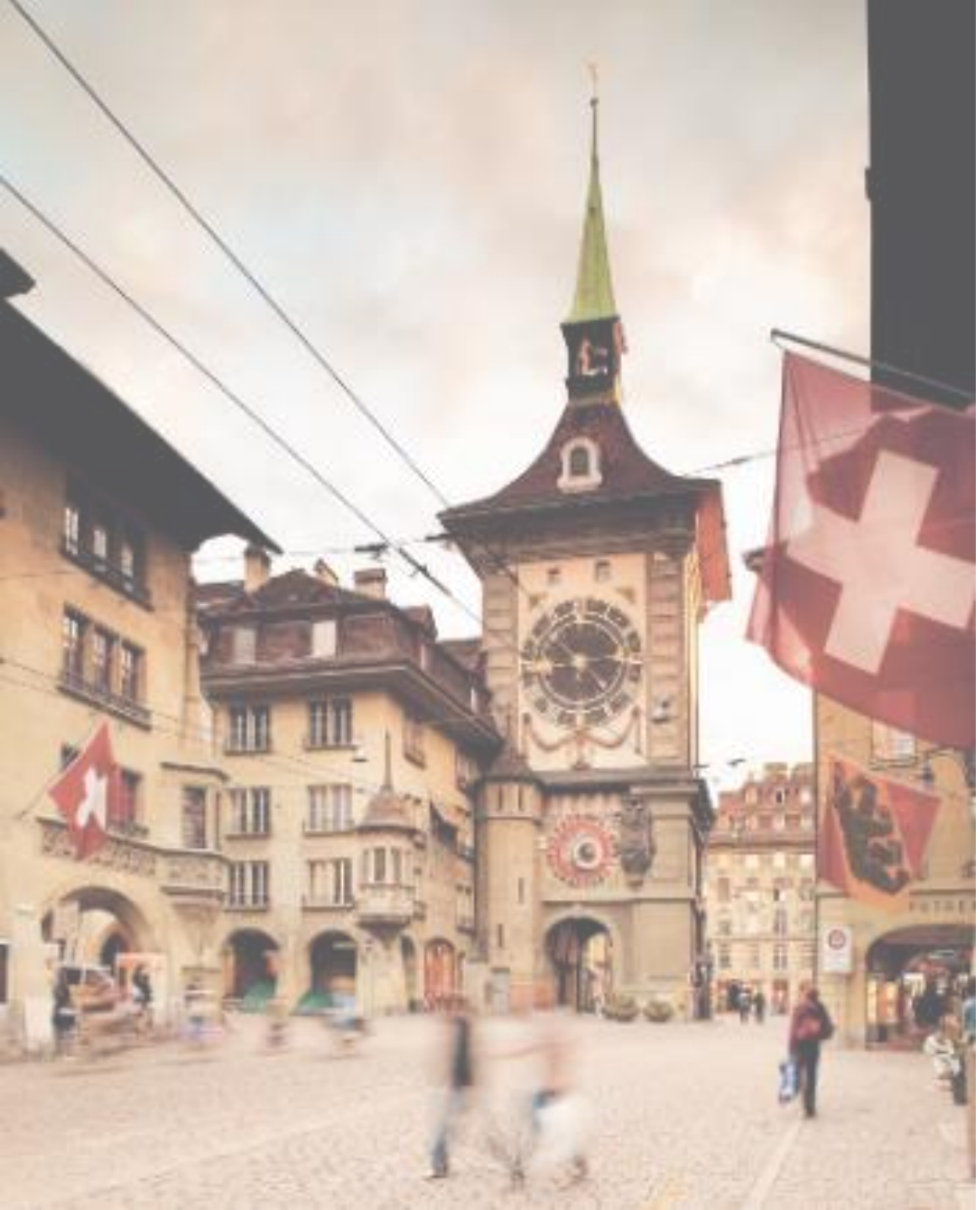


The Treatment of Acromegaly:

Update 2021

Post ADA/Endocrine
16.09.2021, Berne

Dre Maria Mavromati
Médecin Adjointe, Endocrinologie, HUG

Based on:

- ENDO 2020:

Ancillary Symposium ‘Improving Outcomes in Acromegaly: Let patients be your guide’

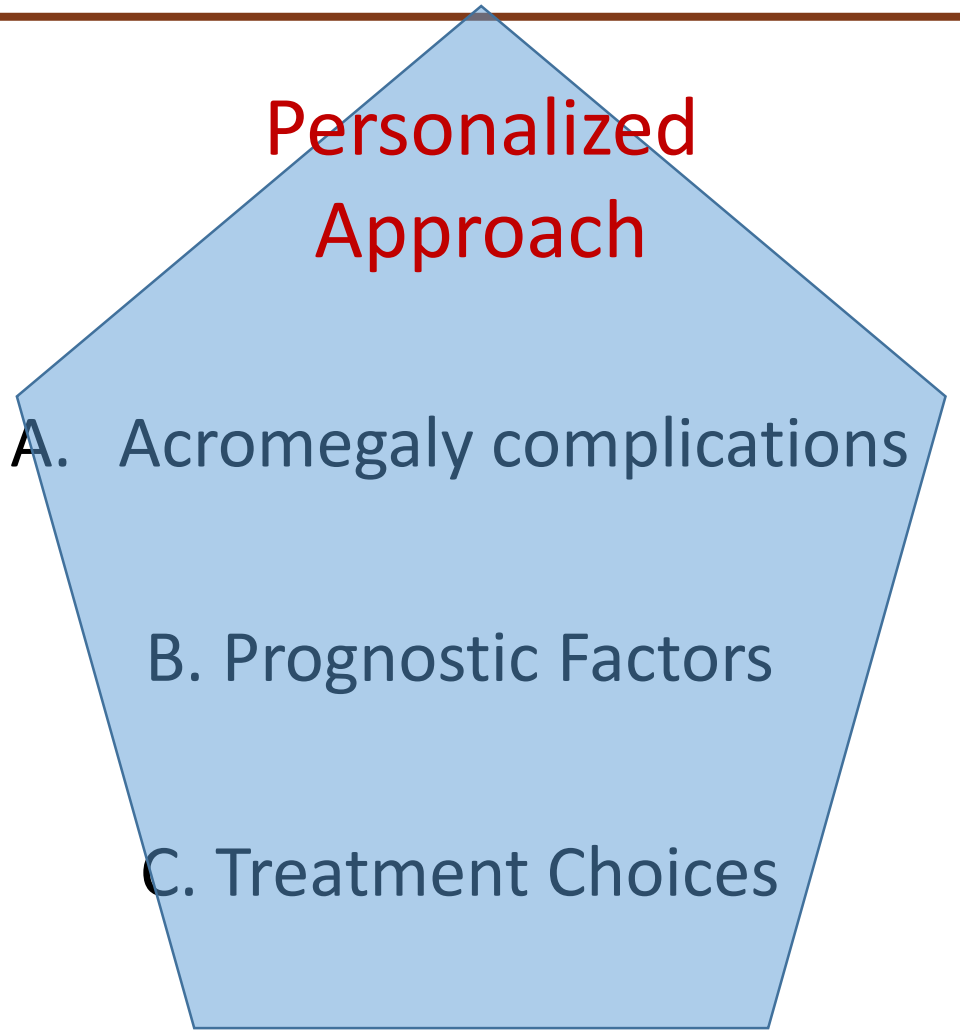
Shlomo Melmed, Lisa Nachtigall

- ENDO 2021:

‘Surveillance and Management of Long-Term Complications of Acromegaly’

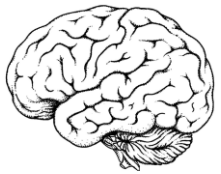
Robert Murray

Menu

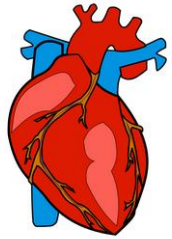

Personalized
Approach
A. Acromegaly complications
B. Prognostic Factors
C. Treatment Choices

