ACROMEGALIA: GESTIONE CLINICA

REAL CLINICAL PRACTICE

Benedetta Zampetti
ASST Grande Ospedale Metropolitano Niguarda Ca' Granda
Milano

La clinica

14 giugno 2010

Donna, 42 aa, una GAT 4 anni fa

FM ogni 21 gg da qualche mese

Cefalea persistente, frontale, quotidiana agli zigomi, occhi, costante, diversa dalla precedente, da 12 mesi

Alterazioni fisionomiche: «mi sento brutta», aumento mani e piedi

Galattorrea da 24 mesi

Parestesie

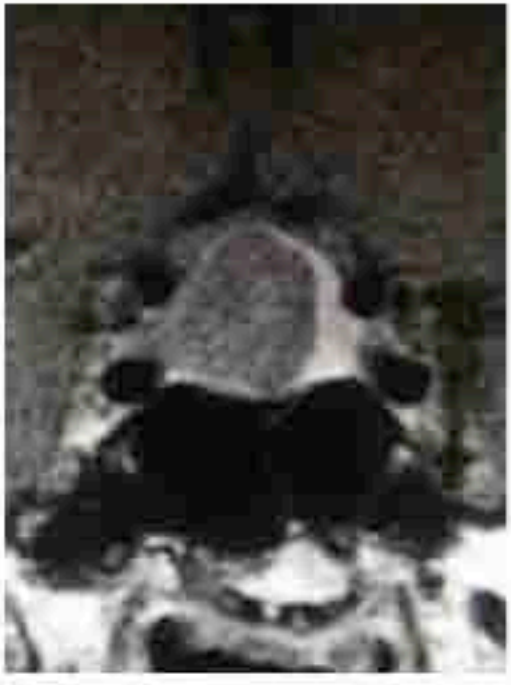
Roncopatia

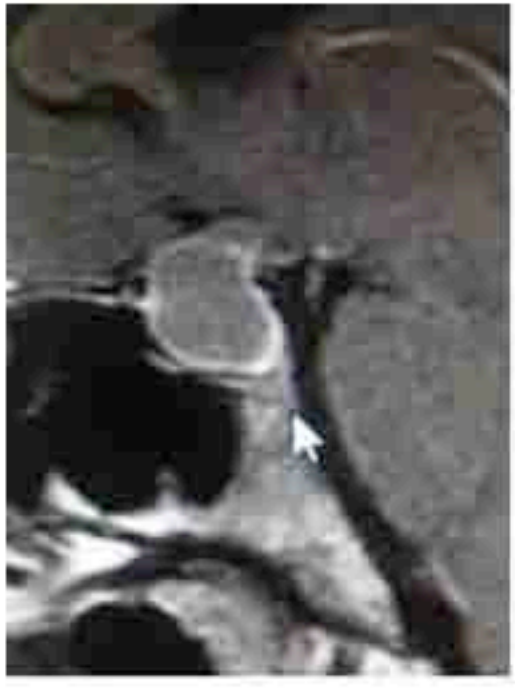
Tunnel carpale bilaterale

Prospettiva di gravidanza

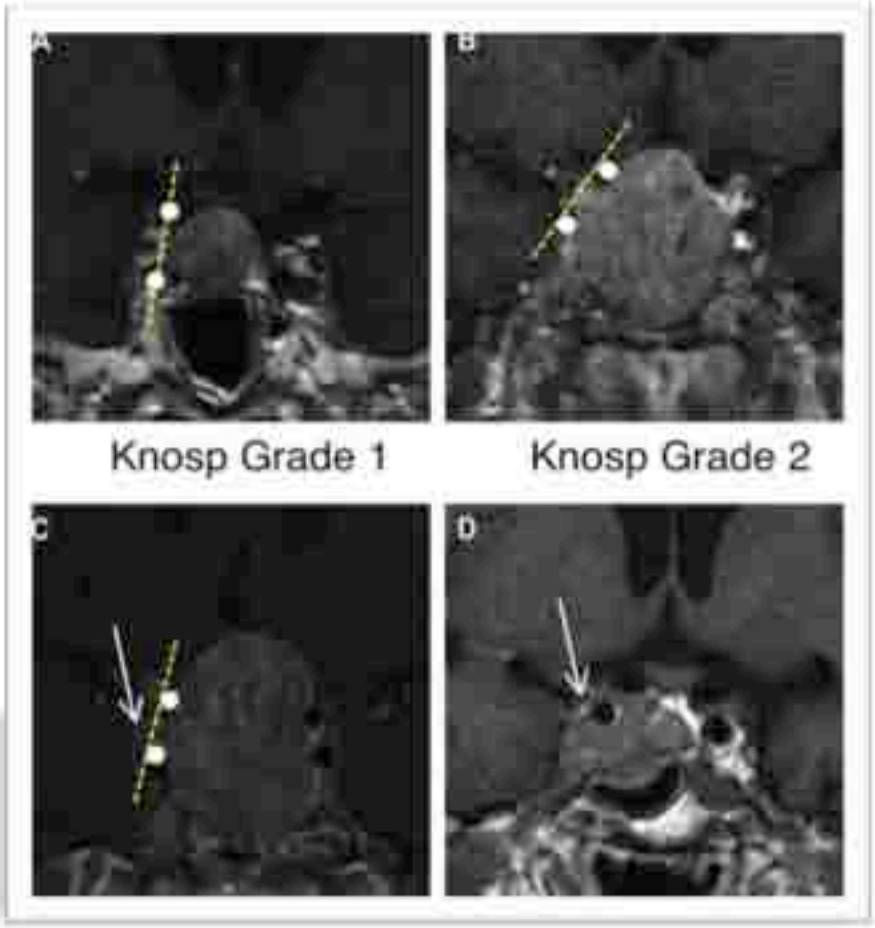
La diagnosi

RM : Voluminoso adenoma intra-sopra sellare, iniziale invasione seno cavernoso destro, a contatto con le vie ottiche





