AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF ACROMEGALY

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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Abbreviations:
GH = growth hormone; **GHRH** = growth hormone-releasing hormone; **IGF-I** = insulin-like growth factor-I; **LV** = left ventricular; **MEN 1** = multiple endocrine neoplasia type 1; **MRI** = magnetic resonance imaging; **OGTT** = oral glucose tolerance test

ACROMEGALY: WHY TREAT?

Acromegaly is an uncommonly diagnosed disorder with an annual estimated incidence of 3 to 4 cases per 1 million people. It is characterized by hypersecretion of growth hormone (GH). In more than 95% of cases, the source of the GH hypersecretion is a pituitary somatotroph adenoma. GH stimulates hepatic production of insulin-like growth factor-I (IGF-I). GH produces some of its somatic effects directly; others are mediated by IGF-I. The morbidity and mortality associated with acromegaly are due to both the metabolic consequences of GH hypersecretion and the direct mass effects from the somatotroph adenoma. Recent studies have shown that many consequences related to soft tissue overgrowth can be reversed, at least in part, with appropriate therapy. In addition, appropriate therapy seems to reverse the apparent increased risk of mortality in patients with acromegaly.

The classic clinical findings in a patient with advanced acromegaly include frontal bossing, coarse facial features, wide nasal bridge, thick lips, protruding jaw with widely spaced teeth, and large hands and feet. Acromegaly is a chronic disease that, because of its slowly progressive, insidious nature, often remains undetected for up to 10 years before formal diagnosis. The delay in diagnosis may exaggerate the complications due to GH hypersecretion. Thus, the alertness of the primary care physician and the availability of endocrine consultation are critical for the timely diagnosis of acromegaly. Mandibular bone enlargement may lead to dental malocclusion, which may necessitate surgical intervention for mandibular reduction. Although successful therapy may decrease the soft tissue excess with reductions in skin thickening and hand and foot size, GH and IGF-I normalization will not reduce the magnitude of bone enlargement. Nevertheless, metabolic control may prevent further bone enlargement and associated complications.

The symptoms of local tumor growth include headache, visual field loss (due to compression of the optic chiasm), and cranial nerve palsies (due to involvement of the cranial nerves within the cavernous sinus). These complications are common because macroadenomas (>10 mm) are detected in approximately 80% of patients with acromegaly, a reflection of the delay in diagnosis. Therefore, tumor debulking and appropriate adjuvant therapy may reverse, reduce, or even prevent mass effects caused by tumor growth.

Patients with acromegaly often complain of headaches and fatigue. Hypertension is present in approximately 30% of cases, presumably attributable to volume overload and structural changes in the vascular system. Because hypertension often persists after successful treatment of acromegaly, other mechanisms, such as essential hypertension, may be present in such patients. Hypertension may lead to cardiac hypertrophy, although there are characteristic cardiac changes that are the result of a more specific form of acromegalic cardiomyopathy (1). In patients with acromegaly, cardiac disease usually begins with a hyperkinetic syndrome characterized by increased heart rate. Left ventricular (LV) function is usually preserved in young patients with a brief duration of disease, although LV mass may be increased and LV function in response to exercise may be reduced. Diastolic dysfunction is prevalent in patients with acromegaly. The degree of cardiomyopathy correlates with the duration of disease. Overt heart failure may occur in advanced disease if hormone excess is left untreated. Successful reduction in serum GH and IGF-I concentrations can lead to reduction in cardiac mass and improvement in LV function (2). The high prevalence of hypertension and diabetes mellitus in association with acromegaly contributes to progression of coronary artery disease. Sleep apnea syndrome is present in most patients with acromegaly; it is detected in up to 90% of patients with symptoms such as snoring. Medical therapy for acromegaly may lead to decreased symptoms of sleep apnea (3).

Hyperhidrosis (excessive perspiration) is a common manifestation of acromegaly as well. Musculoskeletal complications include enlargement of the synovial tissue and cartilage, causing hypertrophic arthropathy. The

arthropathy, primarily of the weight-bearing joints, can lead to degenerative changes and the need for surgical replacement of joints. Recently, investigators showed that joint improvement may be achieved after 12 months of medical therapy, although joint thickening was not completely reversed (4). Median nerve entrapment leads to carpal tunnel syndrome in 20% of patients.

The risk of cancer from GH hypersecretion is controversial. An increased incidence of numerous types of cancer has been suggested, the most common being colon cancer. Patients with acromegaly are at increased risk for premalignant colonic polyps, which are present in up to 30% of such patients. Several retrospective studies have suggested an increased risk of colon cancer in patients with acromegaly (5,6). In contrast, however, a recent prospective controlled study showed no increased prevalence of colorectal cancer in 115 patients with acromegaly (7). Although the risk of neoplasms in patients with acromegaly is unclear, the evidence is sufficiently suggestive to warrant periodic screening by colonoscopy in those with active disease.

The mortality rate of patients with acromegaly is 2 to 4 times higher than the expected rate, primarily attributable to cardiovascular disease (8,9). Treatment that normalizes serum IGF-I levels abolishes this risk (10,11). Similarly, normalization of GH secretion with reduction of circulating GH levels to less than 2.5 ng/mL leads to mortality rates comparable to those of the normal population (12,13). These data emphasize the importance of timely diagnosis and appropriate treatment.

In summary, acromegaly is associated with multiple comorbidities related to GH hypersecretion and tumor enlargement. Biochemical control can lead to reversal of the associated comorbidities. Control of GH and IGF-I hypersecretion appears to reverse the risk of premature mortality.

DIAGNOSIS

The diagnosis of acromegaly is optimally based on both clinical and biochemical evidence. Even in the mildest cases of acromegaly, subtle body changes can usually be detected, especially enlargement of the hands and feet (14). Nonetheless, acromegaly can go unrecognized; such lapses have caused a tragic delay in diagnosing acromegaly, the mean delay being 9 years (15).

Once acromegaly is suspected, measurement of serum IGF-I should be the next step. The high degree of correlation between serum IGF-I and variables of acromegaly had been noted as early as 1979 (14). In addition, a correlation exists between 24-hour mean GH and IGF-I levels in acromegaly (16). Once IGF-I levels have escalated to a certain point, however, they begin to plateau (14). Acromegaly in the absence of high IGF-I levels is extremely rare; therefore, this relationship makes IGF-I an ideal screening test. IGF-I is also useful for monitoring of treatment outcomes, such as after a surgical procedure or during treatment with octreotide or pegvisomant.

