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# Management of hormone-secreting pituitary adenomas

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**Abstract**

Pituitary adenomas are one of the most common primary central nervous system tumors and have an estimated prevalence of 17%. Approximately half of pituitary adenomas secrete distinct pituitary hormones (most often prolactin, growth hormone, or adrenocorticotropic hormone). While these tumors are histologically benign, they have potent endocrine effects that lead to significant morbidity and shortened lifespan. Because of their pathophysiologic endocrine secretion and anatomic location near critical neural/vascular structures, hormone-secreting pituitary adenomas require defined management paradigms that can include relief of mass effect and biochemical remission. Management of hormone-secreting pituitary adenomas involves a multidisciplinary approach that can incorporate surgical, medical, and/or radiation therapies. Early and effective treatment of hormone-secreting pituitary adenomas can reduce morbidity and mortality. Consequently, understanding clinical features as well as therapeutic options in the context of the specific biological features of each type of hormone-secreting pituitary adenoma is critical for optimal management.

**Key words**

acromegaly | Cushing's disease | management | pituitary adenoma | prolactinoma

Pituitary adenomas are one of the most common brain tumors. These neoplasms account for 14% of primary intracranial and central nervous system tumors, and their overall prevalence in the general population (radiographic and autopsy) is estimated at 17%.[1,2] While a portion of pituitary adenomas do not secrete hormones (*nonfunctional*; 36%–54%), approximately half of these tumors are hormone-secreting (*functional*; 46%–64%).[3–5] Secreted hormones frequently include prolactin (32%–51% of pituitary adenomas), growth hormone (GH) (9%–11%), or adrenocorticotropic hormone (ACTH) (3%–6%). Thyroid-stimulating hormone (TSH)-secreting and gonadotropin-secreting adenomas are rare (<1% of pituitary adenomas). Of note, many pituitary adenomas classified as nonfunctional may stain for gonadotropins without resulting in elevated serum hormone levels. While hormone-secreting pituitary adenomas are typically histologically benign, they underlie significant morbidity (via direct mass effect on neurovascular structures and/or hypersecretion of hormones) and result in shortened lifespan.[6,7] Early diagnosis and effective management are critical for reducing morbidity and minimizing mortality. Treatment strategies are tailored to the specific adenoma subtype and can include surgical resection, medical therapy, and/or radiation therapy. Here we describe the treatment paradigms based on each hormone-secreting pituitary adenoma subtype.

## General Treatment Approaches

### Surgical Resection

Successful surgical resection of hormone-secreting pituitary adenomas in carefully selected patients (see below) via microsurgical, endoscopic, or combined (microscopic and endoscopic) approaches can result in immediate tumor eradication and biochemical remission while preserving normal pituitary endocrine function (Table 1). Moreover, surgery can provide direct relief of mass effect and improvement in vision in cases with significant compression of the optic chiasm or nerve.

Risks associated with resection of pituitary adenomas include postoperative cerebrospinal fluid leak (after 3.9% of operations), injury to the normal pituitary gland causing hypopituitarism (13%), transient/permanent diabetes insipidus (DI; 18% and 0.4%, respectively), and transient isolated hyponatremia (21%).[8–11] Less frequent potential risks include neurovascular injury (0%–5.6%) and epistaxis (0.8%–3.4%).[9,10]

### Medical Management

Because functional pituitary adenomas cause morbidity primarily through hormone hypersecretion, medical therapies that inhibit pituitary hormone secretion or target organ response can be an effective temporary or indefinite management paradigm. Medical management is noninvasive and does not carry the anatomic and potentially permanent risks of surgery and radiation. Nevertheless, except for prolactinomas, medical therapy is unlikely to eradicate (ie, control/reduce size) the adenoma and result in permanent cure. Effective medical therapy typically provides biochemical control. Risks of medical therapy for hormone-secreting pituitary adenomas are specific to the medication used (see below). Each therapeutic agent has inherent risks, and understanding patient tolerability is critical because the course of therapy may be prolonged or indefinite.

### Radiation Therapy

Pituitary adenoma radiation therapy includes conventional fractionated radiotherapy (CFRT) (dose: 45–54 Gy over 5–6 weeks), single-treatment stereotactic radiosurgery (SRS; 20–25 Gy), or multi-session, fractionated stereotactic radiation therapy (FSRT: 50.4–54 Gy). While prospective, randomized studies comparing these modalities do not exist, the efficacy of modern, selectively targeted SRS and FSRT appear similar.[12] CFRT and FSRT are preferred for larger lesions and tumors near cranial nerves (including the optic chiasm) as SRS carries the risk of cranial neuropathy (4%–5%).[13,14] SRS is complete in one session and may require less time to achieve biochemical remission compared with CFRT and FSRT.[12,13,15] Radiation often leads to new hormone deficiencies requiring hormone replacement (22% at 3 years and >60% at 5 years).[12] Regardless of technique, hormone-producing pituitary adenomas require higher treatment doses than their nonfunctional counterparts. Proton irradiation has also been applied to hormone-secreting pituitary adenomas with similar efficacy as other radiation modalities and rates of hypopituitarism.[16]

**Table 1** Benefits and risks of treatment modalities for hormone-secreting pituitary adenomas

| Modality | Surgery | Medicine | Radiation |
|---|---|---|---|
| Benefits | Immediate relief of mass effect<br>High rate of durable cure<br>Single treatment | Noninvasive<br>Biochemical control<br>May relieve mass effect | Noninvasive<br>Possible cure<br>Single treatment[a]<br>May relieve mass effect |
| Risks | Invasive<br>Cerebrospinal fluid leak<br>Hypopituitarism<br>Diabetes insipidus<br>Anesthetic risks<br>Postsurgical risks (cardiac, venous thromboembolism)<br>Epistaxis<br>Cranial nerve injury[b]<br>Vascular injury[b] | Life-long therapy<br>Medication-specific side effects | Long latency period to effect<br>Higher rate of recurrence<br>Hypopituitarism<br>Cranial nerve injury[b] |

[a]stereotactic radiosurgery.
[b]infrequent.