La classificazione di Knosp



Minicorso 4
Acromegalia: gestione clinica

Presentazione, diagnosi clinica e complicanze

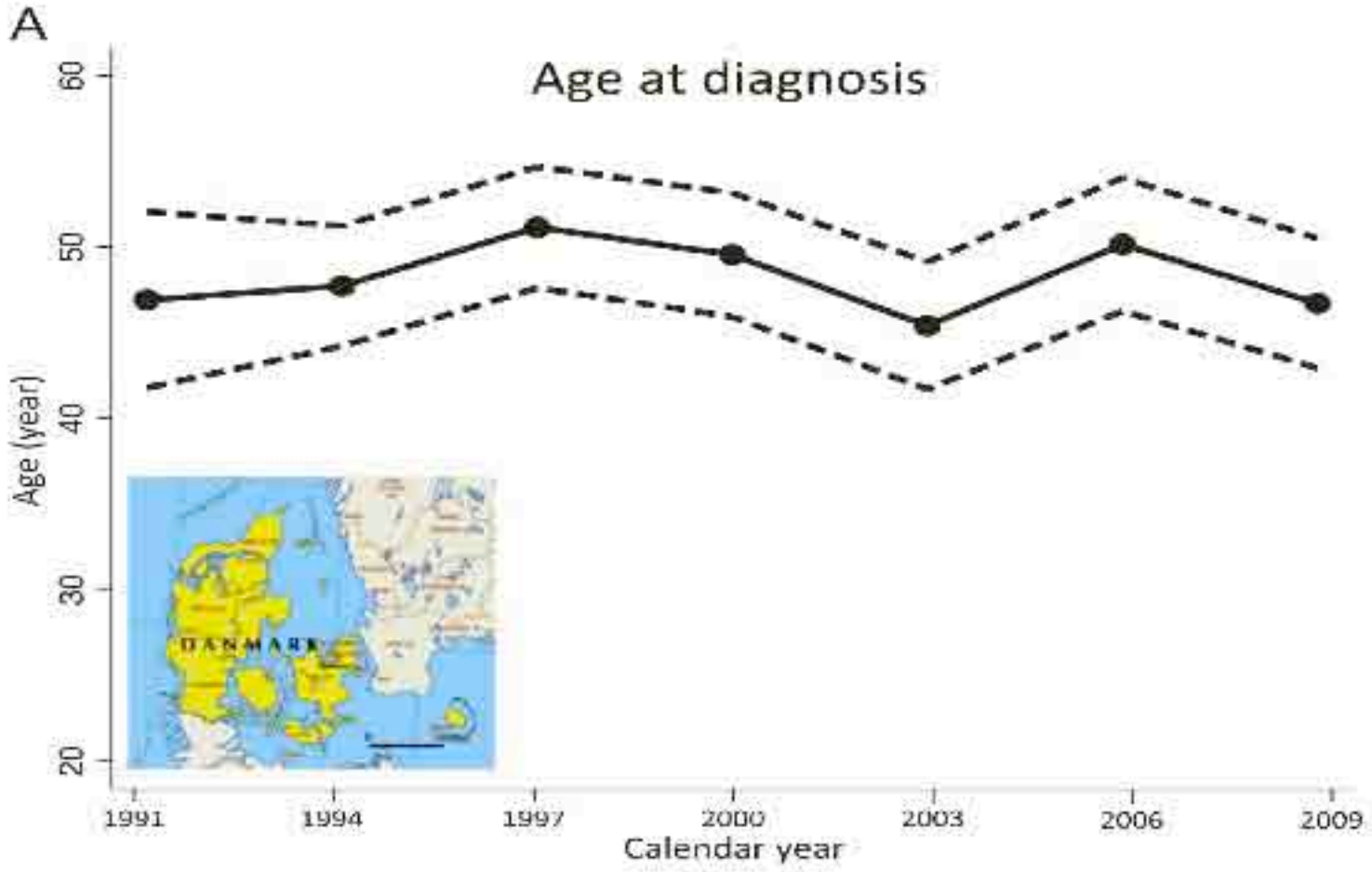
Pietro Maffei,
Clinica Medica 3^, Azienda Ospedaliera Padova
pietromaffei@libero.it
pietro.maffei@aopd.veneto.it

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Novartis, Ipsen, Pfizer, Janssen

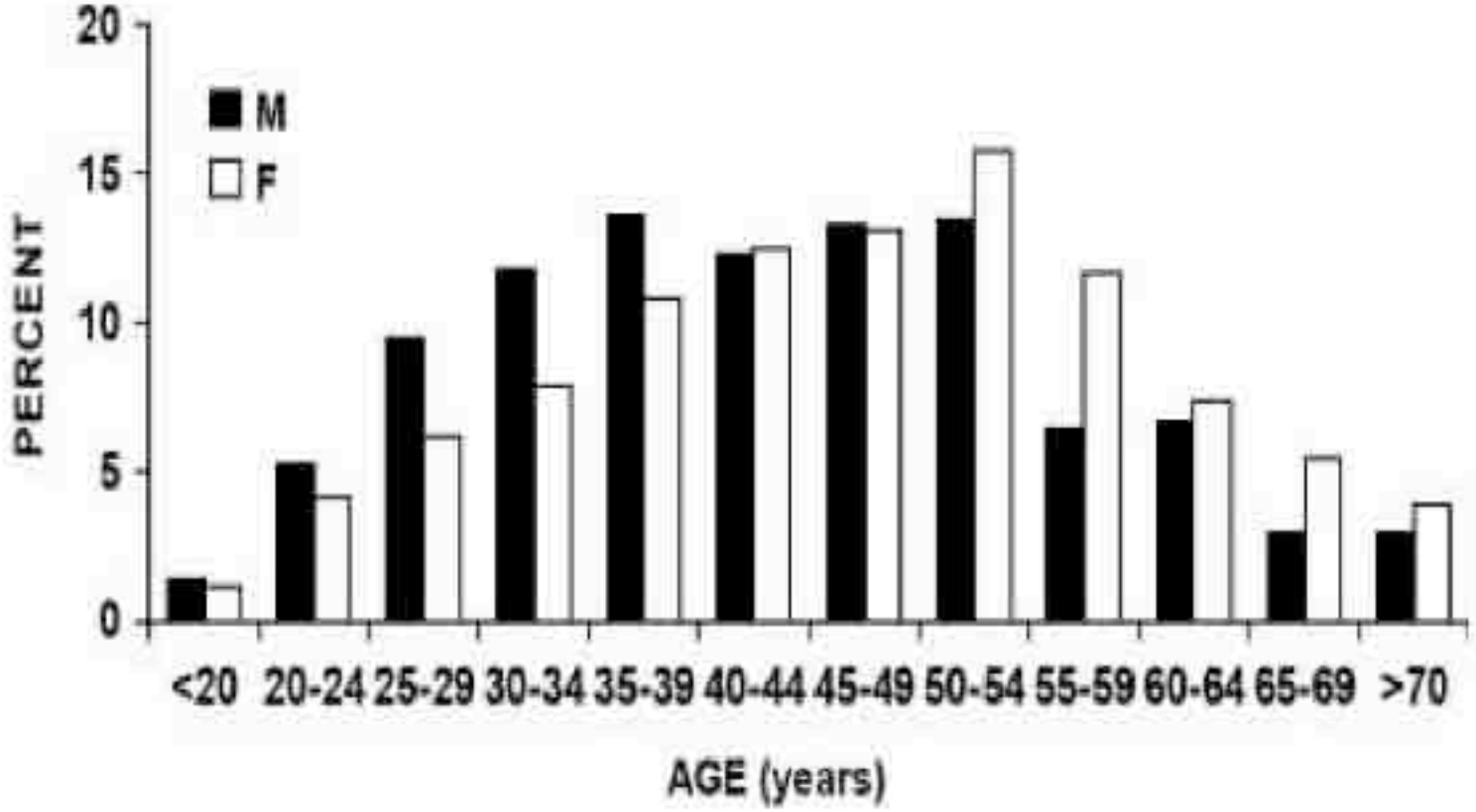
Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study



