
بسم الله الرحمن الرحيم

Management of Acromegaly

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Introduction:

- Acromegaly is almost always caused by a somatotroph adenoma of the pituitary gland
- and is associated with increased morbidity and mortality.

Introduction:

As a result, almost all patients:

- should be treated,
- even those who are asymptomatic
- and those in whom the disorder does not seem to be progressing

Introduction:

- One exception is a patient with a short life expectancy who is not expected to live long enough to benefit from therapy.

Goals of therapy:

The goals of therapy are:

- 1- to lower the serum insulin like growth factor-1 (IGF-1) concentration to within the normal range for the patient's age and gender.

Goals of therapy:

- 2- In addition to lowering IGF-1, another biochemical goal is to lower the GH concentration to <1 mcg/L, as this also correlates with control of acromegaly.

Goals of therapy:

- 3- control adenoma size & reduce mass effects,
- 4- improve symptoms,
- 5- reverse metabolic abnormalities such as DM2

- Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest 2009;119:3189.

Goals of therapy:

- However, the IGF-1 criterion may be better
- since some patients who appear to have active disease clinically and by elevated IGF-1 concentration have serum GH values that suppress to <1 mcg/L .

- Freda PU. Et al. J Clin Endocrinol Metab 1998; 83:3808.
- Dimaraki EV, et al. J Clin Endocrinol Metab 2002; 87:3537.
- Roula Zahr et al. European Endocrinology, 2018;14(2):57–61

Goals of therapy:

- Serum IGF-1 concentrations also correlate better than serum GH with insulin sensitivity in patients with acromegaly.

- Puder JJ, et al. J Clin Endocrinol Metab 2005; 90:1972.

Goals of therapy:

- When serum GH and IGF-1 concentrations decline to normal,
- the characteristic soft tissue overgrowth and related symptoms gradually recede
- and the metabolic abnormalities, such as diabetes mellitus, improve.

- Melmed S. Medical progress: Acromegaly. N Engl J Med 2006; 355:2558.

Goals of therapy:

- In addition, life expectancy returns to that of the general population.
- However, bony abnormalities generally do not regress and joint symptoms persist.

Goals of therapy:

Another goal of treatment is:

- to alleviate symptoms due to the direct effects of the somatotroph adenoma (headaches, vision loss),
- without causing hypopituitarism.

Management of acromegaly:

Overview of approach:

	Surgery		Radiotherapy
	Microadenoma	**Macroadenoma**	
Normal IGF-1	80-90%	40%	50% at 10 years
Adenoma shrinkage	95%	70%	95%
Advantages	Potential cure reduction	Rapid size reduction	
Disadvantages	Recurrence: 5-10%	Regrowth of adenoma	Slow
Complications			
Hypopituitarism	Rare	15%	50% at 10 years
Other	Diabetes insipidus, 5%	Diabetes insipidus, 10%	Neurological deficits

Management of acromegaly:

Overview of approach:

	Octreotide, lanreotide	Cabergoline	Pegvisomant
Normal IGF-1	50%	40%	95%
Adenoma shrinkage	50%	No data	Not expected
Advantages		Oral administration	
Disadvantages	Injection		Injection
Complications			
Hypopituitarism	None	None	None
Other	GI symptoms, gallstones	Nausea, lassitude	Elevated liver enzymes

Potential complications:

- The perioperative mortality rate is less than 1 % in patients with large, invasive adenomas
- and negligible in patients with smaller ones.

Potential complications:

- Long-term deficiency of one or more pituitary hormones has been reported in up to 70 percent of patients.

- Abosch A, et al. J Clin Endocrinol Metab 1998; 83:3411.
- Freda PU, et al. J Neurosurg 1998; 89:353.

Potential complications:

- Patients treated with both surgery and radiation are particularly prone to develop pituitary hormonal deficiencies, including growth hormone (GH) deficiency.

- Ronchi CL, et al.. Eur J Endocrinol 2009; 161:37.

Other major complications

- Other major complications of surgery with experienced neurosurgeons occur in approximately 8 % of patients.
- Rates with less experienced surgeons are much higher.

Other major complications

These include:

- central diabetes insipidus (2 %),
- cerebrospinal fluid rhinorrhea (2 %),
- meningitis (2 %).
- All are more common in patients with macroadenomas.

Postoperative evaluations:

The early cure rate in patients with acromegaly:

- 80 to 90 percent for microadenomas
- and less than 50 percent for macroadenomas

Postoperative evaluations:

We measure IGF-1 levels and a random GH :

- approximately 12 weeks after surgery
- as it may take this long for IGF-1 to normalize.

Postoperative evaluations:

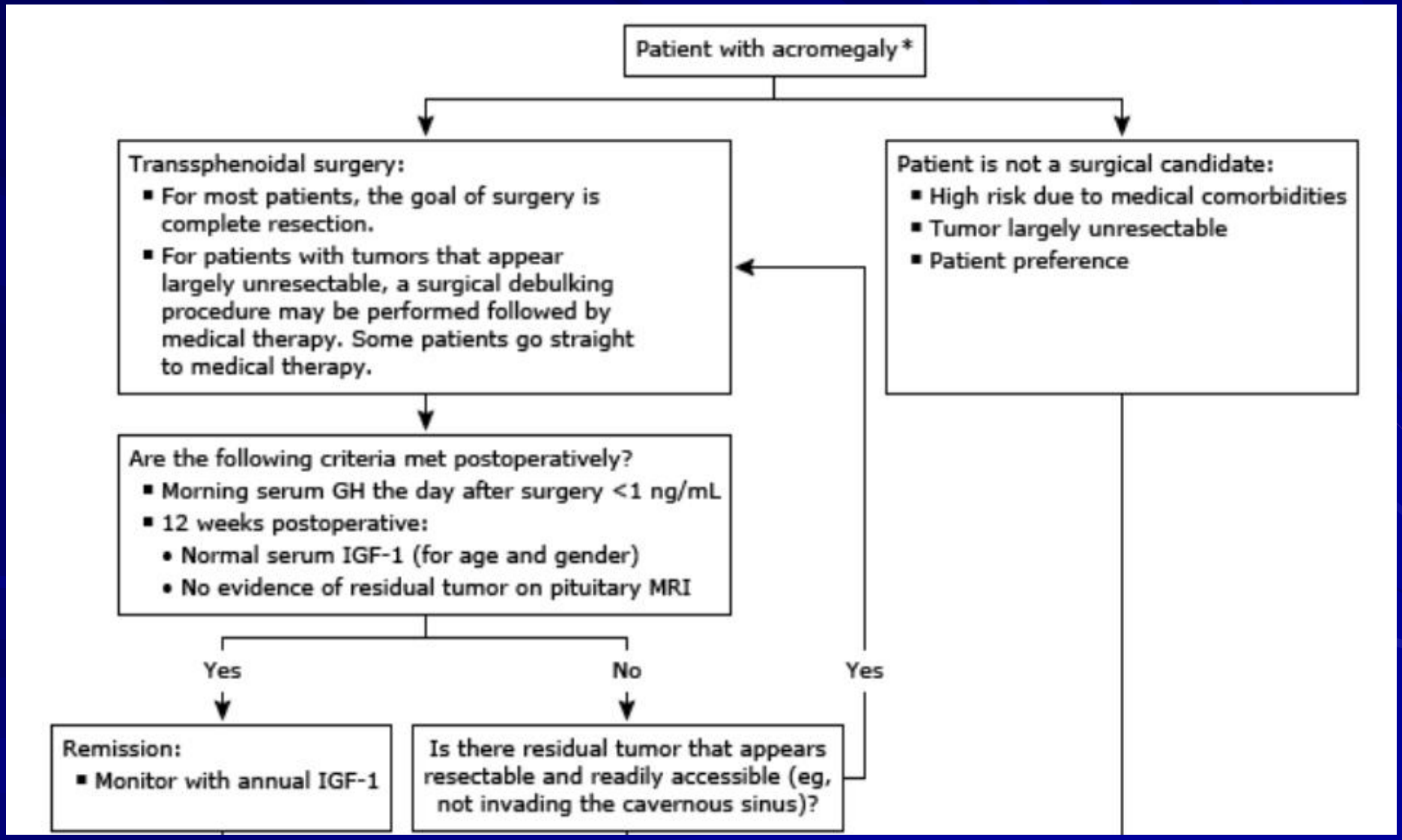
- If a random GH is >1 mcg/L,
- we remeasure GH after a glucose load;
- a post-glucose serum GH <1 or <0.4 mcg/L is consistent with control of acromegaly.

Postoperative evaluations:

- We also suggest performing a pituitary MRI study at least 12 weeks after surgery to look for residual tumor and assess adjacent structures.

- Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99:3933.
- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561

Management of acromegaly:



Postoperative evaluations:

- There is no further therapy needed after trans-sphenoidal surgery with normal IGF-1 and no residual tumor on MRI.

Patients with residual disease:

- Patients with residual disease biochemically or on MRI, need additional treatment.
- This can include repeat surgery, medical therapy, and/or radiation therapy.

Additional therapy for residual disease

- Management of tumor persistence or recurrence after first surgery is still controversial.
- Current practice is to propose medical management
- and/or radiotherapy to patients
- failing to achieve biochemical remission after initial surgical resection.

