Multidisciplinary Management of Acromegaly: A Consensus

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Abstract

The 13th Acromegaly Consensus Conference was held in November 2019 in Fort Lauderdale, Florida, and comprised acromegaly experts including endocrinologists and neurosurgeons who considered optimal approaches for multidisciplinary acromegaly management. Focused discussions reviewed techniques, results, and side effects of surgery, radiotherapy, and medical therapy, and how advances in technology and novel techniques have changed the way these modalities are used alone or in combination. Effects of treatment on patient outcomes were considered, along with strategies for optimizing and personalizing therapeutic approaches. Expert consensus recommendations emphasize how best to implement available treatment options as part of a multidisciplinary approach at Pituitary Tumor Centers of Excellence.

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Introduction

Acromegaly is a chronic, progressive, and potentially lethal disease caused by a growth hormone (GH)-secreting pituitary adenoma and resultant excess in circulating levels of GH and insulin-like growth factor (IGF)-I (1). Facial and acral changes due to soft tissue overgrowth as well as systemic complications affecting bone and joints (2) and the cardio-respiratory system (3), in association with metabolic and oncologic complications, contribute to an increased clinical burden, leading to decreased quality of life and diminished survival rates (4, 5). Unfortunately, most patients already exhibit features of advanced disease at presentation due to a delay in diagnosis from first symptom onset by up to 8-10 years (6). Treatment of acromegaly is targeted to normalizing biochemical parameters as well as improving well being, controlling signs and symptoms, and reducing excess morbidity and mortality (7, 8). A multimodal therapeutic approach comprising neurosurgery, medical therapy, and radiotherapy is often required to attain these goals (9). Therefore, a multidisciplinary team approach is recommended for effective management of acromegaly and its comorbidities, coordinated by pituitary medicine experts to personalize treatment and follow-up, and optimize outcomes (10).

In November 2019, the Acromegaly Consensus Group convened in Fort Lauderdale, Florida, to provide current consensus on the comprehensive multidisciplinary management of acromegaly. Forty-eight acromegaly experts including endocrinologists and neurosurgeons reviewed the current literature and assessed current treatment choices and prioritization for clinical practice. Discussions focused on treatment outcome goals; results and side effects of neurosurgery, radiotherapy, and medical therapy; and the proposed place of each available treatment option in the guidelines. Updated consensus recommendations on treatment of patients with acromegaly were graded using the Grading of Recommendations Assessment, Development

and Evaluation (GRADE) system (11). Key recommendations are presented in Table 1 and outlined in Figure 1.

Methods

Literature searches were performed by meeting participants to identify new data in English language papers published between January 2014 and October 2019, and indexed in PubMed. Search terms included “acromegaly” and terms associated with each topic, including “biochemical control”, “tumor volume”, “clinical symptoms”, “side effects”, “neurosurgery”, “radiotherapy”, “somatostatin analogue”, “somatostatin receptor ligand”, “pegvisomant”, “morbidity”, “mortality”, “quality of life”, and “guidelines”. After brief plenary overviews on the state of the art for each topic, participants were divided into breakout groups for further analysis of the assigned topics and subsequently reported their conclusions to the whole group.

Consensus recommendations were produced based on speaker presentations, subgroup discussions, and reports. After the meeting, the Scientific Committee graded the evidence supporting the recommendations, and then graded the consensus recommendations on the basis of the quality of evidence (Table 2). Final graded consensus recommendations were approved by all meeting participants.

Targets for Therapeutic Approaches

GH and IGF-I

Excess GH and/or IGF-I lead to systemic comorbidities in patients with acromegaly, requiring effective treatment to decrease disease burden and reduce or normalize excess mortality (HQ) (12). Although consideration of tumor and clinical variables is important for clinical

management, biochemical control is the cornerstone on which succesful treatment is built .Thus, at present, normalization of GH and IGF-1 is still the primary goal of acromegaly treatment and biochemical parameters should be used to evaluate activity of disease (SR).

