenomas hypersecrete cortisol and cause Cushing syndrome. Approximately 10 percent of cases of overt Cushing syndrome are due to adrenal adenomas.

Unilateral adrenalectomy — Adenomas are always cured with unilateral adrenalectomy.

- Because of the reduction in postoperative morbidity, hospital stay, and expense compared with open laparotomy, laparoscopic adrenalectomy by an experienced endocrine surgeon is the preferred approach for adrenal adenomas. The laparoscopic approach, which can be done via either the anterior or posterior approaches, has become standard (at least for

patients with adenomas <6 cm in diameter). Hospital stays appear to be shorter with this approach (usually one to five days) and complications fewer, as compared with open surgery. Surgical adrenalectomy and details on the anterior and posterior laparoscopic approach are reviewed separately. (See "Adrenalectomy techniques", section on 'Selection of operative approach'.)

- Cushing syndrome creates a hypercoagulable state due to an activated coagulation cascade and impaired fibrinolysis and patients have more than a 10-fold greater risk of developing venous thromboembolic disease, particularly if undergoing surgery [23,24]. (See "Epidemiology and clinical manifestations of Cushing syndrome", section on 'Thromboembolic events'.)

  We therefore suggest thromboprophylaxis be used in patients with Cushing syndrome undergoing surgery [4]. The approach to prevention of venous thromboembolism in the surgical patient is reviewed separately. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

- There may be cardiovascular and metabolic benefits to surgery for patients with subclinical Cushing syndrome, who often present with adrenal incidentalomas [25]. (See "Evaluation and management of the adrenal incidentaloma", section on 'Subclinical Cushing syndrome'.)

Outcome — Virtually all patients with adrenocortical adenomas are cured by surgery [26-28]. Postoperative glucocorticoid therapy is needed because excess cortisol secretion has suppressed corticotropin-releasing hormone (CRH) and corticotropin (ACTH).

In patients with Cushing syndrome due to adrenal adenomas, the recovery of normal ACTH secretion from pituitary corticotropes after prolonged inhibition may be delayed. There will be secondary atrophy of nontumorous adrenal zona fasciculata and reticularis cells in the contralateral adrenal gland. As a result, the patient often requires glucocorticoid replacement therapy for several months to a year and sometimes even longer after resection of the tumor. The principles of glucocorticoid replacement are similar to those for patients with Cushing disease who are cured by resection of a pituitary adenoma.

Generally, patients are given higher than normal glucocorticoid replacement intraoperatively and postoperatively to avoid symptoms and signs of acute steroid withdrawal. A dose of 150 to 200 mg of hydrocortisone (or dexamethasone equivalent if bilateral adrenalectomy is not done) may be administered by constant infusion or in divided doses intravenously over the first 24 hours after induction of anesthesia. A rapid taper follows over a few days until hydrocortisone

can be given by mouth. A taper may be achieved by decreasing each successive daily dose to 50 percent of the previous day's dose.

The patient with subclinical Cushing syndrome with partial suppression of hypothalamic-pituitary-adrenal axis should also be treated with perioperative glucocorticoid coverage because of the risk of adrenal insufficiency; recovery will usually be faster than for patients with severe Cushing syndrome. (See "Evaluation and management of the adrenal incidentaloma", section on 'Subclinical Cushing syndrome'.)

ACTH-independent bilateral adrenal hyperplasia — There are two forms of ACTH-independent bilateral adrenal hyperplasia: primary pigmented nodular adrenocortical disease (PPNAD, also called micronodular adrenal hyperplasia); and bilateral macronodular adrenal hyperplasia (BMAH). (See "Cushing syndrome due to primary pigmented nodular adrenocortical disease" and "Cushing's syndrome due to primary bilateral macronodular adrenal hyperplasia".)

- Surgical bilateral adrenalectomy is uniformly effective in PPNAD; subtotal or unilateral adrenalectomy should not be performed since recurrence can occur. Bilateral adrenalectomy is also indicated in most patients with macronodular adrenal hyperplasia.

- Bilateral adrenalectomy is now usually performed by laparoscopy and causes permanent adrenal insufficiency, but not Nelson syndrome. In selected cases with macronodular adrenal hyperplasia and aberrant hormone receptors, pharmacologic blockade on the aberrant receptor can result in long-term normalization of cortisol secretion.

- Medical management of patients after bilateral adrenalectomy is reviewed separately. (See "Persistent or recurrent Cushing disease: Surgical adrenalectomy", section on 'Postoperative management'.)

- Although medical treatment does not cure ACTH-independent micronodular or macronodular adrenal hyperplasia, the adrenal enzyme inhibitors (metyrapone or ketoconazole) can be given to reduce cortisol secretion in an attempt to improve the patient's physical condition before surgery. As with adrenocortical tumors, ACTH secretion will not increase and override the pharmacologic blockade. (See "Medical therapy of hypercortisolism (Cushing's syndrome)".)

