6th AME National Meeting

Italian Association of Clinical Endocrinologists

3rd Joint Meeting with AACE

American Association of Clinical Endocrinologist

An Update in the Treatment of Acromegaly

The role of GH and IGF-I in Diagnosis and Cure Criteria

Diego Ferone

Center of Excellence for Biomedical Research
- University of Genoa -

Department of Endocrinological & Metabolic Sciences
University of Genova

Diagnosis of acromegaly

Anamnesis and clinical evaluation

- ✓ Retrospective evaluation (photos)
- ✓ Clinical picture
- ✓ Co-morbidities

Biochemistry

- ✓ Basal GH (?)
- ✓ GH during Oral glucose load (OGTT)
- ✓ Insulin-like growth factor 1 (IGF-I)
- ✓ Study of the residual pituitary function

Imaging

- ✓ Radiology (MRI)
- ✓ Visual perimetry

Criteria for diagnosis and disease control in acromegly

0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism
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Vol. 85, No. 2
Printed in U.S.A.

CONSENSUS

Criteria for Cure of Acromegaly: A Consensus Statement*†

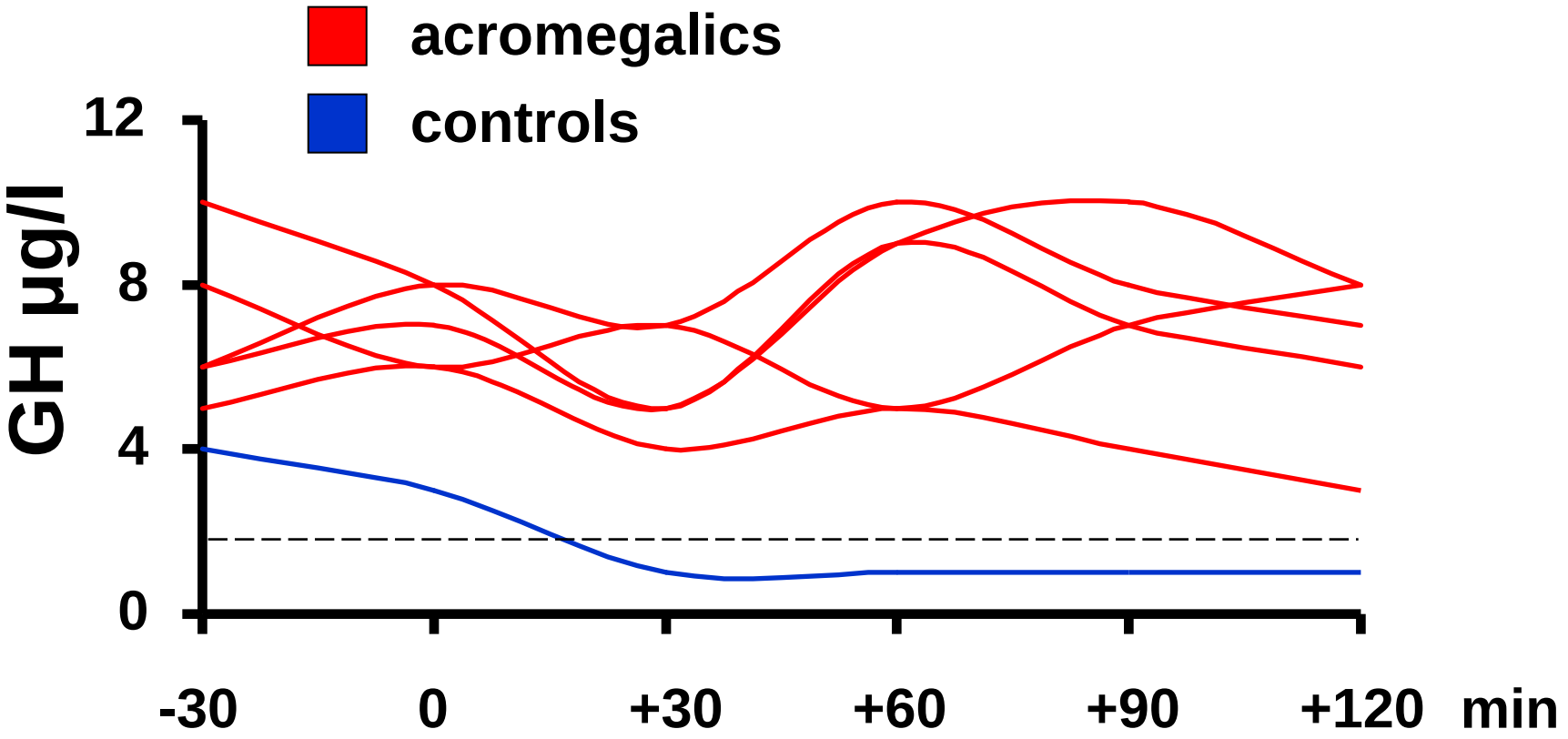
ANDREA GIUSTINA, ARIEL BARKAN, FELIPE F. CASANUEVA,
FRANCO CAVAGNINI, LAWRENCE FROHMAN, KEN HO, JOHANNES VELDHUIS,
JOHN WASS, KLAUS VON WERDER, AND SHLOMO MELMED

– GH

TABLE 1. Acromegaly biochemical diagnosis

Random GH <0.4 μg/L and normal IGF-I
Excludes acromegaly
GH nadir during OGTT <1 μg/L and normal IGF-I
Excludes acromegaly

GH levels during OGTT in acromegalic patients and controls



Assessment of disease activity in acromegaly by means of a single blood sample: comparison of the 120th minute postglucose value with spontaneous GH secretion and with the IGF system

Clinical Endocrinology (2004) **61**, 138–144

Francesco Minuto*,†, Eugenia Resmini*,
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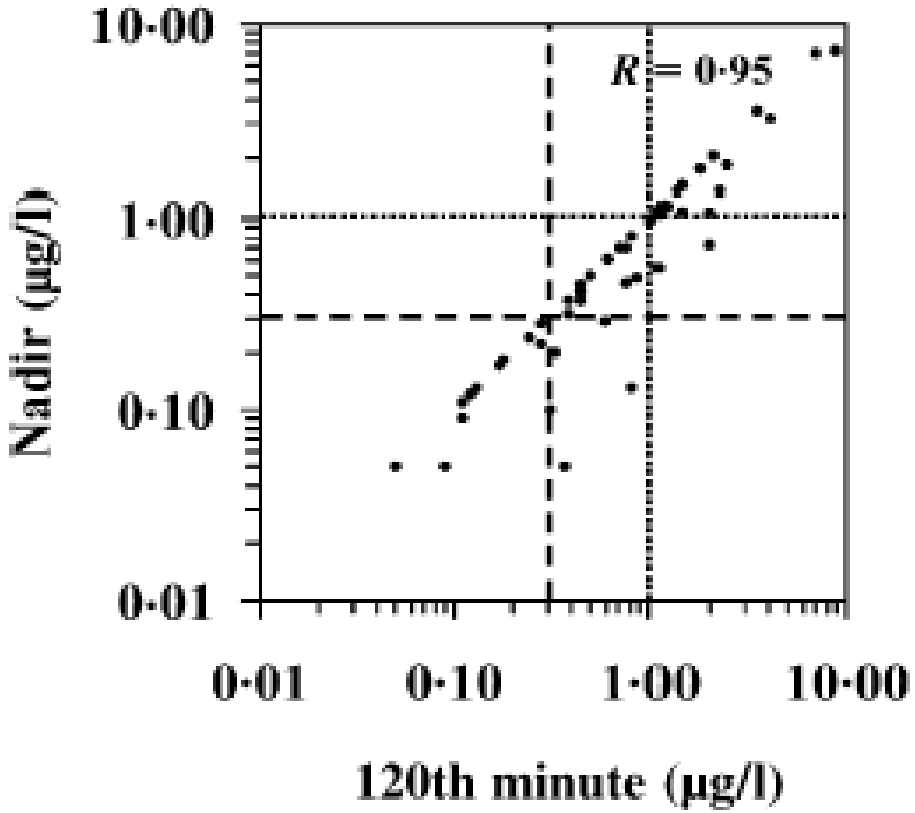
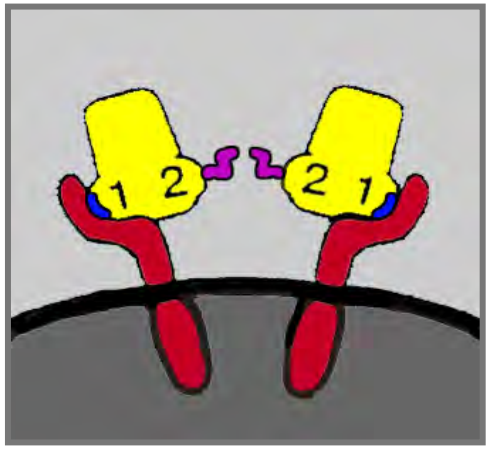
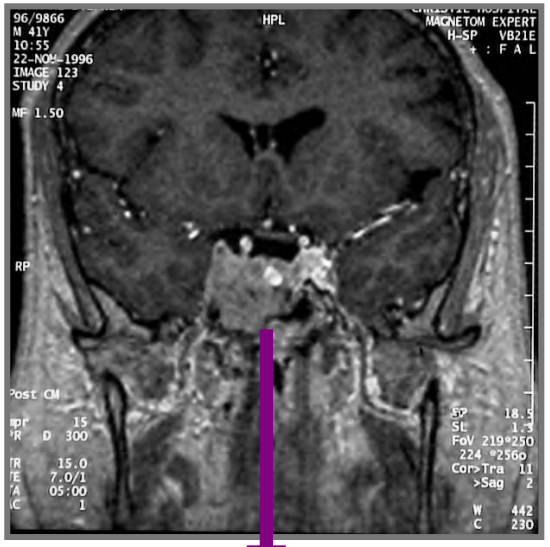


Altered GH levels during OGTT

- Acromegaly
- Adolescents
- Laron syndrome
- Diabetes mellitus
- Liver diseases
- Kidney failure
- Malnutrition

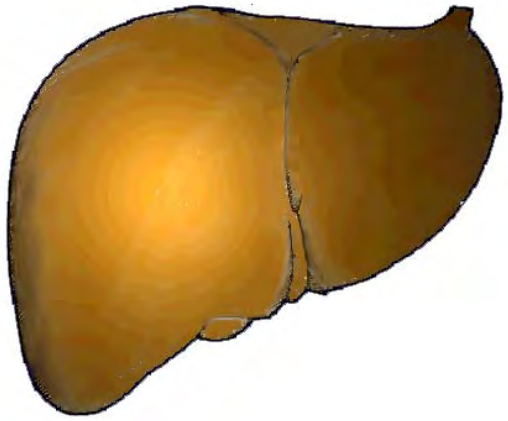


Pegvisomant



- 191 amino acid GH analogue
- 9 amino acid substitutions
- 4-5 PEG moieties
- molecular weight 42-46000 D
- half-life >70 hours
- subcutaneous administration

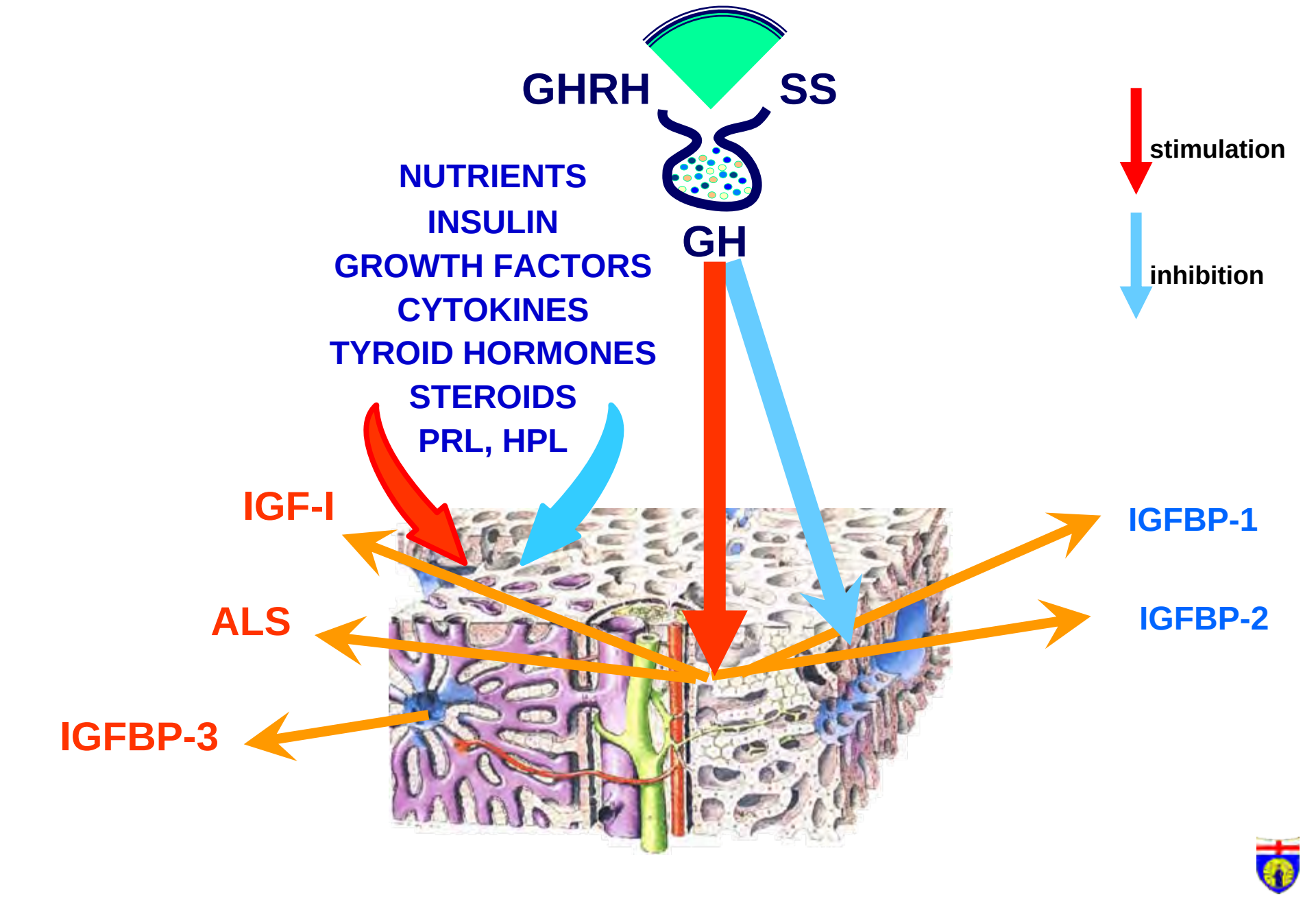
GH



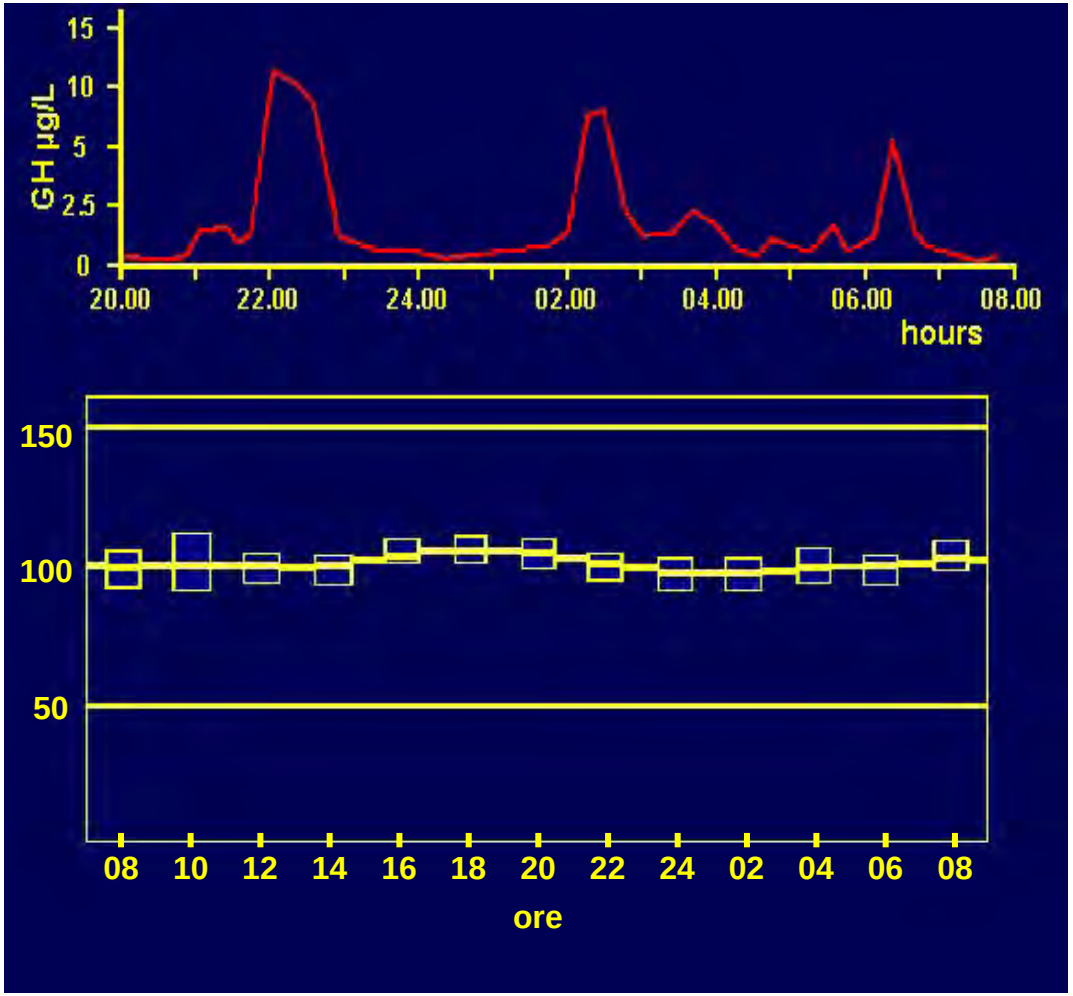
Goal of therapy - to lower IGF-I into the age-related reference range

Serum GH cannot be used as a disease marker

GH-IGF-IGFBP AXIS



150 kDa complex subunits as diagnostic parameters



- Stable circulating concentrations
- Reproduction of the integrated GH secretion
- High circulating levels

Diagnostic Value of the Acid-Labile Subunit in Acromegaly: Evaluation in Comparison with Insulin-Like Growth Factor (IGF) I, and IGF-Binding Protein-1, -2, and -3*

The Journal of Clinical Endocrinology & Metabolism
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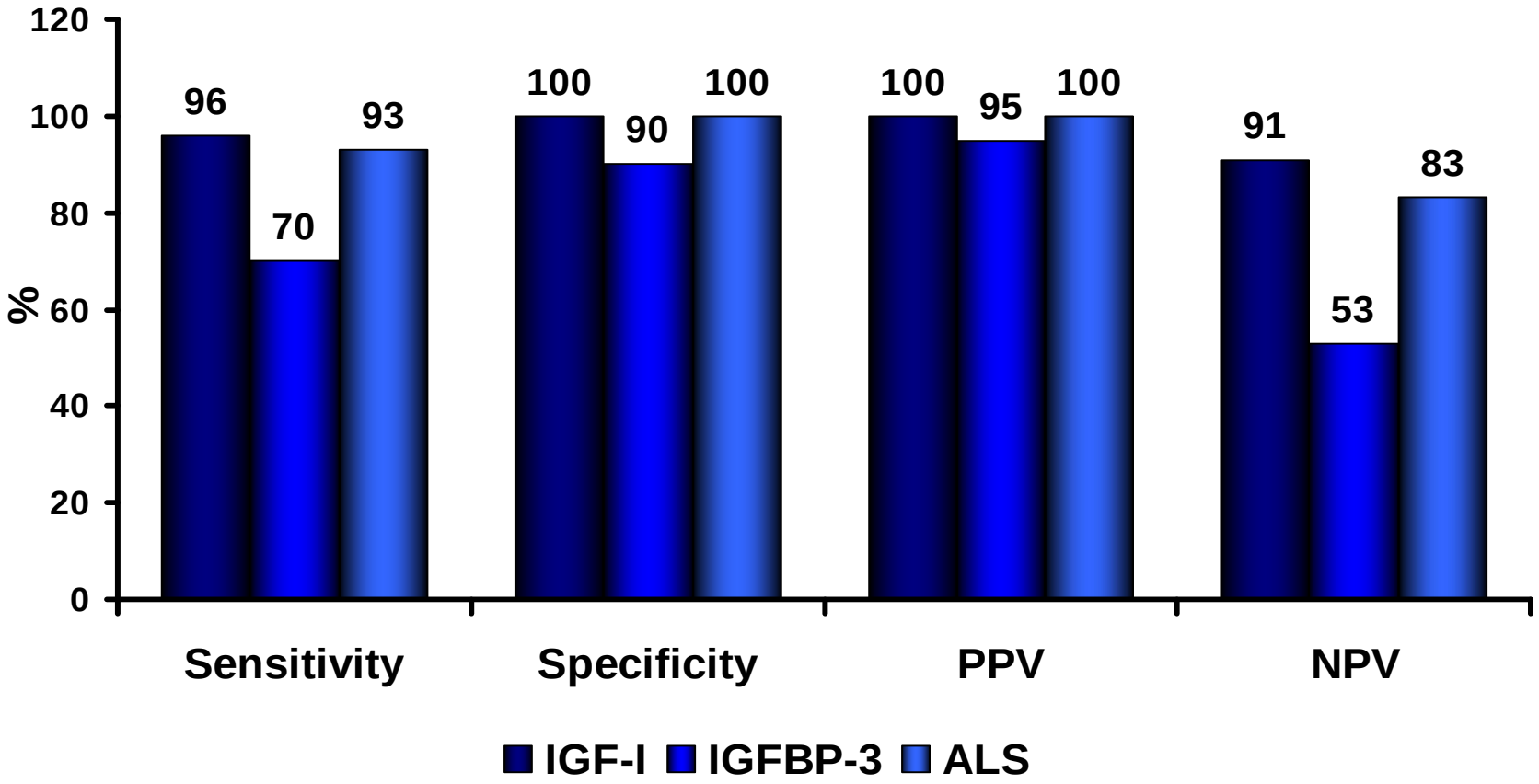
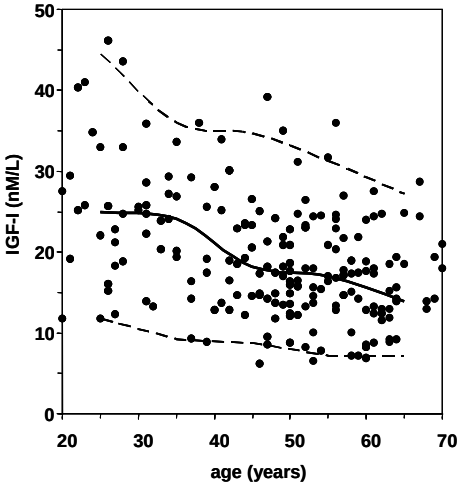
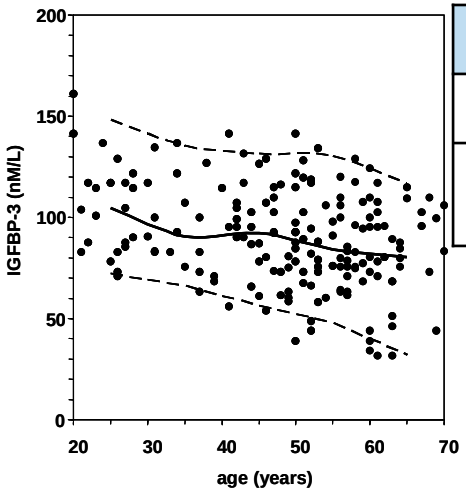
M. AROSIO, S. GARRONE, P. BRUZZI, G. FAGLIA, F. MINUTO, AND A. BARRECA



Aging changes of the IGF system components

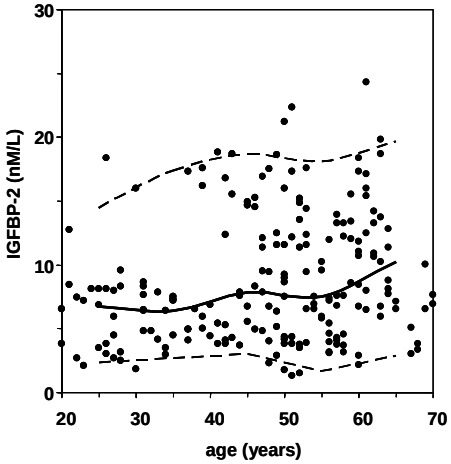
IGF-I	20-40y	50-70 y	δ %
Mean	24.24	16.85	-30.5
SEM	1.23	0.60	

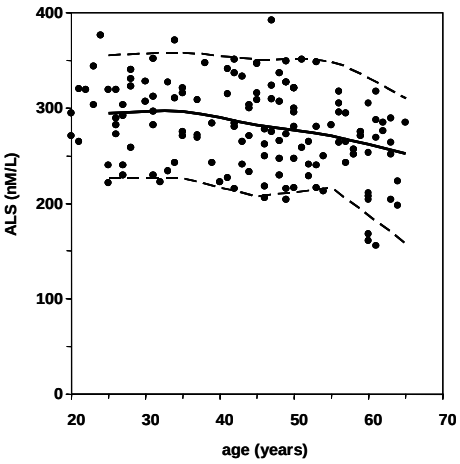




IGBP-3	20-40y	50-70 y	δ %
Mean	101	85	-15.5
SEM	4	2	

IGFBP-2	20-40y	50-70 y	δ %
Mean	6.96	9.35	34.3
SEM	0.57	0.50	





ALS	20-40y	50-70 y	δ %
Mean	293	261	-10.8
SEM	6	6	

Potential pitfalls of IGF system parameters

LIMITES	IGF-I	IGFBP-3	ALS
Methodology	++++	-	-
Age	+++	+++	+
Malnutrition	+++	+++	++
Sepsis	+++	+++	+++++
Diabetes	++	++	?
Hypothyroidism	++	++	+
Kidney failure	++	++	?

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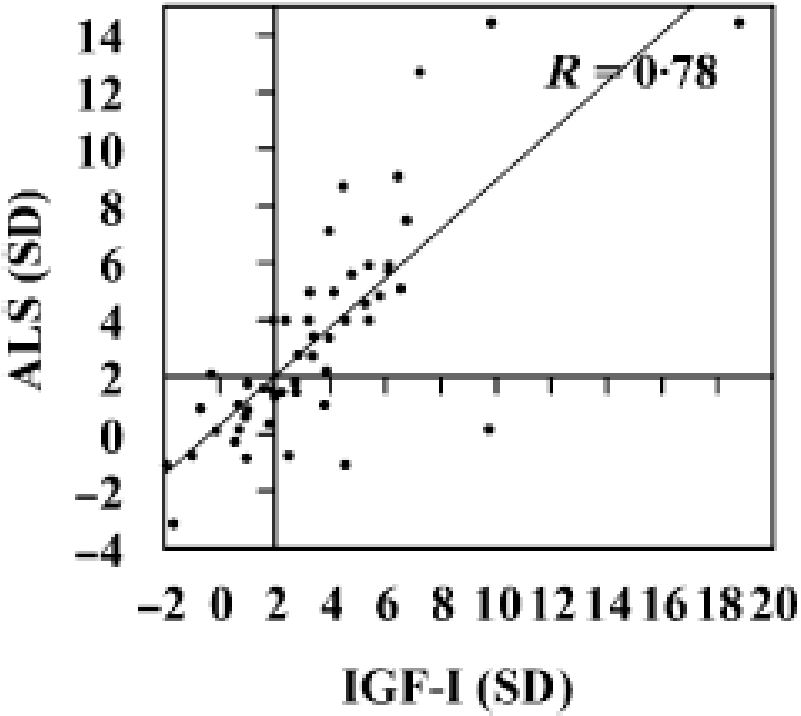

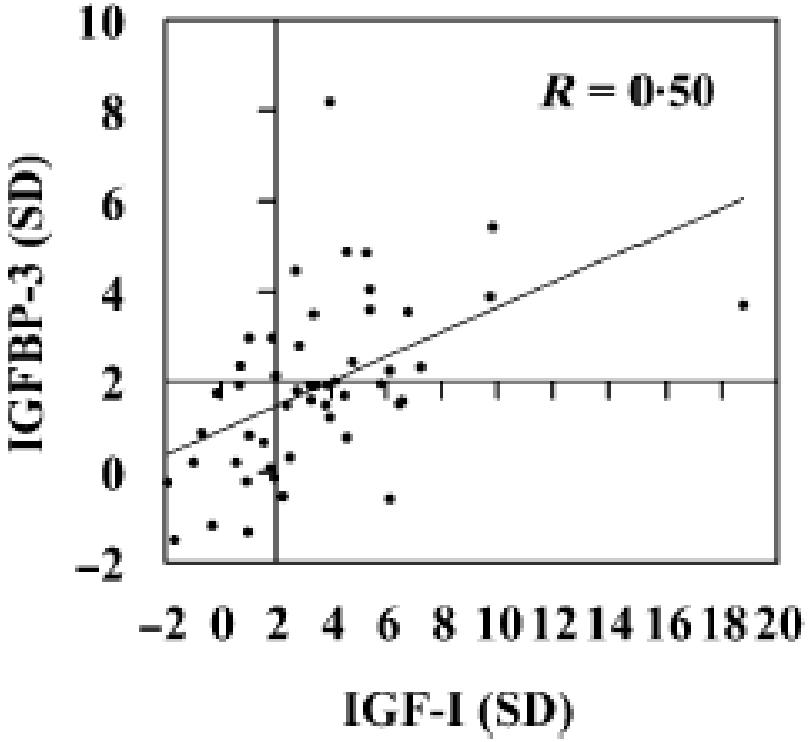

GH and IGF-I discrepancies

Dimaraki *et al*. JCEM 2002:

Subjects with normal GH high IGF-I

Freda *et al*. JCEM 1998:

Subjects with high GH normal IGF-I

Concordance between IGF system parameters and GH after glucose load in acromegly

	OGTT 120 < 1
IGF-I <2 SDS	**52**
ALS <2 SDS	**62**
IGFBP-3 <2 SDS	**56**

Concordance between IGF system parameters and spontaneous GH secretion in acromegaly

	Mean conc. GH < 2.5	Minim. conc. GH < 0.3
IGF-I <2 SDS	**56**	**68**
ALS <2 SDS	**62**	**70**
IGFBP-3 <2 SDS	**60**	**60**

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If 2 parameters of IGF system are normal, then 91% GH daycurve and 73% OGTT are normal

	Mean GH day curve				OGTT 120th minute			
	< 2.5	> 2.5	< 1	> 1	< 1	> 1	< 0.3	> 0.3
2 normal IGF system parameters	20	2	12	10	15	7	7	15

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If post glucose GH is <1 and IGF is normal, then other parameters are useless

	Mean GH day curve				ALS		IGFBP-3	
	< 2.5	> 2.5	< 1	> 1	nl	hi	nl	hi
GH and IGF	11	0	10	1	11	0	9	2

Cure criteria for acromegaly
(post-glucose GH and IGF-I)

GH and IGF-I elevated	Active or uncontrolled disease
GH and IGF-I normal	Inactive or controlled disease
GH normal and IGF-I elevated GH elevated and IGF-I normal	Partially controlled disease
GH normal and IGF-I low	Overcontrolled disease or hypopituitarism

CONCLUSIONS

- **If post-glucose GH is < 1 and IGF-I is normal then no further biochemical assessment is required**
- **The 120th minute post glucose GH value can replace the nadir**
- **Among GH-dependent factors, IGF-I is the most reliable parameter, ALS close next**

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Mara Boschetti
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Federico Bianchi
Alberto Rebora
Massimo Giusti
Francesco Minuto

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University of Genova

Thanks for the attention!

An Update in the Treatment of Acromegaly

The Role of Diagnostic Procedures in Complications

Pietro Maffei,
Clinica Medica 3^, University Hospital, Padua, Italy

3rd AME-AACE Joint Meeting, October 27-29, 2006, Verona, Italy

A Medical Mystery
Which Twin is the Patient ?

2655 responses: 64% correctely diagnosed acromegaly

W-A. Nieuwlaat & G. Pieters, NEJM, 2004

Guidelines & Consensus (Acromegaly)

- 2006 CIM – Canadian Guidelines
- 2005 EJE - Pituitary Society & ENEA (Seville)
- 2004 JCEM – GHRS & Pituitary Society
- 2004 End Pract – AACE (US Guidelines)
- 2003 JEI – Pituitary Society & ENEA (Versailles)
- 2002 JCEM – Treatment Consensus Workshop (Montecarlo)
- 2002 Gut – St Bartholomew's Hospital, London, UK
- 2001 GH & IGF Res. – Scandinavian Guidelines
- 2000 JCEM – Expert panel (Cortina)
- 1998 JCEM – US Guidelines (Four Centers)
- 1994 AJM – Consensus Development Panel

Guidelines & Consensus (General population)

Specifically Mentioned by Acromegaly Guidelines:

- American Cancer Society guidelines
- NIH Clinical Practice guidelines for high BP
- NCEP, ATP III – High Blood Cholesterol in Adult
- CDC – Recommended Adult Immunization schedule

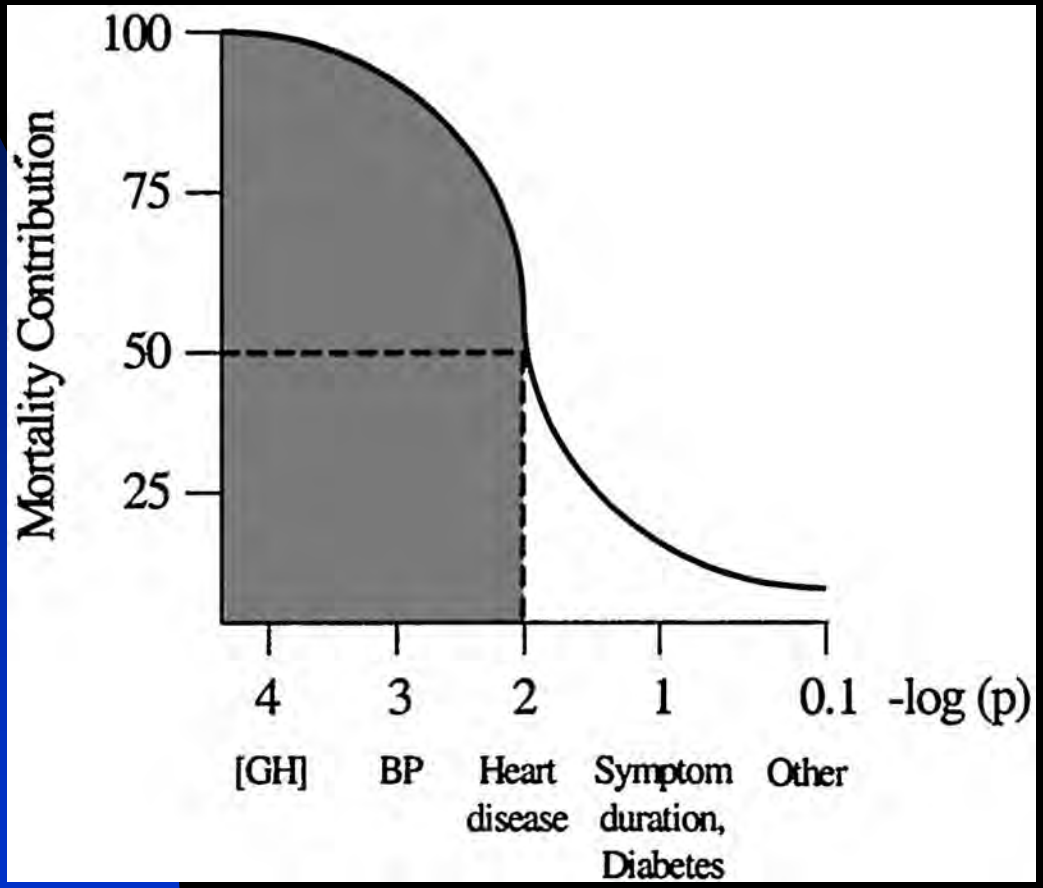
Other Guidelines:

- WHO and ADA (Diabetes)
- IDF, Clinical Guidelines Task Force (Type 2 diabetes)

Guidelines & Complications

	GH-IGF Diag/Ther	Surg Ther	Med Ther	Rad Ther	Complic
ENEA+PS, Seville, EJE ’05	√	√	√	√	√
GHR+PS, JCEM ’04	√	√	√	√	√
AACE, ’04	√	√	√	√	√
ENEA+PS, Versailles, JEI ’03					√
Montecarlo, JCEM ’02		√	√	√	√
Cortina, JCEM ’00	√	√	√	√	√
JCEM ‘98	√	√	√	√	√

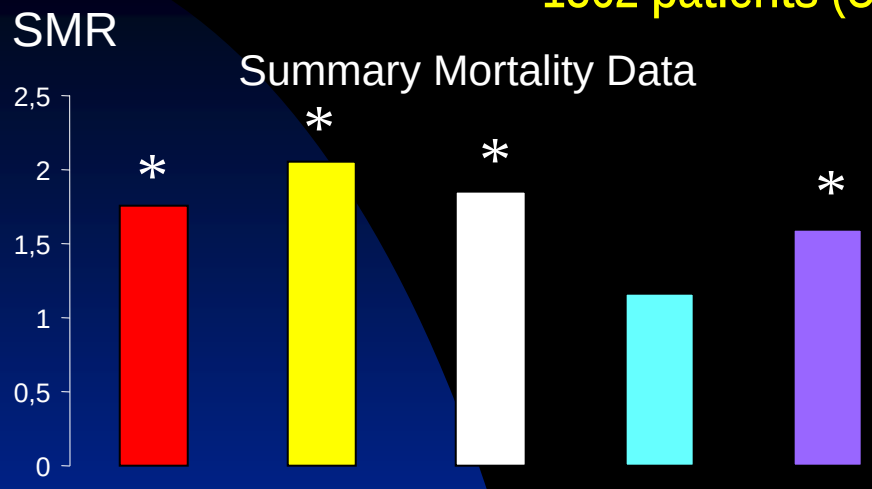
The main problem: Mortality

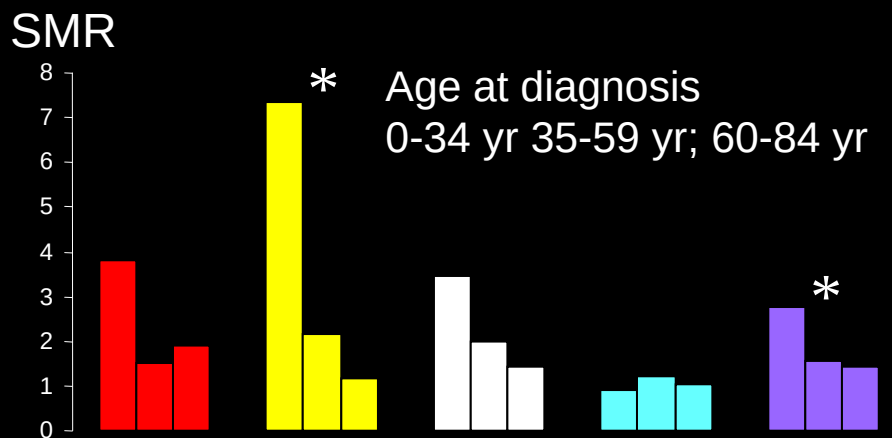


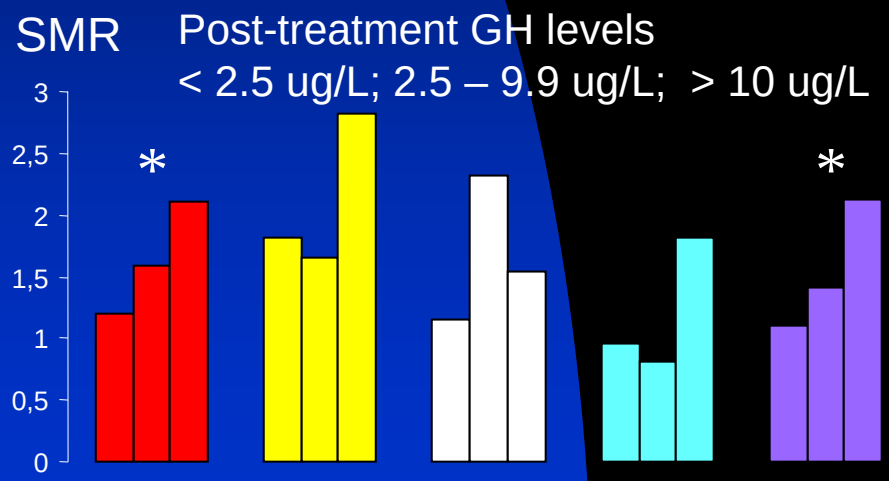
Melmed, JCEM, 2001

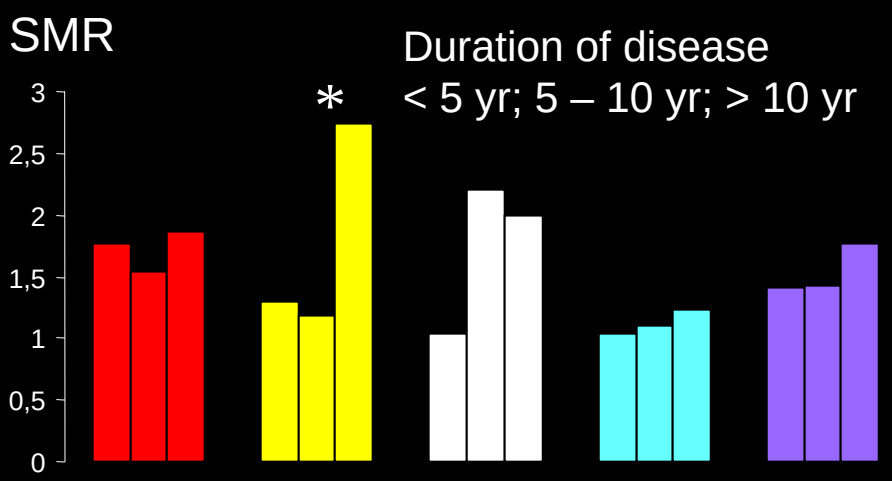
Mortality and Cancer Incidence in Acromegaly: a Retrospective Cohort Study