## Prolactinomas

### Clinical Features

Prolactinomas are the most common hormone-secreting pituitary adenomas (69%–80% of endocrine-secreting pituitary adenomas).[3–5] Prolactinomas occur more frequently in females compared with males (female-to-male ratio,:3:1).[5] Depending on sex, prolactinomas most frequently present with amenorrhea, galactorrhea, headache, infertility, mass effect on adjacent neurovascular structures, premature ejaculation, erectile dysfunction, and/or hypogonadism. However, many of these tumors may be asymptomatic and thus are discovered incidentally. These tumors tend to be larger in men at diagnosis, with up to 41% presenting with visual impairment.[17]

### Diagnosis

Hyperprolactinemia may occur commonly with certain physiologic states (lactation, pregnancy), pathophysiological conditions (sellar/pituitary masses), or pharmacological use (neuroleptic medications). Serum prolactin levels >250 μg/L in combination with adenoma identification on high-resolution and postcontrast gradient echo (GRE) magnetic resonance (MR)-imaging typically confirm a diagnosis of prolactinoma.[18] With large macroadenomas and moderately elevated serum prolactin, a false-negative value maybe observed due to the *hook effect* (oversaturation of antibodies used in the prolactin assay).[19] In such cases, serial dilution of the serum sample may help to confirm the diagnosis. In other cases with macroadenomas and mildly elevated serum prolactin (<96μg/ L), compression of the pituitary stalk may result in decreased tonic inhibition of prolactin by dopamine from the hypothalamus (*stalk effect*).[20] In certain cases of elevated serum prolactin in the absence of symptoms, macroprolactinemia, or the presence of large, low biologic activity forms of prolactin, may be suspected.[21] The presence of macroprolactin may be determined by precipitation with polyethylene glycol and requires no further management.

## Treatment

### *Medical Therapy*

Normally, prolactin secretion by lactotrophs in the anterior pituitary is controlled by the negative (inhibitory) feedback of dopamine secretion from the hypothalamus. Similarly, prolactinomas (comprising lactotroph cells) are often sensitive to negative dopamine stimulation.[22] Consequently, dopamine-agonist therapy is first-line treatment for prolactinomas (Fig. 1) including cases of large prolactinomas that cause symptom/sign-inducing (eg, cranial nerve dysfunction) mass effect. Dopaminergic therapy is effective in reducing adenoma size (62% of patients), resolving infertility (53%), and normalizing prolactin levels (68%).[18] The ergot derivatives bromocriptine and cabergoline are most commonly used. However, quinagolide, a non-ergot–derived dopamine agonist, can also be used.

Cabergoline (D2 receptor-specific) is generally favored over bromocriptine as initial therapy for prolactinomas.[18] Systematic analyses have demonstrated greater efficacy and fewer adverse effects with cabergoline.[23] Standard-dose cabergoline therapy is effective in up to 80% of prolactinoma patients, and a majority of the remainder respond to increases in dosage.[24] After 2 years of medical treatment, dopamine-agonist therapy may be tapered to cessation if no adenoma is visible on MR imaging and serum prolactin levels are normalized.[25] However, medical therapy may need to be reinstituted if hyperprolactinemia recurs.[26]

### *Surgical Treatment*

A small proportion of patients with prolactinomas will be refractory to medical therapy (3%–12%) or will be intolerant of medication side effects (3%–11%).[27] Surgical resection should be considered in such patients, and biochemical remission can be achieved in up to 72% of these cases.[28] Successful resection is associated with smaller size and lower preoperative prolactin level.[29] Some patients prefer the immediate risks of surgical resection to prolonged or life-long medical therapy. A first-line surgical approach has been investigated in prolactinoma patients with small adenomas (≤2 cm in diameter).[30] Eighty-eight percent of these patients experienced normalization of serum prolactin after surgery with minimal complications. Analysis has shown that pituitary surgery may be cost-effective compared with lifelong medical therapy in patients with life expectancy >10 years.[31]

### *Radiation Therapy*

Radiation therapy (SRS, FSRT, or CFRT) provides a therapeutic option for patients who cannot undergo surgery