Dal et al, EJE 2016

Predictors of morbidity and mortality in acromegaly: an Italian survey

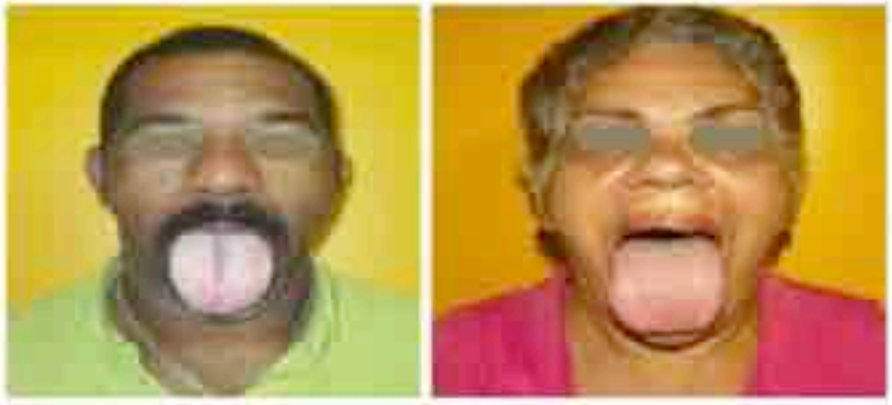
Distribuzione per range di età e sesso alla diagnosi



Arosio et al, EJE 2012

Cosa porta alla diagnosi ?

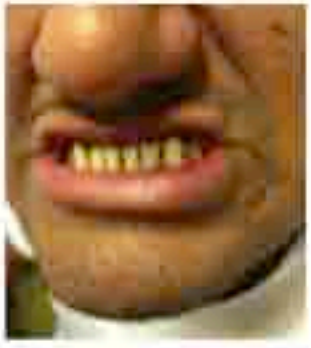
Presenting chief complaint	**310 pazienti**	Frequency (%)
Menstrual disturbances		13
Change in appearance or acral growth		11
Headaches		8
Paresthesias/carpal tunnel syndrome		6
Diabetes mellitus or impaired glucose tolerance		5
Heart disease		3
Visual impairment		3
Decreased libido or erectile dysfunction		3
Arthropathy		3
Thyroid disorder		2
Hypertension		1
Gigantism		1
Fatigue		0.3
Hyperhydrosis		0,3
Somnolence		0,3
Others		5
By chance (detected by unrelated physical or dental examination or radiograph)		40
Total		100



Vilar et al, Pituitary 2017 (Molitch, Clin Endocrinol Metab 1992)

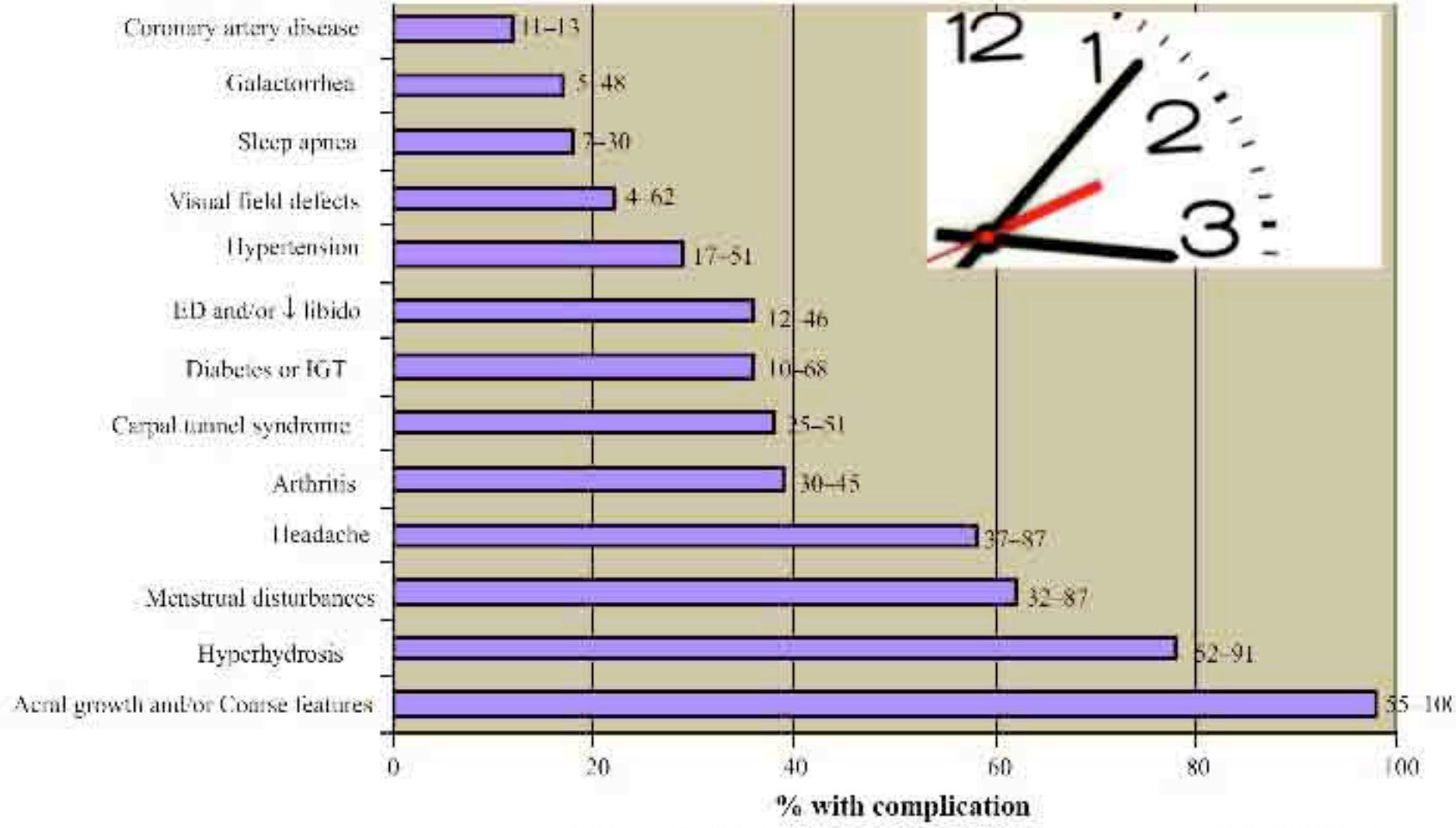
Acromegaly: clinical features at diagnosis