A. Acromegaly Complications

Complications of Long-term Exposure to GH Hypersecretion and Treatment



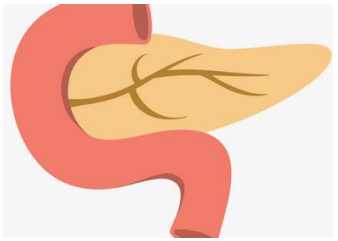
Headache
Stroke



HTA
Cardiomyopathy
Valvular disease

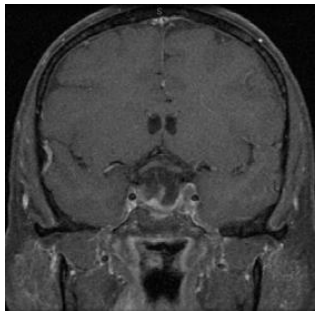
Sleep apnea
Respiratory complications

Glucose intolerance
Diabetes

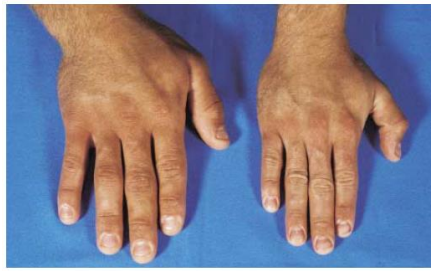


Acromegaly

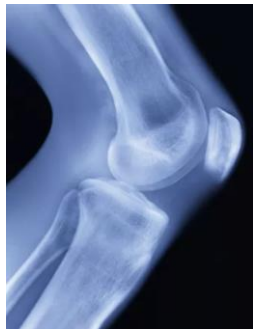
Hypopituitarism



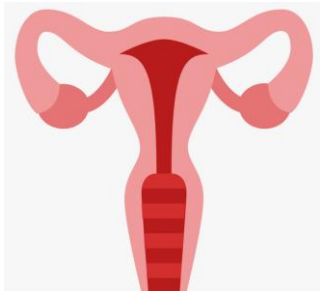
Acral overgrowth



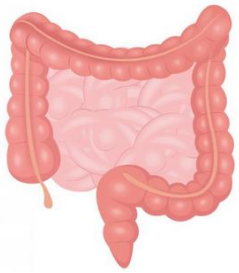
Arthritis
Fractures



Gonadal dysfunction

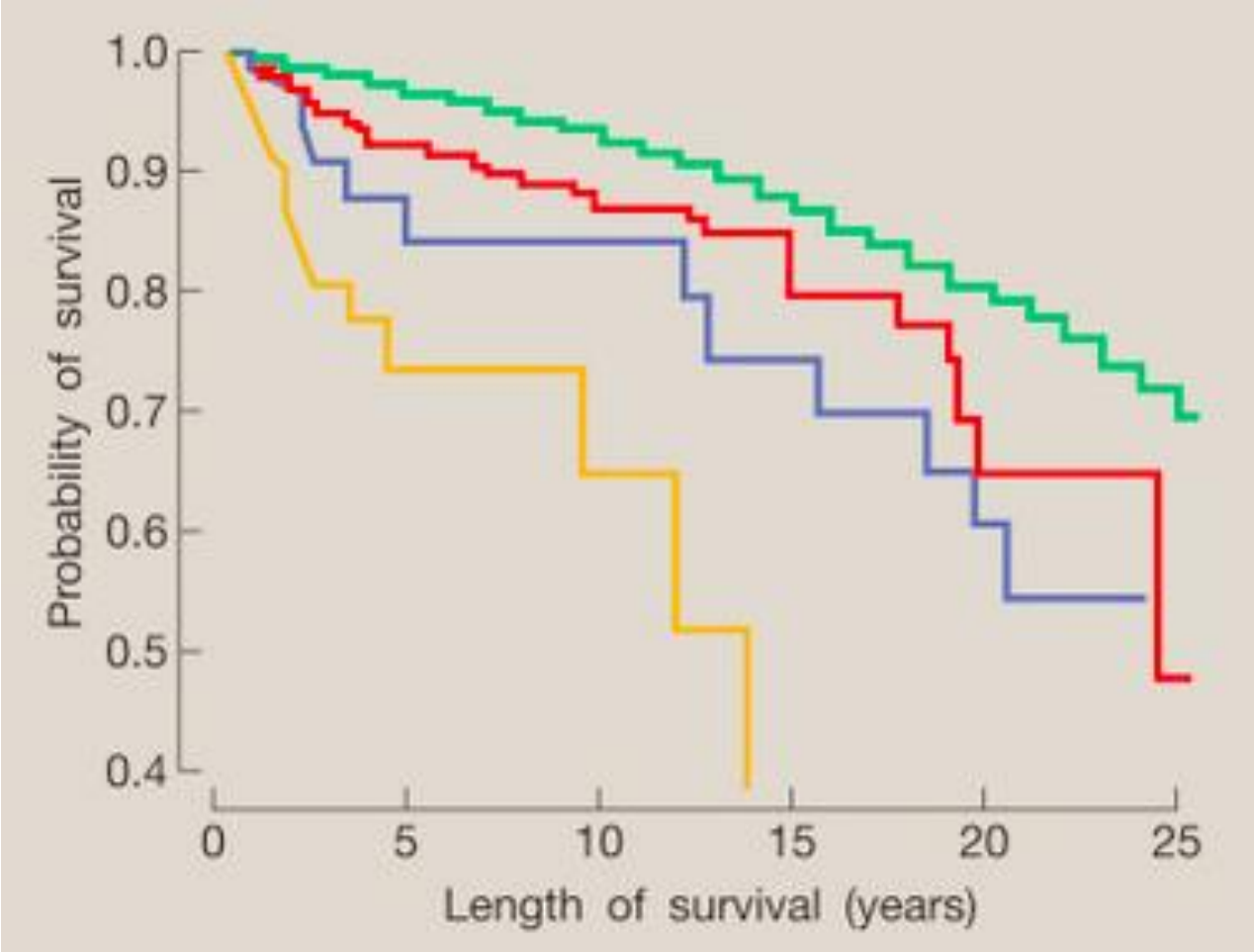


Colon polyps



Colao A. Endocrine Reviews 2004;25:102

Acromegaly Life Expectancy ↓ 10 years



General population

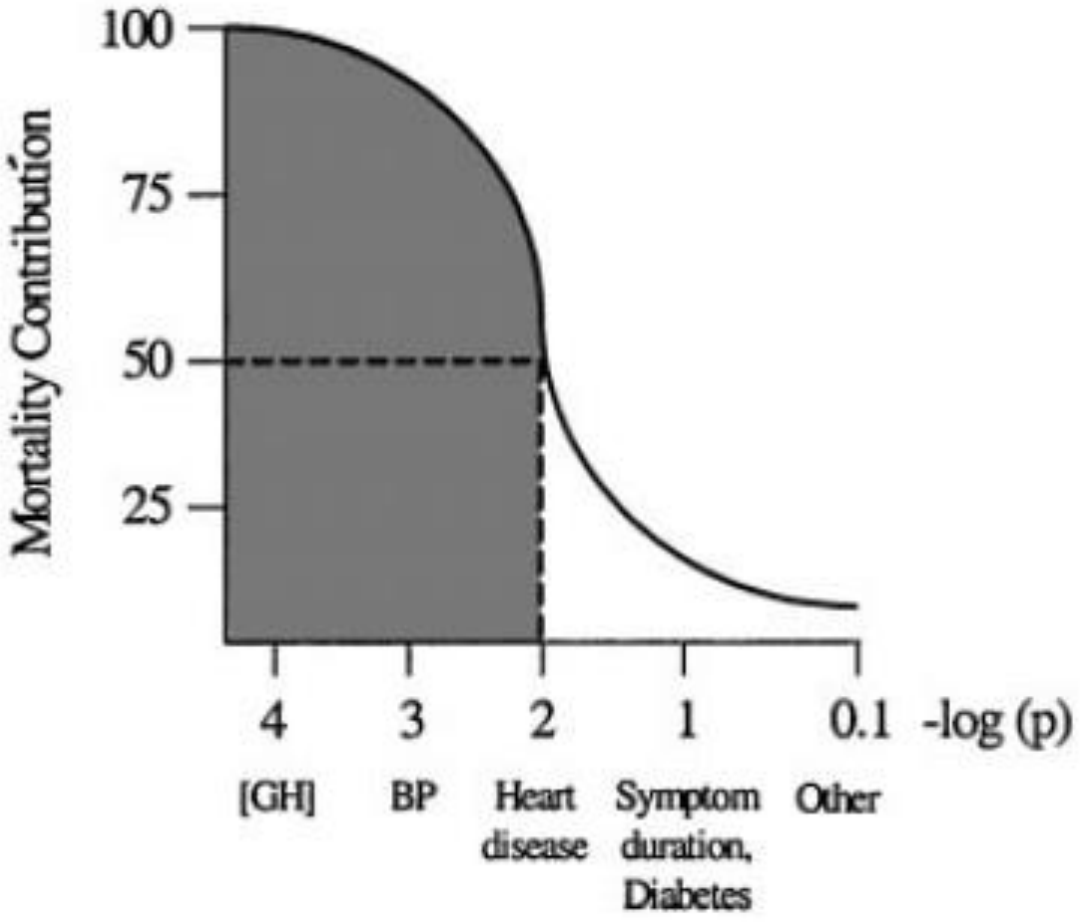
All acromegaly

Acromegaly + diabetes

Acromegaly + cardiac disease

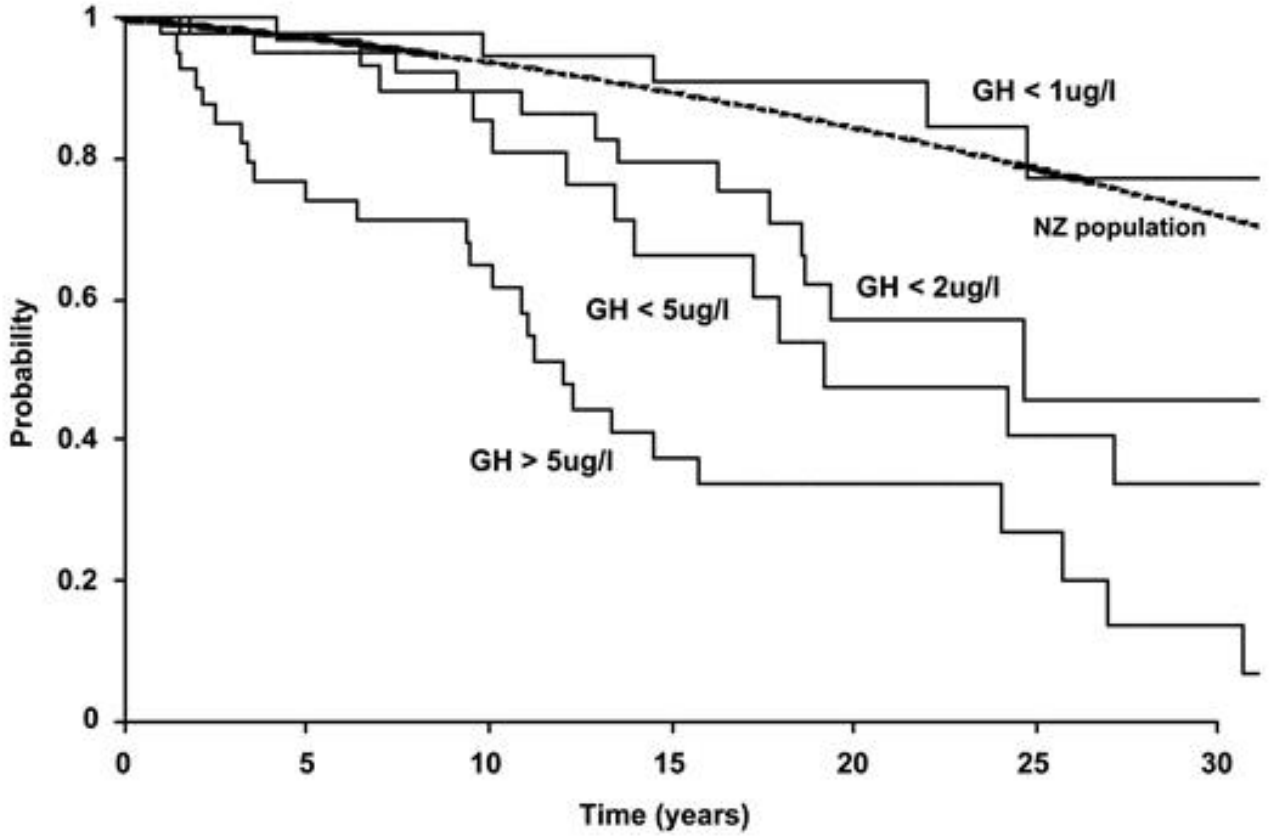
Rajasoorya C. Clin Endocrinol. 1994;41(1):95