1362 patients (UK) - 19.323 yrs follow-up









Cardiovascular
Cerebrovascular
Respiratory
Malignant
Overall

Adapted from Orme et al, JCEM, 1998

Complications & Comorbidities

- Disease-related symptoms
- Skeletal and dental manifestation
- Soft tissue and skin changes
- Cardiovascular disease & Hypertension
- Metabolic disorders
- Cancer
- Respiratory disorders
- Genitourinary comorbidities
- Adverse events of surgery, RT, medical therapy
- Hypopituitarism
- Goitre, thyroid nodule
- Reproductive disorders & Pregnancy
- Neuropsychological complications

Skeletal Manifestations
Assessment
AACE + ENEA & PS*

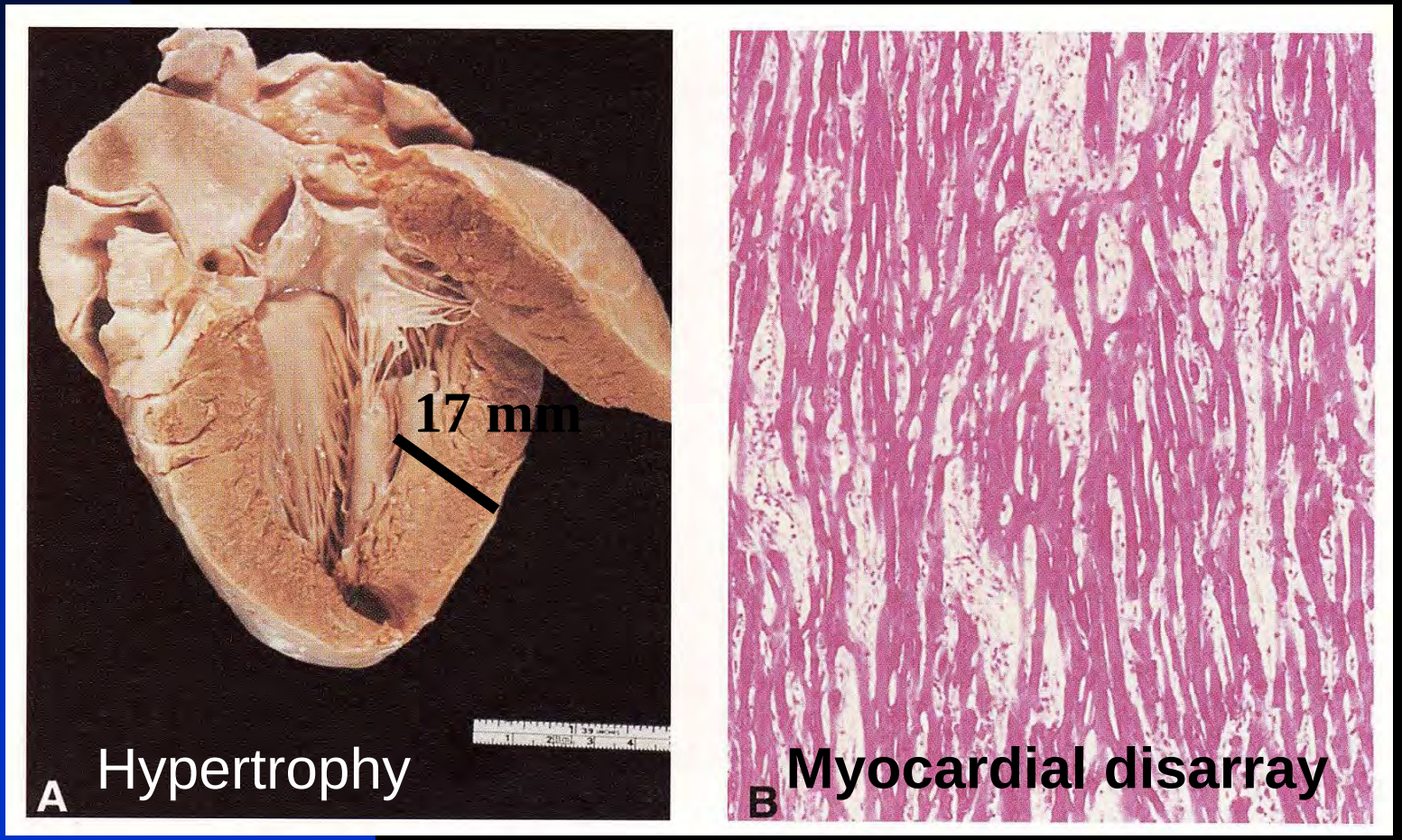
At diagnosis	Long-term follow-up
Bone densitometry (if hypogonadism)*	Every 2-3 years*
Calcium levels	

When persistent hypercalcemia consider (AACE):

Primary Hyperparathyroidism
MEN 1

Cardiovascular disorders

Time is muscle !!

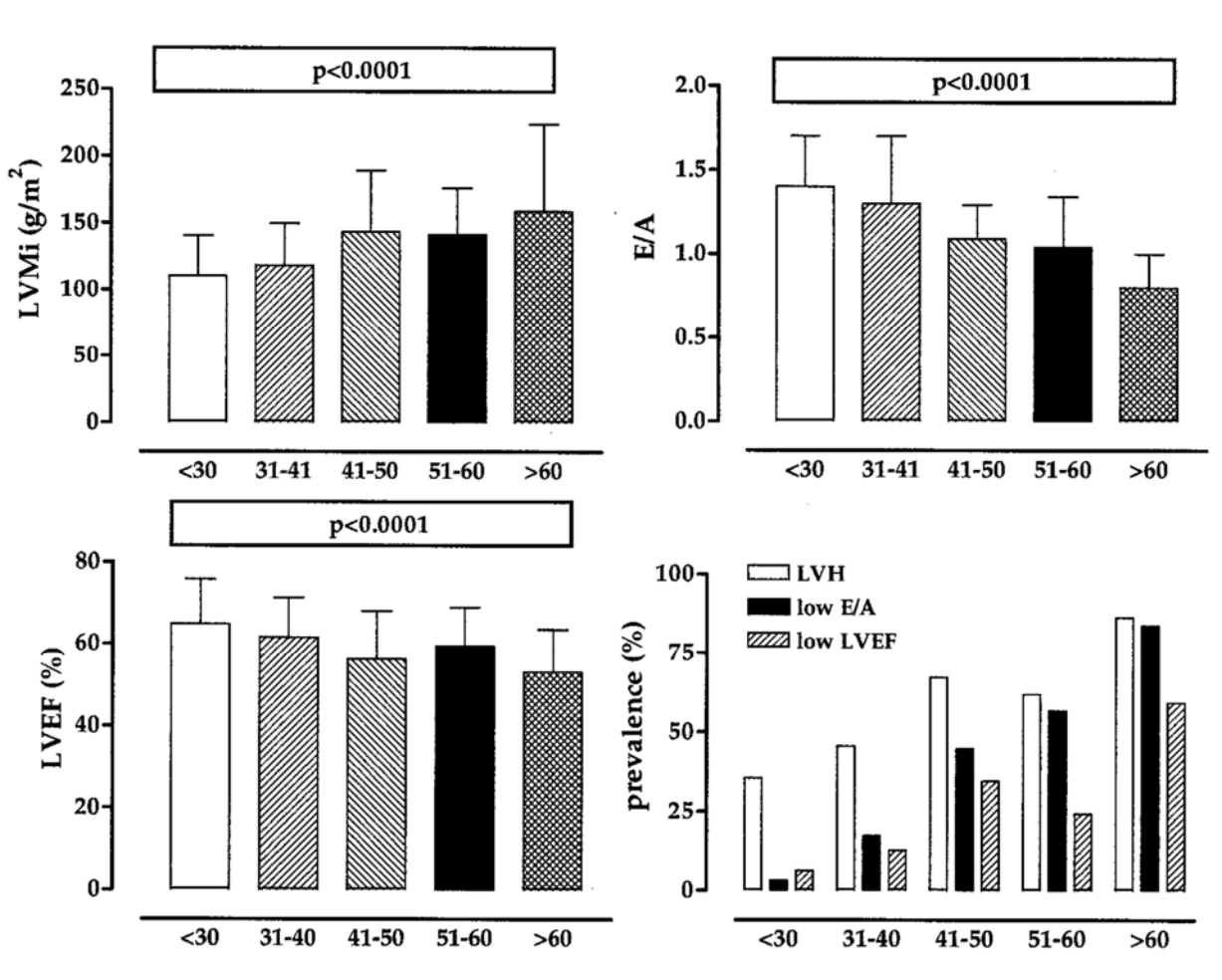


G. Thiene, G Ital Cardiol, 1980

Cardiovascular disorders: Problems

- Hypertension
- Left ventricular hypertrophy
- Impaired systolic and diastolic function
- Cardiac failure
- Arrhythmias
- Conduction abnormalities
- Valvular heart disease
- Sudden death ?
- Ischemic heart disease ?
- Peripheral vascular disease ?
- Cerebrovascular disease ?

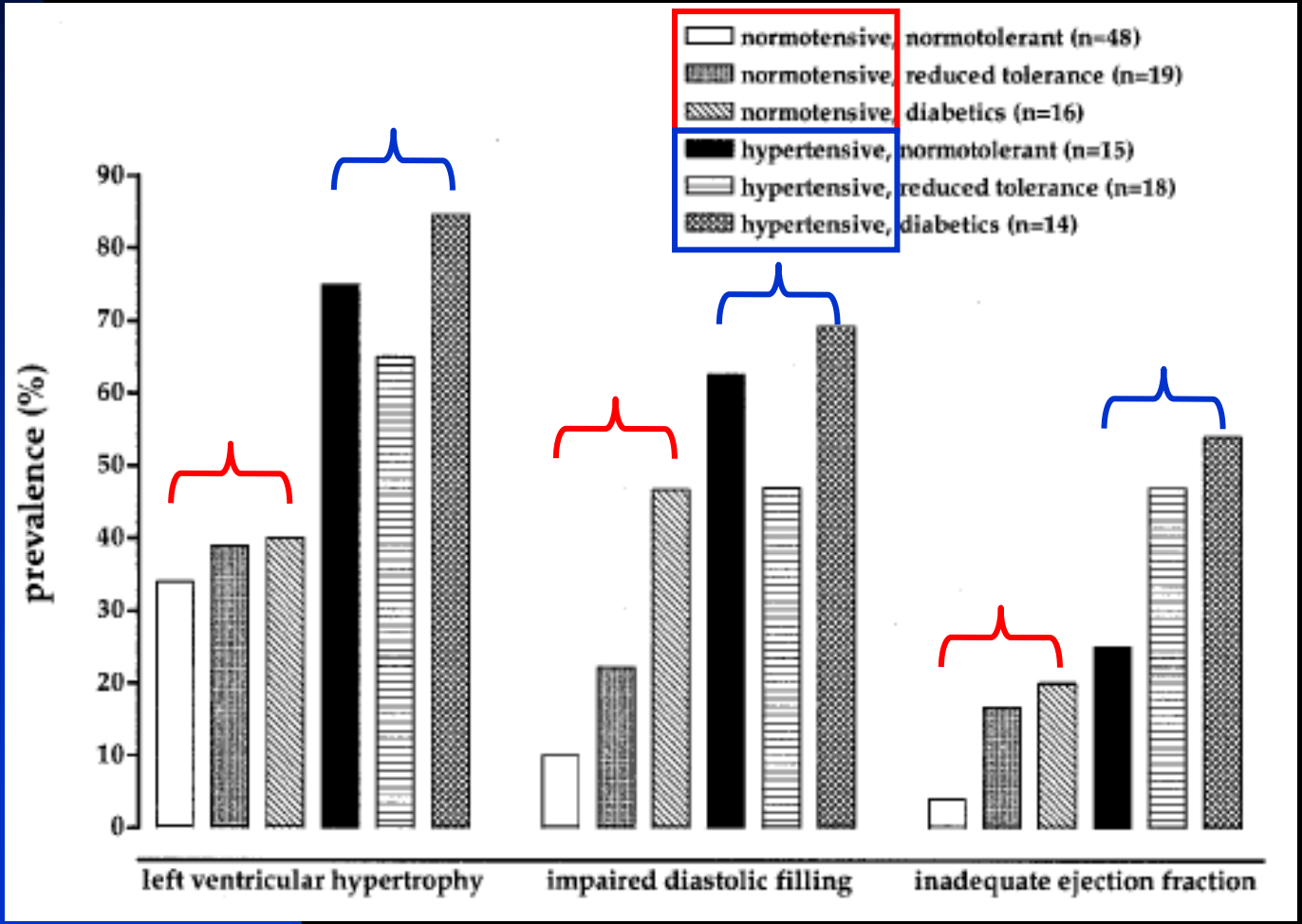
Aging and Echocardiographic Parameters
(200 patients)



Colao et al, Endocr Rev, 2004

Effect of Hypertension and Diabetes on Echocardiographic Parameters

(130 patients)



Colao et al, Endocr Rev, 2004

Assessment of Cardiovascular Complications at Diagnosis and Follow-up

At diagnosis	Long term follow-up
Echocardiography	Annually
Electrocardiogram	Annually
Exercise ECG	If angina is present
BP monitoring	Annually (or in case of change of treatment)
Echodoppler of Carotid	As indicated by clinical features

AACE: Limited information is available about the role of screening cardiac stress tests or echocardiography in patients with acromegly

Adapted from Giustina et al, J Endocrinol Invest, 2003

ACC/AHA/ASE Guideline Update for the Clinical Application of Echocardiography

Screening

Recommendations for Echocardiography to Screen for the Presence of Cardiovascular Disease

Class I

1. Patients with a family history of genetically transmitted cardiovascular disease.
2. Potential donors for cardiac transplantation.
3. Patients with phenotypic features of Marfan syndrome or related connective tissue diseases.
4. Baseline and re-evaluations of patients undergoing chemotherapy with cardiotoxic agents.
5. First-degree relatives (parents, siblings, children) of patients with unexplained dilated cardiomyopathy in whom no etiology has been identified.

Class IIb

Patients with systemic disease that may affect the heart.

Class III

1. The general population.
2. Routine screening echocardiogram for participation in competitive sports in patients with normal cardiovascular history, ECG, and examination.

Cheitlin et al, 2003

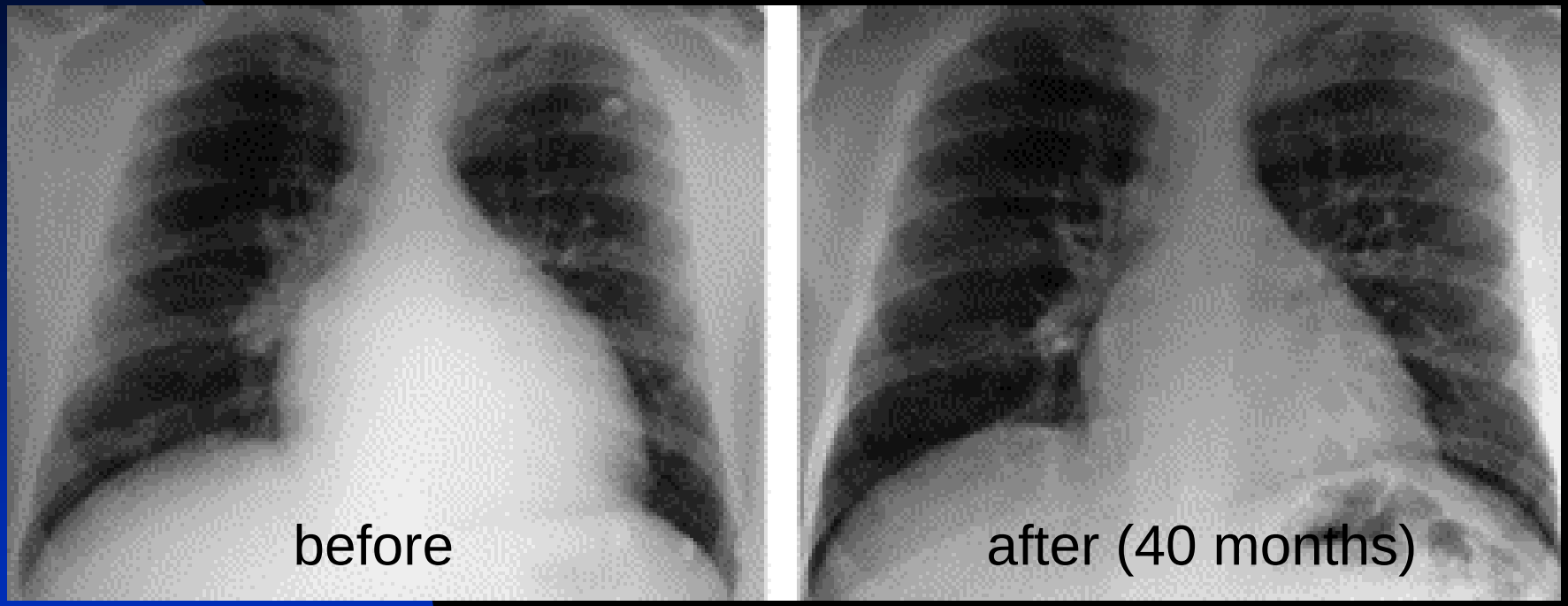
ACC/AHA/ASE Guideline Update for the Clinical Application of Echocardiography

Class I or IIa in the following:

- Heart murmur (stenosis, regurgitation, MV prolapse)
- Dyspnea, edema, cardiomyopathy
- Hypertension
- Neurological events
- Arrhythmias and palpitation

Cheitlin et al, 2003

When head rules heart



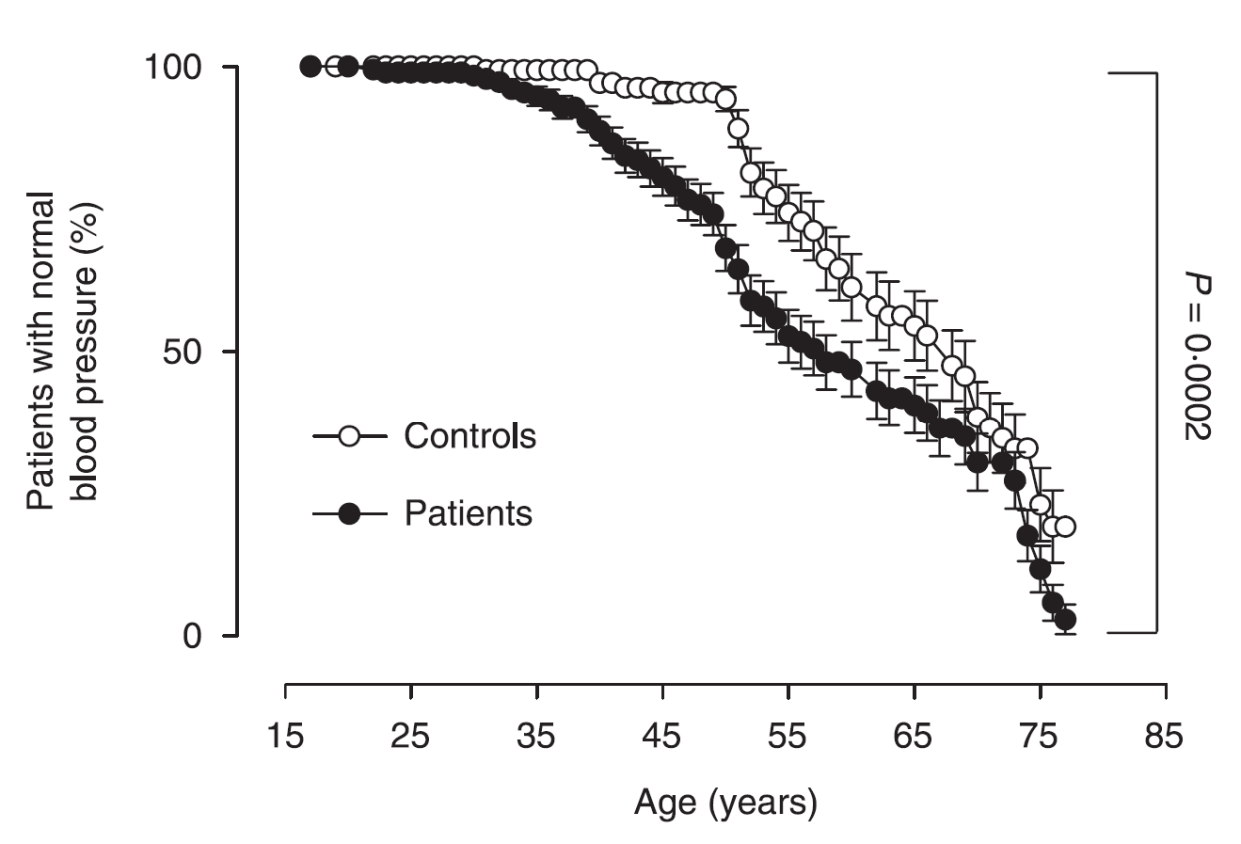
July 2000
40 yr; dyspnea
LVED 90 mm (hypocinetic)
IGF-I 1214 ug/L
BP 100/60; HR 90

2000-2002: octreotide
February 2002: Surg. Therapy
April 2003: LVED 60 mm
IGF-I: 195 ug/L

Flaherty et al, Lancet, 2004

Hypertension in Acromegaly: Prevalence and Determinants

(200 patients)



Independent predictors of hypertension:
Age and glucose

Vitale et al, Clinical Endocrinology, 2005

7th Report of the Joint National Commettee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)

BP Classification	SBP		DBP
Normal	< 120	and	< 80
Prehypertension	120-139	or	80-89
Stage 1	140-159	or	90-99
Stage 2	≥160	or	≤100

AACE guidelines: target < 130/80

JAMA, May 2003

7th Report of the Joint National Commettee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)

Follow-up and Monitoring

- Patients should return for follow-up and adjustment of medication until the BP goal is reached
- More frequent visits for Stage 2 hypertension or with complicating comorbidit conditions
- Serum potassium and creatinine 1-2 times per year
- After BP at goal and stable, follow-up visits at 3 to 6 months intervals
- Comorbidities and the need of laboratory tests influence the frequence of visits

JAMA, May 2003

Global Guideline for Type 2 Diabetes
International Diabetes Federation

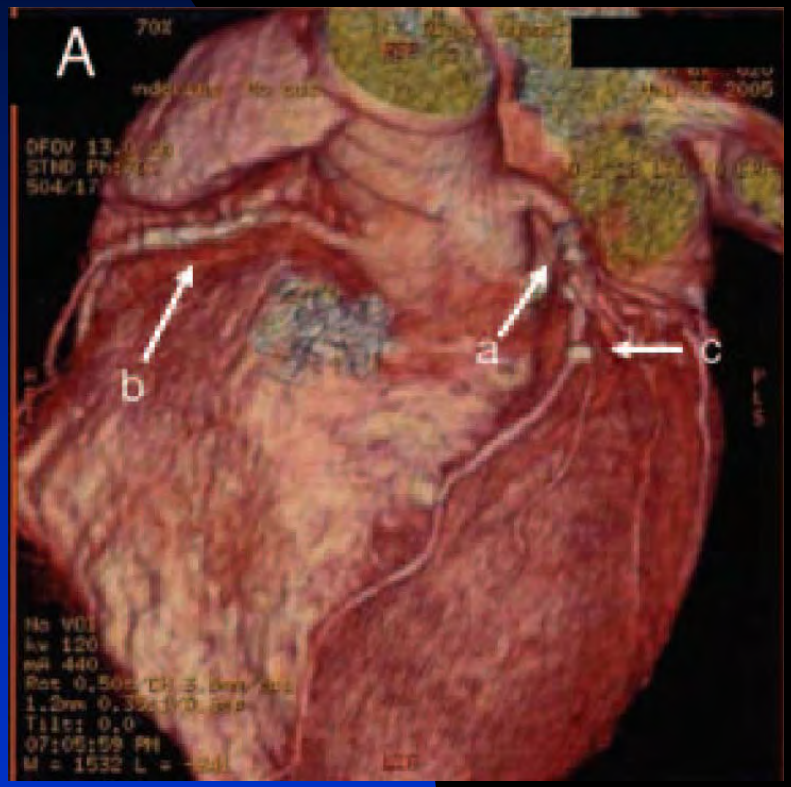
- Glucose control levels:
  - HbA1c < 6.5%*
  - before meals glucose < 6.0 mmo/L (110 mg/dl)
  - 1-2h after meals glucose < 8.0 mmol/L (145 mg/dl)
  - raise targets for people on insulin or sulfonylurea
- Clinical monitoring:
  - HbA1c every 2-6 months (depending on stability, therapy)
- Blood pressure control:
  - measure annually, every routine clinic visit
  - target below 130/80* mmHg (140/80 in some people)

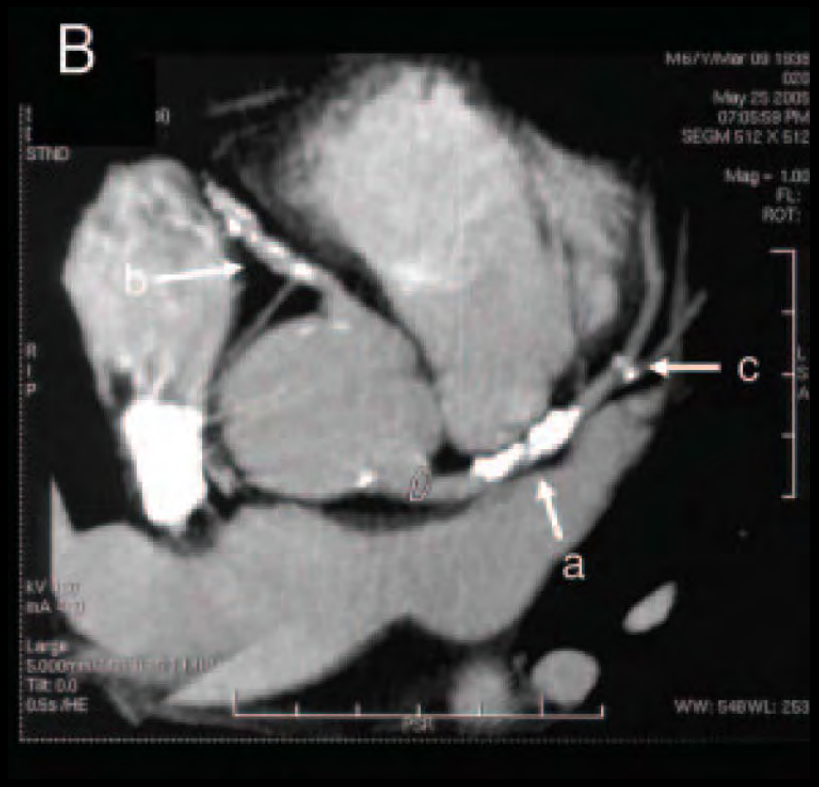
(* same as AACE Guidelines)

IDF Clinical Guidelines Task Force, 2005

Coronary Calcification Detected by Computed Tomography

(34 patients)





Coronary calcium increased with:

Hypertension P <0.002

Diabetes P <0.05

Cannavo et al, JCEM, 2006

NCEP-ATP III
Classification of Total and LDL Cholesterol

	Total	LDL	TG
Optimal		<100	
Desiderable	<200	100-129	<150
Borderline High	200-239	130-159	150-199
High	>240	160-189	200-499
Very High		>190	>500

Low HDL	< 40
High HDL	> 60

NIH Publication, September 2003

NCEP ATP III
Follow-up when LDL Levels are Below Goal Levels

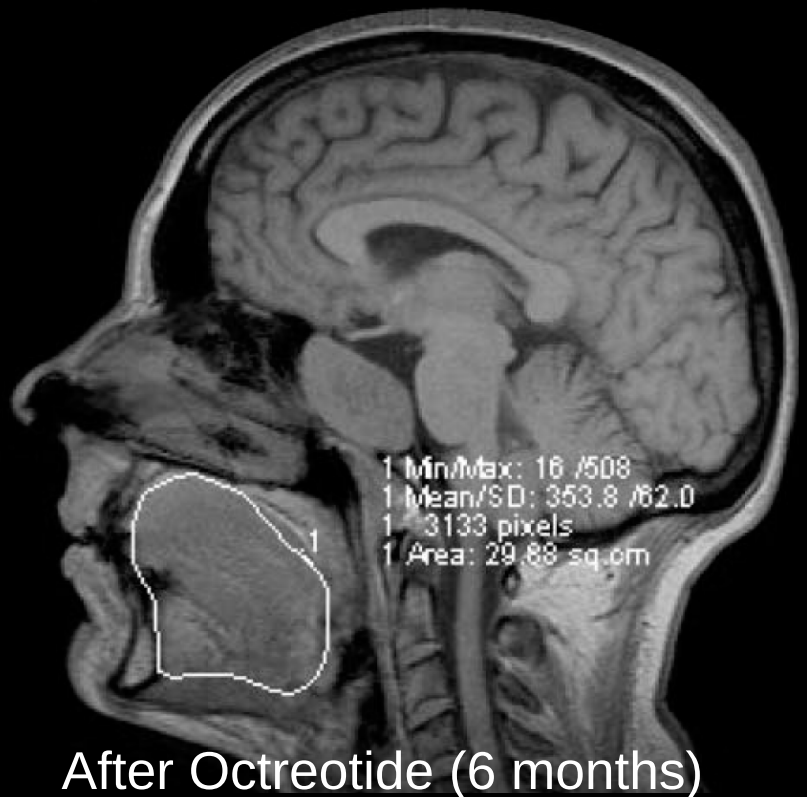
Risk Level	LDL Goal (mg/dL)	LDL Level Observed (mg/dL)	Repeat Lipoprotein Analysis
CHD or CHD risk equivalents	<100	<100	<1 year
2+ risk factors	<130	<130	≤2 years
0–1 risk factor	<160	130–159	≤2 years
0–1 risk factor	<160	<130	≤5 years

RF: age, family hystory of CHD, current smoking, hypertension, low HDL

NIH Publication, September 2002

Sleep Apnoea and Tongue Volume
(14 patients)

Before



After Octreotide (6 months)

Herrmann et al, European Journal of Endocrinology, 2004

Respiratory disorders:
Problems

- Obstructive pulmonary disease
- Higher risk of pulmonary infections
- Sleep apnea (obstructive, central, mixed)
- Impaired airflow transit
- Nocturnal snoring

Respiratory disorders: Assessment

- History and examination
- Chest X-Ray
- Sleep questionnaries
- Overnight oximetry (AACE: screening test)
- Polysomnography

Respiratory disorders:
Assessment
AACE + ENEA & PS

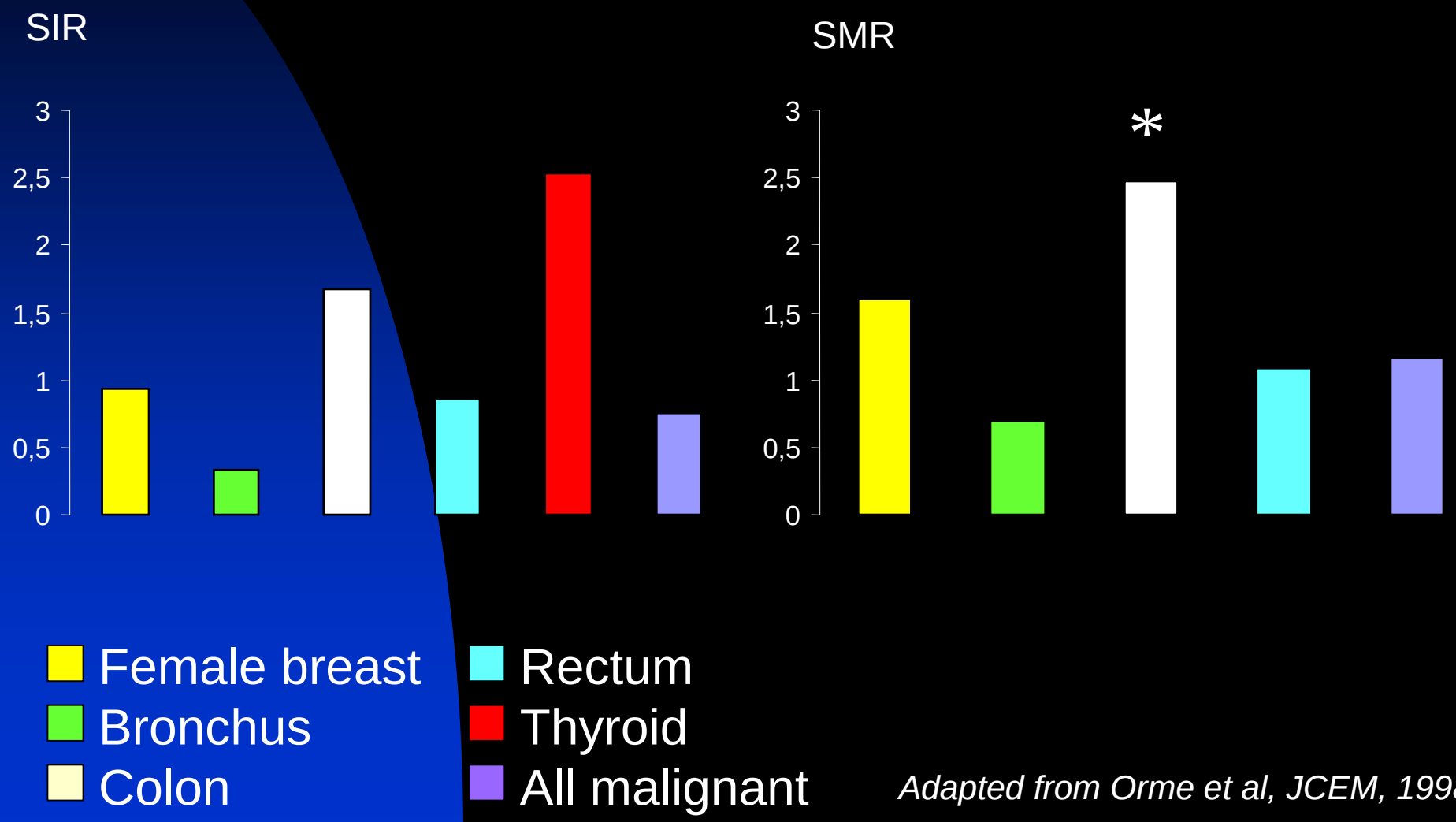
At diagnosis	Long-term follow-up
Sleep assessment	Annually (if altered at diagnosis)
Influenza vaccine	Annually
Pneumococcal vacc.	One time (and > 65 yr)
Smoking cessation	

Cancer:
Problems

- Colon: polyps, cancer ?
- Breast cancer ?
- Prostate cancer ?
- Intracranial neoplasms ?
- Thyroid cancer ?

Summary of Cancer Incidence and Mortality Data

1362 patients (UK) - 19.323 yrs follow-up



Adapted from Orme et al, JCEM, 1998

Colon polyps:
Assessment

St Bartholomew's Hospital, London, UK

- Total colonoscopy
- Screening: start at age 40
- Every 3 yr if adenoma or ↑ IGF
- Every 5 yr if hyperplastic polip or negative

Jenkins and Fairclough, Gut, 2002

Colonoscopy
Assessment

	1st screening	Follow-up (negative)	Follow-up (positive)	Not specified
Cortina 2000	At diagnosis			
London 2002	40 yr	5 yr	3 yr	
Versailles 2002				3-5 yr
ENEA+PS 2003	At diagnosis	2-3 yr		
AACE 2004	At diagnosis	5 yr*	Am Cancer Society*	
GHR+PS 2004	50 yr			

* Like increased risk patients

American Cancer Society Guidelines for the Early Detection of Cancer
Colorectal: average-risk, asymptomatic

Population	Test or Procedure	Frequency (starting age 50)
Men and women, Age 50+	Fecal occult blood test (FOBT) and flexible sigmoidoscopy	Annual FOBT + Sigmoidoscopy every 5 yr
	Flexible sigmoidoscopy	Every 5 yr
	FOBT	Annual
	Colonoscopy	Every 10 yr
	Double contrast barium enema (DCBE)	Every 5 yr

Smith et al, CA Cancer J Clin 2002

Colonoscopy Surveillance after Polipectomy

Consensus Update by the US Multi-Society Task Force On Colorectal Cancer and the American Cancer Society

➢ Rectal hyperplastic polyps*	10 yr
➢ 1 or 2 < 1 cm tubular adenoma (low grade dysplasia)	5-10 yr
➢ 3-10 adenomas Adenoma > 1cm Villous features High-grade dysplasia	3 yr
➢ 10 adenoma	< 3 yr

*patients with small hyperplastic polyps should be considered to have normal colonoscopies

Adapted from Winawer et al, CA Cancer J Clin 2006

Colonoscopy Surveillance after Cancer

Consensus Update by the US Multi-Society Task Force On Colorectal Cancer and the American Cancer Society

Colon and rectal cancer	1 yr
If normal after 1 yr	3 yr
If normal after 3 yr	5 yr

Adapted from Rex et al, CA Cancer J Clin 2006

American Cancer Society Guidelines for the Early Detection of Cancer
Breast and Prostate: average-risk, asymptomatic

Population	Test or Procedure	Frequency
BREAST		
Women, Age 20+	Breast self-examination	Monthly, starting age 20
	Clinical breast examination	Every 3 yr, age 20-39 Annual, starting at age 40*
	Mammography	Annual, starting at age 40
PROSTATE		
Men, age 50+	Digital rectal examination (DRE) and PSA	PSA and DRE annually starting at age 50 for men who have a life expectancy of at least 10 years

Smith et al, CA Cancer J Clin 2002

Monitoring of Men Receiving Testosterone Therapy
Endocrine Society Clinical Practice Guidelines

- Baseline Digital Rectal Examination (DRE) + PSA:
  → 3 months

- Urological Consultation if:
  PSA > 4.0 ng/ml
  PSA increase > 1.4 ng/ml after 12 months of treatment
  PSA velocity > 0.4 ng/ml/yr (1st PSA after 6 m; tot 2yr)
  DRE abnormalities
  Symptom score > 19

- Hematocrit:
  Baseline → 3m → annually
  Cutoff < 54%

The Endocrine Society, 2006

Systematic approach to complications
Conclusion

Consider the following:

- Signs and Symptoms
- Check comorbidities → follow-up
- Age, age at diagnosis, duration of disease
- GH & IGF-I
- Adenoma volume
- Gender & Fertility
- Therapy

Acknowledgements

Clinica Medica 3^

G. Federspil
N. Sicolo
R. Vettor
F. Fallo
C. Martini
E. De Carlo
R. Mioni
C. Pagano
M. Rossato
C. Menegazzo
M. Barban
M. Carli

Laboratorio

G. Milan
C. Pillon
C. Centobene
S. Leandri

Infermieri

L. La Serra
L. Rizzato
A.M. Baldan

Scale 1 (Physical, 8 items)

Item 1	My legs feel weak
Item 3	I get depressed
Item 9	I have problems carrying out my usual activities
Item 13	The illness affects my performance at work or in my usual tasks
Item 14	My joints ache
Item 15	I am usually tired
Item 19	I feel like a sick person
Item 22	I feel weak

Scale 2 (Psychological, 14 items)

Subscale 2·1 (Appearance, 7 items)

Item 2	I feel ugly
Item 4	I look awful in photographs
Item 7	I look different in the mirror
Item 11	Some parts of my body (nose, feet, hands, …) are too big
Item 12	I have problems doing things with my hands, e.g. sewing or handling tools
Item 16	I snore at night
Item 17	It is hard for me to articulate words due to the size of my tongue

Subscale 2·2 (Personal relations, 7 items)

Item 5	I avoid going out very much with friends because of my appearance
Item 6	I try to avoid socializing
Item 8	I feel rejected by people because of my illness
Item 10	People stare at me because of my appearance
Item 18	I have problems with sexual relationships
Item 20	The physical changes produced by my illness govern my life
Item 21	I have little sexual appetite

Surgical Therapy:
Incidence of Complications

- Mortality < 0.5 %
- Major complications 1.5 %
  - Cerebrospinal fluid leak
  - meningitis
  - ischemic stroke
  - vascular injury
  - intracranial hemorrhage
  - new cranial nerve palsy
  - visual loss
- Minor complications 6.5 %
  - sinus disease
  - septal perforation
  - epistaxis
  - wound infections
  - hematomas

Adapted from Nemergut et al, Anesth Anal, 2006

American Cancer Society Guidelines for the Early Detection of Cancer
Colorectal: increased-risk, asymptomatic

Risk Category	Age to begin	Test	Comment
People with a single, small (< 1 cm) adenoma	3-6 years after the initial polypectomy	Colonoscopy*	If the exam is normal, the patient can thereafter be screened as per average-risk guidelines.
People with a large (1 cm +) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 years after the initial polypectomy	Colonoscopy*	If normal, repeat examination in 3 years; If normal then, the patient can thereafter be screened as per average-risk guidelines.
Personal history of curative-intent resection of colorectal cancer	Within 1 year after cancer resection	Colonoscopy*	If normal, repeat examination in 3 years; If normal then, repeat examination every 5 years.
Either colorectal cancer or adenomatous polyps, in any first-degree relative before age 60, or in two or more first-degree relatives at any age (if not a hereditary syndrome)	Age 40, or 10 years before the youngest case in the immediate family	Colonoscopy*	Every 5-10 years. Colorectal cancer in relatives more distant than first-degree does not increase risk substantially above the average-risk group.