500 pazienti: prevalenza segni e sintomi

<30%	30–60%	>60%
Depression	Headache	Acral growth
Reduce libido	Erectyle dysfunction	Deformity of facial features
Carpal tunnel syndrome	Arthritis	Soft tissue swelling
Daytime somnolence	Asthenia/fatigue	Increased sweating
Myopathy	Peripheral neuropathy	
Increased hair growth	Parestesia	
Dyspnea/breathlessness		
Galactorrhea		

Vilar et al, Pituitary 2017 (Ezzat et al, Medicine 1994)

Acromegaly: clinical features at diagnosis



Vilar et al, Pituitary 2017 (Clemmons et al, JCEM 2003)

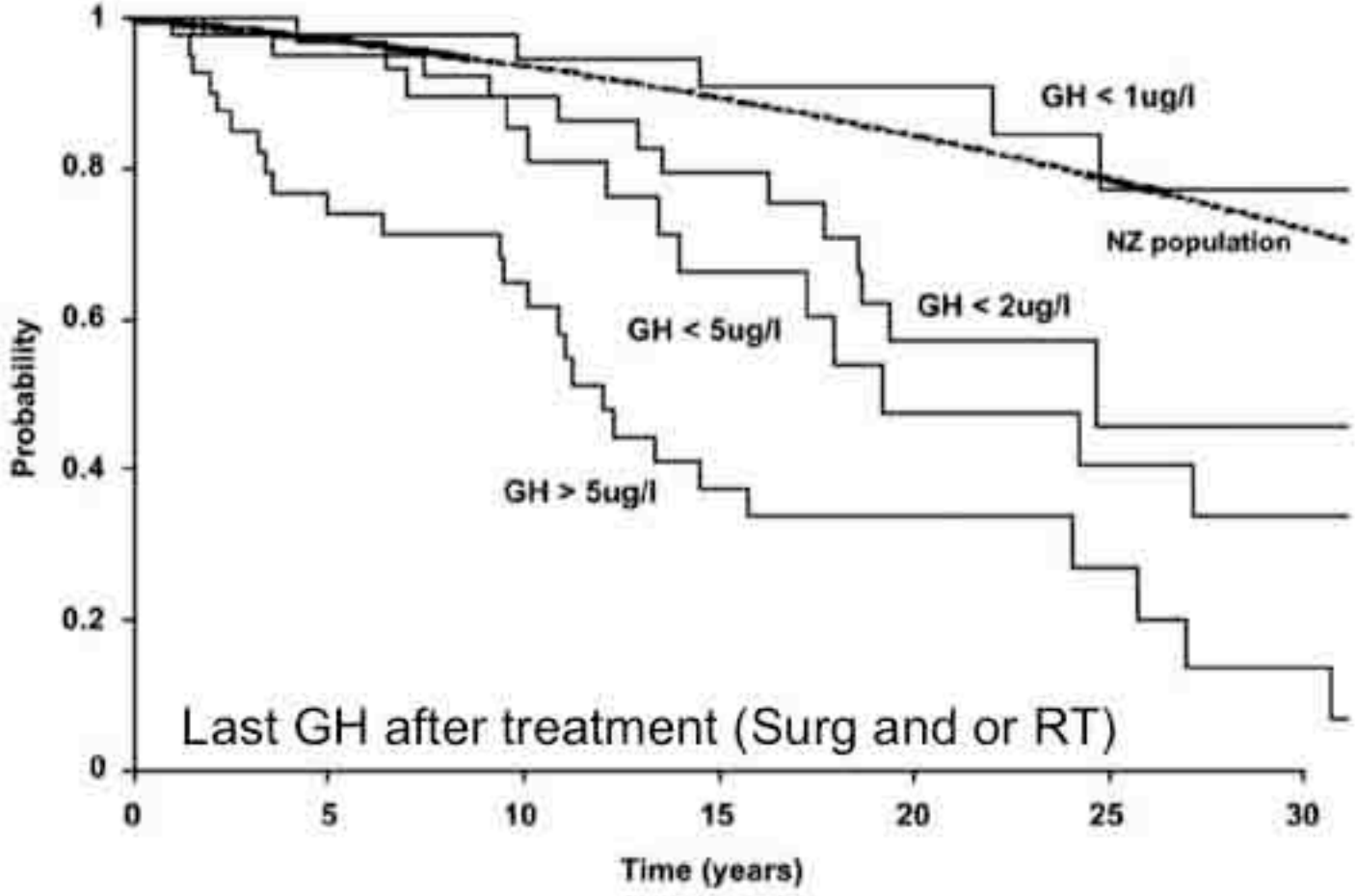
Predictors of morbidity and mortality in acromegaly: an Italian survey

	Number of patients (M/F)	Diabetes mellitus (%)	Hypertension (%)	Disease control (%)	SMR (95% CI)
UK	419 (178/241)	–	–	46	1.26 (1.03–1.54)
Spagna	1219 (478/741)	37.6	39.1	31	–
NZ	208 (125/83)	29.7	54.4	–	2.70 (2.10–3.50)
Finlandia	334 (161/173)	–	–	55	1.16 (0.85–1.54)
Belgio	418 (213/205)	25.3	39.4	49	1.39 (0.96–2.03)
Germania	1485 (677/808)	–	–	–	–
Italia	1512 (624/888)	16	33	65	1.13 (0.87–1.46)

