

Guidelines for Acromegaly Management: An Update

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Objective: The Acromegaly Consensus Group reconvened in November 2007 to update guidelines for acromegaly management.

Participants: The meeting participants comprised 68 pituitary specialists, including neurosurgeons and endocrinologists with extensive experience treating patients with acromegaly.

Evidence/Consensus Process: Goals of treatment and the appropriate imaging and biochemical and clinical monitoring of patients with acromegaly were enunciated, based on the available published evidence.

Conclusions: The group developed a consensus on the approach to managing acromegaly including appropriate roles for neurosurgery, medical therapy, and radiation therapy in the management of these patients. (*J Clin Endocrinol Metab* 94: 1509–1517, 2009)

The Acromegaly Consensus Group has produced several consensus documents on various aspects of acromegaly management since 2000 (1–5). In 2002, the group published comprehensive guidelines for acromegaly management (2), and in November 2007 the group reconvened to update these guidelines. The participants in this sixth meeting of the Consensus Group, sponsored by the Pituitary Society and the European Neuroendocrine Association, developed a consensus and provided a new set of recommendations on acromegaly management that reflect the current knowledge in 2007.

Recommendations were graded, based on the GRADE system (6, 7), depending on the quality of evidence as very low quality (VLQ) expert opinion with one or a small number of uncontrolled studies in support, low quality (LQ) large series of uncontrolled studies, moderate quality (MQ) one or a small num-

ber of large uncontrolled studies or meta-analyses, or high quality (HQ) controlled studies or large series of large uncontrolled studies with sufficiently long follow-up. Recommendations were classed as discretionary recommendations (DR) if based on VLQ or LQ evidence and as strong recommendations (SR) if based on MQ and HQ evidence.

Clinical Background

Although the pituitary tumors associated with acromegaly are nearly always benign, the elevated GH and IGF-I levels lead to a wide range of cardiovascular, respiratory, endocrine, and metabolic morbidities (8, 9). These can range in severity from subtle signs of acral overgrowth or soft-tissue swelling to diabetes and

cardiac failure. Symptoms from an expanding tumor, such as visual-field defects and headache, might accompany the clinical presentation of acromegaly.

In a recent meta-analysis, the weighted mean of the standardized mortality ratio (SMR) from 16 published studies of patients with acromegaly was 1.72 [95% confidence interval (CI), 1.62–1.83] (10) MQ. A meta-regression analysis demonstrated improved survival in more recent studies, presumably due to modern treatment modalities (including transsphenoidal surgery) and more strictly defined cure criteria, but even in recent studies there was a 32% increased risk for all-cause mortality in patients with acromegaly (10). Patients with random serum GH level below 2.5 ng/ml after treatment, mostly measured by standard RIA, had mortality close to expected levels [SMR, 1.1 (95% CI, 0.9–1.4), compared with a SMR of 1.9 (95% CI, 1.5–2.4) for those with a final GH level > 2.5 ng/ml] (11). Similarly, a normal serum IGF-I level for age and sex at last follow-up after treatment was associated with an SMR of 1.1 (95% CI, 0.9–1.4) compared with an SMR of 2.5 (95% CI, 1.6–4.0) for those with elevated IGF-I levels (11) MQ. There was a significant trend for reduced mortality in series reporting frequent use of somatostatin receptor ligands (SRLs) and in studies reporting high rates (>70%) of biochemical remission after treatment (11). In cases where GH and IGF-I results are divergent, it is important to consider the degree of the biochemical abnormality and the clinical context before initiating further therapy (12–14).

Therapies for acromegaly have the aim of reducing or controlling tumor growth, inhibiting GH hypersecretion, and normalizing IGF-I levels. The three approaches to therapy are surgery, medical management, and radiotherapy. Each treatment modality has specific advantages and disadvantages, but the optimal use of these treatments should result in a reduction in mortality in the acromegaly patient population compared to that of the general population. However, conventional fractionated radiotherapy may be associated with increased mortality (13, 15) LQ.

The goal of the Acromegaly Consensus Group meetings is to ensure that patients with acromegaly receive optimal treatment by creating a common understanding of best practice among endocrinologists, neurosurgeons, and radiotherapists. This manuscript presents the consensus on the optimal use of management modalities in patients with acromegaly.

The Role of Neurosurgery

Complete surgical removal of GH-secreting tumors results in hormonal control of acromegaly and improvement of soft tissue changes.

Transsphenoidal surgery is the treatment of choice for intrasellar microadenomas, noninvasive macroadenomas (*i.e.* those without cavernous sinus or bone invasion), and when the tumor is causing compression symptoms. In patients with intrasellar microadenomas, surgical removal provides biochemical control with normalization of IGF-I in 75–95% of patients (16–21) HQ. Control rates are lower in patients with noninvasive macroadenomas, but even in these cases surgical removal provides bio-

chemical control with normalization of IGF-I in 40–68% of patients (16–21). The exact influence of tumor size on surgical outcome is still uncertain. However, as a preliminary guideline, a tumor at least 2 cm in diameter is associated with a greatly reduced success rate (20) HQ. Craniotomy is very rarely indicated in patients with acromegaly.

Expertise in surgical management of acromegaly is very important—the control rates outlined above can only be achieved when surgery is performed by a dedicated and experienced pituitary neurosurgeon conducting at least 50 pituitary operations per year (22–24). Lower control rates in some published papers almost certainly reflect the level of experience of the surgeon(s) involved. In addition, a skilled multimodality team, either in a multidisciplinary center or via a network or virtual team, is required for optimal surgical results. Such a team should include the experienced surgeon using advanced surgical techniques, an endocrinologist with pituitary expertise, and a physician with radiotherapy expertise.

Newer surgical adjuncts such as computerized navigation, endoscopy, and intraoperative magnetic resonance imaging (MRI) may be used with (or instead of) standard equipment, but such decisions depend on the preference of the surgeon. The current evidence on the use of newer endoscopic surgical techniques is promising but limited; more research is needed (25).

In experienced hands, complications of transsphenoidal surgery in acromegaly are rare, including transient oculomotor palsies, deterioration of vision, carotid artery injury, and epistaxis (occurring in less than 1% of patients) (17, 18), and therefore safety can only be marginally improved with new surgical developments (17, 18, 26).

