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CONSENSUS

Guidelines for Acromegaly Management

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In May 2000, an Acromegaly Treatment Workshop was held to develop a consensus statement reflecting the integrated opinions of 68 leading neuroendocrinologists and neurosurgeons worldwide.

Acromegaly is an insidious disorder caused by a pituitary GH-secreting adenoma resulting in high circulating levels of GH and IGF-I (1). Unfortunately, no single therapy is comprehensively successful in controlling the disease and its protean clinical manifestations, and different treatment modes are associated with unique adverse effects and clinical disadvantages (2). Surgery, radiation, and medical treatments are available for lowering GH and IGF-I hypersecretion, controlling pituitary tumor mass effects, and improving morbidity (3). Recent studies provide a compelling rationale for controlling GH and IGF-I secretion as being the most significant determinant of restoring the observed adverse mortality to control rates (4–6). Regardless of the therapeutic mode, the goal of treatment is to control GH levels to less than 1 μg/liter after an oral glucose load (Fig. 1), normalize age- and gender-matched IGF-I levels, ablate or reduce tumor mass and prevent its recurrence, and alleviate significant comorbid features, especially cardiovascular, pulmonary, and metabolic derangements (7, 8).

Achieving Disease Control

Surgery

Transsphenoidal surgery is the procedure of choice for the initial management of acromegaly, and craniotomy is very rarely indicated (4, 5, 9–12). Uniform biochemical and local anatomic outcome criteria should be applied in determining success for all acromegaly treatments. Complete microadenoma resection and maximal removal of locally impinging tumor and hyperfunctioning macroadenomas are desired anatomic outcomes. Reoperation for surgically accessible residual or recurrent tumor remnants visualized by magnetic resonance imaging (MRI) should be considered in patients who fail to achieve surgical remission as defined by rigorous biochemical criteria. Somatostatin receptor ligand (SRL) pretreatment of patients destined for surgery may be useful in patients with serious medical complications of acromegaly (13), but no data are available on influencing surgical outcomes.

Technical surgical adjuncts such as endoscopy, neuronavigation, intraoperative hormone assays, and intraoperative MRI may improve operative outcome, patient satisfaction, and complication rates, but definitive data on the impact of these procedures on surgical outcomes are not yet available.

Early GH assessment after surgery is useful, and oral glucose tolerance testing and IGF-I assessment should be performed within 2–4 months after surgery and interpreted according to established criteria for defining disease control (8, 14). The results of pituitary surgery are optimal when performed in specialized centers encompassing a team approach to therapy, including expertise in endocrinology, neurosurgery, and pathology. Individual surgical expertise is a major determinant of surgical outcomes and may be defined as a record of peer-reviewed publication of surgical results encompassing both endocrine and surgical evaluation and follow-up; training experience of more than 100 pituitary surgery cases, and annual surgical activity of more than 25 cases/surgeon. Specialized pituitary pathology is desirable, and immunostaining is mandatory for rigorous evaluation of surgical results.

Medical

GH-secreting adenomas express somatostatin receptor forms; the SSTR2 receptor subtype appears to be a particularly important mediator for signals suppressing GH secretion (15). SRLs, administered by sc or im injection, effectively control GH axis biochemical parameters in 50–70% of patients (16–18) and provide sustained hormone suppression and alleviation of soft tissue manifestations of acromegaly as long as drug administration is continued (19). SRLs are recommended as the mainstay of medical therapy. Oral dopa-

Abbreviations: MRI, Magnetic resonance imaging; SRL, somatostatin receptor ligand.

