

## Chapter 29

# Multimodality Treatment of Pituitary Adenomas

Nelson M. Oyesiku, M.D., Ph.D.

### ACROMEGALY

Acromegaly is caused by excessive secretion of growth hormone (GH). The average annual incidence of acromegaly is approximately 3.3 per million, and the prevalence is approximately 60 per million (50). GH-secreting adenomas account for 20% of functional adenomas, and 75% of GH adenomas are macroadenomas (50). The mortality in untreated acromegaly is two to three times higher than that of the general population, but with appropriate reduction of GH hypersecretion, it normalizes (50). Treatment is aimed at normalizing GH secretion, eradicating the tumor, preserving normal pituitary function, and managing associated complications. The treatments include transsphenoidal surgery or craniotomy, pharmacotherapy, radiation, or combination therapy.

### Criteria for Cure

Patients that are controlled have a nadir GH  $<1$   $\mu\text{g/L}$  during OGTT, normal age, and sex-normalized IGF-1 and no clinical activity (31). Inadequately controlled patients have a nadir GH  $>1$   $\mu\text{g/L}$  during OGTT or increased IGF-1 and are clinically inactive. Poorly controlled patients have a nadir GH  $>1$   $\mu\text{g/L}$  during OGTT or increased IGF-1 and have clinically active disease (31).

### Surgery

Selective transsphenoidal adenomectomy by an experienced neurosurgeon is a safe procedure that remains the first-line treatment for most patients with acromegaly (1, 80). A craniotomy approach is sometimes required for patients with large tumors with extensive suprasellar or parasellar extension. Sellar and suprasellar tumors can be transsphenoidally removed by a sublabial, transseptal, or direct endonasal approach using the endoscope or microscope. C-arm, computed tomography (CT) scans, or magnetic resonance imaging (MRI) guidance may be used to orient the surgeon during surgery. Some surgeons insert a lumbar drain and instill saline to help manipulate the suprasellar extension. General anesthesia is required, and the supine or semi-sitting position is used.

Rapid reduction in plasma GH concentrations can be achieved within hours after operation (1,26). Plasma IGF-1 concentrations are reduced or normalized over several days or weeks, accompanied by a reduction in headaches, soft-tissue swelling, and blood glucose levels (1). Surgical series using the new stringent criteria for biochemical remission are few. In a study of 103 patients, observed for 1 to 30 years after transsphenoidal surgery, 54% achieved long-term ( $>10$  yr) biochemical remission using older criteria of random GH  $<2.5$   $\mu\text{g/L}$  or GH nadir after OGTT  $<2.5$   $\mu\text{g/L}$  and a normal IGF-1 (5). Microadenomas account for only 20 to 25% of all cases of acromegaly, and because most (75–80%) tumors are macroadenomas with cure rates of only approximately 60%, some 40% of patients treated by operation will require additional treatment. The early and long-term efficacy and safety of a second transsphenoidal surgery for recurrence was retrospectively analyzed in 16 patients. Long-term follow-up data were available in 15 patients. Three of 16 patients (19%) were cured according to the study criteria; moreover, 10 patients (62.5%) developed new pituitary hormone deficiencies. Thus, reoperation for acromegaly has lower success and

higher complication rates. This procedure should be reserved for patients unresponsive to other forms of therapy or with progressive visual impairment despite medical therapy (46).

## Medical Management

Recent advances in the drug treatment of acromegaly include the GH-receptor antagonists and the slow-release depo-injections of somatostatin (SST) analogues (octreotide [Sandostatin LAR; Novartis Pharmaceuticals] and lanreotide [Somatuline; Speywood Pharmaceuticals]) (82).

### Somatostatin Analogs

v Somatostatin is produced in the brain and several peripheral tissues and is an inhibitor of cell proliferation and GH secretion (20). The first-generation analogs had a half-life of 2 hours longer than that of the native hormone but required subcutaneous administration at least three times a day. They reduced GH and IGF-1 levels in 50 to 70% of patients and normalized IGF-1 in approximately 30% of patients after failed pituitary surgery (17). Maximal suppression of GH is reached within 2 hours and usually lasts for 6 hours. A decrease in pituitary tumor size (25–50%) occurs in 20 to 47% of patients with acromegaly on long-term octreotide therapy (17). Preoperative treatment for 8 to 12 weeks shrinks GH macroadenomas by approximately 40%, but whether this affects the surgical outcome is controversial. On the contrary, surgical risk in patients with cardiac and metabolic complications is improved by short-term preoperative octreotide administration.