Contraindications to surgery include patient refusal, severe cardiomyopathy or respiratory disease, or the lack of an available skilled surgeon.

Presurgical treatment

In many studies, the effects of presurgical treatment with a SRL on surgical outcome and postoperative complications have been assessed (27–30). Some authors have concluded that pretreatment with a SRL can improve normalization of GH and IGF-I after surgery and shorten the duration of hospitalization (27), whereas others have found no benefits to SRL pretreatment (28) VLQ. Medical treatment before surgery is certainly not contraindicated, but there is currently insufficient evidence to recommend it for improved surgical outcome or postoperative complications (31).

Tumors unlikely to be controlled by surgery

Although transsphenoidal surgery is the treatment of choice for most microadenomas and some macroadenomas, approximately 40–60% of macroadenomas are unlikely to be controlled with surgery alone (for example, tumors with cavernous sinus invasion lateral to the carotid artery or those with transcapsular intraarachnoid invasion). Options for such tumors are discussed in subsequent sections of this document and include primary medical therapy or primary surgical debulking followed by medical therapy for hormonal control and/or radiation therapy for treatment of residual tumor. Recent studies suggest that surgical

debulking may increase the proportion of patients that subsequently achieves GH control and normalized IGF-I with SRL therapy, especially when more than 75% of the tumor is removed (32–34) LQ.

Ongoing challenges

The success of neurosurgery is dependent upon the availability of skilled and experienced surgeons and multimodality teams. However, the availability of the appropriate personnel is variable even in large cities, and in most countries there is an absence of regional networks to guide referral to expert centers.

Tumor staging classification systems have been proposed [for example, Hardy *et al.* (35)], but these are not in widespread use. A modified classification system for defining adenoma size and invasiveness is needed and may increase the use of such systems. This would provide standardized recommendations on identifying which adenomas are suitable targets for surgical removal.

As with all treatment modalities discussed in this statement, there is a need for cost-effectiveness analyses of surgery and of the relative cost-benefit ratio of pretreatment with an SRL or surgical debulking before using other treatment modalities. Specific cost-effectiveness studies may resolve these issues.

The Role of Medical Therapy

Currently, there are three drug classes available for the treatment of acromegaly: dopamine agonists (DAs), SRLs, and a GH receptor antagonist (GHRA). For women who become pregnant while on medical therapy, cessation of medical therapy during pregnancy is usually advised, primarily based on the lack of a large database demonstrating the safety of such use.

Somatostatin receptor ligands

The SRLs signal predominantly via somatostatin receptor subtypes 2 and 5 (36), leading to a decrease in adenoma GH secretion.

The use of SRLs is most appropriate:

- As first-line therapy when there is a low probability of a surgical cure (for example, large extrasellar tumors with no evidence of central compressive effects) (37–41) DR.
- After surgery has failed to achieve biochemical control SR.
- Before surgery to improve severe comorbidities that prevent or could complicate immediate surgery (the benefits of this are unproven) (42) DR.
- To provide disease control, or partial control, in the time between administration of radiation therapy and the onset of maximum benefit attained from radiation therapy (radiation therapy can take several years to produce disease control—see below) SR.

SRLs are effective in controlling GH/IGF-I hypersecretion and in reducing tumor size. Long-term studies indicate that approximately 70% of patients receiving SRLs have GH levels below 2.5 ng/ml and normalized IGF-I, and maximal benefit may be achieved after 10 yr of therapy (37, 43) MQ. However, these studies often include patients preselected for GH responsivity. In

unselected populations, SRLs reduce GH to less than 2.5 ng/ml and normalize IGF-I in 44 and 34% of patients, respectively (38). Tumor shrinkage of more than 20% occurs in approximately 75% of acromegaly patients receiving these drugs (mean 50% reduction in tumor volume) (39, 44).

These peptide analogs have a proven safety record. Common side effects include abdominal bloating and cramping, with a reduction over the first few months of treatment. Multiple small gallstones and gallbladder sludge commonly occur, but they rarely cause cholecystitis. There have been a small number of cases who have developed pancreatitis with the use of SRLs—a finding that seems paradoxical because of the benefits seen in other settings when these drugs are used to treat pancreatitis.

In well-designed trials, the long-acting formulations of the two SRLs currently available [octreotide LAR and lanreotide Autogel (or Somatuline depot in the United States)] appear to be equivalent in the control of symptoms and biochemical markers in patients with acromegaly (45).

Patients should remain on the same dose for 3 months (assuming the patient tolerates the medication) to properly assess adequacy of treatment and the need for dose titration.

GH receptor antagonist

There is currently a single GHRA available, pegvisomant, for the treatment of acromegaly. The indications for its use are:

- In patients that have persistently elevated IGF-I levels despite maximal therapy with other treatment modalities SR.
- Possibly as monotherapy or in combination with a SRL in other patients DR. However, more data are required before firm guidelines can be given on this.

Pegvisomant is highly effective in acromegaly and significantly improves the quality of life (QoL) in patients that require both SRLs and pegvisomant to achieve biochemical control (46) MQ. Safety issues with GHRA include liver function abnormalities and tumor growth. Tumor growth is infrequent (<2%) (47), and approximately 25% of patients have liver function abnormalities, but these appear to be transient in most patients without changing the GHRA dose (48, 49). Whether the tumor growth is due to the GHRA or merely reflects ongoing tumor growth when there is no therapy directed specifically at the tumor has not been established definitively.

Combination therapy with a SRL and GHRA

Recent publications suggest that GHRA may be useful in combination therapy with a SRL (50–52), but there are no direct comparisons between combination therapy and monotherapy with GHRA. The combination of a SRL and a GHRA may be useful for patients with acromegaly that is resistant to other treatment modalities, for patients who have not achieved biochemical control after surgery, or to improve cost-effectiveness in patients that would otherwise require high-dose GHRA monotherapy.