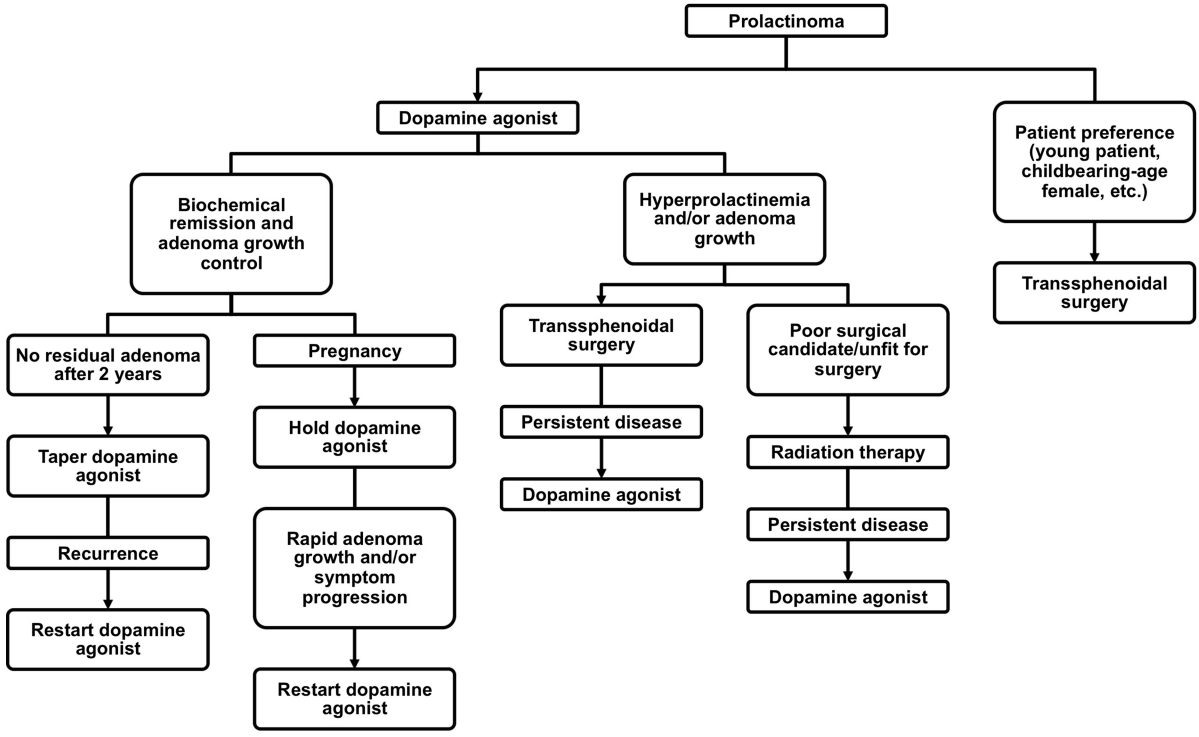


**Fig. 1** Management paradigm for prolactinomas. Persistent disease or recurrent disease is characterized by hyperprolactinemia and/or adenoma growth.

or who have unresectable tumors with elevated prolactin levels. Radiation therapy results in biochemical remission in 17%–26% of patients who did not respond to medical or surgical approaches.[32,33] Biochemical remission after radiation therapy for prolactinomas is associated with smaller adenoma size and adenomas that do not require dopamine-agonist therapy at the time of radiation treatment.[32] Radiation may also permit previous medically refractory adenomas to be better controlled by dopamine agonists (14%).[33]

#### *Pregnancy*

During pregnancy, lactotroph cells are stimulated, and serum prolactin levels rise significantly. Use of dopamine agonists in pregnant prolactinoma patients is associated with increased rates of pregnancy loss and preterm birth.[34] It is recommended that dopamine agonist use be discontinued once pregnancy is confirmed. After discontinuation, <10% of patients will experience adenoma growth during pregnancy.[35] Prolactinoma progression resulting in symptomatic mass effect requires serial visual field exams during pregnancy (and MR imaging as indicated symptomatically) and may necessitate restarting dopamine-agonist treatment. Because macroadenomas or poorly controlled prolactinomas may be more likely to progress during pregnancy, surgical resection can be considered for these patients if they wish to become pregnant.[36]

### Assessment of Biochemical Remission

Biochemical remission after medical, surgical, and/or radiation therapy is determined by normalization of serum prolactin levels. Serial MR imaging is used to assess the effect of various treatments on the adenoma.

## Growth Hormone-secreting Adenomas

### Clinical Features

GH-secreting adenomas account for 13%–20% of endocrine-secreting pituitary adenomas.[3–5] These adenomas occur more frequently in males compared with females (male-to-female ratio: 3:2).[5] GH-secreting pituitary adenomas cause gigantism and acromegaly before and after closure of epiphyseal growth plates, respectively. GH hypersecretion leads to acral enlargement (77%), coarse facial features (54%), profuse sweating (52%), carpal tunnel syndrome (51%), headaches (44%), osteoarthritis (42%), insulin resistance (15%), cardiovascular disease, and early mortality.[6,37]

Symptoms may be insidious, making delay to diagnosis frequent (mean time from first symptom/sign to diagnosis: 7 years).[37] Adenomas are often large at discovery due to this lengthy time to diagnosis. Overall, patients with acromegaly have an estimated standardized mortality ratio of 1.72 compared with the general population. However, this ratio is reduced to 1.32 due to modern management.[6]

### Diagnosis

Elevated serum insulin-like growth factor-1 (IGF-1) typically confirms a diagnosis of acromegaly.[38] In cases of equivocal IGF-1 levels, an oral glucose tolerance test (OGTT) may be performed, and lack of GH suppression to <1 μg /L is diagnostic of acromegaly.[38] High-resolution, postcontrast GRE MR imaging of the pituitary gland is used to assess the size and location of the adenoma. In cases of elevated IGF-1 and no tumor on MR imaging, hormone elevation is likely idiopathic. Rarely, GH-adenomas are small at biochemical diagnosis and not visible on MR imaging.[39] Acromegaly may also be due to ectopic GH-releasing hormone secretion from an extrapituitary source; however, this cause is exceedingly infrequent.[40]