Newer formulations of somatostatin analogs (octreotide-LAR- and lanreotide-sustained release) have extended durations of action, they are administered in single intramuscular injections (10–40 mg every 28 d), with similar efficacy and better compliance (17). These long-acting somatostatin preparations are expensive and require a meticulous reconstitution technique before injection, requiring a physician-nurse team for long-term care. Lanreotide is available only as a slow-release formulation; because of its shorter duration of action (10–14 d), it needs to be injected 2 to 3 times a month. Typically, therapy is initiated with subcutaneous injections of 100 µg of octreotide three times daily, increasing to 250 µg three times daily as required. Relief of symptoms is often seen immediately after starting the injections and before serum GH levels have declined. Side effects associated with the long-term administration of octreotide are relatively minor and include pain at the injection site, abdominal cramps, and mild steatorrhea. There may be a mild impairment of glucose tolerance and biliary sludge.

Somatostatin analogs are indicated in patients with macroadenomas who have persistent disease after transsphenoidal surgery, as interim treatment in patients awaiting the full effects of radiation, and as preoperative treatment to improve the patient's medical condition. They can also be offered as primary therapy in patients who refuse surgery or those with severe medical problems that preclude surgery or who are unlikely to be cured by an operation (57). Poor-risk patients may be reconsidered for surgery if their medical condition improves after 3 to 6 months on octreotide.

### Dopamine Receptor Agonists

Dopamine agonists such as bromocriptine are indicated in mixed GH- and PRL-secreting tumors, which occur in 30 to 40% of patients with acromegaly. These tumors have greater sensitivity to bromocriptine than pure GH adenomas. Bromocriptine should be given initially at a dose of 1.25 mg at bedtime and then increased gradually to a maximum of

20 mg/d in divided doses. Side effects such as nausea, vertigo, and hypotension may result. Bromocriptine has been effective in decreasing GH and IGF-1 levels in only 20% of patients, with only 10% achieving normalization. The newer generation of long-acting dopamine agonists cabergoline and quinagolide seem to be more effective and better tolerated than bromocriptine.

### GH Receptor Antagonist

Growth hormone receptor (GHR) dimerization is a prerequisite to the generation of GH action. Pegvisomant (Sensus Drug Development, Stockholm, Sweden) is a mutant GHR protein antagonist that binds to the GHR and blocks dimerization. Pegvisomant is a highly effective antagonist of GH action in patients with acromegaly and is a potent inhibitor of IGF-1 production (82). Pegvisomant is administered as daily subcutaneous injections. GH antagonists do not act on the pituitary tumor, and a potential risk is an increase in GH secretion and possible tumor enlargement owing to a loss of the negative feedback from circulating IGF-1. Early results, however, suggest that there is no significant increase in GH levels or acceleration of tumor growth for up to 1 year of follow-up for patients on GH antagonist treatment (82).

### Radiotherapy

Currently, the major role for SRS in acromegaly is for treatment of patients who have failed surgery or as primary treatment for patients unwilling to undergo or medical unsuitable for transsphenoidal surgery. The major risk from SRS is radiation damage to the visual pathways; this can be obviated by limiting the radiation dose to the optic chiasm to <10 Gray. In contrast, the neuronal and vascular structures in the cavernous sinus are less radiosensitive, allowing an ablative dose to be administered to tumors with cavernous sinus invasion. SRS induces remission more rapidly than fractionated radiotherapy (66, 87). Conventional radiotherapy is generally delivered in fractionated doses of 1.6 to 1.8 Gray, four to five times per week over 5 to 6 weeks for a total of 45 to 59 Gray. There is a rapid decrease in GH levels during the first 2 years followed by a slower rate of decrease subsequently. GH concentrations less than 5 µg/L are achieved in 80% of patients, but only after 10 to 15 years, and few patients are cured, even after this length of time, if one applies the more stringent contemporary criteria. Furthermore, conventional radiation has a high risk of hypopituitarism and cognitive and neurologic deficits (32). In a recent report of the results of gamma-knife SRS (GKS) by Zhang et al. (87), with GH-producing pituitary as the primary procedure, GH levels decreased with improvement in acromegaly in all cases in the first 6 months after GKS. Normalization of GH levels was achieved in 23 of 58 patients (40%) observed for 12 months and in 96% of cases observed for more than 24 months (43 of 45). The tumor shrank in 30 of 58 patients (52%) who had been observed for 12 months ( $p < 0.01$ ), 39 of 45 patients (87%) for more than 2 years ( $p = 0.02$ ), and 24 of 26 patients (92%) for more than 36 months (87).