Dopamine agonist

Of the two DAs, bromocriptine and cabergoline, only cabergoline has any efficacy in acromegaly, and this is limited—mono-

therapy is effective in less than 10% of patients (53–56) VLQ. Clinical situations in which cabergoline may be useful include:

- When the patient prefers oral medication (DAs are the only oral medication available for acromegaly) DR.
- After surgery (very occasionally as first-line therapy) in selected patients, such as those with markedly elevated prolactin and/or modestly elevated GH and IGF-I levels DR.
- As additive therapy to SRL therapy in patients partially responsive to a maximum SRL dose DR—approximately 50% of such patients may achieve control of GH and IGF-I levels with combination therapy LQ (57–62).

There is evidence that in patients with Parkinson's disease, high doses of cabergoline (higher than doses used for the treatment of pituitary tumors), and a prolonged duration of therapy, are associated with the development of cardiac valvular abnormalities. Valvular disease has not been found in patients receiving the conventional doses used for pituitary tumors (63, 64). It would be prudent, however, to monitor patients receiving higher than conventional doses of cabergoline for prolonged periods of time by performing echocardiography.

Control of comorbidities via biochemical control of acromegaly

In addition to medical therapy for GH/IGF-I hypersecretion, treatment of comorbidities has an important impact on QoL and mortality. A number of comorbidities are present in patients with acromegaly, including arthropathy, hypertension, obstructive sleep apnea (OSA), diabetes, cardiomyopathy, colon polyps, goiter, and headache (9, 65). Successful treatment of GH/IGF-I hypersecretion will control these comorbidities to varying degrees, but some may persist in patients even after biochemical control of acromegaly (and some comorbidities may improve even if biochemical control is not achieved) (66). All comorbidities should be actively diagnosed and treated, irrespective of GH and IGF-I control.

Ongoing challenges

There are certain areas where more data are needed on the use of medical therapies in acromegaly. Firstly, there are no head-to-head studies of the different SRLs of adequate design and power to recommend one drug over the other. Secondly, data on the potential use of GHRA as a first-line treatment or in combination with SRLs are needed. And thirdly, the relative cost-effectiveness of all medical therapies as monotherapy, or in the various combination options discussed above, requires evaluation.

The Role of Radiation Therapy

When radiation therapy for acromegaly is being considered, it should be conducted by an experienced pituitary radiotherapist in a specialized center. Radiation therapy should generally be reserved for third-line treatment, occasionally as second-line treatment, but rarely as first-line treatment. Patients who do not have tumor growth control or normalization of hormone levels

with surgery (for example, after debulking of a nonresectable tumor) and/or medical therapy are possible candidates for radiation therapy. Radiation therapy may be useful in patients receiving GHRA (who have failed other medical therapies) and are at risk of tumor expansion. Some endocrinologists may consider radiotherapy in patients controlled on drug therapy to allow for potential termination of such therapy, which would otherwise be lifelong.

Conventional radiotherapy (conformal fractionated radiotherapy) can lower GH levels and normalize IGF-I in over 60% of patients, but maximum response is achieved 10–15 yr after radiotherapy is administered (67–69) HQ. Medical therapy with a SRL is usually required during this latency period. An alternative to conventional radiotherapy is single-dose, focused radiotherapy such as that achieved with the Gamma Knife or Linear Accelerator. Five-year remission rates with gamma knife radiotherapy in patients with acromegaly (after surgical debulking) range from 29 to 60% (70–73) MQ. However, studies of gamma knife radiotherapy suffer from selection bias because only patients with a smaller tumor size are included. No long-term data are currently available for the use of gamma knife radiotherapy in acromegaly.

If radiation therapy is deemed necessary, the choice of technique is dependent upon the tumor characteristics: conventional radiotherapy is preferred for large tumor remnants or tumors that are too close to optic pathways, whereas stereotactic radiotherapy is preferred when there is a smaller tumor size or when improved patient convenience is desired. Stereotactic radiotherapy may produce beneficial effects on GH and IGF-I sooner than conventional radiotherapy, but this is unproven and may be due to the aforementioned selection bias in trials. At present, there is insufficient evidence to provide definitive recommendations in favor of one particular technique over another.

The main limitation to the use of radiation therapy in acromegaly is safety, especially when other safer treatment modalities exist. Hypopituitarism is observed in over 50% of patients receiving radiation therapy, and after 5–10 yr, the incidence is similar with conventional radiotherapy and stereotactic radiotherapy (68, 71–73). The probability of hypopituitarism appears similar with all types of radiotherapy. However, if hypopituitarism is already present in a patient, this is less of an issue. There is also a small but significant risk of vision defects, especially with focal treatment plans—as many as 5.5% of patients could potentially be affected (68, 70, 71, 74). Conventional radiotherapy may carry a risk of second tumors or cerebrovascular events due to radiation vasculopathy (13–15, 75–77), but long-term data on the risk of these events with stereotactic radiotherapy are not yet available.

Ongoing challenges

Many of the potential safety concerns with radiation therapy for acromegaly remain unresolved. The possible causative link between radiation therapy and cerebrovascular mortality and morbidity is still unclear (77). In addition, although second tumors have been reported (76), data on the effects of newer focused radiation therapy techniques on the development of second tumors are not yet available. The reports of second tumors

may relate to an increased incidence of such tumors in patients with a pituitary tumor, or may be the result of more intensive surveillance.

Long-term complications, particularly neurocognitive defects, of radiation therapy require further evaluation, and especially in young patients, the long-term (>30 yr) effects of radiation therapy are unknown.

It is not possible to provide recommendations on the preferred radiation therapy technique for patients with acromegaly. Studies with more homogeneous patient populations would be required to accurately assess the relative efficacy of conventional radiotherapy *vs.* stereotactic radiotherapy.

Goals of Treatment

Mortality reduction

The appropriate use of modern management modalities reduces mortality from acromegaly to the level in the general population. Thus, normalizing mortality in patients with acromegaly is a key aim of disease management. Based on the fact that basal GH levels above 2.5 ng/ml (15, 78), elevated IGF-I (12, 14, 78), age and disease duration (14, 78), hypertension (78), diabetes, and cardiac disease are the main determinants of mortality HQ, biochemical goals to control mortality are a GH less than 2.5 ng/ml or a normal age and sex-adjusted IGF-I level. Comorbidities that are associated with mortality must also be treated appropriately, and because disease duration determines mortality, early diagnosis of acromegaly and prompt treatment are recommended.