GH is produced by the pituitary gland in a pulsatile fashion (17), with the highest levels produced during sleep in concert with sleep stages. Normal subjects have very low levels of GH throughout much of the day. In patients with acromegaly, increased pulse frequency results in high levels of GH. These GH levels may demonstrate considerable variability, ranging from 1 ng/mL to values in excess of 100 ng/mL. With both extremes, GH concentrations are sustained, without declining to the low concentrations between pulses seen in normal subjects. This sustained elevation of GH levels is presumably the cause of signs and symptoms of acromegaly. Sometimes IGF-I levels may remain high even in the presence of sustained low serum concentrations of GH. Indeed, up to a third of the patients with acromegaly who undergo surgical treatment may demonstrate a persistently high IGF-I level despite a nadir GH level of less than 1 ng/mL during an oral glucose tolerance test (OGTT). This finding indicates that a proportion of patients may continue to experience subtle changes in GH secretion, leading to persistent disease (18).

Measuring GH during an OGTT has been a standard technique for diagnosis of acromegaly for almost 40 years. The nadir GH level that supports the diagnosis has been in flux throughout that time and remains so because of the increasing sensitivity of GH assays and the improvement of IGF-I assays to corroborate the diagnosis. This test is performed by giving 75 g of glucose orally and sampling for glucose and GH levels at 0, 30, 60, 90, and 120 minutes after administration of the glucose. If the GH level does not decline to below 1 ng/mL during the test, the patient has acromegaly (19). This diagnosis must be made in conjunction with the clinical picture and assessment of the serum IGF-I. Recent studies have shown that occasional patients have GH levels as low as 37 pg/mL and still have signs and symptoms of acromegaly and high levels of IGF-I (20).

Low, but nonsuppressible, levels of GH after oral administration of glucose (GH >1 ng/mL) are frequently noted in patients who have undergone surgical treatment and who have normal IGF-I concentrations. In such patients, the acromegaly is considered controlled but not cured. If the patient is asymptomatic, close follow-up without therapy is reasonable. Currently, prophylactic irradiation is not considered warranted in this context. If symptoms such as heat intolerance or glucose intolerance emerge, or if the IGF-I level becomes high, further therapy is warranted.

Although random GH levels are not generally useful in diagnosing acromegaly, they may have to be used under certain circumstances. Patients with diabetes mellitus have GH levels that respond to glucose; however, performance of an OGTT in patients with very high levels of glucose is not always advisable. Some neuroendocrinologists order

24-hour GH sampling, but that approach is usually part of a defined research project. Thyrotropin-releasing hormone and growth hormone-releasing hormone (GHRH) stimulation tests yield discordant GH responses in up to 50% of patients with acromegaly. Thus, these tests are rarely useful in helping to diagnose acromegaly.

Measurement of GHRH can be helpful in detecting an ectopic source of the acromegaly. A GHRH test should be done when a patient has no obvious pituitary tumor, but there is proven acromegaly. Rarely, acromegaly can be part of a genetic syndrome, including multiple endocrine neoplasia type 1 (MEN 1), McCune-Albright syndrome, familial acromegaly, and Carney complex.

ROLE OF SURGICAL THERAPY

Goals of Operative Intervention

Surgical therapy for acromegaly has the following goals:

1. Normalization of GH secretion and IGF-I levels
2. Elimination of mass effect and reversal of associated neurologic problems—for example, optic compression and headaches
3. Alleviation of comorbidities associated with active acromegaly, including sleep apnea, cardiomyopathy, hypertension, and arthritis
4. Preservation of pituitary function and restoration of any endocrine deficits caused by the tumor
5. Prevention of recurrence of the tumor
6. Procurement of tissue for pathologic and scientific analysis

Advantages of Surgical Treatment

In light of the foregoing goals, surgical treatment of acromegaly has many advantages and at the present time has an important role in the successful outcome of most patients with active acromegaly. Effective surgical intervention produces an immediate lowering of GH levels and offers a potential "cure." For those patients in whom a remission is not possible because the tumor is invasive or involves a site too dangerous to approach in a radical fashion, surgical treatment decreases the tumor burden, which may lead to more successful adjunctive use of radiation therapy, pharmacologic therapy, or a combination of both. A major advantage with the option of surgical management is that one can obtain tissue and characterize the tumor by using immunocytochemistry, ultrastructural analysis, and other techniques of molecular neuropathology.

Disadvantages of Surgical Treatment

Clearly, some disadvantages are associated with use of a surgical approach to acromegaly. Risks accompany all types of treatment, but with a surgical procedure, the patient has the risks of general anesthesia, potential damage to vital structures in the brain and to the blood supply to the brain, and the possibility of vision problems, spinal fluid leak, or meningitis. Even in patients who do not have major complications, there is still the possibility of postoperative pituitary insufficiency, which occurs in about 3% of patients treated surgically (21).

Prognostic Factors

Careful review of a series of patients treated surgically for acromegaly has revealed several factors that predict a satisfactory outcome. Clearly, the smaller the tumor, the more likely is the possibility of remission, and small noninvasive tumors (microadenomas) are the most favorable category of tumor for surgical remission (10,11,20-23). Moreover, the basal GH level before surgical treatment predicts the outcome, with favorable results occurring in those patients with basal GH levels of less than 45 ng/mL.

One of the most important factors favoring good outcome is the experience of the surgeon and the surgical team (24-27). Studies have shown that surgeons who are actively involved on a regular basis in performance of pituitary surgical procedures achieve better outcomes (28). The criteria for a qualified pituitary surgeon should include the following:

1. Prior experience with more than 100 pituitary operations
2. An ongoing experience with more than 20 pituitary cases per year
3. Involvement in a team approach with colleagues from other specialties, especially endocrinology, neuropathology, and radiation oncology

Candidates for Surgical Treatment

Surgical treatment should be considered the first therapeutic option in every patient with acromegaly. Medical therapy may be offered as first-line treatment but only after the surgical option has been discussed with the patient. Those patients who present with severe mass effect manifested as visual loss or double vision are appropriate candidates for urgent surgical treatment. Because the rapidity, reliability, and extent of shrinkage of GH-secreting pituitary adenomas by pharmacologic agents are not entirely predictable, presurgical treatment with somatostatin analogues should not postpone surgical intervention in urgent cases. Because the GH-lowering effects of somatostatin analogues seem to be, in part, a function of the initial GH level (29,30), surgically lowering the GH level may improve the possibility of pharmacologic control, even in those patients who cannot be surgically "cured."

Some patients are unsuitable candidates for surgical treatment and should be considered for medical therapy as first-line management. These selected patients include those with medically unstable conditions, those at high risk for complications of anesthesia because of airway difficulties, and those with major systemic manifestations of acromegaly, including cardiomyopathy, severe hyperten-

sion, and uncontrolled diabetes. Some of these patients become more suitable candidates for surgical intervention after pretreatment with pharmacologic agents, and this type of preoperative management has the potential for lowering risks and improving outcomes in patients ultimately treated surgically (31).