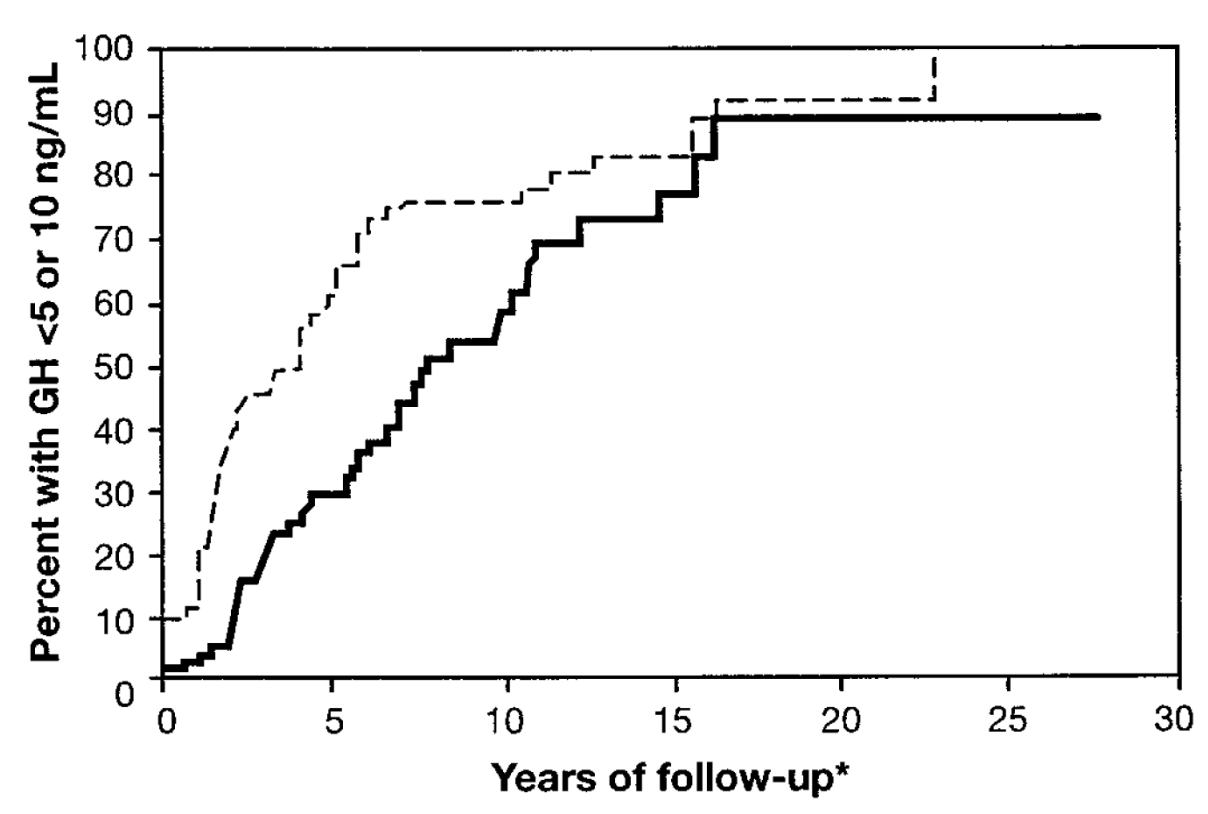
Double contrast barium enema (DCBE) or the combination of DCBE with flexible sigmoidoscopy are acceptable alternatives

Smith et al, CA Cancer J Clin 2002

Disease-Related Symptoms

- Headache
- Visual field loss
- Cranial nerve palsies
- Hypopituitarism
- Hyperprolactinemia

Radiation Therapy

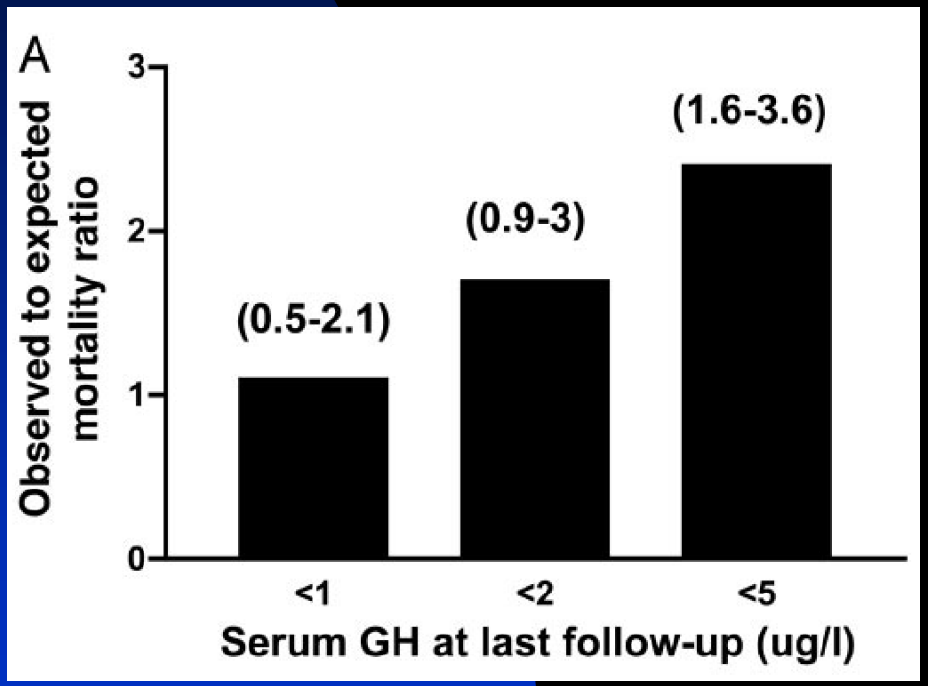


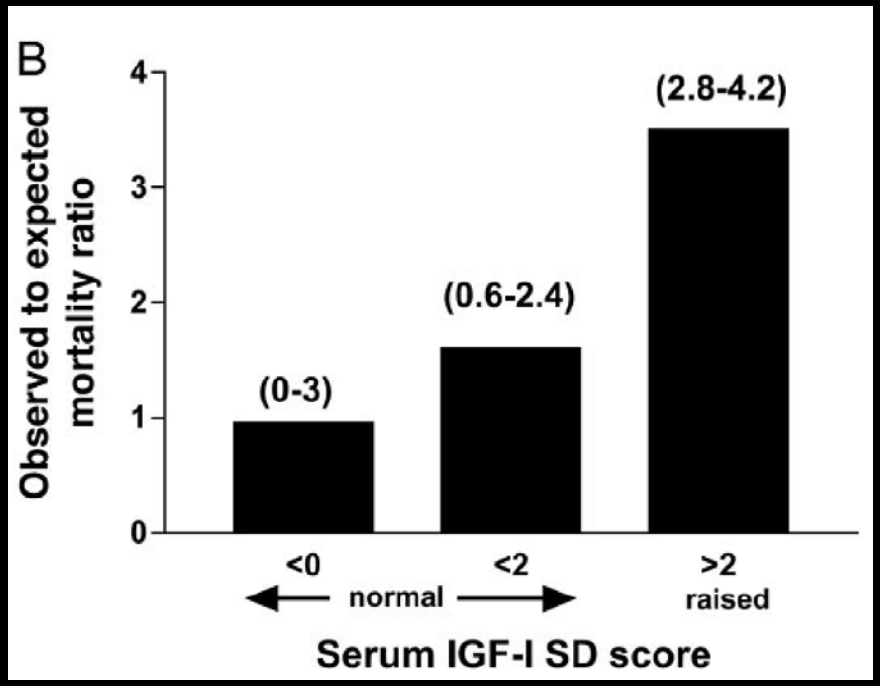
87 75 54 37 15 7 patients

Eastman et al, Endocrinol Metab Clin North Am, 1992

Factors Influencing Mortality in Acromegaly

208 patients (New Zeland), 1964-2000, follow-up 13 yrs, 72 died





Holdaway et al, JCEM, 2004

7th Report of the Joint National Commettee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)

Laboratory tests

- Routine tests:
  - ECG
  - Urinalysis
  - Blood glucose and hematocrit
  - Serum potassium, creatinine (or GFR), and calcium
  - Lipid profile, that includes HDL, LDL and tryglicerides
- Optional tests:
  - Urinary albumin excretion or albumin/creatinine ratio
- More extensive testing for identifiable causes is not generally indicated unless BP control is not achieved

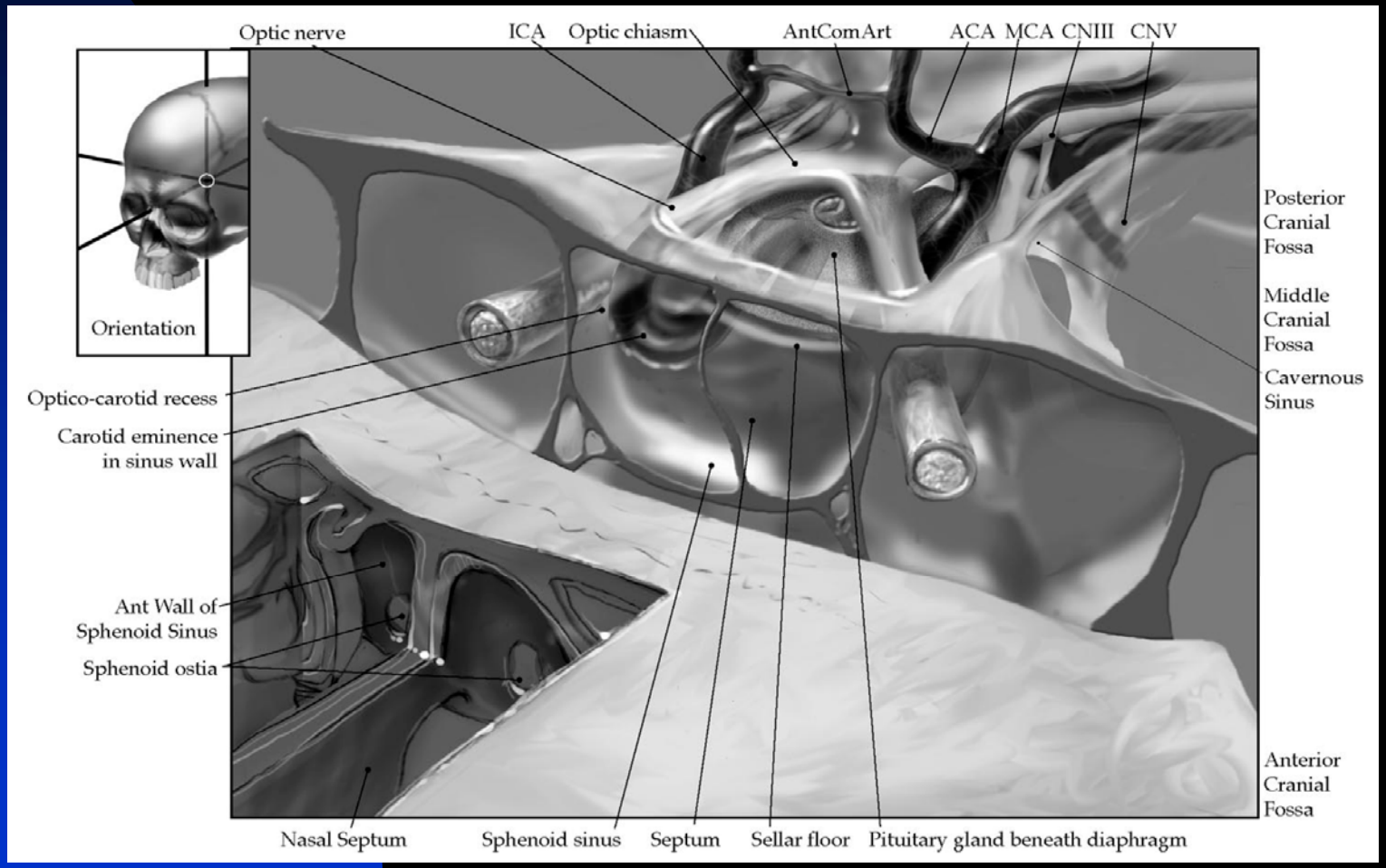
JAMA, May 2003

Global Guideline for Type 2 Diabetes
International Diabetes Federation

- Screening and diagnosis:
  - Target high-risk people
  - Fasting glucose: 5.6-7.0 mmol/L (100-126 mg/dl)
  - OGTT for diagnosis
  - Random glucose: 5.6-11.1 mmol/L (100-200 mg/dl) → Repeat fasting or OGTT
  - Diagnosis by WHO 1999 criteria

IDF Clinical Guidelines Task Force, 2005

Perioperative Management of Patients Undergoing Transsphenoidal Pituitary Surgery



Nemergut et al, Anesth Analg, 2005

AN UPDATE IN THE TREATMENT OF ACROMEGALY

THE ROLE OF SURGERY

Domenico Billeci

Department of Neurosurgery of Treviso

University of Padova

VERONA October 27,2006

GOALS OF OPERATIVE INTERVENTION

AACE Guidelines for Acromegaly 2004

1. Normalization of GH secretion and IGF-I levels
2. Elimination of mass effect and reversal of associated neurologic problems
3. Alleviation of comorbidities associated with active acromegaly
4. Preservation of pituitary function and restoration of any endocrine deficits caused by the tumour
5. Prevention of recurrence of the tumour
6. Procurement of tissue for pathologic and scientific analysis

PREDICTORS OF SURGERY OUTCOME IN ACROMEGALY

- **High basal GH and IGF-1 concentrations before surgery**
- **Tumour size**
  - **Intracavernous extension** (MRI)
  - **Dural invasion** (intraoperative evaluation)
  - **Tumour hardness**
- **Tumour morphology**
- **Mixed tumours** (GH-PRL)
- **Age at diagnosis**
- **SSA (pre)treatment**
- **Skill and experience of the surgeon**

Preoperative GH value

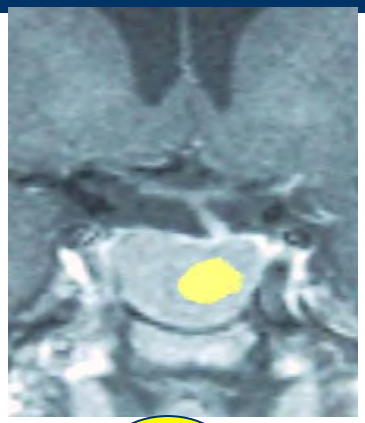
- It is difficult to identify GH threshold values that will predict postoperative results!

  30 ng/ml (Abosh et al.)

  50 ng/ml (Ahmed et al.)

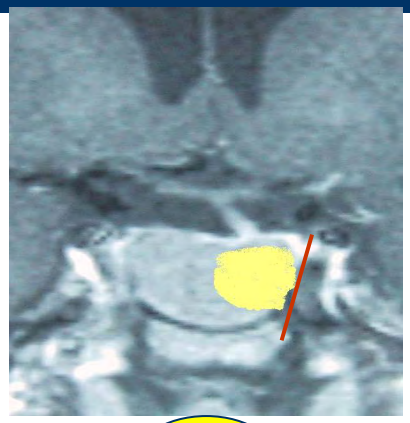
GH > 50ng/ml is predictive for a poor outcome (cure rate 25%)

TUMOUR SIZE
INTRACAVERNOUS EXTENSION (ICE)



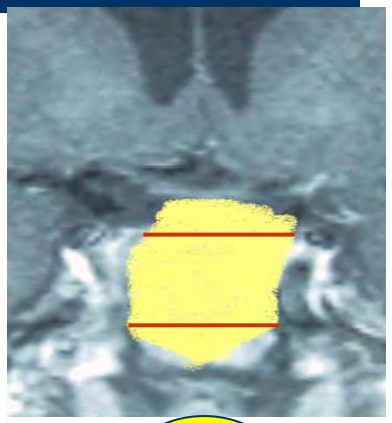
A

Microadenoma



B

Enclosed Macroadenoma



C

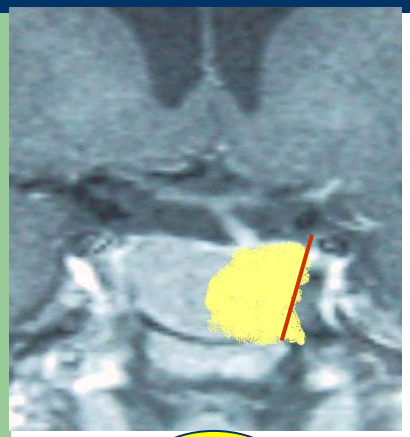
Infra-Suprasellar extension

CURE RATE

A — **B** 70-90%

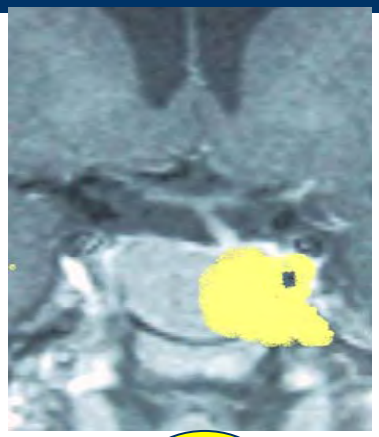
C Depends on hardness/dural invasion

TUMOUR SIZE
INTRACAVERNOUS EXTENSION (ICE)



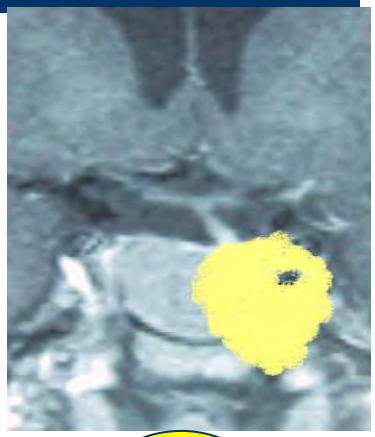
D1

ICE without invasion



D2

Cavernous sinus invasion



D3

Massive invasion

Cure rate

D1 **50-60%**

D2 **D3** **< 40%**

TUMOUR MORPHOLOGY

- **Sparsely granulated GH-cell adenomas** which exhibit **“dot-like cytokeratin staining”**are more invasive, with suprasellar extension and less responsive to pharmacological effect than densely granulated adenomas with a perinuclear, fibrillary cytokeratin pattern
- **Anti Ki-67 monoclonal antibody (MIB-1)** correlates with dural and cavernous sinus invasiveness

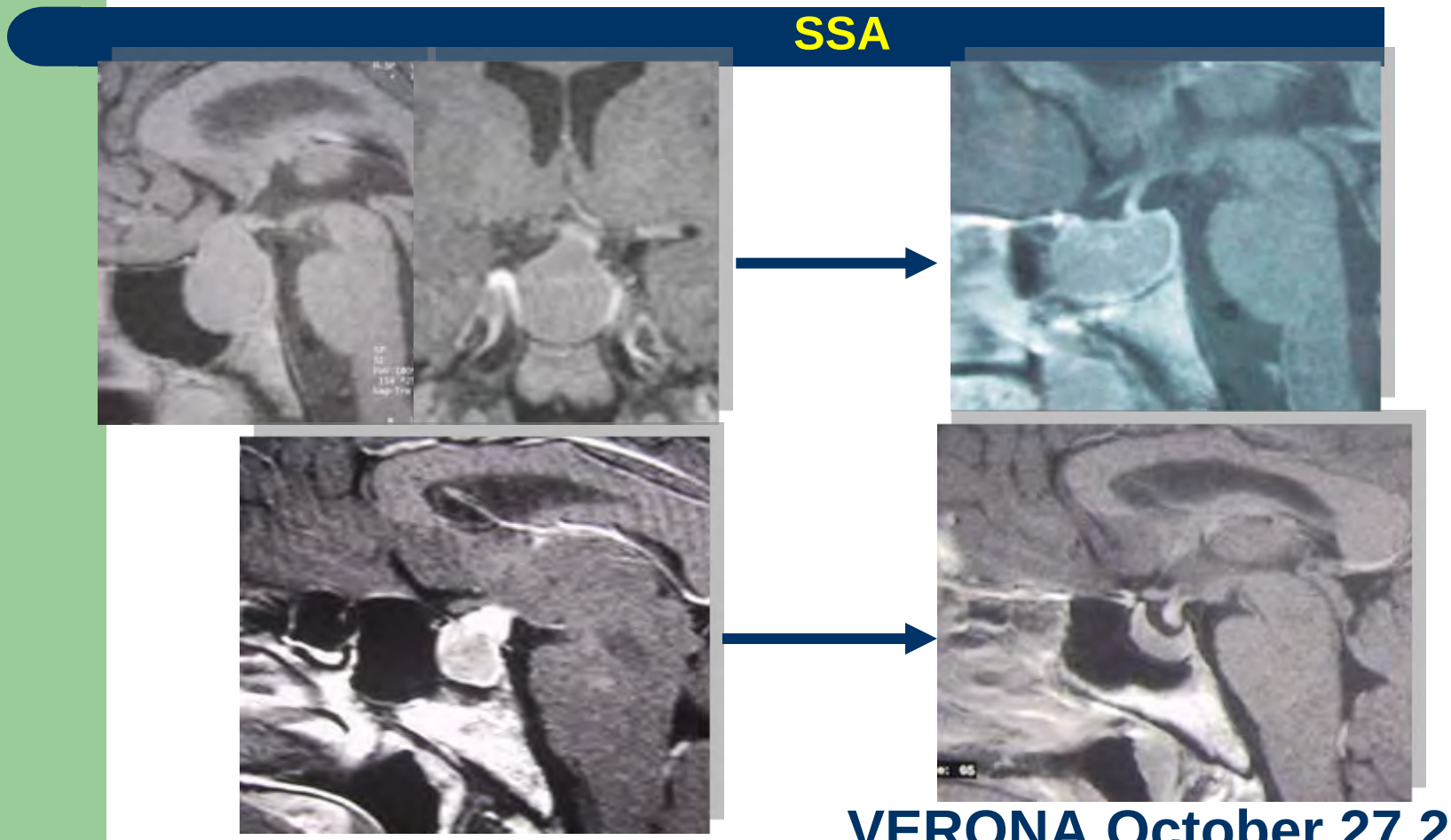
PREDICTORS OF SURGERY OUTCOME IN ACROMEGALY

Sparsely granulated GH-cells adenoma, dot-like cytokeratine pattern and mixed GH-PRL tumour correlate with **young age**, **high GH value** and **larger tumour size (ICE)** and have been associated with poorer outcomes.

AIMS OF PREOPERATIVE SSA SHORT TERM ADMINISTRATION

- Shrinkage of the tumour
- Clinical and biochemical improvement
- More soft or fluid adenoma

Significant Shrinkage (=>30%) around 50%



VERONA October 27,2006

Presurgical use of SSA improves surgical results especially in macroadenomas

"….only a controlled, randomized, and blinded study may give the ultimate answer to this question."

(M.Losa et al J.Neurosurg. 2006)

PROGNOSTIC FACTORS

AACE Guidelines for Acromegaly 2004

1. Tumour size
2. GH level before surgical treatment
3. Experience of the surgeon and the surgical team:

- Prior experience with more than 100 pituitary operations
- An ongoing experience with more than 20 pituitary cases per year
- Involvement in a team approach with colleagues from other specialities, especially endocrinology, neuropathology and radiation oncology. (neuroradiology)

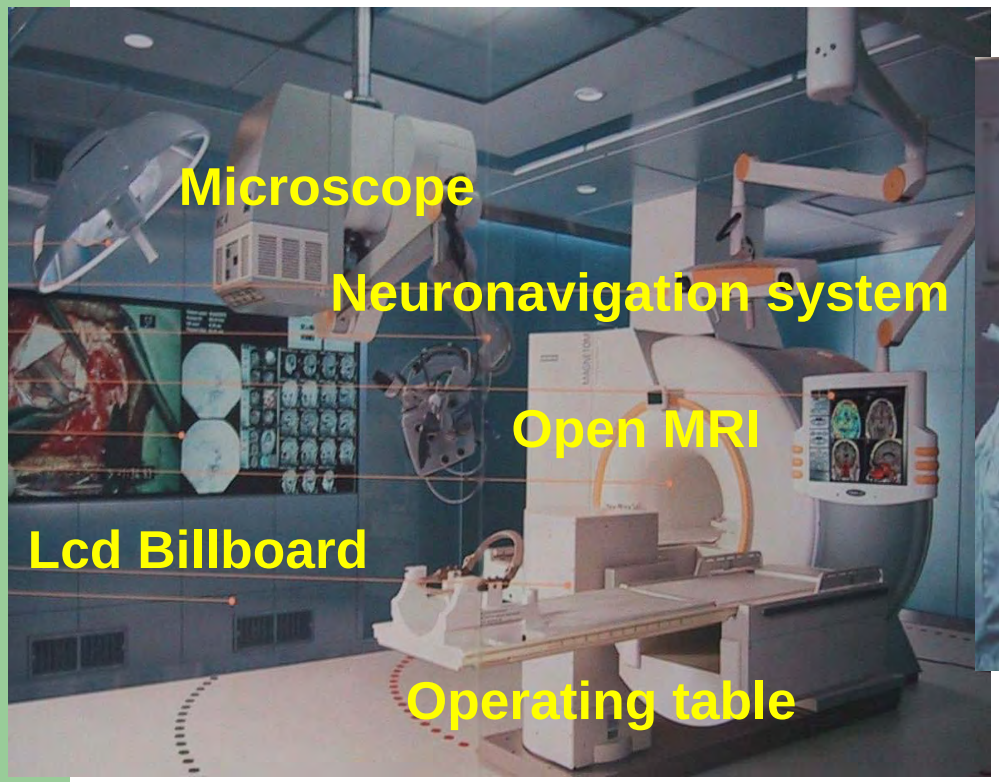
EXPERIENCE OF THE SURGEON

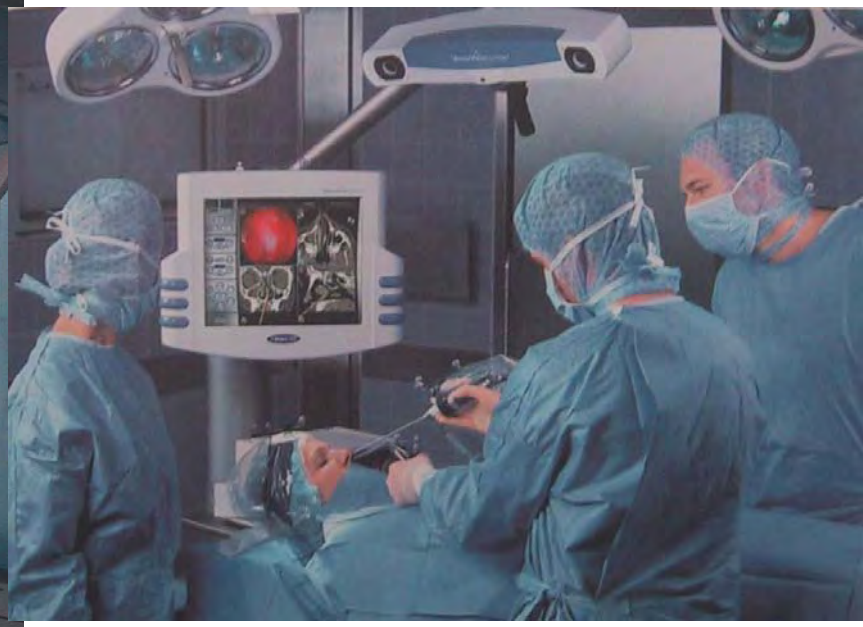
- The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone(GH) secreting adenoma (Lisset CA.; Clin. Endocr. 1998)
- Outcome of surgery for acromegaly; the experience of a dedicated pituitary surgeon(N.J.L. Gittoes;J Med. 1999)
- Outcome of transsphenoidal surgery for acromegaly and its relationship to surgical experience.(Wass JA; Clin. Endocr.1999)
- Outcome of surgery for acromegaly performed by different surgeons: importance of surgical experience (Erturk E.; Pituitary 2005)

Technical Advances
Imaging Quality and Surgical Equipment

- High resolution Magnetic Resonance Imaging
- Minimally invasive procedures (Endoscopic technique)
- Image guidance and navigation
- Intraoperative MRI

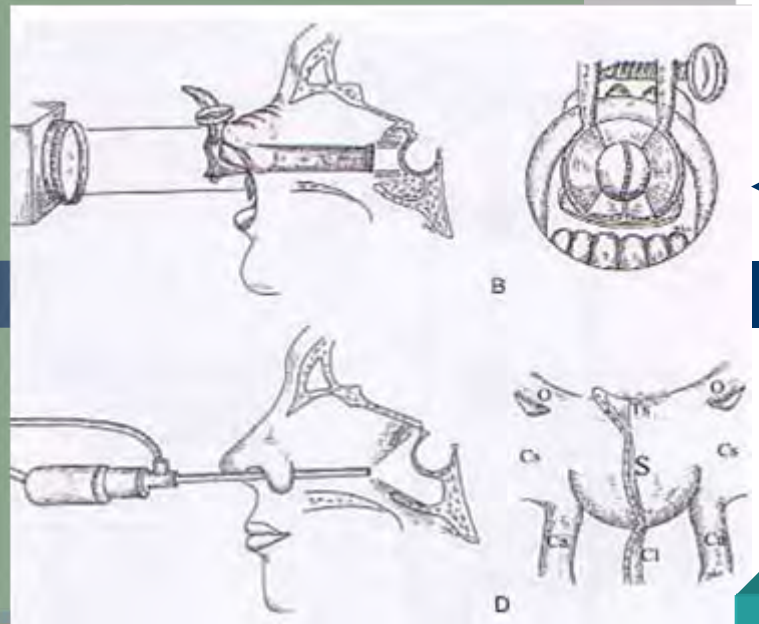
Technical Advances
Imaging Quality and Surgical Equipment





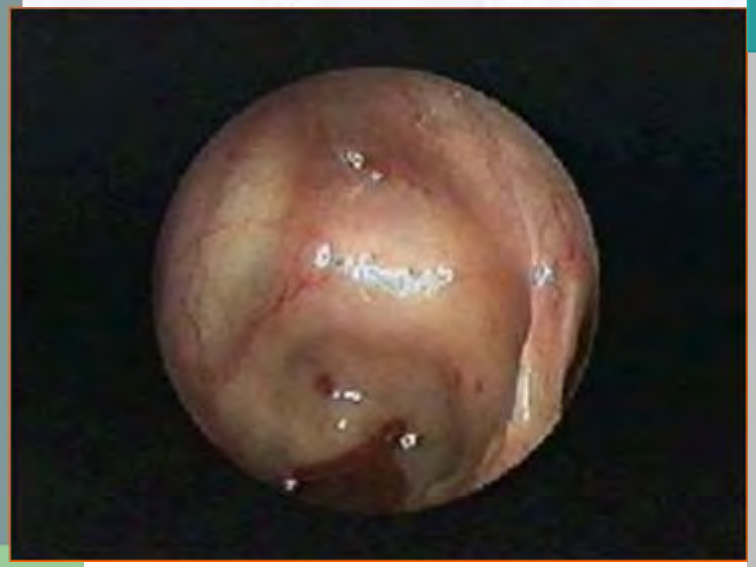
VERONA October 27,2006

SURGICAL APPRROACHES

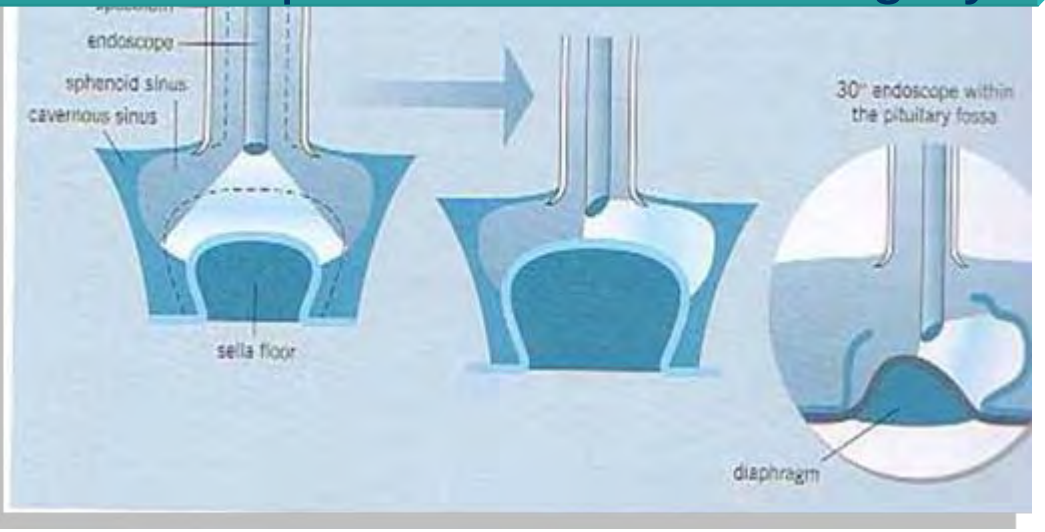


Microsurgery

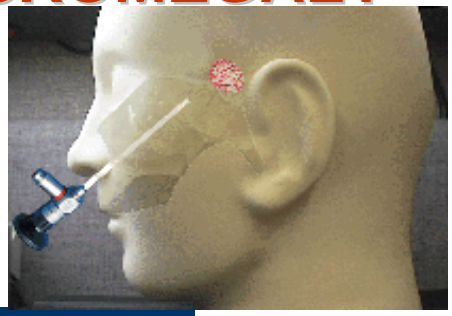
Endoscopic technique



Endoscope-assisted microsurgery



Endoscopic Endonasal Transsphenoidal Surgery Minimally invasive technique



- Approach trough a single nostril
- Excellent vision of surgical field
- Better debulking of tumour specially in macroadenomas
- Easier access in recurrent lesions
- Nasal buffering not required

Endoscopic Endonasal Transsphenoidal Surgery

- Absence of nasal bleeding
- No need of long bed rest
- No patient indisposition
- No need of long hospital stay (3 days)
- No mortality and Low morbidity
- No cases of infection
- No nasal complications

Debulking of invasive macroadenomas improves hormonal control by SSA

Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs

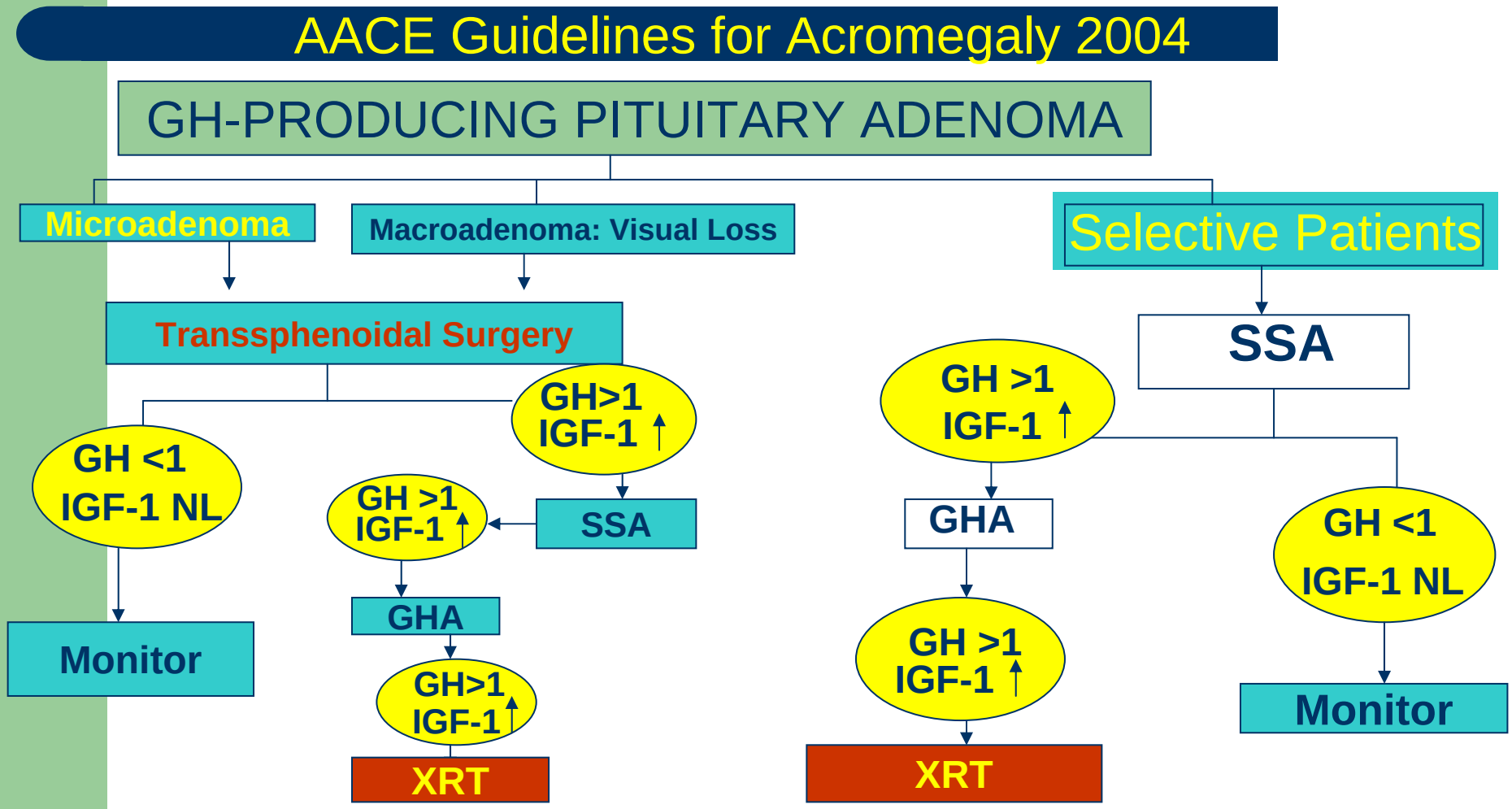
P. Petrossian et al. European Journal Of Endocrinology 2005

Partial surgical removal of growth hormone-secreting pituitary tumors enanches the response to somatostatin analogs in acromegaly

