Acromegaly

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INTRODUCTION

Acromegaly is a *chronic*, *progressive* disease generally caused by a somatotroph pituitary adenoma with excess production of GH and IGF-I, characterized by disfiguring facial and acral changes . Systemic and metabolic comorbidities of the disease may lead to poor quality of life and increased mortality .

Persisting diagnostic delay (up to 10 years) highly contributes to the severity of the disease and complicates its treatment

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

INTRODUCTION

Adult patients with acromegaly have the characteristic facial features of a large lower jaw, a prominent forehead, and large hands and feet.

This occurs are after the growth plates fused, distinguishing acromegaly from *gigantism*, which occurs before the fusion of growth plates.

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EPIDEMIOLOGY

Acromegaly has a worldwide prevalence of about 4,600 per million population, with about 116.9 new cases per million per year, and its incidence is increasing further.

The mean age of diagnosis is 40 for men and 45 for women.

Acromegaly usually presents in the third decade of life.

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ETIOLOGY

The causes of acromegaly divided int

- primary GH excess
- ectopic
- iatrogenic GH excess
- Excess GHRH

most commonly (>95%) caused by a somatotroph GH-secreting adenoma of the anterior pituitary gland.

The most commonly associated mutation involves activating the alpha subunit of the guanine nucleotide stimulatory protein gene.

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ETIOLOGY

Other causes of primary GH excess include pituitary adenomas that secrete multiple hormones and GH-cell carcinomas.

In addition, acromegaly is also associated with some disorders such as:

Carney complex (CNC), McCune-Albright syndrome (MAS), and MEN type 1 and 4

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
Published online 2022 Sep 3

ETIOLOGY

Rarer causes of acromegaly are related to GHRH excess.

These can be further divided into central and peripheral causes:

- Central causes include: hypothalamic hamartomas, chorist Oma, and ganglioneuroma.
- Peripheral causes include: secretion of GHRH by bronchial carcinoid tumors

small cell lung cancer, adrenal adenoma, and even production by some MTCs or

pheochromocytoma has been described

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Presentation, comorbidities, and mortality

Although men present at a younger age than women, women may show both increased incidence and mortality risk.

presence of comorbidities as a significant part of diagnosing and managing acromegaly.

These comorbidities include:

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

Presentation, comorbidities, and mortality

Cardiovascular Complications

Histologically there is necrosis of myocardial cells, interstitial fibrosis, and infiltration of lymphocytes. this presents as a hyperkinetic heart, then evolving to biventricular hypertrophy and, eventually, diastolic and systolic dysfunction.

Arrhythmias can also occur but are seldom symptomatic.

Valvular abnormalities can also occur with increased in acromegalic patients.

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Presentation, comorbidities, and mortality

Hypertension

Excess GH in circulation leads to insulin resistance, endothelial dysfunction, and increased sodium and water retention, resulting in increased plasma volume and hypertension .

There is a predominance of diastolic blood pressure revelation, which increases in prevalence with age.

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Presentation, comorbidities, and mortality

Respiratory Complications

The most common respiratory complication (one-third of patients) is sleep apnea due to craniofacial anatomic changes such as macroglossia, soft tissue overgrowth of the palate and uvula, and alterations of the jaw.

Other abnormalities can Occur due to anatomic changes related to the ribcage, thus altering ventilatory mechanics.

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Presentation, comorbidities, and mortality

Obstructive Sleep Apnea (OSA)

OSA is a common finding in acromegaly due to pharyngeal soft-tissue hypertrophy.

Therefore, it is *necessary to evaluate for OSA once a diagnosis* of acromegaly is made by formal overnight polysomnography or home overnight oximetry.

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Presentation, comorbidities, and mortality

Metabolic Complications

Diabetes Mellitus

The etiology of diabetes in acromegaly is increased in circulating GH and IGF-1, leading to *insulin resistance*, *increased gluconeogenesis*, and *hyperinsulinemia*.

Therefore, the management of diabetes secondary to acromegaly is similar to that of the general population, and metformin should be considered first-line therapy.

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Presentation, comorbidities, and mortality

Pasireotide is, contraindicated in patients with uncontrolled DM.

✓ Adding GLP1RA or DPP4I can prevent this complication.

GH stimulates the hydrolysis of triglycerides into free fatty acids and glycerol so patients commonly have **elevated triglyceride levels and low HDL**.

Other complication addition to the above, the laboratory finding of **hypercalcemia**

✓ necessitates the evaluation of primary hyperparathyroidism and, if present, MEN 1

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Presentation, comorbidities, and mortality

Musculoskeletal Complications

Both GH and IGF-1 stimulate the production of periosteal bone formation.

In the craniofacial region, this manifests as characteristic features such as prognathism, teeth separation, jaw thickening, frontal bossing, and nasal bone hypertrophy.

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Presentation, comorbidities, and mortality

Musculoskeletal Complications (continued)

The changes noted in the extremities are due to a combination of *increased soft tissue, cartilage, bone overgrowth, and deformity* results in the widening of joint spaces, and the widening of the phalanges .

The spine is also affected: the phenotype of which is dorsal kyphosis and lumbar hyper lordosis and widening of the ribs.

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Presentation, comorbidities, and mortality

Vertebral Fractures

Vertebral fractures resulting from osteoporosis are a frequent consequence of acromegaly and *increased bone turnover* or h*ypogonadism* .

Therefore, antiresorptive therapy should be considered if osteoporosis does not resolve or improve after medical and surgical management of acromegaly .

Dual-energy X-ray absorptiometry is repeated every two years to monitor progress .

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Presentation, comorbidities, and mortality

Hypopituitarism

This results from the mass effect of an enlarging tumor.

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Presentation, comorbidities, and mortality

Skin Manifestations

The major changes seen with the skin result from *hyperhidrosis*, and patients may complain of excessive *sweating* and general *oiliness* of their skin.

Additional findings may include *skin tags*. Skin is also generally *thickened* as a result of glycosaminoglycan deposition and connective tissue overgrowth.

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Presentation, comorbidities, and mortality

Neurologic Complication

Carpal tunnel remains the most common neuropathy. the mechanism is thought to be edema of the median nerve, not external nerve compression from soft tissue and bone over growth.

cerebral aneurysms increase frequency in patients with acromegaly, often found incidentally on imaging, but they can also rupture, present as cerebral hemorrhage .

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Presentation, comorbidities, and mortality

Neoplastic Complications

Studies have shown that acromegaly increases the risk of *colonic polyps*.

There remains *no true consensus* among different guidelines concerning *colonoscopy surveillance*.

Some guidelines recommend screening at the time of *diagnosis*, and others starting at *age 40*. Repeat colonoscopies depend on the findings of the initial colonoscopy.

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Presentation, comorbidities, and mortality

Neoplastic Complications (continued)

Thyroid nodules can also occur. Sometimes these patients can develop a multinodular goiter and become clinically *thyrotoxic*.

Differential Diagnosis

Carney complex

McCune-Albright syndrome

MEN type 1

Sotos syndrome

Beckwith-Wiedemann syndrome

Malan syndrome

Tatton-Brown-Rahman syndrome

Berardinelli–Seip lipodystrophy

Abnormalities of natriuretic peptide C pathway

Pachydermoperiostosis

Minoxidil use

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ASSAY

Screening is biochemical.

IGF-1 is used as it does not vary with sleep patterns, exercise, or throughout the day like GH. Increased IGF-1 level confirms GH excess, and imaging should be done next to localize the source. If the *IGF-1 is normal*, acromegaly can essentially be *ruled out* at this point.