Technical Advances

Certain technical advances have helped improve the outcome of surgical management of acromegaly. Many strides have been made in the area of instrumentation, such as the latest generation of operating microscopes with excellent optics that improve visualization and the operating endoscope that lends versatility and facilitates minimally invasive procedures (32,33). Other technical innovations that have improved surgical management include advances in image guidance and navigation. The preoperative characterization of pituitary tumors can be exquisitely done with use of high-resolution magnetic resonance imaging (MRI). Furthermore, various computer-based navigational systems will allow real-time tracking of the operative procedure on MRI or computed tomographic images obtained preoperatively—a technique that is extremely helpful in patients who have undergone a prior surgical procedure and in whom important anatomic landmarks may now be obscured (34). The use of intraoperative MRI is another relatively new method that allows the surgeon to have imaging control throughout the entire operative procedure and offers the combination of navigational capabilities with intraoperative imaging to aid in determining the extent of resection (35,36).

For standard pituitary surgical procedures, the translabial or the transnasal approach can be used. The transnasal approach is a recent development, which may be the procedure of choice with smaller pituitary tumors for surgeons experienced with this technique. The advantages and disadvantages of these two approaches are summarized in Table 1.

Summary

Surgical treatment remains the first management option for virtually all patients with acromegaly. Medical therapy may be selected as first-line treatment in patients who refuse to undergo or are too ill to undergo a surgical procedure or who prefer the medical option over an operation. An experienced pituitary surgeon should be selected whenever possible, so that the need for reoperations can be minimized.

ROLE OF MEDICAL THERAPY

During the past decade, major progress has been seen in the development of highly specific and selective pharmacologic agents, which have considerably facilitated aggressive management of patients with persistently active acromegaly. In this section, current evidence is summarized for each of the major classes of pharmacotherapeutic agents, with special emphasis on their recognized benefits and risks.

Somatostatin Analogues

Derived from the native inhibitory hormone somatostatin, the somatostatin analogues constitute a true physiologically based approach to treating GH excess. The first-generation analogues had an extended half-life over the native hormone of 2 hours, necessitating subcutaneous administration at least three times a day. This class of analogues successfully reduces GH and IGF-I levels in 50 to 70% of patients, with an IGF-I normalization rate ranging from approximately 41 to 67% (37-39). Maximal suppression is attained within 2 hours and usually lasts for 6 hours. Because the GH response is rapid, this assessment can be done at the outset to identify potential responsiveness. In patients whose GH levels return to baseline before the end of the dosing interval, the frequency of administration can be increased.

In an effort to address some of the shortcomings of first-generation somatostatin analogues, newer formulations of somatostatin analogues (octreotide, lanreotide) with more extended durations of action have been developed. Administered as a single intramuscular injection (10 to 30 mg every 28 days), octreotide results in clinical benefits similar to those achieved with the subcutaneously administered formulations (40). Because the effects are

Table 1
Comparison of Approaches for Standard Pituitary Surgical Procedures

Approach	Advantages	Disadvantages
Translabial	Improved visibility	More invasive Potential injuries of teeth and mouth
Transnasal	Less discomfort Less invasive	Limited visibility Poorer control of hemostasis

more sustained than those with the subcutaneously given preparations, patient compliance is enhanced. The GH inhibitory effects of octreotide are significantly better in patients harboring densely granulated somatotroph adenomas in comparison with those harboring sparsely granulated adenomas (41). Adverse events include transient abdominal cramps and malabsorptive diarrhea. Although an increased incidence of gallbladder sludge and stone formation has been noted, they are not typically of clinical significance. These long-acting preparations, however, are expensive (42) and necessitate meticulous reconstitution technique immediately before injection in comparison with the subcutaneously administered preparations. Accordingly, a dedicated physician-nurse care provider team is essential for continuity of care.

The effect of somatostatin analogues on acromegaly-related complications has been studied in terms of impaired cardiovascular function. Glucose-suppressed GH levels to less than 1 ng/mL together with normalization of plasma IGF-I levels for 1 year have been shown to be associated with significant improvement, but not complete normalization, of LV cardiac function (2). In contrast, persistence of high GH levels was associated with increased systolic blood pressure and impaired cardiac performance. In observational studies involving relatively small numbers of patients with persistently active acromegaly, octreotide treatment was shown to reduce prostatic size and volume (43). Similarly, several indices of sleep apnea severity have been shown to respond favorably to at least 6 months of continuous treatment with octreotide-LAR (long-acting release) (44). Somatostatin analogues alleviate symptoms of acromegaly, including headaches, sweating, and arthralgias, in almost 75% of patients. Reduction of pituitary tumor size, however, is limited to a much smaller subset (only 30 to 50% of patients) (36,45-47). Furthermore, when it does occur, reduction of tumor size is usually of a modest degree. These findings have supported the use of somatostatin analogues as secondary therapy in patients who have undergone a pituitary surgical procedure and who continue to have high GH and IGF-I levels. In addition, medical therapy has been advocated for patients with acromegaly who refuse surgical treatment or who are poor surgical candidates. Whether medical therapy should be considered as a *primary* treatment modality for other patients with acromegaly is controversial. Patients whose tumors are too large or too invasive to be removed completely by surgical treatment are specifically at issue. No published randomized trial has compared the efficacy of surgical debulking followed by somatostatin analogues versus somatostatin analogues alone. Some clinicians use somatostatin analogues as primary therapy—especially if the patient finds this a preferable option to an operation (36). Limited data from nonrandomized studies demonstrate that somatostatin analogues are effective as long-term agents in normalizing GH and IGF-I levels in approximately two-thirds of patients who have not undergone operative treatment (37). The incidence of normalization of IGF-I levels was not different in patients receiving surgical or radiation therapy (or both) than in those given octreotide as primary therapy.

Of note, the effect of somatostatin analogues on long-term acromegaly-related complications and mortality remains to be demonstrated. Nevertheless, these agents are currently the drugs of first choice in the medical treatment of acromegaly. Determining their optimal use in the scheme of management of various patients, however, necessitates individual considerations (Fig. 1). The use of somatostatin analogues is of obvious potential benefit to those patients with persistently nonsuppressible GH and high IGF-I levels after a pituitary surgical procedure. They may also constitute *primary* therapy for those patients who are not surgical candidates. Less clear is the potential role of these agents as primary therapy for those with invasive lesions and low likelihood of a surgical cure. If somatostatin analogues are used as primary therapy, their effective control of GH and IGF-I levels may qualify them for long-term use consideration.