### Postoperative Monitoring and Management

After surgery, GH and IGF-1 levels should be assessed, and if they are normal, the patient can be followed up annually or as required. Patients with persistent disease should be treated with Sandostatin-LAR with monitoring of GH and IGF-1 levels until the dose is optimized. They can then be followed up every 6 months. If GH levels remain increased despite a maximum dose of octreotide, then combined medical therapy with octreotide and dopamine agonists, preferably cabergoline, should be tried. Radiotherapy should be considered when medical therapy with

octreotide and dopamine agonists fails to achieve a biochemical remission. A colonoscopy is recommended for all patients at diagnosis, and every 3 to 5 years thereafter, if polyps are found.

## NONFUNCTIONING PITUITARY ADENOMAS

Nonfunctioning (NF) pituitary adenomas account for approximately 30% of pituitary tumors (4). NF reflects the fact that these tumors do not cause clinical hormone hypersecretion (38). They typically are quite large and cause hypopituitarism or visual loss from regional compression.

Unlike the functional pituitary tumors, there is no available effective medical therapy for the NF tumors. Enlargement of a NF adenoma causes progressive bitemporal visual field loss and hypopituitarism, and occasionally large pituitary adenomas become suddenly apparent, secondary to hemorrhage or infarction (apoplexy) (8).

MRI and CT scans help show the exact anatomical configuration of the adenoma (22, 51), which is essential for surgical planning. Visual examinations are required before and after surgery to document visual deficit and monitor changes. Endocrine function testing is required to determine loss of hormonal function—basal levels by themselves may not reveal hypofunction.

### Treatment

The usual treatment of a NF pituitary adenoma in a medically stable patient is transsphenoidal removal of the tumor (23, 33, 38). If vision loss is rapid or the adenoma is associated with hemorrhage or infarction, a more urgent surgical approach is required (8).

Radiation therapy can be used in patients with NF pituitary adenomas who have a significant amount of residual tumor or recurrence (52). If the patient is elderly or medically unstable, radiation therapy may be the only viable treatment. Stereotactic radiosurgery is preferable to conventional external surgery when the tumor configuration, relative to the chiasm and optic nerves, is favorable. Radiation therapy controls tumor growth in 80 to 98% of patients with NF tumors (52). Hypopituitarism is the most common side effect of pituitary irradiation, with an incidence of 13 to 56%. Long-term overall risk for brain necrosis is estimated at 0.2%. Other side effects are rare and include optic neuropathy in 1.7%, vascular changes in 6.3%, neuropsychological problems in 0.7%, and secondary malignancies in 0.8% (6). Despite the frequent dural invasion of these tumors, many patients do well for long periods of time without radiation therapy.

### Surgical Outcome

v After operative decompression of NF adenomas, vision improves in approximately 80% of patients. Generally, endocrine function is the same before and after surgery, although transsphenoidal surgery usually stops progressive loss of hormonal function. Unfortunately, approximately one third of patients with NF adenomas have some hypopituitarism before their surgical treatment (29).

Postoperative evaluation with MRI and CT scans is best delayed for 2 to 3 months after surgery because of postoperative changes. Persistent mass effect seen in the early postoperative period will generally resolve. The gradual resolution of the mass effect can be documented with serial MRI studies (67). If vision is stable or improved

after transsphenoidal surgery, it may be best simply to follow the patient, even if there is persistent suprasellar mass effect.