If the test is equivocal, a GH suppression test should be performed.

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ASSAY

75g of glucose is administered to the patient orally, and GH levels are measured before and 2 hours after the glucose load.

The diagnosis of acromegaly is confirmed if GH concentration is >1ng/mL after the glucose load.

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ASSAY

Other dynamic tests exist but are seldom necessary. They can be done if acromegaly is suspected ,but the IGF-1 and GH suppression test with OGTT are both normal .

✓ Thyrotropin-releasing hormone (TRH) 500 mg can be given intravenously, and in about half of acromegalic patients, the GH level would increase by 50% within 30 minutes. This effect is not observed in the general population.

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ASSAY

AACE guideline emphasizes that Raised IGF-1 levels must be followed by the measurement of GH levels (OGTT :GH measurements every 30 minutes for 120 minutes after 75 g glucose).

Serum GH nadir after glucose administration could also be lowered to 0.4 ng/mL to increase the sensitivity of testing .

Failure to suppress GH confirms the diagnosis of acromegaly.

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

ASSAY

it is important to be aware of confounding effects when interpreting the results.

basal GH and nadir GH following OGTT are affected by various physiological factors,

Furthermore, different assays may yield different results.

Therefore, laboratories must keep the same assays uniform for all patients,

corrected according to gender and age, and ensure that the same assay is used

from diagnosis and through the management of a specific patient

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2022 Sep; 14(9)

ASSAY

pre-menopausal women had higher GH nadir vs men and mean GH nadir in

OCP-using females exceeded by more than threefold the GH nadir mean of

premenopausal women not using OCP

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

ASSAY

Conditions affecting IGF-1 and GH levels.

Condition	IGF-1	Basal GH	Nadir GH
Puberty	High	High	High
Pregnancy	High	High	High
Diabetes mellitus	Low/Normal	High	High
Renal failure	Low/Normal	High	High
Liver disease	Low/Normal	High	High
Malnutrition/Anorexia	Low/Normal	High	High
Oral estrogen	Low/Normal	High	High
Critical illness	Low/Normal	High	High

A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly
2022 Sep; 14(9)

Conditions affecting IGF-1 and GH levels	IGF-1	Growth hormone
Anorexia and malnutrition	Decrease	Increase
Liver and kidney disease	Decrease	Increase
Poorly controlled diabetes	Decrease	Increase
Critical illness (eg, sepsis or multiorgan failure)	Decrease	Increase
Use of oral oestrogen and selective oestrogen receptor modulators	Increase	Increase
Pregnancy	Increase	Increase
Late puberty	Increase	Increase
Use of parenteral testosterone	Increase	Increase
Age >60 years	Decrease	Decrease
Severe obesity	Decrease	Decrease
Assay inaccuracies (eg, assay interference or inappropriate reference ranges)	Might increase or decrease	Might increase or decrease

Acromegaly: pathogenesis, diagnosis, and managementLancet Diabetes Endocrinol 2022; 10: 804–26

ASSAY

The next step in evaluating these patients is a pituitary MRI as a somatotroph adenoma is the most common cause of acromegaly. If imaging does not identify a mass, the adenoma may be too small to be visualized or indicate an alternate GH excess source.

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ASSAY

At this point, alternative imaging should be done, including a CT of the chest and abdomen or DOTATE PET scan.

This should be done in conjunction with serum measurement of GHRH

- elevated levels, usually >300ng/mL, are suggestive of extra-pituitary sources.

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ASSAY

Other tests to be done include evaluating other pituitary hormones.

- Adenomas can co-secrete more than one hormone
- Also, depending on the size of the adenoma, compression of the normal pituitary gland can result in deficiencies of other hormonal cell lines.
- ✓ Prolactin can be elevated either due to stalk compression from the pituitary adenoma or due to a co-secreting adenoma.

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ASSAY

As appropriate, one should check ACTH, early morning cortisol, free T4, FSH, and LH with either testosterone or estradiol and prolactin.

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ASSAY

As a result of common comorbidities, a HbA1c should be measured and a lipid panel.

- ✓ If they have symptoms suggestive of sleep apnea, they should be referred for a sleep study.
- ✓ Any concerning heart failure symptoms on physical examination should prompt referral to a cardiologist and an electrocardiogram and echocardiogram.

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ASSAY

- ✓ Any visual concerns or adenomas close to or compressing the optic chiasm should be referred to an ophthalmologist for formal visual field testing.
- ✓ Depending on the guidelines followed, a colonoscopy should be done at diagnosis (or age 40). After screening colonoscopy at diagnosis, further testing should be performed similar to the general population.

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Comparison of the ES, AACE, PS, and ACG diagnostic recommendations

ES: Endocrine Society; AACE: American Association of Clinical Endocrinologists; PS: Pituitary Society; ACG: Acromegaly Consensus Group . **A Comprehensive Review of Four Clinical Practice Guidelines of Acromegaly2022 Sep; 14(9)**

Diagnostic criteria/tests	ES	AACE	PS	ACG
IGF-1	First test of choice	First test of choice	First test of choice	First test of choice
GH as an initial diagnostic test	Not recommended	To be interpreted in the clinical context	Not recommended	Not recommended
OGTT-induced GH suppression	Confirms diagnosis	Confirms diagnosis. Nadir of GH suppression <1 advised to increase sensitivity	Confirms diagnosis. Physiological factors can confound results	Confirms diagnosis (it is recommended that 75 g be used to achieve a level of standardization)
Other biochemical tests	Not mentioned.	IGF-binding protein-3 or TRH tests are explicitly named to be irrelevant	IGF-binding protein 3 or acid-labile subunit can be used to evaluate equivocal GH and IGF-1 results	TRH and GnRH stimulation tests of GH secretion have been used as a second-tier evaluation but are not recommended due to the risk of side effects
Radiological tests	MRI/CT scan of the pituitary gland	MRI/CT scan of the pituitary gland	MRI/CT scan of the pituitary gland	MRI/CT scan of the pituitary gland
Visual tests	Recommended if the optic chiasm is involved	Recommended if the optic chiasm is involved	Recommended if the optic chiasm is involved	Recommended if the optic chiasm is involved
Other tests	None recommended	Prolactin levels and pituitary function tests	None recommended	None recommended

TREATMENT

Surgical management

In the most recent guidelines, surgery is recommended as primary treatment for most patients with acromegaly, and to maximize surgical cure, experienced pituitary surgeons are recommended to perform the procedure .

Recent large series have reported surgical cure rates in less than half of the patients.

Long-term control of acromegaly after pituitary surgery in South-Eastern Norway.
Acta Neurochirurgica 17 August 2023

TREATMENT

Although the overall surgical cure rates remain modest, mortality in patients with acromegaly has decreased over the last two decades, approximating mortality rates of the general population reflecting the development of new treatment approaches and modalities.