- Wilson TJ, et al. Pituitary. 2013;16(4):459–464.
- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561

Postoperative evaluations:

Resistance to SRL therapy can be defined as:

- failure to achieve biochemical control associated with tumor shrinkage or even an increased tumor volume.

- Colao A, et al. Endocr Rev. 2011;32 (2):247–271.

Postoperative evaluations:

Resistance is partial when:

- SRL therapy results in a reduction of IGF-1 levels by more than 50% compared to baseline, without normalization.

- Colao A, et al. Endocr Rev. 2011;32 (2):247–271.
- Gadelha MR, et al. Pituitary. 2017;20(1):100–108.

Postoperative evaluations:

- A treatment duration of at least 12 months and a correct dose titration (maximum tolerated dose) should be reached before considering a patient uncontrolled.

- Fleseriu M. Pituitary. 2011;14(2):184–193.

Postoperative evaluations:

- It is important to wait 12 weeks to allow for involution of gel foam and fat packing.

- Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99:3933.

Additional therapy for residual disease: re-operation

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).

- Almeida JP, et al. Reoperation for growth-hormone secreting pituitary adenomas: endonasal endoscopic series and systematic review of the literature. J Neurosurg. 2018;129:404–16

Additional therapy for residual disease: re-operation

- Residual intra sellar mass that compresses vital structures eg.optic chiasm after initial surgery
- Significant residual tumor in the sella that is resectable

Additional therapy for residual disease: re-operation

- Debulking purposes to increase the likelihood of remission with adjuvant medical therapies

- Mathioudakis Net at al, Neurosurg Clin N Am. 2012;23 (4):621–638.

Additional therapy for residual disease: re-operation

- Severe adverse events during pharmacological treatment
- or in case of cost-related issues.

- Yamada S, et al. Neurosurgery 2010;67(4):949–956
- Del Porto La, et al.. J Clin Neurosci. 2011;18(2):181–190.

Additional therapy for residual disease: re-operation

- Overall remission rate after a re-operation is highly variable between series (ranging from 8% to 59%).
- acromegaly success rate of a second surgery is similar to first surgery

- Yamada S, et al. Neurosurgery 2010;67(4):949–956
- Mathioudakis Net at al, Neurosurg Clin N Am. 2012;23 (4):621–638.
- Wilson TJ, et al.Pituitary. 2013;16(4):459–464.
- Almeida JP, et al .J Neurosurg. 2018;129(2):404–416.

Additional therapy for residual disease: re-operation

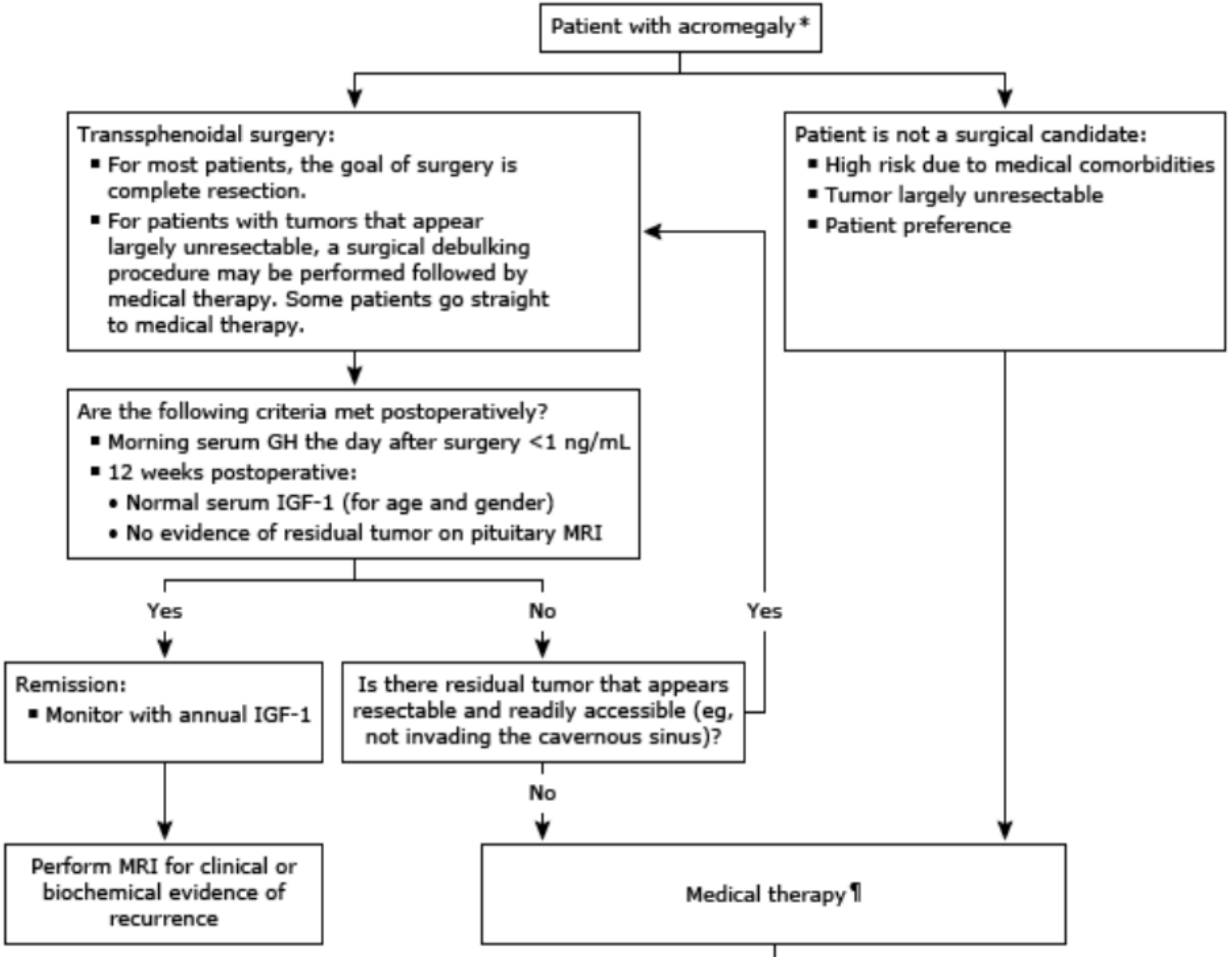
- Complication rate of secondary transsphenoidal surgery is greater than that of primary surgery.

- Yamada S, et al. Neurosurgery 2010;67(4):949–956
- Long H, et al.J Neurosurg. 1996;85(2):239–247.

Additional therapy for residual disease: re-operation

- meningitis 1.8–6%,
- cerebrospinal fluid leak/fistula 2–9%,
- vascular injury 0.1–6%,
- ophthalmopathy 6%
- and hormone deficiencies 1.9%.

- Mathioudakis Net at al, Neurosurg Clin N Am. 2012;23 (4):621–638.


Patient with acromegaly*
Transsphenoidal surgery:
For most patients, the goal of surgery is complete resection.
For patients with tumors that appear largely unresectable, a surgical debulking procedure may be performed followed by medical therapy. Some patients go straight to medical therapy.
Patient is not a surgical candidate:
High risk due to medical comorbidities
Tumor largely unresectable
Patient preference
Are the following criteria met postoperatively?
Morning serum GH the day after surgery <1 ng/mL
12 weeks postoperative:
Normal serum IGF-1 (for age and gender)
No evidence of residual tumor on pituitary MRI
Yes
No
Yes
Remission:
Monitor with annual IGF-1
Is there residual tumor that appears resectable and readily accessible (eg, not invading the cavernous sinus)?
No
Perform MRI for clinical or biochemical evidence of recurrence
Medical therapy¶

Medical therapy:

First-line medical therapy in patients with persistent disease after surgery:

- A long-acting somatostatin analog (SRL)
- Or Cabergoline if IGF1 <2.5 times the upper limit of normal

- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561*

Medical therapy:

Second-line medical therapy if first generation SRL is not successful in normalizing IGF1:

- Increase first-generation SRL dose and/or increase dose frequency
- Add cabergoline to SRL if IGF1 is moderately elevated

Medical therapy:

Second-line medical therapy if first generation SRL is not successful in normalizing IGF1:

- If there is tumor concern:
- Switch to pasireotide LAR

Medical therapy:

Second-line medical therapy if first generation SRL is not successful in normalizing IGF1:

- Minimal or no response and impaired glucose metabolism:
- Switch to pegvisomant

Medical therapy:

Second-line medical therapy if first generation SRL is not successful in normalizing IGF1:

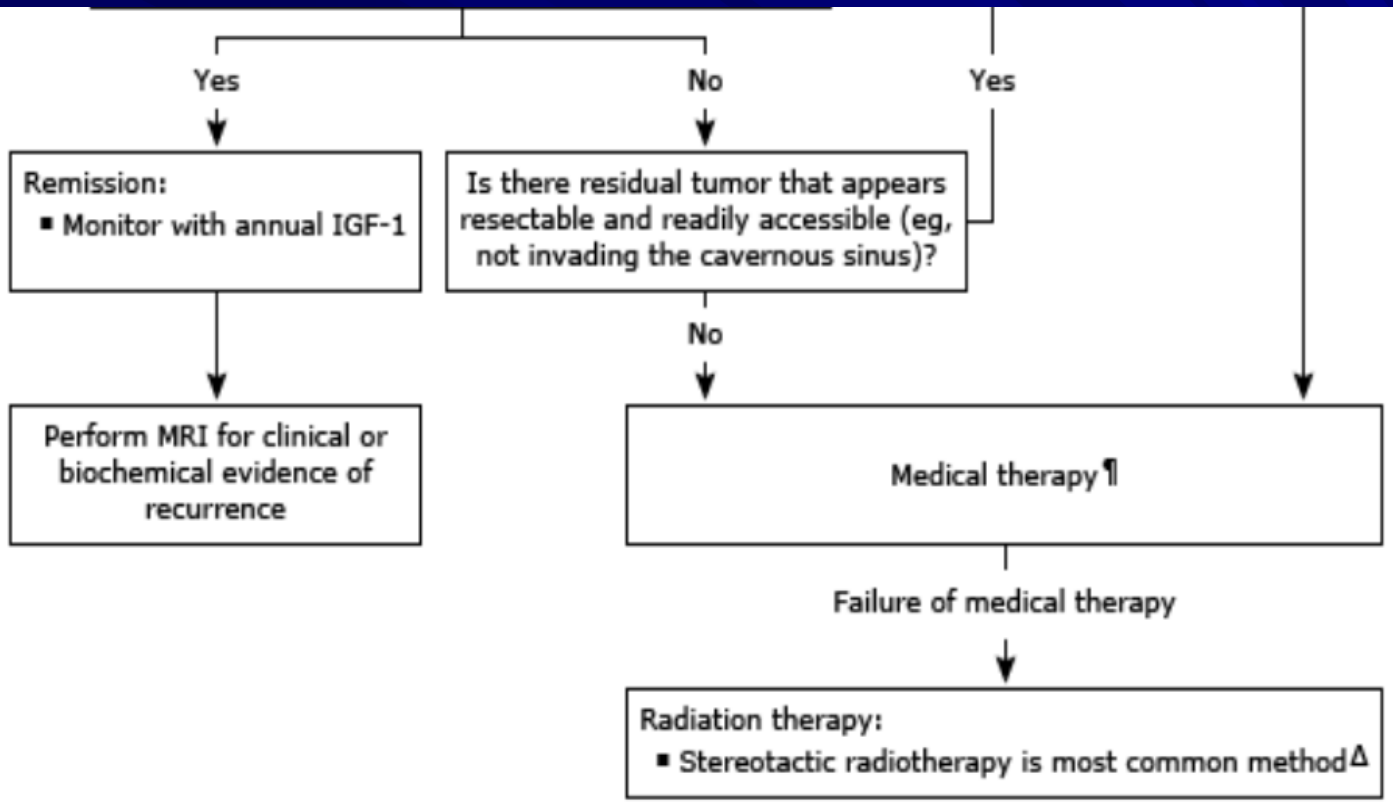
- Minimal or no response, tumor concern and impaired glucose metabolism:
- Add pegvisomant to first-generation SRL

Stereotactic radiation therapy:

Therapy if biochemical control is not achieved after second-line therapy:

- Stereotactic radiosurgery or reoperation
- Temozolomide for unusually aggressive or proven malignant tumors (in close cooperation with a neuro-oncologist)

Stereotactic radiation therapy:



Stereotactic radiation therapy:

Other indications for RT include:

- An adenoma increasing in size despite medical therapy (ie, somatostatin analog plus pegvisomant)

Stereotactic radiation therapy:

Other indications for RT include:

- Aggressive or atypical adenomas
- Patient desire to avoid the cost and administration of long-term medical therapy

Role of primary medical therapy:

- Some patients benefit from preoperative medication to allow easier intubation by reducing severe laryngeal swelling and macroglosia and to improve sleep apnea or cardiac dysfunction.

Role of primary medical therapy:

- Following initial treatment, patients should be evaluated every three to four months by both clinical examination and measurement of serum IGF-1 concentration for at least the first year.

Role of primary medical therapy:

- Medication dose is titrated upwards as needed every 2 months;
- if IGF-1 is not normalized at the maximum dose of somatostatin analog,
- alternative therapy should be considered.

Long-term management:

- Several steps are involved in the long-term management of patients with acromegaly.

Monitoring:

Clinical and biochemical:

- Even if the nadir of the serum GH concentrations after an OGTT is only slightly above the target values, the risk of recurrence is greater.
- Thus, patients with even subtle abnormalities in post-suppression GH levels may have a greater risk of recurrence.

- Freda PU, et al. J Clin Endocrinol Metab 2004; 89:495.

Monitoring:

Clinical and biochemical:

- Following initial treatment, patients should be evaluated every three to four months by both
- clinical examination and
- measurement of serum IGF-1 levels.

Monitoring:

- An elevated level suggests that the treatment has not been sufficient.
- If the IGF-1 level is normal after the initial treatment,
- it should be measured again in six months and then annually.

Monitoring:

If IGF-1 levels are normal,

- measuring random GH or OGTT nadir GH levels may not add helpful information.
- Medical therapy dose adjustments should be made using the IGF-1 levels.

Monitoring:

The Endocrine Society guidelines suggest that:

- an age-normalized serum IGF-1 and
- a random GH <1 mcg/L
- should both be therapeutic goals as they correlate with control of acromegaly.

- Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99:3933.

Imaging:

- MRI should be repeated 12 weeks after surgery
- and then yearly for the first several years after initial treatment and less often thereafter.
- Visual field assessment is indicated for patients whose adenomas threaten the optic chiasm.

- Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99:3933.

Systemic evaluation:

- In recent studies, cancer has been reported as the leading cause of death in acromegaly,
- likely related to longer life expectancy due to better control of the disease rather than a specific increased risk of cancer

- Kasuki L, et al. Arch Endocrinol Metab 2019. 63(6):630–637. 39.
- Bolfi F,et al.. Eur J Endocrinol 2018.179(1):59–71
- Arosio M, et al Eur J Endocrinol 2012.167(2):189–198.

Systemic evaluation:

- However, studies of the two cancers most associated with acromegaly, namely colon and thyroid cancer
- suggest that this risk might not be clinically significant.

- Lai NB, Garg D, et al.Endocr Pract 2020.26(1):16–21.
- Gadelha MR, et al.Endocr Rev 2019. 40(1):268–332.

Systemic evaluation:

- The rate of thyroid malignancies is not greater among acromegaly patients than among those without the condition.

Systemic evaluation:

Based upon different observations:

- Acromegaly appears to be associated with an excess risk of colonic polyps.

Systemic evaluation:

In a study comparing 178 patients and 356 controls, colorectal polyps were found in:

- 67% of patients in the acromegaly group
- and in 24% of the control group ($p < 0.001$),
- but there was no difference in histology subtypes .

- Ochiai Y, et al. Eur J Endocrinol 2020.182(3):313–318.

Systemic evaluation:

Colonoscopy is suggested to be performed:

- at baseline & then every five years thereafter in
- patients in those found to have a polyp
- or those with persistently elevated IGF-1 levels
- and every 10 years in those without polyps and with normal IGF-1 levels.

- Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99:3933.

Systemic evaluation:

- Comprehensive cardiovascular evaluation should be performed regularly,
- and hypertension and heart failure should be treated.

- Katznelson L, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99:3933.

Amelioration of symptoms:

- There is a rapid diuresis, and soft-tissue swelling
- and hyperglycemia can diminish remarkably in a few days.
- Vision, if impaired, and headaches can also improve in days.
- Sleep apnea and cartilaginous overgrowth also improve but often persist.

Amelioration of symptoms:

- Sleep apnea, tissue swelling, headache, and arthralgias resolve or improve in approximately 70 percent of patients controlled on medical therapy or surgery.

- Wolters TLC, et al. J Clin Endocrinol Metab 2020; 105.

Amelioration of symptoms:

- Skeletal, jaw, and joint changes are not reversible.
- Mortality outcomes appear to be more favorable with rigorous biochemical control.

Should GH deficiency be treated?

- It is estimated that 50 to 70 percent of patients with acromegaly treated with surgery alone or surgery combined with RT develop GH deficiency,

- Ronchi CL, et al. Eur J Endocrinol 2009; 161:37.

Should GH deficiency be treated?

- A complication that is associated with a decreased quality of life & mortality
- However, the impact of GH therapy in those who develop GH deficiency is still unclear.

- Wexler T, et al. J Clin Endocrinol Metab 2009; 94:2471.