GH Receptor Antagonists

GH receptor antagonists are a relatively new class of pharmaceutical agents. The currently available agent (pegvisomant) was developed to compete with natural GH for binding with the GH receptor. Unlike native GH, however, this antagonist prevents GH receptor dimerization and signaling. Thus, GH action is directly blocked, and the result is reduced IGF-I synthesis. Clinical trials have demonstrated that daily administration (10 to 20 mg) of pegvisomant results in not only reduction but normalization of circulating IGF-I levels in more than 90% of patients with acromegaly (48,49). Its long-term effects on pituitary tumor growth as well as other acromegaly-associated comorbid conditions remain to be assessed. Currently, this agent can be recommended for use in patients for whom surgical treatment, dopaminergic agents, and somatostatin analogues have proved ineffective or for those who are intolerant of somatostatin analogues, those who have extremely high IGF-I values (that is, more than 900 ng/mL), or those in whom glucose tolerance is worsened by somatostatin analogue therapy (Table 2) (50).

Dopamine Agonists

Recent studies have suggested that cabergoline, a dopamine-2 receptor selective agonist, may provide greater benefit than other previously tested dopaminergic agents. In dose-adjusted studies, cabergoline was shown to suppress IGF-I levels below 300 μg/L in approximately 35% of patients, depending on baseline IGF-I levels. Furthermore, the cosecretion of prolactin portended a better response, with almost 50% of such cases achieving an IGF-I level of less than 300 μg/L (51,52). Tumor shrinkage of significant degree was demonstrated in approximately half of the patients. Drug-related adverse events include gastrointestinal discomfort and orthostatic

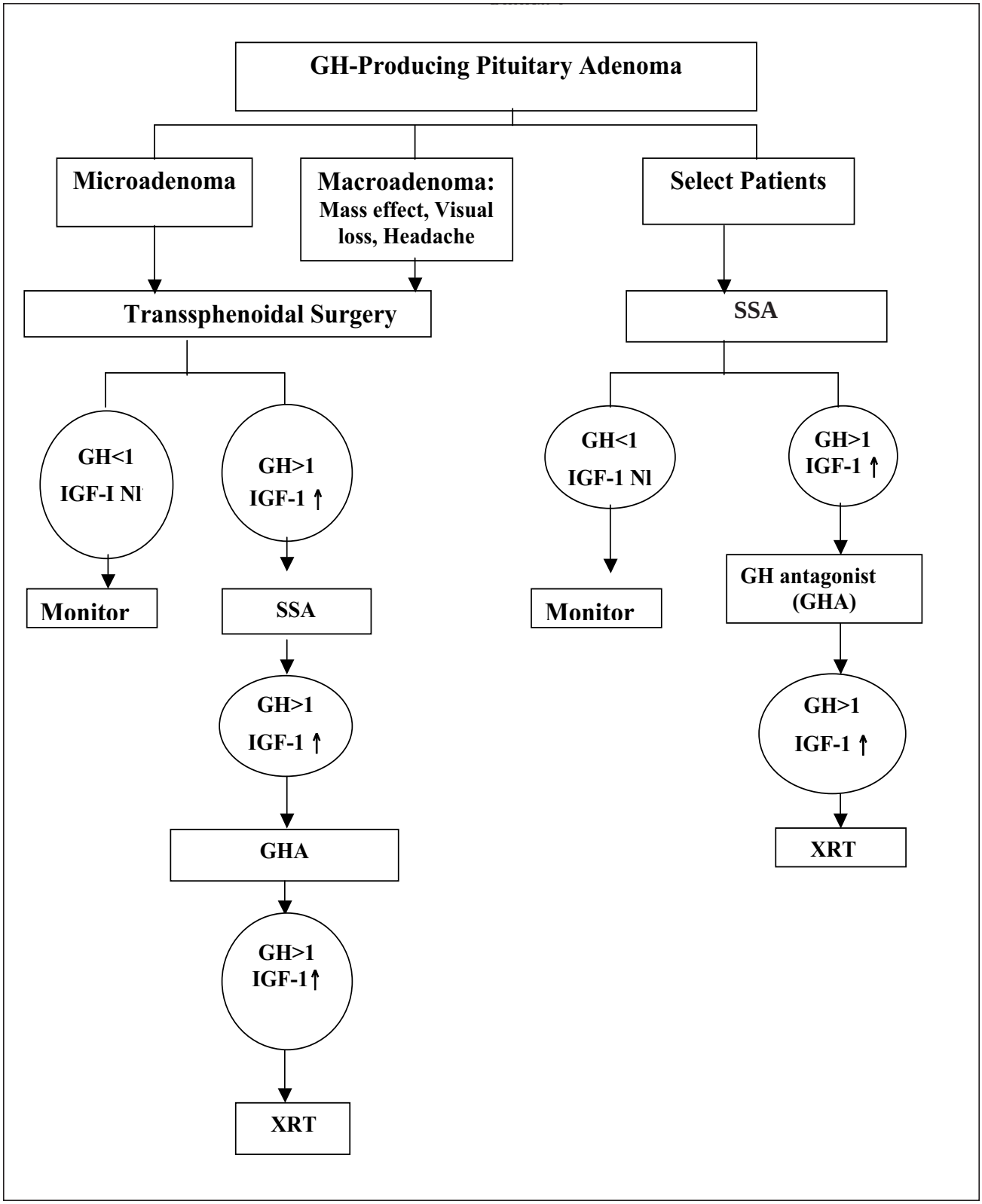

Fig. 1. Recommended scheme for management of growth hormone (*GH*)-producing pituitary adenomas. *GHA* = growth hormone antagonist; *IGF-I* = insulin-like growth factor-I; *Nl* = normal; *SSA* = somatostatin analogue; *XRT* = radiation therapy.