COURSE AFTER EFFECTIVE THERAPY

Resolution of symptoms and complications — Physical symptoms and signs of Cushing syndrome disappear gradually over a period of 2 to 12 months. Overweight, hypertension, and

glucose intolerance improve but may not disappear.

The osteoporosis of Cushing syndrome begins to improve approximately six months after the hypercortisolemia is cured, improves rapidly during the ensuing two years, and more gradually thereafter, but may not normalize [29-31]. For patients with marked bone loss, oral bisphosphonate therapy is recommended; calcium supplementation, vitamin D, and gonadal steroid replacement may also be useful [32]. (See "Prevention and treatment of glucocorticoid-induced osteoporosis".)

In adults, psychiatric symptoms improve, but need for psychopathology may persist, and one study found an increase in the frequency of suicidal ideation and panic [33]. Cognitive deficits persist despite improvement, but not normalization, of apparent brain volume [34,35]. One study of 11 children found a decline in intelligence quotient (IQ) and cognitive performance at one year after curative surgery, in the absence of psychopathology, despite reversal of cerebral atrophy [36].

In children, bone density and growth rate both increase after treatment, although neither returns to normal [37].

Quality of life — Cushing syndrome also impairs health-related quality of life (HRQL), which partially, but not completely resolves after transsphenoidal surgery. This was illustrated in a study of 23 patients with Cushing disease who completed a SF (short-form) 36 survey (which evaluates HRQL) before and after transsphenoidal surgery, and in a group of 343 Cushing patients who were in remission for up to 25 years after surgery (mostly pituitary, but some had adrenal or ectopic Cushing) [38]. Active Cushing disease was associated with low physical and mental summary scores on the HRQL survey; after transsphenoidal surgery, all HRQL parameters improved, but did not normalize in these patients.

Similar results were observed in a meta-analysis of 47 studies in 2643 patients treated for Cushing syndrome [39]. The majority of patients had Cushing disease, but patients with ectopic ACTH secretion and adrenal Cushing were also included. When compared with a healthy control population (n = 2335), all quality-of-life domains improved, but did not normalize. One domain of cognitive functioning normalized after treatment (intelligence), while attention and executive functioning did not. Similar results were seen in a subgroup analysis of patients with Cushing disease. Additional strategies are needed to improve outcomes for patients with persistent impairment of quality of life and/or cognitive functioning after treatment.

Clinicians typically underestimate the time it takes for patients to recover after surgery [40]. In addition, clinicians perceive that work and exercise are the most important coping mechanisms

during recovery. In contrast, most patients consider spending time with family and rest to be the most important activities for recovery.

PROGNOSIS

Untreated Cushing syndrome is often fatal, with most deaths being due to cardiovascular, thromboembolic, or hypertensive complications or bacterial or fungal infections. Years ago there was a 50 percent mortality five years after the development of symptoms [41], but the prognosis is much better now. No patient with Cushing syndrome of any cause should die from persistent hypercortisolism, since cortisol production can always be controlled by adrenal enzyme inhibitors, mitotane, or adrenalectomy.

Cushing disease is virtually always curable, although rarely patients may die of perioperative or other complications [42].

Patients with ectopic corticotropin (ACTH) secretion or adrenocortical carcinoma may have a poor prognosis associated with the underlying tumor. The prognosis is dictated by the nature of the tumor and the severity of the hypercortisolism. Most patients with overt metastases at the time of presentation die of the cancer within one year, although patients with indolent tumors may survive for many years. Patients with small-cell lung cancer, medullary thyroid cancer, and gastrinoma have a particularly poor prognosis [13,14]. Regardless of the prognosis, no patient should suffer from the effects of persistent hypercortisolism, because it can readily be controlled.

Patients with severe Cushing syndrome may die from opportunistic infections before completion of diagnostic studies [43-45]. Increased coagulability is also associated with deep vein thrombosis, pulmonary edema, and myocardial infarction [23].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis and treatment of Cushing syndrome".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Cushing syndrome (The Basics)")
- Beyond the Basics topics (see "Patient education: Cushing syndrome (Beyond the Basics)" and "Patient education: Cushing syndrome treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Goal of treatment** – The goal of treatment of all patients with Cushing syndrome is to achieve normalization of hypothalamic-pituitary-adrenal function and subsequent reversal of Cushingoid signs/symptoms and comorbidities.
- **Surgery** – Optimal treatment involves localization and complete surgical removal of a corticotropin (ACTH)-secreting pituitary or ectopic tumor or cortisol-secreting adrenal tumor(s). (See 'General principles' above.)
- **Medical therapy** – In patients with Cushing disease who were not cured by pituitary surgery, medical therapy targeting the corticotroph tumor such as cabergoline or pasireotide can result in normalization of 24-hour urinary free cortisol in 20 to 40 percent of them, especially if they have only mild hypercortisolism. (See 'Medical therapy' above.)