GH nadir <1 μg/L after an oral glucose tolerance test (OGTT) was initially defined by our Consensus Group as a marker of postsurgical remission (13); subsequently, this recommendation was revised to 0.4 μg/L taking into account use of ultrasensitive GH assays (14). However, GH nadir levels during an OGTT are impacted by factors such as patient age, BMI, sex, and estrogen status (15) (LQ), as well as glucose intolerance and diabetes mellitus or preexisting use of antidiabetic and somatostatin receptor ligand (SRL) therapy (VLQ) (16). Nevertheless, as these cutpoints correlate well with long-term outcomes (17), we recommend that ultrasensitive assays be used for diagnosis, and post-surgical evaluation using the 0.4 μg/L threshold for cut-off (SR).

During follow-up, IGF-I levels reflect clinical activity of disease (MQ) (1). However, wide variability between assays has been reported due to several preanalytical and analytical confounding factors (MQ) (18), and fluctuation of circulating IGF-I levels may be seen, particularly in the early postoperative period or after treatment changes (MQ) (19). It is therefore recommended that the same well-validated IGF-I assay be used throughout patient follow-up (SR). Further, although the absolute cut-off for defining biochemical control is the upper limit of normal (ULN) (SR), values slightly higher than this cut-off (e.g., within 1.2-1.3 × ULN) could be considered as a target of treatment depending on the clinical scenario (20, 21) (DR). Serum GH values can be used to assess control, with the goal of achieving a fasting level <1.0 μg/L. Close follow-up is recommended for patients with discrepant GH and IGF-1 levels observed at 3 months postoperatively; most commonly, patients show controlled GH and elevated IGF-I, but

the opposite may also occur (22, 23). In these cases, we recommend relying on IGF-I values (SR).

Tumor Volume

Tumor growth control, and ideally, decreasing tumor size, are clinically important goals for patients with acromegaly (SR) (4). We recommend to continue evaluating reduction in mass maximal dimension, rather than overall tumor volume, which is not standardized (24) (DR). As the latter is a better measure of response, a consensus on methodology for measuring tumor volume would be welcomed by the physician community.

T2-weighted MRI hypointensity may be helpful for predicting SRL therapy responsiveness (MQ) (25-27), along with adenoma granularity and other histological markers (VLQ) (7), but are not currently validated for guiding treatment. Tumor characteristics, such as the degree of adenoma fibrosis and consistency may be evaluated by texture analysis which is currently restricted to clinical trial settings to evaluate clinical precision.

Clinical Symptoms

As symptoms and comorbidities associated with acromegaly impact quality of life and survival, their prevention and control is a major goal of treatment (SR) (4). We recommend assessing and aggressively managing disease-associated comorbidities (SR). However, symptoms and clinical manifestations can be dissociated from biochemical values (LQ) (28), and specific assessment and clinical monitoring is recommended beyond biochemical parameters (SR).

Clinician-reported instruments such as SAGIT (Signs and symptoms, Associated comorbidities, GH levels, IGF1 levels and Tumour profile) (29) and ACRODAT (Acromegaly Disease Activity Tool) (30) as well as patient-reported outcome assessment measures have been proposed to standardize follow-up over time (VLQ) (31-33), and their use can be considered in therapeutic decision-making (DR).

Neurosurgery

Techniques

Tumor resection via transsphenoidal surgery is the optimal primary treatment in most patients (HQ) (34) (Figure 1). Data supporting use of endoscopic over microscopic approaches remain incomplete and further comparative outcome studies are needed before one approach can be recommended over the other. Currently, the choice of technique depends on neurosurgeon expertise and preference. Craniotomy is very rarely indicated in patients with acromegaly (HQ) (35). Intraoperative MRI and other techniques to aid in intraoperative visualization of tumor remnants remain investigational (LQ) (36, 37).

Results

The primary predictor of the likelihood of achieving surgical remission remains tumor size and invasiveness of surrounding structures, particularly the cavernous sinus (HQ) (38, 39). Knosp grading may be correlated to outcomes (40). Preoperative serum GH level is also an important determinant of surgical remission (41, 42).

In specialized referral centers, remission can be achieved in 80-90% of microadenomas and about 50% to 75% of macroadenomas, although these figures dramatically decrease when

the tumor is invasive or very large (e.g., >4 cm). (HQ) (43, 44). Remission rates are likely lower at less experienced centers

Surgical tumor debulking prior to medical therapy can be considered in appropriate candidates if the patient cannot be surgically cured (MQ), if a substantial amount of the mass can be successfully removed and/or there are symptoms of mass effect (45). Debulking may also be appropriate prior to radiotherapy to decrease target volume (DR).