Table 2
Comparison of Various Drugs for Treatment of Acromegaly*

Drug type and agents	Starting dose	Maximal dose	Side effects	Monitoring suggestions	Preferred indication
Dopamine agonist					
Cabergoline	1 mg/wk orally	4 mg/wk	Nausea, GI cramps, headache	GH, IGF-I	GH and prolactin cosecreting tumors
Somatostatin analogues					
Octreotide	50 μg SC tid	200 μg tid	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analogue-responsive tumor
Octreotide LAR	10 mg IM every 4 wk	30 mg every 4 wk	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analogue-responsive tumor
Lanreotide	60 mg IM every 2 wk	120 mg every 7 days	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analogue-responsive tumor
Lanreotide Autogel	60 mg IM every 4 wk	120 mg every 4 wk	Nausea, GI cramps, gallstones	GH, IGF-I, ultrasonography of gallbladder (if symptoms)	Somatostatin analogue-responsive tumor
GH antagonist					
Pegvisomant	10 mg SC daily	40 mg daily	Headache, fatigue, abnormal liver enzymes	Liver function tests monthly for 6 mo, then every 6 mo; MRI yearly; IGF-I only (not GH)	High IGF-I levels not responsive to somatostatin analogue therapy

*GH = growth hormone; GI = gastrointestinal; IGF-I = insulin-like growth factor-I; IM = intramuscularly; LAR = long-acting release; MRI = magnetic resonance imaging; SC = subcutaneously; tid = three times a day.

hypotension. Dopamine agonists are far less effective than either somatostatin analogues or GH receptor blockers. They are most helpful in patients with acromegaly and associated hyperprolactinemia. Because of the modest degree of GH and IGF-I suppression mediated by these agents, they may also be indicated in patients with relatively minimal IGF-I elevations. These uncontrolled studies suggest that dopamine agonists at least warrant further investigation and should be considered in some patients with persistently active acromegaly. One study suggested that somatostatin analogues in combination with dopamine agonist therapy might provide control of acromegaly in some patients in whom somatostatin analogue therapy alone has been ineffective (53).

ROLE OF RADIATION THERAPY

Pituitary irradiation is most commonly used as adjunctive therapy after surgical resection of as much of the adenoma as possible. The fact that up to 80% of patients at the time of diagnosis of acromegaly have a large tumor with dural, bone, or cavernous sinus invasion (or involvement of some combination of these three) indicates that multimodality therapy will be necessary for achievement of clinical remission and a normal serum IGF-I concentration. Conventional fractionated radiation therapy may take 10 to 20 years to be fully effective and has traditionally been used in an attempt to achieve control of tumor growth and ultimate biochemical remission.

More recently, focused methods of delivering a high radiation dose to the residual pituitary tumor have been used; these delivery systems include the gamma knife, proton beam, and Linac (linear accelerator). No direct comparisons of the results among these methods of pituitary radiation delivery are available, but reports suggest that focused radiotherapy yields biochemical remission earlier than does conventional fractionated radiotherapy (54-56) (Table 3).

Candidates for Radiation Treatment

Which patients should receive radiation therapy? In light of the delay in effectiveness, pituitary irradiation is not usually administered as the initial therapy. Patients who have residual GH hypersecretion after surgical treatment are candidates for pituitary irradiation. A combined program of medical therapy to control GH and IGF-I production while the effects of irradiation are awaited is the most logical and beneficial for the patient. Medical therapy should be withdrawn every 6 to 12 months for evaluation of endogenous GH secretion (serum IGF-I and OGTT) and development of any new pituitary hormone deficiencies.

Which patients are not suitable candidates for pituitary irradiation? Essentially all patients qualify, but the method of radiation delivery is determined by the volume and site of the residual pituitary tumor. As a general guideline, stereotactic, focused radiation methods are used only if the distance between the residual tumor and the optic chiasm or an optic nerve is more than 5 mm—because of the potential for damage to vision. Although medical therapies (somatostatin analogues, a GH receptor antagonist, and, rarely, a dopamine agonist) may lower serum IGF-I levels to normal, they are not definitive treatments for permanent control of GH hypersecretion. A specific consideration is the issue of fertility. In young adults who desire fertility, the patients (men and women) must be informed that any type of pituitary irradiation may impair gonadotropin function. Although fertility is possible with administration of exogenous gonadotropin, this technique is expensive, may require several months of treatment, and is not always successful.

Types of Radiation Treatment

Which type of radiation therapy should be recommended? No direct comparisons of results among the various modes of radiation delivery (conventional versus different types of focused, stereotactic delivery) have been published. Reports of efficacy and complications are available, however, and they suggest that stereotactic, focused methods of delivery (gamma knife) result in remission earlier than does conventional fractionated radiation therapy. As noted, not all patients are candidates for stereotactic radiotherapy because of the concern about radiation exposure to the optic apparatus. Most available reports of the efficacy of conventional fractionated radiotherapy did not use current criteria to define remission (normal age-adjusted serum IGF-I levels and serum GH level less than 1 ng/mL after oral administration of glucose). In older studies, a "successful" response was considered a serum GH level of less than 10 ng/mL or less than 5 ng/mL. These criteria are no longer acceptable because of the availability of more sensitive GH assays, the reliability of serum IGF-I as an overall indicator of GH secretion, and the current knowledge about the importance of reducing GH and IGF-I values to normal levels to decrease the risk of premature mortality (10). In one study, conventional fractionated radiotherapy reduced serum GH to levels less than 5 ng/mL in 77% of 87 patients 15 years after treatment (57). Other studies have reported a reduction in GH levels to less than 2.5 ng/mL in 7 of 28 patients (25%) 5 years after radiotherapy (58) and a normal level

Table 3
Comparison of Advantages and Disadvantages of Various Types of Pituitary Radiation Therapy

Type of radiation therapy	Advantages	Disadvantages
Conventional	Can be used when tumor is near the optic chiasm	25 to 30 therapy visits Delayed remission
Proton beam (stereotactic)	Single session or fractionated	Limited availability Tumor must be >5 mm from optic chiasm No data on time of remission
Linac (stereotactic)	Single session or fractionated	Tumor must be >5 mm from optic chiasm No data on time of remission
Gamma knife (stereotactic)	Single session Early remission	Limited availability Tumor must be >5 mm from optic chiasm

of serum IGF-I achieved in 2 of 38 patients (5%) after a mean follow-up period of 6.8 years (59). Gamma knife radiosurgery reduced IGF-I concentrations to normal in 14 of 31 patients (45%) 2 years after treatment (51), in 11 of 26 patients (42%) at a mean of 42 months after treatment (52), and in 23 of 64 patients (36%) at a mean of 28 months after therapy (54).

Potential Complications

What are the potential complications of pituitary irradiation? The most common is loss of normal pituitary function, necessitating hormone replacement. With long-term follow-up, loss of pituitary function has been noted in up to 100% of patients given conventional radiation therapy (60). Gamma knife radiosurgery resulted in new hormone deficiency in 18 of 64 patients (28%) (54). Less common complications of all types of pituitary irradiation include loss of vision, radiation necrosis, and development of a secondary malignant lesion in the radiation field.

Prevention of Tumor Recurrence

Should pituitary irradiation be given to prevent recurrence of acromegaly? A risk of pituitary tumor recurrence always exists, regardless of the type of adenoma. The reported recurrence rate in patients with acromegaly ranges from 2 to 14% (61). With this low risk of recurrence, no precedent is available for recommending prophylactic irradiation for the patient who has undergone successful surgical treatment and who has a normal serum IGF-I level. Every patient, however, should be scheduled for regular follow-up examinations every 6 to 12 months, for detection of any recurrence and implementation of prompt treatment, if necessary.