#### Follow Up

Most patients with NF pituitary adenomas should have annual MRI or CT, visual, and endocrine evaluations whether or not they have had surgical or radiation treatment. If these tumors are not treated, they continue to grow over months or years. There is a significant recurrence rate after transsphenoidal surgery (approximately 10–20%). A significant number of patients who undergo postoperative radiation therapy develop hypopituitarism and therefore should be monitored.

#### PROLACTINOMAS

Prolactinomas account for approximately 30% of pituitary adenomas and 50 to 60% of functional pituitary tumors (85). They are the most common type of functioning pituitary tumor and are second in frequency to nonfunctioning adenomas in overall incidence (85). Prolactinomas can cause reproductive and sexual dysfunction and local mass effect resulting in visual compromise and hypopituitarism (54). Masses in the sellar and parasellar region can compress the pituitary stalk and interrupt the dopaminergic inhibition of PRL (stalk effect); this results in increased PRL levels in the range of 50 to 125 ng/mL and should not be confused with a prolactinoma. When other causes of hyperprolactinemia have been excluded, an MRI should be obtained to confirm the diagnosis. In most cases, serum PRL levels correlate with the size of the prolactinomas. When the tumor has invaded the cavernous sinus, the serum PRL level may be several thousand nanograms per milliliter. A falsely low serum PRL level (25–150 ng/mL) in the face of a giant and invasive prolactinoma is known as the “hook effect” (19, 30, 78) and warrants a high index of suspicion. The objectives for treatment of prolactinomas are to normalize PRL levels and remove the tumor. Dopamine agonists are the treatment of choice in most cases (55) and are effective in normalizing PRL levels in >90% of patients, but long-term treatment is usually required. Transsphenoidal surgery is indicated when medical therapy fails or cannot be tolerated.

#### Medical Treatment

The dopamine agonists bromocriptine and cabergoline are very effective in normalizing serum PRL levels within days, shrinking the tumor, and restoring gonadal function. Cabergoline is more expensive than bromocriptine, but it is better tolerated and more effective. Visual examination should be repeated approximately 1 month after initiation of therapy, and MRI should be repeated at 6 weeks and again at 3 months after initiation of treatment. Once normalized, serum PRL levels should be monitored annually (7, 15). Bromocriptine is started at 1.25 to 2.5 mg orally once a day and increased during 2 to 3 weeks to 5 to 10 mg daily in divided doses. After normalization of serum PRL levels, bromocriptine can be reduced to the smallest effective dose. Cessation of the drug usually results in recurrent hyperprolactinemia and reexpansion of the tumor (58, 79), although some studies suggest long-term normalization can be attained even after discontinuing the drug (60). Some 10 to 25% of patients are partially or totally resistant to bromocriptine (11, 61), and 5 to 10% of patients are intolerant of bromocriptine because of side effects. In women, intravaginal administration (2.5–5 mg daily) may reduce gastrointestinal side effects (37). Combined medical and surgical therapy may be indicated if the patient fails to respond to cabergoline; after surgical debulking, medication may be more effective. Cabergoline may be administered at doses ranging between 0.5 and 1.5 mg once or twice per

week (55). If the patient is pregnant or wanting to become pregnant, bromocriptine should be used preferentially because it is safe for pregnant women (76), and experience with cabergoline in these patients is limited (68). Once pregnancy is established, bromocriptine should be discontinued, and the patient should be monitored for tumor expansion. The risk of symptomatic tumor enlargement of a microadenoma during pregnancy ranges from 0.5 to 1%, and for patients with macroadenomas, the risk of symptomatic tumor enlargement ranges from 15 to 35% (81). If the patient experiences symptomatic tumor enlargement, bromocriptine therapy can be safely initiated during pregnancy.