Serum IGF-I levels to reliably define remission should be assessed at least 3 months postoperatively (HQ) (43, 44). Early indication of remission may be obtained by measuring fasting GH on postoperative day 1 or 2, with lowest levels (<1 µg/L) having the best sensitivity to predict outcomes. However, these data need to be interpreted with caution if patients are treated with preoperative SRL therapy (VLQ) (43).

Expertise in surgical management of acromegaly, together with initial tumor dimension, has a dramatic impact on disease control rates (HQ) (10). A high volume of pituitary operations per individual surgeon per year with monitoring of outcome data is recommended to maintain sufficient surgical expertise (DR) (46).

Preoperative SRL therapy

Randomized studies suggest improvement in postoperative remission after pretreatment with SRL for 3-6 months (MQ). However, data are conflicting and, in many instances, results were not sustained during long-term follow-up (LQ) (47-50). The role of SRL pretreatment in improving anesthetic risk is not clear and current data do not support a general recommendation for preoperative SRL treatment (SR) (51).

Reoperations

Reoperation may be considered in patients with significant residual tumor who have not adequately responded to postoperative SRL or in patients with a potentially resectable residual tumor after an unsuccessful first surgery (LQ) (52). Reoperation, as for primary surgery, should be done in a specialized center and after multidisciplinary evaluation (53) (SR).

Complications

Surgical complications after transsphenoidal surgery are well-recognized, although they occur less commonly with experienced surgeons (46). Post-surgical hypopituitarism can occur in 5-10% of cases and persistent CSF leakage in 2-3%. (54) Other serious complications (e.g., visual deterioration, carotid artery injury, transient oculomotor palsies, and meningitis) are rarely observed (MQ) (55-57). Diabetes insipidus occurs at a rate similar to surgically treated pituitary tumors (10-15%), and is usually transient. The syndrome of inappropriate antidiuretic hormone secretion may occur 5-14 days after surgery and requires vigilance, with frequent monitoring of serum sodium levels and possibly fluid restriction (LQ) (58, 59).

Advanced age, severe cardiomiopathy, and poorly controlled diabetes mellitus are relative contraindications to surgery (VLQ).

Radiotherapy

Techniques

Modern radiotherapy continues to have a place in the treatment algorithm, typically as a third-line option after surgery and optimal medical therapy. There are two indications for radiotherapy: control of tumour growth and/or lowering GH secretion (60) (MQ). The earlier era of

conventional radiotherapy was associated with complications, particularly cerebrovascular disease and secondary tumours, as well as hypopituitarism (9) (MQ). Modern stereotactic radiotherapy techniques are localised accurately in 3-dimensions, and are delivered either as a single fraction or fractionated. The relatively small number of patients undergoing pituitary radiotherapy and the long latency for an observed effect make it difficult to draw definitive conclusions about complication rates. However, single-fraction stereotactic radiosurgery appears to be associated with similar but fewer side effects as compared to fractionated radiotherapy (LQ) (60-65).

Radiation therapy should be administered in specialized centers where patient selection is guided by discussion within a multidisciplinary team, and treatment should be delivered by radiotherapists experienced in treating pituitary disease to both maximize efficacy and prevent long-term complications (SR).

Results

Radiotherapy is reserved for patients that have failed, are unfit for, or declined surgical and/or medical therapy (SR) (Figure 1), and may be considered as second-line treatment in select patients (VLQ). Radiotherapy can control biochemical parameters in more than 60% of patients, and is highly efficacious (>90%) in controlling tumor growth, offering the prospect of stopping high-cost lifelong medical therapy (MQ). However, full response may not be realized until up to 10-15 years after administration (MQ) (60-66). Given the delay in suppressing GH and IGF-I levels, medical therapy is indicated in the intervening years (SR).