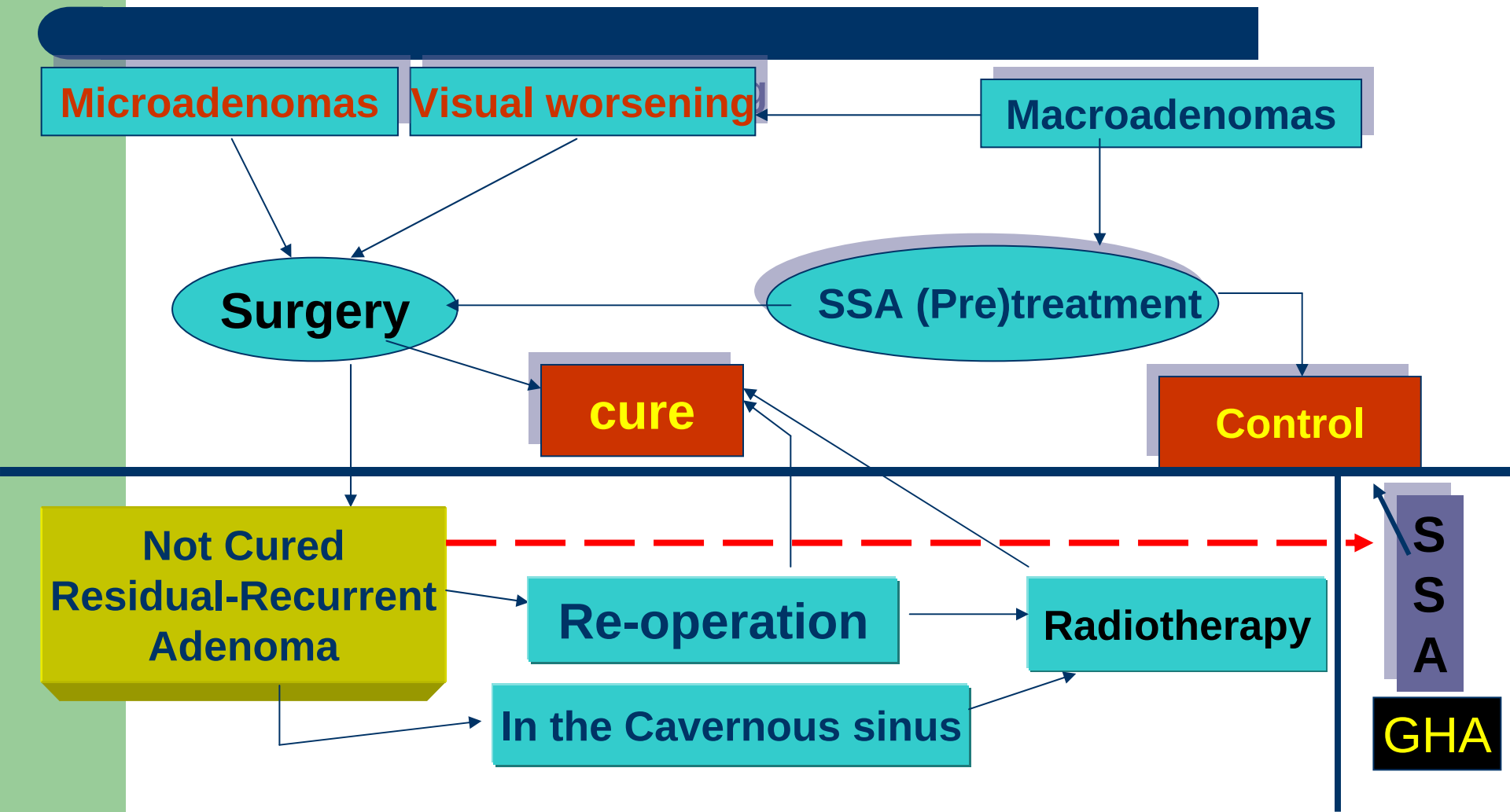
Colao A. et al. J. Clin. Endocrinol. Metab. 2006

AN UPDATE IN THE TREATMENT OF ACROMEGALY

Recommended scheme for management of GH-producing pituitary adenomas



Multimodal Therapy for Acromegaly



6th AME Italian Meeting, 3rd Joint Meeting with AACE
October 27-29, 2006
Update in Clinical Endocrinology
Pre Congress Symposia
An update in the treatment of acromegaly

The role of medical treatments

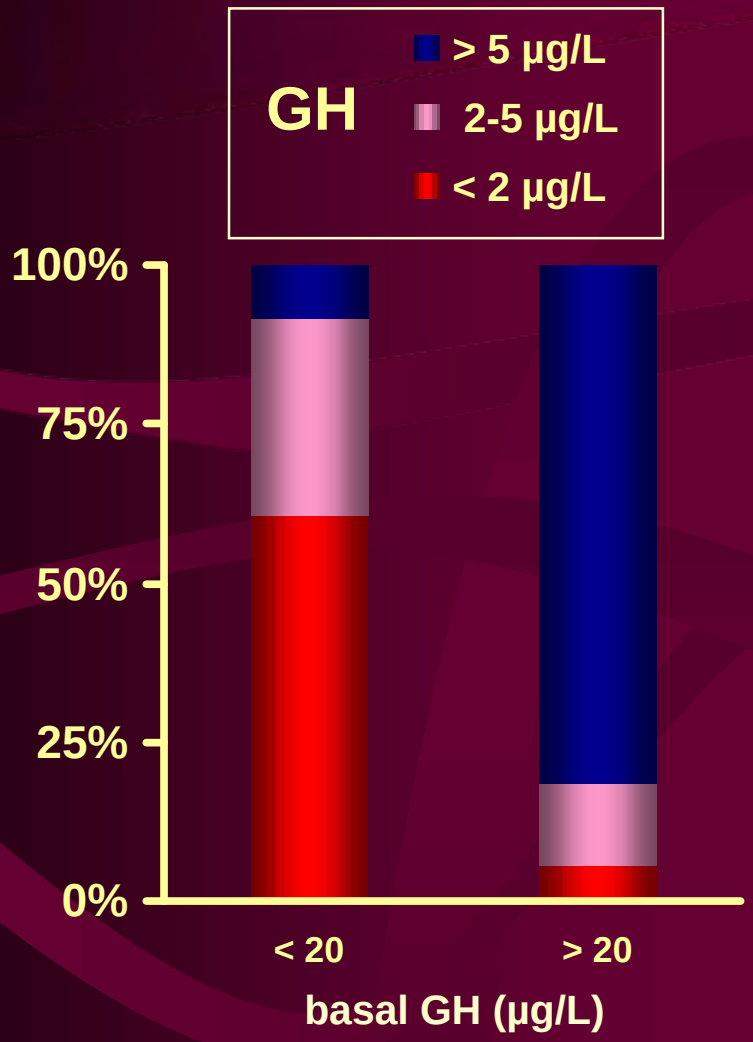
Renato Cozzi

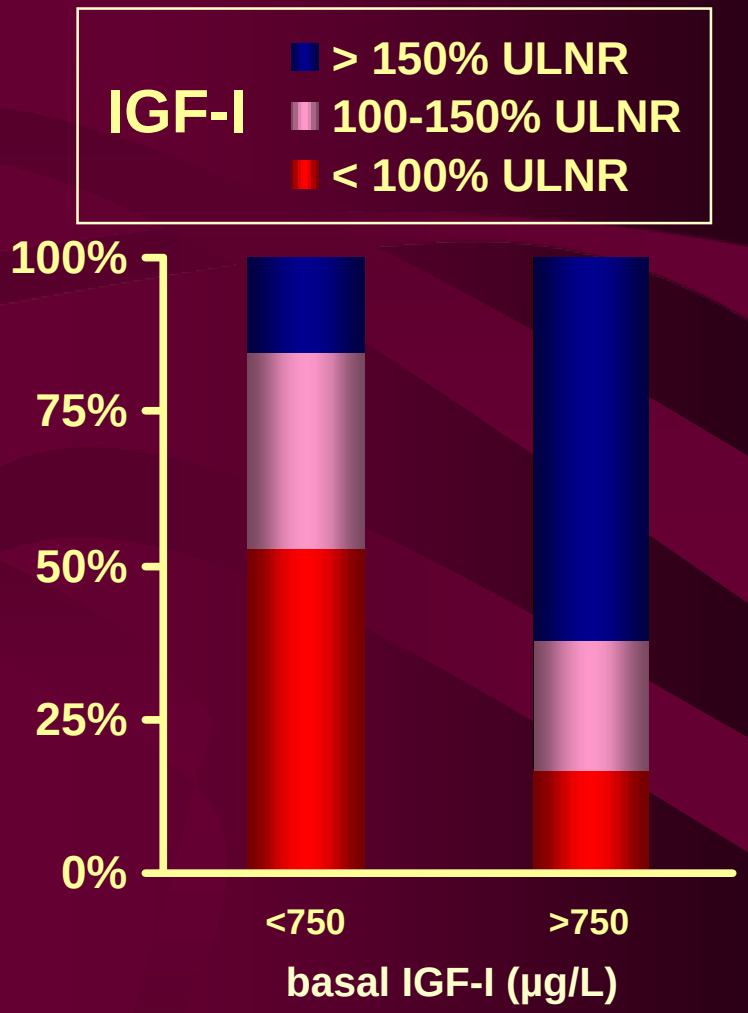
S.C. Endocrinologia Ospedale Niguarda Milano

Medical treatments

- Dopamine agonists
- Somatostatin analogs
- Pegvisomant

Cabergoline
(1-3.5 mg/week)





Abs et al, JCE&M 1998

Indications for cabergoline

- ***Who*** **mild disease, both mixed GH/PRL and pure GH secretion; intolerance to SA**
- ***When*** **adjuvant/primary**
- ***How long*** **long-lasting, safe**

Medical treatments

- Dopamine agonists
- Somatostatin analogs
- Pegvisomant

SA work at different levels

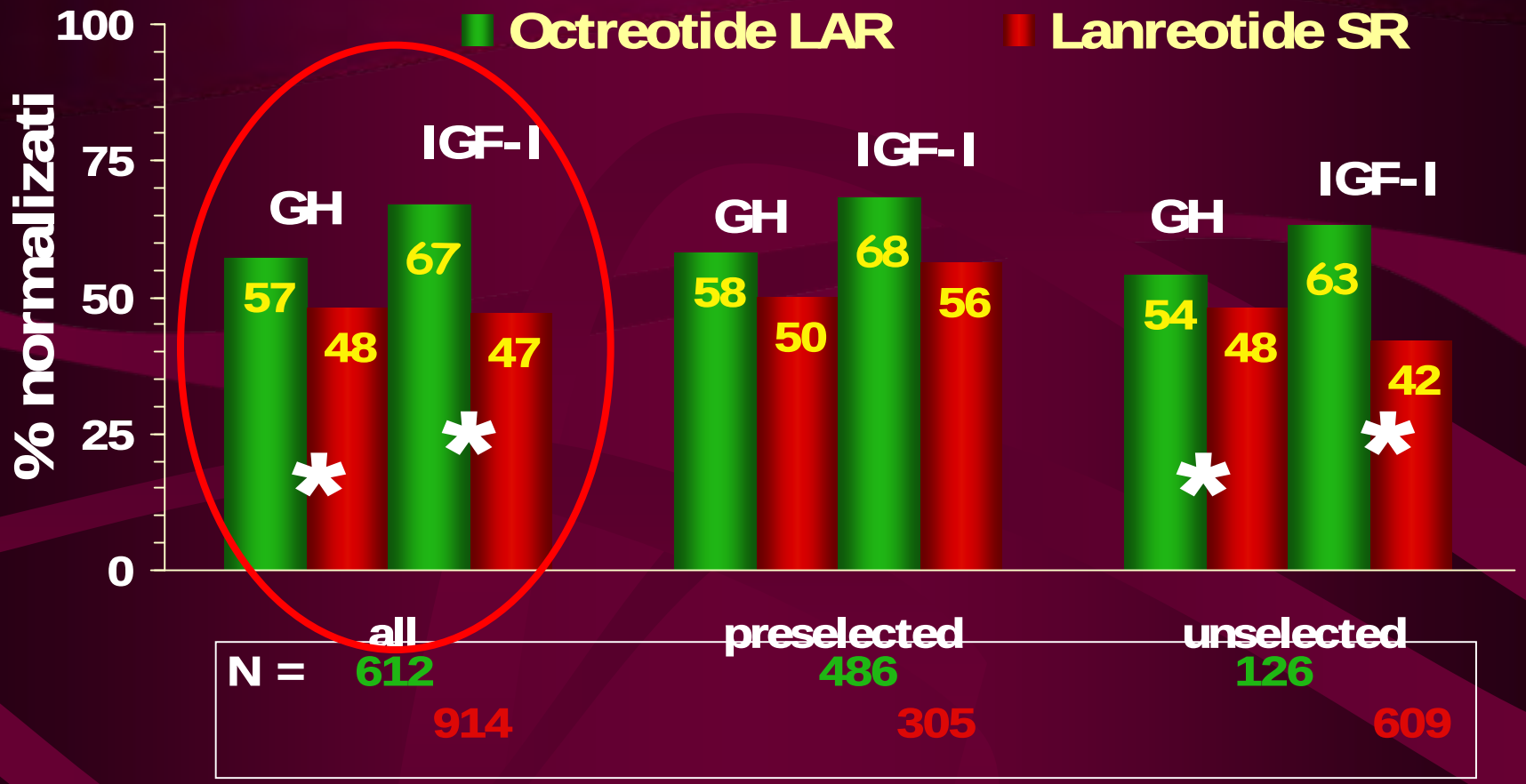
Central and peripheral actions of somatostatin on the growth hormone–IGF-I axis

Robert D. Murray,[1] Kiwon Kim,[1] Song-Guang Ren,[1] Marjorie Chelly,[2]
Yutaka Umehara,[2] and Shlomo Melmed[1]

[1]Department of Medicine and [2]Department of Surgery, Cedars Sinai Research Institute, UCLA School of Medicine, Los Angeles, California, USA.

The Journal of Clinical Investigation http://www.jci.org Volume 114 Number 3 August 2004

Meta-analysis on the efficacy of SA



Freda et al, JCE&M, 2005

Clinical context

- **Comorbidities**
- **Increased surgical risk**
- **Intubation may be difficult**

Somatostatin analogs improve comorbidities

Is the Acromegalic Cardiomyopathy Reversible? Effect of 5-Year Normalization of Growth Hormone and Insulin-Like Growth Factor I Levels on Cardiac Performance*

ANNAMARIA COLAO, ALBERTO CUOCOLO, PAOLO MARZULLO, EMANUELE NICOLAI, DIEGO FERONE, ANNA MARIA DELLA MORTE, ROSARIO PIVONELLO, MARCO SALVATORE, AND GAETANO LOMBARDI

European Journal of Endocrinology (2004) **151** 309–315 ISSN 0804-4643

CLINICAL STUDY

Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly

B L Herrmann, T E Wessendorf[1], W Ajaj[2], S Kahlke, H Teschler[1] and K Mann

Neurosurgery

Invasiveness of adenoma and high GH levels are independent and additive negative predictors of surgical outcome (90 patients)

basal GH (µg/L)	micro	intrasellar macro	invasive macro	**Total (micro & macro)**
< 10	10/12 (83%	5/5 (100%)	3/4 (75%)	**18/21 (86%)**
10-25	9/10 (90%)	6/10 (60%)	1/4 (25%)	**16/24 (67%)**
> 25	4/7 (57%)	16/21 (76%)	3/17 (18%)	**23/45 (51%)**
Total	23/29 (79%)	27/36 (75%)	7/25 (28%)	**57/90 (63%)**

Rees et al, JCEM 2003

Main surgical series

Surgery by microscopy by transnasal route

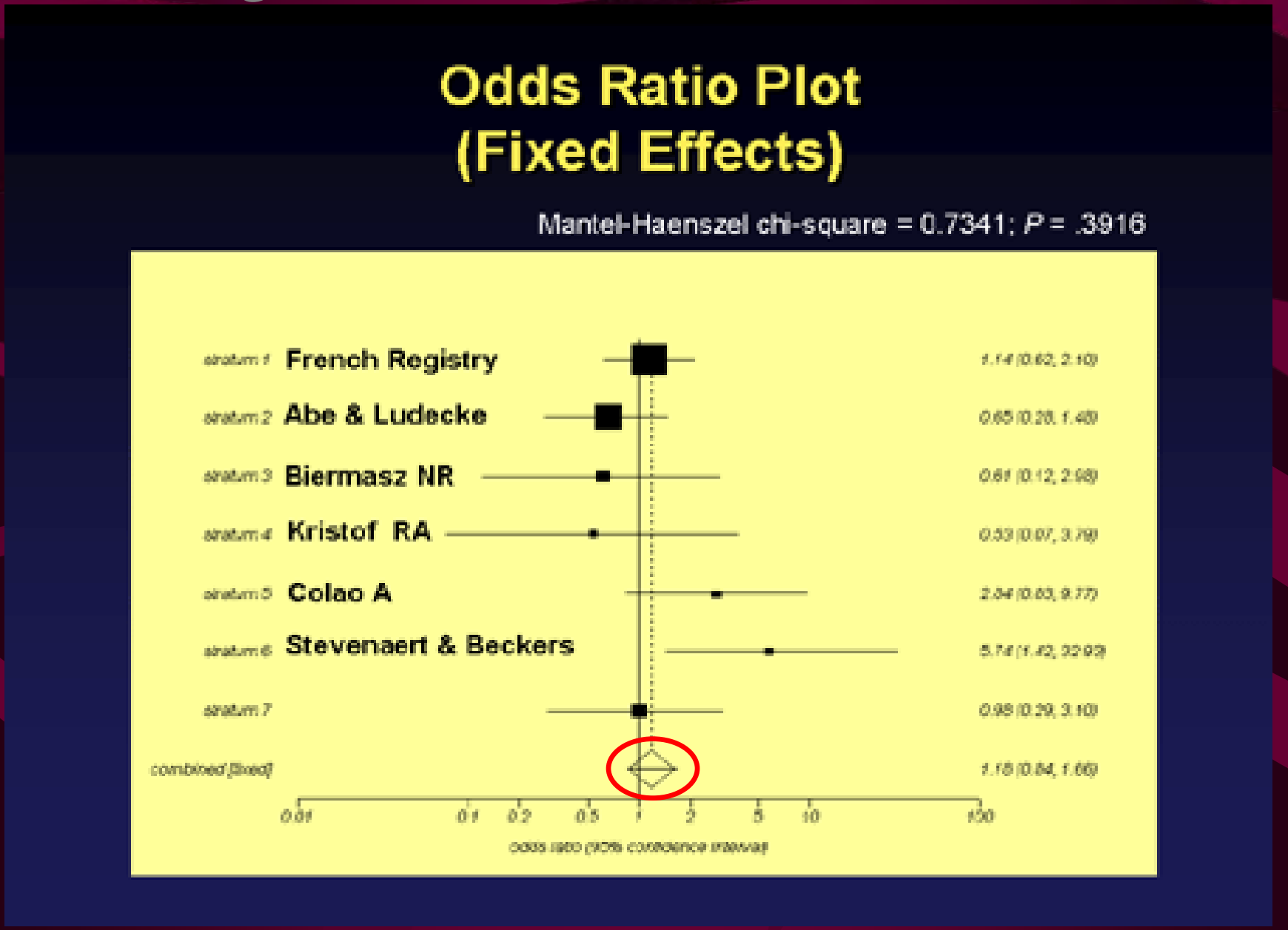
Series	No	total % cure	micro % cure	macro % cure
Ross, 1988	153	56	nd	nd
Falbush,1992	222	57	72	49
Davis,1993	174	52	nd	nd
Swearingen, 1998	162	57	91	48
Gittoes,1999	160	64	86	52
Laws, 2000	117	67	87	50
Beauregard, 2003	103	52	82	60
Falbush, 2006	506	57	75	50

Do somatostatin analogues enhance the role of surgery?

or

does surgery enhance the role of somatostatin analogues

Pre-surgical treatment on remission rate



Results of s.c. octreotide pre-surgical treatment

Significant <u>improvement</u> of clinical parameters:

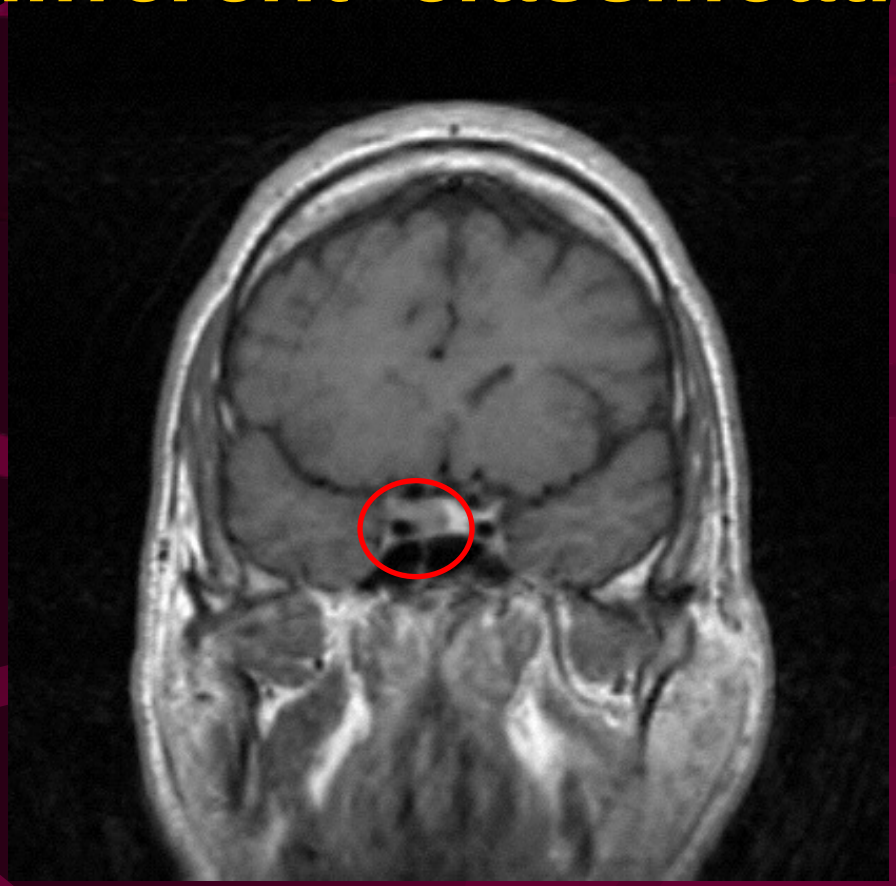
- Arrhythmic events and blood pressure
- Glucose and lipids homeostasis
- Tumor mass shrinkage
- Anesthesiological procedures / surgical outcome

Significant <u>reduction</u> of:

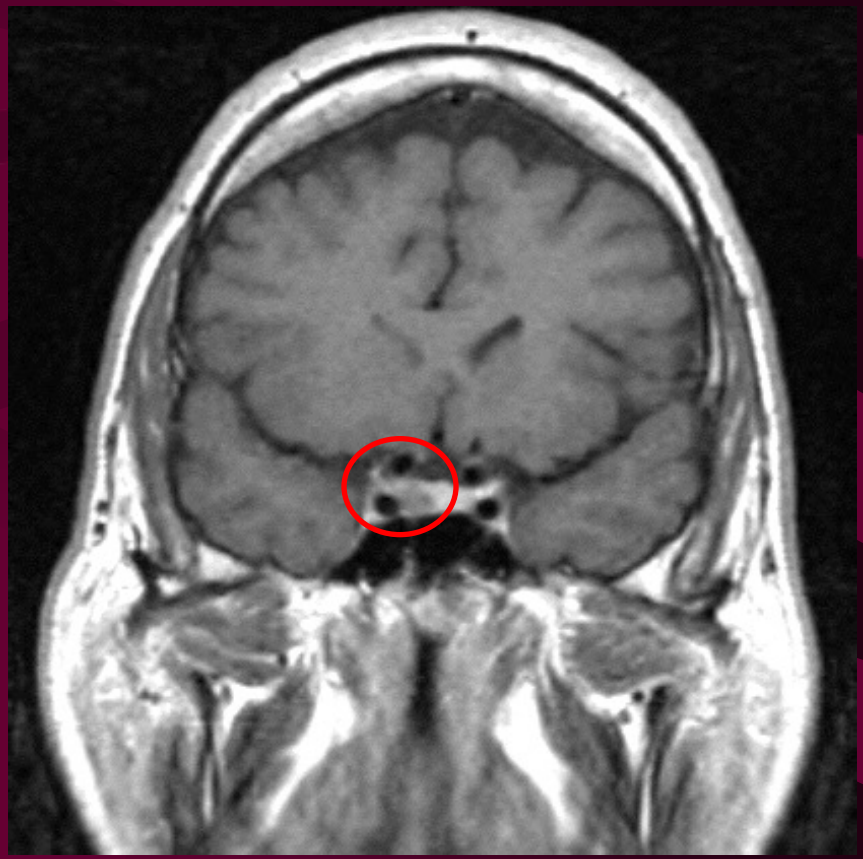
- Hospitalization time

Colao et al, JCE&M 1997

Does the pretreatment lead to a different classification of the tumour ?

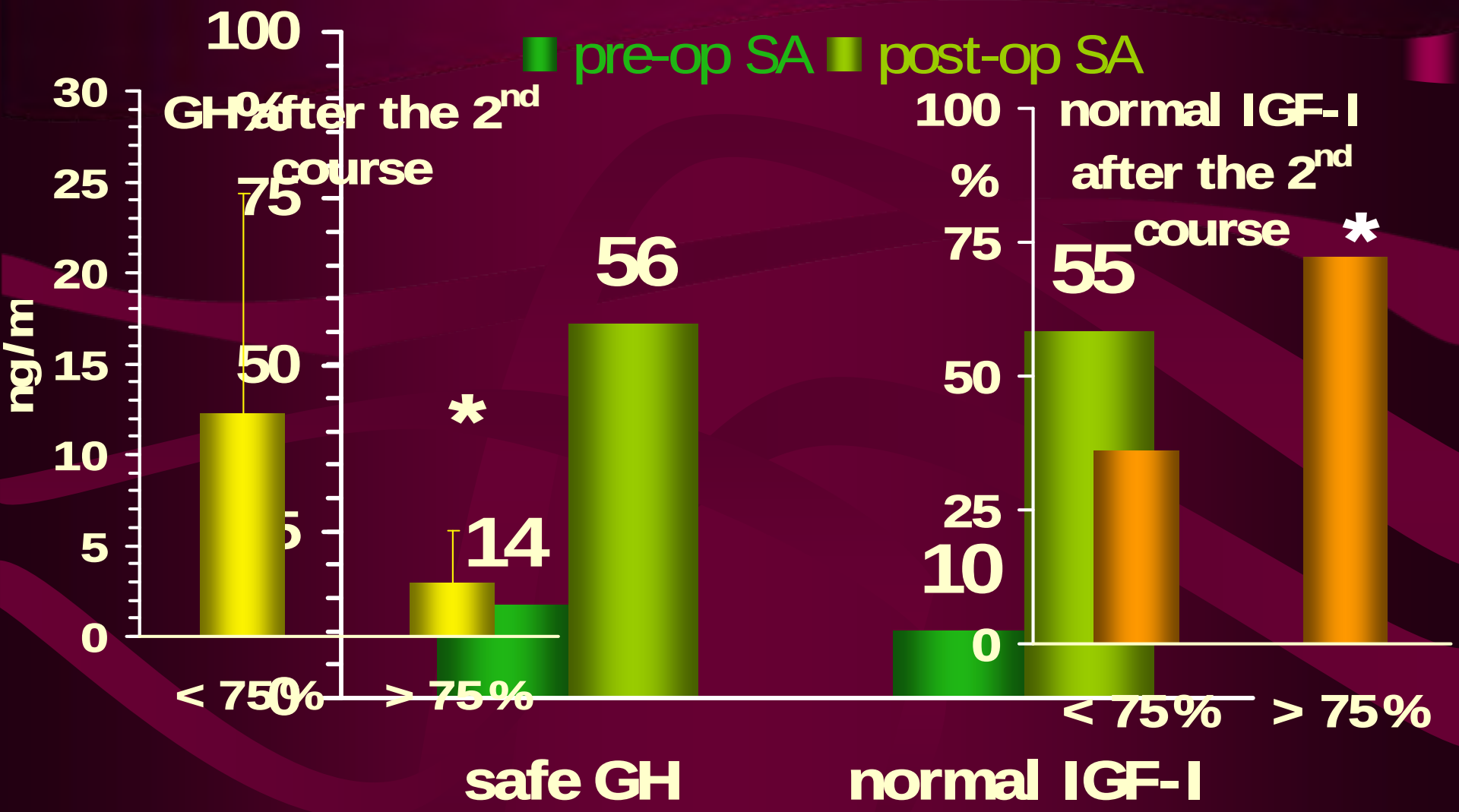


basal



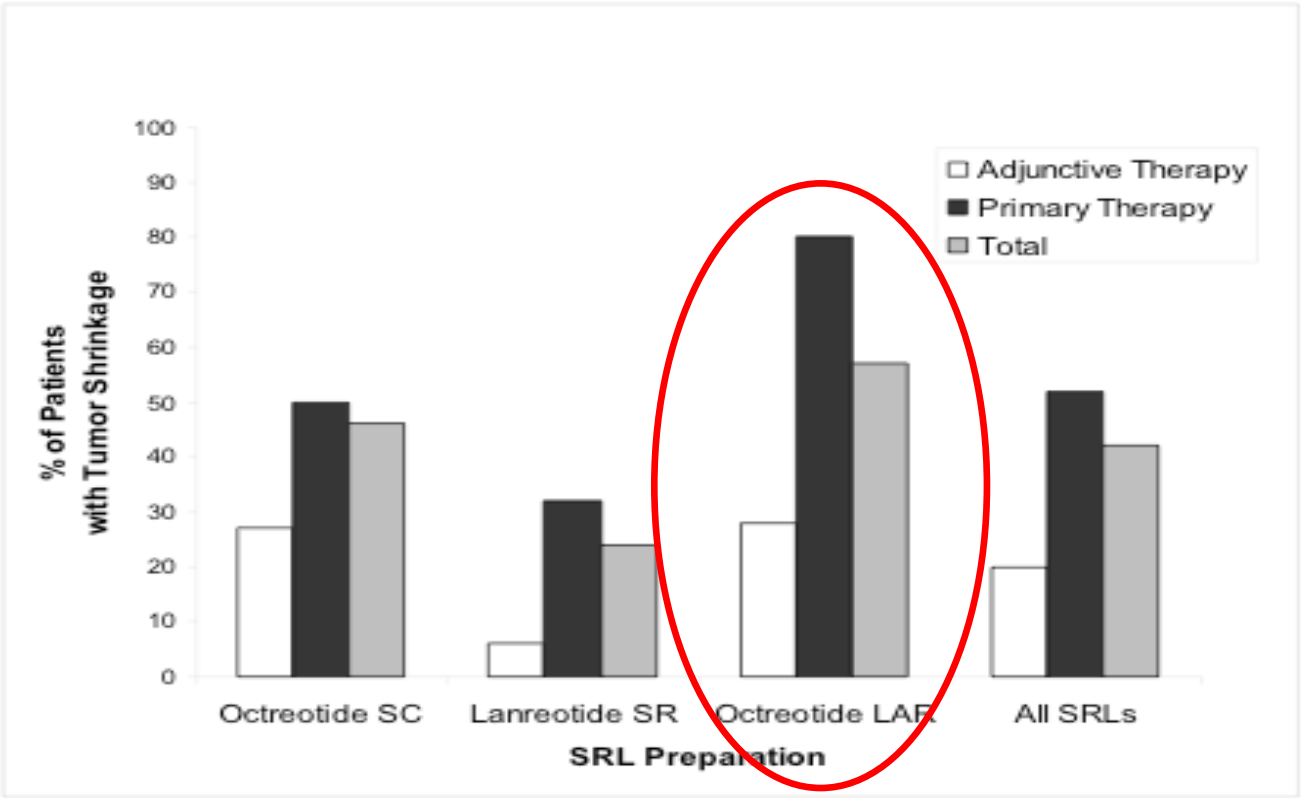
on treatment

Surgical debulking



Colao et al, JCEM 2006

Somastostatin analogs and tumour shrinkage



Bevan et al, JCE&M 2005

Primary Treatment of Acromegaly with Octreotide LAR: A Long-Term (Up to Nine Years) Prospective Study of Its Efficacy in the Control of Disease Activity and Tumor Shrinkage

Renato Cozzi, Marcella Montini, Roberto Attanasio, Mascia Albizzi, Giovanni Lasio, Sandro Lodrini, Paola Doneda, Liana Cortesi, and Giorgio Pagani

Divisions of Endocrinology (R.C., R.A.) and Neuroradiology (P.D.), Ospedale Niguarda, I-20162 Milan, Italy; Department of Neurosurgery (G.L., S.L.), Neurological Institute Carlo Besta, I-20133 Milan, Italy; and Division of Endocrinology (R.A., M.M., M.A., L.C., G.P.), Ospedali Riuniti, I-24100 Bergamo, Italy

Context: Neurosurgery is regarded as the first-line treatment of acromegaly. Because of its low cure rate in macro and invasive adenoma, the role of primary medical treatment is debated.

Objective: Our objective was to evaluate primary pharmacological treatment in acromegaly.

Design and Setting: We conducted an open prospective study at two Italian tertiary level centers.

Patients: We studied 67 consecutive patients (36 women; age, 54.9 ± 14.2 yr; 72% bearing macroadenoma).

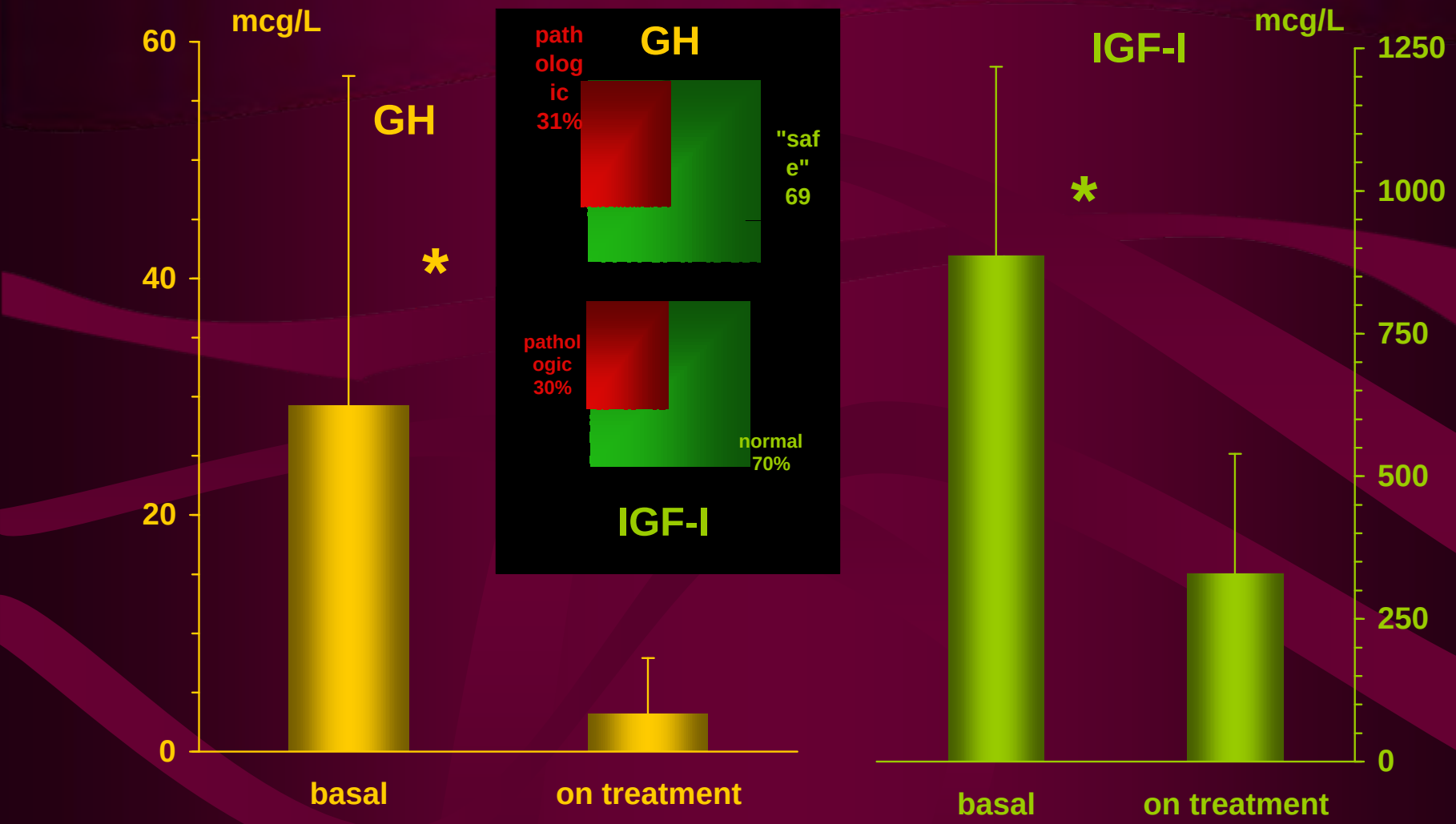
Intervention: Individually tailored octreotide LAR (OCLAR) was administered.

Main Outcome Measures: Outcomes included safe GH (<2.5 μg/liter), normal age-matched IGF-I levels, and tumor shrinkage.

Results: After a median follow-up of 48 months (range, 6–108 months), safe GH levels and normal age-matched IGF-I values were obtained by 68.7 and 70.1% of patients, respectively. Hormonal endpoints were achieved regardless of basal levels, and early results were predictive of outcome. Tumor shrank in 82.1% of patients by 62 ± 31% (range, 0–100%), decreasing from 2101 ± 2912 to 1010 ± 2196 mm^3 ($P \leq 0.0001$). The higher the basal GH values and the greater the GH/IGF-I changes on treatment, the greater the tumor shrinkage. Tumor disappeared in three patients and was progressively reduced to empty sella in five patients; apparent magnetic resonance imaging cavernous sinus invasion disappeared in three. In males, testosterone increased, restoring eugonadism in 64% of hypogonadal patients.