Summary

Pituitary irradiation for residual GH hypersecretion is an important part of the treatment of acromegaly and should be used as an adjunctive therapy in conjunction with medical treatment to control the disease. Development of pituitary deficiency should be anticipated and treated accordingly.

MONITORING AND TREATING COMORBIDITIES

The morbidities associated with GH-secreting pituitary adenomas are due to local mass effects of the tumor, sequelae of GH and IGF-I excess, and sequelae of other pituitary hormone deficiencies. In an effort to decrease the excess mortality attributable to cardiovascular disease, respiratory disease, and cancer, aggressive modification of risk factors and screening for early diagnosis should be implemented.

Skeletal and Dental Manifestations

Unlike the soft tissue changes, the bone enlargement that occurs with excess secretion of GH is not readily reversible with successful treatment (62-64). Any corrective surgical procedure, such as maxillofacial correction of dental malocclusion, should be postponed until GH and IGF-I levels normalize or stabilize. Joint discomfort and carpal tunnel syndrome may, in part, be due to enlargement of soft tissues and retention of fluid. This component of acromegaly often improves with reduction of excess GH secretion. Established degenerative arthritis, however, if present, is irreversible and should be managed appropriately with physical therapy, anti-inflammatory medications, and surgical joint replacement, as indicated. Patients should also be screened (with bone densitometry and determination of serum calcium levels) for coexisting metabolic bone disease. If osteoporosis is present and bone densitometry findings do not improve with correction of any associated hypogonadism or hypercalciuria, antiresorptive therapy should be considered. Hypercalcemia and hypercalciuria can occur with GH excess and are due to altered vitamin D metabolism. These abnormalities should diminish with successful treatment. If hypercalcemia persists, further evaluation for primary hyperparathyroidism and MEN 1 syndrome should be undertaken.

Hypopituitarism

In patients with acromegaly, the time frame and the possibility of developing hypopituitarism depend on the treatment used. Pituitary insufficiency that manifests preoperatively from tumor compression of the normal gland may diminish with successful surgical debulking. Alternatively, new hormonal deficits may occur as a result of the surgical procedure. The integrity of the hypothalamic-pituitary-adrenal axis and posterior pituitary function should be assessed during the immediate postoperative period. The integrity of the thyroid and gonadal axes is assessed 6 to 12 weeks postoperatively. Occasionally, dynamic testing will be necessary to determine partial deficiencies. Patients who have received radiation therapy need lifelong monitoring of pituitary function, inasmuch as new deficits can occur up to 15 years or more after radiation treatment.

Respiratory Disorders

Successful treatment of acromegaly, with reduction in the size of soft tissues of the upper airway, may improve or eliminate sleep apnea; however, many patients with acromegaly who have sleep apnea have not only a central component but also an obstructive component (65). Home overnight oximetry can be used as a screening test for sleep apnea, and if abnormal results are found, formal overnight polysomnography should be performed.

Patients with acromegaly should be considered to have higher than normal risk for pulmonary infections because of the high prevalence of obstructive pulmonary disease (59) and increased respiratory mortality in such patients. Vaccinations for influenza and pneumococcal pneumonia should be given, as recommended by the

Centers for Disease Control and Prevention, for persons with medical indications—that is, annual influenza vaccine and one-time pneumococcal vaccine, with revaccination after age 65 years if more than 5 years have elapsed since the initial vaccination (66). For those patients who use tobacco, aggressive intervention for cessation of tobacco use should also be initiated.

Cardiovascular Disease and Cardiovascular Risk Factors

Standard therapy for patients with LV hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease (67), and ischemic heart disease should be used. Limited information is available about the role of screening cardiac stress tests or echocardiography in patients with acromegaly. With lowering of GH concentrations, LV size and function may improve (68).

Hypertension and diabetes mellitus, if present, may improve with lowering of GH and IGF-I levels. Standard dietary strategies and medical therapies for hypertension, diabetes mellitus, and hyperlipidemia should be used. In the absence of definitive interventional studies in this patient population, it seems prudent to attempt to achieve the goals for high-risk cardiac patients: blood pressure, less than 130/80 mm Hg (69); hemoglobin A1c, less than 6.5%; low-density lipoprotein cholesterol, less than 100 mg/dL; triglycerides, less than 150 mg/dL; and high-density lipoprotein cholesterol, more than 40 mg/dL (70).

Cancer

Colon cancer develops from malignant transformation of benign colon polyps—a process believed to involve from 5 to 10 years. Early detection and treatment of colon cancer improve survival, and the removal of premalignant polyps will prevent the development of colon cancer. Although data regarding the risk of benign or malignant colon lesions in patients with acromegaly are conflicting, the risk of death from colon cancer is increased in patients with acromegaly in whom colon cancer develops (71). The onset of GH hypersecretion is difficult to ascertain; it usually precedes a diagnosis of acromegaly by many years (72). Therefore, it is prudent to screen patients for colorectal cancer and polyps with colonoscopy at the time of diagnosis of acromegaly and then follow the American Cancer Society guidelines for patients with increased risk (colonoscopy every 5 years if no cancer or polyps are detected, with more frequent follow-up if any lesions are detected, depending on the number, size, and histologic features of the lesions) (73).

Screening for other cancers should follow the standard guidelines established by national organizations. Because patients with acromegaly may receive treatments that, in and of themselves, alter the risk for cancers (such as hormone replacement therapy and breast cancer, testosterone replacement and prostate cancer, and cranial irradiation and intracranial neoplasms), the screening guidelines should be adjusted accordingly.

CONCLUSION

Acromegaly is often a chronic debilitating condition that, if left uncontrolled, is associated with increased morbidity and mortality. The diagnosis is established by substantiating autonomous GH hypersecretion and by imaging of the pituitary gland. Traditionally, surgical resection of the responsible pituitary adenoma has been the cornerstone of management, and an experienced pituitary surgeon should be selected when possible. Because complete resection is not always possible, adjunctive therapy is frequently necessary. This situation has prompted the view that primary medical therapy may be a suitable option to consider for some patients. Persistently active disease is now well documented to be associated with increased morbidity and mortality. New pharmacologic therapies will most certainly emerge and prove superior to those currently available. New guidelines for the management of acromegaly will necessitate ongoing reassessment.