### Treatment

#### *Surgical Treatment*

First-line therapy for GH-secreting adenomas is resection (Fig. 2). Overall, surgical resection results in biochemical remission in up to 70% of patients.[41] Size is inversely associated with surgical success, which is more likely with microadenomas (87%; <1 cm in diameter) than with macroadenomas (66%).[41] Other factors associated with surgical success include lower preoperative serum GH and IGF-1 and a lower degree of parasellar extension.[41]

#### *Medical Therapy*

Medical therapy may be used if resection (or re-resection) fails to provide biochemical remission. It may also be considered a first-line therapy in patients unlikely to be cured by surgery. Pituitary somatotroph cells normally secrete GH and are inhibited by somatostatin. GH-secreting adenomas are composed of somatotroph cells that can be inhibited by somatostatin analogues. Consequently, medical approaches include activating somatostatin receptors via somatostatin analogues (receptor ligands for inhibition), which inhibits GH production/excretion and/or antagonizing end-organ GH receptors. Somatostatin analogues including octreotide (LAR, long-acting release form) and lanreotide can both be administered monthly. Octreotide and lanreotide result in normalization of both serum IGF-1 and GH in 25% and 38% of patients at one year, respectively.[42–44] Both medications may cause gastrointestinal symptoms, which are often self-limited. Somatostatin analogues can lead to development of gallstones and/or sludge in up to 22% of patients without gallstones at baseline.[43] Pasireotide (another injectable somatostatin analogue), may result in normalization of IGF-1 in ~25% of patients who do not respond to either octreotide or lanreotide.[45] Up to 33% of these patients on pasireotide will experience hyperglycemia that can be difficult to control in the context of acromegaly-induced insulin resistance.

For patients refractory to somatostatin analogues, pegvisomant, a GH-receptor antagonist, may be used. Unlike somatostatin analogues, pegvisomant requires daily dosing.Therapy may result in IGF-1 normalization in up to 63% of patients.[46] A small fraction of patients (2.5%) experience hepatotoxicity. Due to lack of negative feedback of IGF-1

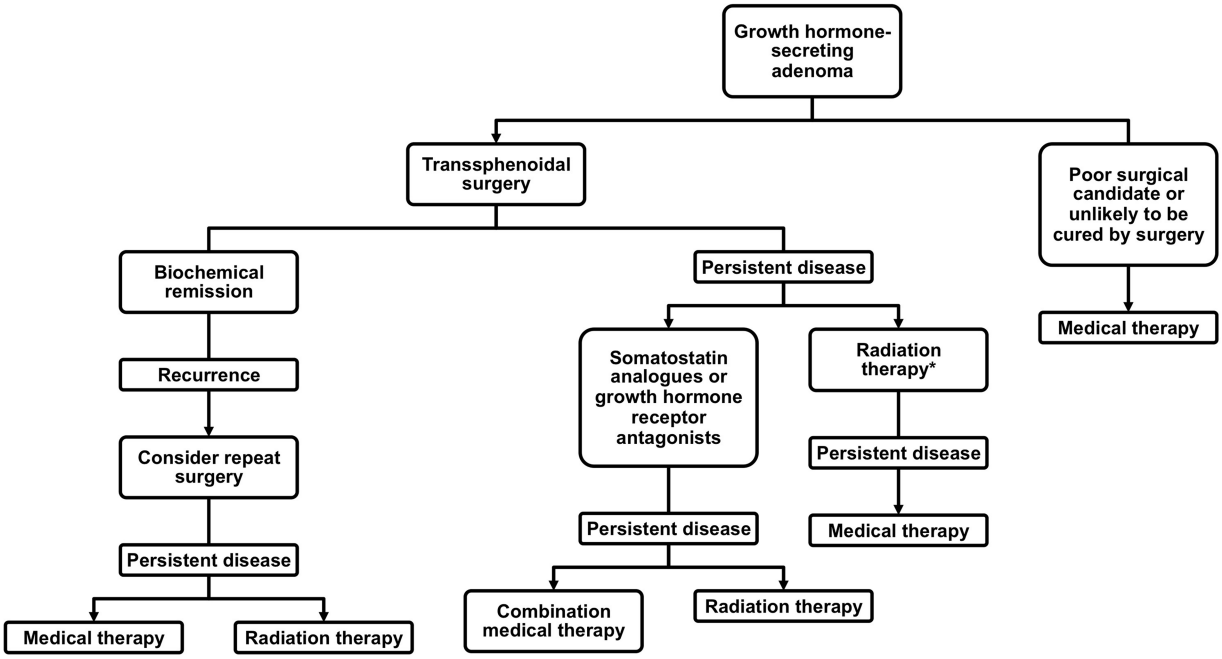


**Fig. 2** Management paradigm for growth hormone-secreting pituitary adenomas. Persistent disease is characterized by lack of biochemical remission and/or adenoma growth. *Radiation therapy may be considered after failed transsphenoidal surgery (second-line) in the appropriately selected patient.

on pituitary somatotrophs with pegvisomant therapy, it has been suggested that accelerated adenoma progression could occur; however, this has not been seen with long-term analysis.[46] Patients refractory to monotherapy of GH-reducing medications may respond to combination therapy (pegvisomant with a somatostatin analogue or in combination with dopamine agonists), which may result in IGF-1 normalization in up to 97% of patients.[47,48] Elevated liver transaminases were as high as 14% in the pegvisomant plus somatostatin analogue cohort.[48]