Tumor shrinkage

Control of tumor mass, which may impinge on vital central structures, is an essential goal of acromegaly therapy.

The different treatment modalities have different effects on tumor mass. Surgery achieves immediate and substantial debulking, radiotherapy takes years to reduce tumor mass, therapy with GHRA does not induce tumor shrinkage (and in a small proportion of cases may induce tumor growth), and DAs only reduce tumor mass in approximately 5% of patients, whereas SRLs reduce tumor mass more than 20% (on average approximately 50%) in 75% of patients (37–41, 44) MQ. Tumor shrinkage in patients receiving SRLs is independent of age and initial tumor size. There is, in general, a concordance between biochemical and anatomical response, but tumor shrinkage may occur even in the absence of a biochemical response (79). Increased tumor size has not been reported in patients achieving biochemical control except in patients taking GHRA.

Tumor mass should be monitored with MRI, and the frequency of MRI should be decreased after tumor growth control is established LQ.

Treatment of comorbidities

Hypertension, cardiac dysfunction, diabetes, osteoarthritis, and OSA are the most important comorbidities of acromegaly and can all lead to significant functional disability (80–86). Surgical removal of pituitary tumors and biochemical control of

acromegaly (by any treatment modality) may reverse or halt progression of these comorbidities in some patients, but a significant proportion will need additional management (84, 87–89). Comorbidities should be managed (that is, treatment of abnormal lipid levels, and elevated glucose and blood pressure, especially to prevent stroke and other cardiovascular problems) and response to treatment monitored, as they would be for the general population with these morbidities LQ.

Some studies have shown that SRLs have a suppressive effect on β -cell function (90) and could potentially decrease insulin secretion VLQ. The reduction in GH levels usually achieved with SRL therapy tends to outweigh any effect on β -cell function and leads to an overall improvement in insulin resistance, but if diabetes control worsens while the patient is on therapy, substituting with a GHRA can be considered.

The incidence of premalignant colonic lesions may be increased in acromegaly (83, 91), and therefore, at diagnosis, all patients should have a colonoscopy SR. Subsequent follow-up investigation should be implemented as in the general population. The evidence for a link between an increased risk of colorectal malignancies and uncontrolled acromegaly is controversial.

Monitoring the Patient with Acromegaly

A regular transparent audit of outcomes and complications [combined surgical and endocrinological (hormonal) follow-up] in all centers managing patients with acromegaly is recommended. To aid such audits, the promulgation of a uniform tumor staging classification system (of size and invasiveness)—for example, the system proposed by Hardy (35)—is needed to standardize monitoring of tumor response.

Biochemical markers of response

Both GH and IGF-I should be measured to assess the biochemical response to any medical treatment SR (except when patients are receiving GHRA therapy, in which case only IGF-I should be measured). Measurement of GH during an oral glucose tolerance test (OGTT; measurement of GH and glucose at 0, 30, 60, and 120 min after glucose load) may be preferred to a random GH measurement and should be performed 3–6 months after surgery. Thereafter, IGF-I, a random GH or GH during an OGTT should be measured at follow-up visits SR. OGTT is not helpful in monitoring therapeutic responses while patients are receiving SRL therapy (92, 93).

Studies of patients with acromegaly have used a number of different treatment endpoints to define response, and therefore, different cutoff values for GH and IGF-I have been suggested. However, biochemical control is generally defined as a normal IGF-I for age and gender and a GH less than 1.0 ng/ml during an OGTT. The cutoff value for GH used within each individual center depends upon the reliability of the assay used and the ability of the laboratory to provide normative data with very high sensitivity assays (92). Using sensitive assays, a GH of less than 0.4 ng/ml would be consistent with remission. Retrospective studies measuring GH using RIA (which is no longer routinely

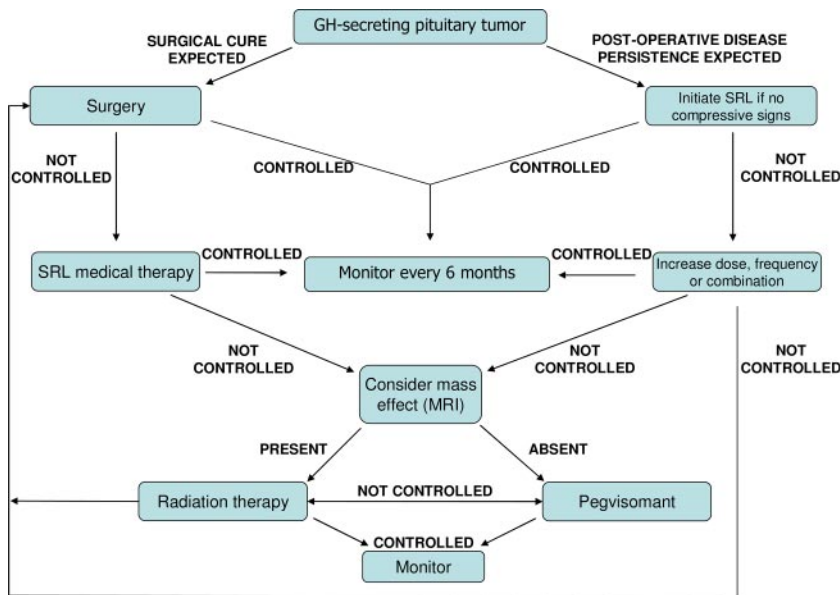


FIG. 1. Summary of management strategy for patients with acromegaly. First level, Surgery SR; SRL DR. Second level, SRL SR; monitor SR; increase dose DR. Third level, MRI DR. Fourth level, Radiation DR; Pegvisomant DR. Fifth level, Monitor SR; back to surgery SR. Control is defined by GH and IGF-I measurements as outlined in the text.

used to measure GH) indicate that a random GH below 2.5 ng/ml is associated with a normal life expectancy (11, 14, 78).

Therapeutic decisions should be made according to individualized biochemical and clinical assessment—if IGF-I and GH are elevated, additional therapy should be considered; if IGF-I and GH measurements are discrepant, clinical judgment should be used.