Side Effects and Contraindications

Safety is the main limiting factor for use of radiation therapy in acromegaly, especially as safety of other treatment modalities has improved. There are currently no comparative studies of side effects caused by different modalities of radiotherapy. Reduced incidence of non-endocrine complications (i.e., secondary tumors, cerebrovascular disease, optic neuritis, cranial nerve palsy) may be observed with more focused techniques (LQ) (60-65). Hypopituitarism is the most frequent complication, regardless of technique, and increases over time, with rates approaching 25-50% after 5 years (MQ) (67). Routine monitoring of endocrine function should be conducted lifelong (SR).

Medical Therapy

Medical therapy is recommended for patients who do not achieve biochemical control after surgery (SR). Primary medical therapy is reserved for those with contraindication to or who refuse surgery, and may be considered in select patients considered at poor risk for good outcomes and surgical success (DR) (68) (Figure 1).

SRL

Octreotide LAR and lanreotide are used as first-line medical therapy due to their favorable risk/benefit profiles (SR). Thirty to 55% of patients achieve normal IGF-I on long-term treatment with these SRLs (MQ) (68-72) and >20% reduction in tumor size is seen in more than half of treated patients (MQ) (73, 74). Lower baseline IGF-I level and older age are strong predictors of response (MQ) (75-77). Increasing dose and/or dose frequency of octreotide LAR and lanreotide can improve biochemical control rates in patients inadequately controlled on standard doses, but sensitive to SRL therapy (LQ) (78, 79). An oral formulation of octreotide was recently approved

in the United States as long-term maintenance treatment in patients who have responded to and tolerated treatment with octreotide or lanreotide (80). Pasireotide LAR can be effective in normalizing IGF-1 levels in some patients inadequately controlled by octreotide LAR or lanreotide (MQ) (81-83), and may yield a higher rate of tumor shrinkage (LQ) (82).

Side effects of SRL include mainly gallstones and GI symptoms (1). Long-term octreotide LAR and lanreotide generally have an overall neutral effect on glucose metabolism (MQ), although in some patients mild hyperglycemia is observed (84). By contrast, pasireotide LAR causes hyperglycemia in up to 70% of patients, including secondary diabetes in 25-40% of patients (LQ) (85). Candidates for pasireotide LAR should therefore be carefully screened and monitored for glycemic adverse effects (SR). Controlled studies on the best treatment of pasireotide-induced hyperglycemia are not available. Patients not controlled on oral antidiabetic medications, including metformin, could be better managed with glucagon-like peptide-1 receptor agonists rather than insulin (DR) (86).

Cabergoline

Cabergoline, a relatively long acting dopamine agonist, has the advantages of limited cost and oral route of administration compared to SRL. However, its positioning in the therapeutic algorithm is limited by its relatively modest effect on inducing biochemical control, primarily restricted to patients who have mild-GH/IGF-I elevations postoperatively (IGF-I levels <2.5 x ULN) (7), as well as an escape phenomenon that can occur (87, 88). Some studies have suggested that cabergoline may be useful as add-on therapy in patients who do not achieve biochemical control with maximal doses of SRL (89) or pegvisomant (90) (VLQ) (DR).

Pegvisomant

Unlike all other medical therapies, the GH receptor antagonist pegvisomant is not dependent on tumor characteristics for efficacy (91). Pegvisomant is generally used as second-line therapy in patients who do not achieve biochemical control with maximal doses of SRL (SR), although observational data suggest that it is also effective when used as first-line therapy (VLQ) (92). As higher rates of control are often seen as the dose is increased (93-97), treatment should be started at low doses and uptitrated as tolerated until control can be achieved (SR). Potentially, any patient can be controlled with adequate dose titration (MQ), but the high cost of treatment is often an obstacle to adequate dose titration (98) (VLQ).Younger patients with more aggressive disease, higher baseline IGF-I levels, and associated comorbidities may require higher doses to acheive biochemical control (LQ) (97). Loss of biochemical control due to tumor regrowth, previous treatment modifications, concomitant menopause, and changes in testosterone administration, can be corrected by increasing the dose (LQ) (99, 100).