Acromegaly Mortality Determinants



Melmed S. JCEM 2001;86(7):2929-34

Acromegaly Mortality Determinants



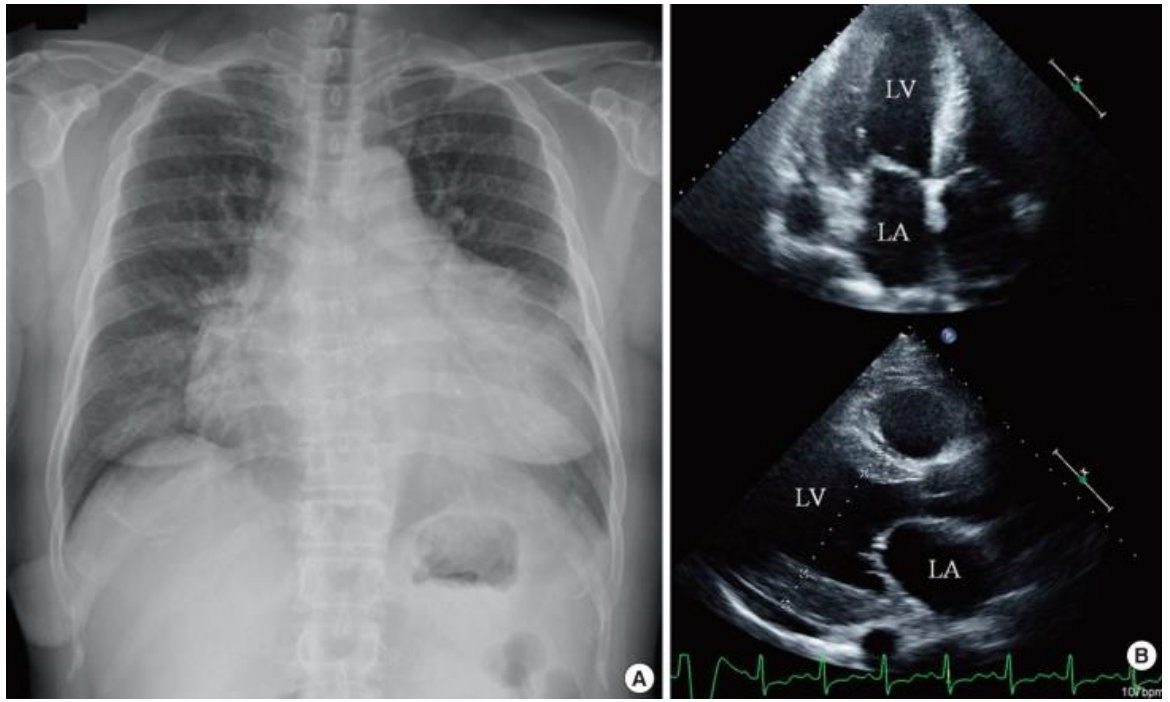
Holdaway I.M. JCEM. 2004; 89: 667
Sherlock M. Endocrine Reviews 2010; 31: 301

Cardiovascular Comorbidities in Acromegaly

CVD: Leading cause of premature mortality

GH associated with:

- HTA
- Cardiomyopathy
- LVH
- Valvulopathy
- Arrythmias



Cardiomegaly LVEF 25% in a 47-year-old female patient

Lee HM. Endocrinol Metab (Seoul) 2015; 30(3): 395

Respiratory Complications

- Sleep apnea in 50-70% of patients

- GH hypersecretion associated with:
  - enlarged pharyngeal & laryngeal soft tissues
  - macroglossia
  - pulmonary tissue hypertrophy

- Predictive factors:
  - duration of GH excess
  - obesity
  - gender (males)

Cancer Incidence in Acromegaly

Italian Registry (N=1512) :
increase in thyroïd, kidney and colorectal cancer

Cancer Type	Observed	Expected	SIR	95% CI	P value
All	124	88	1.41	1.18-1.68	
Colorectal	20	12	1.67	1.07-2.58	0.022
Kidney	10	3.5	2.87	1.55-5.34	< 0.001
Thyroid	13	3.3	3.99	2.32-6.87	< 0.001

Predictive Factors

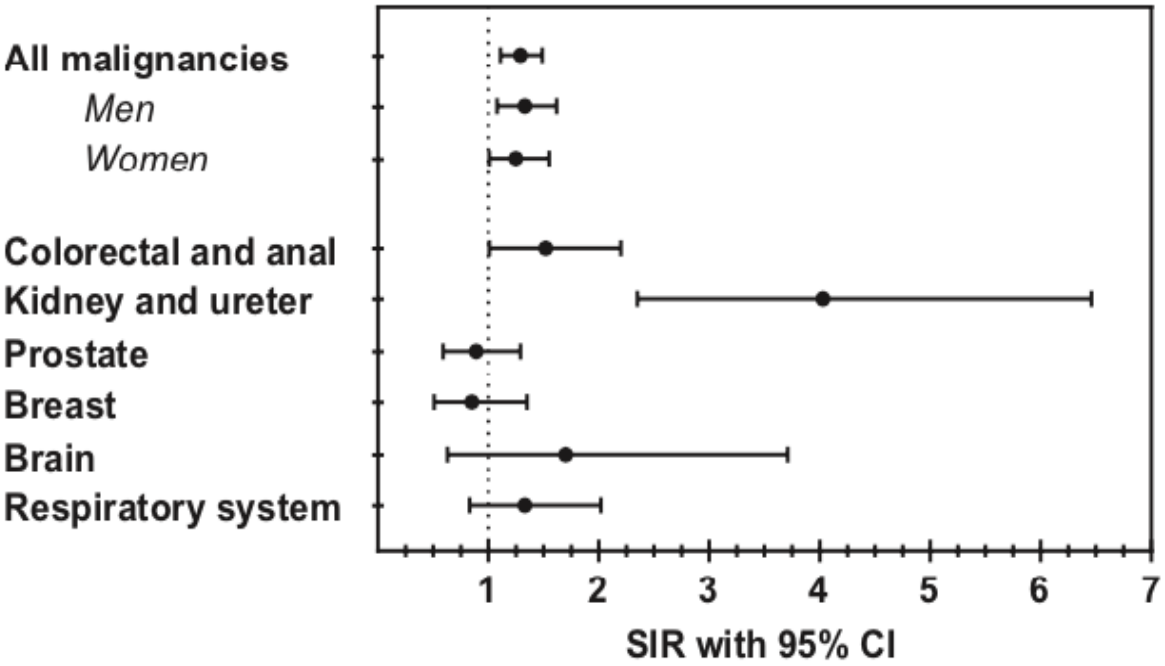
	OR	P value
Age	5.39	< 0.001
Family cancer history	1.73	0.04
Disease duration	1.27	0.08
Radiotherapy	1.76	0.10
IGF-1 at last visit	1.03	0.87

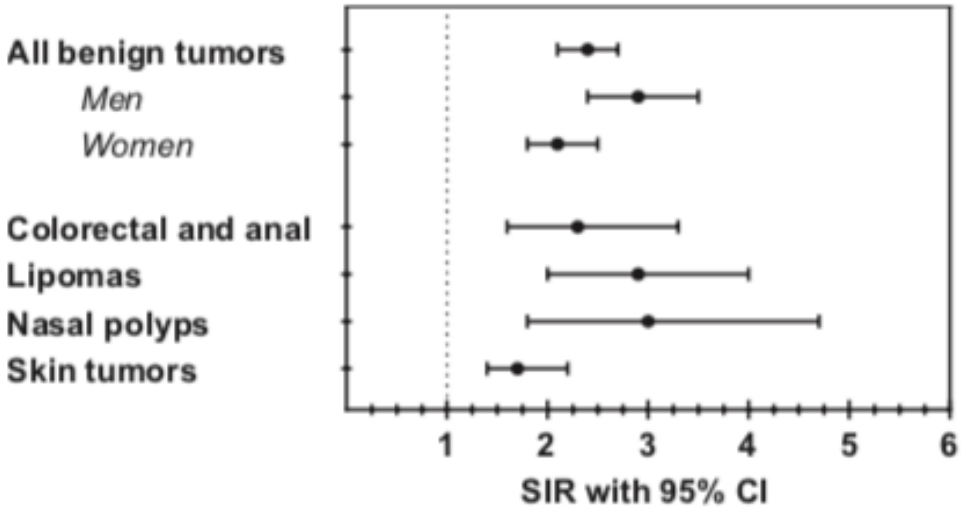
German Acromegaly Registry shows no increase (N=446)

Petroff D. JCEM 2015; 100: 3894
Terzolo M. Endocrine Related Cancer 2017;24(9):495

Cancer Incidence in Acromegaly

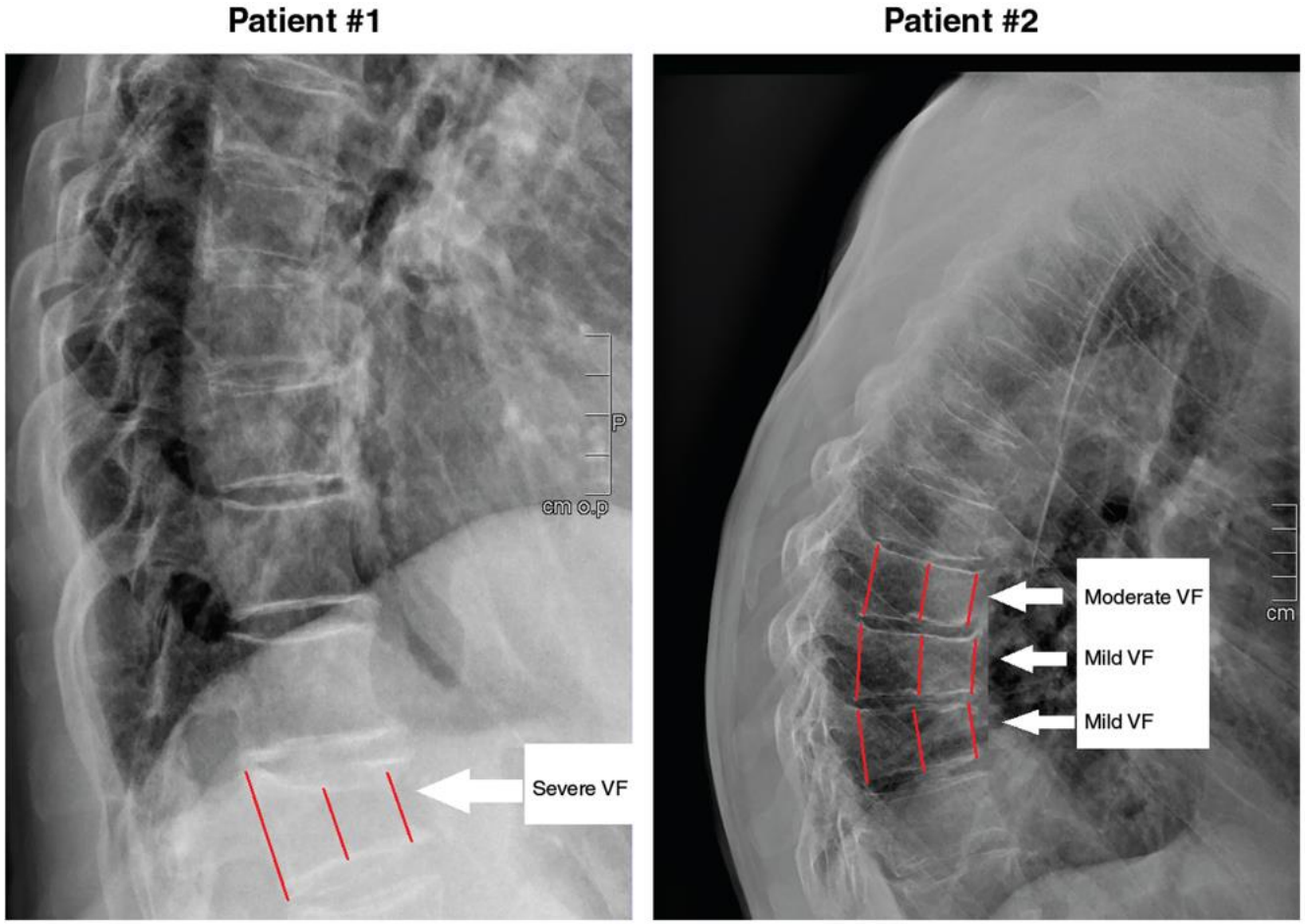
Swedish Registry (N=1296, 30 years) :
increase in benign and malignant tumors (colorectal, anal, renal, ureteral cancer)