MRI

Postoperative MRI is recommended 3–4 months after surgery to establish a baseline for future follow-up. Similarly, patients receiving medical therapy should be assessed by MRI 3–6 months after starting therapy DR.

The subsequent timing of MRI in patients with acromegaly, after surgery and during medical therapy, depends on disease control. If the patient is surgically “cured,” then MRI may not be necessary (94); however, this is not clearly established and an alternative may be to reduce the frequency of MRI after 2–3 yr of tumor growth control. In patients receiving SRL therapy, if biochemical control is achieved at 1 yr [when most tumor shrinkage will take place (95)], then MRI can be used according to clinical judgment. If disease is not fully controlled with SRL therapy at 1 yr, MRI should be performed 6 months later, then annually. In patients receiving GHRA therapy, MRI should be conducted 6 months after starting therapy, then once per year (because of the potential risk of tumor enlargement).

An important concern with contrast-enhanced MRI is the emerging evidence of associated nephrogenic systemic fibrosis (caused by the gadolinium contrast dye) in certain clinical settings (96). Therefore, renal function should be evaluated before considering the use of gadolinium with MRI.

Pituitary function

After surgery for acromegaly, pituitary function should be measured to assess restoration/preservation of pituitary function

and adrenal insufficiency or posterior pituitary dysfunction (which occurs in a small percentage of patients after transsphenoidal surgery) (18) SR. On the other hand, preoperative hypopituitarism may resolve after surgery. Follow-up assessment should include full pituitary function assessment 3 months after surgery. If this test gives normal results, there is no need for repeat pituitary function tests. However, after radiation therapy, repeated assessment of pituitary function over the years is needed because hypopituitarism can take 10 or more years to develop (69, 97). In patients receiving medical therapy, pituitary function should be assessed as clinically required.

Echocardiography

In patients with no underlying heart disease, echocardiography could be performed at baseline. In the presence of cardiomyopathy, the patient should be referred to a cardiologist for appropriate management.

Sleep disturbance

OSA is a comorbidity of acromegaly that may occur in 25–60% of patients. Sleep quality and disturbances in patients with acromegaly require detailed assessment and appropriate referral for management.

Colonoscopy

At least one baseline colonoscopy assessment is required in all patients with acromegaly. Patients with colonic polyps should be followed according to the international guidelines for colon cancer (98–100) SR.

Summary

Significant progress has been made in the management of acromegaly in recent years. If managed appropriately by a multimodality team with specific experience in managing pituitary tumors, there is no reason for patients to have reduced life expectancy or frequent morbidity. However, unresolved issues exist: the aim of ensuring that patients are managed by appropriately experienced healthcare professional teams is not yet a reality; little is known about the cost-effectiveness of the various management options for acromegaly; and combining treatments may improve patient morbidity and QoL, but more data are needed.

These consensus recommendations are summarized in Fig. 1, but as with most medical management decisions, treatment needs to be individualized and an experienced team should evaluate risks and benefits for each patient. These updated guidelines are aimed to provide clear advice for achieving optimum management and enhancing the health and QoL of all patients with acromegaly.

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References

- Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S 2000 Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab* 85:526–529
- Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A 2002 Guidelines for acromegaly management. *J Clin Endocrinol Metab* 87:4054–4058
- Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, Ghigo E, Ho K, Jaquet P, Kleinberg D, Lamberts S, Laws E, Lombardi G, Sheppard MC, Thorner M, Vance ML, Wass JA, Giustina A 2005 Consensus statement: medical management of acromegaly. *Eur J Endocrinol* 153:737–740
- Giustina A, Casanueva FF, Cavagnini F, Chanson P, Clemmons D, Frohman LA, Gaillard R, Ho K, Jaquet P, Kleinberg DL, Lamberts SW, Lombardi G, Sheppard M, Strasburger CJ, Vance ML, Wass JA, Melmed S 2003 Diagnosis and treatment of acromegaly complications. *J Endocrinol Invest* 26:1242–1247
- Giustina A, Barkan A, Chanson P, Grossman A, Hoffman A, Ghigo E, Casanueva F, Colao A, Lamberts S, Sheppard M, Melmed S 2008 Guidelines for the treatment of growth hormone excess and growth hormone deficiency in adults. *J Endocrinol Invest* 31:820–838
- Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young Jr WF, Montori VM 2008 Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 93:3266–3281
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ 2008 GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336:924–926
- Melmed S 2006 Medical progress: acromegaly. *N Engl J Med* 355:2558–2573
- Colao A, Ferone D, Marzullo P, Lombardi G 2004 Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 25: 102–152
- Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP 2008 Mortality in acromegaly: a metaanalysis. *J Clin Endocrinol Metab* 93: 61–67
- Holdaway IM, Bolland MJ, Gamble GD 2008 A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol* 159:89–95
- Swearingen B, Barker 2nd FG, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N, Black PM, Zervas NT 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab* 83:3419–3426
- Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS 2004 Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. *J Clin Endocrinol Metab* 89:1613–1617
- Biermasz NR, Dekker FW, Pereira AM, van Thiel SW, Schutte PJ, van Dulken H, Romijn JA, Roelfsema F 2004 Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. *J Clin Endocrinol Metab* 89:2789–2796
- Kauppinen-Makelin R, Sane T, Reunanen A, Valimäki MJ, Niskanen L, Markkanen H, Lyytyniemi E, Ebeling T, Jaatinen P, Laine H, Nuutila P, Salmela P, Salmi J, Stenman UH, Viikari J, Voutilainen E 2005 A nationwide survey of mortality in acromegaly. *J Clin Endocrinol Metab* 90:4081–4086
- De P, Rees DA, Davies N, John R, Neal J, Mills RG, Vafidis J, Davies JS, Scanlon MF 2003 Transsphenoidal surgery for acromegaly in Wales: results based on stringent criteria of remission. *J Clin Endocrinol Metab* 88:3567–3572
- Ludecke DK, Abe T 2006 Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1,000 operations. *Neuroendocrinology* 83:230–239
- Nomikos P, Buchfelder M, Fahlbusch R 2005 The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical ‘cure’. *Eur J Endocrinol* 152:379–387
- Kaltsas GA, Isidori AM, Florakis D, Trainer PJ, Camacho-Hubner C, Afshar F, Sabin I, Jenkins JP, Chew SL, Monson JP, Besser GM, Grossman AB 2001 Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in assessing postoperative disease activity. *J Clin Endocrinol Metab* 86:1645–1652
- Shimon I, Cohen ZR, Ram Z, Hadani M 2001 Transsphenoidal surgery for acromegaly: endocrinological follow-up of 98 patients. *Neurosurgery* 48: 1239–1243; discussion 1244–1245
- Beauregard C, Truong U, Hardy J, Serri O 2003 Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. *Clin Endocrinol (Oxf)* 58:86–91
- Ahmed E, Stratton P, Adams W 1999 Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. *Clin Endocrinol (Oxf)* 50:561–567
- Gittes NJ, Sheppard MC, Johnson AP, Stewart PM 1999 Outcome of surgery for acromegaly—the experience of a dedicated pituitary surgeon. *QJM* 92:741–745
- Bates PR, Carson MN, Trainer PJ, Wass JA 2008 Wide variation in surgical outcomes for acromegaly in the UK. *Clin Endocrinol (Oxf)* 68:136–142
- Frank G, Pasquini E 2006 Endoscopic cavernous sinus surgery with special reference to pituitary adenomas. In: Laws ER, Sheehan JP, eds. *Pituitary surgery—a modern approach*. Basel, Switzerland: Karger; 64–82
- Abbassioun K, Amirjamshidi M, Mehrazin A, Khalatbary I, Keynama M, Bokai H, Abdollahi M 2006 A prospective analysis of 151 cases of patients with acromegaly operated by one neurosurgeon: a follow-up of more than 23 years. *Surg Neurol* 66:26–31; discussion, 31
- Colao A, Ferone D, Cappabianca P, del Basso De Caro ML, Marzullo P, Monticelli A, Alfieri A, Merola B, Cali A, de Divitiis E, Lombardi G 1997 Effect of octreotide pretreatment on surgical outcome in acromegaly. *J Clin Endocrinol Metab* 82:3308–3314
- Losa M, Mortini P, Urbaz L, Ribotto P, Castrignano T, Giovanelli M 2006 Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates. *J Neurosurg* 104:899–906
- Plockinger U, Quabbe HJ 2005 Presurgical octreotide treatment in acromegaly: no improvement of final growth hormone (GH) concentration and pituitary function. A long-term case-control study. *Acta Neurochir (Wien)* 147: 485–493; discussion, 493
- Abe T, Ludecke DK 2001 Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. *Eur J Endocrinol* 145:137–145