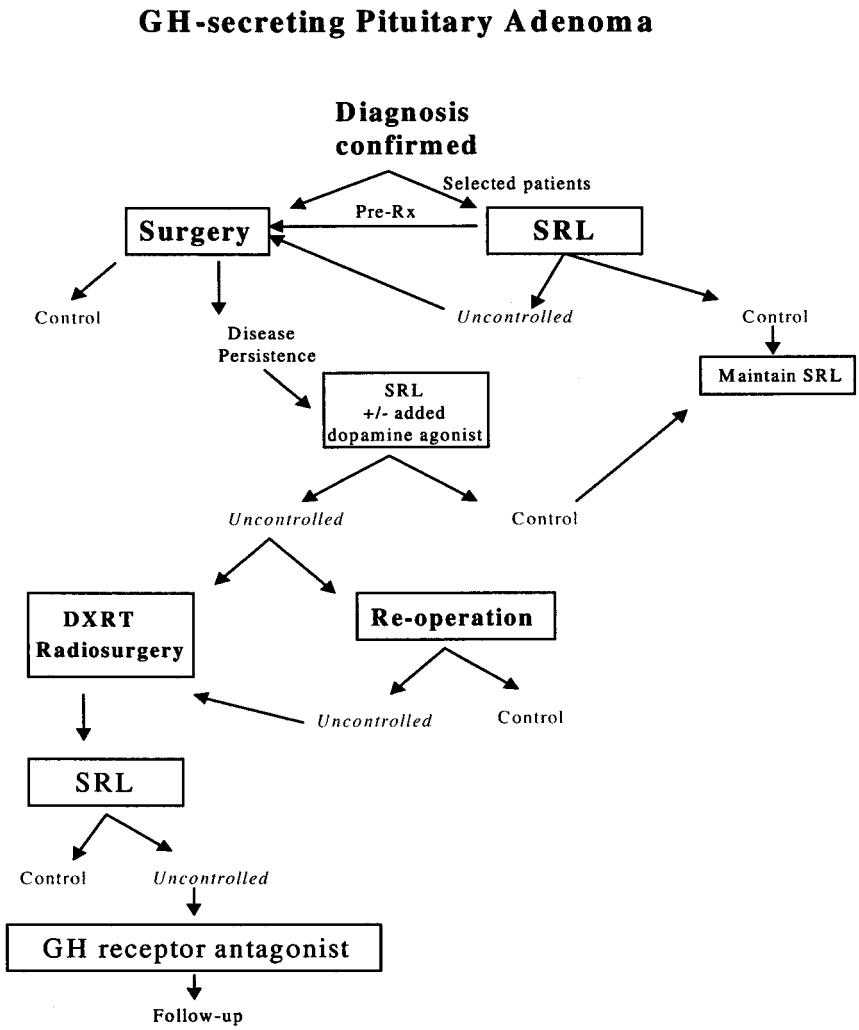

FIG. 1. Control implies GH less than 1 ng/ml after an oral glucose load and normalized age- and gender-matched IGF-I levels. DXRT, Radiation therapy.

mine agonists are only effective in about 10% of patients, and in selected patients with coexistent hyperprolactinemia, dopamine agonists may be a preferable therapeutic choice, whereas combined use of SRL and dopamine agonist therapy may improve therapeutic efficacy (20). Long-acting depot SRL preparations and longer acting dopaminergic agents are preferred over the short-acting agents (21–24).

The GH receptor antagonist (25) represents a novel approach for the treatment of acromegaly, particularly in somatostatin analog-resistant patients (26). Although the drug is investigational, and its long-term safety profile remains to be established, it will be especially useful for patients with persistently elevated IGF-I levels.

Radiotherapy

Radiotherapy administered by conventional means (~45–50 Gy total dose) is associated with relatively few adverse events other than hypopituitarism. Administered in fractionated doses not exceeding 1.75 Gy/session, radiotherapy can be considered for nonresectable or residual pituitary disease, medical therapy failure, and/or patient refusal of other modalities. GH and IGF-I levels decrease slowly after fractionated conventional radiotherapy (27, 28), and the most rapid GH decrease occurs in the first 2 yr. Medical therapy, usually with SRLs, is often required to bridge the latency period before the onset of radiation effectiveness. Tumor regrowth after radiotherapy is rarely encountered, but the time course of tumor shrinkage is variable. Radiation therapy choices should be carefully evaluated with an informed team approach, including the patient, endocrinologist, experienced radiation oncologist, and neurosurgeon.

Several forms of radiation therapy are available, including use of the linear accelerator, gamma knife and proton beam, and their efficacy has been enhanced by the availability of stereotactic techniques achieved by computerized imaging and stereotactic technologies to maximize targeting, minimize radiation field scatter, reduce treatment times, and shorten latency to onset of effects (29–31). Most available data rely on therapy administered a decade or more ago, when criteria for control were not well established, and older technologies were in use. Therefore, it is anticipated that data will become available to ascertain whether advantages provided by the stereotactic approach achieve or improve efficacy and safety. Overall, radiotherapy modalities are viewed as adjunctive therapies to primary surgical and medical interventions (29–31).

Control of Mass Effects

The expanding pituitary mass may impinge on vital central structures, and alleviation of these effects is an important goal of disease management. Improved standardization for tumor volume assessment is recommended, including the use of three-dimensional tumor analysis and accurate measurement of tumor diameter and distance from critical structures (32). Surgery is immediately effective in debulking tumor mass, and particularly relieves pressure on visual tracts and improves headache. Pretreatment with SRLs may be helpful in shrinking tumor size and potentially improving surgical outcomes, but controlled prospective data are required (13). Tumor shrinkage is rarely observed with dopamine agonists, but occurs with SRLs in approximately 50% of patients who experience a moderate (<50%) decrease in volume, with dramatic shrinkage only in sporadic cases. Shrinkage usually occurs within 3 months of initiating therapy, but some changes are seen even after 1 yr. Doses may be decreased with time, and no evidence of tumor regrowth is apparent if drug treatment is maintained (17). The probability of tumor regrowth occurring if drug treatment is discontinued should be considered, however. Radiotherapy often produces tumor shrinkage, but the very slow onset of action usually requires many years to be manifest. Focused radiotherapy is probably at least as effective as standard techniques and is possibly more rapid in onset, but more data are required.