Long-term control of acromegaly after pituitary surgery in South-Eastern Norway.
Acta Neurochirurgica 17 August 2023

TREATMENT

	ES (endocrine society)	AACE(American Association of Clinical Endocrinologists)
SRL/SSA	Recommended as first line. SRL is used as primary therapy in a patient who cannot be cured by surgery, has extensive cavernous sinus invasion, does not have chiasmal compression, or is a poor surgical candidate	Recommended as first line. SSAs are effective in normalizing IGF-1 and GH levels in approximately 55% of patients. SSAs reduce pituitary tumor size modestly in about 25% to 70% of patients, depending on whether they are used as adjuvant or de novo therapy, respectively. The short-acting subcutaneously administered SSA octreotide is effective, especially when low cost and rapid onset of action is the goal
Pegvisomant	It is also recommended as first line	It is recommended as second line. Pegvisomant is often used in patients who respond poorly or are unable to tolerate SSAs. It is extremely effective in normalizing IGF-1 values (>90%). This includes patients who are partially or entirely resistant to other therapies

TREATMENT

	PS(Pituitary Society)	ACG(Acromegaly Consensus Group)
SRL/SSA	Recommended as first line. Extended-dosing intervals (>4 weeks) for 120 mg lanreotide may be effective among selected patients previously controlled with long-acting SRLs. Older age, female sex, lower IGF-1 levels, and tumor T2 MRI hypo intensity at baseline predict more favorable long-term biochemical responses to primary lanreotide 120 mg therapy every 4 weeks (MQ, SR). They recommend that pasireotide LAR is an effective alternative for patients who did not receive much benefit from lanreotide or octreotide LAR. For patients who have shown complete or partial biochemical response on injectable octreotide or lanreotide, oral octreotides are suitable (HQ, SR)	recommended as first line. For patients who are on SRL therapy, tumor shrinkage was observed in up to 80% of subjects. Tumor shrinkage did not show any link to biochemical remission (MQ). Response to SRL therapy was more pronounced after surgical debulking (MQ)

TREATMENT

	PS	ACG
pegvisomant	It is recommended as second line. Studies have shown a 73% biochemical control rate. For patients who are diabetic, it improves glucose metabolism independent of IGF-1 control but does not have the same effects in patients without diabetes (MQ)	It is recommended as second line in patients with persistently elevated IGF-1 levels after high doses of SRLs

TREATMENT

	ES	AACE
Dopamine agonists	Cabergoline is first line in patients with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess. In such cases, ES suggests a trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy	Recommended as first line. Cabergoline has been shown to yield better clinical results than bromocriptine. Dopamine agonists are recommended as first line. because of their oral availability and cheaper price. They recommend using dopamine agonists in patients with modestly elevated serum IGF-1 levels
Combination therapy	They recommend the addition of pegvisomant or cabergoline in a patient with inadequate response to SRLs. Combining medical therapies may improve efficacy, reduce side effects associated with an individual medication, decrease the frequency of injections and total drug dose, and potentially offer a cost benefit and improved compliance during long-term treatment	In patients with a partial response to SSA therapy, the addition of cabergoline may be useful. In patients with a partial response to SSA therapy, pegvisomant can also be considered as daily or weekly doses

TREATMENT

	PS (Pituitary Society)	ACG (Acromegaly Consensus Group)
Dopamine agonists	Not specified	They recommend using dopamine agonists as first line occasionally in patients who prefer oral formulations, have markedly elevated prolactin, or those with modestly raised GH or IGF-1 levels
Combination therapy	Combination therapy of SRL and pegvisomant is already being used and has shown impressive results with up to 96% biochemical control rate achieved	They recommend SRL and pegvisomant combination therapy in patients with poor response to first and second-line management modalities, improve cost-effectiveness in patients who require high-dose pegvisomant monotherapy or patients with an inability to achieve biochemical control after surgery

TREATMENT

	ES	AACE	PS	ACG
Radiotherapy	The third line of treatment. It is recommended in the setting of a residual tumor mass following surgery and if medical treatment is unavailable, unsuccessful, or not tolerated	The third line of treatment. It is recommended as an adjunctive treatment in patients not fully responding to medical or surgical treatments	The third line of treatment. It can be used after a response to prior surgery or medical treatments	The third line of treatment; however, is occasionally used as second line. It is indicated in patients with poor tumor growth control or failure of normalization of hormone levels with surgical or medical therapy

TREATMENT

Debulking of macroadenomas without mass effect can also be done and has been described as a modality to allow for better response to medical treatment, even if a surgical cure is not likely.

neoadjuvant medical treatment with octreotide before surgery results in higher remission rates; however, larger studies are needed to ascertain whether this should be routinely done or which patient may benefit from this approach.

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TREATMENT

In general, this type of surgery should be performed at a center with an experienced pituitary neurosurgeon who performs at least 50 cases per year.

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TREATMENT

Preoperative SRL therapy

Randomized studies suggest improvement in postoperative remission after pretreatment with SRL for 3–6 months .

data are conflicting and, 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.

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

Medical Therapy

- This is considered for patients who do not desire surgery
- are too high risk for surgery
- are not a surgical candidate as the tumor may be unresectable
- those with recurrent disease after initial surgical management who do not qualify for repeat surgery
- there may also be a role for neoadjuvant medical therapy before surgery.

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TREATMENT

Medical Agents

Somatostatin analogs (octreotide, Lanreotide, pasireotide):

these drugs bind to somatostatin receptors.

This results in the suppression of GH secretion from both normal

pituitary gland and somatotroph adenomas.

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TREATMENT

it also acts at the level of the liver inhibiting GH action by reducing GH binding to hepatocytes and reducing the production of IGF-1 from the liver.

✓ Thus, these drugs control hormonal overproduction as well as tumor growth.

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TREATMENT

Somatostatin analogs are usually administered as once-monthly IM injections, although 3 to 4 times per day, SC injections are also available.

Recently, an oral formulation of somatostatin has been FDA-approved.

58% of patients with acromegaly taking the oral formulation of octreotide had controlled levels of IGF-1 as opposed to only 19% of those taking a placebo.

Somatostatin analogs are generally well tolerated.

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TREATMENT

Injectable Lanreotide:

predict more favorable long-term biochemical responses to primary lanreotide:

- Older age
- female sex
- lower IGF-I levels
- tumor T2 MRI hypo intensity at baseline

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

TREATMENT

Oral octreotide capsules

it is expect that patients who respond to injectable octreotide LAR or lanreotide in this setting would also respond to OOC.

OOC is not currently recommended for patients who have tumor characteristics predictive of octreotide resistance:

e.g., MRI T2 hyperintensity, sparsely granulated tumors

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

TREATMENT

Pasireotide is a second-generation somatostatin analog; that have a much higher affinity for the somatostatin receptor SSTR5 in addition to some action on SSTR2 and SSTR3.

most somatotroph adenomas have high expression of both SSTR2 and SSTR5.

with octreotide and lanreotide having effects predominantly via SSTR2 and pasireotide with the highest affinity for SSTR5.

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TREATMENT

When pasireotide was compared to octreotide , pasireotide resulted in better control of both the hormonal profile and tumor size.

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TREATMENT

Side effects that have been reported are:

Mainly gastrointestinal such as diarrhea, vomiting, and abdominal pain,

they can also result in biliary sludge or cholelithiasis.

These drugs can also affect glucose homeostasis resulting in hyperglycemia; this

result seems more pronounced with pasireotide.

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TREATMENT

pasireotide LAR causes:

- hyperglycemia in up to 70% of patients
- secondary diabetes in 25–40% of patients.

Patients should be carefully screened and monitored for glycemic adverse effects

Patients not controlled on oral antidiabetic medications, including metformin,

could be better managed with GLP1RA rather than insulin

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

monitoring

IGF-1 level should be measured 3 months after administering a long-acting SRL

Treatment efficacy is described as one or a combination of the following:

- Random GH level <2ng/mL
- GH nadir <1ng/mL after OGTT
- normalization of IGF-1 levels

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TREATMENT

Dopamine receptor agonists (cabergoline, bromocriptine):

These act on dopamine 2 receptors (D2R) in the pituitary gland and are less effective than somatostatin analogs.