## Surgery

The effectiveness and safety of medical therapy has limited the need for surgery. Transsphenoidal adenectomy is the preferred surgical treatment given its effectiveness and its low morbidity and mortality (16). An extended transsphenoidal approach may be used if the tumor is beyond the sella (36). Craniotomy should be considered if there is a significant supratentorial tumor extension (44). Surgical results are predicated on tumor size and PRL level. The higher the PRL level, the lower the chance of cure. In patients with microprolactinomas and serum PRL levels <200 ng/mL, transsphenoidal surgery performed by experienced pituitary surgeons at high-volume centers offers more than a 90% chance of cure (2), with minimal risks of morbidity and mortality of less than 1% (16) and is cost-effective in the long term (83). Patients with preoperative PRL levels >200 ng/mL, harboring larger and more invasive prolactinomas, tend to have poorer outcomes (37–41% cure rate) (84). Surgery is rarely curative in patients with macroprolactinomas and is usually reserved for patients who cannot tolerate medical therapy, for whom medical therapy is ineffective (84), or in patients who do not wish to receive long-term medical therapy (45). Even if surgery is not curative (2, 84), tumor cytoreduction may enhance the efficacy of medication or reduce the target for stereotactic radiosurgery. Long-term treatment with dopamine agonists may alter the consistency of the tumor and make surgery more difficult (42). In patients with giant or invasive prolactinomas, pretreatment with a dopamine agonist may improve the success of subsequent surgery (86).

## Stereotactic Radiosurgery

Stereotactic radiosurgery is an option for patients with prolactinomas after failed transsphenoidal surgery or failed medical therapy (43) and may be a primary treatment for prolactinomas in patients who are reluctant to undergo long-term medical therapy or surgery (59). There is a risk of hypopituitarism, and there may be a radioprotective effect of dopamine agonist therapy; therefore, these medications should be stopped temporarily during radiosurgical treatment (42). Pan and Zhang (59) described 164 patients with prolactinomas who underwent primary treatment with GKS. A mean follow-up period of 33.2 months was available in 128 patients, tumor growth was controlled in all but 2 patients who eventually underwent surgery, biochemical cure was attained in 52% of patients, and an improvement was noted in 28% of patients (59).

## CUSHING'S DISEASE

Cushing's disease accounts for approximately 80% of all cases of Cushing syndrome. Multiple organ systems are affected, and the mortality rate, if untreated, is 50% within 5 years (63). Disease remission is defined as a normal, 24-hour urinary-free cortisol level, a normal or subnormal morning serum cortisol level, regression of clinical features, and cessation of tumor growth (75). Therapeutic options include microsurgical resection, conventional radiotherapy, and chemotherapy. Microsurgical resection remains the best primary therapy; it has the potential for long-term cure

potential and a small incidence of complications.

## Surgery

Transsphenoidal adenomectomy is the therapy of choice, achieving a 70 to 80% cure rate; recurrence occurs in nearly 13 to 25% of the cases and progressively increases over time (3, 10). Transsphenoidal surgery for Cushing's disease can be accomplished with infrequent levels of mortality and morbidity (74). The primary goal of surgical management is removal of an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor and preservation of normal pituitary function; some cases will have negative explorations where no adenoma is found (13, 48). Remission is achieved in 70 to 94% of patients with microadenomas and 45 to 58% of patients with macroadenomas. The clinical recovery after remission often takes at least 6 months and sometimes a year or more.

Virtually all the operations performed for relief of Cushing's disease are accomplished using the transsphenoidal approach. Operative adjuncts include endoscopy, detection of tumors using ultrasonic probes, IPSS to guide intraoperative exploration, and the recognition that locally ectopic areas may hide a small tumor within the dura of the cavernous sinus, the suprasellar compartment, the pituitary stalk, or the sphenoid bone. Complete exploration of the gland should be from one cavernous sinus to the other and from the tuberculum sellae down to the clivus. The dura is opened, and a subdural dissection should be performed to expose all surfaces of the gland. Occasionally, a tumor is encountered at or relatively near the surface of the gland, and it can be removed. If a surface tumor is not uncovered, intraglandular exploration begins with a horizontal incision in the pituitary gland and then external compression from the gland surface in the hope that compression will allow the tumor to extrude through the incision.