Arosio et al, EJE 2012

Factors Influencing Mortality in Acromegaly

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

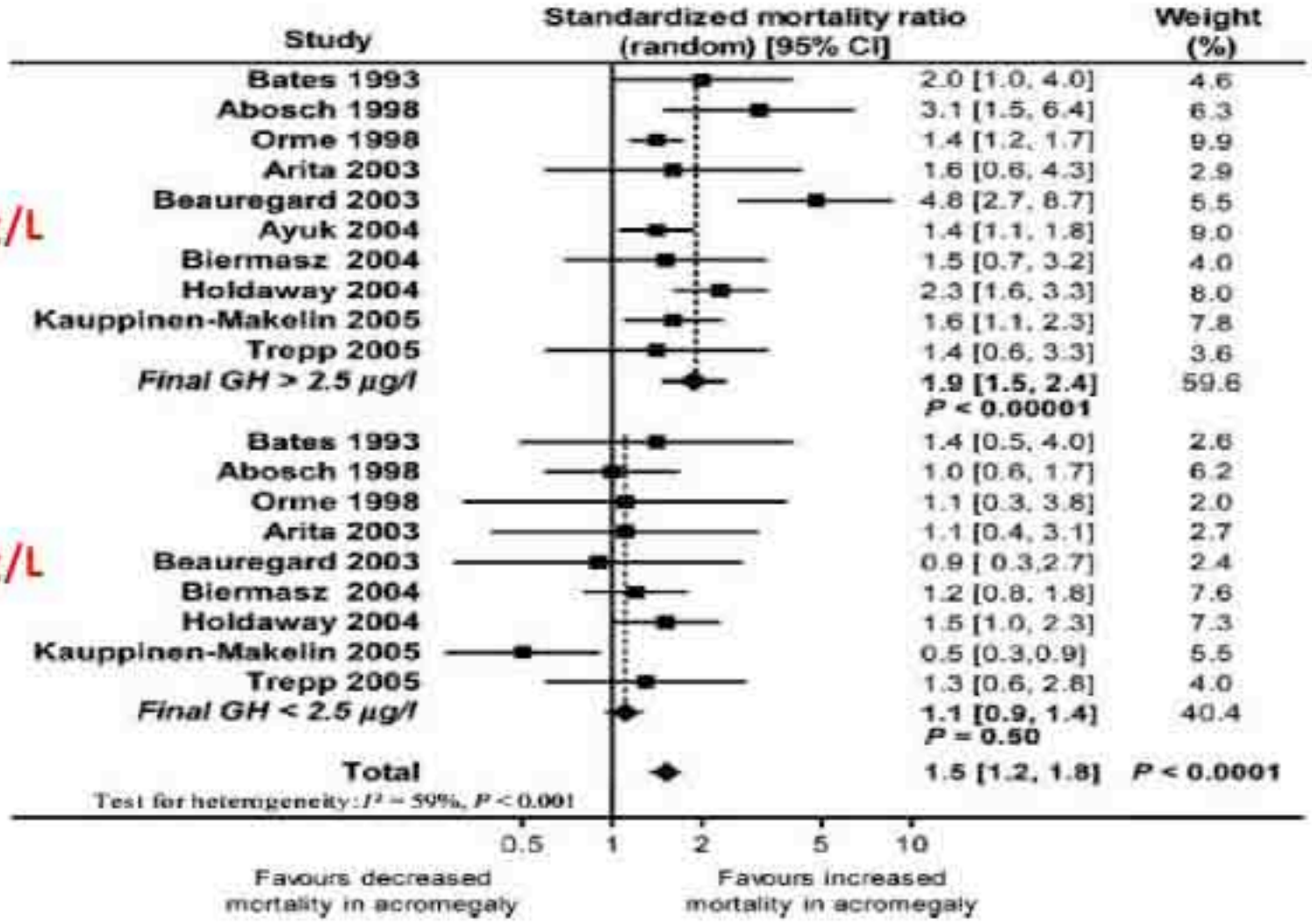


Holdaway et al, EJE 2008

Factors Influencing Mortality in Acromegaly

GH > 2.5 ug/L

GH < 2.5 ug/L



Holdaway et al, EJE 2008

Factors Influencing Mortality in Acromegaly

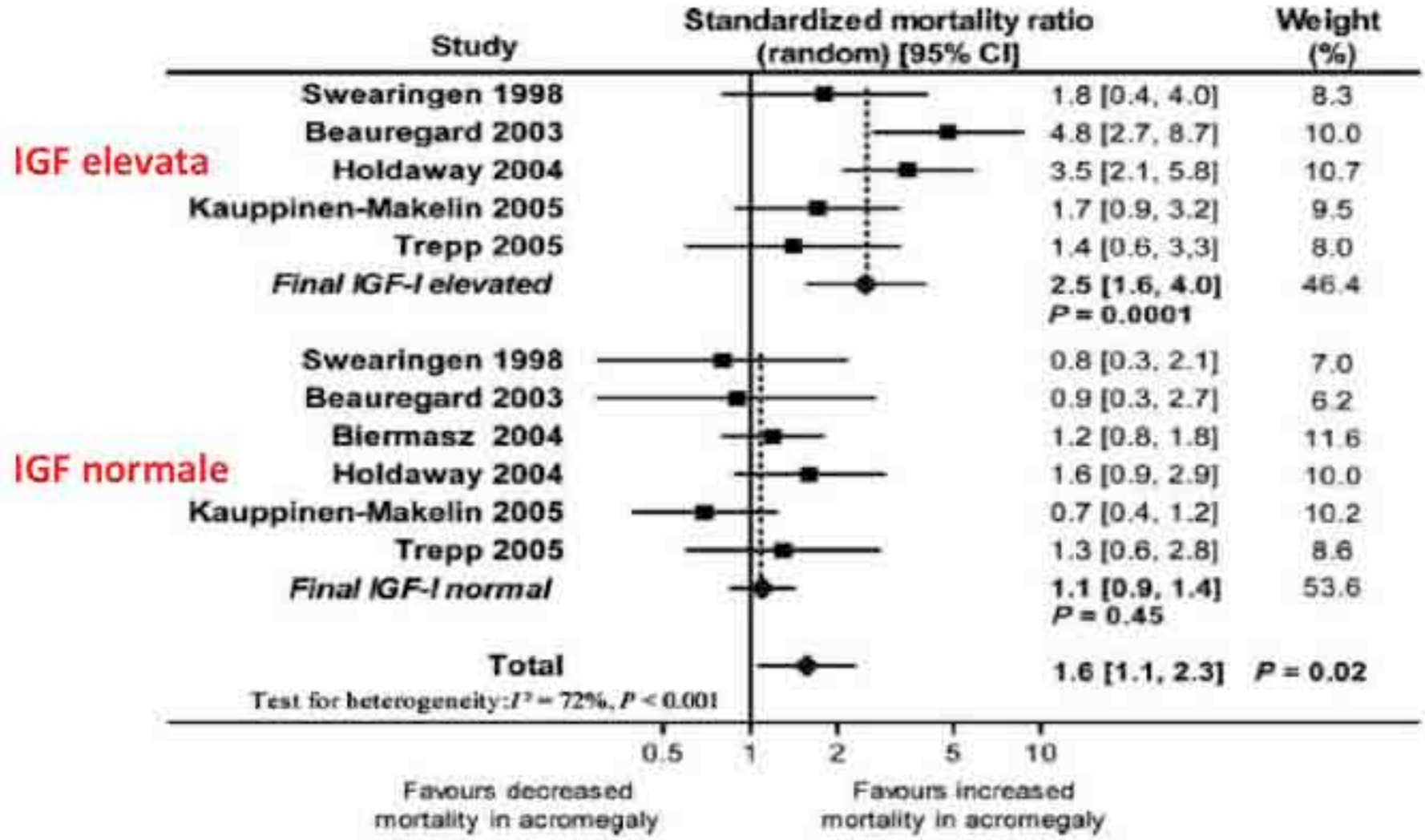


Table 2. Value of each symptom: multivariate logistic model

Variable	OR	95% CI	Ln(OR)	Score
Type 2/secondary diabetes	2·1	1·0–4·5	0·747	1
Hyperhidrosis	3·6	1·9–6·8	1·276	2
Thyroid hyperplasia	8·7	4·7–16·0	2·164	3
Carpal tunnel syndrome	2·3	0·9–5·8	0·853	1
Spaced teeth	15·7	6·7–36·7	2·752	4
Colorectal polyps	7·3	3·1–17·1	1·983	3

Prencipe et al, CEN 2017

Acromegaly: An Endocrine Society Clinical Practice Guideline