Relative benefits of treatments for determining disease complications and mortality

Reductions in GH and IGF-I levels are valuable and accurate markers for improvement of the comorbidity associated with acromegaly. Successful surgical adenoma resection significantly and promptly results in mass reduction. Surgery is also of value in debulking selected invasive or large tumors even if they are not completely resectable. Medical therapy may be offered to patients before surgery in an attempt to reduce tumor bulk and lower GH levels, with a comprehensive discussion outlining potential risks *vs.* benefits of each treatment approach. Clinical judgment should be used as to whether medical therapy should be continued or surgical intervention recommended after evaluation of initial responses to primary SRL treatment. It is recommended that GH and IGF-I assessment be undertaken 2–3 months after medical therapy to establish dose adequacy. Medical therapy has the advantage of not inducing hypopituitarism, and selective long-term sustained GH suppression portends a favorable mortality outcome. However, the potential benefits of preoperative medical therapy in enhancing surgical outcomes are as yet unknown. MRIs should be performed within 6–9 months after surgery, and after initiating medical treatment, MRI should be performed after biochemical parameters have been stabilized.

Comorbidities of acromegaly should be evaluated and treated during and after specific therapy within the clinical context. Aggressive management of cardiovascular disorders, especially hypertension, arrhythmias, and cardiac failure, should be ongoing. Sleep studies should be undertaken in patients with documented respiratory disorders. In patients with sleep apnea, respiratory function should be monitored during and after therapy initiation. Colonoscopy should be performed every 3–5 yr depending upon clinical indications, including family history and previous polyp detection. The presence of other serious comorbidities should be diagnosed and aggressively treated, especially diabetes, arthritis, renal disease, and mandibular dysfunction.

Limitations of Treatment Modes

Surgery

In experienced hands, surgery is not life-threatening, and cumulative major complications, including mortality, visual impairment, and meningitis, occur in less than 2% of patients. Cerebrospinal fluid leak, permanent anterior lobe deficits, diabetes insipidus, and local nasal complications occur in approximately 5% of patients. In inexperienced surgical hands, 3- to 4-fold higher complication rates are encountered (32, 33). Relative contraindications to surgery include patient frailty and physical illness, and comorbidity of acromegaly. Medical pretreatment can be offered to patients with cardiomyopathy, cerebrovascular disease, and/or airway obstruction before undertaking surgery.

Medical

When initiating dopamine agonist therapy, patients should be instructed to start with low, albeit less efficacious, doses of dopamine agonists, because of gastrointestinal side-effects. SRLs are associated with transient gastrointestinal disturbances and the development of asymptomatic gallstones of limited clinical significance primarily during the first 2 yr of therapy. Ultrasound evaluation before treatment initiation is not routinely recommended. However, a commitment to open-ended, long-term SRL therapy is required. Limitations of medical treatment include severe drug intolerance and ongoing drug cost. To date, no serious side-effects of SRLs or dopamine agonists have been encountered that would limit their use (24).

Radiotherapy

In more than 60% of patients, hypopituitarism develops within 5–10 yr. Rarely encountered, but serious, complications occur, including optic neuropathy, temporal lobe radiation injury, and secondary extrapituitary neoplasms, especially in patients with cerebrovascular or organic brain disease (34, 35). The potential neuropsychological effects of radiation and incidence of secondary tumor development require further study. Disadvantages of radiation include the slow rate of GH attenuation (36) and the potential for optic nerve damage when the adenoma is contiguous with optic tracts.

Summary

Treatment of acromegaly is determined by the availability of local neuroendocrine, imaging, and surgical expertise as well as patient access to costly evaluations and therapeutic choices, which may be unique for regions and countries. Nevertheless, controlled GH suppression should be optimized (37). In deciding on appropriate means to achieve

biochemical control and relieve mass effects, the treating physician team should balance risk and benefits, and treatment contraindications and side-effects for each patient (2, 38). Factors to be considered include disease severity, tumor mass effect on central structures, tumor expression of somatostatin receptor subtypes, and potential for long-term pituitary damage, especially in younger reproductive-aged patients. In patients who have low GH levels and already have irreversible hypopituitarism, radiation therapy may be preferred because there is no further risk for this complication, although tumor resection often relieves compressive hypopituitarism.

The depicted flowsheet recommends surgery as the first line therapy followed by medical therapy should surgery not be curative. In selected patients with unacceptable anesthetic risk, cardiovascular or pulmonary complications, and macroadenomas not impinging on the optic chiasm, primary SRL therapy may be offered (13, 39). If control is inadequately achieved with maximal doses of SRLs and added dopamine agonists, radiotherapy should be considered or no further action should be proposed, depending on clinical disease activity and degree of biochemical disease persistence. Reoperation or treatment with investigational GH receptor antagonists (25) should be considered for patients resistant to surgical, medical, and radiotherapeutic approaches (26).

In conclusion, considering the potentially serious treatment adverse effects that limit their efficacy, there is consensus that integrated treatment decisions should be made by a team including endocrinologists, surgeons, and radiation therapists. The patient's choice of therapy should be based upon an informed understanding of the potential disadvantages of therapeutic approaches *vs.* their effectiveness in managing this complex metabolic disorder, reducing its comorbidities, and ultimately achieving favorable mortality outcomes.

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