  Metastatic or occult ectopic ACTH-secreting tumors may respond to somatostatin analog treatment, adrenal enzyme inhibitors, or mitotane. (See 'Ectopic ACTH and CRH syndromes' above.)
- **Pituitary irradiation** – Pituitary irradiation is another second-line treatment for persistent or recurrent Cushing disease. Adrenal enzyme inhibitors must be used to control hypercortisolism until RT is effective. Conventional RT will correct the hypercortisolism in

up to 85 percent of adults when used after debulking surgery. (See 'Pituitary irradiation' above.)

- **Bilateral adrenalectomy** – Bilateral adrenalectomy is a definitive treatment for ACTH-secreting pituitary or ectopic tumors. (See 'Adrenalectomy' above.)

- **Resolution of signs and symptoms** – The physical symptoms and signs of Cushing syndrome resolve gradually over a period of 2 to 12 months after effective cure of Cushing syndrome. Hypertension, osteoporosis and glucose intolerance improve but may not disappear. (See 'Course after effective therapy' above.)

  Patients may have impaired quality of life for many years despite remission of hypercortisolism. However, the long-term prognosis of cured patients who had benign disease is excellent. The prognosis of patients with malignancy is variable and relates to the ability to control hypercortisolism and treat the cancer. (See 'Prognosis' above and 'Ectopic ACTH and CRH syndromes' above.)

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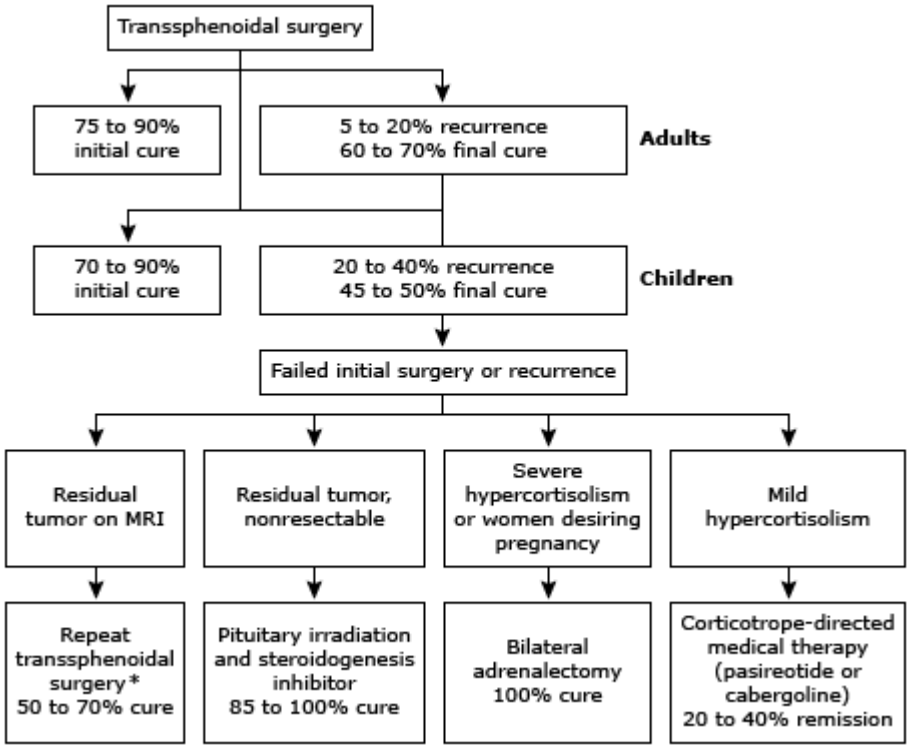
GRAPHICS

Treatment of Cushing disease

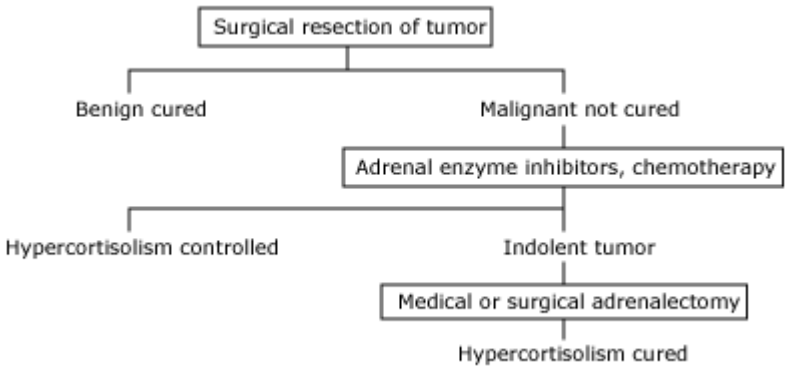


MRI: magnetic resonance imaging.

* The choice of treatment after failed transsphenoidal surgery should be individualized for each patient based upon the presence of dural or cavernous sinus invasion, the presence of a surgical target on MRI, the location of tumor in relationship to optic nerves, the need for prompt resolution of hypercortisolism, contraindication to specific medical therapy, and the patient's values and preferences.

Graphic 76949 Version 4.0

Treatment of ectopic ACTH syndrome



Graphic 68665 Version 1.0