2.1 We suggest evaluating all patients presenting with acromegaly for associated comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnea. (2|⊕⊕◯◯)

2.2 We also recommend that such comorbidities be longitudinally monitored and rigorously managed. (Ungraded recommendation)

2.5 We recommend assessing for hypopituitarism and replacing hormone deficits. (1|⊕⊕⊕◯)

Katznelson et al, JCEM 2014

Predictors of morbidity and mortality in acromegaly: an Italian survey

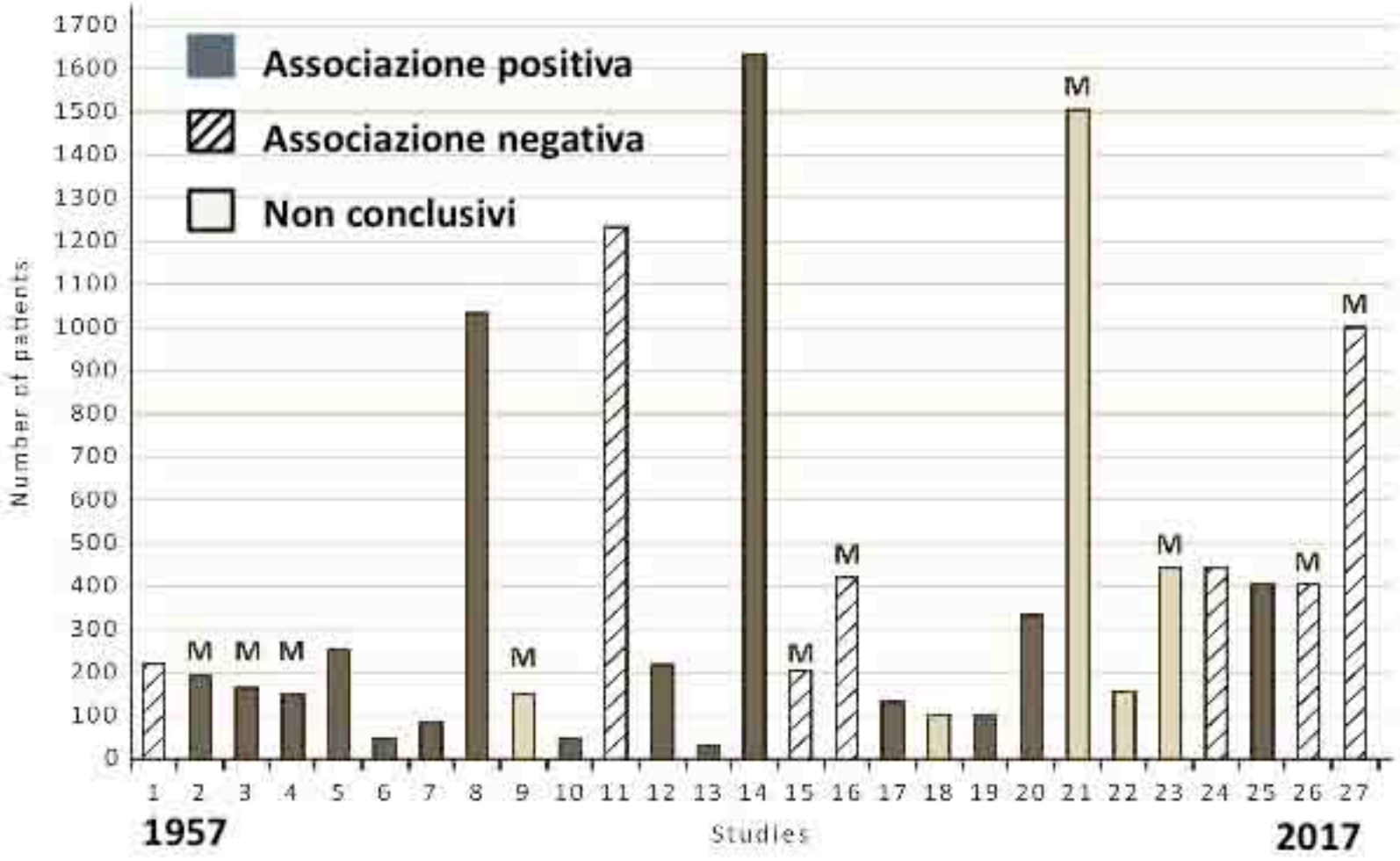
Causes of death	61/1512
Malignant tumors	36%
Cardiovascular	27.9%
Cerebrovascular	9.8%

Predittori indipendenti di mortalità:

- ✓ Età avanzata
- ✓ GH ultimo follow-up
- ✓ IGF alla diagnosi
- ✓ Neoplasie
- ✓ Radioterapia

Arosio et al, EJE 2012

Rischio oncologico ?