Mortality in GH-deficient adults

with or without GH treatment

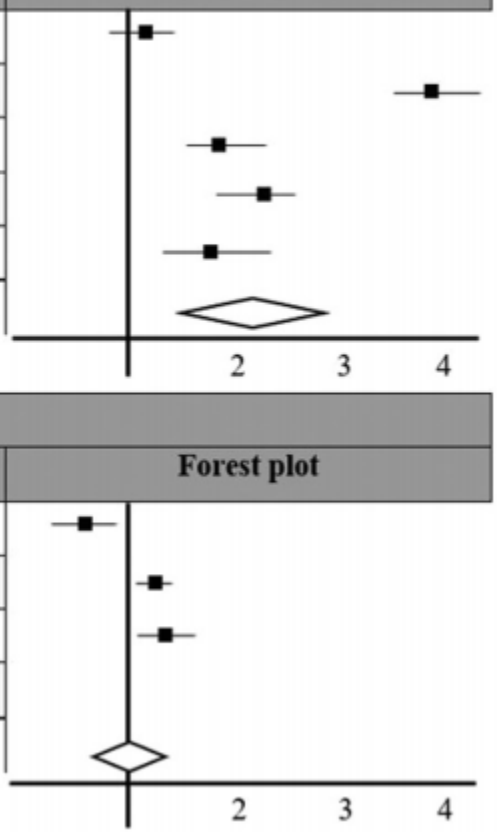
Figure 4. **Forest plots showing the difference in SMR among hypopituitary adults without and with GH treatment**

Studies without GH-treatment

Study	Year	Observed, *n*	Expected	SMR [95% CI]	Forest plot
Olsson *et al.*[90]	2017	93	80.2	1.16 [0.94-1.42]	
Svensson *et al.*[29]	2004	399	105.1	3.80 [3.43-4.19]	
Tomlinson *et al.*[26]	2001	181	96.7	1.87 [1.61-2.17]	
Bülow *et al.*[27]	1997	188	87.0	2.16 [1.86-2.49]	
Bates *et al.*[28]	1996	50	28.9	1.73 [1.28-2.28]	
Total				**2.14 [1.30-2.98]**	

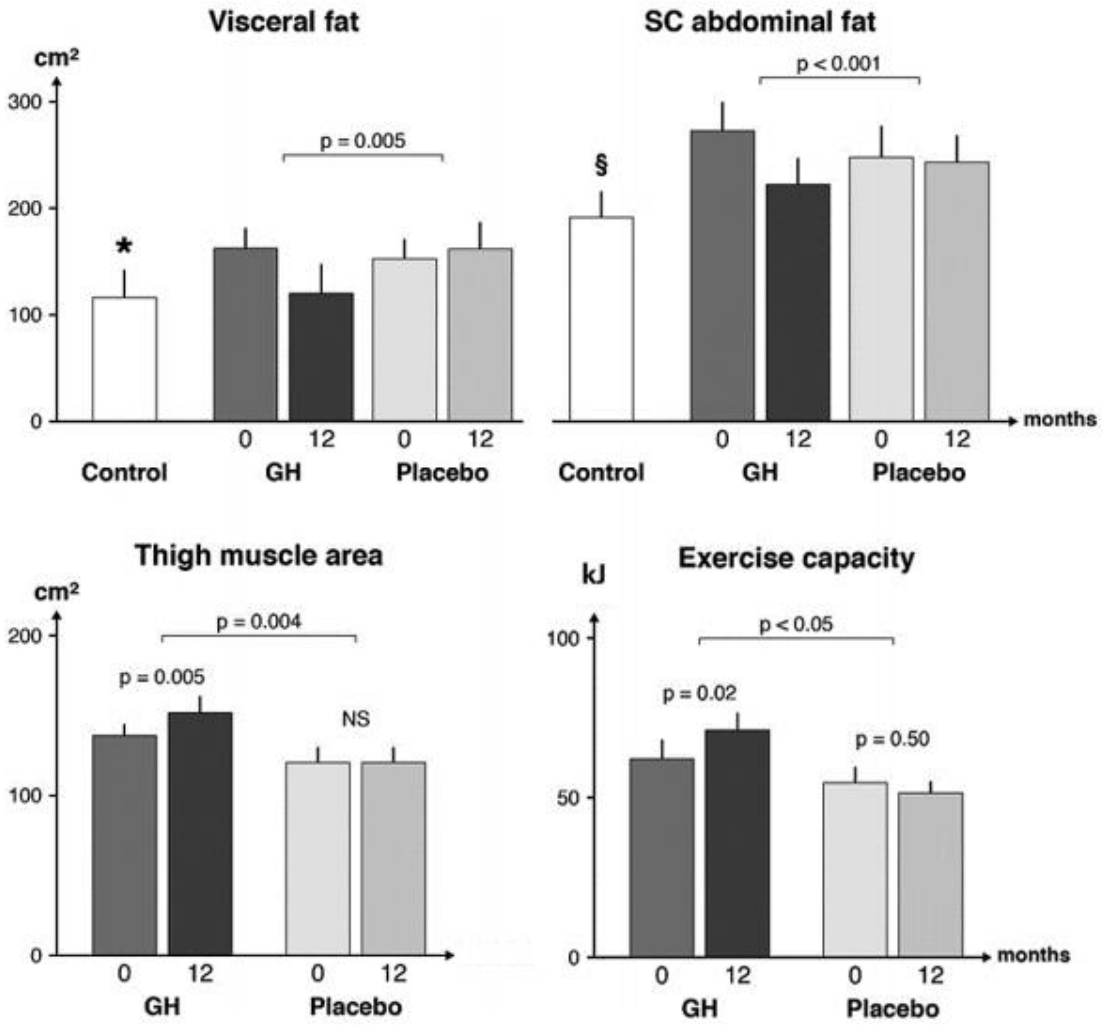
Studies with GH treatment

Study	Year	Observed, *n*	Expected	SMR [95% CI]	Forest plot
Olsson *et al.*[90]	2017	29	44.4	0.65 [0.44-0.94]	
Gaillard *et al.*[93]	2012	528	465.5	1.13 [1.04-1.24]	
Van Bunderen *et al.*[92]	2011	95	74.6	1.27 [1.03-1.56]	
Svensson *et al.*[29]	2004	8	9.5	0.84 [0.36-1.66]	
Total				**1.00 [0.72-1.28]**	



- Jorgensin JOLm,et al. European Society of Endocrinology. 2022,186:1

Should GH deficiency be treated?



Body composition & exercise capacity in GH-deficient patients.

Effect of GH therapy after one year

\HDU*+UHSODFHPHQWRU SODFHER

Endocrine guidelines:

Testing for GHD should only be down in adults with a reasonable probability of GHD

- patients with a history of hypothalamic & pituitary disorders
- and those that had undergone surgery
- and/or cranial irradiation to the brain
- with the intention to offer treatment when the diagnosis is established

- Kevin C J Yuen .European Journal ofEndocrinology (2021) 184, C5–C7

Endocrine Society Clinical Practice Guideline

- We recommend offering GH replacement to those patients with proven GHD and no contraindications.

- Fleseriu M, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016; 101:3888.

Endocrine guidelines:

- Recombinant human GH was approved over 25 years ago in Europe and the United States,
- there are now extensive efficacy and safety data supporting its use in adults with GHD.

- Kevin C J Yuen .European Journal ofEndocrinology (2021) 184, C5–C7

Should GH deficiency be treated?

- GH cannot lower CVD morbidity & mortality in adults with GH deficiency
- It improves lipid profile & increased bone mass,
- & muscle mass not strength

- Jorgensin JOLm,et al. European Society of Endocrinology. 2022,186:1

Should GH deficiency be treated?

- We do not suggest the routine use of growth hormone (GH) therapy in patients with acromegaly who develop GH deficiency, as available data are conflicting.

Review of treatment options:

Transsphenoidal surgery:

Selective transsphenoidal surgical resection is the treatment of choice for patients with:

- somatotroph adenomas that are small,
- large but still resectable,
- or large and cause visual impairment

Review of treatment options:

Transsphenoidal surgery:

- large adenomas that are not entirely accessible surgically (eg, those with cavernous sinus extension), with the goal of removing a sufficient mass to increase the likelihood that somatostatin analog treatment will be effective postoperatively.

Review of treatment options:

Transsphenoidal surgery:

- Some authorities recommend somatostatin analog treatment preoperatively, although the studies do not conclusively support this approach.

- Ben-Shlomo A, Melmed S. J Clin Endocrinol Metab 2003; 88:963.
- Albarel F, at al. Pituitary. 2018;21:615–23
- Lv L et al Clin Neurol Neurosurg. 2018;167:24–30.
- Losa M, et al. Endocrine. 2016;52:451–7.

Recurrence:

- Women, especially when postmenopausal, may exhibit lower surgical remission rates from TSS,
- as they tend to have larger and more invasive tumors that are less amenable to total resection.

Recurrence:

- Patient age is likely not a predictor of surgical outcomes, nor does it impact the favorable effects of postsurgical remission on alleviating disease comorbidities.

- Park SH, Ku CR, et al. J Clin Endocrinol Metab 2018.103(3):909–916.
- Ioachimescu AG, et al. Endocrine 2020. 67(2):423–432.
- Spina A, et al. Endocrine 2019.65(3):637–645.

Medical therapy:

Pharmacologic treatment is used when:

- surgery alone has not reduced serum GH and IGF-1 to normal.

Somatostatin analogs:

Octreotide and lanreotide

- Inhibit GH secretion more effectively than native somatostatin because of their greater potency and longer plasma half-life (two hours versus two minutes).

Somatostatin analogs:
Octreotide and lanreotide

- Their effect is greater when the number of receptors is high;
- repetitive administration does not result in desensitization or loss of therapeutic efficacy.

- Taboada GF, et al. Eur J Endocrinol 2008; 158:295.
- Fougner SL, et al. Clin Endocrinol (Oxf) 2012; 76:96.
- Melmed S. Nat Rev Endocrinol Nat Rev Endocrinol 2016; 12:90.