Degree of improvement in clinical outcomes with pegvisomant is variable and is dependent upon the specific comorbidity and the duration of disease (101-103) (LQ). Compared to other forms of medical therapy, pegvisomant is the most likely to achieve maximal improvement in glucose tolerance and insulin sensitivity (MQ) (102, 103). Accordingly, pegvisomant is the preferred medical therapy for patients with preexisting hyperglycemia or diabetes mellitus who do not respond to octreotide LAR/lanreotide (SR). Abnormal liver function can occur early and should be monitored (SR) (97). Tumor size may rarely increase in patients switching from SRL, possibly as a rebound after stopping SRL but more likely due to the absence of a pituitary-targeting therapy (97, 104) (LQ). Pegvisomant is therefore preferred for patients with no clinically relevant residual tumor (SR).

Combination Pegvisomant and SRL Therapy

Higher rates of biochemical control are seen in patients treated with combination pegvisomant and octreotide/lanreotide compared to those on SRL alone (MQ) (104,105), and the combination may be considered in patients with a concern for residual tumor control and impaired glucose tolerance instead of switching to pasireotide LAR (DR) (8). The combination of pegvisomant and pasireotide LAR is effective in achieving biochemical control with lower pegvisomant doses but no clear advantage has yet been shown in attenuating the hyperglycemic effects of pasireotide (LQ) (106, 107). Nevertheless, this combination, although costly, may be an option among those with observed tumor growth if radiotherapy is either contraindicated or not available or while awaiting tumor-shrinking effects of radiation in more aggresive tumors (DR).

Temozolomide

Use of temozolomide and other chemotherapeutic agents should be limited to patients with highly aggressive or truly malignant pituitary tumors (108) and should be administered under supervision of a neuro-oncologist (109) (DR).

The Multidisciplinary Treatment Approach

The availability of increased management options has enabled a more effective multimodality treatment of acromegaly, requiring a higher degree of treatment personalization. Treatment of acromegaly is best determined by a multidisciplinary team of experts within the structure of a Pituitary Tumors Center of Excellence (PTCOE), preferably in a single institution where feasible (SR) (9) (MQ). The PTCOE should have a sufficiently large referral population to

allow neurosurgeons to have post-residency training in a high-volume pituitary center, a continuous multidisciplinary experience, and a possibility to publish outcomes for pituitary tumor operations (DR) (46). Ideally, more than one surgeon per center should be available. In addition to experts in transsphenoidal pituitary surgery and pituitary disease endocrine management, the multidisciplinary team should include neuroradiologists, neuropathologists, radiation oncologists, and nurses with specific expertise in pituitary medicine (9) (LQ). A multidisciplinary treatment approach at a PTCOE where current guidelines are implemented and up-to-date and validated laboratory and clinical tools are routinely used offerrs the best opportunity for optimizing outcomes and quality of life while also ensuring that disease-associated morbidity and mortality are minimized (110) (SR).

Declarations

Ethical approval

No original data from studies on patients are reported in this manuscript and therefore no ethical approval or informed consent was needed.

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Conflicts of Interest/Competing Interests

AG is consultant for Chiasma, Genevant, Ipsen, Pfizer and Recordati and received research grants from Ipsen, Novartis and Pfizer to his Institution.

AB has received research funding from Pfizer and travel and speaker grants from Novartis and Ipsen

BMKB is PI of research support to Massachsuetts General Hospital from Crinetics, Ionis and Novartis, occasional consulting honoraria from Chiasma, Crinetics and Novartis.

CLB has served as consultant/speaker for Novartis and Ipsen.

MB has served as speaker for Novartis, Ipsen, Pfizer and Recordati

VB has received research grants from Pfizer, and has served on advisory boards for Pfizer

MDB is Member of Steering Committees and Advisory Boards of Chiasma, Ipsen, Novartis; Speaker for Ipsen, Novartis; and has received grants as PI for clinical trials from Crinetics, Ipsen, and Novartis

PC has received unrestricted research and educational grants from Ipsen, Novartis, Crinetics and Pfizer on behalf of the Service of Endocrinology and Reproductive Diseases, Hôpitaux Universitaires Paris-Saclay and Association Recherche Endocrinologie Bicêtre, and has served as investigator (principal or coordinator) for clinical trials funded by Novartis, Pfizer, Ipsen, Italpharmaco, Chiasma. PC gave lectures for Ipsen, Novartis, and Pfizer. All the fees and honoraria are paid to his Institution or Research Association.