### *Radiation Therapy*

Although previously considered a third-line treatment option after both failed surgery and medical therapy, improving outcomes with radiation therapy suggest that it may be an appropriate second-line alternative (after transsphenoidal surgery) in carefully selected patients.[49] After CFRT, IGF-1 levels normalize in 61% of patients at 15 years, and adenoma control is 95%. Hypopituitarism, however, can occur in 85% of patients.[50] With more conformal FSRT, hypopituitarism may be reduced.[12] SRS results in less endocrinopathy (32%) and biochemical remission for up to 65% of patients (median time to remission: 36 mo), but nearly 8% of patients will experience an endocrine recurrence.[14] It has been suggested that somatostatin receptor ligands may be radioprotective and should be suspended before radiation therapy.[51] Conversely, patients for whom medical therapy is continued before radiotherapy tend to have greater serum IGF-1 levels before treatment and are less likely to achieve remission after radiation therapy.[51,52]

### Assessment of Biochemical Remission

Biochemical remission is achieved with normalization of serum IGF-1 and random GH 12 weeks after surgery.[53] If serum GH is >1 μg/L, then OGTT should be performed. Biochemical remission is defined as a nadir GH after an OGTT <0.4 μg/L.[53] Radiation and medical therapy may be assessed by evaluation of serum IGF-1 and adenoma response on MR imaging.

## ACTH-Secreting Adenomas

### Clinical Features

ACTH-secreting pituitary adenomas (Cushing disease) account for 4.8%–10% of endocrine-secreting pituitary adenomas and occur more frequently in females compared with males (female-to-male ratio is 3:1).[3–5] Cushing disease is characterized by weight gain (central obesity), diabetes, hypertension, moon facies, facial plethora, psychiatric and neurocognitive changes, decreased libido, and osteoporosis. Pathophysiologic ACTH-secretion in Cushing disease causes supraphysiologic cortisol secretion from the adrenal glands. High circulating levels of cortisol cause potent clinical effects and can prompt diagnostic evaluation and detection of ACTH-adenomas when they are small (microadenomas, <1 cm diameter). Cushing disease, if not effectively treated, results in morbidity

associated with cardiac, cerebrovascular, immunosuppressive, osteoporosis, psychiatric disturbances, and diabetic events. Untreated Cushing disease has an estimated standardized mortality ratio of up to 5 compared with the general population.[7]

## Diagnosis

Once endogenous hypercortisolism (Cushing syndrome) is identified, biochemical diagnosis of Cushing disease is made by confirming a pituitary source and excluding other sources (ectopic ACTH-secreting and adrenocortical tumors). Elevated ACTH can rule out an adrenocortical tumor. High-dose dexamethasone suppression and corticotropin-releasing-hormone stimulation tests may be used to differentiate between pituitary and ectopic sources of ACTH hypersecretion, but both tests have false-negative response rates of ~10%.[54] Because adenomas are often small at biochemical diagnosis (mean adenoma size: 6 mm), high-resolution, postcontrast, GRE MR imaging confirmation may be complicated by lack of a visible tumor in 25%–40% of cases.[55] In cases with negative or equivocal (adenoma size <6 mm) imaging but biochemical testing suggestive of a pituitary source, inferior petrosal sinus sampling may be used to localize ACTH hypersecretion (pituitary vs ectopic) more precisely.[56]

## Treatment

### *Surgical Treatment*

Once an ACTH-secreting pituitary adenoma is confirmed, the treatment of choice is surgical resection (Fig. 3). Pituitary surgery results in biochemical remission in the majority of cases, with rates of remission at experienced centers >80%.[57,58] Successful surgery is associated with preoperative MR-imaging evidence of an adenoma, smaller adenoma size, and the absence of dural invasion.[57–59] When an adenoma is found at the time of surgery, biochemical remission is typically durable. However, when adenoma recurs, it is at the site of resection and/or invasion of immediately adjacent dura.[59] Consequently, adjacent dura (including the medial wall of the cavernous sinus) should be inspected at the time of surgery and resected when safe. Postoperative remission often results in hypocortisolemia, and patients should be given glucocorticoid replacement and should be instructed to observe for signs and symptoms of adrenal insufficiency until recovery of normal corticotroph function (typically 6–18 months after surgery).[60]

Preoperative identification of adenoma location by MR imaging informs the surgeon precisely where to begin surgical exploration of the pituitary gland for adenomectomy. (Imaging location correlates with surgical adenoma location in 86% of cases).[61] In cases without MR evidence of a tumor, adenomas can be found and resected using systematic exploration of the pituitary gland, which results in biochemical remission in 65%–95% of patients.[62,63] When no adenoma is identified at surgery, partial hypophysectomy may allow approximately half of patients to achieve biochemical remission.[63] In cases without biochemical remission after surgery, early repeat transsphenoidal surgery may be performed to explore the remainder of the pituitary gland and/or perform partial hypophysectomy.[64]

### *Radiation Therapy*

Radiation therapy should be considered in patients with persistent hypercortisolism after surgical management or known residual disease that cannot be resected (eg, within the cavernous sinus). CFRT results in biochemical remission in 83% of patients after failed transsphenoidal surgery.[15] Similarly, SRS results in biochemical remission in 70% of patients, but the risk of cranial neuropathy is greater with SRS (5%).[13] Median time to remission was under 18 months with fractionated radiation, and the median time to remission was 16.6 months with SRS. Medical therapy is often continued during the time it takes radiation to control the effects of cortisol excess. No specific pretreatment factors have been associated with lasting endocrine remission after radiation.[15] Radiologic control is observed in the majority of patients treated with radiation (up to 98% with SRS).[13]