If unsuccessful, one can explore the gland by vertical incisions using the IPSS data or the central mucoid wedge where most corticotrophs reside. If the tumor is still not found, the posterior pituitary should be examined, because some tumors arise at the junction between the anterior and posterior pituitary or in the posterior lobe. If a spinal fluid leak has occurred through the diaphragm, then Duraseal or Tisseal can be used to seal the leak and reconstruct the floor of the sella with bone or cartilage and a free-fat graft from the abdomen. Virtually no patients with Cushing's disease require intraoperative corticosteroid administration; therefore, one can assess the results of surgery after the operation by measuring plasma cortisol levels and 24-hour UFC. Cortisol levels will usually decrease to an undetectable level within a day of surgery if the operation has been successful. Some patients require preliminary treatment with ketoconazole because of medical complications. When surgery is successful, there is hypocortisolemia, and cortisol replacement must be maintained until the patient recovers normal corticotroph function.

If the patient is not in remission, one should reassess the diagnosis by reviewing all laboratory data, imaging, and histopathology. An important factor is whether an ACTH-staining pituitary tumor has been removed. If it is certain that a pituitary source is the cause, the immediate reexploration of the pituitary is indicated because this may uncover residual tumor or a previously undetected adenoma. Alternately, reexploration can be deferred. If the tumor cannot be completely resected, then radiotherapy or stereotactic radiosurgery may be recommended. In patients who have serious medical problems and cannot be treated effectively by medication, adrenalectomy should be considered. Because postadrenalectomy Nelson's syndrome may result, radiation therapy to the pituitary should also be performed. Favorable prognostic features for surgery include definitive laboratory data, a positive MRI scan, and the discovery of an ACTH-staining tumor at surgery (9).

Negative prognostic factors include severe, rapidly progressing Cushing's disease, invasive tumors, and macroadenomas. In those patients with microadenomas, the absence of a positive MRI scan is not of great concern because the results are nearly as good in this situation as when the scan is interpreted as positive.

### Nelson's Syndrome

The development of a particularly aggressive ACTH-producing adenoma after bilateral adrenalectomy is known as Nelson's syndrome (56). These frequently invasive tumors are unlikely to be cured with TSA. For example, only 5 (45%) of 11 patients with Nelson's syndrome experienced disease remission after surgery in one study (39). Pollock and Young (64) reported their experience with 11 patients who underwent SRS for Nelson's syndrome. In this series, tumor growth was controlled in nine patients (82%).

### Conventional Radiation Therapy

Although conventional fractionated radiotherapy is effective in reducing the hypercortisolemia of Cushing disease, there is a significant delay of up to several years after radiotherapy for a beneficial clinical and biochemical effect. Conventional radiotherapy results in up to a 90% remission rate by 5 years after treatment (25); however, if observed long enough, a large proportion of patients begin to experience hypopituitarism, and approximately 5% of patients experience a radiation optic neuropathy (62). Remission rates range from 50 to 83% (18). The latent period ranges from 4 to 60 months, remission usually starts after 9 months of treatment, and most patients are in remission within 2 years (18).

### Stereotactic Radiosurgery

Stereotactic radiosurgery is more effective than conventional radiotherapy and can be administered using either a linear accelerator or gamma knife. SRS is preferable in patients with adenomas smaller than 30 mm that are located at least 3 to 5 mm from the optic chiasm. Radiosurgery can be used as a primary treatment for patients who are not good candidates for surgery (35). A marked decrease in the serum cortisol level is obtainable within 3 months after treatment; however, a biochemical cure may be delayed up to 3 years. Complications after SRS for pituitary adenomas are uncommon, particularly in patients with microadenomas, which are most often seen with Cushing's disease. The most common complication is hypopituitarism, which occurs in up to 50% of patients with a mean latency period of 5 years. Radiation-induced optic neuropathy has been reported in less than 2% of cases and induction of a secondary neoplasm in less than 1% of cases. Radiosurgical hypophysectomy is a viable option in patients with severe refractory Cushing's disease without a definite imaging abnormality. Kobayashi et al. (40) reported on 20 of 25 patients with Cushing's disease who underwent GKS. Among the 20 patients, there was complete resolution of the tumor on MRIs in six patients (30%). Levels of ACTH and cortisol became normal in seven patients (35%) (40). In contrast to surgery, in which the risk of diabetes insipidus is approximately 18% (16), this risk seems to be negligible with SRS. In contemporary series, the incidence of new-onset hypopituitarism requiring replacement therapy after SRS has been reported to range between 16 and 55% with a median period of between 50 and 60 months (27).