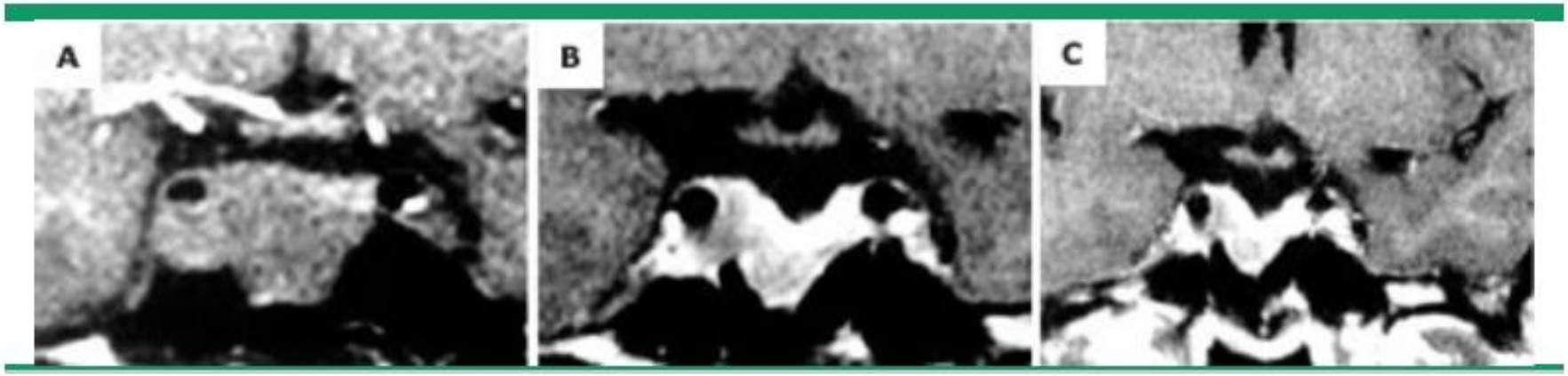
Somatostatin analogs:

Octreotide and lanreotide

- They also cause pituitary adenoma shrinkage in some patients.
- The mechanism of the shrinkage remains unclear.

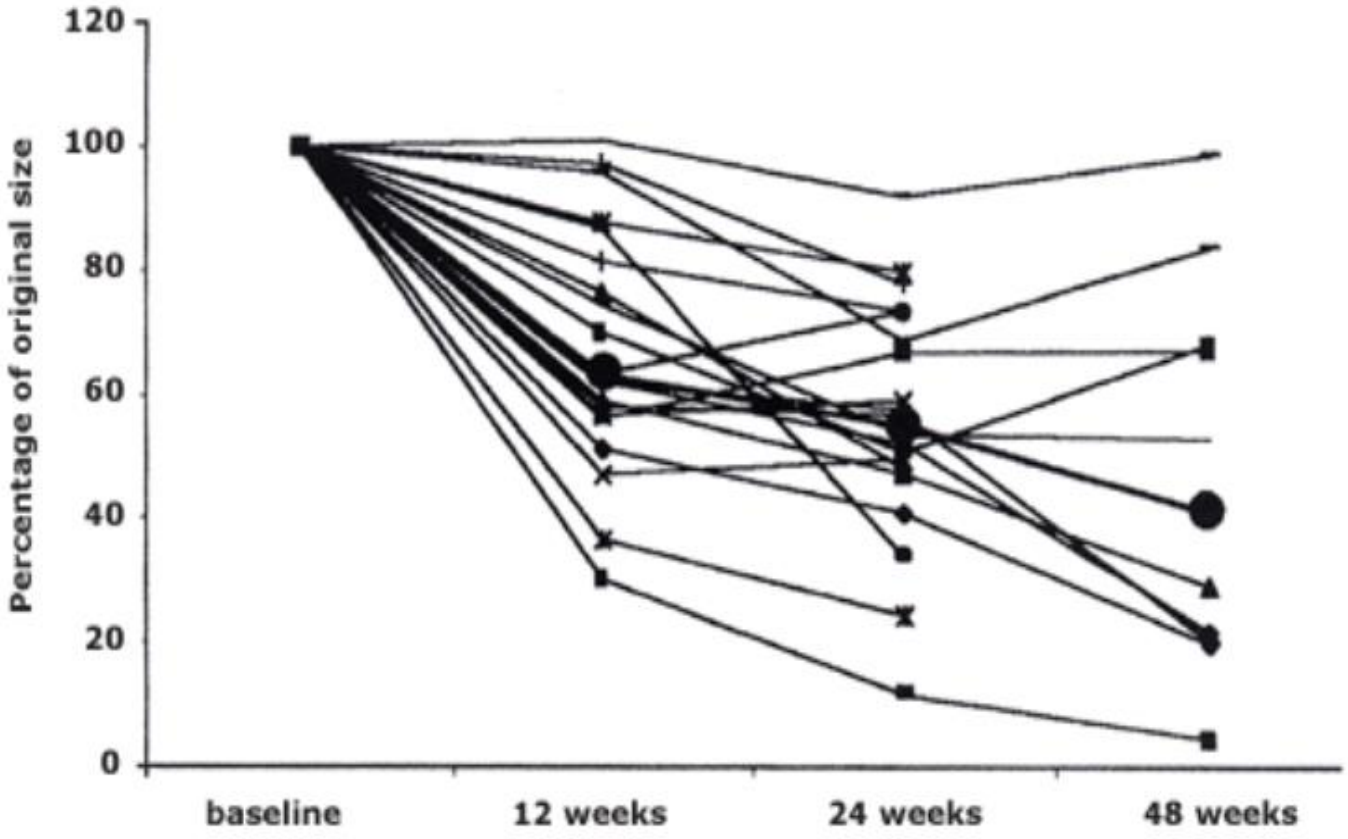
Somatostatin analogs:

Octreotide and lanreotide



- Effect of octreotide on the size of a somatotroph adenoma before (A) and after 12 weeks (B) and 24 weeks (C) of treatment with short-acting octreotide

Effect of octreotide on adenoma size

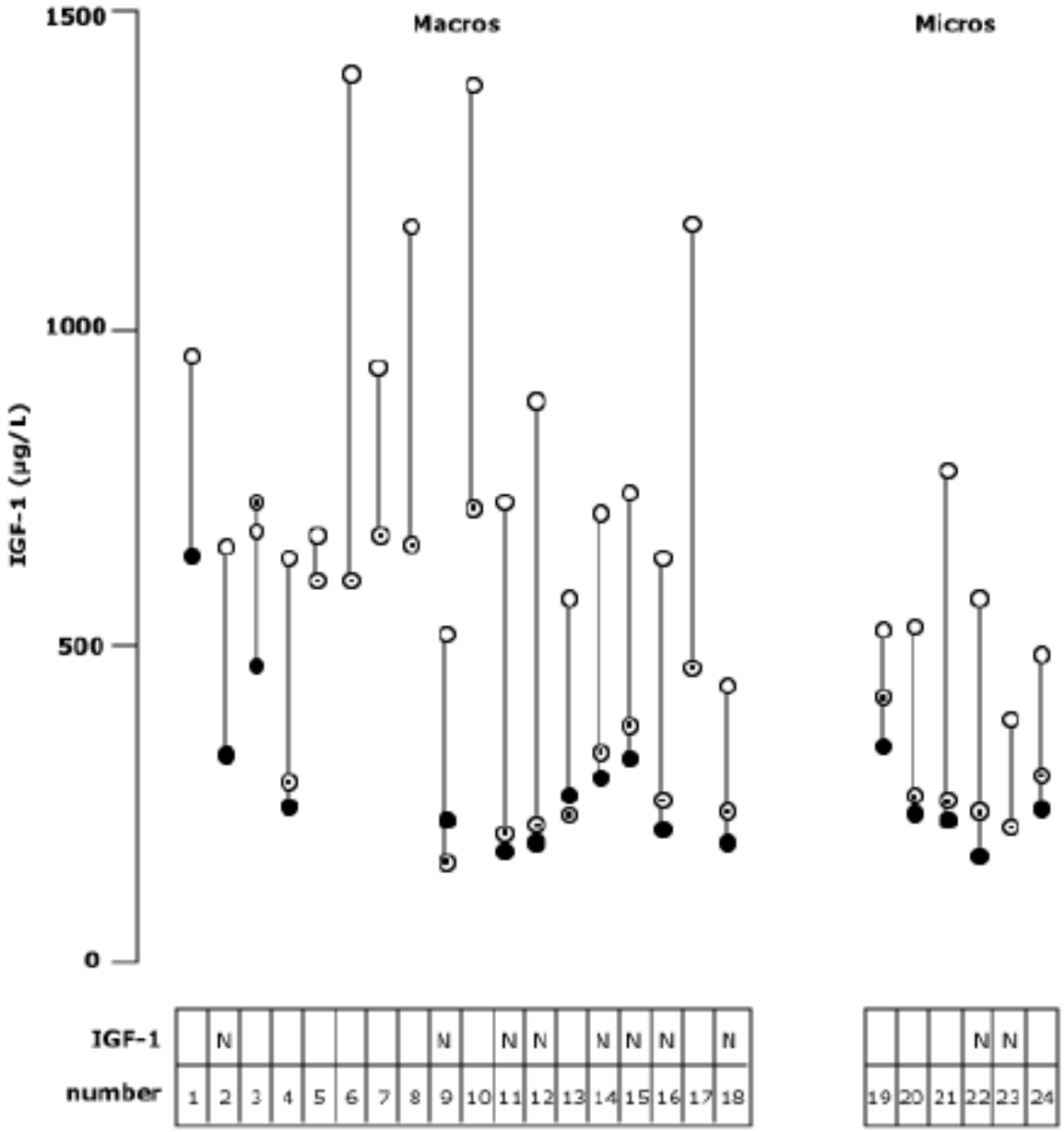


In 20 previously untreated acromegalic patients with macroadenomas, short-acting octreotide was administered for 24 weeks and then long-acting octreotide for another 24 weeks to 10 patients.