### *Medical Therapy*

Medical therapy is an alternative approach to treating patients who cannot undergo surgical treatment or have not achieved biochemical remission after surgery. In these situations, medical therapy is used adjunctively with radiation therapy to achieve eucortisolism until the therapeutic effects of radiation take effect or indefinitely if radiation therapy fails. Medical therapies include steroidogenesis inhibitors, corticotroph-directed agents, and glucocorticoid receptor blockers. Adrenal steroidogenesis inhibitors including ketoconazole, metyrapone, mitotane, and etomidate can be used. Ketoconazole results in control of cortisol excess in 49% of patients.[65] Hepatotoxicity can occur with ketoconazole treatment (16%) but can be reversed upon medication withdrawal.[65] Metyrapone may be also used and can result in normalization of urine free cortisol in 43% of patients with Cushing syndrome (all causes).[66] Metyrapone can cause gastrointestinal upset (23%) but is otherwise generally well-tolerated. Mitotane is no longer used widely as it is highly teratogenic and causes gastrointestinal upset in >50% of patients.[67] Finally, intravenous etomidate may be used for emergent control of severe cortisol excess, but it requires intensive care monitoring for administration.[68] Medical therapy may also be directed at the pituitary directly by targeting somatostatin receptors on corticotrophs with pasireotide. Up to 25% of patients who received pasireotide (higher dose group) experienced biochemical remission at 12 months.[69] The majority of patients experience hyperglycemia, which may be a limiting factor for many with Cushing disease. Mifepristone inhibits the glucocorticoid receptor directly and can be used to block systemic effects but does not result in a reduction in cortisol.[70] Given the morbidity associated with persistent hypercortisolemia, improved medical therapy remains an area of active research, and novel therapeutics are being applied to patients with Cushing disease. For example, with

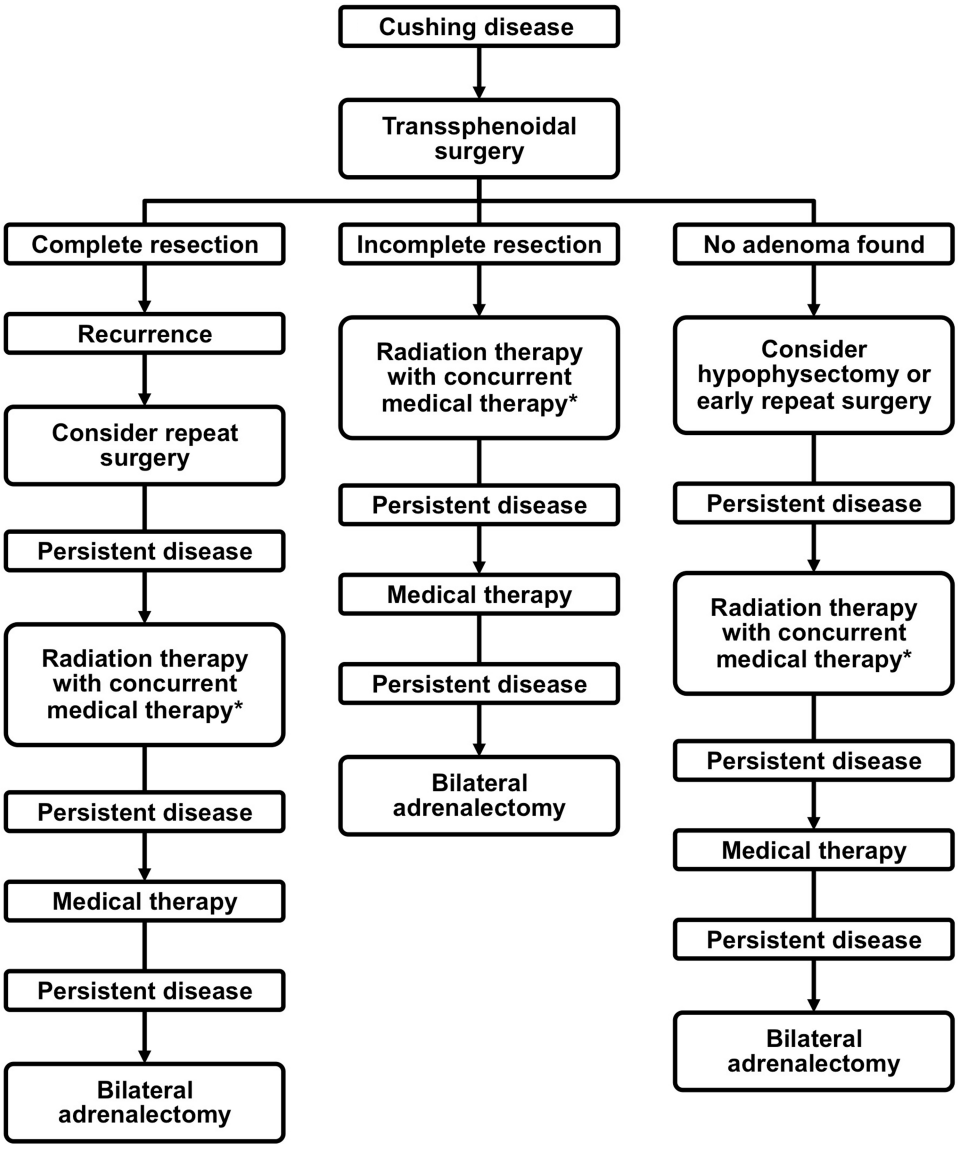


**Fig. 3** Management paradigm for Cushing disease. Persistent disease is characterized by hypercortisolemia (majority of cases) and/or adenoma growth. *In most cases, medical therapy should be initiated concurrently with radiation therapy to limit the morbidity of hypercortisolemia until biochemical remission is achieved.

invasive, treatment-resistant adenomas, temozolomide (an oral alkylating agent frequently used for malignant brain tumors) has been shown to have antitumor effects in case reports and small series.[71] Further clinical trials are required to determine its utility in such tumors.