They are often used as adjuncts.

Cabergoline is more potent than bromocriptine in lowering GH levels.

Doses of cabergoline (up to 7mg weekly) are much higher than those used in prolactinomas to effectively reduce GH levels.

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TREATMENT

»These drugs are considered for those patients with only mild biochemical abnormalities (GH >1 but <1.3ng/mL) and mild symptoms or in conjunction with somatostatin analogs.

cabergoline can reduce GH and IGF-1 levels in 40% of patients.

With bromocriptine reduction in the tumor size in conjunction with control of IGF-1 levels only occurs in about 10 to 20% of people using.

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TREATMENT

Cabergoline

It has 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) , and has an escape phenomenon that can occur.

Some studies have suggested that cabergoline maybe useful as add-on therapy in patients who do not achieve biochemical control with maximal doses of SRL or pegvisomant .

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

The most common side effects related to these drugs are:

- nausea
- abdominal pain
- Constipation
- rarely dizziness
- orthostatic hypotension.

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TREATMENT

GH-Receptor antagonist (pegvisomant):

- ✓ is a human growth hormone analog
- ✓ blocks endogenous growth hormone at the receptor level
- ✓ lowering IGF-1 levels while GH levels can be increased
- ✓ IGF-1 levels are the only biochemical marker used to monitor response to treatment

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TREATMENT

treatment should be started at low doses and up titrated as tolerated until control

can be achieved .

Potentially, any patient can be controlled with adequate dose titration, but the high

cost of treatment is often an obstacle to adequate dose titration .

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TREATMENT

This drug does not have anti-proliferative effects and thus does not affect tumor Size so preferred for patients with no clinically relevant residual tumor.

pegvisomant have a beneficial effect on glucose homeostasis and can improve insulin sensitivity.

Is the preferred medical therapy for patients with preexisting hyperglycemia or DM who do not respond to octreotide LAR/lanreotide.

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TREATMENT

require higher doses of Pegvisomant in:

- Younger patients with more aggressive disease
- higher baseline IGF-I levels
- associated comorbidities may to acheive biochemical control
- Loss of biochemical control due to tumor regrowth
- concomitant menopause
- changes in testosterone administration

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Springer Nature 2020

TREATMENT

- require higher doses of **pegvisomant** and more rapid up-titration to achieve IGF-I normalization.
  - Patients with DM
  - those with a higher BMI

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

TREATMENT

Adverse reactions associated with this drug include:

- diarrhea
- Nausea
- abnormal hepatic function tests (should be monitored)
- infections
- pain.

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TREATMENT

Combination medical therapy has also been described

Combining cabergoline with a somatostatin analog has been seen to be effective .

In a study adding Pegvisomant to a somatostatin analog in patients seemingly resistant to the somatostatin analog, IGF-1 levels normalized in 95% of patients.

this combination needs to monitor hepatic function, as liver derangement is more common with the combination of drugs than with Pegvisomant alone.

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TREATMENT

A combination of a low-dose somatostatin analog with weekly pegvisomant is effective in biochemical control in addition to being cost-effective in those requiring combination therapy for the management of their acromegaly

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TREATMENT

Combination of Pegvisomant and SRL therapy:

may be considered in patients with a concern for residual tumor control and impaired glucose tolerance.

this combination, 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 aggressive tumors

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

Combination of pasireotide plus pegvisomant :

can yield biochemical control rates exceeding 70% even when pegvisomant doses are kept low.

The addition of pegvisomant does not ameliorate the high rates of pasireotide-induced hyperglycemia.

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

TREATMENT

Reoperations

Reoperation may be considered in patients with significant residual tumor:

- Who have not adequately responded to postoperative SRL
- patients with a resectable residual tumor after an unsuccessful first surgery .

Reoperation, as for primary surgery, should be done in a specialized center and after multidisciplinary evaluation

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

Complications

- ✓ Post-surgical hypopituitarism in 5–10% of cases
- ✓ persistent CSF leakage in 2–3%.
- ✓ Other rarely serious complications: visual deterioration, carotid artery injury, transient oculomotor palsies, and meningitis

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

- ✓ Diabetes insipidus :10–15%usually transient .
- ✓ SIADH may occur 5–14 days after surgery and require frequent monitoring of serum sodium levels and possibly fluid restriction .
- ✸ relative Surgery contraindications: Advanced age, severe cardiomyopathy, poorly controlled DM

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

Radiotherapy

Radiotherapy is considered a third-line option in those patients in whom medical management is ineffective in controlling disease, recurrence after surgery, and, the failure of medical therapy.

The patients treated with radiotherapy need to be closely monitored for hypopituitarism.

patient selection is guided by discussion within a multidisciplinary team

TREATMENT

There are two indications for radiotherapy:

a) control of tumor growth

b) lowering GH secretion

Multidisciplinary management of acromegaly: A consensus
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TREATMENT

1) Conventional fractionated radiotherapy:

It is associated with the risk of irradiating adjacent brain tissues.

It is provided at small daily doses five days a week, usually for 5 to 6 weeks duration.

Remission can take up to 10 years, and these patients require medical management in the interim.

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TREATMENT

2) Stereotactic radiosurgery:

Precision radiotherapy are localized accurately in *3-dimensions* directs a *single* *high-dose* radiation to the tumor and minimizes risk to nearby healthy brain tissues.

The adenoma needs to be *multiple millimeters away from the optic chiasma* to avoid damage to utilize this technique.

The *remission rate* with this modality ranges from *17 to 50%* in the absence of medical management for *2 to 5 years*.

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TREATMENT

Results

Radiotherapy can

- ❑ control biochemical parameters in more than 60% of patients,
- ❑ is highly efficacious (>90%) in controlling tumor growth,
- ❑ offering the prospect of stopping high-cost lifelong medical therapy .
- ✖ BUT full response maybe realized up to 10–15 years after administration .

so medical therapy is indicated in the intervening years .

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Springer Nature 2020

TREATMENT

Side effects

single-fraction stereotactic radiosurgery to be associated with similar but fewer side effects as compared to fractionated radiotherapy .

Hypopituitarism is the most frequent complication, regardless of technique, and increases over time, with rates approaching 25–50% after 5 years .

Routine monitoring of endocrine function should be conducted lifelong

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

TREATMENT

Side effects

non-endocrine complications observed with more focused techniques included:

- secondary tumors
- cerebrovascular disease
- optic neuritis
- Cranial nerve palsy

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Springer Nature 2020

TREATMENT

Temozolomide

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

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Springer Nature 2020

TREATMENT

Management of Acromegaly in Pregnancy

GH-secreting tumors have estrogen receptors, particularly those that co-secrete prolactin. in some studies, it has been found that tumor size does not change significantly during pregnancy in most women. But, given that the risk is still present, women need to be monitored closely with serial visual field monitoring.

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TREATMENT

Acromegaly in Pregnancy (continued)

In a microadenoma, the clinician should discontinue medical management, and these patients can just be closely monitored. The same applies to those with macroadenomas not affecting the optic chiasm with very close monitoring of visual fields.

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TREATMENT

If a woman were to develop worsening symptoms related to acromegaly, medical management could be reinstituted to help decrease those symptoms

(no biochemical monitoring due to alterations of IGF-1 and GH during pregnancy).