Terzolo et al, Endocrine-Related Cancer 2017

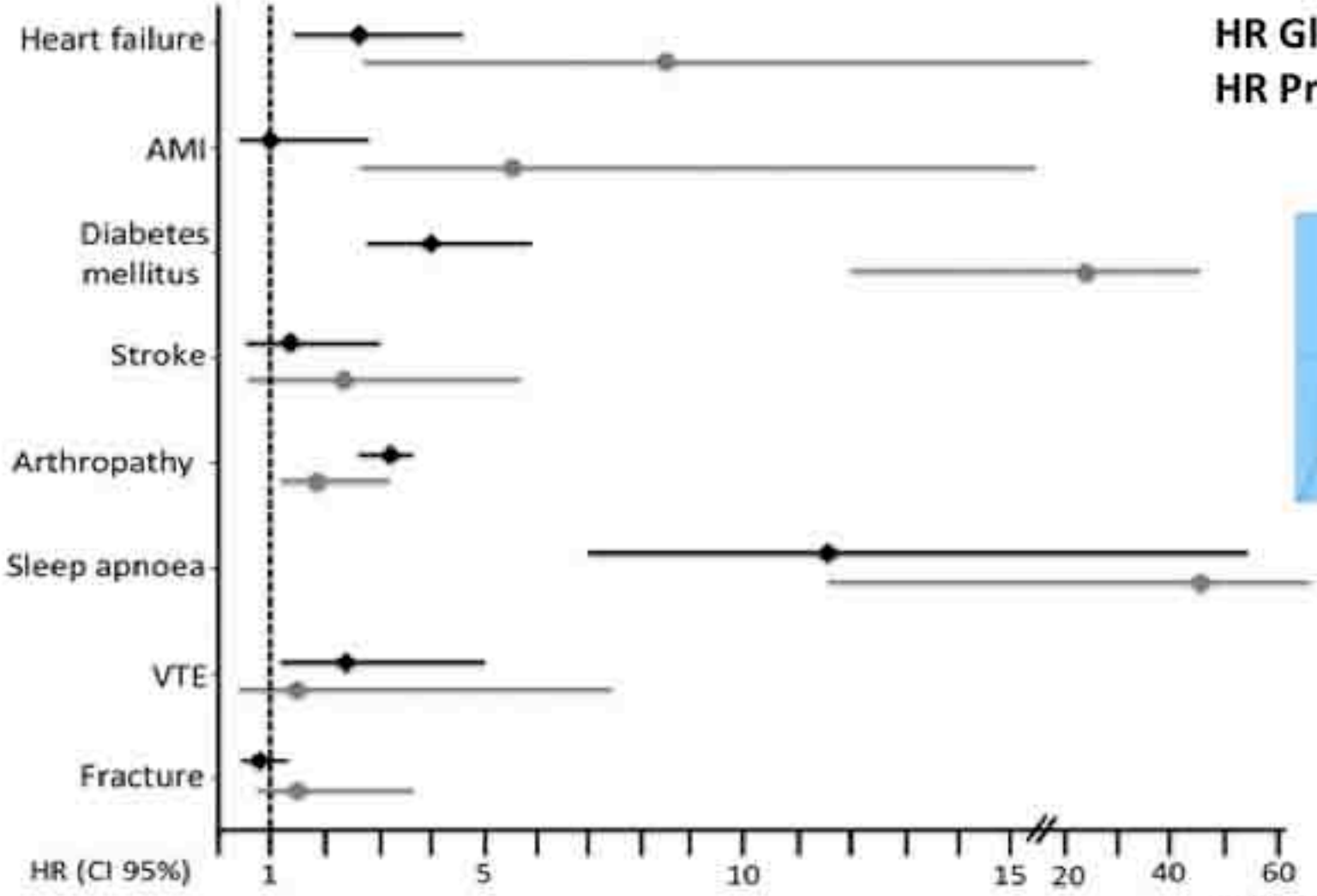
Acromegaly is associated with increased cancer risk: a survey in Italy

OR Età P < 0.001, Storia familiare P = 0.04

Cancer type	Observed	Expected	SIR	95% CI	*P* value
Female					
All malignancies	72	47.6	1.51	1.2–1.91	<0.001
Breast cancer	22	16.8	1.31	0.86–1.99	0.21
Colorectal cancer	12	6.4	1.86	1.06–3.28	0.03
Thyroid cancer	8	2.5	3.22	1.61–6.44	0.01
Male					
All malignancies	52	40.2	1.29	1.0–1.7	0.06
Colorectal cancer	8	5.6	1.44	0.72–2.88	0.31
Kidney cancer	7	1.9	3.73	1.78–7.83	<0.001
Thyroid cancer	5	0.8	6.51	2.71–15.65	<0.001
Overall					
Colorectal cancer	20	12	1.67	1.07–2.58	0.022
Kidney cancer	10	3.5	2.87	1.55–5.34	<0.001
Thyroid cancer	13	3.3	3.99	2.32–6.87	<0.001

Terzolo et al, Endocrine-Related Cancer 2017

Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study



HR Globale

HR Pre-diagnosi

Dal et al, EJE 2016

La diagnosi biochimica

IGF-1	521% ULNR	Upper Limit Normal Range
GH	36	ng/ml
Prolattina	27.3	4 - 15 ng/ml
Cortisolo PI	5.3	6 – 22 mcg/dL
Cortisolo Dopo ACTH Test	8-18-14	> 18 mcg/dL
ACTH	14	7-63 pg/ml
fT4	9.7	7-18 ng/dl
TSH	1.8	0.5-4.78 mU/ml
Glicemia	107	70-110 mg/dl
HbA1c	5.7	4.8-6 %

Andrea Lania

UO. Endocrinologia & Pituitary Unit
Istituto Clinico Humanitas
Dipartimento di Scienze Biomediche
Humanitas University

HUMANITAS UNIVERSITY

European Reference Network

ENETS

GH e IGF-I
Quale ricadute cliniche…

ACROMEGALIA

Diagnosi

Valutazione guarigione /remissione

Valutazione controllo attività

SPECIAL FEATURE
CLINICAL PRACTICE GUIDELINE

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Edward R. Laws, Jr., Shlomo Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass

1.3 We recommend measuring serum IGF-1 to rule out acromegaly in a patient with a pituitary mass. (1|⊕⊕⊕◯)

1.4 We recommend against relying on the use of random GH levels to diagnose acromegaly. (1|⊕⊕⊕◯)

episodic GH secretion from both normal and adenomatous pituitaries

the commercially available immunoassays produce heterogeneous values, and results from one laboratory cannot be compared with findings from another

SPECIAL FEATURE
Clinical Practice Guideline

Acromegaly: An Endocrine Society Clinical Practice Guideline

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1.0 Diagnosis

1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features. (1|⊕⊕⊕◯)

1.2 We suggest the measurement of IGF-1 in patients without the typical manifestations of acromegaly, but who have several of these associated conditions: sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension. (2|⊕⊕◯◯)

IGF-I…?