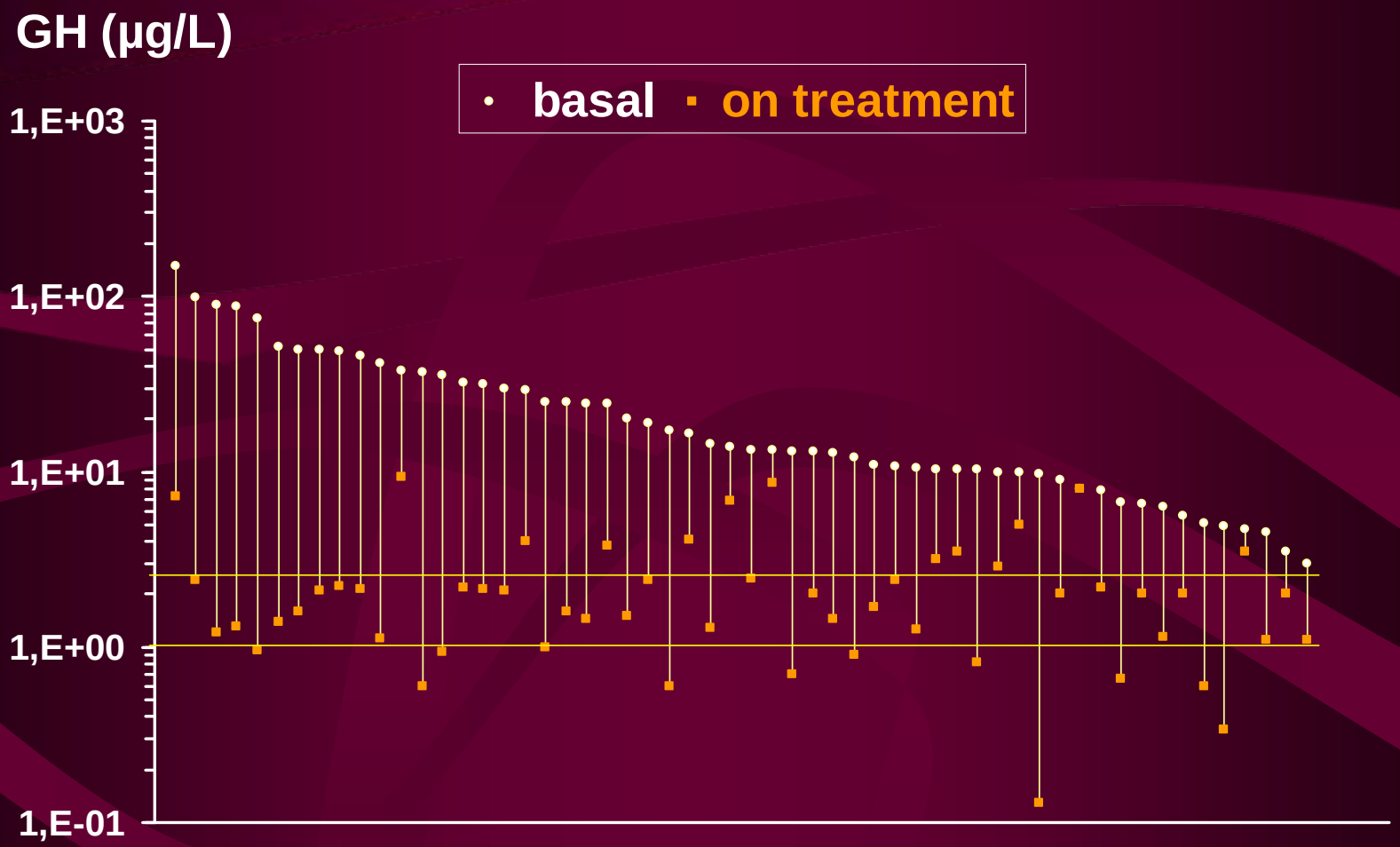
Conclusions: The efficacy on GH/IGF-I levels in unselected patients and the outstanding volumetric control indicate that treatment with OCLAR may be the first therapeutic approach to all acromegalic patients not amenable to surgical cure. Tumor shrinkage might also encourage the evaluation of primary OCLAR adoption in patients with initial visual field defects. (*J Clin Endocrinol Metab* 91: 0000–0000, 2006)

Primary Treatment with Octreotide LAR



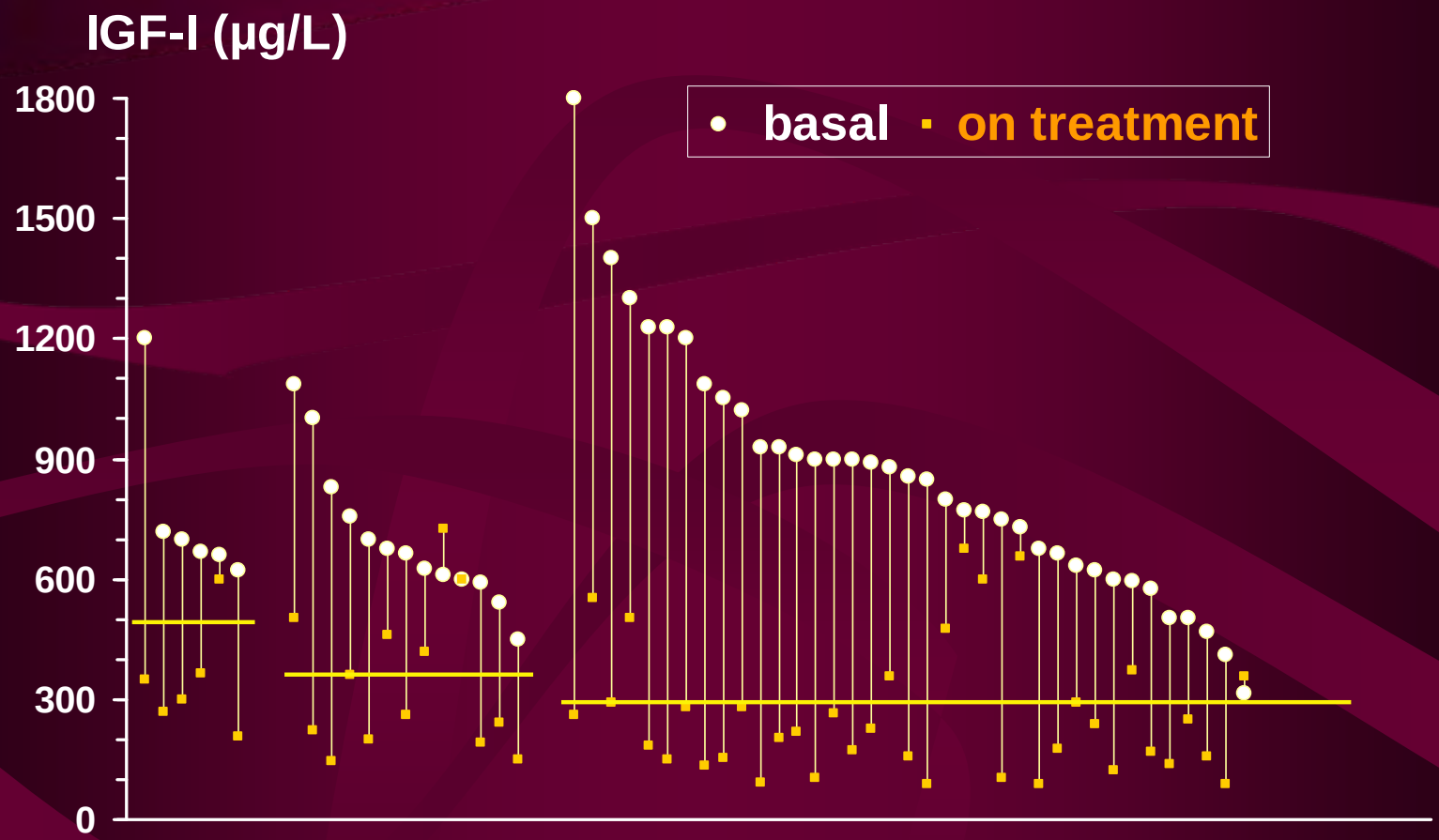
Cozzi et al, JCEM 2006

Safe GH



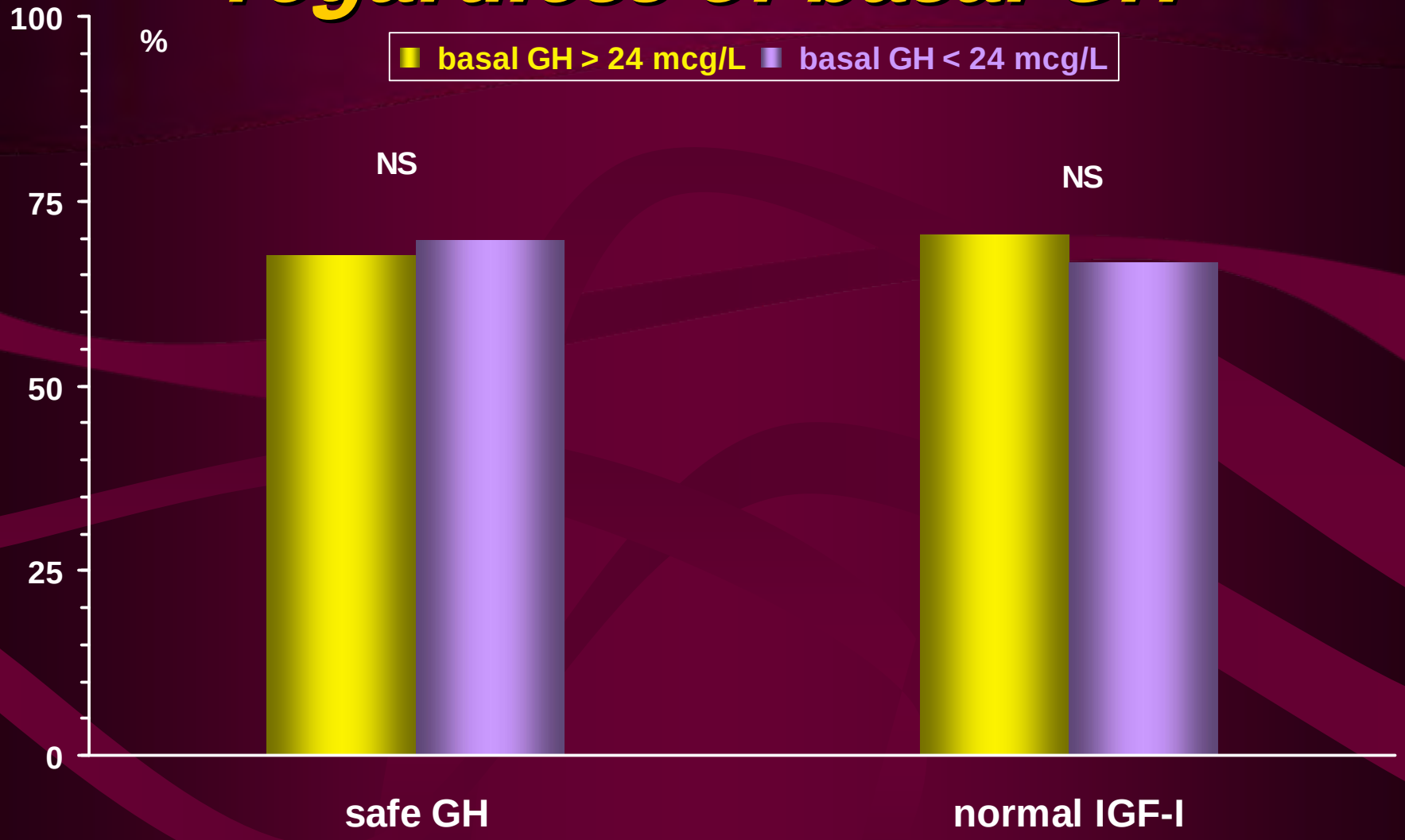
Cozzi et al, JCEM 2006

normal IGF-I



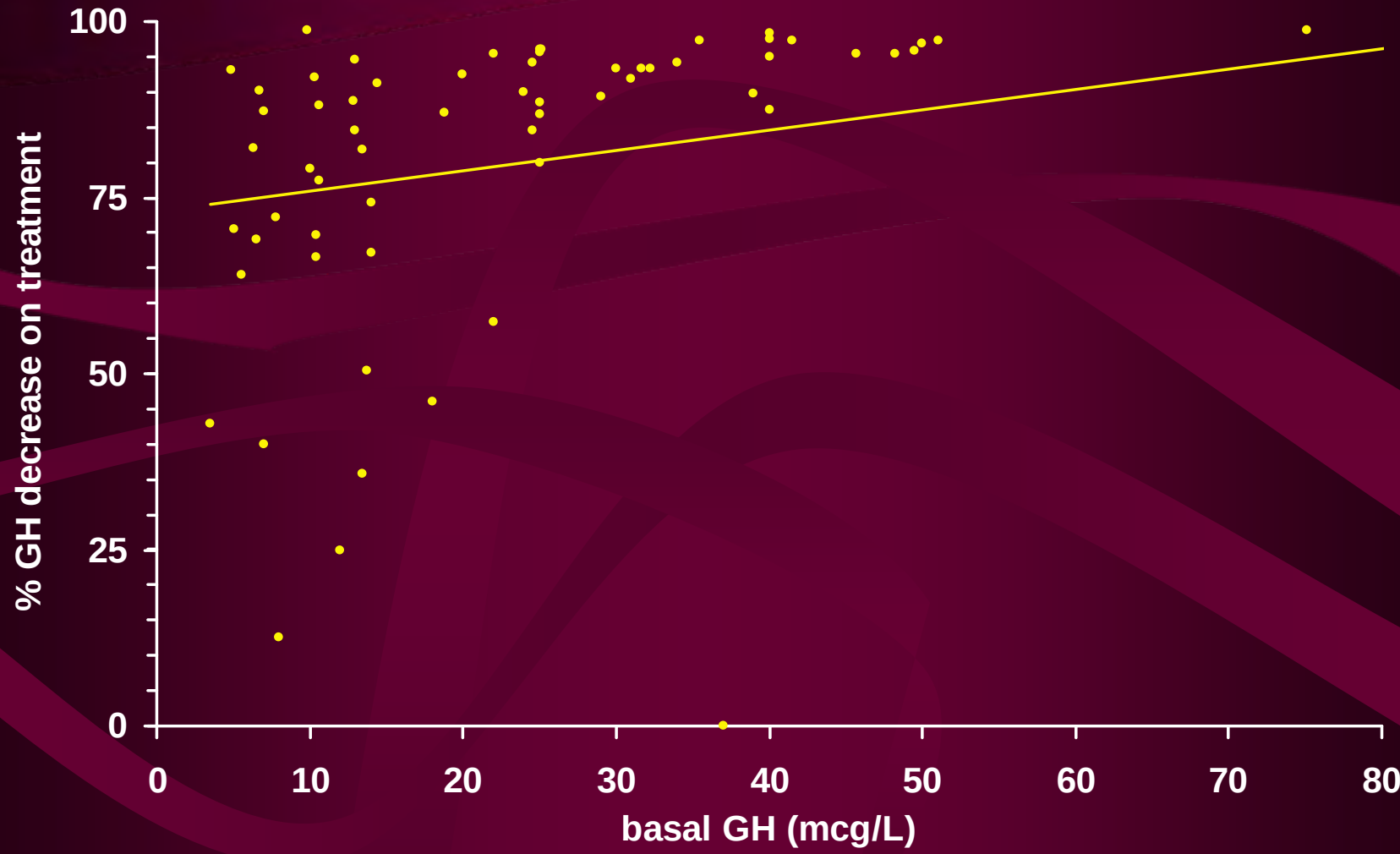
Cozzi et al, JCEM 2006

Hormonal normalization regardless of basal GH



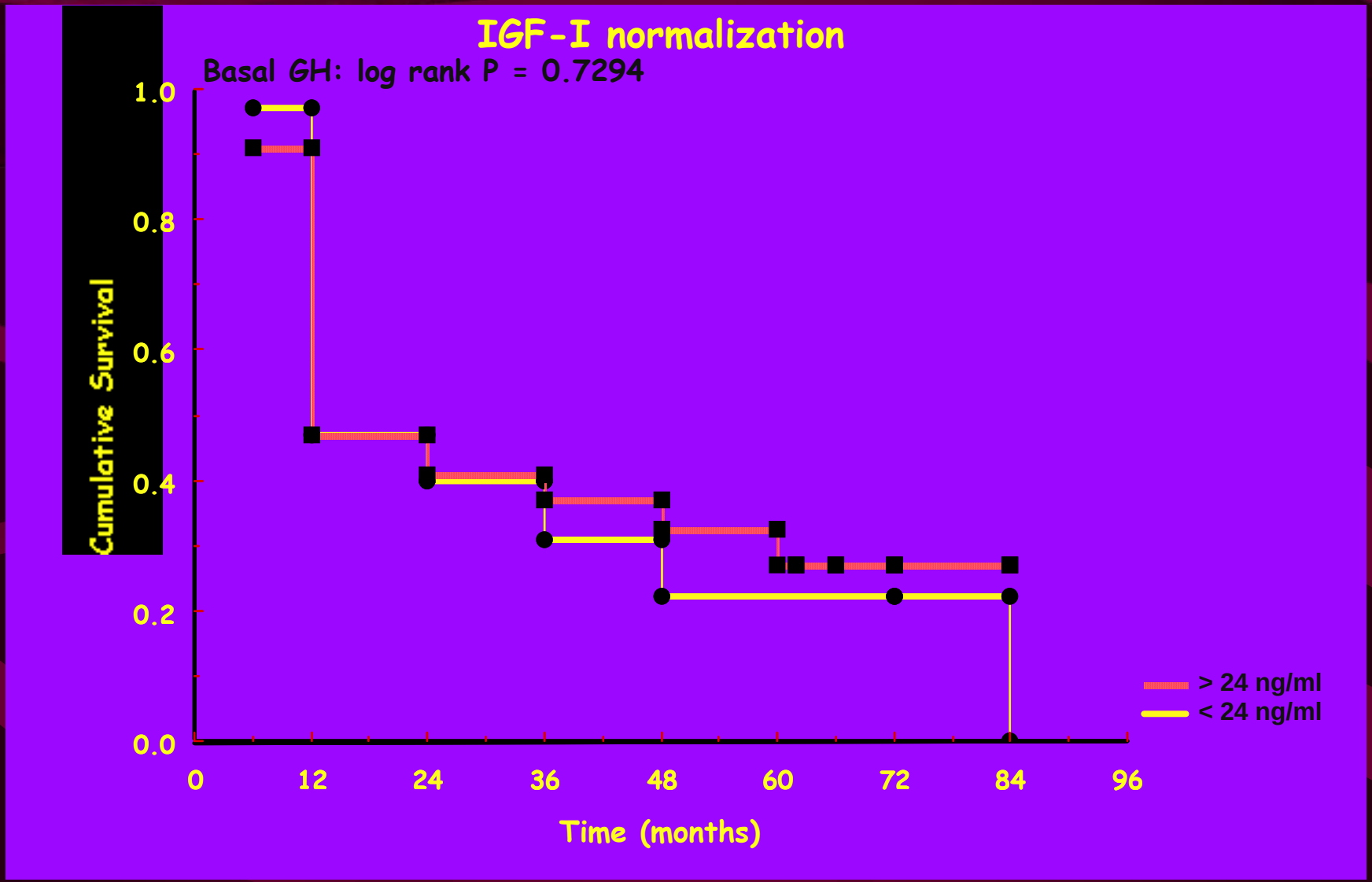
Cozzi et al, JCEM 2006

Positive relation between basal GH levels and GH suppression on treatment



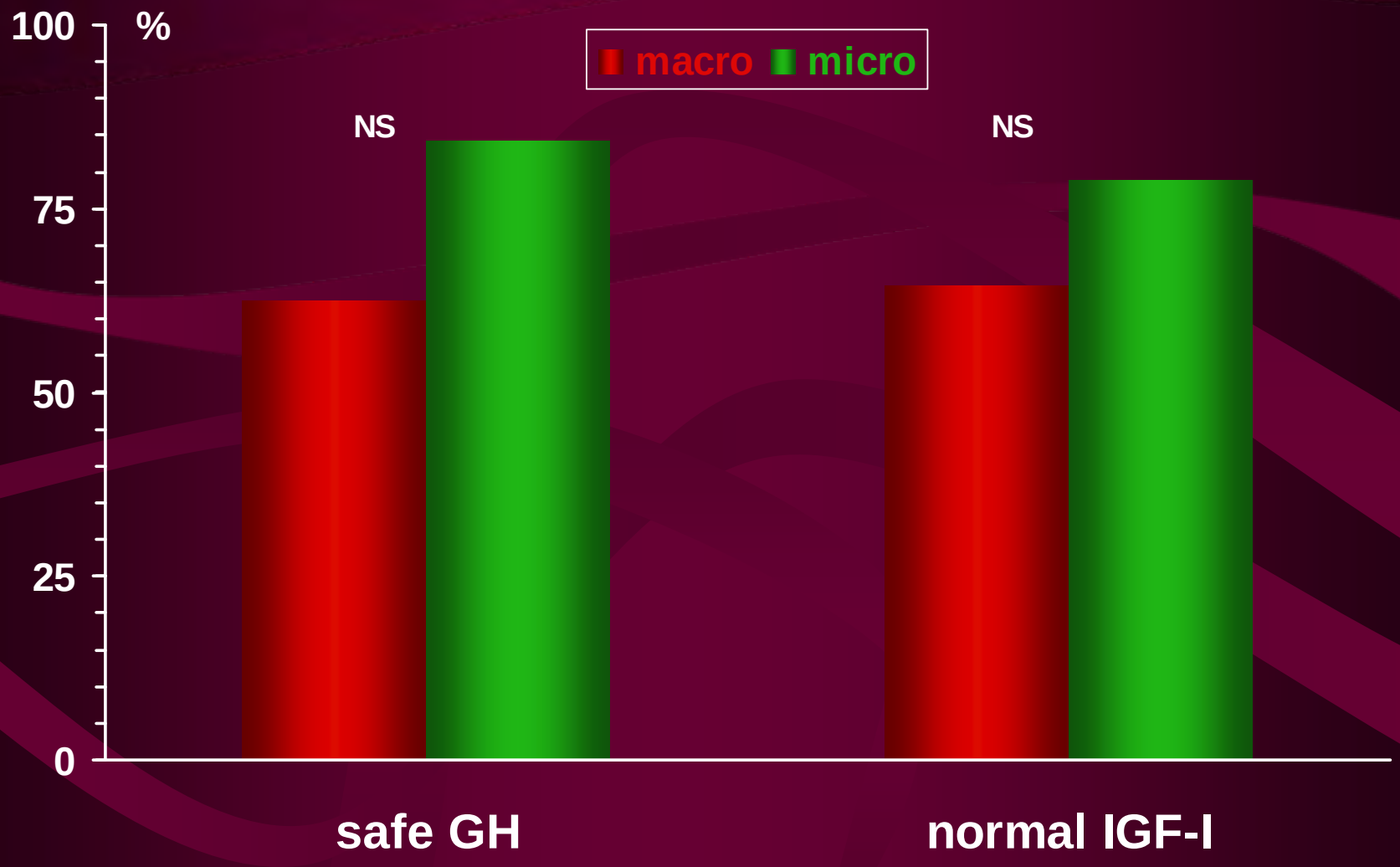
Cozzi et al, JCEM 2006

Time course of IGF-I normalization



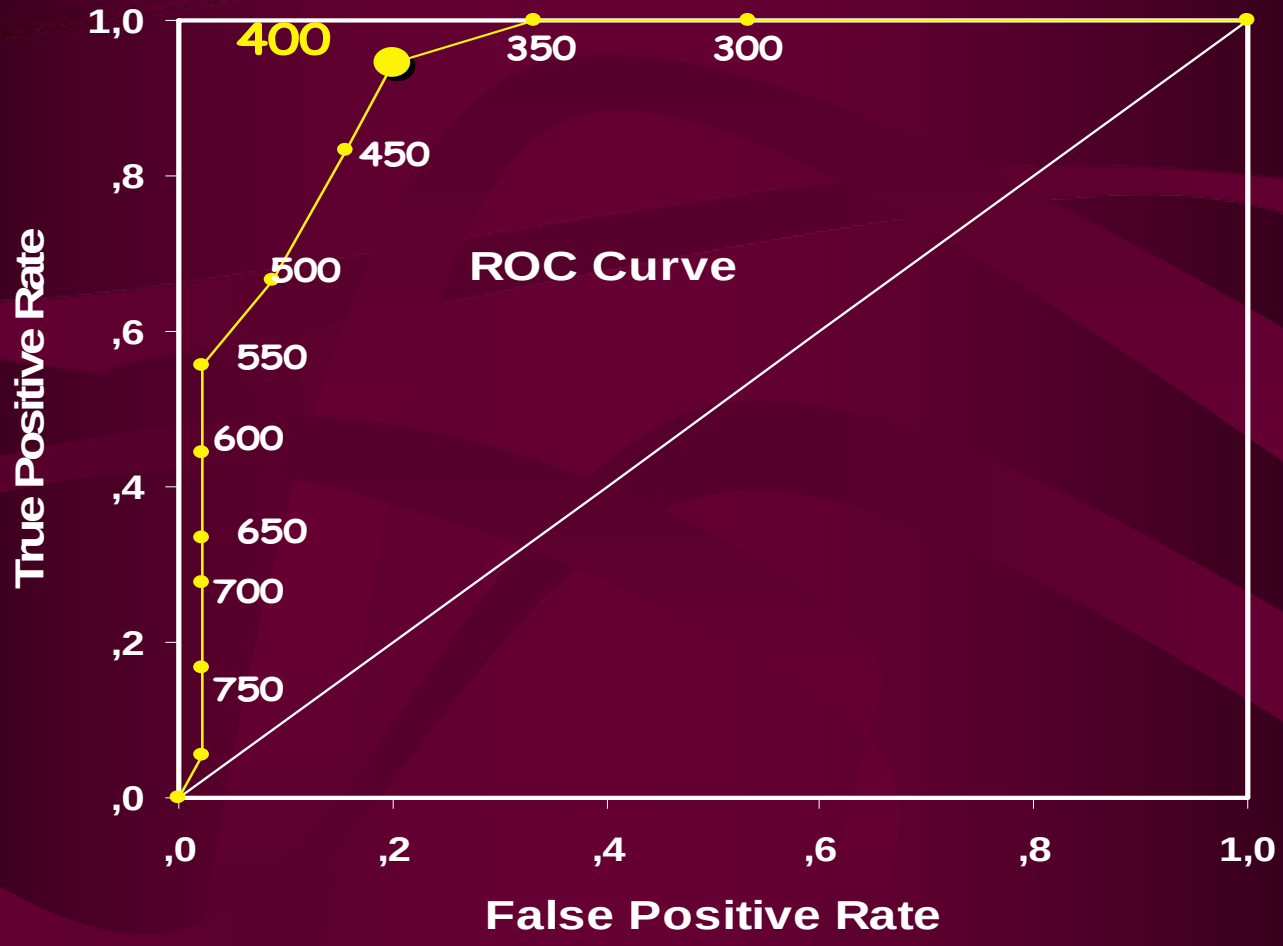
Cozzi et al, JCEM 2006

Hormonal normalization and adenoma size



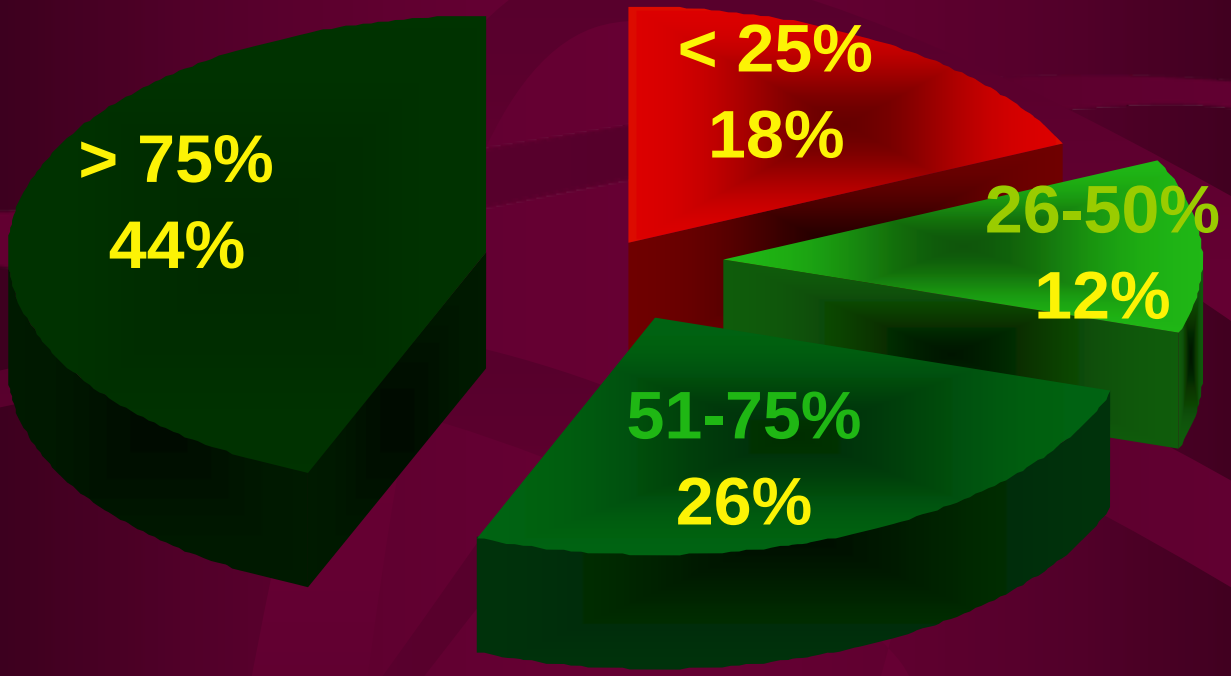
Cozzi et al, JCEM 2006

12 m IGF-I value predicts its normalization



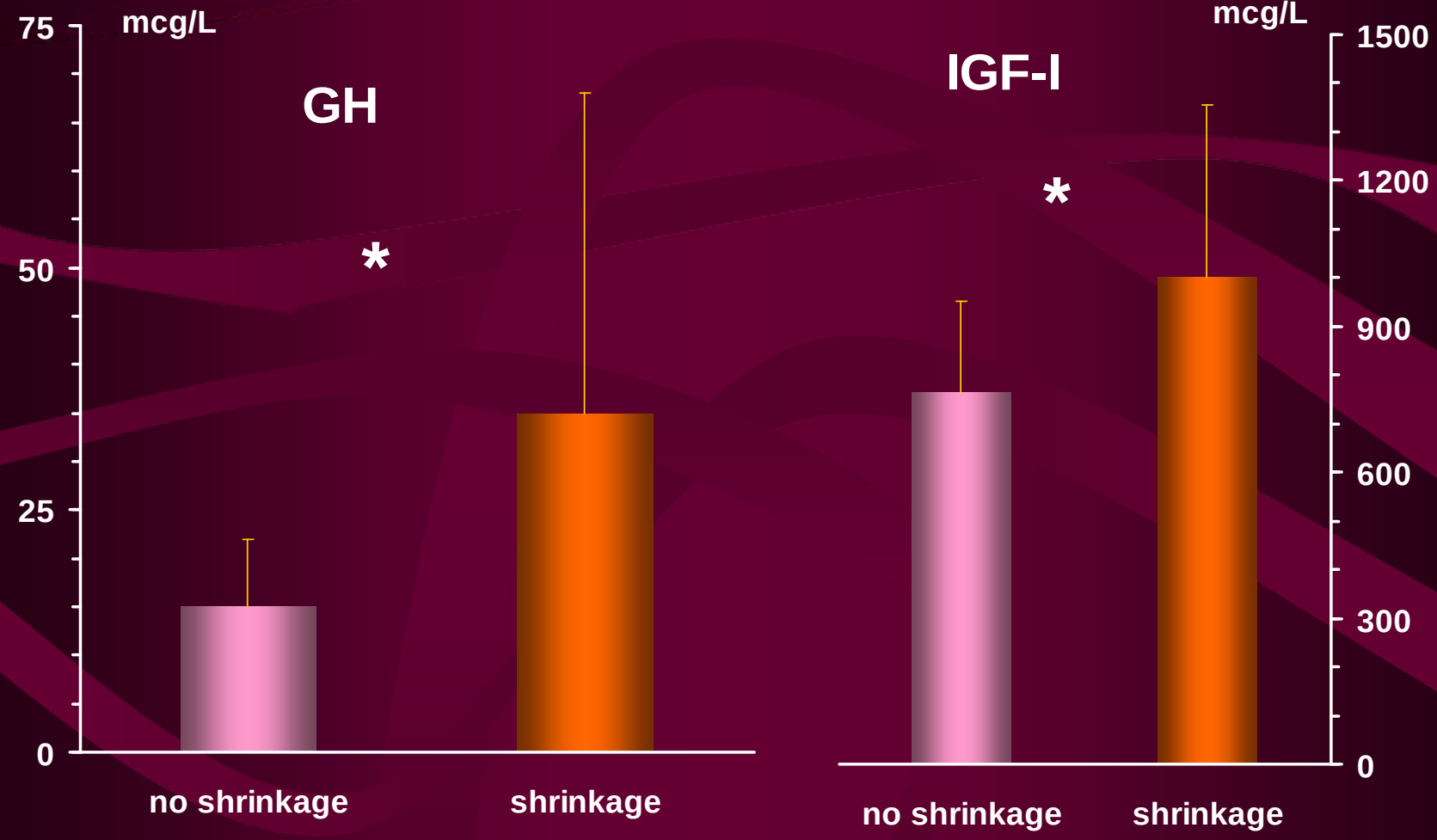
Cozzi et al, JCEM 2006

The tumor shrinks irrespective of its aspect



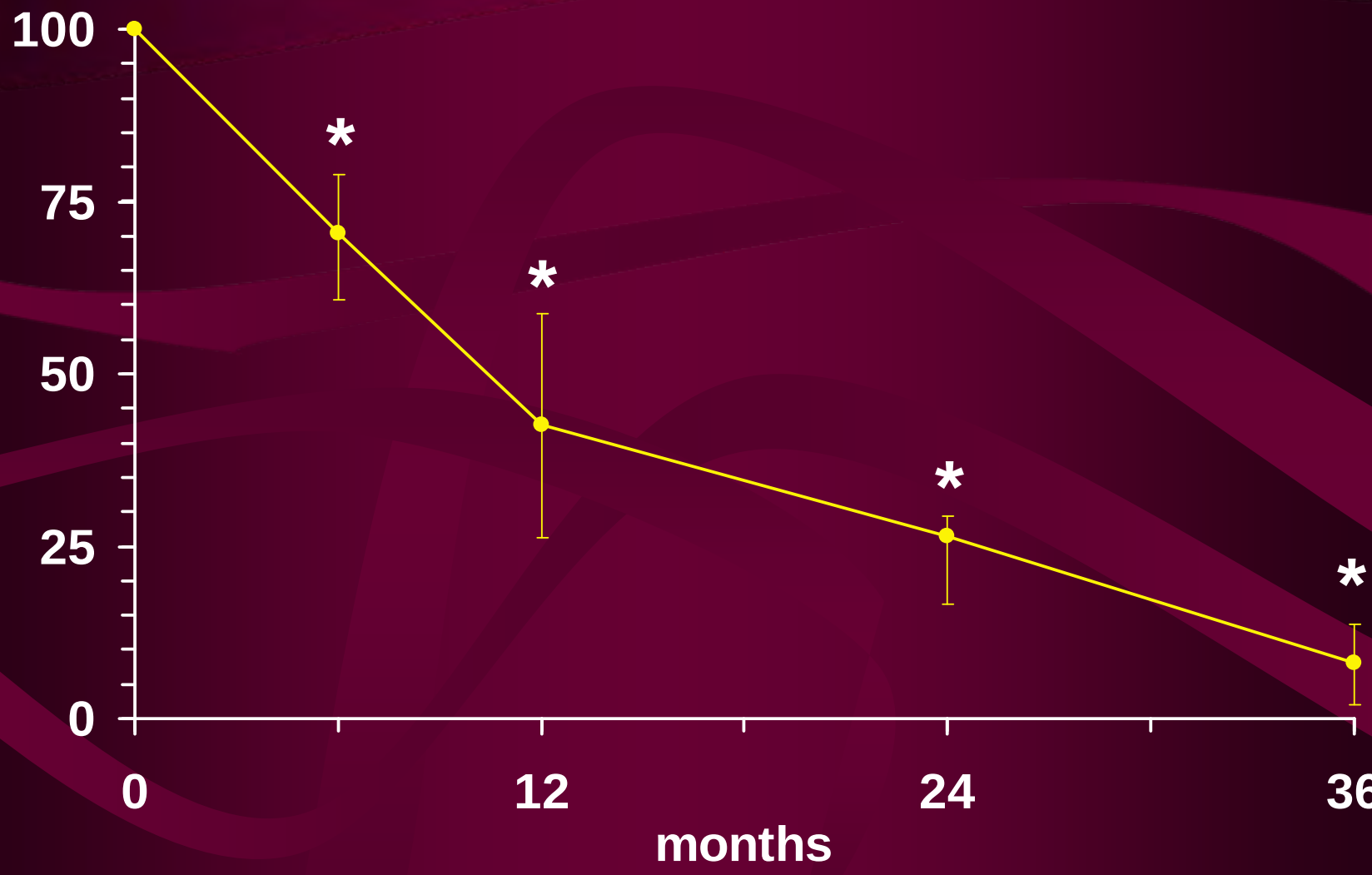
Cozzi et al, JCEM 2006

The higher GH/IGF-I levels, the better the chance of tumor shrinkage



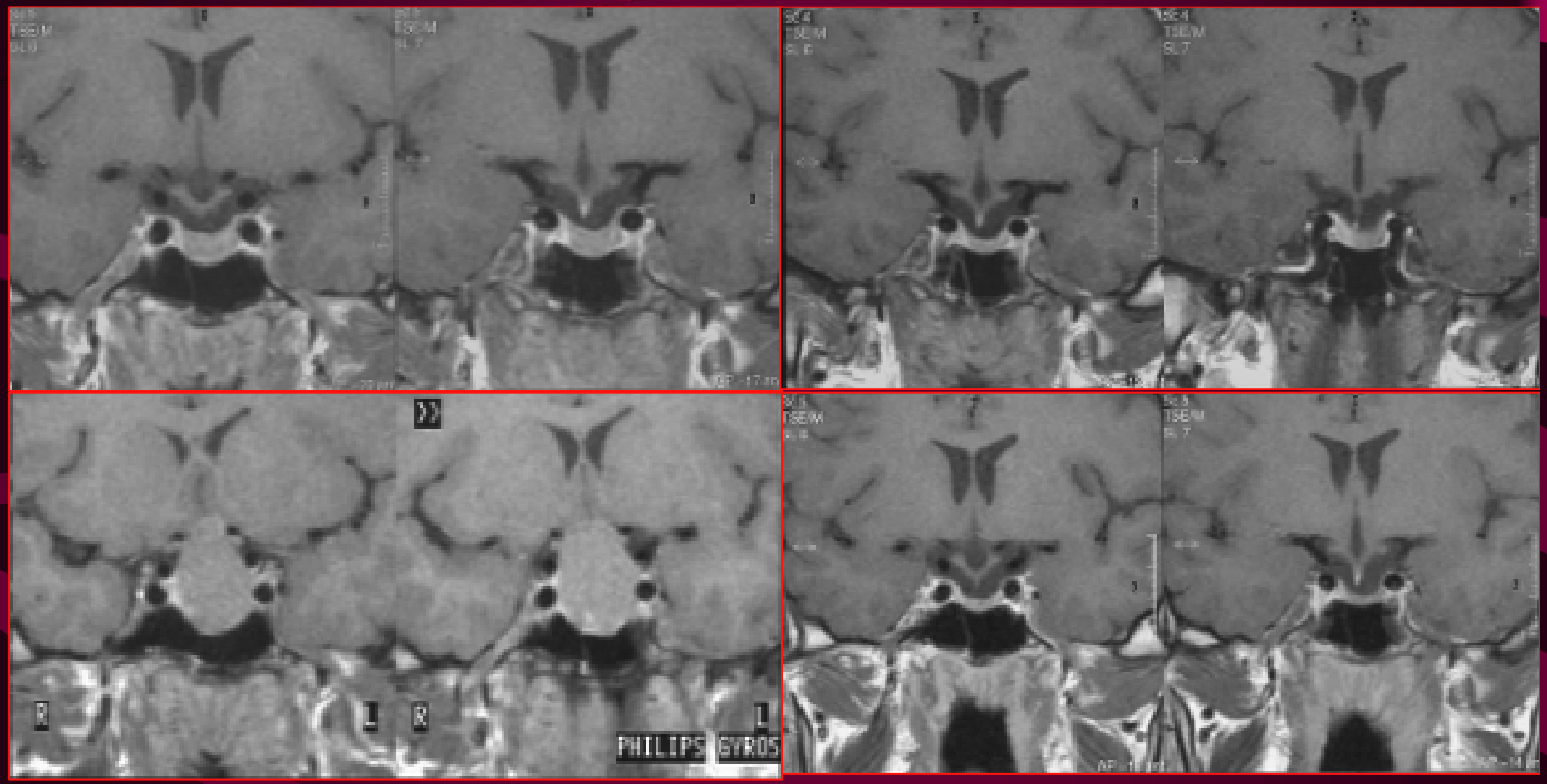
Cozzi et al, JCEM 2006

Progressive tumor shrinkage



Cozzi et al, JCEM 2006

Octreotide LAR: tumor shrinkage



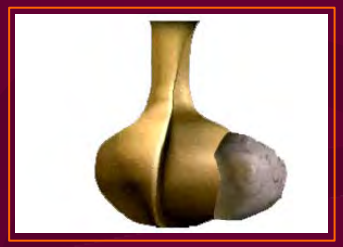
Indications for somatostatin analogs

- ***Who*** **virtually all patients with active disease (warning in diabetics)**
- ***When*** **both primary (the only treatment in selected cases; the first-line treatment) and adjuvant (persistent disease, after debulking > 75%)**
- ***How long*** **long-lasting, safe**

Medical treatments

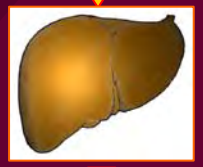
- Dopamine agonists
- Somatostatin analogs
- Pegvisomant