Bromocriptine has been used to manage the signs and symptoms without causing adverse fetal harm.

cabergoline has not been extensively studied in pregnancy.

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TREATMENT

Somatostatin analogs can cross the placenta and potentially decrease uterine blood flow, but longer use of octreotide does not seem to adversely affect the pregnancy fetal development.

Pegvisomant is not recommended as it has not been studied in pregnancy,

If visual complaints arise, an MRI is necessary to determine whether medical management or surgery is needed.

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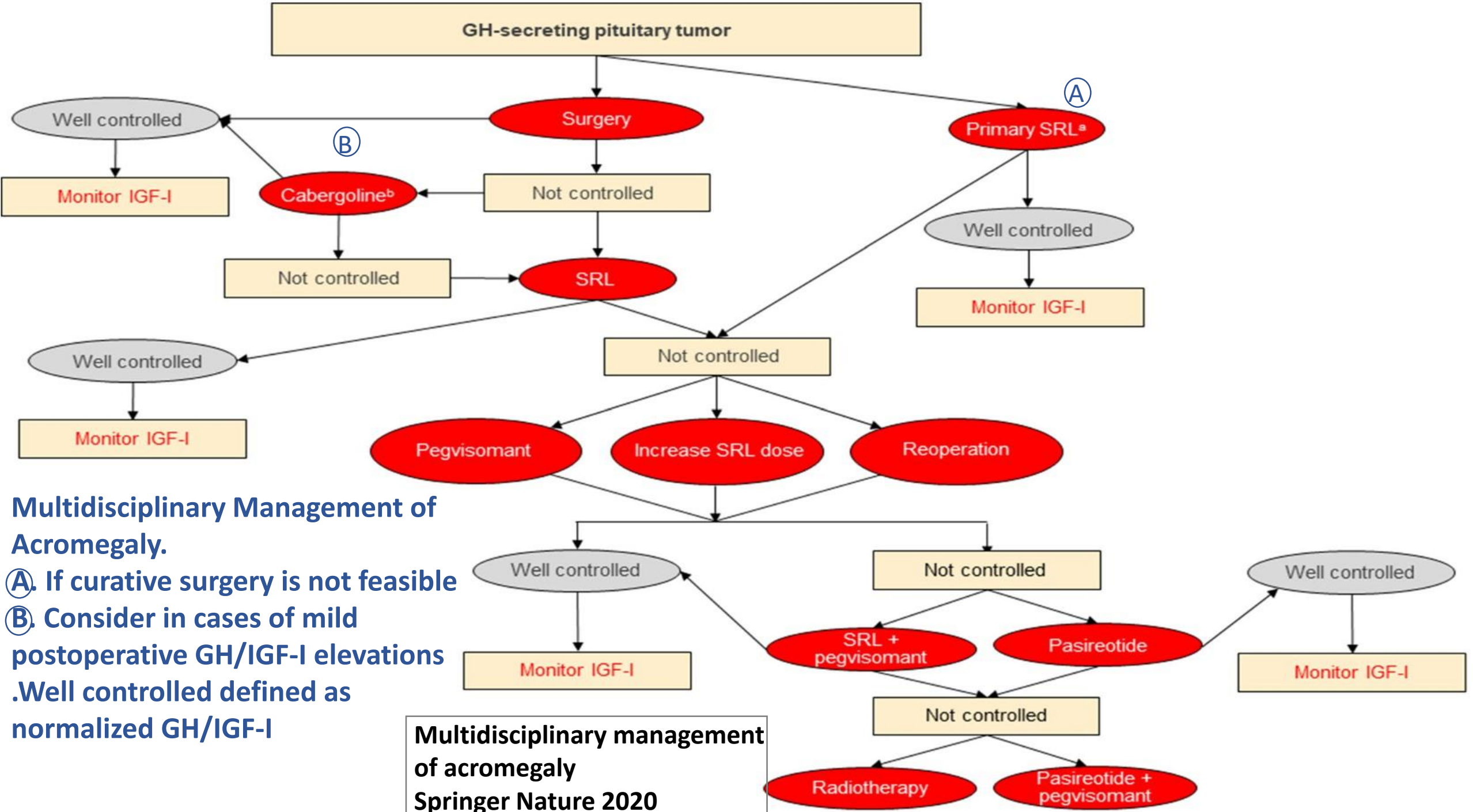

Multidisciplinary Management of Acromegaly.

Ⓐ. If curative surgery is not feasible

Ⓑ. Consider in cases of mild postoperative GH/IGF-I elevations .Well controlled defined as normalized GH/IGF-I

Multidisciplinary management of acromegaly
Springer Nature 2020

RESISTANT ACROMEGALY

Neurosurgery

primary factors predicting surgical remission in acromegaly:

- Tumor size
- cavernous sinus invasion
- preoperative GH levels

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

surgical remission rate in pituitary tumor centers of excellence should be 80–90% of microadenomas and 50–75% of macroadenomas but it dramatically drops for invasive very large (>4 cm) adenomas

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Definition of first-generation somatostatin receptor ligands treatment resistance:

(Included octreotide and lanreotide)

This should be based on three pillars:

(a) hormonal (GH levels should be less than 1 ng/ml and age normalized IGF-I)

(b) oncological (adenoma shrinkage <20% or tumor growth of pituitary adenomas,

which can be dissociated from the biochemical effects

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Definition (continued):

(c) clinical: progression of acromegaly comorbidities as recorded by holistic tools

such as SAGIT

[signs and symptoms (S)

GH levels (G)

tumor features (T)]

associated comorbidities (A)

IGF-1 levels (I)

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Resistance to first-generation somatostatin receptor ligands treatment divided to:

- partial resistance: defined as at least 50% decrease in GH and IGF-1 vs pre-treatment levels
- complete resistance

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Springer Nature 2023

RESISTANT ACROMEGALY

First-generation somatostatin receptor ligands(SRLs):

Injectable octreotide and lanreotide are effective in the control of:

- ✓ GH hypersecretion and tumor growth In ~ 50% of the patients
- ✓ As primary treatment or after surgical failure.

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Resistance to first-generation SRLs has been associated with:

1. low expression of survivin

   (a protein regulating apoptosis and cell proliferation)

2. hyperintense signal on T2 weighted MRI

3. young age

4. sparse adenoma granularity

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Resistance to first-generation SRLs has been associated with: (continued)

5. elevated post-surgery GH/IGF-I levels

6. large tumor remnants.

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Springer Nature 2023

RESISTANT ACROMEGALY

Other predictors of responsiveness to first-generation SRLs:

a. Cytokeratine patterns

b. proliferative markers (such as Ki-67)

c. other molecules as beta-arrestin, filamin A, ZAC-1 and E-cadherins w.

Interestingly, somatostatin receptor subtype (SSTR)2 expression was reported to be a good predictor of response to octreotide

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Other two possible drug-specific factors leading to attenuated response to first-generation SRLs:

Ⅰ. conventional doses used may not be the maximally effective doses, as demonstrated by trials with high doses of either octreotide or lanreotide .

Ⅱ. chronic treatment with SRLs injections may not be well tolerated by the patients, leading to inadequate compliance and persistence on treatment.

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

In this respect, oral octreotide may represent a relevant step toward a better compliance and preserved efficacy of acromegaly treatment with first-generation SRLs

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Second-line medical treatment : Second-generation SRL : Pasireotide LAR:

- ✓ biochemical control in patients resistant to first-generation SRLs .
- ✓ have a more pronounced tumor shrinkage effect than previously used SRLs.