Esposito D. JCEM 2021; 20(20): 1-10

Skeletal Fragility… a neglected surveillance

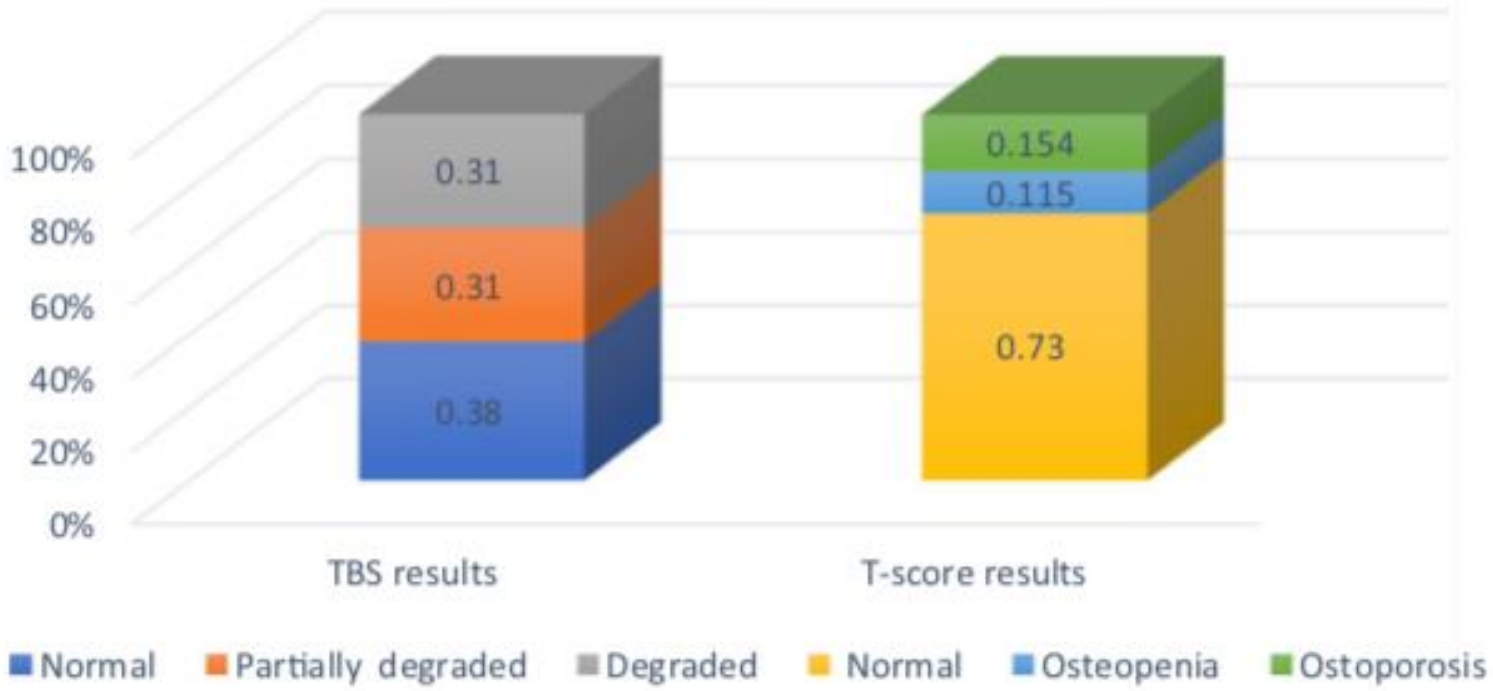


Vertebral fracture prevalence in acromegaly:

40% (M > F)

Mazziotti G. Eur J Endocrinol 2019;181(2):R45
Mazziotti G. J Clin Endocrinol Metab 100: 384 –394, 2015

Skeletal Fragility… a neglected surveillance



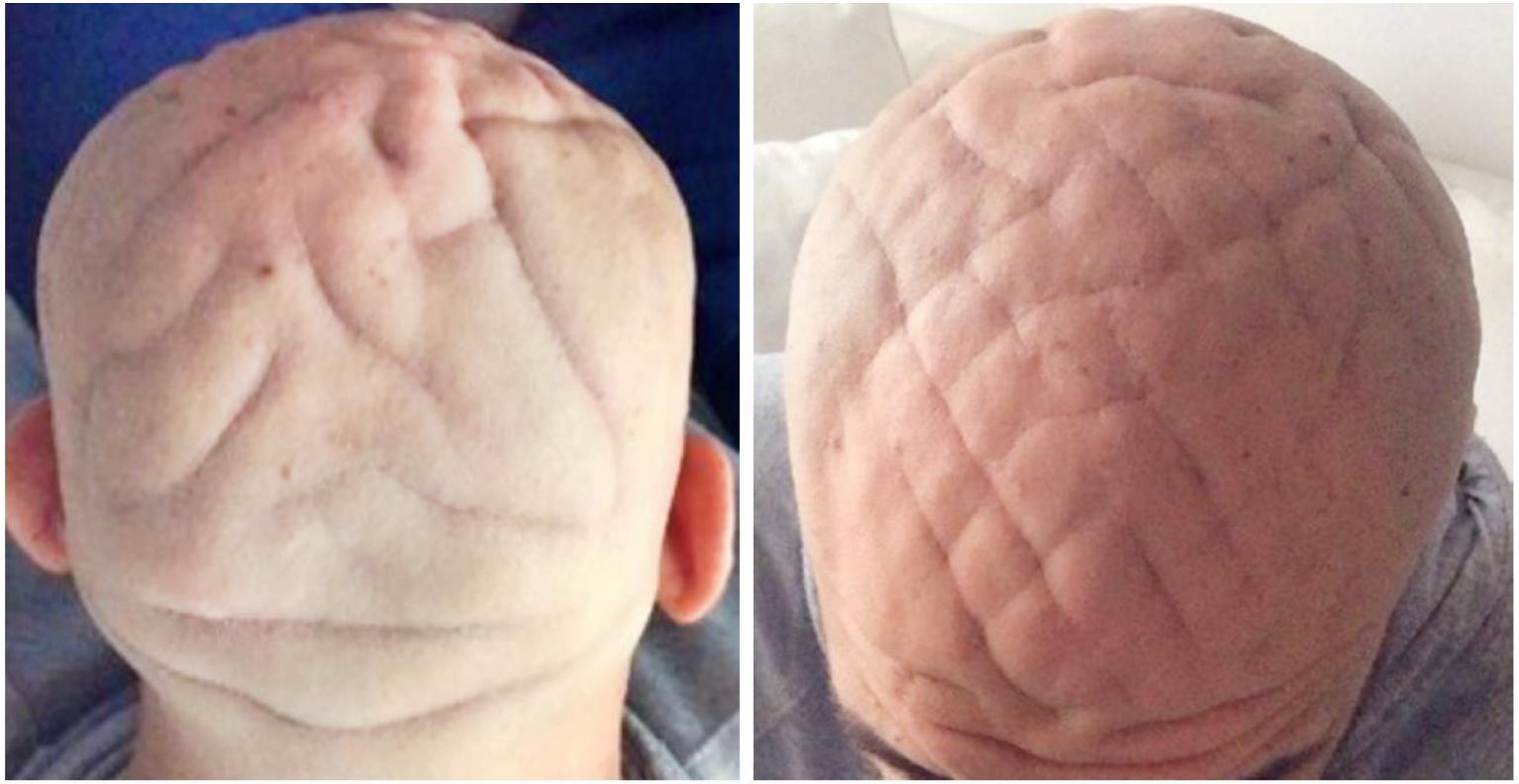
Trabecular Bone Score (TBS):