31. Ben-Shlomo A, Melmed S 2003 Clinical review 154: the role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab* 88:963–968
32. Petrossians P, Borges-Martins L, Espinoza C, Daly A, Betea D, Valdes-Socin H, Stevenaert A, Chanson P, Beckers A 2005 Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs. *Eur J Endocrinol* 152:61–66
33. Colao A, Attanasio R, Pivonello R, Cappabianca P, Cavallo LM, Lasio G, Lodrini A, Lombardi G, Cozzi R 2006 Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 91:85–92
34. Karavitaki N, Turner HE, Adams CB, Cudlip S, Byrne JV, Fazal-Sanderson V, Rowlers S, Trainer PJ, Wass JA 2008 Surgical debulking of pituitary macroadenomas causing acromegaly improves control by lanreotide. *Clin Endocrinol (Oxf)* 68:970–975
35. Hardy J 1973 Transsphenoidal surgery of hypersecreting pituitary tumors. In: Kohler PO, Ross GT, eds. *Diagnosis and treatment of pituitary tumors*. Amsterdam: Excerpta Medica; 179–198
36. Shimon I, Yan X, Taylor JE, Weiss MH, Culler MD, Melmed S 1997 Somatostatin receptor (SSTR) subtype-selective analogues differentially suppress in vitro growth hormone and prolactin in human pituitary adenomas. Novel potential therapy for functional pituitary tumors. *J Clin Invest* 100:2386–2392
37. Maiza JC, Vezzosi D, Matta M, Donadille F, Loubes-Lacroix F, Cournot M, Bennet A, Caron P 2007 Long-term (up to 18 years) effects on GH/IGF-1 hypersecretion and tumour size of primary somatostatin analogue (SSTa) therapy in patients with GH-secreting pituitary adenoma responsive to SSTa. *Clin Endocrinol (Oxf)* 67:282–289
38. Mercado M, Borges F, Bouterfa H, Chang TC, Chervin A, Farrall AJ, Patocs A, Petersenn S, Podoba J, Safari M, Wardlaw J 2007 A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. *Clin Endocrinol (Oxf)* 66:859–868
39. Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A 2005 A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. *J Clin Endocrinol Metab* 90:4405–4410
40. Cozzi R, Montini M, Attanasio R, Albizzi M, Lasio G, Lodrini S, Doneda P, Cortesi L, Pagani G 2006 Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. *J Clin Endocrinol Metab* 91:1397–1403
41. Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F, Caranci F, Cirillo S, Lombardi G 2006 Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. *J Clin Endocrinol Metab* 91:2112–2118
42. Carlsen SM, Lund-Johansen M, Schreiner T, Aanderud S, Johannesen O, Svartberg J, Cooper JG, Hald JK, Fougner SL, Bollerslev J 2008 Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *J Clin Endocrinol Metab* 93:2984–2990
43. Caron P, Bex M, Cullen DR, Feldt-Rasmussen U, Pico Alfonso AM, Pynka S, Racz K, Schopohl J, Tabarin A, Valimaki MJ 2004 One-year follow-up of patients with acromegaly treated with fixed or titrated doses of lanreotide Autogel. *Clin Endocrinol (Oxf)* 60:734–740
44. Bevan JS 2005 Clinical review: the antitumoral effects of somatostatin analog therapy in acromegaly. *J Clin Endocrinol Metab* 90:1856–1863
45. Murray RD, Melmed S 2008 A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. *J Clin Endocrinol Metab* 93:2957–2968
46. Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, Webb SM, van der Lely AJ 2008 Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. *J Clin Endocrinol Metab* 93:3853–3859
47. Frohman LA, Bonert V 2007 Pituitary tumor enlargement in two patients with acromegaly during pegvisomant therapy. *Pituitary* 10:283–289
48. Parkinson C, Burman P, Messig M, Trainer PJ 2007 Gender, body weight, disease activity, and previous radiotherapy influence the response to pegvisomant. *J Clin Endocrinol Metab* 92:190–195
49. Schreiber I, Buchfelder M, Droste M, Forssmann K, Mann K, Saller B, Strasburger CJ 2007 Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. *Eur J Endocrinol* 156:75–82
50. Neggers SJ, van Aken MO, Janssen JA, Feelders RA, de Herder WW, van der Lely AJ 2007 Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. *J Clin Endocrinol Metab* 92:4598–4601