Mechanism of action of Pegvisomant



Pegvisomant works regardless of somatostatin receptors on the adenoma

GH



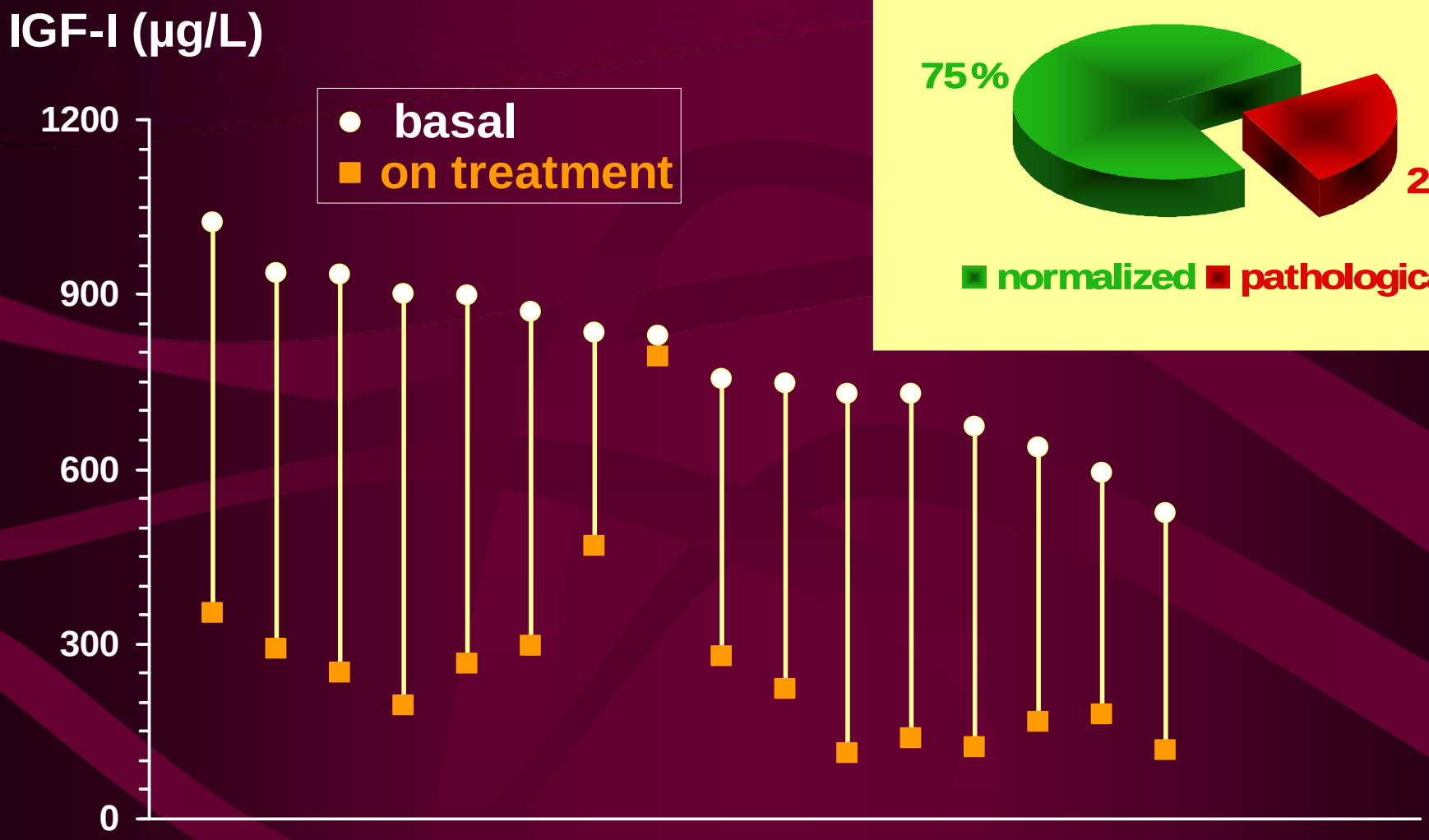
Pegvisomant

it blocks GH action at the level of the peripheral receptor

IGF-I normalization

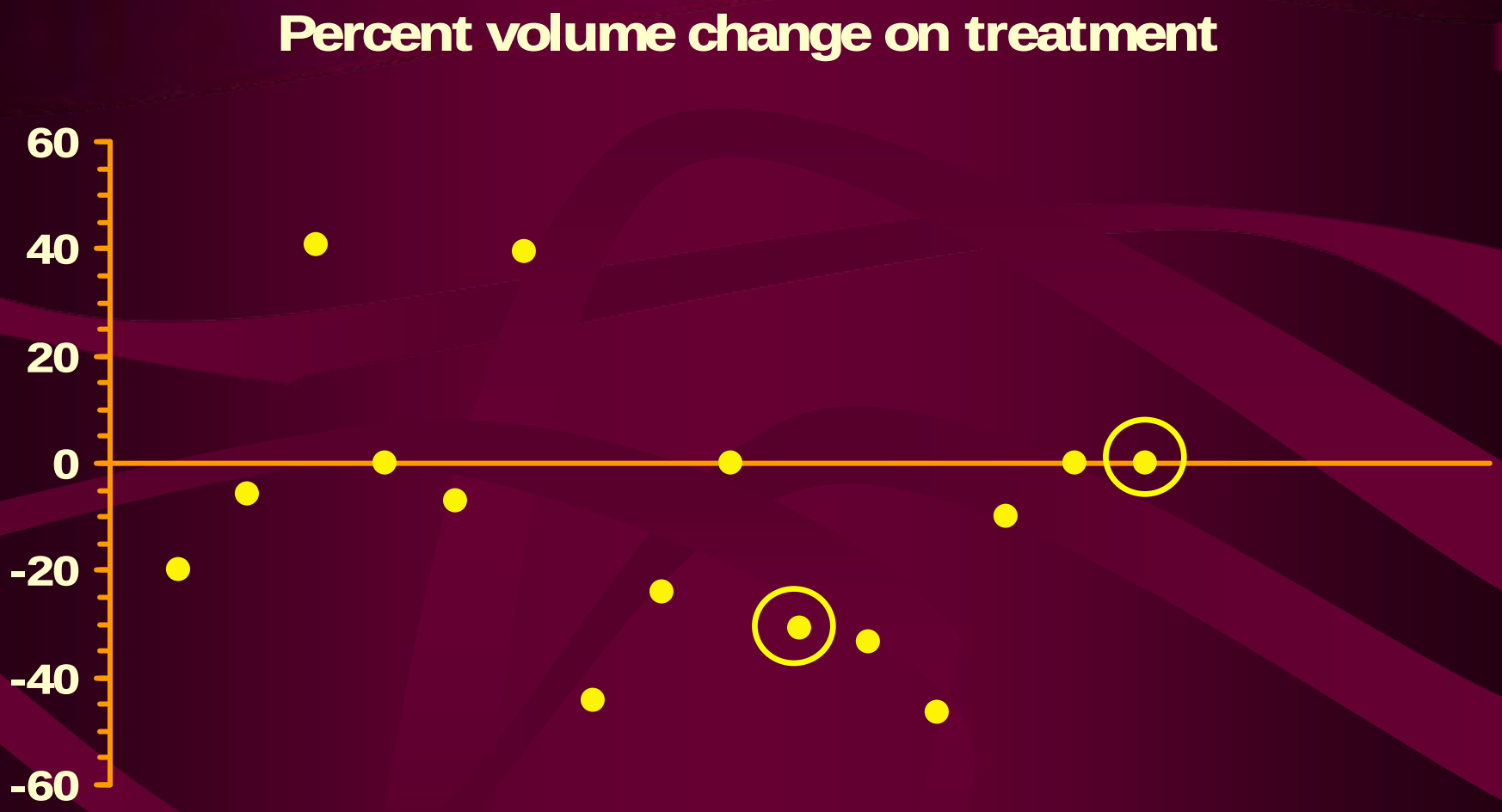
only IGF-I must be monitored

Pegvisomant treatment

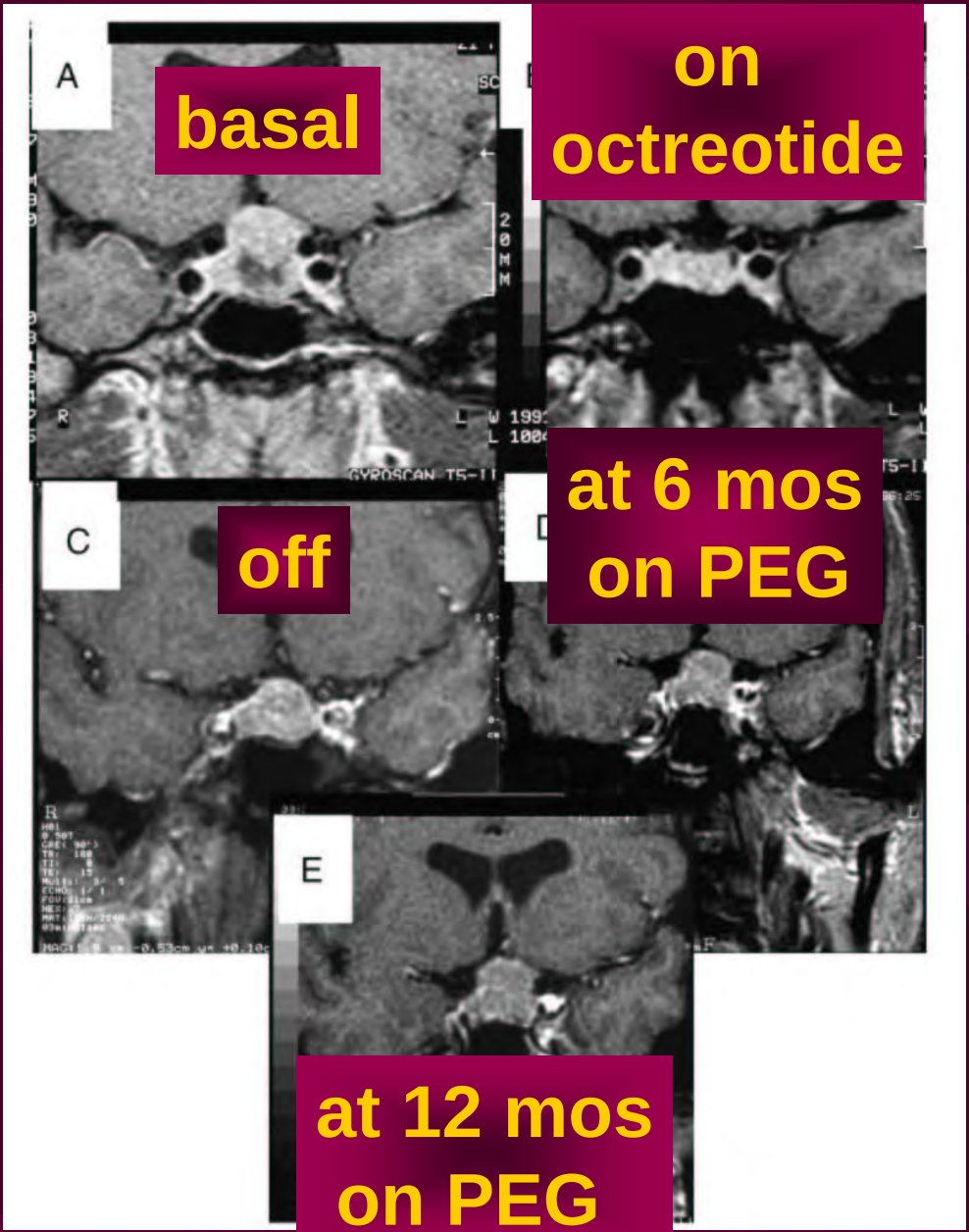


Modified from Colao et al, Eur J Endocrinol 2006

Pegvisomant treatment

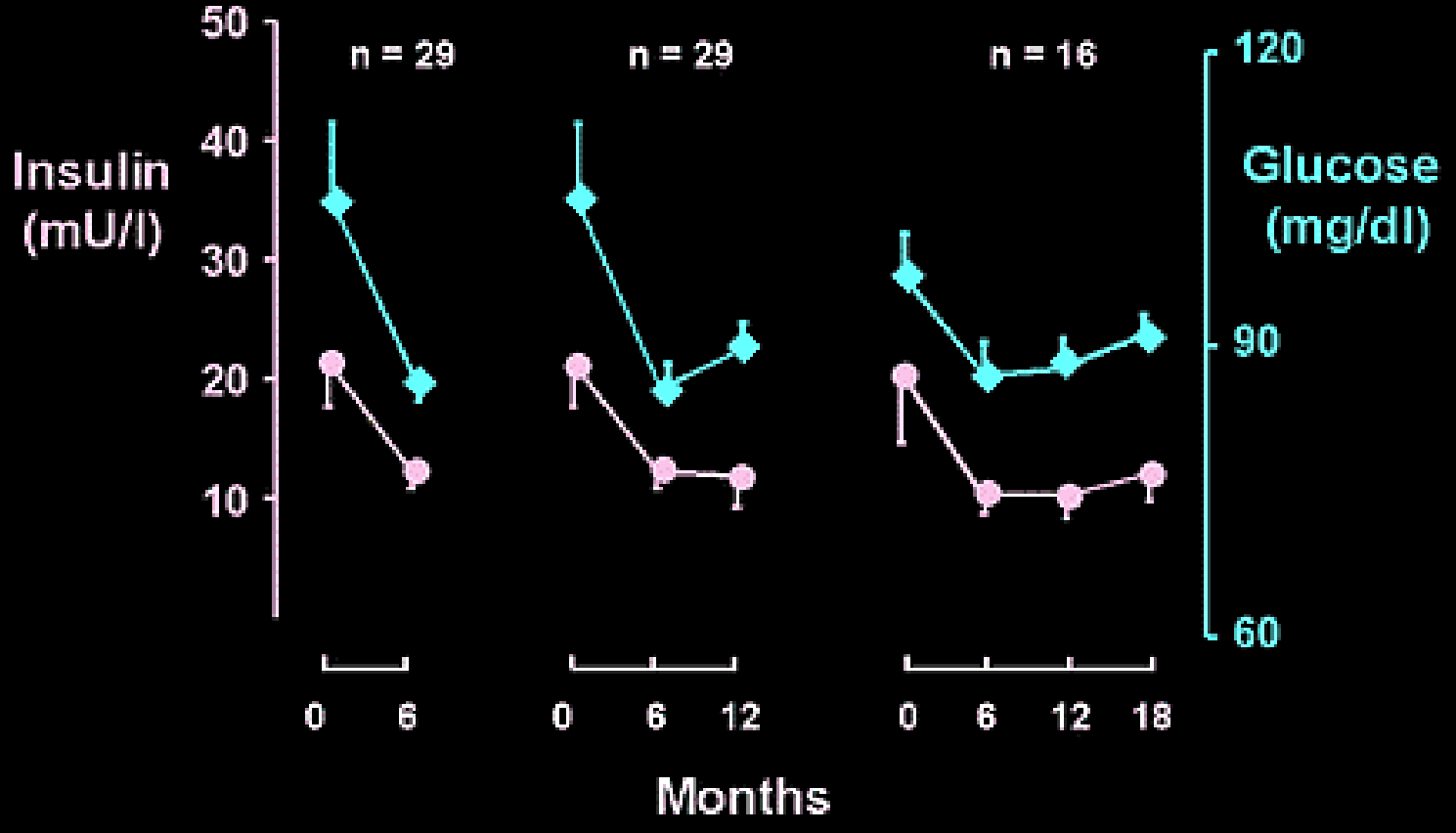


Modified from Colao et al, Eur J Endocrinol 2006



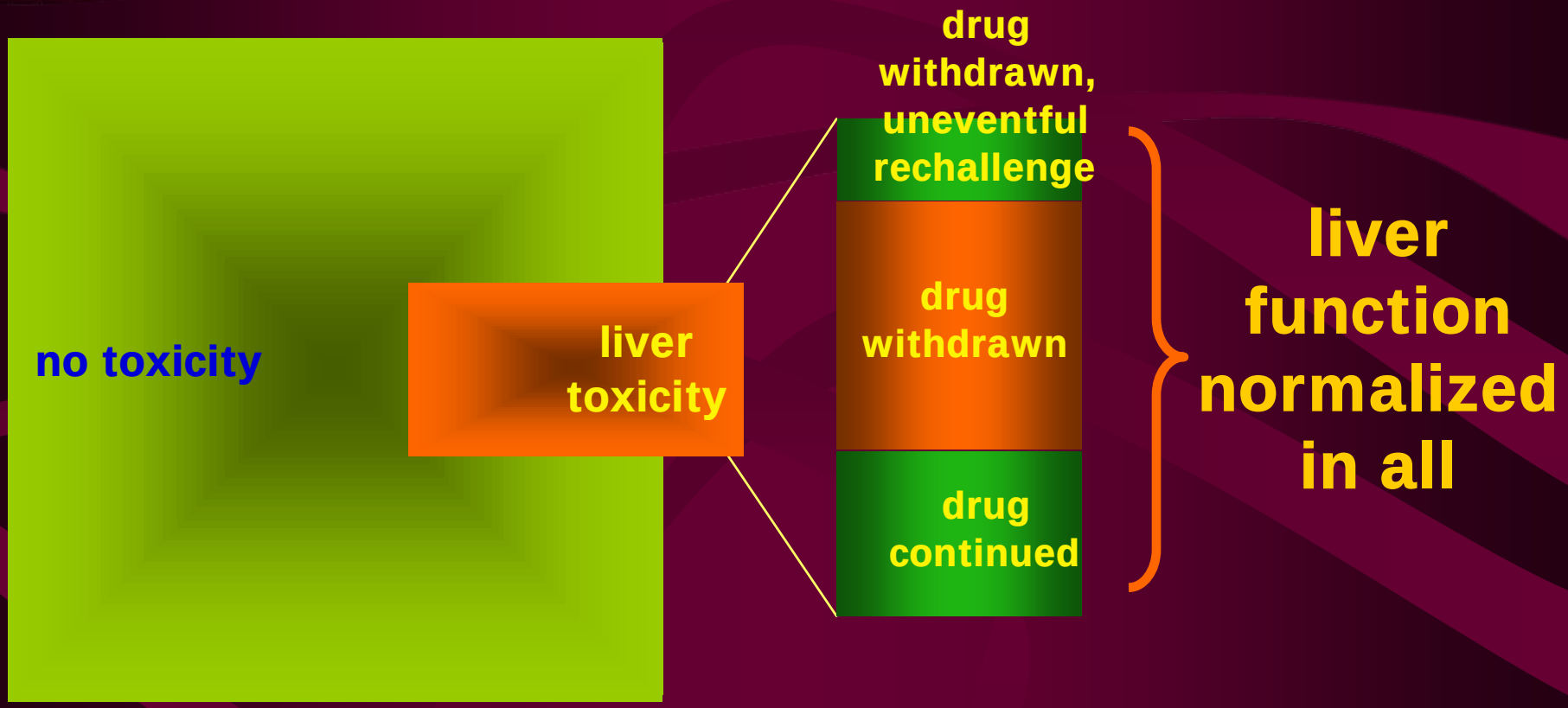
Colao et al, Eur J Endocrinol 2006

Mean fasting insulin and glucose after 6, 12 and 18 months therapy with pegvisomant



Liver toxicity

miulticentric German study (n = 142)



Biering et al, Eur J Endocrinol 2006

Indications for pegvisomant

- ***Who*** **active disease after surgery /radiotherapy in pts resistant to SA; diabetic acromegalics**
- ***When*** **adjuvant**
- ***How long*** **more data are needed**

Medical treatments

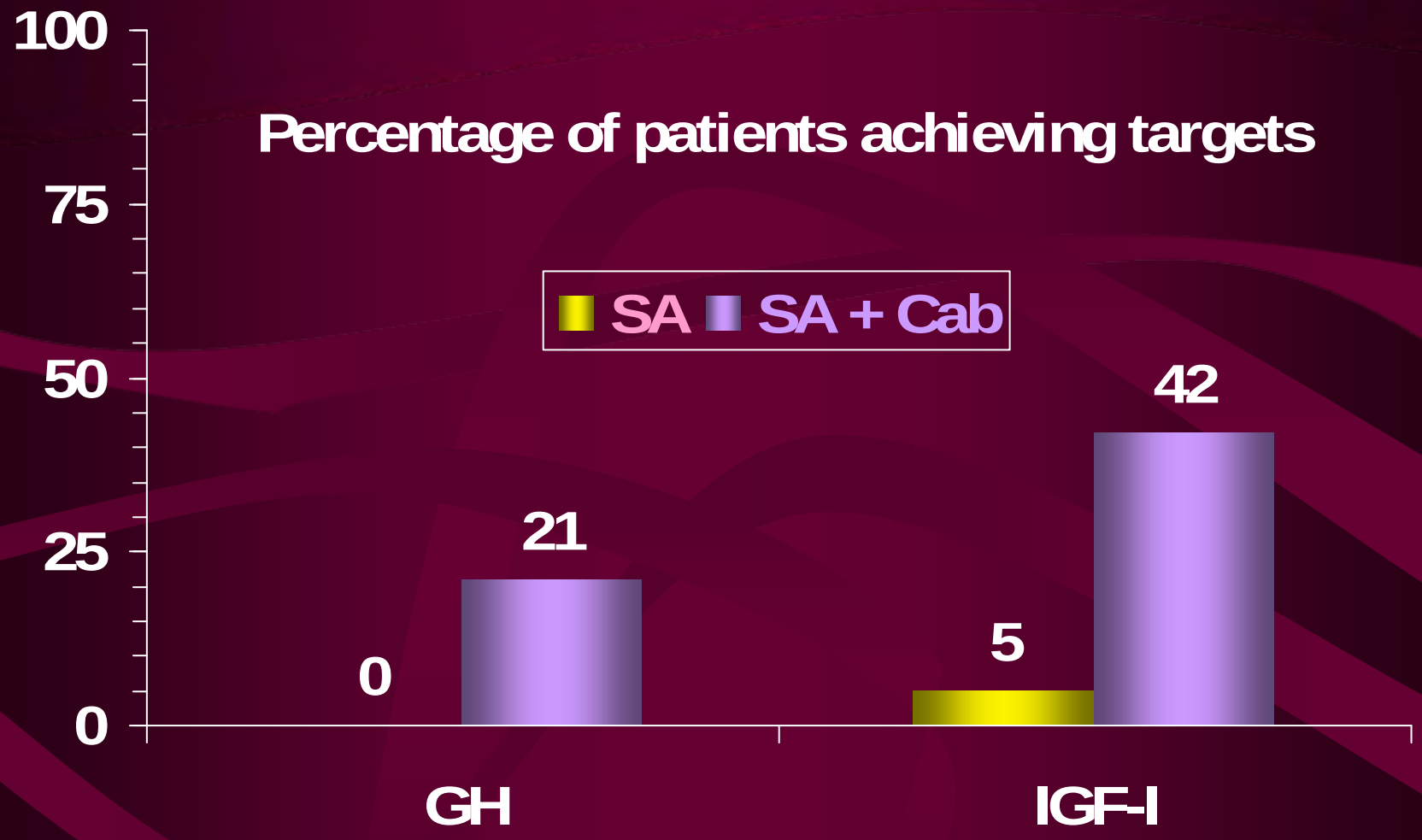
- Dopamine agonists

Combined treatments

- Somatostatin analogs

- Pegvisomant

octreotide + cabergoline



Cozzi et al, Clin Endocrinol 2004

Pegvisomant + octreotide

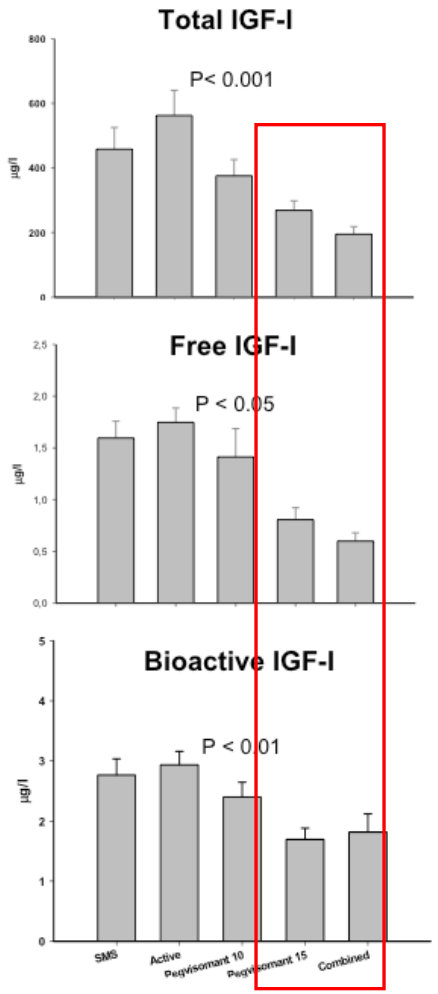
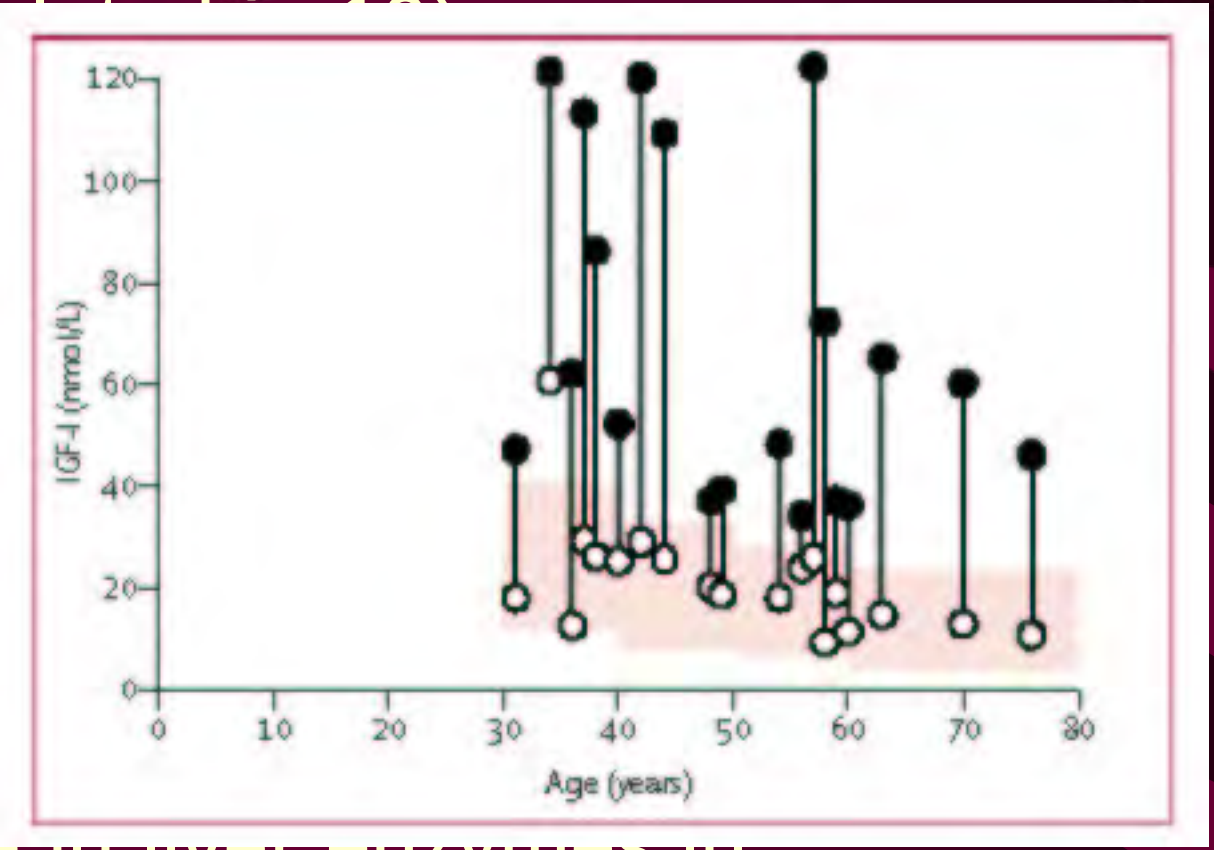


Figure 1

Jorgensen et al, JCE&M 2005

Weekly Peg + monthly OC

- 26 pts (comp
- 42 weeks
- Peg dose esc
  normalizatio
- Final Peg do
  (median 60)
- No tumor gr
- Mild increase in liver enzymes in 38%



Feenstra et al, Lancet 2005

The role of medical treatments

PRIMARY

- Pts not amenable of surgical cure:
- poor clinical conditions
- hormonal and MRI negative determinants
- Refusal of surgery
- Desire of preservation of fertility

ADJUVANT

- Persistent disease after surgery/rx-therapy

Divisione di Endocrinologia,
Ospedali Riuniti, Bergamo

Thanks to *Roberto Attanasio*

Divisione di Neurochirurgia,
Istituto Neurologico Carlo Besta, Milano

Thanks for your attention

6th AME Congress
Verona, October 27-29, 2006

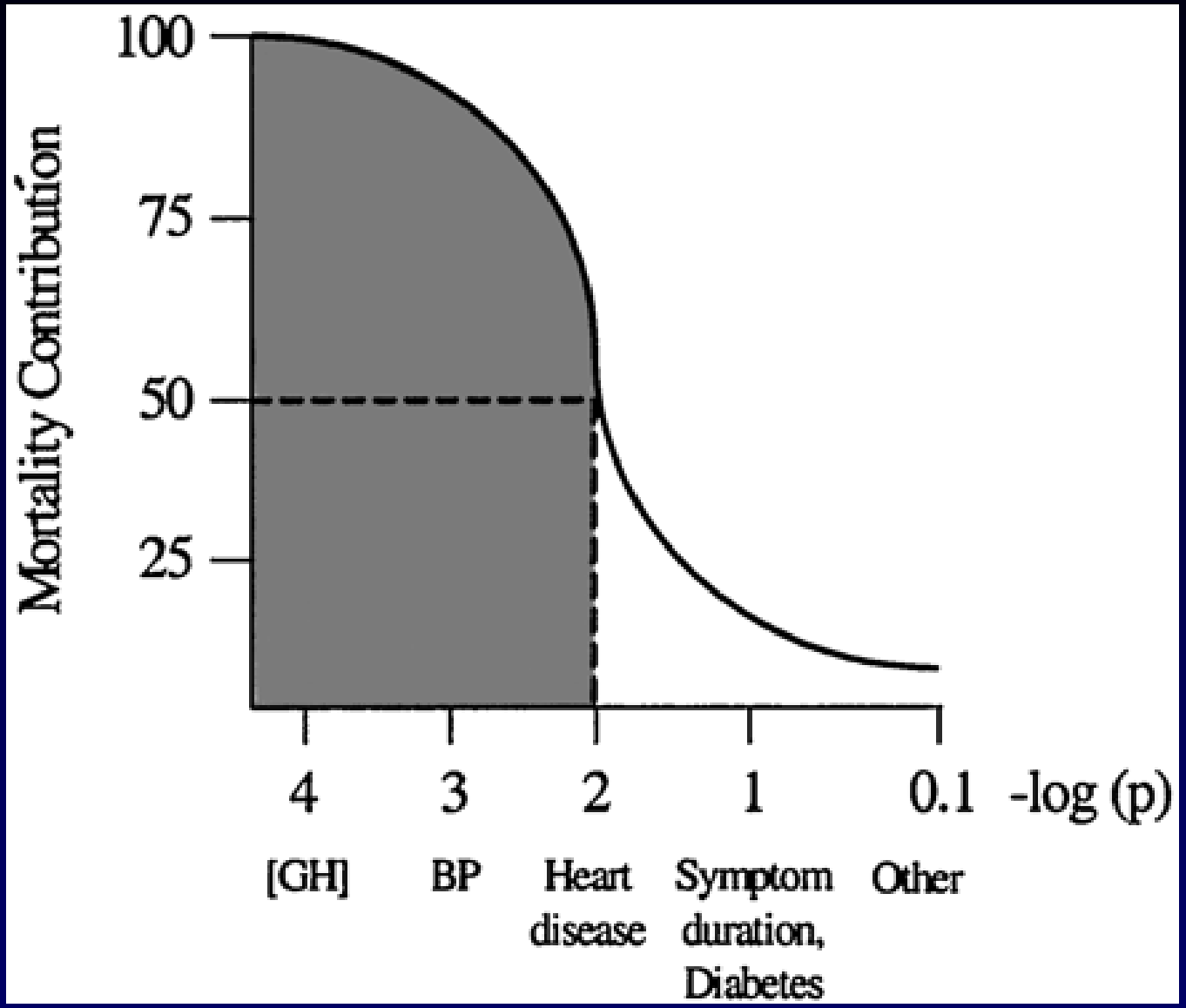
6th AME National Meeting
Italian Association of Clinical Endocrinologists

3rd Joint Meeting with AACE
American Association of Clinical Endocrinologist

Reversal of systemic complications of acromegaly

Gaetano Lombardi

Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica,
Università "Federico II" di Napoli



Melmed S *JCE&M* 2001; 96: 2929-2934

Acromegaly: Mortality

Survival determinants	*P*
Last GH	< 0.0001
Hypertension	< 0.02
Cardiac disease	< 0.03
Diabetes	< 0.03
Symptom duration	< 0.04

Causes of death	
Cardiovascular	60%
Respiratory	25%
Malignancy	15%

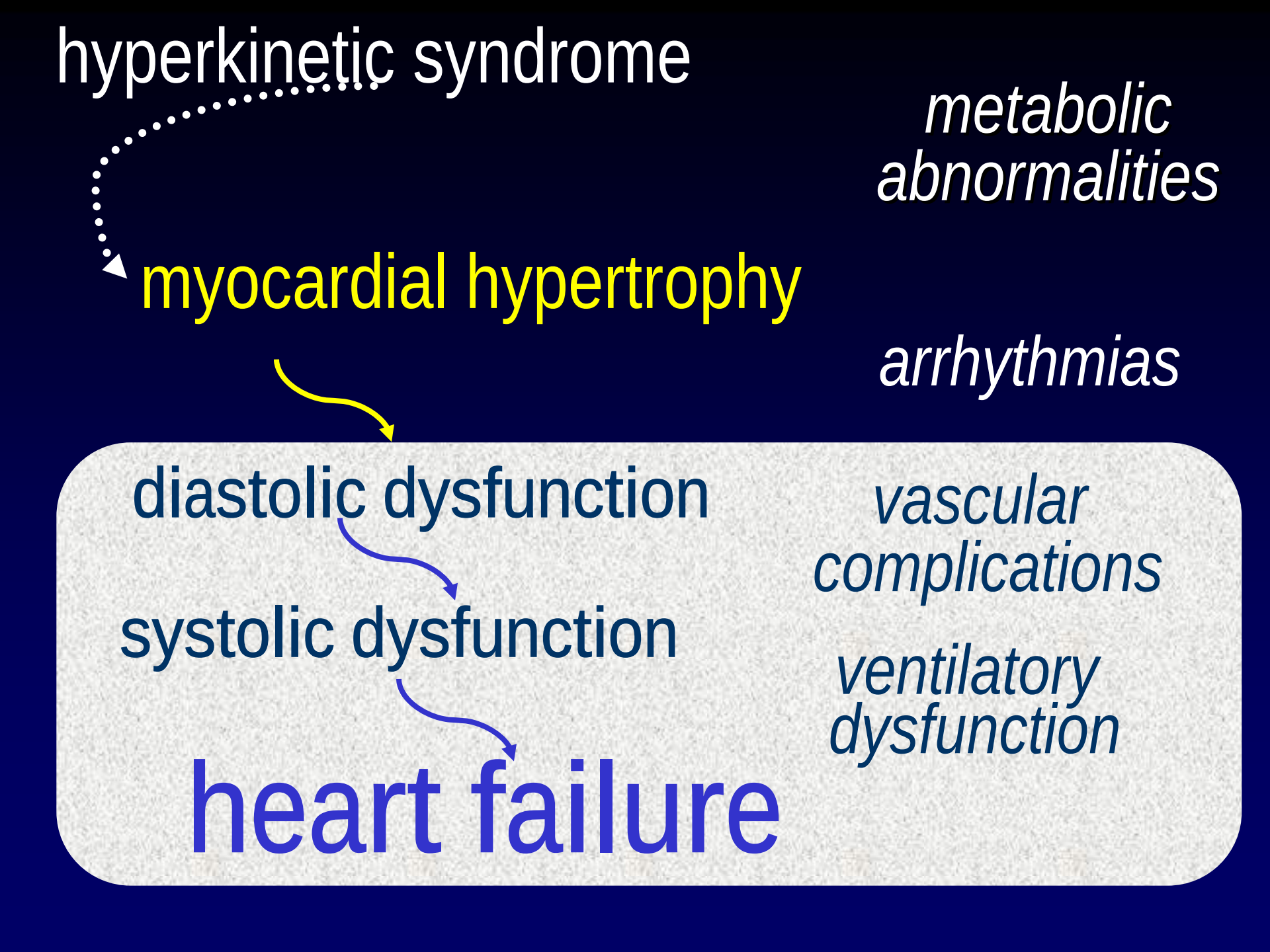
Derived from Wright 1969; Alexander 1980; Nabarro 1987; Bengtsson 1988; Bates 1993; Etxabe 1993; Rajasoorya 1994; Swearingen 1998; Abosch 1998; Freda 1998; Holdaway 2003;
GES Barcelona 2003

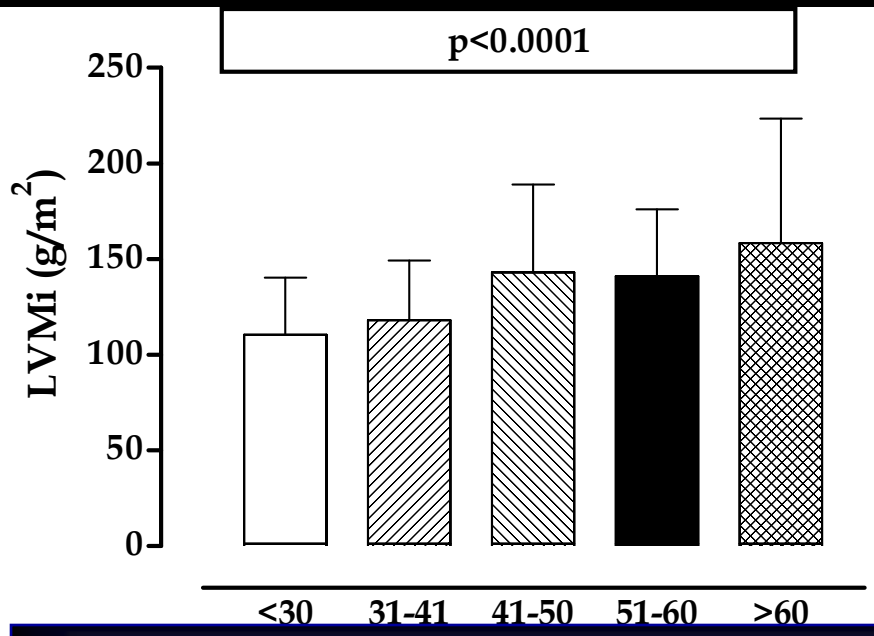
To normalize mortality:

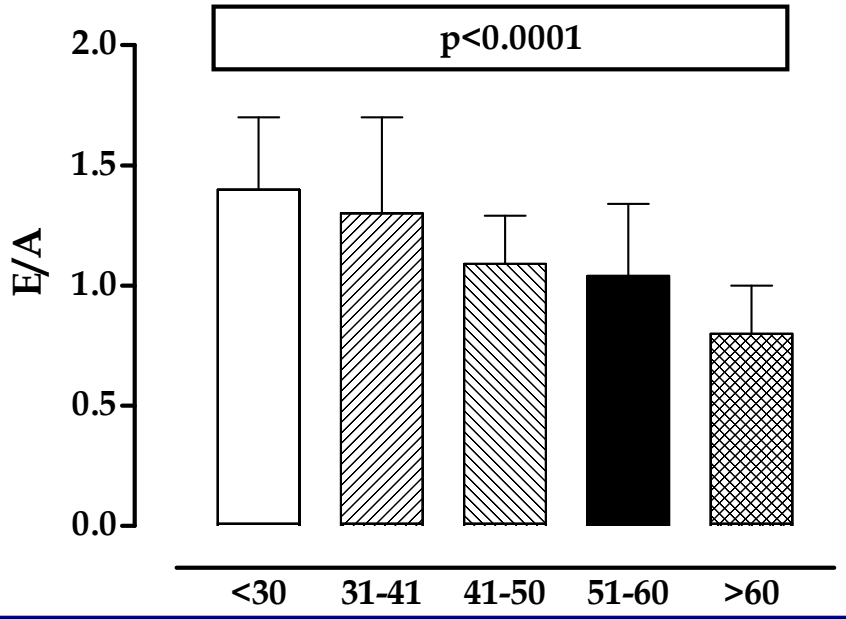
1. Suppress GH levels <1-2.5 µg/liter
2. Normalize IGF-I levels for age and gender
3. No radiotherapy
4. Absence of hypertension and/or cardiac disease at diagnosis

Reversal of systemic complications of acromegaly

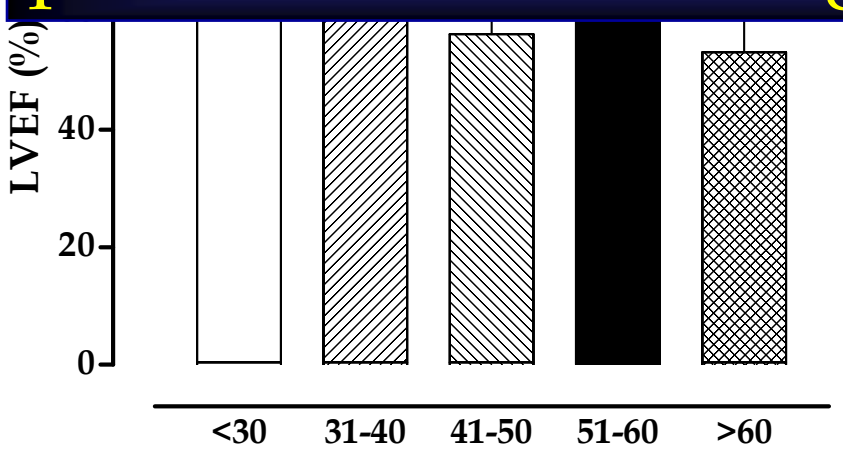
- → The cardiovascular system
- → The respiratory system
- → The osteo-skeletal system
- → The oncological risk