Guidelines recommend that pasireotide LAR should preferably be used in those with normal glucose tolerance, although pasireotide-mediated hyperglycemia can be well pharmacologically controlled.

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Pegvisomant

Daily GH antagonist pegvisomant subcutaneous injections with appropriate dose can obtain hormonal control in about 90% of patients not controlled by first-generation SRLs.

Guidelines recommend pegvisomant use in second-line treatment preferably in patients with diabetes and without a clinically relevant post-operative tumor Remnant.

Modern approach to resistant acromegaly
Springer Nature 2023

RESISTANT ACROMEGALY

Pegvisomant+SRLs:

Once or twice weekly pegvisomant combined with first- generation SRLs may be effective in reaching biochemical control and improving quality of life .

Interestingly, this synergistic combination acting both centrally and peripherally may also be able to control tumor growth .

Guidelines recommend its use when diabetes and relevant tumor mass are concomitant in the same patient .

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Springer Nature 2023

RESISTANT ACROMEGALY

combination of pegvisomant with pasireotide:

☺ may improve glucose metabolism in selected cases .

☺ Could be effective in controlling the disease in selected resistant.

SO patients with acromegaly allowing a further improvement in the personalized approach to treatment

Modern approach to resistant acromegaly
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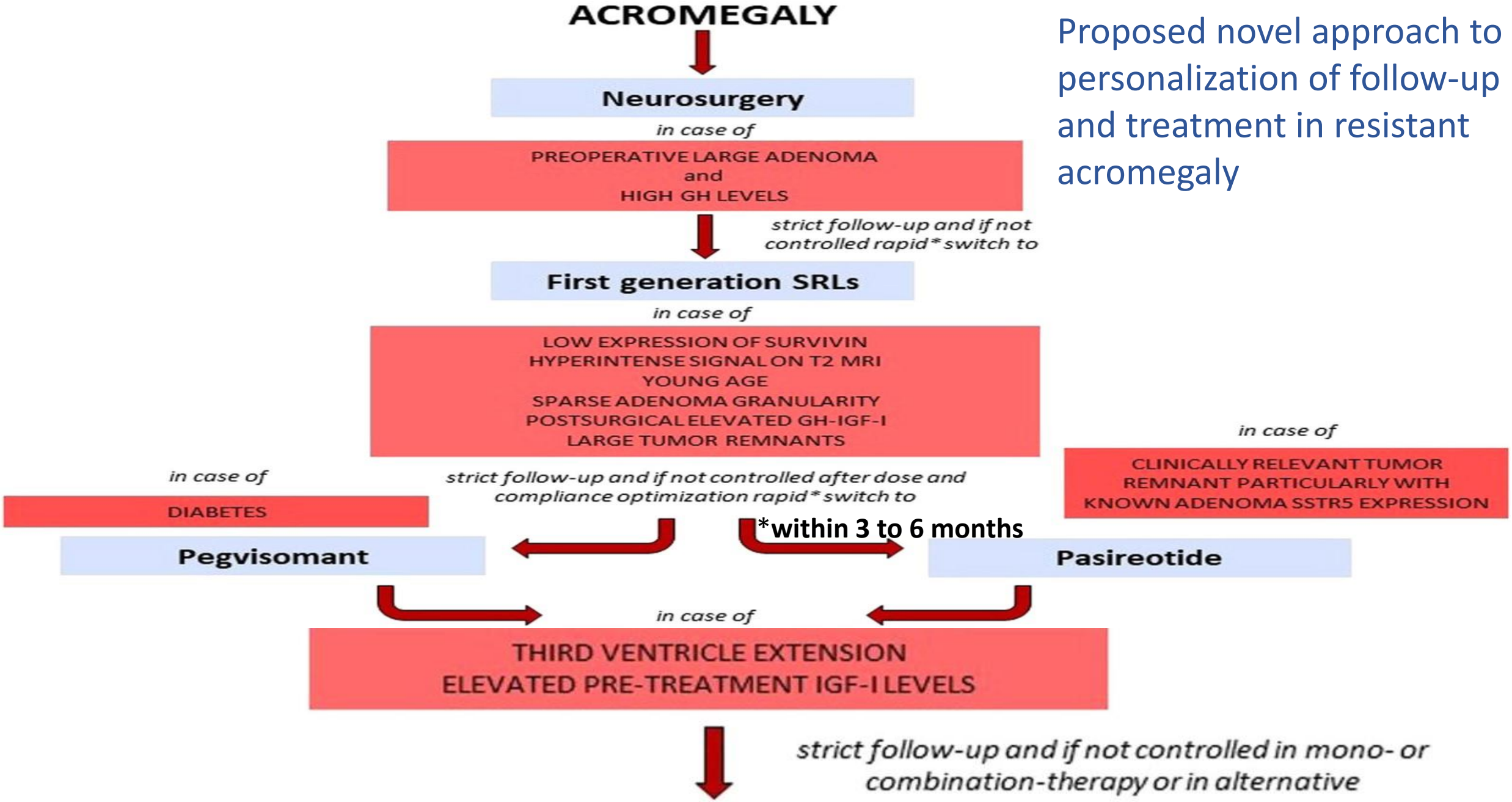
Proposed novel approach to personalization of follow-up and treatment in resistant acromegaly



Modern approach to resistant acromegaly
Springer Nature 2023

PREDICTORS OF PATIENT OUTCOME

lower absolute IGF-1 levels at diagnosis were associated with biochemical control after surgery at short-term in corroboration with other studies but not at long-term follow-up. But of the few studies reporting long-term follow-up data exceeding 3years postoperatively, preoperative GH and IGF-1 levels, tumor size and invasiveness, and age at diagnosis were among factors predicting long-term biochemical control after surgery .

Long-term control of acromegaly after pituitary surgery in South-Eastern Norway
ActaNeurochirurgica 17 August 2023

PREDICTORS OF PATIENT OUTCOME

Presurgical medical treatment may improve control rates , but medical pretreatment as a systematic approach in unselected patients remains controversial

Long-term control of acromegaly after pituitary surgery in South-Eastern Norway.
ActaNeurochirurgica 17 August 2023

PREDICTORS OF PATIENT OUTCOME

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).

Remission rates are likely lower at less experienced centers.

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

PREDICTORS OF PATIENT OUTCOME

Predictors of response to second-line

comparison of the biochemical response to pasireotide versus pegvisomant showed a slightly higher control rate with pegvisomant (85.4%) than with pasireotide LAR (69.7%) .

Modern approach to resistant acromegaly
Springer Nature 2023

PREDICTORS OF PATIENT OUTCOME

In a study, a poor pegvisomant response was prevalently linked to:

- tumor-associated factors
- extension to the third ventricle
- Ki67 > 4%
- high pre-treatment IGF-I levels.

Modern approach to resistant acromegaly
Springer Nature 2023

PREDICTORS OF PATIENT OUTCOME

poor pasireotide LAR response was also related to:

- tumor extension to the third ventricle
- elevated pre-treatment IGF-I levels
- absent/low SSTR5 somatotroph expression
- d3-deleted isoform of GH receptor, which influence the biochemical assessment of acromegaly after treatment and to independently predict GH and IGF-I discrepancy during acromegaly follow-up.

Modern approach to resistant acromegaly
Springer Nature 2023

PREDICTORS OF PATIENT OUTCOME

pre-existing diabetes and vertebral fractures, may impact on the choice of second-line treatment.

pasireotide may have a more pronounced fracture protective effect as compared to pegvisomant .