51. Feenstra J, de Herder WW, ten Have SM, van den Beld AW, Feelders RA, Janssen JA, van der Lely AJ 2005 Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. *Lancet* 365:1644–1646
52. Jorgensen JO, Feldt-Rasmussen U, Frystyk J, Chen JW, Kristensen LO, Hagen C, Orskov H 2005 Cotreatment of acromegaly with a somatostatin analog and a growth hormone receptor antagonist. *J Clin Endocrinol Metab* 90:5627–5631
53. Bevan JS, Webster J, Burke CW, Scanlon MF 1992 Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev* 13:220–240
54. Colao A, Ferone D, Marzullo P, Di Sarno A, Cerbone G, Sarnacchiaro F, Cirillo S, Merola B, Lombardi G 1997 Effect of different dopaminergic agents in the treatment of acromegaly. *J Clin Endocrinol Metab* 82:518–523
55. Abs R, Verhelst J, Maiter D, Van Acker K, Nobels F, Coolens JL, Mahler C, Beckers A 1998 Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab* 83:374–378
56. Cozzi R, Attanasio R, Barausse M, Dallabonzana D, Orlandi P, Da Re N, Branca V, Oppizzi G, Gelli D 1998 Cabergoline in acromegaly: a renewed role for dopamine agonist treatment? *Eur J Endocrinol* 139:516–521
57. Wagenaar AH, Harris AG, van der Lely AJ, Lamberts SW 1991 Dynamics of the acute effects of octreotide, bromocriptine and both drugs in combination on growth hormone secretion in acromegaly. *Acta Endocrinol (Copenh)* 125:637–642
58. Sadoul JL, Thyss A, Freychet P 1992 Invasive mixed growth hormone/prolactin secreting pituitary tumour: complete shrinking by octreotide and bromocriptine, and lack of tumour growth relapse 20 months after octreotide withdrawal. *Acta Endocrinol (Copenh)* 126:179–183
59. Cremonini N, Graziano E, Chiarini V, Sforza A, Zampa GA 1992 Atypical McCune-Albright syndrome associated with growth hormone-prolactin pituitary adenoma: natural history, long-term follow-up, and SMS 201–995—bromocriptine combined treatment results. *J Clin Endocrinol Metab* 75:1166–1169
60. Marzullo P, Ferone D, Di Somma C, Pivonello R, Filippella M, Lombardi G, Colao A 1999 Efficacy of combined treatment with lanreotide and cabergoline in selected therapy-resistant acromegalic patients. *Pituitary* 1:115–120
61. Cozzi R, Attanasio R, Lodrini S, Lasio G 2004 Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clin Endocrinol (Oxf)* 61:209–215
62. Selvarajah D, Webster J, Ross R, Newell-Price J 2005 Effectiveness of adding dopamine agonist therapy to long-acting somatostatin analogues in the management of acromegaly. *Eur J Endocrinol* 152:569–574
63. Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, Bax JJ, Pereira AM 2008 Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *J Clin Endocrinol Metab* 93:3348–3356
64. Vallette S, Serri K, Rivera J, Santagata P, Delorme S, Garfield N, Kahtani N, Beauregard H, Aris-jilwan N, Houde G, Serri O 2 2008 Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. *Pituitary* 10.1007/s11102-008-0134-2
65. Webb SM, Badia X 2007 Quality of life in growth hormone deficiency and acromegaly. *Endocrinol Metab Clin North Am* 36:221–232
66. Maison P, Tropeano AI, Macquin-Mavier I, Giustina A, Chanson P 2007 Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. *J Clin Endocrinol Metab* 92:1743–1747
67. Barrande G, Pittino-Lungo M, Coste J, Ponvert D, Bertagna X, Luton JP, Bertherat J 2000 Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. *J Clin Endocrinol Metab* 85:3779–3785
68. Jenkins PJ, Bates P, Carson MN, Stewart PM, Wass JA 2006 Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. *J Clin Endocrinol Metab* 91:1239–1245
69. Minniti G, Jaffrain-Rea ML, Osti M, Esposito V, Santoro A, Solda F, Gargiulo P, Tamburrano G, Enrici RM 2005 The long-term efficacy of conventional radiotherapy in patients with GH-secreting pituitary adenomas. *Clin Endocrinol (Oxf)* 62:210–216
70. Attanasio R, Epaminonda P, Motti E, Giugni E, Ventrella L, Cozzi R, Farabola M, Loli P, Beck-Peccoz P, Arosio M 2003 Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study. *J Clin Endocrinol Metab* 88:3105–3112
71. Castinetti F, Taieb D, Kuhn JM, Chanson P, Tamura M, Jaquet P, Conte-Devolx B, Regis J, Dufour H, Brue T 2005 Outcome of gamma knife radio-