Indirect Measure of Trabecular Microarchitecture

Calatayud M. Clinical Endocrinology. 2021;95:58–64

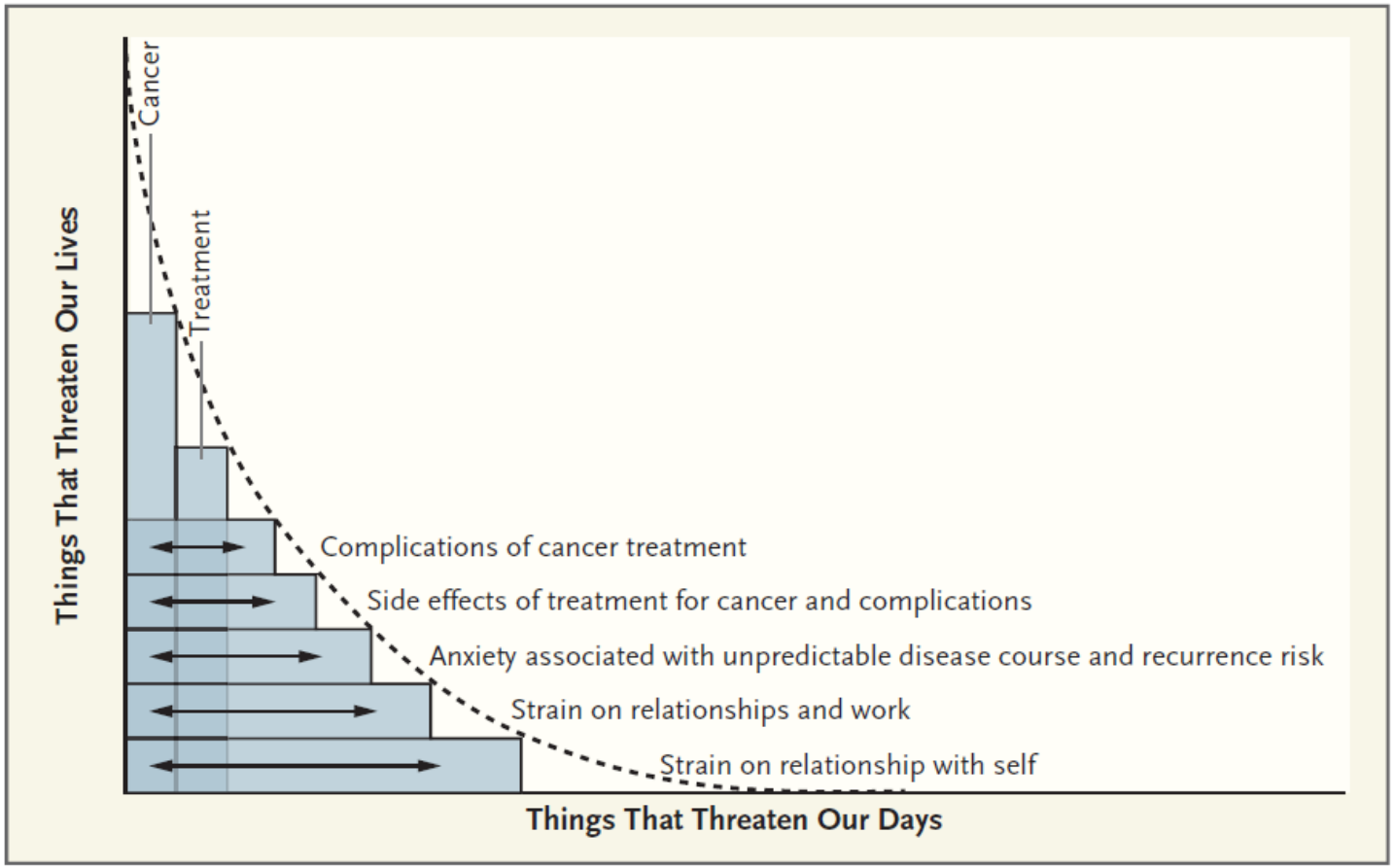
GH-induced Soft Tissue Proliferation

Cutis verticis gyrata in a 37-year-old patient



Parolin M. NEJM 2019;380(18):e31

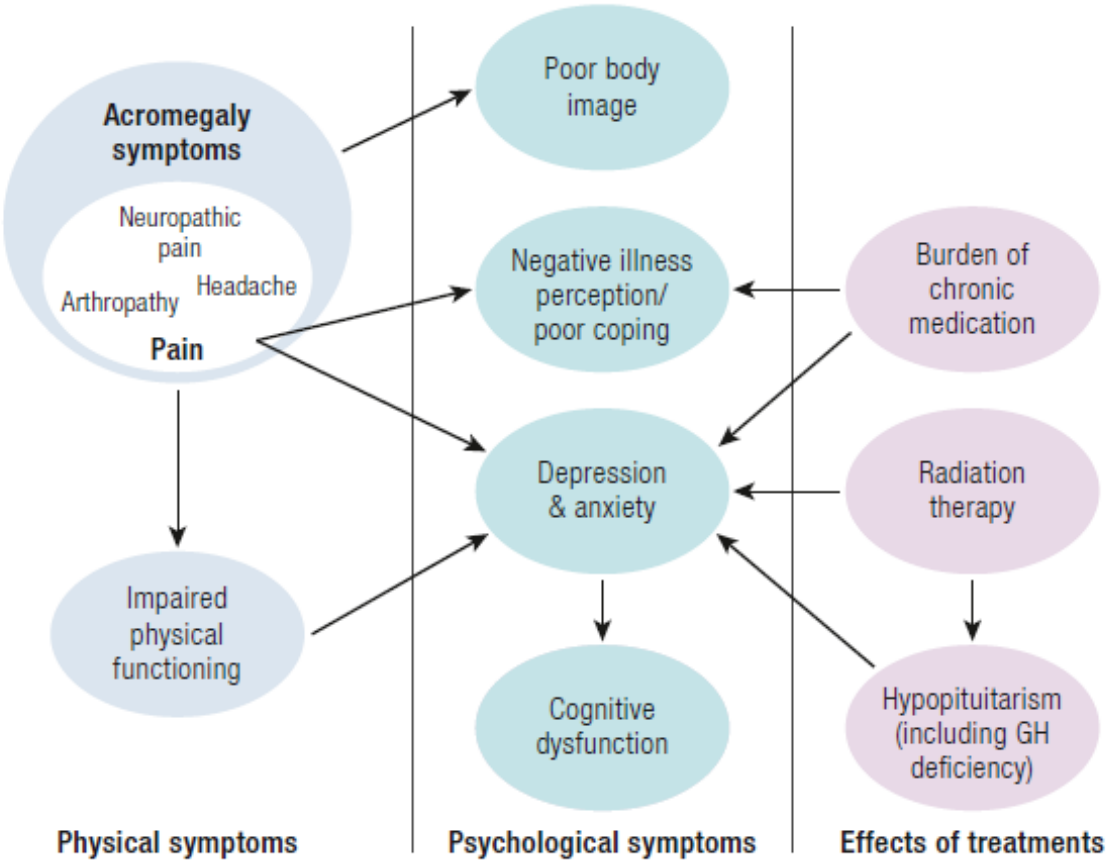
Life Challenges Curve



The Reality of Cancer (ROC) Curve.

Walker SP. NEJM 2019;380(17): 1594

Quality of Life



Gadelha M. Endocrine Reviews 2019; 40: 268

Monitoring Patient-Focused Outcomes

Endocrine replacement

Side effects of therapy

Arthralgias and Headache

Interpret laboratory testing

Cardiac failure
HTA
Diabetes
Sleep apnea
Other complications

Fertility

Maxillofacial surgery

QoL

Melmed S. JCEM 2009;94:1509

Screening of Complications

Complication	Screening and Diagnosis
Cardiovascular	Ambulatorial BP
	24-h monitoring BP
	ECHO
	ECG (if rhythm abnormality at physical exam)
	Referral to cardiologist if symptoms
Respiratory	Epworth scale
	Polysomnography (if symptoms ?)
Bone	Thoracic and lumbar x-ray or VFA
Articular	Clinical evaluation
Cancer	Colonoscopy (especially if > 40 yrs)
	Thyroid US (if palpable nodule)
Metabolic	Glucose level and lipid profile
Endocrine	Pituitary function
QoL	AcroQoL (repeat yearly)

Gadelha M. Endocrine Reviews 2019; 40: 268

S	SIGNS & SYMPTOMS	Which of the symptoms (S) from the list below is your patient experiencing?	Score S	Score S *from 0 to 4* *(0 = no Signs & Symptoms ticked)*
		Headache ☐ Sweating ☐ Joint symptoms ☐ Swelling ☐	Sum up the number of symptoms (S) ticked	S = ...
A	ASSOCIATED COMORBIDITIES	Which of the associated comorbidities (A) from the list below is your patient experiencing?	Score A	Score A *from 0 to 6* *(0 = no Comorbidities ticked)*
		Altered carbohydrate metabolism ☐ Hypertension ☐ Sleep apnea ☐ Heart disease ☐ Hypopituitarism ☐ Active malignant tumor ☐	Sum up the number of comorbidities (A) ticked	A = ...
G	GH NADIR WITH OGTT	Report concentration result of GH nadir with OGTT	Corresponding score	Score G *from 0 to 4*
		≤ 0.4 µg/l ○ > 0.4 to < 1.0 µg/ ○ ≥ 1.0 to < 2.5 µg/l ○ ≥ 2.5 to < 5 µg/ ○ ≥ 5 µg/l ○	G = 0 G = 1 G = 2 G = 3 G = 4	G = ...
	OR	OR	OR	OR
	GH RANDOM OR MEAN CONCENTRATION OF GH SERIES	Report concentration result from the test (GH random or mean concentration of GH series)	Corresponding score	Score G *from 0 to 4*
		≤ 1.0 µg/l ○ > 1.0 to < 2.5 µg/l ○ ≥ 2.5 to < 5 µg/l ○ ≥ 5 to < 10 µg/l ○ ≥ 10 µg/l ○	G = 0 G = 1 G = 2 G = 3 G = 4	G = ...
I	IGF-I	Report level relative to age-adjusted upper limit of normal *(ULN)*	Corresponding score	Score I *from 0 to 3*
		Normal ○ < 1.3 ULN ○ ≥ 1.3 to < 2 ULN ○ ≥ 2 ULN ○	I = 0 I = 1 I = 2 I = 3	I = ...
T®	TUMOR	Describe the tumor *(tick the worst choice by default)*	Corresponding score	Score T *from 0 to 5*
		No visible tumor ○ Micro tumor intrasellar < 10 mm ○ Macro tumor intrasellar ≥ 10 mm ○ Extrasellar tumor < 40 mm ○ Invasive tumor ○ Giant tumor ≥ 40 mm ○	T = 0 T = 1 T = 2 T = 3 T = 4 T = 5	T = ...