DC served as an advisory board member for Crinetics

MF has received research support to OHSU as principal investigator from Chiasma, Crinetics, Ionis, Novartis and has received occasional scientific consulting from Chiasma, Crinetics, Ionis, Novartis, Pfizer.

PUF has received research grant to her institution for clinical research studies from Pfizer, Novartis, Ipsen and Chiasma.

MRG has been principal investigator in clinical trials from Novartis and Crinectics, has served on advisory boards for Novartis and Crinectics and served as apeaker for Novatis and Ipsen

EBG is an investigator for research grants to MSKCC from Ionis, Novartis, Corcept, Strongbridge Biopharma, and Bristol-Myers Squibb. She has received a speaker's fee for an educational presentaion for Chiasma.

APH has served as consultant/ speaker for Ipsen and Chiasma

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SP has served as an advisory board member for Ipsen, Novartis, and Crinetics, and as speaker for Ipsen, Novartis, and Pfizer.

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IS has served as consultant and speaker for Novartis, Pfizer and Medison Pharma

CS served as an advisor to and received speaker's fees from Pfizer, Ipsen, Chiasma and Crinetics

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MEW has received research grants to her institution for clinical research studies from Ionis and reviewed investigator-initiated research proposals for Pfizer.

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Authors' contributions

AG and SM served as Program Coordinators of the 13th Acromegaly Consensus Conference. MB, FC, DC, MF, PM, SS, CS, and JW served as Scientific Committee Members. All authors researched data for the Conference. AG and SM wrote the manuscript and all authors reviewed and/or edited the manuscript before submission.

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Table 1. Key Recommendations*

1. During follow-up, measurement of IGF-I levels with the same well-validated assay is recommended. Values slightly higher than a standard cut-off for age-adjusted normalization (e.g.,within 1.2-1.3 × ULN) may be considered sufficient for control of acromegaly.
2. Prevention and control of symptoms and comorbidities is a major goal of treatment. Assessing and aggressively managing disease-associated comorbidities is recommended, with use of clinician- and patient-reported outcome measures to help standardization of follow-up strategies.

3. Tumor resection via transsphenoidal surgery (either endocscopic or microscopic) is a safe and effective primary treatment for most patients. The primary predictors of surgical remission are tumor size, invasiveness (Knosp grade), and experience of the neurosurgeon.
4. Medical therapy is recommended for patients who do not achieve biochemical control after surgery. Choice of therapy among dopamine agonist, SRL, and GH receptor antagonist should be individualized based on disease- and patient-specific factors known to affect therapeutic efficacy and safety.
5. Radiotherapy is reserved for patients that have failed, are unfit for, or declined surgical and/or medical therapy. It should be administered in specialized centers to maximize efficacy and minimize long-term complications
6. Treatment of acromegaly is best determined by a multidisciplinary team of experts within the structure of a PTCOE, preferably in a single institution with a sufficiently large referral population. Such an approach is more likely to optimize outcomes and quality of life while minimizing disease-associated morbidity and decreasing mortality.

*These recommendations were selected among all the recommendations included in the text based on a formal vote from all authors and reflect the consensus reached within the group.