### *Bilateral Adrenalectomy*

For patients with severe refractory disease, bilateral adrenalectomy can be used as a definitive treatment. Because the adrenal glands are the target organ for ACTH, this therapy can resolve cortisol excess in nearly all patients.[72] Persistent disease is typically related to the presence of adrenal remnants after surgery. Although effective, bilateral adrenalectomy may carry significant morbidity, with up to 20% of patients experiencing an Addisonian crisis after surgery. Patients who undergo bilateral adrenalectomy for refractory Cushing disease may develop Nelson's syndrome (8%–28% of patients) due to lack of the negative feedback effect of cortisol on pituitary corticotrophs leading to rapid, unchecked adenoma growth.[73,74]

Nelson's syndrome is characterized by adenoma growth, hyperpigmentation, and rising ACTH values; however, a recent study has demonstrated corticotroph tumor progression in up to 47% of patients following bilateral adrenalectomy.[75] Rapid growth of adenomas can cause

significant morbidity from mass effect.[74] Pituitary surgery is effective in reducing tumor mass and serum ACTH levels in the majority of patients with Nelson's syndrome.[76] Adenomas without significant mass effect can be managed by radiation therapy. SRS has resulted in a decrease in lesion size in 55% of patients and lesion stability in an additional 36% of patients.[77] Recent reports have suggested that pituitary radiation before bilateral adrenalectomy may diminish the eventual rate of corticotroph tumor progression.[72,78]

### Assessment of Biochemical Remission

Postsurgical biochemical remission may be assessed by morning serum cortisol, serum ACTH levels, and urine free cortisol within the first week after surgery. A morning serum cortisol < μg /dL 3–5 days after surgery is associated with the highest positive predictive value (96%) of lasting remission.[58] Assessment of remission after either radiation or medical therapies is typically confirmed by normalization of urine free cortisol.

## Other Endocrine-secreting Adenomas

### TSH-secreting Adenomas

TSH-secreting pituitary adenomas are rare (1%–2% of pituitary adenomas).[79] Patients with TSH-secreting pituitary adenomas can present with symptoms of hyperthyroidism (most often with palpitation or tachycardia, excess sweating, and goiter).[80] Some patients may undergo thyroid-directed treatment before a pituitary adenoma is recognized, and the presence or absence of a functioning thyroid gland can affect the thyroid function test profile and diagnosis. In some patients with an intact thyroid gland, TSH may be normal, and a combination of thyrotropin-releasing hormone stimulation test (lack of response of TSH), serum α-subunit (elevated), and the α-subunit/TSH molar ratio (elevated) may be needed to make a diagnosis.[81]

Because these adenomas are encountered infrequently, management paradigms and outcomes have not been defined. Surgical resection is typically the first-line therapy. Because these adenomas can be particularly fibrous, large, and invasive at the time of diagnosis, reported biochemical remission rates are variable (35%–84%).[79–81] Radiation therapy may be used in patients who do not achieve biochemical remission after surgery.[80] For patients not suitable for surgery or not cured by surgery or radiation, medical therapy with somatostatin analogues such as octreotide have been used with reduction in serum thyroxine levels (73% patients) and a reduction in adenoma size (21%).[82] Biochemical remission is generally determined by free thyroxine and no residual adenoma on pituitary MR imaging. However, recurrence is frequent, and long-term follow-up is necessary.[81] As an adjunct, undetectable serum TSH 7 days after pituitary surgery is specific for successful outcome.[83]

### Gonadotroph Adenomas

While silent gonadotroph pituitary adenomas (follicle-stimulating hormone [FSH] or luteinizing hormone [LH]-secreting) make up the majority of nonfunctional lesions, functional gonadotroph-secreting tumors are rare (0.2% of pituitary adenomas).[3,84] Premenopausal women with functional gonadotroph adenomas typically present with oligo- or amenorrhea, infertility, or galactorrhea. Men typically present with testicular enlargement or hypogonadism. Diagnosis is made by clinical features and pituitary MR imaging in combination with diverse biochemical findings that may include hyperestrogenism (LH-secreting) in premenopausal women and elevated serum FSH in men as well as elevated α-subunit in both groups. Surgical resection has been the first-line approach in most cases, but defined outcomes have not been established.[85] Radiation therapy may be used in isolated refractory cases, but outcomes are not defined.[85] Medical therapy (dopamine agonists and somatostatin analogues) has been largely unsuccessful, and adenoma size reduction has been elusive.[85] Assessment of biochemical remission includes normalization of the preoperatively elevated hormones and the absence of residual adenoma on postoperative pituitary MR imaging.