SAGIT Ipsen Pharma

Pituitary (2016) 19:39–49
DOI 10.1007/s11102-015-0681-2

CrossMark

SAGIT®: acromega from a pi

Andrea Giusti
Philippe Chans
Caroline Sert[7]
The SAGIT In

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. XX, No. XX, 1–14
https://doi.org/10.1210/clinem/dgab536
Clinical Research Article

ENDOCRINE SOCIETY

OXFORD

Clinical Research Article

International Multicenter Validation Study of the SAGIT® Instrument in Acromegaly

Andrea Giustina,[1] Marcello D. Bronstein,[2] Philippe Chanson,[3] Stephan Petersenn,[4] Felipe F. Casanueva,[5] Caroline Sert,[6] Aude Houchard,[6] and Shlomo Melmed[7]

Pituitary (2017) 20:692–701
DOI 10.1007/s11102-017-0835-5

CrossMark

Development of ACRODAT®, a new software medical device to assess disease activity in patients with acromegaly

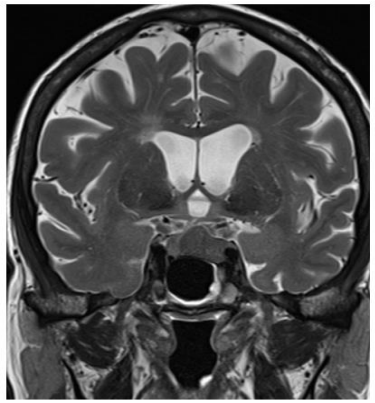
Aart J. van der Lely[1] · Roy Gomez[2] · Andreas Pleil[3] · Xavier Badia[4] · Thierry Brue[5] · Michael Buchfelder[6] · Pia Burman[7] · David Clemmons[8] · Ezio Ghigo[9] · Jens Otto Lunde Jørgensen[10] · Anton Luger[11] · Joli van der Lans-Bussemaker[12] · Susan M. Webb[13] · Christian J. Strasburger[14]

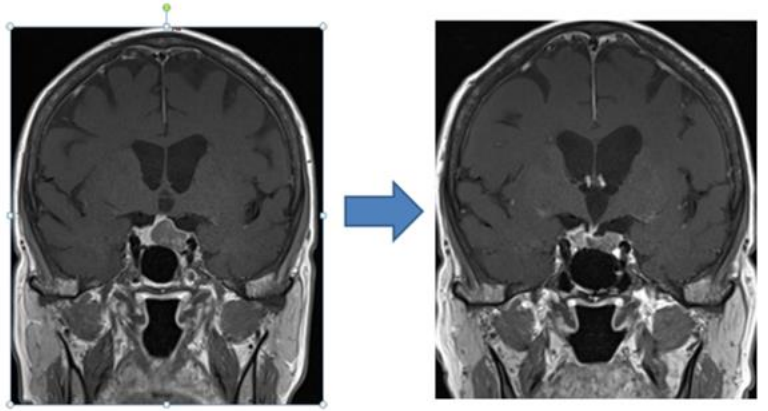
B. Prognostic Factors

Personalized Prognostic Factors

1. **Genetics:** AIP
2. **Age:** young
3. **Proliferation: size, invasion**
4. **MRI: T2 intensity**

   T2 hypo-intensity en T2 associated with better response on SRL



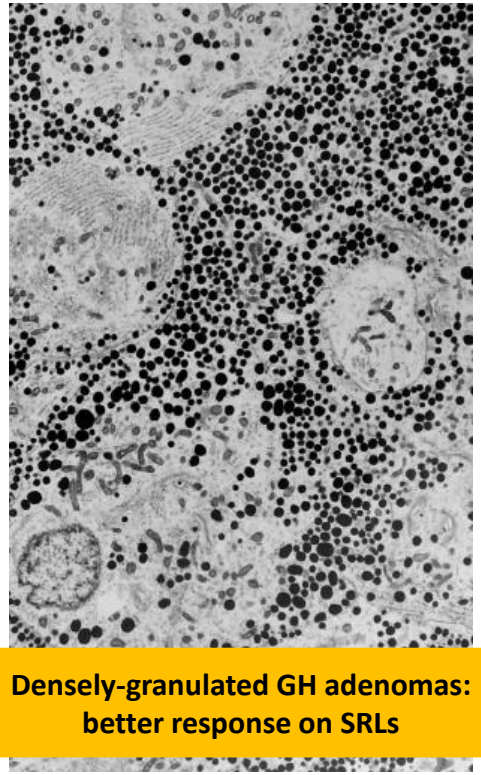


Melmed S. JCEM 2016;101:769

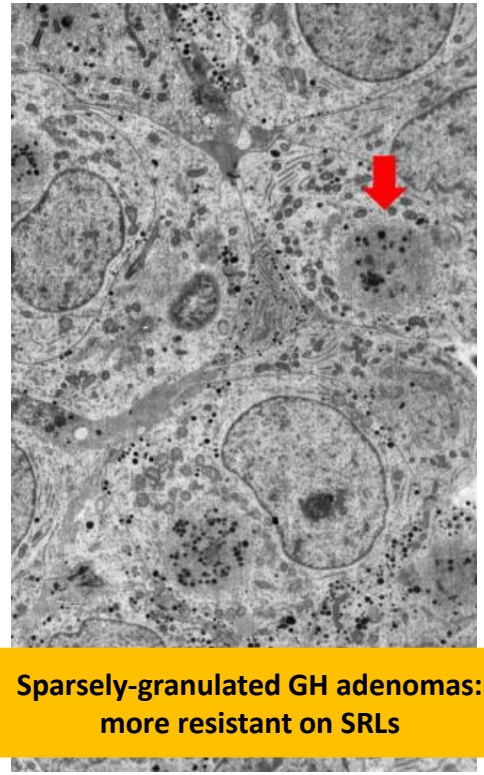
GH Granulation Pattern: Determinant of Treatment Resistance

5. Histology:

- Hormone granularity:
  densely granulated (respond better on SRLs) vs sparsely granulated
- Specific receptor expression: SST2, SST5, D2
- Cell cycle markers: Ki67, p21
- Cell-specific transcription factors: POU1F1



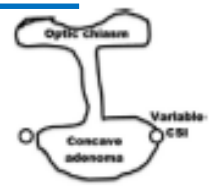
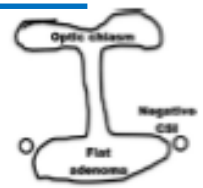
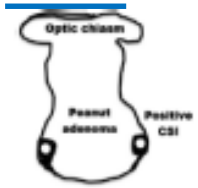
Densely-granulated GH adenomas: better response on SRLs



Sparsely-granulated GH adenomas: more resistant on SRLs

Syro LV, Pituitary 2017;20:84–92

Acromegaly Classification: Personalized Approach to Optimal Outcomes

	Acromegaly Types		
	1	**2**	**3**
Frequency order	1	3	2
Tumor			
Shape and CSI	Concave	Flat	Peanut
			
Size	Micro- or macroadenomas	Macroadenomas	Macroadenomas
Invasiveness by MRI	Intermediate	Never	Always
Aggressive behavior	Intermediate	No	Yes
Suprasellar extension	Intermediate	Rare	Common
Sphenoid sinus extension	Common	Rare	Intermediate
Optic chiasm compression	Rare	Rare	Common
Granulation	Dense	Both	Sparse
Immunoreactivity			
GH	Strong	Weak	Weak
α-Subunit	Positive	Positive or Negative	Negative
Ki-67 index < 3%	90%	33%	42%
SSTR2	58%	30%	22%
p16	0.0%	0.2%	0.5%
p21	38%	15%	4%
Biochemistry			
IGF-1 levels at diagnosis	Lower	Intermediate	Higher
Prolactin at diagnosis	Intermediate	Lower	Higher
Management and outcomes			
No. of medications	2 or less	2 or less	2 or more
No. of surgeries	1	1 or 2	2 or more
Disease control	Frequent	Intermediate	Rare
IGF-1 levels at follow-up	Normal	Intermediate	Elevated

Cuevas-Ramos D, JCEM 2015;100:122-31

C. Treatment Choices

Treatment of Acromegaly

- Surgical
- Medical
- Radiation

Two Transsphenoidal Techniques

❑ Microscopic

- A single continuous unobstructed 3D view
- May be more familiar to surgeons
- Better control of bleeding
- Narrower field

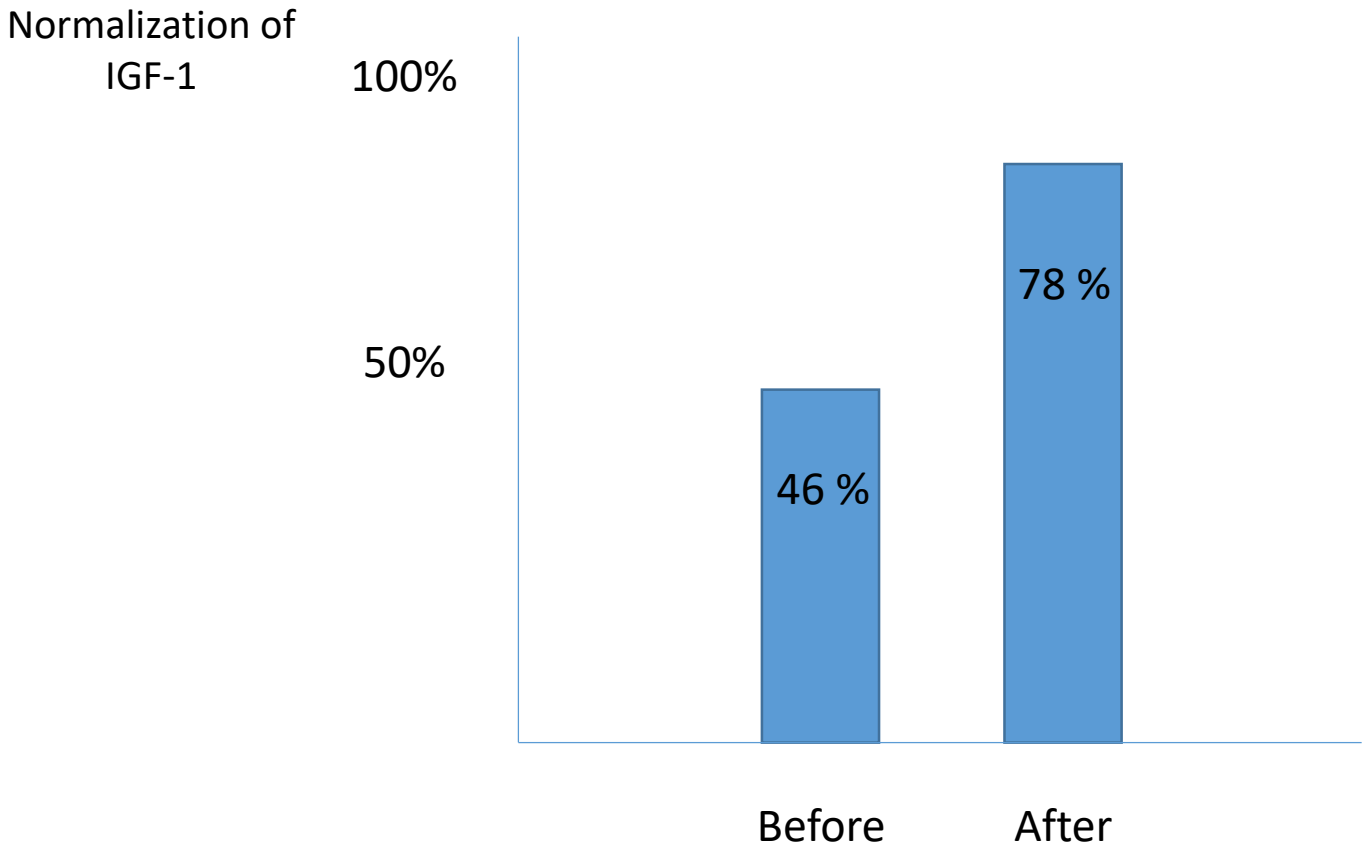
❑ Endoscopic

- A more panoramic view
- Transient surgical debris obstruct view
- A speculum is not used, limits free movent of instruments
- The suprasellar compartement and latteral aspect of the cavernous sinus may be more accessible