REFERENCES

1. **Fazio S, Cittadini A, Cuocolo A, et al.** Impaired cardiac performance is a distinct feature of uncomplicated acromegaly. *J Clin Endocrinol Metab*. 1994;79:441-446.
2. **Colao A, Marzullo P, Ferone D, et al.** Cardiovascular effects of depot long-acting somatostatin analog Sandostatin LAR in acromegaly. *J Clin Endocrinol Metab*. 2000;85:3132-3140.
3. **Grunstein RR, Ho KK, Sullivan CE.** Effect of octreotide, a somatostatin analog, on sleep apnea in patients with acromegaly. *Ann Intern Med*. 1994;121:478-483.
4. **Colao A, Marzullo P, Vallone G, et al.** Ultrasonographic evidence of joint thickening reversibility in acromegalic patients treated with lanreotide for 12 months. *Clin Endocrinol (Oxf)*. 1999;51:611-618.
5. **Bari D, Gridley G, Ron E, et al.** Acromegaly and cancer risk: a cohort study in Sweden and Denmark. *Cancer Causes Control*. 2002;13:395-400.
6. **Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr.** Acromegaly and gastrointestinal cancer [erratum in *Cancer*. 1992;69:549]. *Cancer*. 1991;68:1673-1677.
7. **Renehan AG, Odwyer ST, Shalet SM.** Screening colonoscopy for acromegaly in perspective. *Clin Endocrinol (Oxf)*. 2001;55:731-733.
8. **Bengtsson BA, Eden S, Ernest I, Oden A, Sjogren B.** Epidemiology and long-term survival in acromegaly: a study of 166 cases diagnosed between 1955 and 1984. *Acta Med Scand*. 1988;223:327-335.
9. **Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R.** Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)*. 1980;12:71-79.
10. **Swearingen B, Barker FG II, Katznelson L, et al.** Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab*. 1998; 83:3419-3426.

11. **Holdaway IM, Rajasoorya RC, Gamble GD.** Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab*. 2004;89:667-674.
12. **Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB.** Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. *J Clin Endocrinol Metab*. 1998;83:3411-3418.
13. **Melmed S.** Tight control of growth hormone: an attainable outcome for acromegaly treatment. *J Clin Endocrinol Metab*. 1998;83:3409-3410.
14. **Clemmons DR, Van Wyk JJ, Ridgway EC, Kliman B, Kjellberg RN, Underwood LE.** Evaluation of acromegaly by radioimmunoassay of somatomedin-C. *N Engl J Med*. 1979;301:1138-1142.
15. **Nabarro JD.** Acromegaly. *Clin Endocrinol (Oxf)*. 1987;26:481-512.
16. **Barkan AL, Beitins IZ, Kelch RP.** Plasma insulin-like growth factor-I/somatomedin-C in acromegaly: correlation with the degree of growth hormone hypersecretion. *J Clin Endocrinol Metab*. 1988;67:69-73.
17. **Winer LM, Shaw MA, Baumann G.** Basal plasma growth hormone levels in man: new evidence for rhythmicity of growth hormone secretion. *J Clin Endocrinol Metab*. 1990;70:1678-1686.
18. **Freda PU, Post KD, Powell JS, Wardlaw SL.** Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. *J Clin Endocrinol Metab*. 1998;83:3808-3816.
19. **Giustina A, Barkan A, Casanueva FF, et al.** Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab*. 2000;85:526-529.
20. **Dimaraki EV, Jaffe CA, DeMott-Friberg R, Chandler WF, Barkan AL.** Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. *J Clin Endocrinol Metab*. 2002;87:3537-3542.
21. **Kreutzer J, Vance ML, Lopes MB, Laws ER Jr.** Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *J Clin Endocrinol Metab*. 2001;86:4072-4077.
22. **Tindall GT, Oyesiku NM, Watts NB, Clark RV, Christy JH, Adams DA.** Transsphenoidal adenomectomy for growth hormone-secreting pituitary adenomas in acromegaly: outcome analysis and determinants of failure. *J Neurosurg*. 1993;78:205-215.
23. **Freda PU, Wardlaw SL, Post KD.** Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. *J Neurosurg*. 1998;89:353-358.
24. **Gittoes NJ, Sheppard MC, Johnson AP, Stewart PM.** Outcome of surgery for acromegaly—the experience of a dedicated pituitary surgeon. *QJM*. 1999;92:741-745.
25. **Clayton RN.** How many surgeons to operate on acromegalic patients? *Clin Endocrinol (Oxf)*. 1999;50:557-559.
26. **Clayton RN, Stewart PM, Shalet SM, Wass JA.** Pituitary surgery for acromegaly: should be done by specialists. *BMJ*. 1999;319:588-589.
27. **Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA.** Outcome of transsphenoidal surgery for acromegaly and its relationship to surgical experience. *Clin Endocrinol (Oxf)*. 1999;50:561-567.
28. **Ciric I, Ragin A, Baumgartner C, Pierce D.** Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. *Neurosurgery*. 1997;40:225-236.
29. **Colao A, Ferone D, Lastoria S, et al.** Prediction of efficacy of octreotide therapy in patients with acromegaly. *J Clin Endocrinol Metab*. 1996;81:2356-2362.
30. **Newman CB, Melmed S, Snyder PJ, et al.** Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients—a clinical research center study [erratum in *J Clin Endocrinol Metab*. 1995;80:3238]. *J Clin Endocrinol Metab*. 1995;80:2768-2775.
31. **Ben-Shlomo A, Melmed S.** Clinical review 154: the role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab*. 2003; 88:963-968.
32. **Jho HD.** Endoscopic transsphenoidal surgery. *J Neurooncol*. 2001;54:187-195.
33. **Cappabianca P, Cavallo LM, Colao A, et al.** Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. *Minim Invasive Neurosurg*. 2002;45:193-200.
34. **Cappabianca P, de Divitiis E.** Image guided endoscopic transnasal removal of recurrent pituitary adenomas. *Neurosurgery*. 2003;52:483-484.
35. **Bohinski RJ, Warnick RE, Gaskill-Shipley MF, et al.** Intraoperative magnetic resonance imaging to determine the extent of resection of pituitary macroadenomas during transsphenoidal microsurgery. *Neurosurgery*. 2001;49: 1133-1143.
36. **Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C.** Intraoperative magnetic resonance imaging during transsphenoidal surgery. *J Neurosurg*. 2001;95: 381-390.
37. **Newman CB, Melmed S, George A, et al.** Octreotide as primary therapy for acromegaly. *J Clin Endocrinol Metab*. 1998;83:3034-3040.
38. **Ezzat S, Snyder PJ, Young WF, et al.** Octreotide treatment of acromegaly: a randomized, multicenter study. *Ann Intern Med*. 1992;117:711-718.
39. **Chanson P, Leselbaum A, Blumberg J, Schaison G (French Multicenter Study Group on Lanreotide in Acromegaly).** Efficacy and tolerability of the long-acting somatostatin analog lanreotide in acromegaly: a 12-month multicenter study of 58 acromegalic patients. *Pituitary*. 2000;2:269-276.
40. **Colao A, Ferone D, Marzullo P, et al.** Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab*. 2001;86:2779-2786.
41. **Ezzat S, Kontogeorgos G, Redelmeier DA, Horvath E, Harris AG, Kovacs K.** In vivo responsiveness of morphologic variants of growth hormone-producing pituitary adenomas to octreotide. *Eur J Endocrinol*. 1995;133:686-690.
42. **Wilson LS, Shin JL, Ezzat S.** Longitudinal assessment of economic burden and clinical outcomes in acromegaly. *Endocr Pract*. 2001;7:170-180.
43. **Colao A, Marzullo P, Spiezia S, et al.** Effect of two years of growth hormone and insulin-like growth factor-I suppression on prostate diseases in acromegalic patients. *J Clin Endocrinol Metab*. 2000;85:3754-3761.
44. **Ip MS, Tan KC, Peh WC, Lam KS.** Effect of Sandostatin LAR on sleep apnoea in acromegaly: correlation with computerized tomographic cephalometry and hormonal activity. *Clin Endocrinol (Oxf)*. 2001;55:477-483.
45. **Lombardi G, Colao A, Ferone D, et al.** Cardiovascular aspects in acromegaly: effects of treatment. *Metabolism*. 1996;45(8 Suppl 1):57-60.