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Springer Nature 2023

Acromegaly: pathogenesis, diagnosis, and management
Lancet Diabetes Endocrinol 2022; 10: 804–26

Panel: Predictive factors for incomplete or inadequate response to acromegaly treatment

Surgery[23,143,144,146]

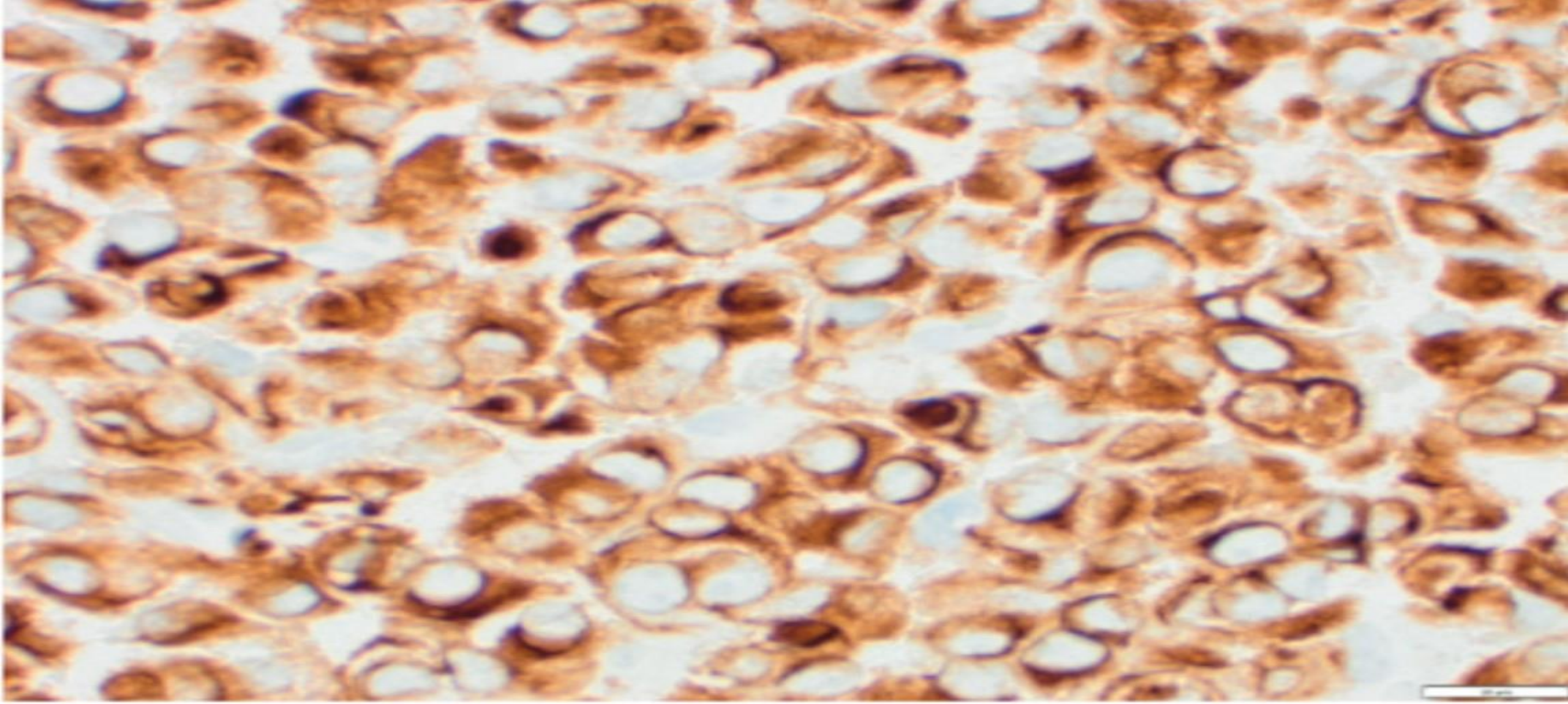
- Cavernous sinus invasion
- Wider tumour diameter
- Increased preoperative growth hormone concentrations
- Younger age (age varies by study)
- No consistent association between preoperative insulin-like growth factor (IGF-1) concentrations and postoperative remission

Lanreotide or octreotide[56,147–149]

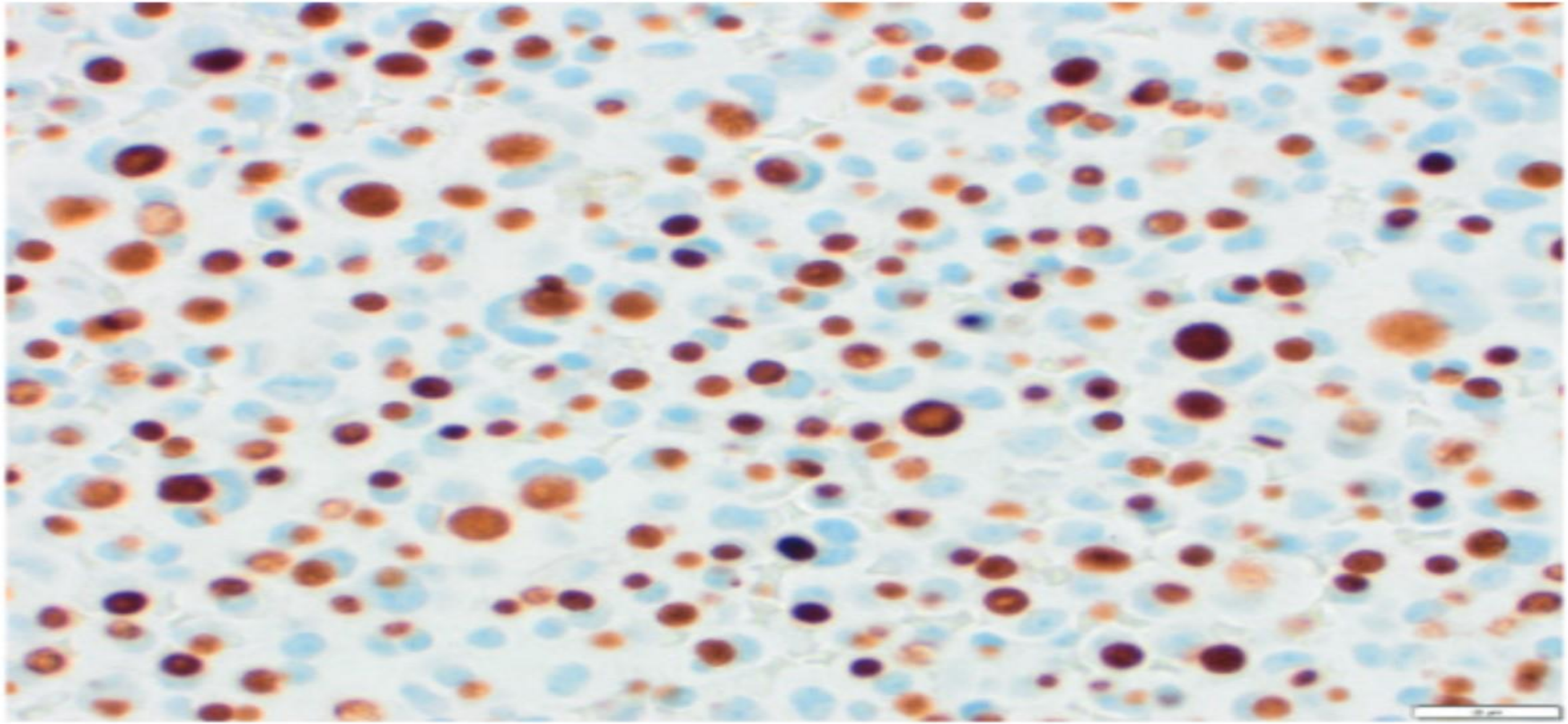
- Sparsely granulated immunohistochemistry pattern and low expression of somatostatin receptor 2
- Age <40 years
- Germline *AIP* mutation (for select patients with familial acromegaly)
- Hyperintensity on T2-weighted pituitary MRI