Both techniques provide comparable results regardless of the size or degree of invasion

Starcke RM, JCEM 2013;98:3190-8

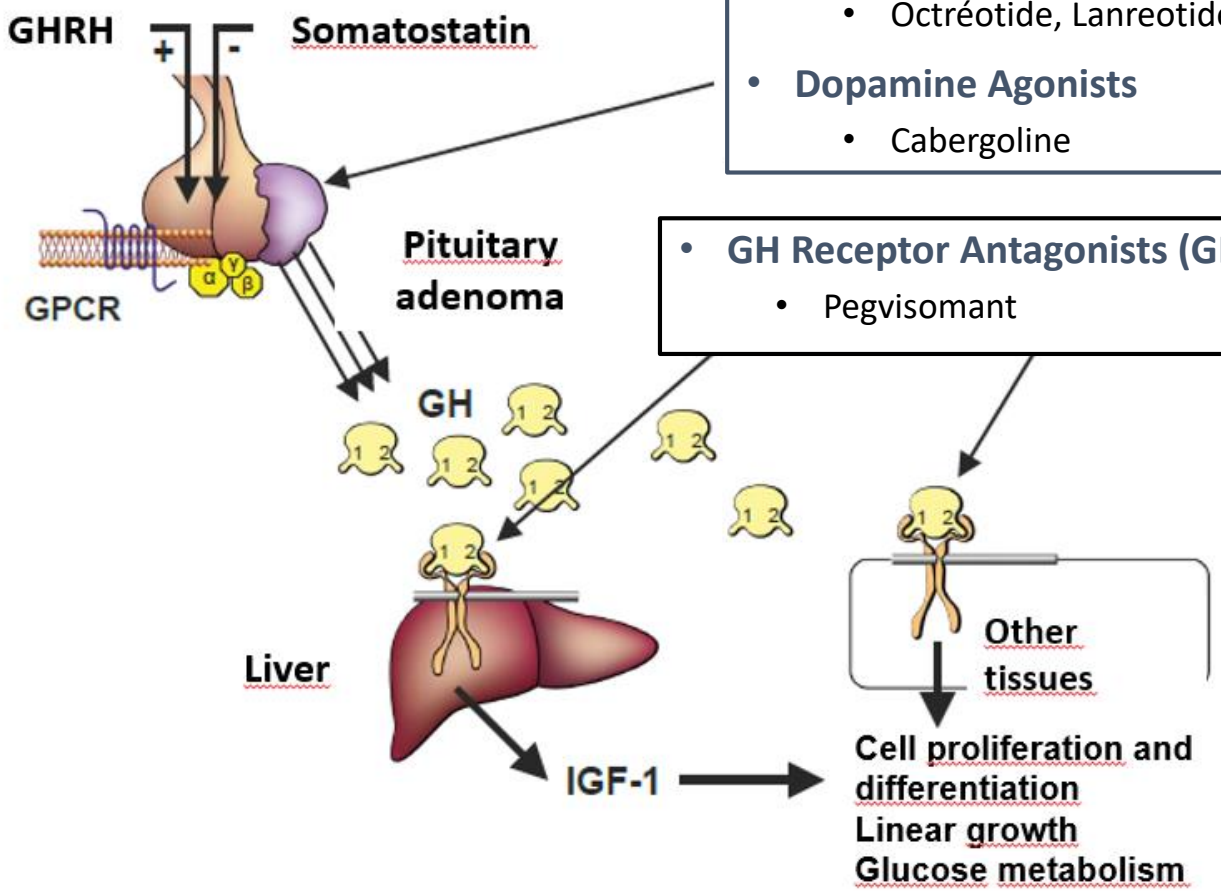
Surgical Debulking Enhances Efficacy of SRL Therapy



Prevalence of Normal IGF-1 during SRL treatment before and after surgical debulking

Petrossians P, EJE, 2005;152 61-6

Options for Medical Treatment



- **Somatostatin Receptor Ligands (SRL)**
  - Octréotide, Lanreotide, Pasireotide
- **Dopamine Agonists**
  - Cabergoline

- Directly inhibit GH secretion
- Indirectly inhibit IGF-1 secretion

- **GH Receptor Antagonists (GHRA)**
  - Pegvisomant

- Does not supress GH secretion
- Directly inhibit IGF-1 secretion

Katznelson L, JCEM 2014;99:3933-51
Melmed S, J Clin Invest 2009;119:3189-202

Somatostatin Receptor Ligand Therapy Efficacy

- Controls GH or IGF-1 in 50-66%

  but studies vary greatly (20-80% depending on patients and study design)

- Tumor shrinkage: 20-50%

- Octreotide LAR: IM
  10, 20, 30, 40 mgr/month
- Lanreotide Autogel: SC
  60, 90, 120 mgr/month (up to every 8 weeks)
- Pasireotide: IM
  20, 40, 60 mgr/month

Freda PU, JCEM 2002;87(7):3013–18
Melmed S, Pituitary 2010;13:18–28
Dabrh AMA, JCEM 2014;99:4003-14
Katznelson L, JCEM 2014;99:3933-51

Adverse Events of 1st gen. SRLs

- GI (diarrhea, nausea, abdominal discomfort)
  - early < 50%
  - persistent < 10%
- Biliary tract abnormalities
  - all types, 50%
  - new gallstones, 15%
- Abnormalities of glucose metabolism
  - hypoglycemia, 2%
  - hyperglycemia, 7-15%
- Injection site pain, 24%
- Transient hair loss, 3-6%
- Hypothyroidism, 2%
- Other
  - Sinus bradycardia
  - Vitamine B12 deficiency
  - altered absorption of orally administered drugs

Freda PU, JCEM 2002;87(7):3013–18

Pasireotide LAR vs Octreotide LAR: Safety during 12 months

	Pasireotide LAR, n = 178[a]		Octreotide LAR, n = 180[a]	
	All Grades, n (%)	Grade 3/4, n (%)	All Grades, n (%)	Grade 3/4, n (%)
Diarrhea	70 (39.3)	1 (0.6)	81 (45.0)	4 (2.2)
Hyperglycemia	51 (28.7)	6 (3.4)	15 (8.3)	1 (0.6)
Cholelithiasis	46 (25.8)	1 (0.6)	64 (35.6)	2 (1.1)
Diabetes mellitus	34 (19.1)	9 (5.1)	7 (3.9)	0
Headache	33 (18.5)	2 (1.1)	46 (25.6)	5 (2.8)
Abdominal pain	32 (18.0)	1 (0.6)	40 (22.2)	0
Alopecia	32 (18.0)	0	35 (19.4)	0
Nasopharyngitis	28 (15.7)	0	28 (15.6)	0
Nausea	24 (13.5)	1 (0.6)	39 (21.7)	0
Increased blood creatine phosphokinase	23 (12.9)	3 (1.7)	21 (11.7)	4 (2.2)
Abdominal distension	21 (11.8)	1 (0.6)	21 (11.7)	1 (0.6)
Arthralgia	17 (9.6)	1 (0.6)	22 (12.2)	1 (0.6)
Fatigue	17 (9.6)	1 (0.6)	18 (10.0)	0
Dizziness	17 (9.6)	0	19 (10.6)	0
Back pain	14 (7.9)	0	20 (11.1)	2 (1.1)

Colao A, JCEM 2014;99:791-9

Primary Medical Therapy for Acromegaly

- Should be considered if surgery is contraindicated or refused

- May be appropriate for:
  - inaccessible invasive tumors
  - tumors unlikely to be surgically curable (?)
  - tumors not compressing optic chiasm

Katznelson L, JCEM 2014;99:3933-51

Pegvisomant: Administration and Dosing

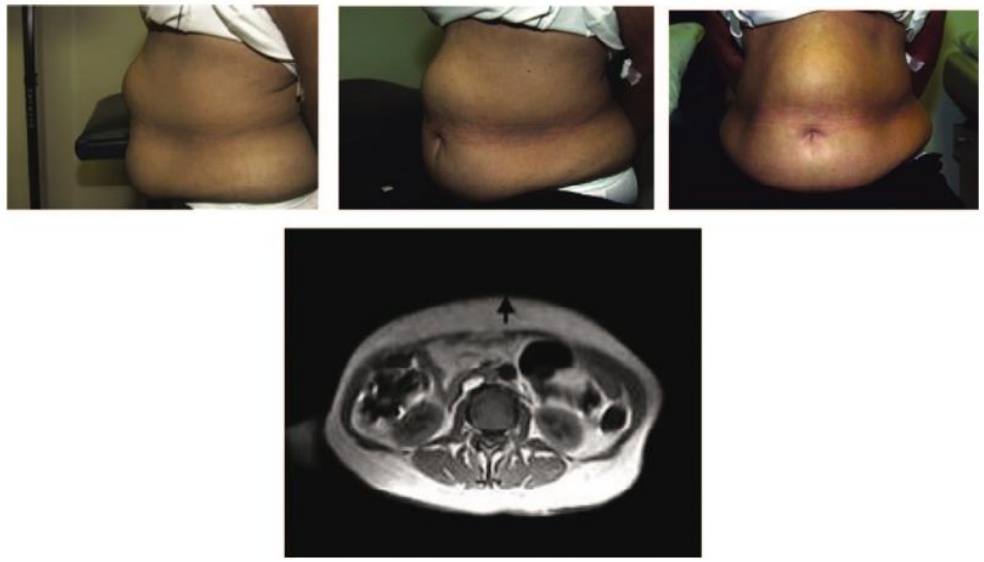
- Daily sc injections
- Investigational evidence for efficacy of weekly use
- May be used as first-line therapy

➢ Pegvisomant: SC
10, 15, 20, 25, 30 mgr/daily

Neggers, JCEM 2008;93:3853-59

Pegvisomant: Adverse events

	AE, *n* (%)
Injection site reactions (erythema, swelling, lipohypertrophy)	17 (7.4)
Elevated liver enzymes	9 (3.9)
Increase of pituitary tumor volume	–
Headache	4 (1.7)



Schreiber I, EJE 2007;156:75-82
Bonert VS, JCEM 2008;93:3515-18

Pegvisomant: ACROSTUDY Results

- Global, multicenter, post-authorization safety surveillance study

- N=2221, mean of 9.3 year follow-up
  - % N IGF1 improved over time: 11.4% at start, 53.7% at year 1, 75.4% at year 10
  - 96.3% had received other acromegaly treatments before
  - 16.5% of patients had treatment related adverse events, 1.3% led to drug withdrawal