## Special Considerations

### Pituitary Apoplexy

Patients with pituitary adenomas (nonfunctional and functional) can present with sudden clinical symptoms due to hemorrhage or infarction of the tumor. This is known as *pituitary apoplexy*. Pituitary apoplexy can result in sudden headache (90%), hypopituitarism (84%), visual disturbances (47%; including complete blindness), and other cranial nerve paresis (39%).[86] Diagnosis of pituitary apoplexy is confirmed by MR imaging or computed tomography. Once pituitary apoplexy has been identified, serum hormone levels should be drawn, and empiric corticosteroids should be administered immediately to treat potential adrenal insufficiency. If laboratory results are negative for adrenal insufficiency, high-dose corticosteroids may still be beneficial in the setting of mass effect causing visual changes.[87] Treatment of pituitary apoplexy includes hormone replacement and emergent surgical resection of the hemorrhagic pituitary adenoma in the setting of visual loss and altered mental status. Surgical resection typically results in improvement or resolution of symptoms.[86,88] Nevertheless, the comparative effectiveness of surgery versus conservative management (corticosteroid treatment) is not defined. A retrospective analysis of 30 patients with apoplexy demonstrated that medical management (corticosteroids alone) resulted in outcomes similar to surgery.[87] Irrespective of treatment choice, patients require monitoring for endocrinopathy including diabetes insipidus. Because apoplexy can result in tissue death, spontaneous biochemical remission of hormone-secreting adenomas may occur.[89]

### Pediatric Patients

Endocrine-secreting pituitary adenomas have unique considerations in the pediatric populations. Compared with lesions in adults, nonfunctioning tumors are relatively infrequent, whereas prolactinomas and ACTH-secreting adenomas predominate.[90] Risks associated with therapy, particularly hypopituitarism, can be significant in prepubertal patients. Further, surgery is complicated by narrow nasal apertures via the transsphenoidal route and a frequently non-pneumatized sphenoid sinus that must be carefully drilled to reach the pituitary gland. Prolactinomas in children are typically responsive to dopamine agonist therapy, which is generally well-tolerated.[91] Second-line therapy is surgery, which results in hormonal control with or without adjuvant dopamine-agonist therapy in the majority of remaining cases.[90,91] Similarly Cushing disease can be treated effectively with surgery as first-line therapy, resulting in biochemical remission at rates similar to those in adults and minimal complications.[58] In the majority of patients who undergo selective adenomectomy, native pituitary gland function is maintained. Among pediatric patients who experience surgical remission of Cushing disease, ~3% demonstrate signs and symptoms of pseudotumor cerebri that may require treatment within a year of cure.[92] Finally, radiation for pediatric patients should be used cautiously, given the relatively high rates of hypopituitarism associated with this therapy.

### Tumor Predisposition Syndromes

Hormone-secreting pituitary adenomas may also occur in the setting of tumor predisposition syndromes, which have significant implications for management. Among the most frequent is multiple endocrine neoplasia syndrome Type I (MEN1). In this syndrome, patients are predisposed to parathyroid adenomas, pancreatic islet cell tumors, and pituitary adenomas. Pituitary adenomas in MEN1 are most frequently prolactinomas but may be nonfunctional, growth hormone-secreting, ACTH-secreting, gonadotroph-secreting, or co-secreting.[93] As these patients are predisposed to developing multiple endocrine tumors over their lifetimes—and tumors may be multiple—conservative therapy is preferred when possible.[93] Some pituitary tumors such as ACTH-secreting adenomas carry significant morbidity from endocrine hyperactivity and benefit from surgical resection. In these cases, selective adenomectomy in some cases of multiple tumors, or hemi-hypophysectomy if no tumor is found, can result in biochemical remission.[94]

McCune-Albright syndrome (MAS) is caused by sporadic *GNAS* mutations that occur in a mosaic fashion in susceptible patients. This syndrome predisposes patients to developing multiple endocrine tumors, disfiguring fibrous dysplasia, and growth hormone-secreting pituitary adenomas. Pituitary surgery may be challenging in these patients as fibrous dysplasia can significantly increase the amount of bony removal required to reach the sella. Recent evidence has shown that nontumorous pituitary gland in MAS often harbors widespread pathologic, hyperplastic tissue.[95] Due to this feature, simple adenomectomy is often insufficient to achieve biochemical remission. Therefore, medical therapy with a long-acting somatostatin analogue or a GH receptor antagonist should be first-line therapy.[96] If medical therapy does not control GH excess, transsphenoidal surgery with a total hypophysectomy should be considered.[95]

Carney complex (CNC) is an autosomal-dominant familial tumor syndrome caused by mutations in *CNC1* or *CNC2*. It results in spotty pigmentation, myxomas, nerve sheath tumors, and endocrine hyperactivity including growth hormone- and prolactin-secreting pituitary adenomas.[97] Pituitary adenomas in CNC may be single or multiple and may be treated by selective adenomectomy if the patient is a suitable candidate for surgery. Similar to MAS, recent evidence has shown that, in some cases, nontumorous pituitary gland in CNC can harbor widespread pathologic, hyperplastic tissue that may also require medical therapy with a long-acting somatostatin analogue or transsphenoidal surgery with a total hypophysectomy.[98]

Familial isolated pituitary adenoma (FIPA) is a term that encompasses any familial syndrome resulting in only pituitary adenomas. As such, patients with MEN1 or CNC who present only with pituitary adenomas can be considered to have FIPA. The growing understanding of this entity has identified mutations in the aryl hydrocarbon receptor-interacting protein *(AIP*) gene in 15% of families with FIPA.[99,100] Patients with *AIP* mutations most commonly harbor GH-secreting pituitary adenomas (78%).[101] Treatment outcomes are still poorly defined, and surgery may remain an appropriate first-line option as these patients are relatively resistant to medical therapy. Regardless, pituitary surgery may be less effective in these patients than in those with sporadic tumors, and adjuvant radiation should be considered if biochemical remission is not achieved.[101]

## Conclusions

Hormone-secreting pituitary adenomas require both control of tumor growth and hormone excess. An understanding of multimodal management is critical for approaching and delivering high-quality care to patients with these lesions.

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