Pegvisomant[19,150–154]

- Younger age (age varies by study) with aggressive disease
- Increased baseline IGF-1 concentrations
- Increased weight or obesity (increased doses are usually required)
- Female sex (increased doses are usually required)



Densely granulated somatotroph adenoma (cytoplasmic staining)



Sparsely granulated somatotroph adenoma (fibrous bodies)

FOLLOW-UP

Post-surgical Follow-up and Management Immediately post-surgery

urine output monitoring and

sodium levels are vital for rule out of SIADH or, conversely, diabetes insipidus .

The adrenal function should be monitored and treated appropriately immediately

postoperatively.

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FOLLOW-UP

Patients with sleep apnea should not use their CPAP device postoperatively for a while to reduce the risk of pneumocephalus and infections as a result of the high nasal pressures.

Thyroid and gonadal axes can undergo testing 6 to 12 weeks after surgery.

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FOLLOW-UP

Immediate day-one post-operative measurement of GH can be done to assess remission.

However, the remaining normal pituitary gland may produce excess GH in response to surgical stress.

fluctuation of circulating IGF- I levels may be seen, particularly in the early postoperative period or after treatment changes (with preoperative SRL therapy).

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FOLLOW-UP

An OGTT can be done one week post-operatively.

A GH value of <0.4ng/mL defines disease control.

Serology of GH and IGF-1 can be measured by 3 to 6 months post-operatively as it can take this long for IGF-1 levels to normalize.

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FOLLOW-UP

Remission is then defined when normal IGF-1 levels are seen, OGTT is necessary to determine if GH-nadir levels are elevated.

GH after OGTT is measured at <1ng/mL (some recommend using <0.4ng/mL).

IGF1 Values slightly higher than a standard cut-off for age-adjusted normalization (e.g. within 1.2–1.3 × ULN) is considered sufficient for control of acromegaly data need to be interpreted with caution with preoperative SRL therapy.

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FOLLOW-UP

If remission is confirmed, serology should be repeated at least annually, as relapse has been known to occur in some patients even as long as ten or more years later.

Post-operative imaging should be done a minimum of 3 months after surgery as the fat and gel foam packing can take that long to be resorbed.

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FOLLOW-UP

Post treatment Follow-Up

Patients with postoperative GH levels under 1 ng/mL (47 pmol/L) should have follow-up GH and IGF-1 determinations at 6-month intervals for 2 years and yearly thereafter to rule out recurrences.

Recurrent elevations in IGF-1 should prompt a repeat MRI of the sella.

Greenspan's Basic & Clinical Endocrinology
10th edition 2018 p114

FOLLOW-UP

If residual disease is noted the patient may need further treatment with repeat surgery , medical management or radiotherapy.

- ✓ Pathology specimens are helpful for further management:
- ✓ when the tumor is densely granulated , predict response to octreotide.
- ✓ if the adenoma stains positive for prolactin , predict a response to dopamine agonists.

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FOLLOW-UP

Close follow-up is recommended for patients with discrepant GH and IGF-1 levels

observed at 3 months post-operatively.

most commonly, patients show controlled GH and elevated IGF-I, but the opposite

may also occur .

In these cases, we recommend relying on IGF-I values.

Multidisciplinary management of acromegaly: A consensus
Springer Nature 2020

FOLLOW-UP

Tumor size

Tumor growth control, and ideally, decreasing tumor size, are clinically important goals for patients with acromegaly .

We recommend to continue evaluating reduction in mass maximal dimension, rather than overall tumor volume, which is not standardized.

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Springer Nature 2020

Prognosis, comorbidities, and mortality

Acromegaly is associated with high mortality rates(1.2 to 3.3 times), chiefly due to malignancies and cardiovascular and respiratory disorders.

post-operative GH levels correlate the best with overall survival. Thus, if GH/IGF-1 levels are controlled, the life expectancy becomes the same as in age- matched controls.

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Prognosis, comorbidities, and mortality

Biochemical control remains the strongest predictor of patient outcomes, reflecting improvements in glucose metabolism, OSA, cardiovascular disease, and vertebral fractures.

However, structural heart and joint changes are unlikely to resolve.

Rate of thyroid malignancies is not greater among acromegaly patients than among those without the condition.

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

Prognosis, comorbidities, and mortality

Although men present at a younger age than do women, women may show both increased incidence and mortality risk.

postmenopausal women, may exhibit lower surgical remission rates from TSS, as they tend to have larger and more invasive tumors.

A Pituitary Society update to acromegaly management guidelines
Pituitary (2021) 24:1–13

Prognosis, comorbidities, and mortality

Factors associated with a worse prognosis:

- high GH/IGF-1 levels,
- Cardiomyopathy
- hypertension

Morbidity related to the condition often remains despite normalizing GH/IGF-1 levels, but treatment can ameliorate the severity and partially improves the quality of life.

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Prognosis, comorbidities, and mortality

Other prognostic factors included:

Patient factors such as: age

Biochemical factors such as: how high GH/IGF-1 levels are at diagnosis

Tumor factors including: tumor granularity, receptor expression (SSTR2,5, and D2)

Markers such as: Ki67 and p21

Specific mutations: how the tumor behaves in terms of its size and invasion

The T2 intensity of the tumor on MRI

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Prognosis, comorbidities, and mortality

Using this information, a classification of acromegaly into three subtypes has been proposed, guiding prognosis, predicting treatment responsiveness, and thus patient outcomes.

Prognosis, comorbidities, and mortality

★Type 1 (best prognosis):

- Older patients
- fewer symptoms
- lower levels of IGF-1

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Prognosis, comorbidities, and mortality

They have densely granulated micro or macroadenomas that are less aggressive, as evidenced by lower Ki67 , high p21 (a marker of senescence), and very uncommonly have a suprasellar extension.

Instead, they tend to exhibit extension laterally to the sphenoid sinuses, which are more accessible to surgery.

These tumors more frequently express SSTR2 predicting a better response to medical treatment.

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Prognosis, comorbidities, and mortality

★ Type 2 (intermediate prognosis):

- These macroadenomas can be either dense or sparsely granulated but do not
- demonstrate invasive features
- Compared with type 1, IGF-1 levels are higher at diagnosis.

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Prognosis, comorbidities, and mortality

★ Type 3 (worst prognosis):

- These patients are young, experience severe symptoms, and have high levels of IGF-1 at diagnosis.
- Their tumors are macroadenomas and are sparsely granulated and more aggressive, as supported by low levels of p21.

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Last Update: February 2, 2023

Prognosis, comorbidities, and mortality

These tumors also extend to both the sphenoid sinus and the suprasellar region

and frequently compress the optic chiasm.

Low expression of SSTR2 may indicate poor response to medical therapy

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Last Update: February 2, 2023

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