Fleseriu M. EJE 2021; 185, 525–38

Pegvisomant: Effect on Tumor Size

- N=61 on pegvisomant, 5 to 30 mgr/day:

  3 tumors with significant increase, but:

  - all tumor growth in 1st year of treatment
  - all were associated with discontinuation of SRL

- N=

  3

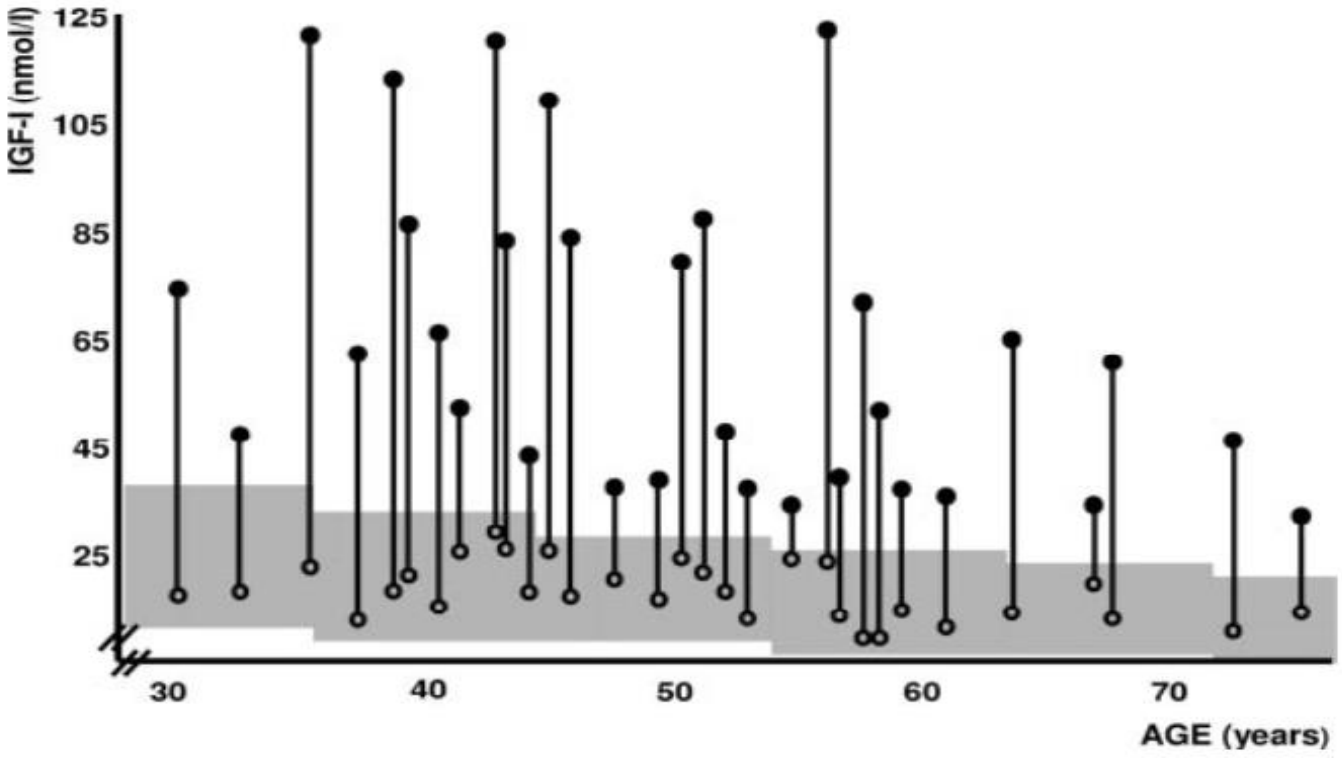
Rare and probably represents the natural history of adenomas without treatment effective on tumor growth

Buhk JH, JCEM 2010;95:552-8
Van Der Lely AJ, JCEM 2012;97:1589-97

Efficacy of SRL + Pegvisomant combination treatment

N=31

Follow-up 35-148 weeks



Meta-analysis
(90 studies, 2020):

Co-treatment with
SRL+ Pegvisomant
was the more effective treatment

Neggers S, JCEM 2007;92:4598-601
Quiao N, Endocrine Practice 2020;26(4):454-62

A Retrospective Analysis of 352 Patients Treated with Radiotherapy: The German Acromegaly Registry

- ✓ 75 % normalized IGF-1 in 10 years, no difference between the two techniques
- ✓ slightly faster achievement of control observed after stereotactic radiosurgery

Variables	Fractionated Radiotherapy (FRT)	Stereotactic Radiosurgery (SRS)	P value
GH (ngr/ml) moyenne avant radiotherapie	6.3 (IR: 2.9-16.2)	3.5 (IR: 1.8-6.9)	< 0.001
Nombre de patients	233	119	
Durée du suivi	13 +/- 8 ans	9+/- 5 ans	< 0.001
Temps jusqu'à rémission	3 ans	2 years	0.021
% remission à 10 ans	48%	52%	0.74

Less adrenal and thyroid insufficiency after radiosurgery ?
Odds Radio 0.54 (95% CI: 0.3-1, P=0.049)

Knappe UJ, EJE 2020;182:275-84

Biochemical Control in Acromegaly with Multimodality Therapies: Outcomes from a Pituitary Center (Mass General) and Changes over Time

N=266 patients followed-up from 1980 to 2019 at Mass General, USA

- 93% achieved normal IGF-1 in 9.9 years (R: 5-15) years

- Factors predicting long-term sustained IGF-1 control after surgery without adjuvant therapies:
  - male
  - older age
  - smaller tumor
  - lower IGF-1 at diagnosis

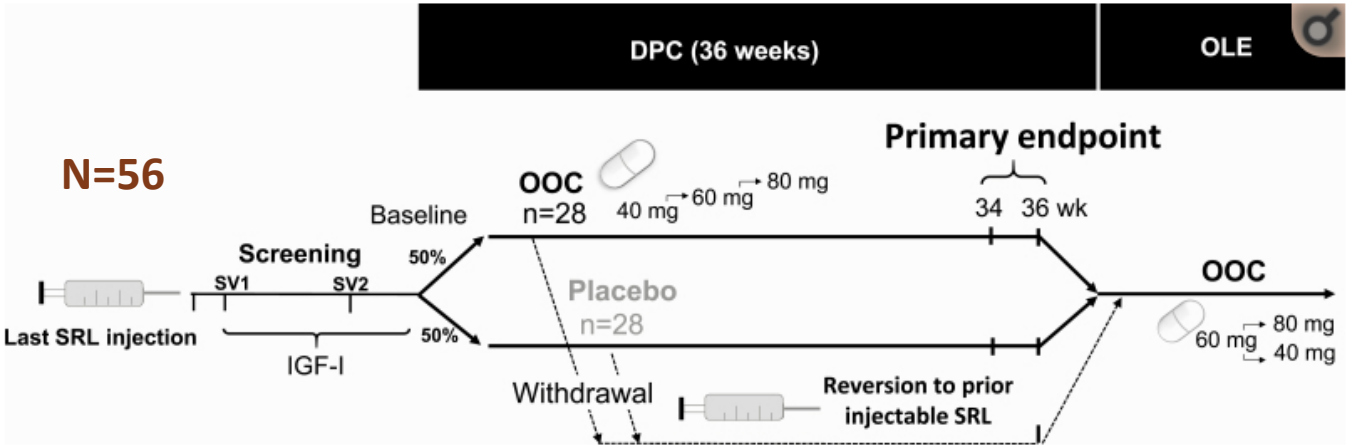
- Better treatment quality after 2006 compared to earlier era:
  → normalization of IGF-1 achieved in a shorter time after 2006 (14 vs 28 months, P=0.002)
  → radiation therapy was rarer after 2006: 22% after 2006 vs 47% before (P< 0.001)
  → second surgery was rarer: 9% after 2006 vs 22% before (P=0.01)

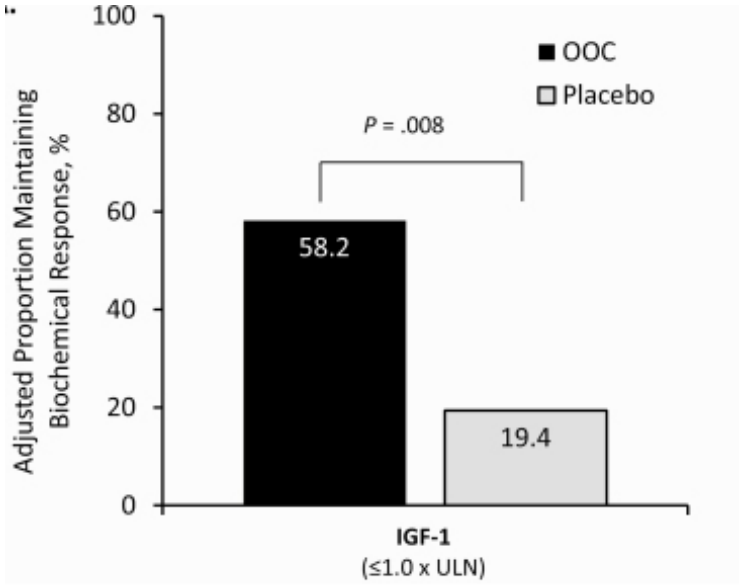
- Age at diagnosis increased over time periods (possibly reflecting increased detection of acromegaly in older patients with milder disease)

Ghajar A, JCEM 2020;105:e532-43
Coopmans E.C. JCEM 2021;106(6): 1783-92

Emerging treatments: Oral Octreotide

CHIASMA OPTIMAL TRIAL





Efficacity obtained with injectable octreotide was maintained after switch on oral octreotide, in a phase III study

FDA Approved June 2020

Samson SL, JCEM 2020;105(10): e3785-97

Take-Home Message (1)

- Acromegaly treatment must include disease activity markers (headache, IGF-1 values), chronic complications but also treatment adverse events, and QoL

- Monitoring tools are available (e.g., SAGIT), for a patient-centered outcome assessment approach

- Certain prognostic factors are useful in order to adapt management (e.g., patient age, size and local invasion on MRI, T2 hypo-intensity associated with a better response to SRLs, granulation pattern on histology, etc.)

Take-Home Message (2)

- Surgery remains the first-line treatment, even if cure is unlikely (improvement in SRL response after debulking). The two transphenoidal techniques are equivalent
- Efficacy of SRLs is 50-70% (GI side effects for octreotide and lanreotide / hyperglycemia for pasireotide)
- Efficacy of the pegnisomant is 80-90% (to be avoided as monotherapy in patients with large residual tumors and non-compliant patients)
- The combined SRL + pegvisomant treatment seems to be the most effective
- Radiotherapy should be considered for difficult cases (75% biologic control at 10 years)