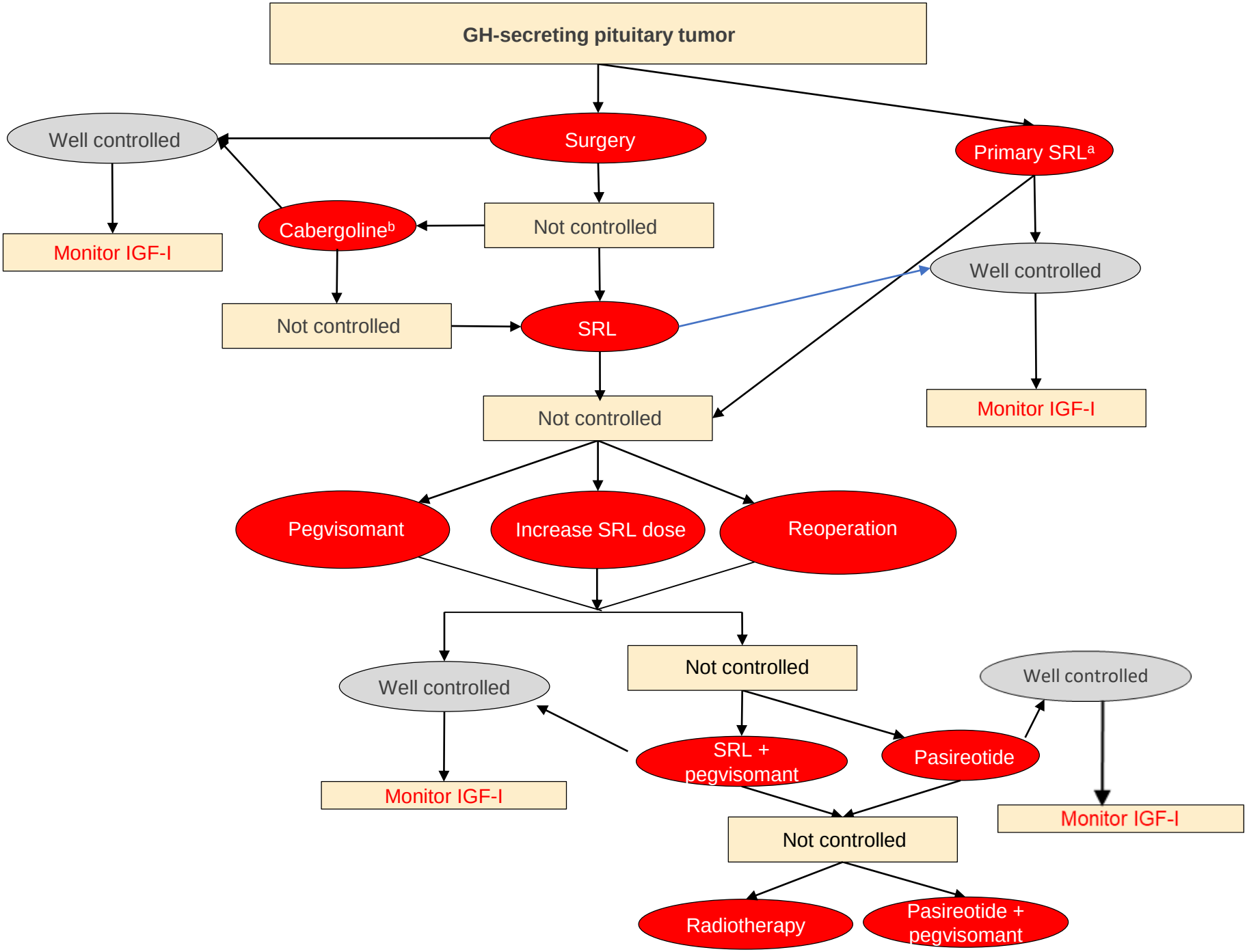
Table 2. Grading of Evidence and Recommendations

Grading the evidence	Grading the recommendations
• Very low quality (VLQ): expert opinion supported by one or few small uncontrolled studies • Low quality (LQ): supported by large series of small uncontrolled studies • Moderate quality (MQ): supported by one or few large uncontrolled studies or meta-analyses • High quality (HQ): supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up	• Discretionary recommendation (DR): based on VLQ or LQ evidence • Strong recommendation (SR): based on MQ or HQ evidence

Adapted with permission from Melmed et al (7)

Figure 1. Algorithm for the Multidisciplinary Management of Acromegaly

[a]If curative surgery is not feasible; [b]Consider in cases of mild postoperative GH/IGF-I elevations. Well controlled defined as normalized GH/IGF-I; not controlled defined as other than well-controlled. Abbreviations: IGF-I, insulin-like growth factor- I; SRL, somatostatin receptor ligand octreotide or lanreotide.


GH-secreting pituitary tumor
Surgery
Well controlled
Monitor IGF-I
Not controlled
Cabergoline[b]
Not controlled
SRL
Primary SRL[a]
Well controlled
Monitor IGF-I
Not controlled
Pegvisomant
Increase SRL dose
Reoperation
Well controlled
Monitor IGF-I
Not controlled
SRL + pegvisomant
Pasireotide
Well controlled
Monitor IGF-I
Not controlled
Radiotherapy
Pasireotide + pegvisomant