- surgery in 82 patients with acromegaly: correlation with initial hypersecretion. *J Clin Endocrinol Metab* 90:4483–4488
72. Jezkova J, Marek J, Hana V, Krsek M, Weiss V, Vladyka V, Lisak R, Vymazal J, Pecan L 2006 Gamma knife radiosurgery for acromegaly—long-term experience. *Clin Endocrinol (Oxf)* 64:588–595
 73. Pollock BE, Jacob JT, Brown PD, Nippoldt TB 2007 Radiosurgery of growth hormone-producing pituitary adenomas: factors associated with biochemical remission. *J Neurosurg* 106:833–838
 74. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML 2007 Gamma knife surgery for Cushing's disease. *J Neurosurg* 106:980–987
 75. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, Gomez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, de Pablos P, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora J, Albareda M, Gilabert M 2004 Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). *Eur J Endocrinol* 151:439–446
 76. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M 2005 Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab* 90:800–804
 77. Erfurth EM, Hagmar L 2005 Cerebrovascular disease in patients with pituitary tumors. *Trends Endocrinol Metab* 16:334–342
 78. Holdaway IM, Rajasoorya RC, Gamble GD 2004 Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab* 89:667–674
 79. Gola M, Bonadonna S, Mazziotti G, Amato G, Giustina A 2006 Resistance to somatostatin analogs in acromegaly: an evolving concept? *J Endocrinol Invest* 29:86–93
 80. Pereira AM, van Thiel SW, Lindner JR, Roelfsema F, van der Wall EE, Morreau H, Smit JW, Romijn JA, Bax JJ 2004 Increased prevalence of regurgitant valvular heart disease in acromegaly. *J Clin Endocrinol Metab* 89:71–75
 81. Bonadonna S, Mazziotti G, Nuzzo M, Bianchi A, Fusco A, De Marinis L, Giustina A 2005 Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. *J Bone Miner Res* 20:1837–1844
 82. Bogazzi F, Battolla L, Spinelli C, Rossi G, Gavioli S, Di Bello V, Cosci C, Sardella C, Volterrani D, Talini E, Pepe P, Falaschi F, Mariani G, Martino E 2007 Risk factors for development of coronary heart disease in patients with acromegaly: a five-year prospective study. *J Clin Endocrinol Metab* 92:4271–4277
 83. Bogazzi F, Cosci C, Sardella C, Costa A, Manetti L, Gasperi M, Rossi G, Bartalena L, Martino E 2006 Identification of acromegalic patients at risk of developing colonic adenomas. *J Clin Endocrinol Metab* 91:1351–1356
 84. Bex M, Abs R, T'Sjoen G, Mockel J, Velkeniers B, Muermans K, Maiter D 2007 AcroBel the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. *Eur J Endocrinol* 157:399–409
 85. Nemes A, Gavalier H, Csajbok E, Julesz J, Forster T, Csanady M 2008 Aortic stiffness is increased in acromegaly—a transthoracic echocardiographic study. *Int J Cardiol* 124:121–123
 86. Coculescu M, Niculescu D, Lichiardopol R, Purice M 2007 Insulin resistance and insulin secretion in non-diabetic acromegalic patients. *Exp Clin Endocrinol Diabetes* 115:308–316
 87. Ronchi CL, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A, Giavoli C, Ferrante E, Lania A, Spada A, Arosio M 2006 Comparison between six-year therapy with long-acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. *J Clin Endocrinol Metab* 91:121–128
 88. Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Della Morte AM, Pivonello R, Salvatore M, Lombardi G 2001 Is the acromegalic cardiomyopathy reversible? Effect of 5-year normalization of growth hormone and insulin-like growth factor I levels on cardiac performance. *J Clin Endocrinol Metab* 86:1551–1557
 89. Tolis G, Angelopoulos NG, Katounda E, Rombopoulos G, Kaltzidou V, Kaltsas D, Protonotariou A, Lytras A 2006 Medical treatment of acromegaly: comorbidities and their reversibility by somatostatin analogs. *Neuroendocrinology* 83:249–257
 90. Strowski MZ, Parmar RM, Blake AD, Schaeffer JM 2000 Somatostatin inhibits insulin and glucagon secretion via two receptors subtypes: an in vitro study of pancreatic islets from somatostatin receptor 2 knockout mice. *Endocrinology* 141:111–117
 91. Matano Y, Okada T, Suzuki A, Yoneda T, Takeda Y, Mabuchi H 2005 Risk of colorectal neoplasm in patients with acromegaly and its relationship with serum growth hormone levels. *Am J Gastroenterol* 100:1154–1160
 92. Arafat AM, Mohlig M, Weickert MO, Perschel FH, Purschwitz J, Spranger J, Strasburger CJ, Schoff C, Pfeiffer AF 2008 Growth hormone response during oral glucose tolerance test: the impact of assay method on the estimation of reference values in patients with acromegaly and in healthy controls, and the role of gender, age, and body mass index. *J Clin Endocrinol Metab* 93:1254–1262
 93. Carmichael JD, Bonert VS, Mirocha JM, Melmed S 2009 The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly. *J Clin Endocrinol Metab* 94:523–527
 94. Zirkzee EJ, Corssmit EP, Biermasz NR, Brouwer PA, Wiggers-De Bruine FT, Kroft LJ, Van Buchem MA, Roelfsema F, Pereira AM, Smit JW, Romijn JA 2004 Pituitary magnetic resonance imaging is not required in the postoperative follow-up of acromegalic patients with long-term biochemical cure after transsphenoidal surgery. *J Clin Endocrinol Metab* 89:4320–4324
 95. Amato G, Mazziotti G, Rotondi M, Iorio S, Doga M, Sorvillo F, Manganella G, Di Salle F, Giustina A, Carella C 2002 Long-term effects of lanreotide SR and octreotide LAR on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. *Clin Endocrinol (Oxf)* 56:65–71
 96. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA 2007 Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am J Roentgenol* 188:586–592
 97. Vik-Mo EO, Oksnes M, Pedersen PH, Wentzel-Larsen T, Rodahl E, Thorsen F, Schreiner T, Aanderud S, Lund-Johansen M 2007 Gamma knife stereotactic radiosurgery for acromegaly. *Eur J Endocrinol* 157:255–263
 98. Sung JJ, Lau JY, Young GP, Sano Y, Chiu HM, Byeon JS, Yeoh KG, Goh KL, Sollano J, Rerknimitr R, Matsuda T, Wu KC, Ng S, Leung SY, Makharia G, Chong VH, Ho KY, Brooks D, Lieberman DA, Chan FK 2008 Asia Pacific consensus recommendations for colorectal cancer screening. *Gut* 57:1166–1176
 99. Van Cutsem EJ, Oliveira J 2008 Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* 19(Suppl 2):ii29–ii30
 100. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ 2008 Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 134:1570–1595