Data from: Bevan, JS, Atkin, SL, Atkinson, AB, et al. J Clin Endocrinol Metab 2002; 87:4554.

Graphic 65053 Version 1.0

Effect of octreotide on serum IGF-1



Octreotide and lanreotide:

Dose and administration

- The long-acting form of octreotide is given IM once a month.
- The initial dose is 20 mg once a month.
- If the serum IGF-1 concentration does not decrease to normal within two months,
- The dose can be increased to 30 mg and then to 40 mg a month.

Octreotide and lanreotide:

Dose and administration

- Lanreotide is given as a deep subcutaneous injection 60 to 120 mg every four to six weeks.

Octreotide and lanreotide:

Dose and administration

- In a study of 30 patients with a partial response to a somatostatin analog,
- use of high dose (180 mg/28 days) or high frequency (120 mg/21 days)
- both resulted in normalization of IGF-1 in approximately 30 percent of subjects.

- Giustina A, et al. J Clin Endocrinol Metab 2017; 102:2454.

Octreotide and lanreotide:

Dose and administration

- These regimens were well tolerated, and adverse events were similar between the groups.

Octreotide and lanreotide:
efficacy

- Appear to be equivalent for control of biochemical markers and symptoms.

- Murray RD, Melmed S. J Clin Endocrinol Metab 2008.93:2957
- Melmed S, et al. Nat Rev Endocrinol. 2018;14 (9):552–561

Octreotide and lanreotide:
Predictors of response:

Tumor subtypes may be a predictor of response to somatostatin analog therapy:

- The densely granulated tumors are typically smaller and more active (produce more GH)
- and respond well to somatostatin analogs.

- Larkin S, et al. Eur J Endocrinol 2013; 168:491.
- Kiseljak-Vassiliades K, et al. Endocrine 2012; 42:18.

Octreotide and lanreotide:

Predictors of response:

In contrast, the sparsely granulated subtype tumors:

- tend to be larger,
- more common in females and in younger patients,
- more invasive,
- and are relatively less responsive to somatostatin analogs.

Octreotide and lanreotide:

Predictors of response:

- A hypointense T2 signal on magnetic resonance imaging (MRI)
- also appears to be associated with a better response to somatostatin analog therapy

- Heck A, et al. Clin Endocrinol (Oxf) 2012; 77:72
- Puig-Domingo M, et al. J Clin Endocrinol Metab 2010; 95:4973.
- Potorac I, et al. Endocr Relat Cancer. 2016;23(11):871–881.

Octreotide and lanreotide:
Improvement in symptoms

- Patients experience more improvement in symptoms with somatostatin analogs than exhibit IGF-1 normalization,
- because even a partial decrease in GH results in some degree of symptomatic improvement.

- Colao A, et al. Endocr Rev 2004; 25:102

Octreotide and lanreotide:
Improvement in symptoms

Successful therapy is associated with an improvement in several signs and symptoms:

- Soft-tissue swelling,
- carpal tunnel syndrome,
- and snoring
- Sleep apnea
- Left ventricular mass and left ventricular function

Octreotide and lanreotide:
Side effects

Well tolerated but one third of patients have:

- nausea,
- abdominal discomfort,
- bloating,
- loose stools,
- and fat malabsorption during the first several weeks of therapy, after which the symptoms usually subside spontaneously with continued use.

- Lamberts SW, et al. N Engl J Med 1996; 334:246.

Octreotide and lanreotide:
Side effects

Somatostatin analogs are associated with:

- an increased risk of gallstone disease.
- Up to 56 percent of patients develop asymptomatic cholesterol gallstones or sludge during the first 18 months of therapy.

- Freda PU. J Clin Endocrinol Metab 2002; 87:3013.
- Grasso LF, et al. Expert Opin Drug Saf 2015; 14:1213.

Octreotide and lanreotide:
Side effects

- Octreotide and lanreotide transiently inhibit insulin secretion,
- but their clinical impact on glucose homeostasis is minimal.
- In a meta-analysis, there were no significant changes in fasting glucose or glycated hemoglobin (A1C) values.

- Mazziotti G, et al. J Clin Endocrinol Metab 2009; 94:1500.

Somatostatin analogs:
Pasireotide

- Several studies confirm efficacy of pasireotide LAR for some patients uncontrolled on lanreotide or octreotide LAR.
- Pasireotide LAR resultes in higher rates of hormonal control and tumor size reduction compared to octreotide LAR.

- Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014;2(11):875–884
- Colao A, et al. J Clin Endocrinol Metab.2014;99:791–9

Somatostatin analogs:
Pasireotide

- However, rates of treatment-induced hyperglycemia and DM are high, requiring careful monitoring for glycemic side effects.

- Gadelha MR, et al.Lancet Diabetes Endocrinol 2014. 2(11):875–884.
- Colao AAL, et al. Eur J Endocrinol 2020.182(6):583
- Giustina A, et al. J Clin Endocrinol Metab. 2019. 105(4):937–946.

Somatostatin analogs:
Pasireotide

In a 12-month trial of 358 patients with acromegaly:

- receiving pasireotide LAR (40 mg/month/IM)
- or octreotide LAR (20 mg/month IM)
- biochemical control was achieved in more patients receiving pasireotide when compared with octreotide (31.3 versus 19.2 percent, respectively).

- Colao A, et al. J Clin Endocrinol Metab 2014; 99:791

Somatostatin analogs:
Pasireotide

- Hyperglycemia (often requiring insulin treatment) was more common with pasireotide LAR than octreotide LAR (57.3 versus 21.7 percent).
- Baseline glucose status (FBS>100 mg/dL) is a potential predictive factor to higher glucose after treatment.

- Schmid HA, et al. Endocrine. 2016;53:210–9

Somatostatin analogs:
Pasireotide

- Results of these studies support pasireotide use, in octreotide/lanreotide-refractory patients with normal glucose metabolism.

- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561

Somatostatin analogs:
combination therapy

In patients with a partial response to SRL and impaired glucose metabolism adding:

- Pegvisomant to somatostatin analogs, has a high efficacy and a good safety profile.

- Neggers SJ, et al. J Clin Endocrinol Metab. 2014;99 (10):3644–3652.
- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561

Somatostatin analogs:
combination therapy

Coopmans et al suggest:

- Switching from first-generation SRLs plus PEG therapy to the combination of PAS LAR plus PEG
- in non-diabetic patients, with active acromegaly

- Coopmans EC, et al. J Clin Endocrinol Metab. 2019;104(6):1978–1988

Oral octreotide:

- An oral formulation of octreotide (delayed-release capsules) has been approved for use for the management of acromegaly.

- Fleseriu M, et al. A Pituitary Society update to acromegaly management guidelines. Pituitary 2021; 24:1.

Oral octreotide:

- This agent is indicated for long-term maintenance therapy in patients with acromegaly
- who have complete or partial biochemical response to treatment with either octreotide or lanreotide.

Oral octreotide:

- Is not currently recommended for patients who have tumor characteristics predictive of octreotide resistance.
- Should be initiated at the time of the previously scheduled SRL injection.

Oral octreotide:

- Is initiated at a dose of 40 mg/day, given as 20 mg capsules twice per day.
- can be up-titrated by an increment of 20 mg every 2–4 weeks based on IGF-I and clinical symptoms.
- This is a more rapid escalation than is used with injectable SRLs, which often are up-titrated every 2- 3 months.

Oral octreotide:

- It appears to be effective in some patients with acromegaly,
- but perhaps less than long-acting injectable preparations
- adverse event profile was similar to that observed for injectable somatostatin analogs.

- Melmed S, et al. J Clin Endocrinol Metab 2015; 100:1699.

Pegvisomant:

- Pegvisomant is a GH receptor antagonist that blocks native GH from binding but does not activate the intracellular signaling that mediates its action.

Pegvisomant:

- Pegvisomant is a valid treatment alternative in patients not responsive to SRLs
- showing a good efficacy and a satisfactory safety profile.

- Grottoli S, et al. Endocrine. 2015;48(1):334–341

Pegvisomant:

- Is indicated in patients resistant to therapy with first-generation SRLs,
- particularly in diabetic patients
- because of its positive impact on glucose
- metabolism.

- Feola T, et al. J Clin Endocrinol Metab. 2019;104 (7):2892–2902
- Melmed S, et al. J Clin Endocrinol Metab 2015; 100:1699.

Pegvisomant:

Patients receiving pegvisomant should be monitored by:

- measuring IGF-1 levels (but not GH levels),
- as well as serial MRIs,
- to assure that there is no continued tumor growth.

Pegvisomant:

- In clinical trials of patients treated
- with pegvisomant and the incidence of increase in pituitary tumor size was 3.2%.