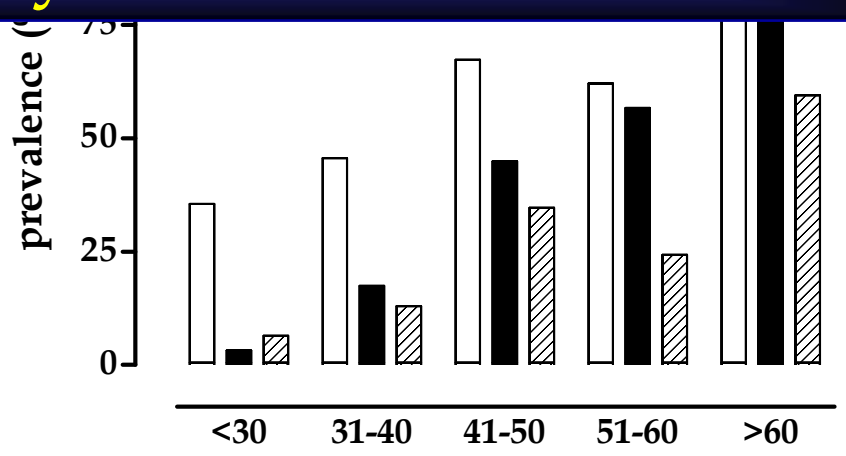

hyperkinetic syndrome
metabolic abnormalities
myocardial hypertrophy
arrhythmias
diastolic dysfunction
vascular complications
systolic dysfunction
ventilatory dysfunction
heart failure





Survey study by echocardiography in 200 patients with acromegaly





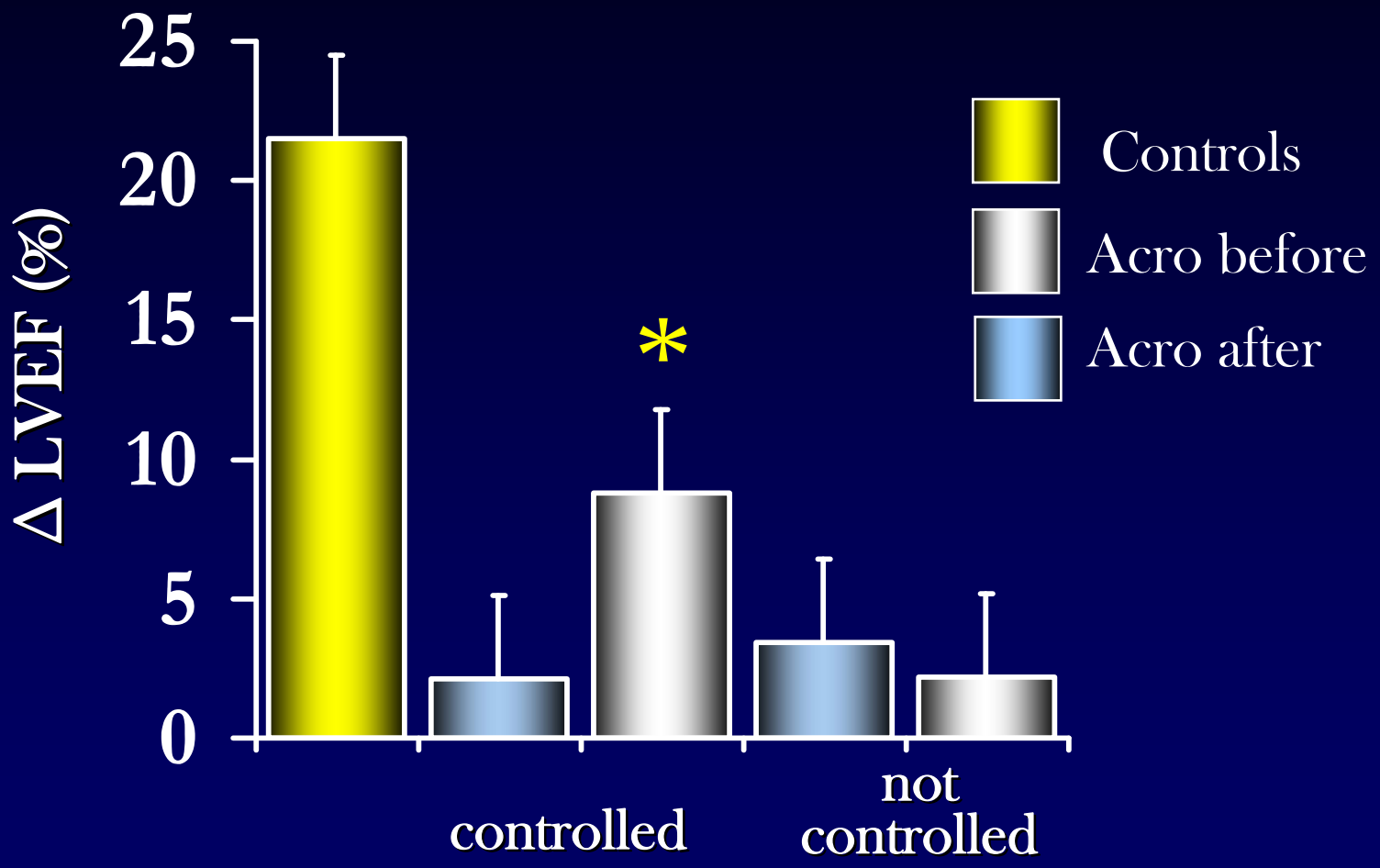
Colao A et al, Endocr Rev 2004

Control of acromegaly by SSA *vs.* cardiac diseases

Author	n.		LVM	DF	SF
Thuesen, 1989	9	OCT	↓	n.d.	n.d.
Pereira, 1991	5	OCT	↓	↑	n.d.
Lim, 1992	16	OCT	↓	n.d.	n.d.
Merola, 1993	11	OCT	↓	↑	Unchanged
Tokgözoglu, 1994	6	OCT	↓	n.d.	Unchanged
Colao, 1999	30	OCT	n.d.	Unchanged	↑
Baldelli, 1999	13	LAN	↓	↑	Unchanged
Hradec, 1999	13	LAN	↓	Unchanged	Unchanged
Colao, 2000	15	LAR	↓	Unchanged	↑
Colao, 2002	25	LAR	↓	Unchanged	↑

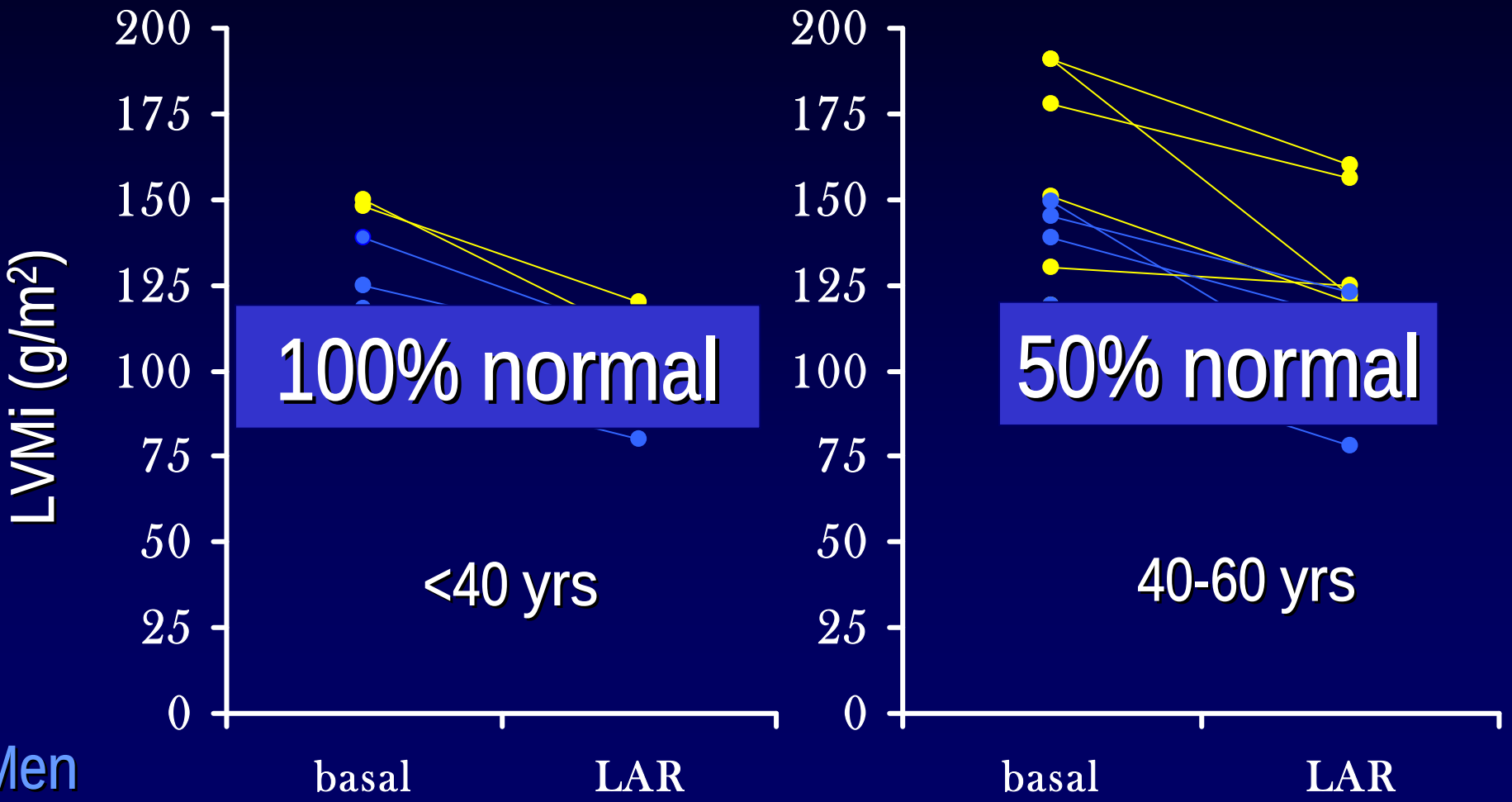
Colao A, et al., *Clin Endocrinol*, 2001

Control of acromegaly by SSA *vs.* cardiac diseases



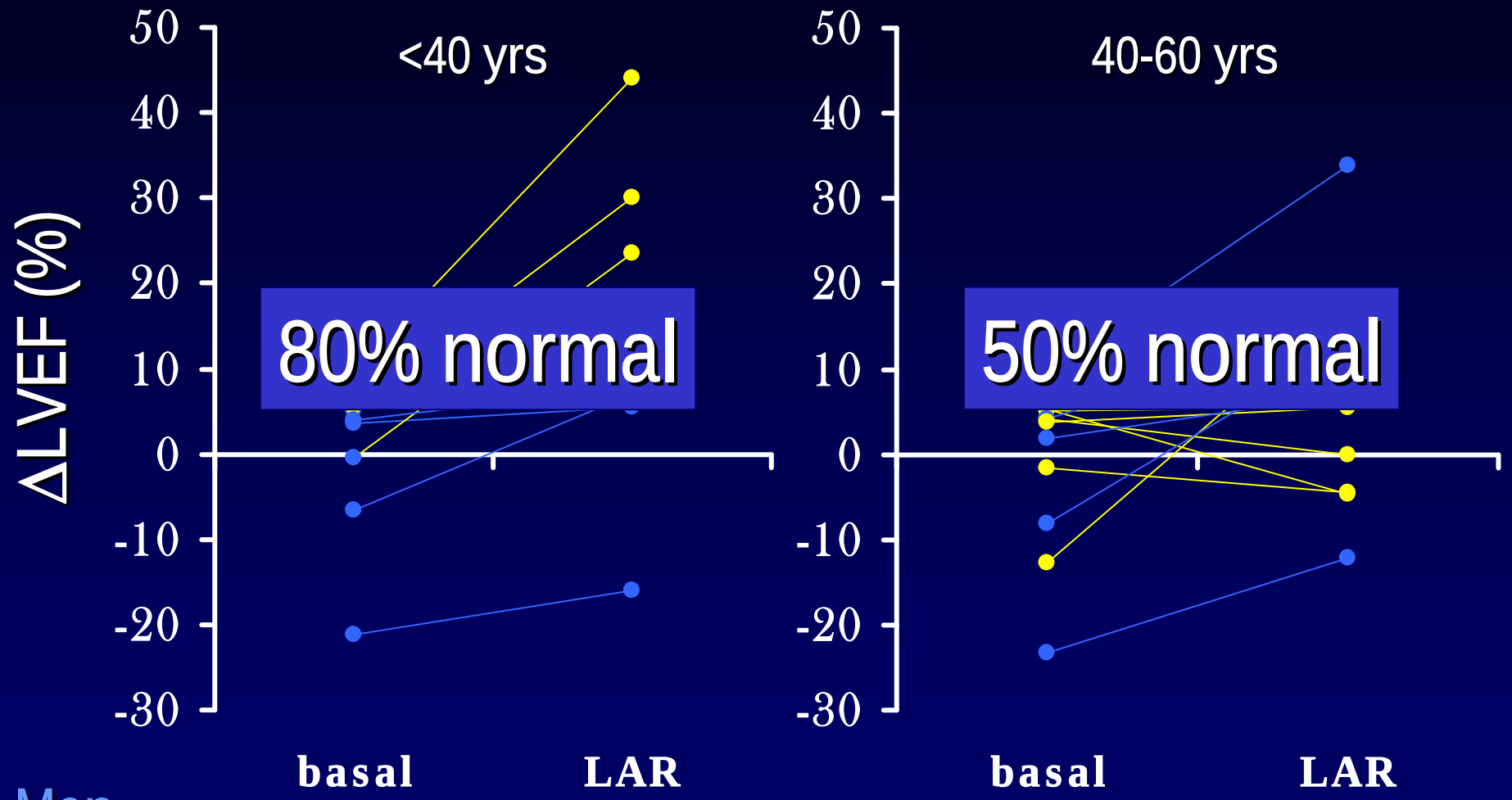
Colao A, et al., *JCE&M*, 1999;84:17-23 *JCE&M* 2000;86: 3132-3140 and new data

Control of acromegaly by SSA *vs.* age & cardiac diseases



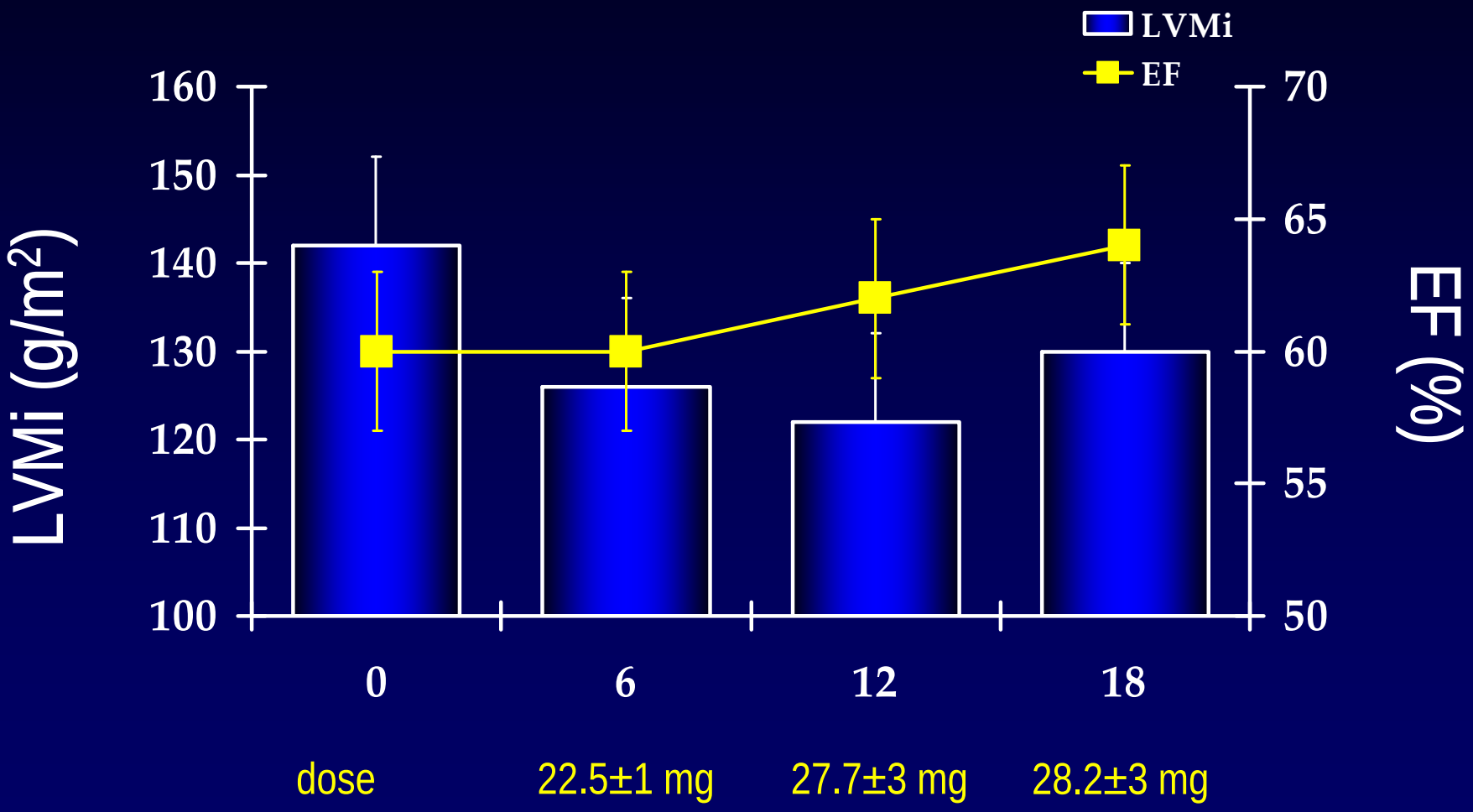
Colao A et al, *Clin Endocrinol* 2003

Control of acromegaly by SSA *vs.* age & cardiac diseases



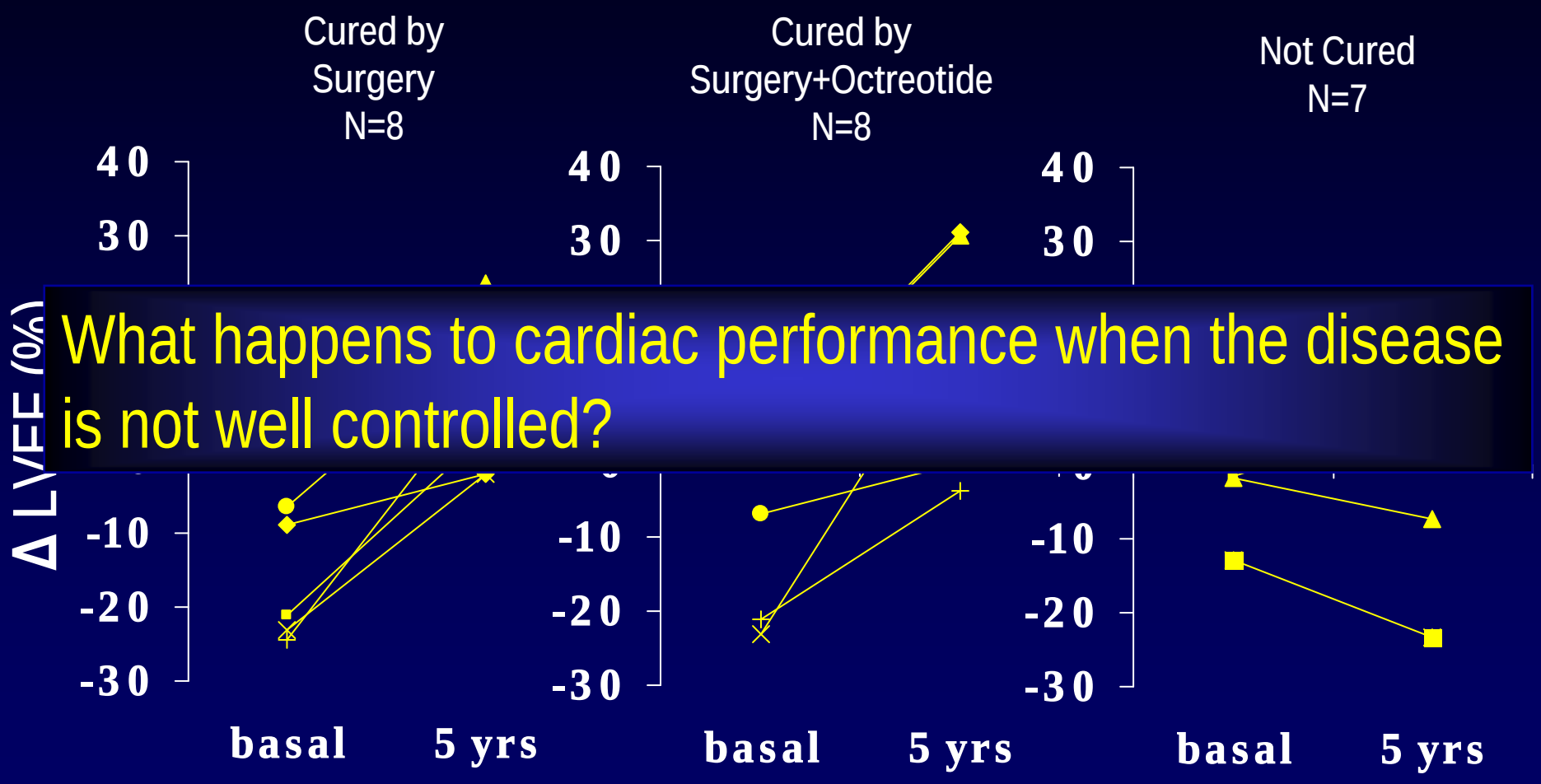
Colao A et al, *Clin Endocrinol* 2003

Control of acromegaly by pegvisomant in 12 SSA-resistant patients



Pivonello et al. JCE&M 2007 in press

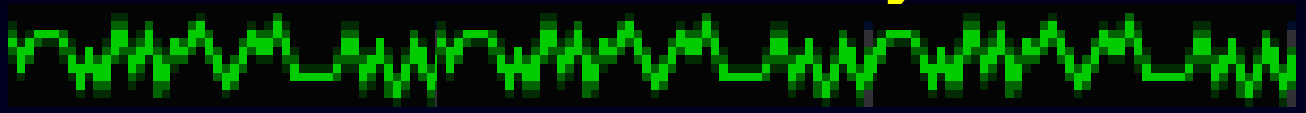
Cardiac performance on effort before and 5 yrs after treatment in acromegaly



What happens to cardiac performance when the disease is not well controlled?

Colao A, et al., *JCE&M* 2001

Arrhythmias



causes

- anatomical uncoupling of cardiomyocytes
- re-entry events + zig-zag propagation of transverse waveform
- adaptational phenotypic changes in membrane proteins

events

atrial-ventricular ectopic beats
paroxysmal atrial fibrillation
paroxysmal ventricular tachyarrhythmia
paroxysmal supraventricular tachyarrhythmia
sick sinus syndrome
bundle branch block

Italian Study Group on Lanreotide

- Mean 24 hour heart rate decreased from 71.5±20 to 66.5±11 beats/min ($p<0.05$)
- Supra-ventricular premature beats (>50/24 hours) were found in 16.6% of patients and showed scarce variation
- Ventricular premature beats (>50/24 hours) were found in 33.3% of the patients before treatment and in 16.5 % after treatment with lanreotide 60-90 mg/mo for 6 mos

Lombardi G. et al. *JEI*, 2002; 25

Cardiac Valve Disease

Degenerative aortic disease with regurgitation

Mitral stenosis & regurgitation

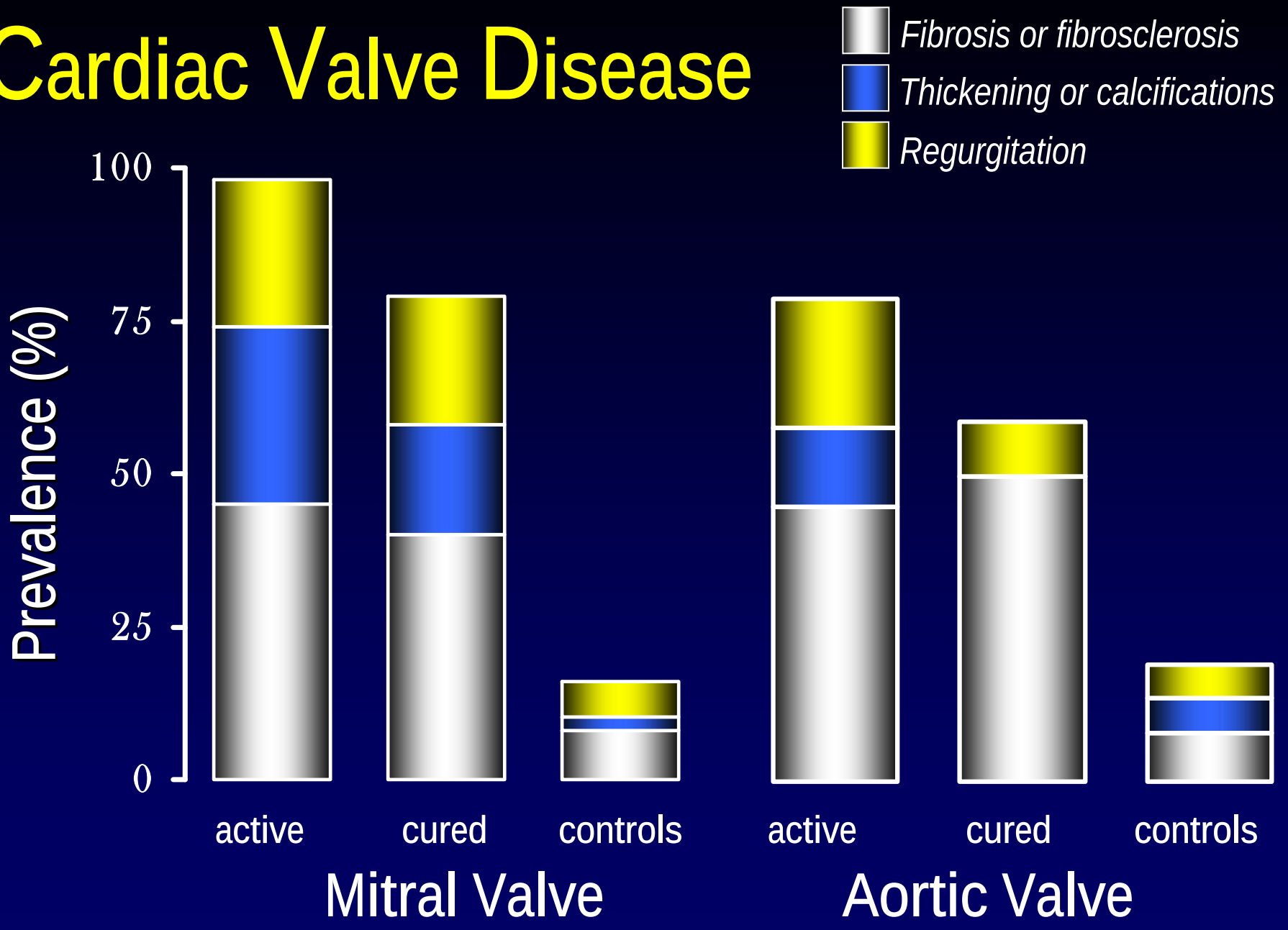
Mitral and aortic dilatation

“Frail” annulus and mucopolisaccaridic deposit on valve leaflets

Calcified stenosis of the aortic valve by endocarditis

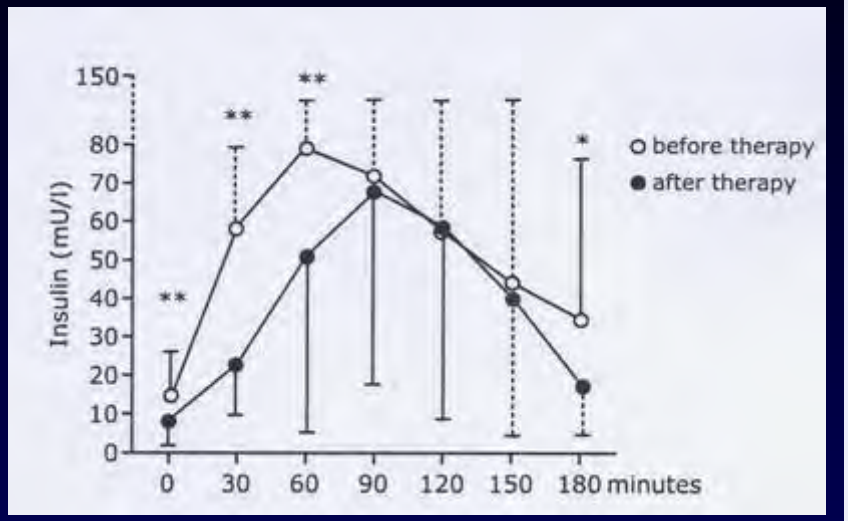
Lie and Grossman, *Am Heart J*, 1980

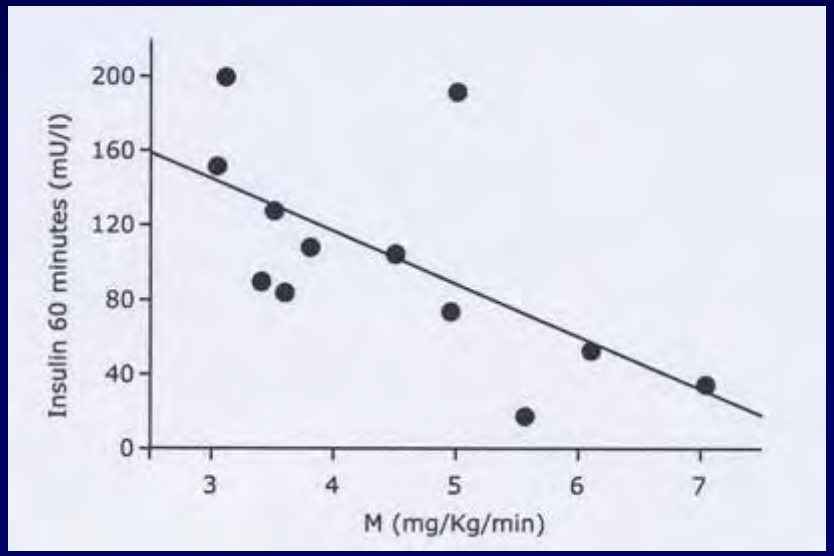
Cardiac Valve Disease

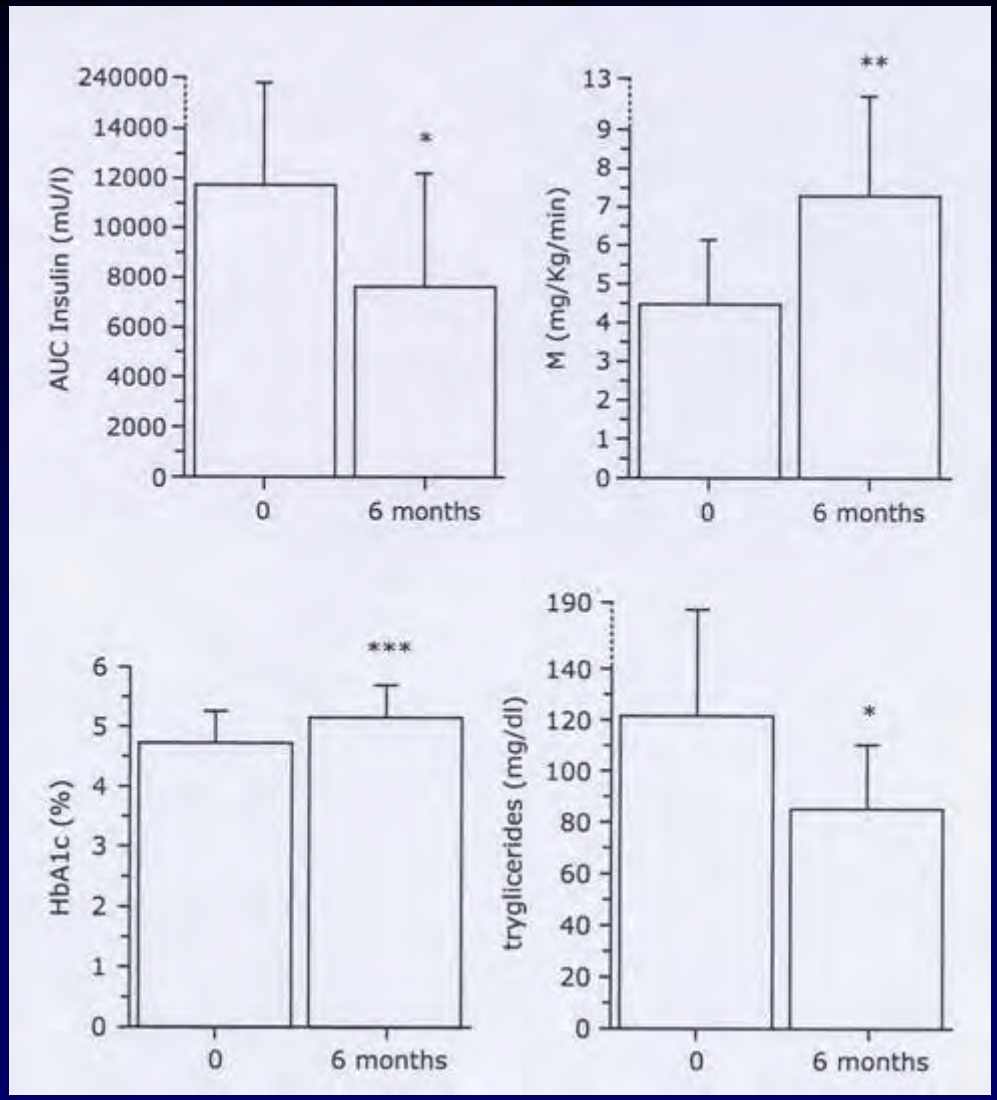


Colao A, et al. *JCE&M* 2003, ; 88: 3196-201

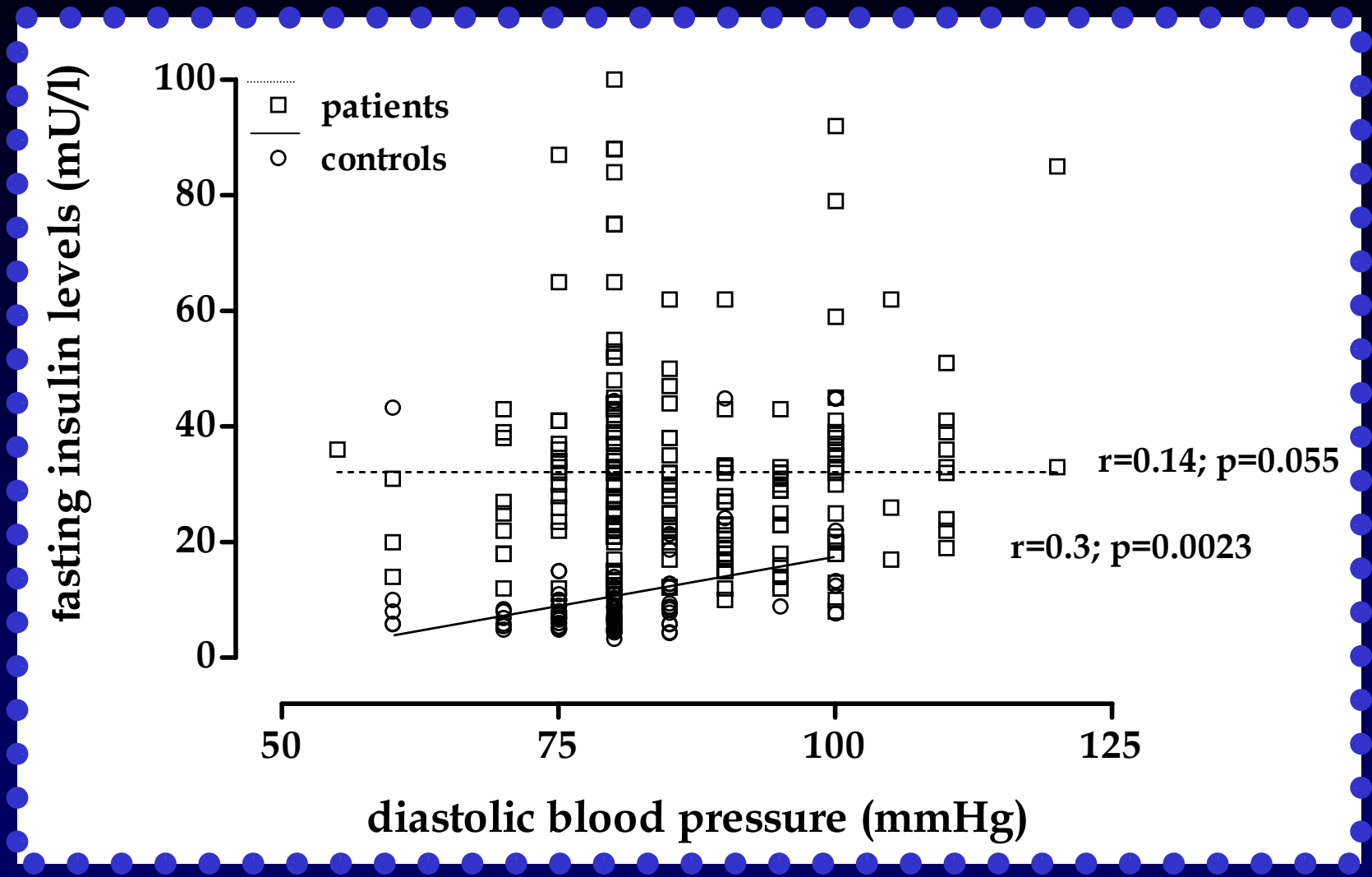
Glucose Homeostasis







Baldelli R et al. *Clin Endocrinol*, 2003



Colao et al., *Endocr Rev*, 2004

European Journal of Endocrinology (2006) 154 467–477 ISSN 0804-4643

CLINICAL STUDY

Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance

Annamaria Colao, Rosario Pivonello, Renata S Auriemma, Maria Cristina De Martino, Martin Bidlingmaier[1], Francesco Briganti[2], Fabio Tortora[2], Pia Burman[3], Ione A Kourides[3], Christian J Strasburger[4] and Gaetano Lombardi

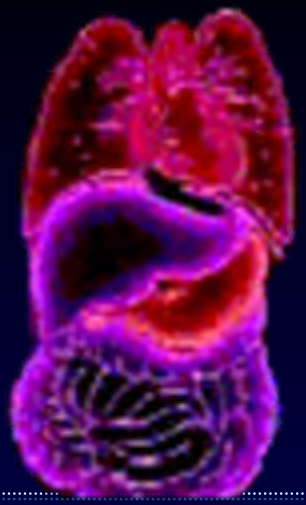
Table 2 Effect of pegvisomant treatment on clinical, biochemical and endocrine findings. Data are shown as mean±S.D. and *P* values refer to Wilcoxon matched *t*-test. The two patients noncompliant with treatment (nos 9 and 14 described in Table 1) were excluded from the calculation.