46. **Bevan JS, Atkin SL, Atkinson AB, et al.** Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab*. 2002;87:4554-4563.
47. **Abe T, Ludecke DK.** Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. *Eur J Endocrinol*. 2001;145:137-145.
48. **van der Lely AJ, Hutson RK, Trainer PJ, et al.** Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet*. 2001;358:1754-1759.
49. **Trainer PJ, Drake WM, Katznelson L, et al.** Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med*. 2000;342:1171-1177.
50. **Clemmons DR, Chihara K, Freda PU, et al.** Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. *J Clin Endocrinol Metab*. 2003;88:4759-4767.
51. **Abs R, Verhelst J, Maiter D, et al.** Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab*. 1998;83:374-378.
52. **Cozzi R, Attanasio R, Barausse M, et al.** Cabergoline in acromegaly: a renewed role for dopamine agonist treatment? *Eur J Endocrinol*. 1998;139:516-521.
53. **Flogstad AK, Halse J, Bakke S, et al.** Sandostatin LAR in acromegalic patients: long-term treatment. *J Clin Endocrinol Metab*. 1997;82:23-28.
54. **Landolt AM, Haller D, Lomax N, et al.** Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. *J Neurosurg*. 1998;88:1002-1008.
55. **Pollock BE, Nippoldt TB, Stafford SL, Foote RL, Abboud CF.** Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. *J Neurosurg*. 2002;97:525-530.
56. **Jane JA, Vance ML, Woodburn CJ, Laws ER Jr.** Stereotactic radiosurgery for hypersecreting pituitary tumors: part of a multimodality approach. *Neurosurg Focus*. 2003;14:1-5.
57. **Eastman RC, Gorden P, Glatstein E, Roth J.** Radiation therapy of acromegaly. *Endocrinol Metab Clin North Am*. 1992;21:693-712.
58. **Thalassinos NC, Tsagarakis S, Ioannides G, Tzavara I, Papavasiliou C.** Megavoltage pituitary irradiation lowers but seldom leads to safe GH levels in acromegaly: a long-term follow-up study. *Eur J Endocrinol*. 1998;138:160-163.
59. **Barkan AL, Halasz I, Dornfeld KJ, et al.** Pituitary radiation is ineffective in normalizing plasma insulin-like growth factor I in patients with acromegaly. *J Clin Endocrinol Metab*. 1997;82:3187-3191.
60. **Flickinger JC, Rush SC.** Linear accelerator therapy of pituitary adenomas. In: Landolt AM, Vance ML, Reilly PL, eds. *Pituitary Adenomas*. London, England: Churchill Livingstone, 1996: 475-483.
61. **Giovanelli M, Losa M, Mortini P.** Acromegaly: surgical results and prognosis. In: Landolt AM, Vance ML, Reilly PL, eds. *Pituitary Adenomas*. London, England: Churchill Livingstone, 1996: 333-351.
62. **Bluestone R, Bywaters EG, Hartog M, Holt PJ, Hyde S.** Acromegalic arthropathy. *Ann Rheum Dis*. 1971;30:243-258.
63. **Detenbeck LC, Tressler HA, O'Duffy JD, Randall RV.** Peripheral joint manifestations of acromegaly. *Clin Orthop*. 1973;91:119-127.
64. **Dons RF, Rosselet P, Pastakia B, Doppman J, Gorden P.** Arthropathy in acromegalic patients before and after treatment: a long-term follow-up study. *Clin Endocrinol (Oxf)*. 1988;28:515-524.
65. **Fatti LM, Scacchi M, Pincelli AI, Lavezzi E, Cavagnini F.** Prevalence and pathogenesis of sleep apnea and lung disease in acromegaly. *Pituitary*. 2001;4:259-262.
66. From the Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States, 2002-2003. *JAMA*. 2002;288:2258-2260.
67. **Colao A, Spinelli L, Marzullo P, et al.** High prevalence of cardiac valve disease in acromegaly: an observational, analytical, case-control study. *J Clin Endocrinol Metab*. 2003; 88:3196-3201.
68. **Colao A, Merola B, Ferone D, Lombardi G.** Acromegaly. *J Clin Endocrinol Metab*. 1997;82:2777-2781.
69. **National Heart, Lung, and Blood Institute, National Institutes of Health.** Clinical practice guidelines for high blood pressure. 2003. Available at: http://www.nhlbi.nih.gov/guidelines/hypertension/jncintro.htm.
70. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285: 2486-2497.
71. **Orme SM, McNally RJ, Cartwright RA, Belchetz PE (United Kingdom Acromegaly Study Group).** Mortality and cancer incidence in acromegaly: a retrospective cohort study. *J Clin Endocrinol Metab*. 1998;83:2730-2734.
72. **Ezzat S, Forster MJ, Berchtold P, Redelmeier DA, Boerlin V, Harris AG.** Acromegaly: clinical and biochemical features in 500 patients. *Medicine (Baltimore)*. 1994;73:233-240.
73. **American Cancer Society.** Cancer reference information. 2003. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_Can_colon_and_rectum_cancer_be_found_early.asp?sitearea=CRI.