### Stereotactic Radiosurgery with Proton Beam Therapy



Proton beam therapy in patients with Cushing's disease generally has a high efficacy, produces remission rates up to 94%, is relatively safe, and causes few cases of hypopituitarism. It can be used alone or in combination with unilateral adrenalectomy (49). Ninety percent of 98 patients showed normal biochemical indices and the absence of any clinical signs of the disease within 6 to 36 months of receiving 80 to 90 Gray of proton beam therapy (49).

#### Fractionated Stereotactic Radiation Therapy

Fractionated stereotactic radiation therapy

(FSR) reduces the risk of damage to the optic chiasm (18). A dose of approximately 50 Gray in 1.8 to 2 Gray per fraction is delivered using multiple convergent radiation beams. Complete remission occurred in nine (75%) patients after a median of 29 months; the other three patients (25%) had partial remission (18).

#### Interstitial Pituitary Irradiation

Interstitial irradiation of pituitary adenomas is a safe and effective treatment for Cushing's disease. Yttrium-90 or gold-198 radioactive-labeled rods are transsphenoidally implanted into the sella. In general, interstitial therapy has a high remission and causes complications in less than 1% of patients. The treatment induces remission faster than all other types of treatments except for surgery (12, 71). The largest study of interstitial therapy consisted of 86 patients with Cushing's disease who were treated with interstitial irradiation as the sole therapy (71). In this study, the 1-year remission rate was 77%. There were no clinical or radiological relapses, but 37% of the patients developed hypopituitarism.

#### Medical Treatment

To date, no pharmacologic drugs have proven to be effective in the management of Cushing's disease. Chemotherapy is reserved for adjuvant therapy of treatment-resistant Cushing's disease or for the occasional mild form of the disease, which may respond to medications.

Medical therapy may have either a primary or adjunctive role if the patient cannot safely undergo surgery, if surgery fails, or if the tumor recurs. When medication is the only therapy, a major disadvantage is the need for life-long therapy; in general, recurrence follows discontinuation of treatment. These compounds work through three broad mechanisms of action. Neuromodulatory compounds modulate corticotropin (ACTH) release from a pituitary tumor, steroidogenesis inhibitors reduce cortisol levels by adrenolytic activity or direct enzymatic inhibition, and glucocorticoid antagonists block cortisol action at its receptor. In general, neuromodulatory compounds (bromocriptine, cyproheptadine, somatostatin, and valproic acid) are not very effective drugs for Cushing's disease. Treatment with a glucocorticoid antagonist and radiation therapy has been reported on a single patient only. Steroidogenesis inhibitors, including mitotane, metyrapone, ketoconazole, and aminoglutethimide, are the drugs of choice for medical therapy of Cushing's disease. In general, ketoconazole is the best tolerated of these drugs and is effective as monotherapy in approximately 70% of patients. Mitotane and metyrapone may be effective as single drugs, whereas aminoglutethimide generally must be given in combination. The intravenously administered etomidate may be used when patients cannot take medications by mouth.

## Drugs that Modulate Pituitary ACTH Release

These compounds have been evaluated as single therapeutic agents for Cushing's disease. Response rates are poor, but no large-scale, placebo-controlled trials have been reported. Daily doses and side-effects show cyproheptadine decreases ACTH secretion in healthy volunteers. The response rate was approximately 20% in 15 patients (41) treated with up to 24 g of cyproheptadine daily. Valproic acid decreases ACTH concentrations in patients receiving the agent to inhibit seizures. However, despite case reports suggesting efficacy, placebo-controlled studies of the agent do not support its use as sole therapy (53). Dopamine agonists have been evaluated for their ability to reduce ACTH secretion and cortisol production in Cushing's disease. As reviewed by Miller and Crapo (53), approximately 40% of patients in case reports and small series normalized urine or plasma glucocorticoids during chronic bromocriptine therapy (53).