- Tritos NA, et al. Eur J Endocrinol. 2017;176:213–20.
- van der Lely AJ, et al. J Clin Endocrinol Metab. 2012;97:1589–97

Pegvisomant:

- In addition, liver function tests (LFTs) should be measured every six months,
- and if more than threefold elevated,
- the drug should be discontinued

Pegvisomant:

- Pegvisomant is administered as a daily, subcutaneous injection.
- The initial daily dose is 10 mg.

Pegvisomant:

- The serum IGF-1 concentration should be measured every four to six weeks and the dose adjusted, in 5 mg increments, to a maximum of 30 mg/day,
- to keep the serum IGF-1 within the normal range.

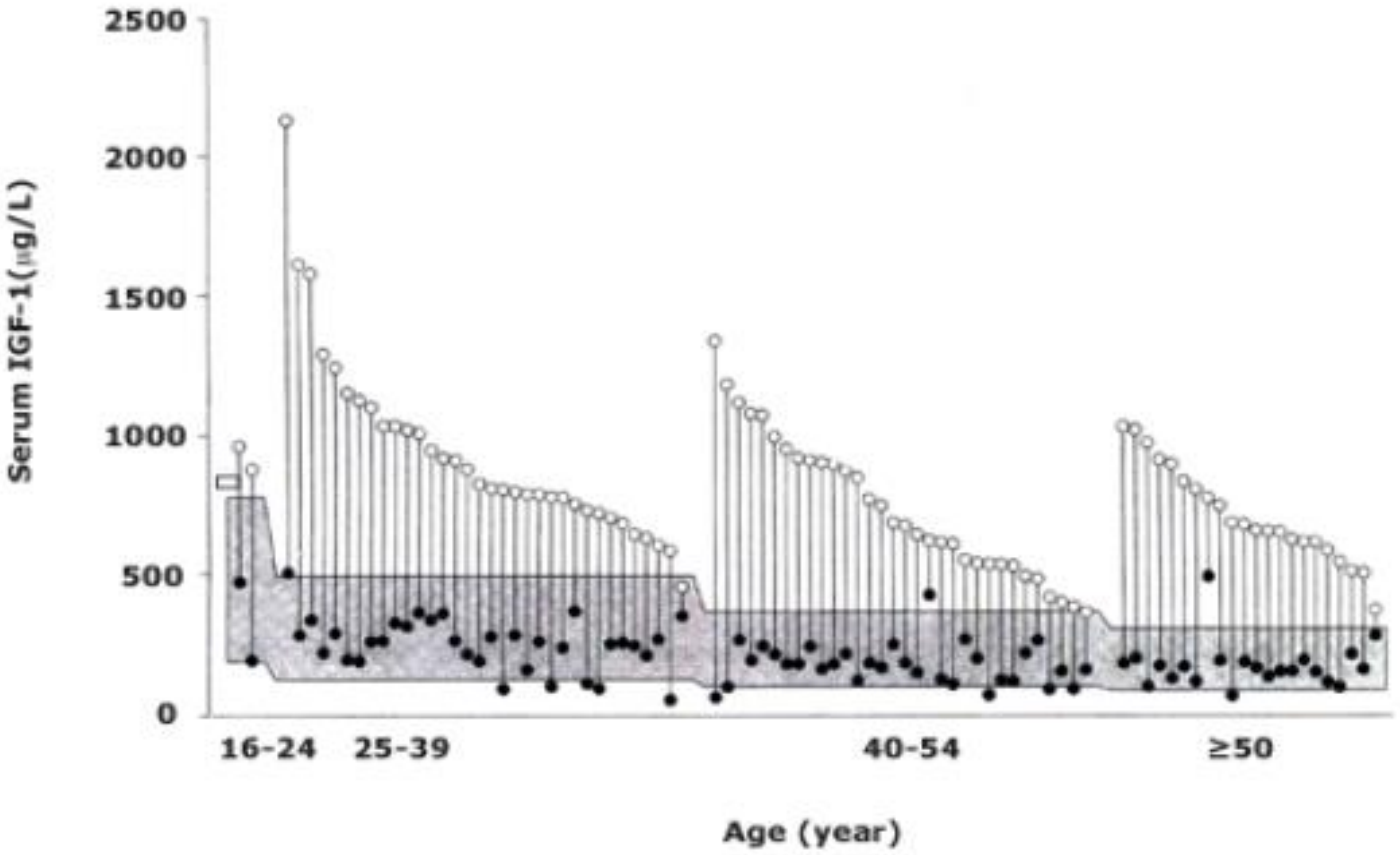
Pegvisomant:

- Serum GH cannot be used to monitor the effectiveness of treatment,
- Since pegvisomant inhibits the action of GH rather than its secretion.

Efficacy:

- 97 percent of those treated for 12 months or more with up to 40 mg/day achieved normal IGF-1 concentrations.

Effect of pegvisomant on serum IGF-1 concentrations



Results in 90 patients with acromegaly who were treated with the growth hormone receptor antagonist pegvisomant for 12 to 24 months. The open circles represent the pretreatment values and the closed circles the lowest post-treatment values. The shaded areas represent the normal ranges for age.

IGF-1: insulin-like growth factor-1.

Efficacy:

- Because pegvisomant does not inhibit GH secretion
- and its use is associated with an increase in the serum GH concentration,
- somatotroph adenoma size presumably could continue to grow during its use.
- However, this appears to be uncommon (3-6.8%).

- van der Lely AJ, et al. J Clin Endocrinol Metab 2012; 97:1589.
- Buchfelder M, ET AL. Eur J Endocrinol 2018. 179(6):419–427

Efficacy:

- Based upon such observations, patients receiving pegvisomant should have adenoma size assessed by MRI at least once a year.

- Buhk JH, et al. J Clin Endocrinol Metab 2010; 95:552.

Safety:

In the registry study noted above:

- 3 percent of patients developed elevated liver enzymes greater than three times the upper limit of normal.
- for whom follow-up data were available, liver enzymes returned to normal after decrease or discontinuation of pegvisomant.
- There were no reports of liver failure.

- van der Lely AJ, et al. J Clin Endocrinol Metab 2012; 97:1589
- Buchfelder M, ET AL. Eur J Endocrinol 2018. 179(6):419–427

Safety:

- Pegvisomant should therefore not be prescribed to patients who have clearly abnormal liver function,

Safety:

- and patients who are treated should be monitored by LFTs
- once a month during the first six months of treatment
- and every four to six months thereafter.

Pegvisomant:
Combination therapy

- Low-dose octreotide LAR or lanreotide plus weekly pegvisomant is a cost-effective and efficacious option for patients requiring combination therapy

Pegvisomant:
Combination therapy

- Combination of pasireotide plus pegvisomant can yield biochemical control rates exceeding 70%
- However, the addition of pegvisomant does not ameliorate the high rates of pasireotide-induced hyperglycemia

Dopamine agonists:

- Dopamine agonists, especially cabergoline, may inhibit GH secretion in some patients with acromegaly
- but do not work as well as somatostatin analogs.
- However, their oral route of administration is an advantage over the other treatments, which are administered parenterally.

Dopamine agonists:

- Cabergoline is the most effective dopamine agonist for the adjuvant management of acromegaly
- and is therefore the drug of choice in this category .

- Sandret L, et al. J Clin Endocrinol Metab 2011; 96:1327

Dopamine agonists:

- A trial of cabergoline is suggested in patients with modest biochemical abnormalities, eg, GH concentrations >1 mcg/L but <1.3 mcg/L and only mild symptoms of GH excess.

Dopamine agonists:
compination therapy

- We also suggest cabergoline in combination with a somatostatin analog in partial responders

- In whom with IGF-1 levels <2.5 times the upper limit of normal, with the greatest benefit seen in those with IGF-1 levels ≤1.5

- Melmed S, et al. Nat Rev Endocrinol. 2018;14 (9):552–561

Dopamine agonists:

Cabergoline could also be tried as primary therapy in:

- the occasional patient who has only a mild elevation of IGF-1
- and a small adenoma,
- is not a good candidate for surgery,
- and refuses monthly injections of a somatostatin analog.

- Melmed S, et al. Nat Rev Endocrinol. 2018;14 (9):552–561

Cabergoline dosing:

- The initial dose of cabergoline should be 0.5 mg once a week or 0.25 mg twice a week.
- The dose should be increased, if necessary, to 1.5 mg twice a week.

Cabergoline dosing:

- The presence of hyperprolactinemia does not consistently predict GH and IGF- 1 response.

Side effects:

The most common side effects of cabergoline are:

- nausea,
- light headedness,
- and mental fogginess.
- Less common are nasal stuffiness,
- depression,
- and constipation.

Radiation therapy:

- RT is effective in reducing the size of somatotroph adenomas (95%)
- and decreasing GH and IGF-1 concentrations, often to normal,(50-70%)

Different types of radiation therapy:

- Fractionated radiotherapy refers to radiation therapy delivered over multiple small doses in multiple sittings

- Del Porto LA, et al.J Clin Neurosci. 2011;18(2):181–190.
- Shih HA, et al.Rev Endocr Metab Disord. 2008;9(1):59–65.

Different types of radiation therapy:

- Stereotactic radiosurgery (SRS) is highly precise delivery of radiation in a single session targeted at the tumor,
- minimizing the dose received by surrounding critical neural structures, such as the optic nerve.