	Before	After	*P*
Weight (kg)	83.5±15.0	85.7±13.6	0.055
Serum GH levels (μg/l)	22.9±24.0	34.5±40.4	0.29
Serum IGF-I levels (μg/l)	775.1±141.4	237.8±106.7	<0.0001
Tumor volume (mm^3)	1198±1234	1196±1351	0.37
Ring size (mm)	12.7±2.2	12.2±2.3	0.78
Systolic blood pressure (mmHg)	133.9±16.2	129.6±10.1	0.13
Diastolic blood pressure (mmHg)	87.1±13.6	86.2±7.1	0.70
Heart rate (bpm)	72.8±7.6	76.8±7.9	0.14
Total cholesterol levels (mmol/l)	5.3±1.0	5.5±0.8	0.43
HDL-cholesterol levels (mmol/l)	1.2±0.3	1.5±0.2	0.0017
Total/HDL-cholesterol ratio	4.5±1.0	3.7±0.6	0.0012
Triglyceride levels (mmol/l)	1.5±0.9	1.5±0.7	0.86
Glucose levels (mmol/l)	5.6±1.2	4.4±1.4	0.0012
HbA1c levels (%)	5.3±0.7	5.3±0.5	0.24
Insulin levels (mU/l)	12.4±6.7	8.1±3.0	0.0023
HOMA index	3.4±2.1	1.9±1.0	0.0017
Fibrinogen levels (mg/dl)	342.1±75.2	361.6±63.6	0.58
AST levels (U/l)	19.4±8.6	22.9±15.1	0.64
ALT levels (U/l)	18.6±14.0	40.1±61.2	0.017
Albumin levels (g/dl)	3.8±0.4	4.4±0.3	0.0002

Reversal of systemic complications of acromegaly

- → The cardiovascular system
- → The respiratory system
- → The osteo-skeletal system
- → The oncological risk

Respiratory disorders



Sleep apnea

Central/obstructive

- macroglossia
- thickened soft palate
- thickened hypopharynx
- laringeal cartilage hypertrophy
- thickened vocal cords
- reduced motility of vocal cords

Pulmonary function

total lung capacity
residual volume
residual capacity of nitrogen

inspiratory pressure
expiratory pressure

TABLE 4. Morphological and functional alteration of upper and lower respiratory airways, thoracic cage, and lungs in patients with acromegaly

Site	Pathological findings	Clinical disorder
Craniofacial region and upper respiratory tract		
Soft tissues and muscles	Macroglossia (283)	
	Swelling/lengthening of the soft palate (266, 267, 273–275, 277)	Impaired airflow transit
	Swelling/collapse of the pharyngeal walls (277)	Obstructive sleep apnea
	Thickening of true and false vocal cords (275, 278)	Nocturnal snoring
Bones	Overgrowth of mandible, maxilla and ioid (266, 267, 273, 277)	Fragmented sleep
	Mandible protrusion (266, 267, 273, 277)	Daytime somnolence
	Dorsocaudal rotation of the mandible (273)	Morning sleepiness
Organs	Thyroid overgrowth (283, 374, 375)	Morning headache
	Submandibular salivary gland hyperplasia (276)	
Neck/thoracic cage and lower respiratory tract		
Soft tissues and muscles	Small airway narrowing (253–255)	
	Derangement of respiratory muscles (286, 287)	Impaired airflow transit
Cartilages and bones	Enlargement/elongation of vertebral bodies (283)	Stiffened rib cage
	Thickened intervertebral discs of the neck (283)	Impaired breathing movements
	Thinned intervertebral discs of the thorax (283)	Respiratory muscle impairment
	Thoracic spine kyphoscoliosis (283)	Short inspiratory time
	Elongation and divergence of the ribs (283, 285)	Emphysema
Organs	Lung overgrowth (253–255, 288)	Bronchiectasis
	Increased lung volume (253–255)	
	Increased lung compliance (253–255)	

Colao A, *Endocr Rev* 2004

Improvement of sleep apnea in 14 pts after LAR 6 mos

	Basal	LAR	P
Sleep efficiency	86.1±13.3	83.8±9.7	NS
Stage 1 sleep (%)	27.7±12	11.6±4.3	0.02
Stage 2 sleep (%)	51.6±18.6	63.9±10.4	NS
Stage 3-4 sleep (%)	8.4±8.1	7.7±6.1	NS
Stage REM sleep (%)	11.8±7.7	16.6±5.7	NS
Apnea/Hypopnea index	29.4±22.6	13.4±11.1	0.03
Obstructive Apnea index	15.3±13.3	3.9±5	0.01
Mixed Apnea index	4.9±8	2.6±4.6	NS
Central Apnea index	3±5.8	1.1±2.1	NS
Snoring episodes	486±239	165±170	0.05
Total time snoring (min)	95.6±30.6	46.6±48.7	0.06

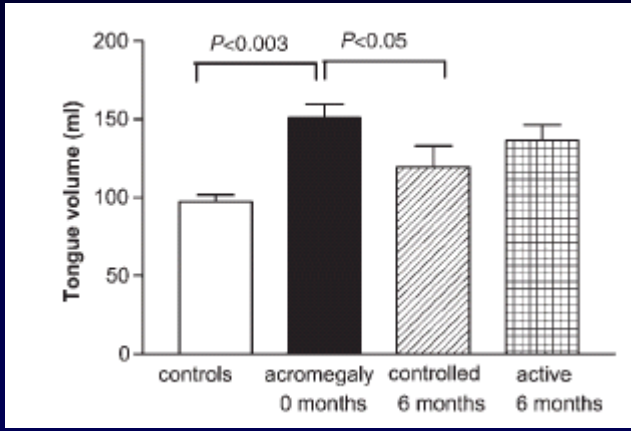
Ip MSM, *Clin Endo* 2001

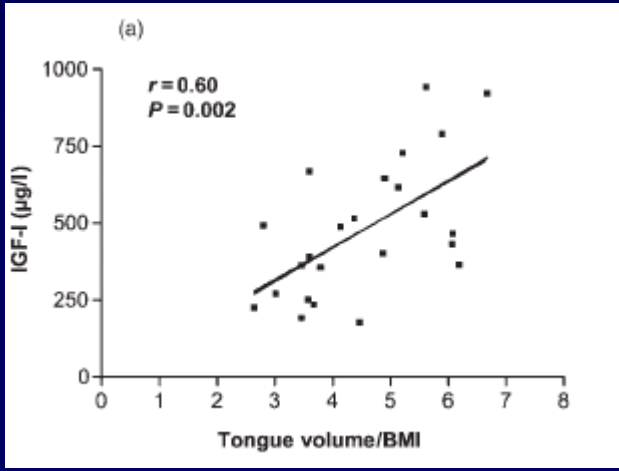
European Journal of Endocrinology (2004) **151** 309–315 ISSN 0804-4643

CLINICAL STUDY

Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly

B L Herrmann, T E Wessendorf[1], W Ajaj[2], S Kahlke, H Teschler[1] and K Mann





Patients: 14 newly diagnosed patients with active acromegaly

Methods:Tongue volume and signal intensity by MRI and sleep apnoea by polysomnography before and after 6 months of treatment Sandostatin LAR (10–30mg every 4 weeks i.m.)

Results: After treatment with octreotide, IGF-I was normalised in 50%. In controlled patients, tongue volume significantly decreased in comparison to uncontrolled. The BMI-adjusted tongue volume correlated with IGF-I levels.

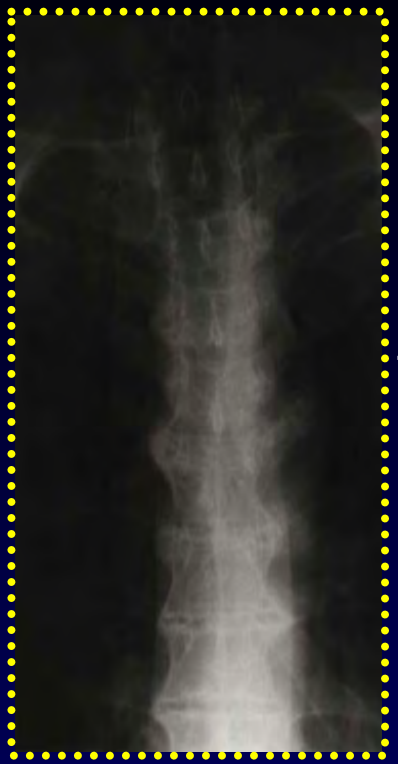
Reversal of systemic complications of acromegaly

- → The cardiovascular system
- → The respiratory system
- → The osteo-skeletal system
- → The oncological risk

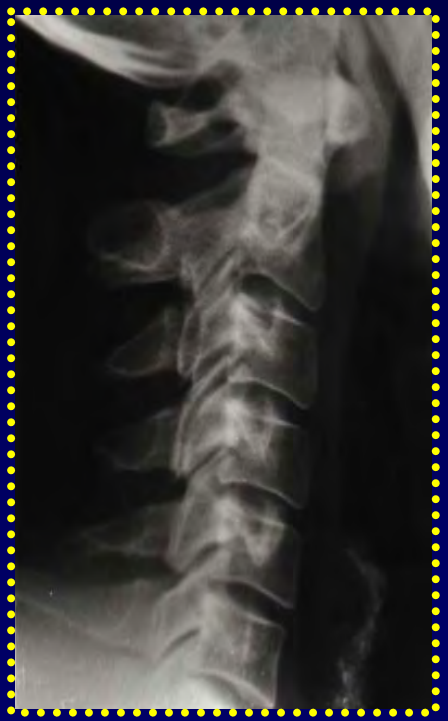
The skeletal complications

- Symptoms or signs referable to joints occur in 53-76%
- The appendicular skeleton is involved in up to 74%
- The delay between estimated onset of acromegaly and appearance of joint disease is about 10 yrs
- No correlation between duration of acromegaly and presence or severity of arthropathy
- Predisposition towards osteoporosis (*Bell, 1967*)
- Bone mass decreased (*Diamond, 1989; Ezzat 1993*), normal (*Ho, 1992; Kotzmann , 1993; Lesse, 1998*), increased (*Seeman, 1982; Hubush, 1993*)

- 54 patients (18-67 aa)
- Axial arthropathy in 51.9%
- Spinal mobility reduced in 56%
- Thoracic cage involvement in 11%
- Alteration of spinal profile in 69%
- DISH features in 21%



Dysphagia, directly due to calcification close to the area of normal oesophageal fixation, in 13% of patients



Arthropathic vs. Non-arthropatic groups:
basal insulin p=0.04

	Vs	R	P
DD	Height of the vertebral body	0.63	0.001
	Height of intervertebral space	0.45	0.02
	Insulin levels	-0.33	0.01

Scarpa R. et al *JCE&M* 2004

Acromegalic Arthropathy

local IGF-I production
proteoglycan synthesis
glycosaminoglican synthesis
cell replication

GH/IGF-I excess

cartilage changes

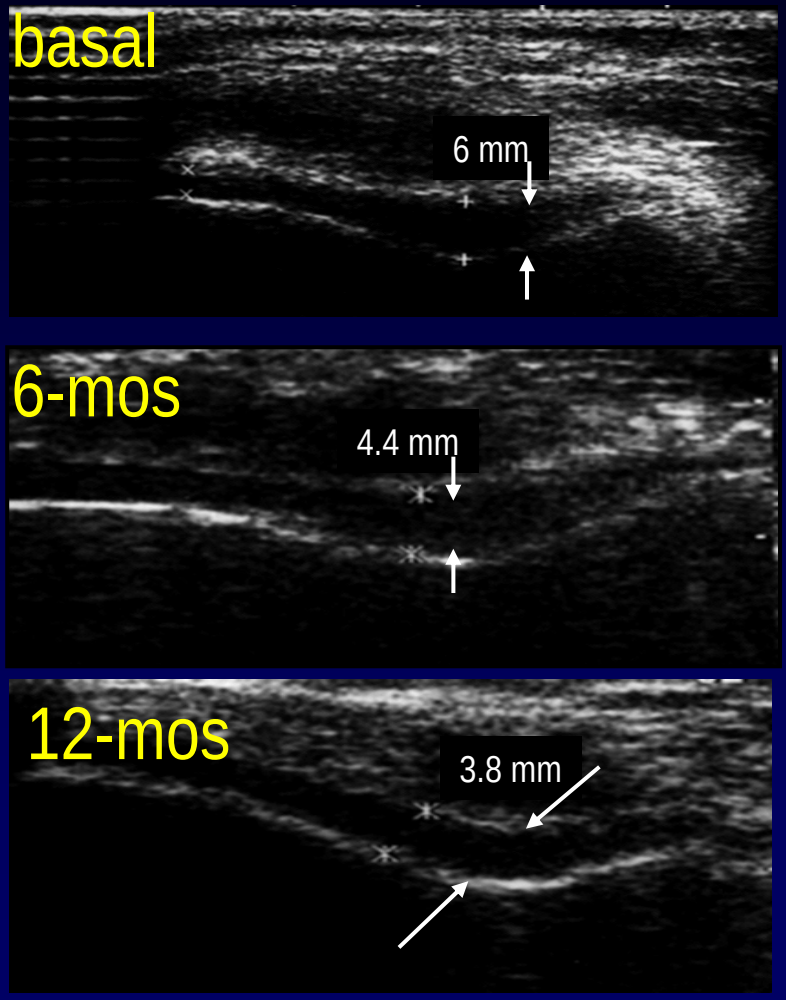
arthicular widening
soft tissues hypertrophy
cartilage ulcers
subchondral cysts
arthicular thickening

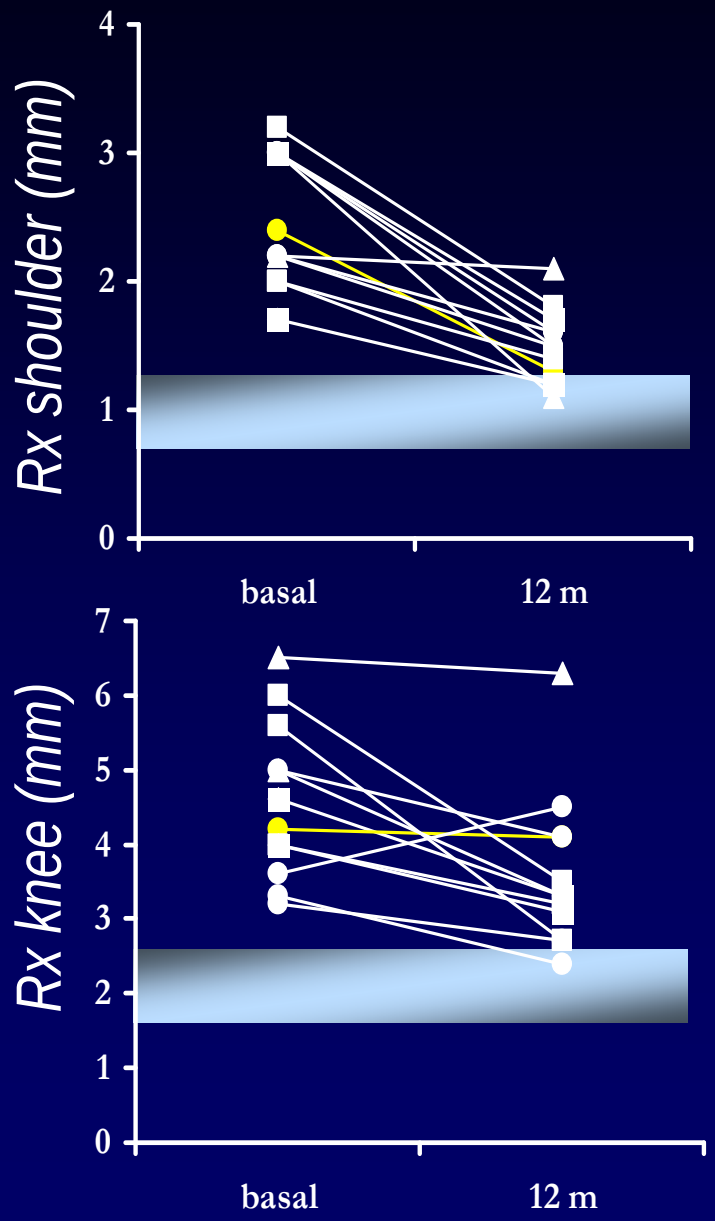
arthicular narrowing

degenerative osteoarthritis

Colao A et al. *Endocr Rev* 2004

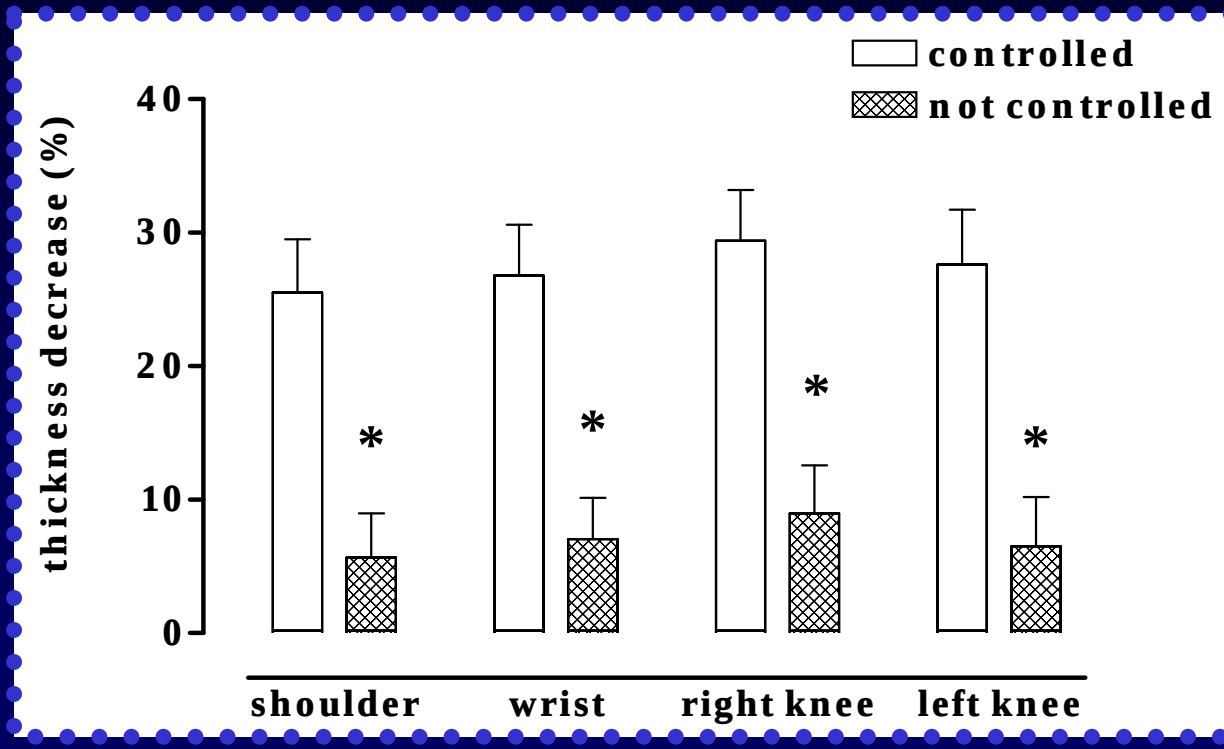
Treatment with SSA reduces the thickness of articular cartilage





Colao A et al., 1998; 1999; 2003

Decrease in the thickness of articular cartilage after Octreotide-LAR is greater in controlled than in non-controlled patients



Colao A, et al. *Eur J Endocrinol* 2003

Increased Prevalence of Radiological Spinal Deformities in Active Acromegaly: A Cross-Sectional Study in Postmenopausal Women

Bonadonna S et al. J Bone Min Res 2005:20:1837-1844

- 36 postmenopausal acromegalic Pts (15 with active and 21 with controlled disease) vs. 36 nonacromegalic postmenopausal women, matched for age, (selected among Pts consulting the Bone Center).

Conclusion:

"This cross-sectional study shows that high numbers of postmenopausal women with acromegaly develop vertebral fractures in relation to the activity of disease. Furthermore, our study shows that, in patients with active acromegaly, vertebral fractures occur even in the presence of normal BMD, whereas in patients with controlled acromegaly, vertebral fractures are always accompanied by a pathological BMD"

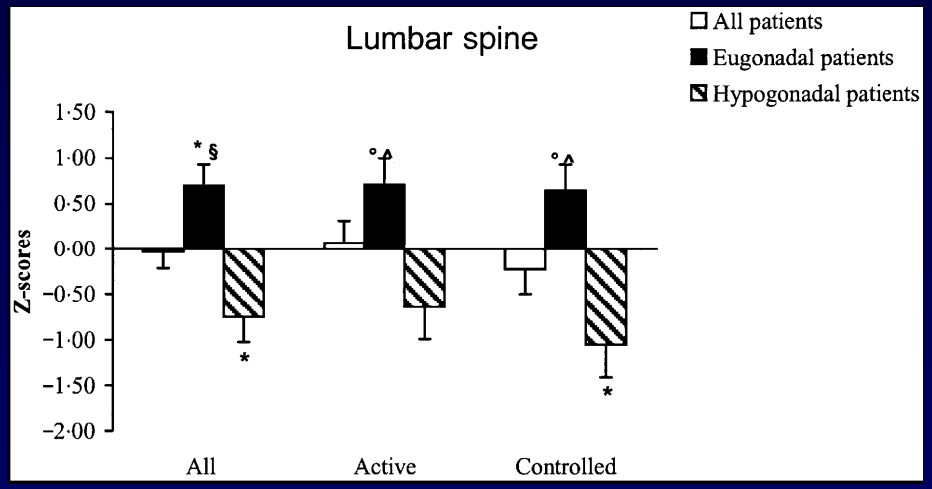
41.7% of women whose fractures were associated with active disease had a normal T score (>−1.0 SD), whereas osteopenia and osteoporosis were found only in 33.3% and 25.0% of them, respectively.

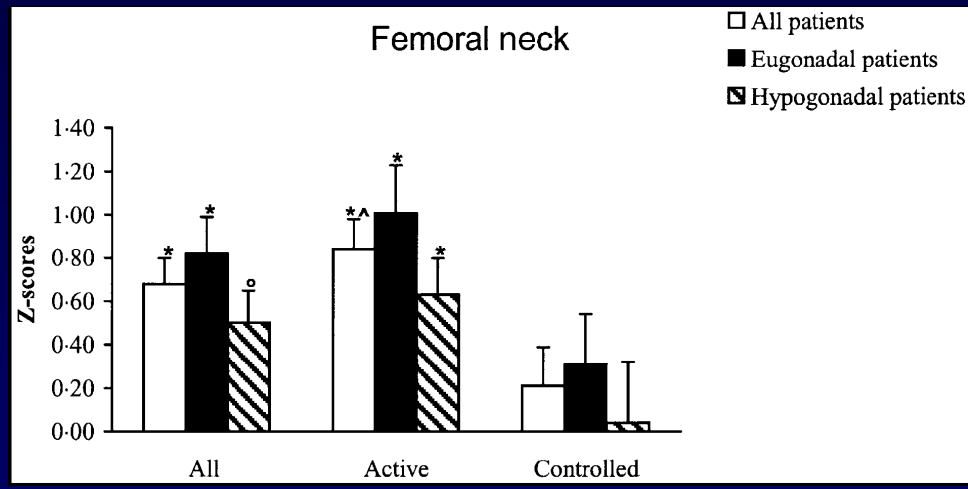
Bone mineral density in acromegaly: the effect of gender, disease activity and gonadal status

Alfredo Scillitani*, Claudia Battista*, Iacopo Chiodini*,***, Vincenzo Carnevale*, Saverio Fusilli*, Enrica Ciccarelli†, Massimo Terzolo‡, Giuseppe Oppizzi§, Maura Arosio¶, Maurizio Gasperi**, Giorgio Arnaldi††, Annamaria Colao‡‡, Roberto Baldelli§§, Maria Rosaria Ghiggi*¶¶, Daniela Gaia†, Carolina Di Somma††, Vincenzo Trischitta* and Antonio Liuzzi†††

Clinical Endocrinology (2003) 58, 725–731

152 acromegalic patients (99 F aged 26–72 yrs, 53 M aged 21–75 yrs), 107 active and 45 controlled.
85 Pts eugonadal status, 67 hypogonadal

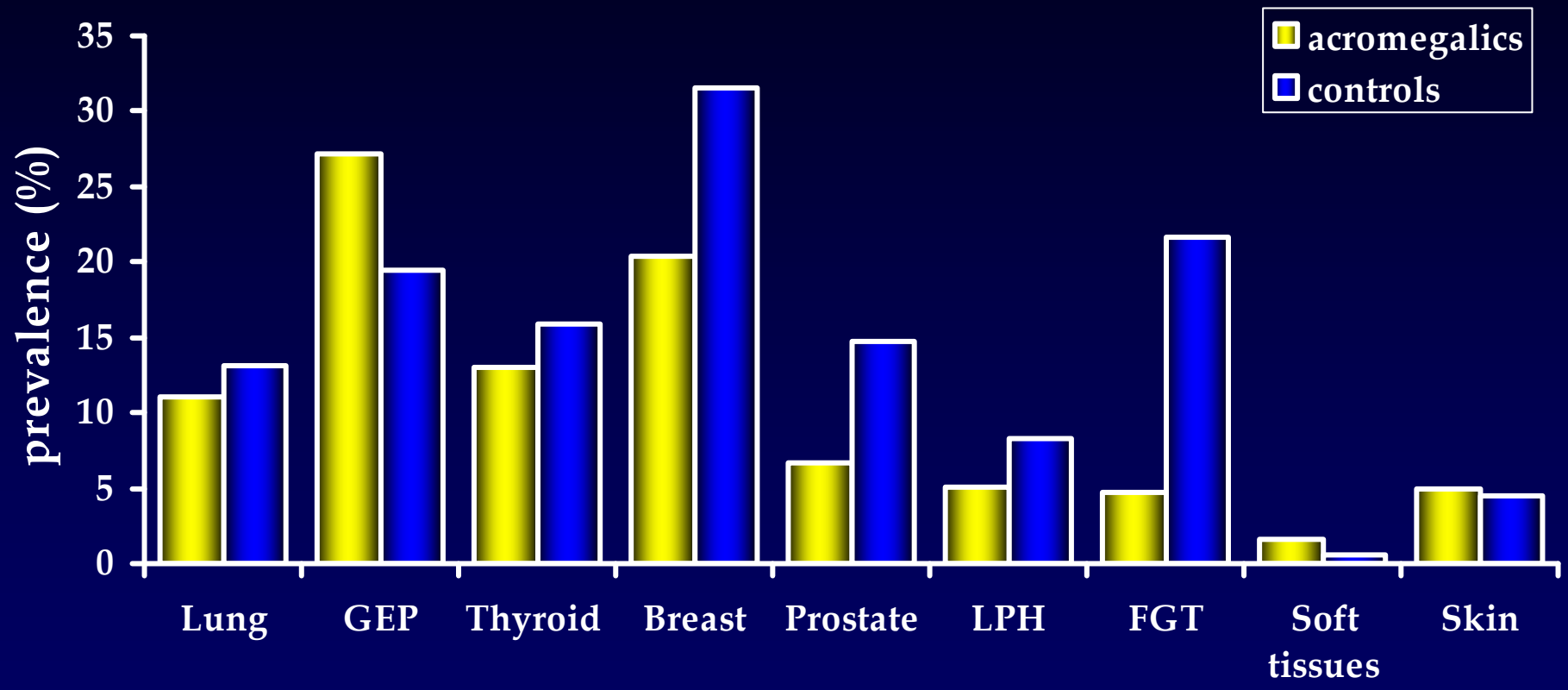




Reversal of systemic complications of acromegaly

- → The cardiovascular system
- → The respiratory system
- → The osteo-skeletal system
- → The oncological risk

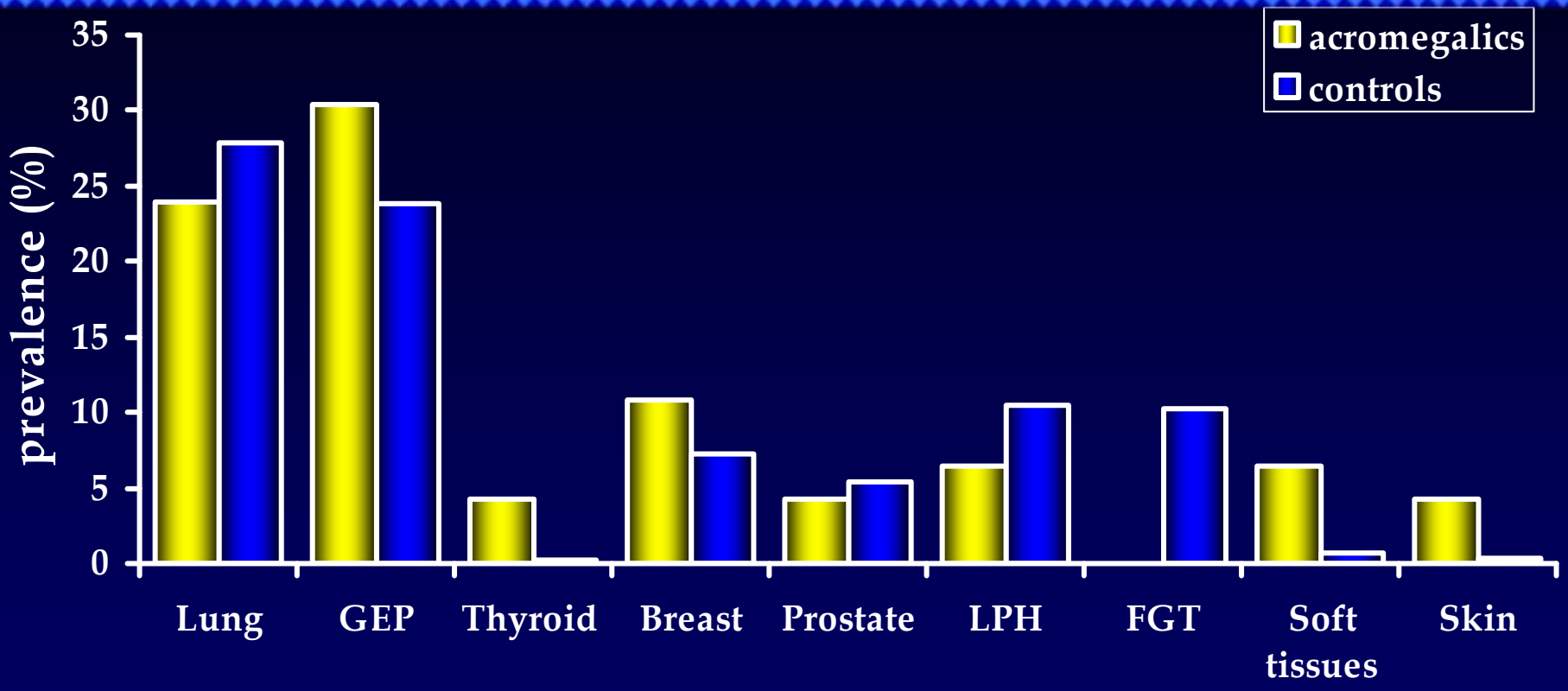
Prevalence of cancer compared to epidemiological data



Colao A et al. *Endocr Rev* 2004

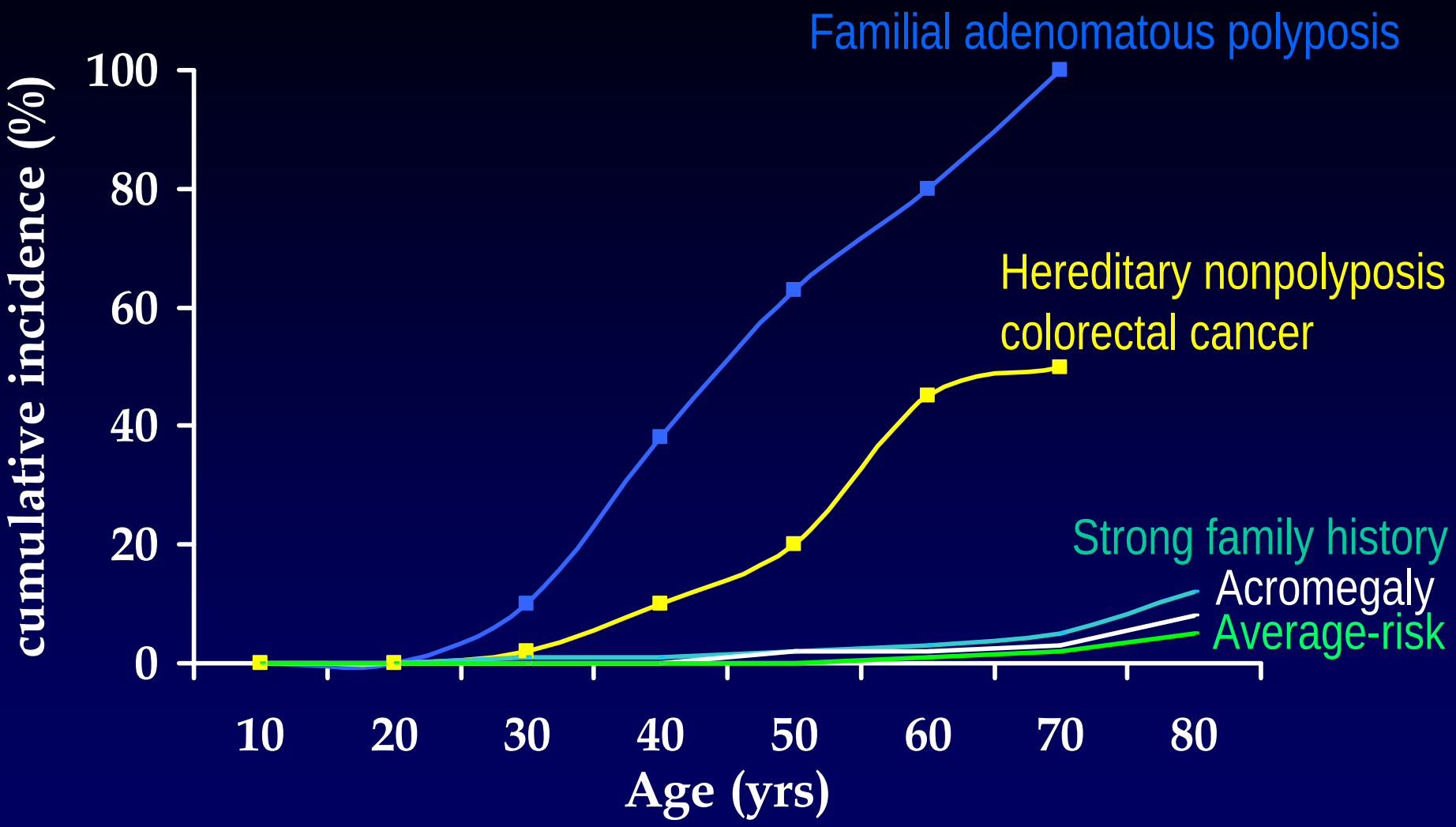
Comparative prevalence is 2002 estimates in U.S. population based on rates collected in 1978-1998 (American Cancer Society Atlanta, Georgia, 2002; published in NCI SEER Program 1979-1998 , available at: htpp://seer.cancer.gov/csr/1973-1999/overview.pdf).

Mortality from cancer compared to epidemiological data



Colao A et al. *Endocr Rev* 2004

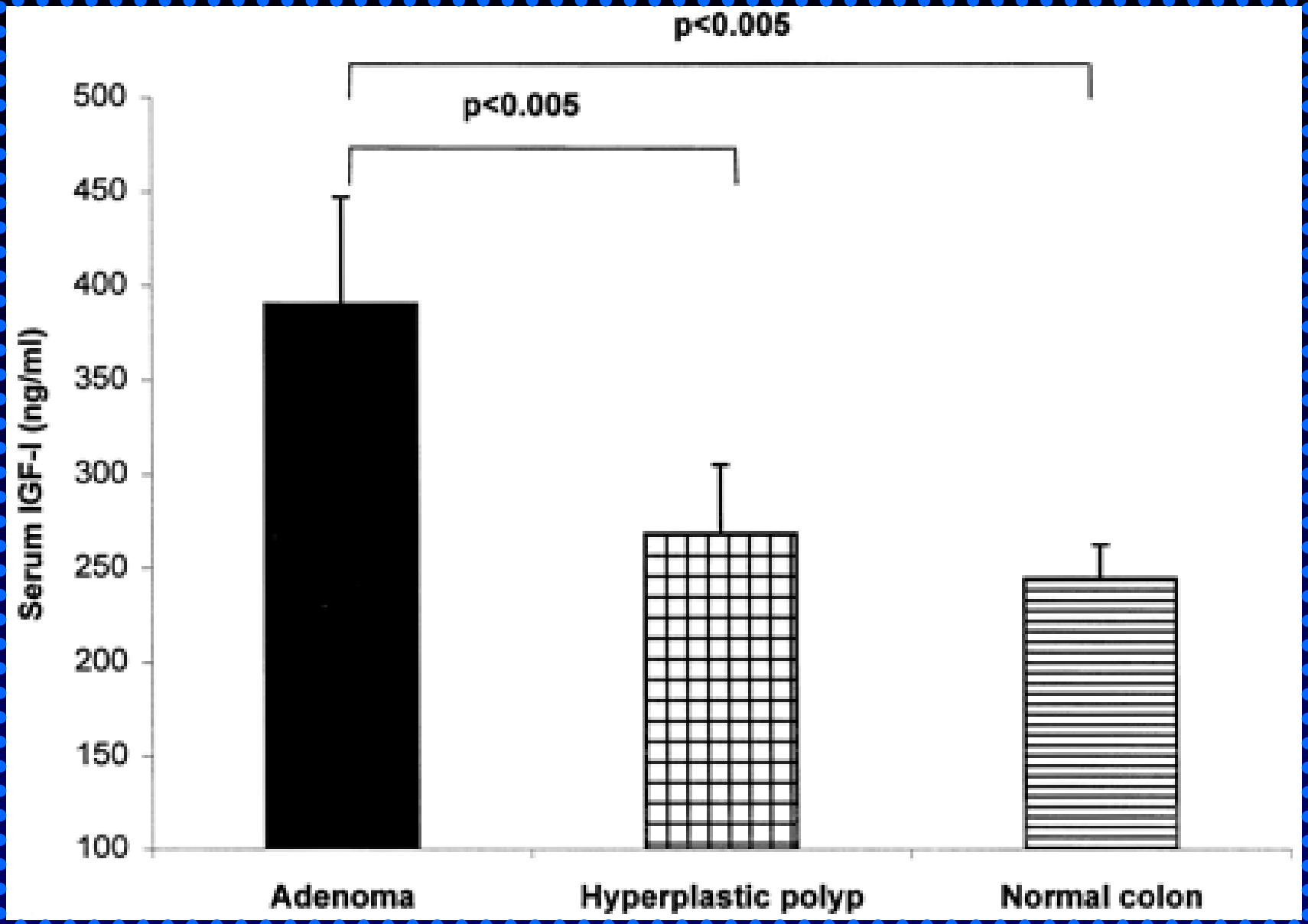
Mortality rates are 2002 estimates in U.S. population based on rates collected in 1978-1998 (American Cancer Society Atlanta, Georgia, 2002; published in NCI SEER Program 1979-1998 , available at: htpp://seer.cancer.gov/csr/1973-1999/overview.pdf).



Renehan AG, et al. Clin Endocrinol (Oxf). 2001; 55: 731-733

Factors pros colonic polyps

- Patients' age above 50 years
- Disease duration longer than 10 years
- Number of skin tags ≥3
- Male gender
- Family history of colonic cancer



Jenkins PJ, et al. JCE&M 2000; 85: 3218-3221

Colonoscopic Screening and Follow-Up in Patients with Acromegaly: A Multicenter Study in Italy

Massimo Terzolo, Giuseppe Reimondo, Maurizio Gasperi, Renato Cozzi, Rosario Pivonello, Giovanni Vitale, Alfredo Scillitani, Roberto Attanasio, Elisabetta Cecconi, Fulvia Daffara, Ezio Gaia, Ennio Martino, Gaetano Lombardi, Alberto Angeli, and Annamaria Colao

The Journal of Clinical Endocrinology & Metabolism 90(1):84–90
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doi: 10.1210/jc.2004-0240

TABLE 2. Colonoscopic findings according to the most advanced lesion

Finding	Patients	Controls	*P*
No polyp	125 (53.2)[a]	175 (75.1)	0.0001
Hyperplastic polyp	45 (19.1)	22 (9.4)	0.003
Adenoma	55 (23.4)	34 (14.6)	0.001
Cancer	10 (4.3)	2 (0.9)	0.036

[a] Number (percentage).

TABLE 4. Association of age with colon neoplasia

Age (yr)	Patients	Controls	*P*
<40	11/57 (19.3)[a]	2/45 (4.4)	0.035
40–49	14/56 (25.0)	6/62 (9.6)	0.047
50–59	23/74 (31.1)	15/75 (20.0)	NS
≥60	17/48 (35.4)	13/51 (25.4)	NS

1. The risk of colonic neoplasia was higher for younger Pts with acromegaly vs.age-matched controls;
2. Pts with acromegaly with or without colonic neoplasia had similar IGF-I levels or duration of disease;
3. Neoplastic recurrence was found in 16.5% of Pts who underwent follow-up.

Identification of Acromegalic Patients at Risk of Developing Colonic Adenomas

Fausto Bogazzi, Chiara Cosci, Chiara Sardella, Aurelio Costa, Luca Manetti, Maurizio Gasperi, Giuseppe Rossi, Luigi Bartalena, and Enio Martino

The first colonoscopy helps to identify acromegalic patients at high risk of developing colonic adenomas. If colonic adenomas are not present initially, it is unlikely that they develop thereafter,independently of metabolic control of acromegaly. Conversely, new lesions are frequent (and often multiple) in patients who already have colonic adenomas at baseline, particularly if acromegalic disease is poorly controlled by treatment.

Conclusion-1

- Biventricular hypertrophy with diastolic and/or systolic dysfunction is associated with acromegaly
- The acromegalic cardiomyopathy is improved by the control of GH & IGF-I excess
- Reversal of cardiac abnormalities is more likely to occur in young patients with short disease duration
- Sleep apnea significantly improve after treatment in analogy with the cardiomyopathy

Conclusion-2

- Decrease in thickening of articular cartilages is observed in patients controlled after treatment with somatostatin analogues
- Skeletal changes are hardly reversed and thus bony consequences are the most important negative factor of QoL
- Decrease of IGF-I is associated with a lower rate of development of colonic lesions
- No data are available for other cancer types

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