## Agents that Inhibit Steroidogenesis

Mitotane, trilostane, ketoconazole, aminoglutethimide, and metyrapone decrease cortisol by direct inhibition of steroidogenesis at one or more enzymatic steps. Some, such as trilostane (3 $\beta$ -hydroxysteroid dehydrogenase) (65) and metyrapone (11 $\beta$ -hydroxylase) primarily block a single enzyme; others, such as aminoglutethimide (72) and ketoconazole (28) act at a number of sites. Medications are given orally and in divided doses, except for mitotane, which may be given once daily. Unfortunately, only etomidate can be given parenterally. A disadvantage of these agents for the treatment of Cushing's disease is the need to increase the dose to maintain eucortisolism. This must be done because corticotrope tumors have a higher than normal setpoint for cortisol negative feedback, so they increase ACTH production as cortisol concentrations decrease. When this occurs, larger amounts of inhibitor may be required to maintain target cortisol levels. An additional drawback is that patients rarely remain in remission when medical therapy is discontinued unless radiation therapy to decrease ACTH production has been given.

Clinicians using steroidogenesis inhibitors must set a goal of either complete or partial inhibition of cortisol production. Full adrenal blockade results in nearly undetectable cortisol concentrations so that patients require glucocorticoid replacement to prevent adrenal insufficiency. In contrast, partial inhibition of cortisol production (adjusted adrenal blockade) aims for normalization of cortisol production so that exogenous glucocorticoids are not required. Both approaches, if properly monitored and managed, can result in eucortisolemia. If it can be achieved, adjusted adrenal blockade is optimal. If adrenal insufficiency occurs, medication should be stopped for one day (except for mitotane) and then re-started at a smaller dose. Either approach requires frequent monitoring of plasma or urine cortisol to identify a dose that maintains the correct level of glucocorticoid suppression.

Mitotane alone can achieve remission in up to 83% of patients with Cushing's disease, but only about a third have a sustained remission after discontinuation of treatment (47). More often, mitotane is used with radiation therapy, where it is quite effective (73). The dose should be advanced very gradually to minimize toxicity. Mitotane has significant gastrointestinal and neurological side effects. These may be avoided by gradual increases in dose and administration with meals or at bedtime with food. Mitotane is relatively contraindicated in women desiring fertility within 2 to 5 years. It may induce spontaneous abortion and act as a teratogen, effects that may persist for a number of years after discontinuation because of gradual release from adipose tissue.

Trilostane is a relatively weak inhibitor of steroidogenesis. At maximal daily doses of 1440 mg, none of five patients achieved remission (21). Its use in combination therapy has not been reported. Side effects include abdominal discomfort, diarrhea, and paresthesias. Metyrapone may be useful as monotherapy or in combination with radiation therapy of the pituitary for Cushing's disease (70). Most published experience reports on metyrapone's use with radiation therapy. Nausea and dizziness also may limit its use. In Cushing's disease, aminoglutethimide is not useful as monotherapy but can be very effective when given with other agents—usually metyrapone.

v Ketoconazole inhibits cytochrome P450 enzymes (77). In general, ACTH levels increase in patients with Cushing's disease during chronic therapy with ketoconazole, suggesting that its major effect in these patients is on the adrenal cortex rather than the corticotrope. A meta-analysis of 82 patients with presumed Cushing's disease showed that single-agent treatment with ketoconazole effectively reduces plasma cortisol levels in 70% (24).

#### Agents that Block Cortisol Action

Mifepristone (RU 486) is a steroid that binds competitively to the glucocorticoid, androgen, and progestin receptors and inhibits the action of the endogenous ligands. Its use in Cushing's syndrome has been limited to a few investigational studies of patients with ectopic ACTH secretion and one patient with Cushing's disease (14).

#### Rosiglitazone

Rosiglitazone, a thiazolidinedione compound with peroxisome proliferator-activated receptor-g (PPAR-g)-binding affinity, suppresses ACTH secretion in treated mice and in AtT20 pituitary tumor cells (69) and also inhibits tumor cell growth (34).

Rosiglitazone reduces cortisol secretion and decreases plasma ACTH, and cortisol level normalizes UFC 30 to 60 days after administration in patients with Cushing's disease. Whether the activation of PPAR-g by rosiglitazone will be effective as chronic pharmacologic treatment of Cushing's disease needs more investigation (34).

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