- Kim EH, et al. World Neurosurg 2018;110:e534–e545

Different types of radiation therapy:

- While the control of tumor growth is similar
- between the two techniques, with 95% of stable tumors observed at 5 years,
- stereotactic radiosurgery seems to result
- in a faster biochemical control compared to fractionated radiation.

- Shih HA, et al.Rev Endocr Metab Disord. 2008;9(1):59–65.

Different types of radiation therapy:

- Since SRS presents lower risk of complications,
- such as hypopituitarism, currently this approach is preferred to fractionated radiotherapy.

- Ding D, et al. Neurosurgery. 2019;84(3):717–725.

Monitoring:

- Because the full therapeutic effect of the RT may take many years and some patients may have limited response,
- it is important to perform annual reassessment of radiation efficacy.

Monitoring:

- Once a normal serum IGF-1 level is achieved,
- medical therapy should be withdrawn annually for one to three months (depending on the specific drug) for reassessment

Adverse effects:
Hypopituitarism

- Gonadotropin deficiency is most common,
- followed by corticotropin (ACTH)
- and then thyroid-stimulating hormone (TSH) deficiency.

Other complications:

- are cranial-nerve palsies,
- loss of vision,
- and memory deficits.
- Second intracranial tumors
- All are rare and usually occur only when the dose is high .

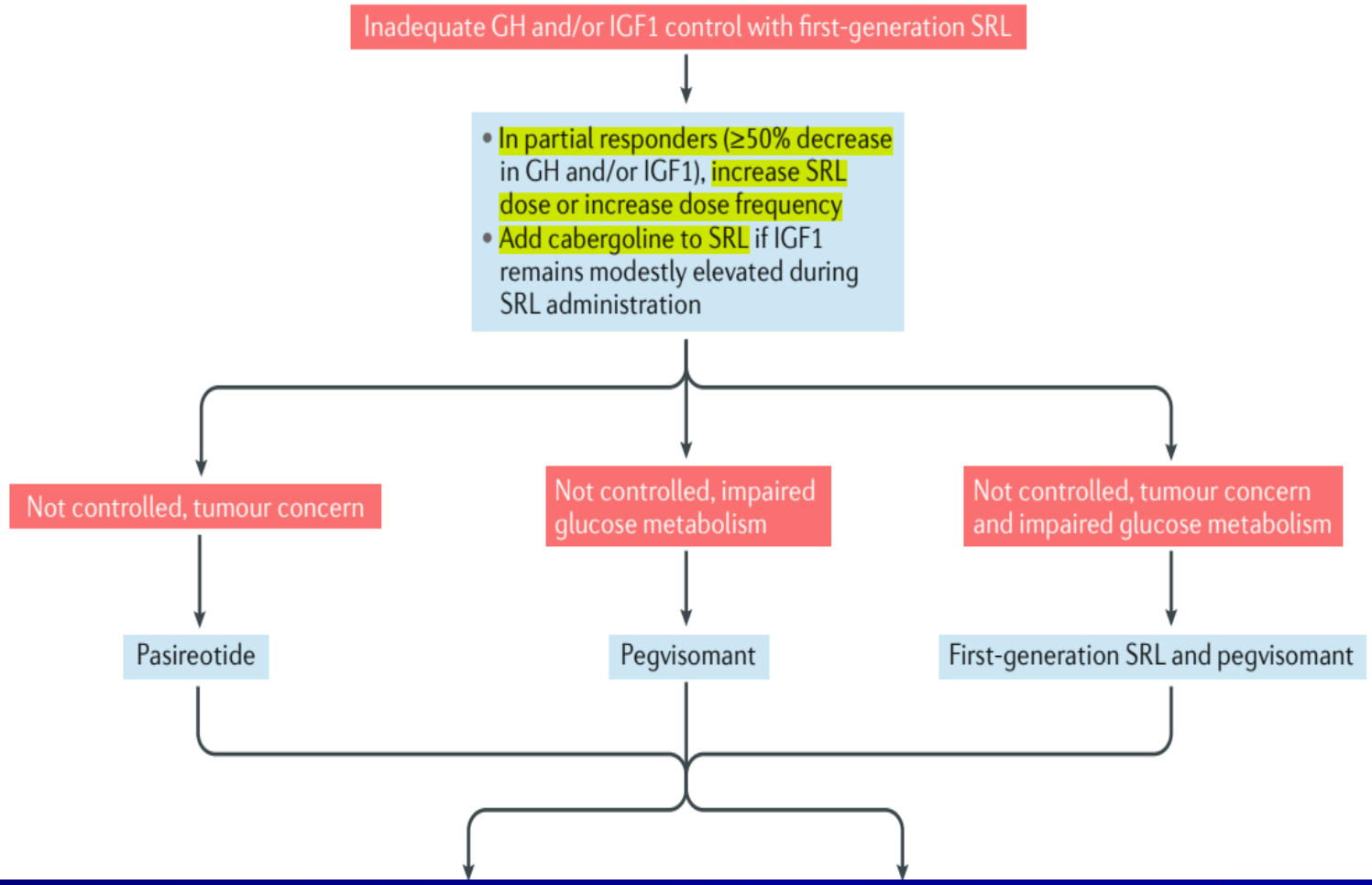
Aggressive tumors:

- Temozolomide for unusually aggressive or proven malignant tumors (in close cooperation with a neuro-oncologist)

- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561

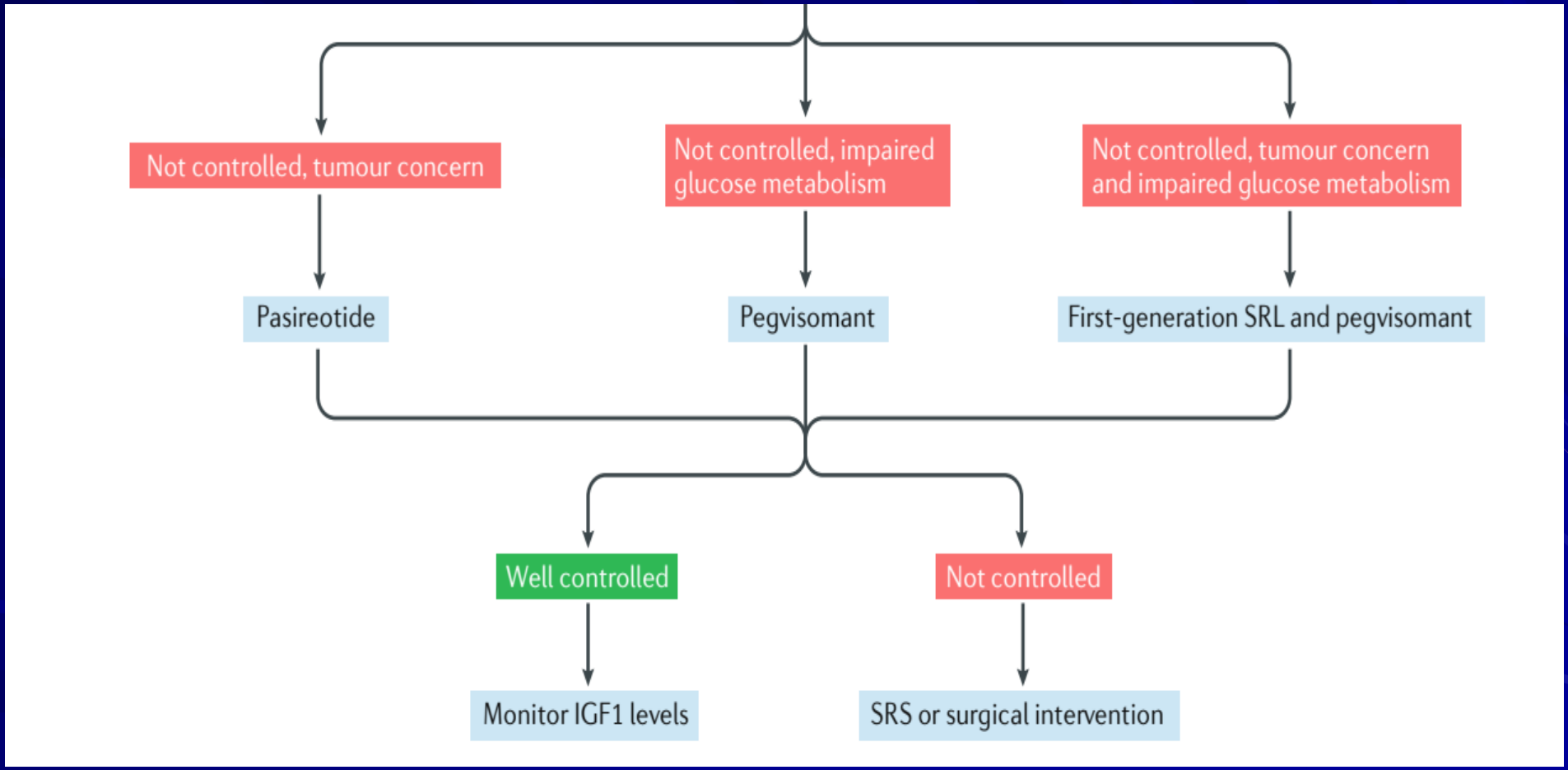
Management of acromegaly

summary:



Management of acromegaly

summary:



- Melmed S, et al. Nat Rev Endocrinol 2018. 14(9):552–561