It is a marker of integrated GH secretion

IGF-1 levels exhibit a log-linear relationship with GH levels

Circulating IGF-1 half-life is approximately 15 hours, and serum levels are relatively stable

- Genetica
- Età
- Sesso
- Ritmo circadiano
- Nutrizione
- IGFBPs
- Estrogeni
- Androgeni
- Tiroxina
- Cortisolo

Specifici range di normalità

Stabilire range di riferimento età-correlati è indispensabile

PS. Non esistono range di riferimento BMI-dipendenti

Non esistono differenze sostanziali sesso-dipendenti (ad eccezione di donne post menopausali in HRT)

Bidlingmaier et al Reference Intervals for IGF-I J Clin Endocrinol Metab, May 2014, 99(5):1712-1721

Brabant et et al Hormone Research, 2003, 60:53-60

Roma

ITALIAN CHAPTER

Table 1
Prevalence of normal IGF-I values measured with the four immunoassays in 52 sera from 40 treated acromegalic patients

Reference range	Nichols assay	Immunotech assay	DiaSorin assay	Schering assay
Manufacturer (age-matched controls)	30/52 (57.7%)	19/52 (36.5%) $\chi^2=4.67$; $p=0.0307$	16/52 (30.8%) $\chi^2=7.64$; $p=0.0057$	15/52 (28.8%) $\chi^2=8.81$; $p=0.003$
	n=1902	*n=125*	*n=258*	*n=233*
Manufacturer (age- and sex-matched controls)	30/52 (57.6%) *n=1169 (men)* *n=733 (women)*			
Normal values on large number of subjects (age-matched controls)		33/52 (63.5%) $\chi^2=0.36$; NS *n=728*	29/52 (55.8%) $\chi^2=0.04$; NS *n=728*	
Normal values on large number of subjects (age- and sex-matched controls)		32/52 (61.5%) $\chi^2=0.16$; NS *n=360 (men)* *n=368 (women)*	28/52 (53.9%) $\chi^2=0.16$; NS *n=360 (men)* *n=368 (women)*	

Acromegalia: buon controllo

Il numero di soggetti utilizzati per stabilire i limiti di normalità è un parametro molto importante per la performance di un metodo

Per una corretta interpretazione dei risultati i valori di normalità devono essere stabiliti sulla base di un ampio gruppo di controllo

Clinica Chimica Acta 373 (2006) 176–179

Quali fattori influenzano la determinazione dei livelli di IGF-I?

- **Modalità di raccolta e conservazione del campione**
- **Entità popolazione di controllo**
- **Anticorpi**
- **BPs (metodi di rimozione)**
- **Standard**

Stabile conservato a -80° (2 aa)
Instabile conservato a -20° (IGF-I proteolisi)

Stabilità 24h **siero** a temperatura ambiente
Instabilità **sangue** a temperatura ambiente

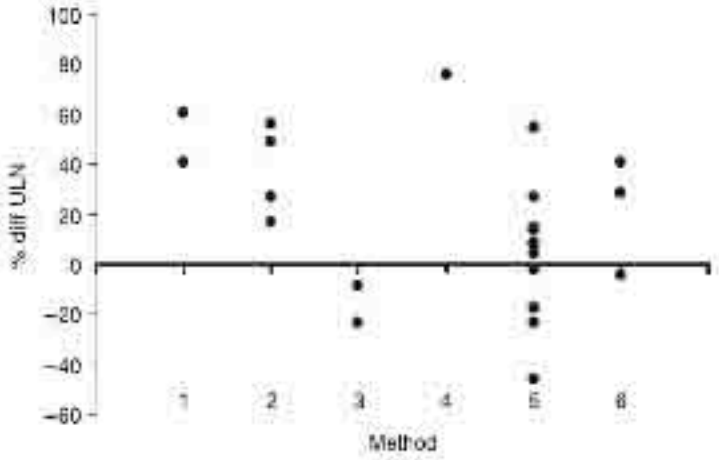
Clinical Endocrinology (2007) 67, 65–70 doi: 10.1111/j.1365-2...

ORIGINAL ARTICLE

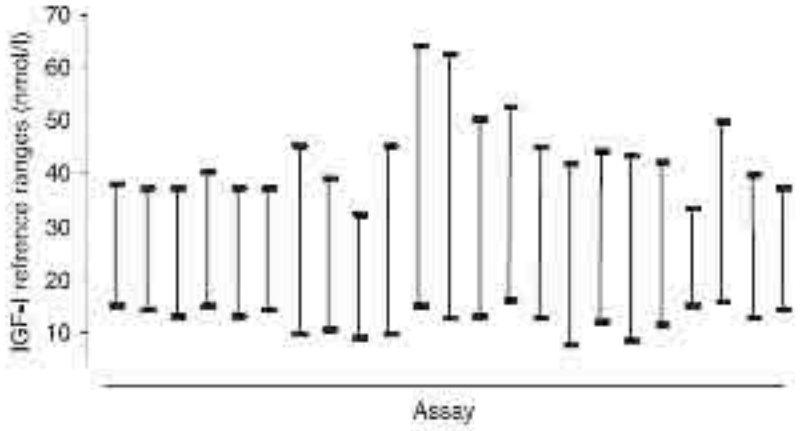
Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice

A. Rakmjar, G. Wark, A. R. Ellis, J. Weor, G. F. Wieringa and P. J. Trainer

No.	Method
1	Immunotech IRMA
2	Wallac Delfia
3	NETRIA IRMA
4	Nichols Allegro IRMA
5	Tosoh AIA
6	Nichols Advantage
7	Nichols ICMA
8	Beckman Access
9	DSL ELISA
10	DPC Immulite
11	DPC Immulite 2000
12	In-house ELISA
13	DiaSorin IRMA
14	In-house IRMA



Differenza % vs ULN di IGF-I in 23 laboratori UK con 6 metodiche differenti



Variabilità del range reference di un singolo campione di IGF-I con diverse metodiche

SPECIAL FEATURE
Clinical Practice Guideline

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Edward R. Laws, Jr, Shlomo Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass

1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 μg/L following documented hyperglycemia during an oral glucose load. (1|⊕⊕⊕◯)

Lo screening delle complicanze

CV OO: normale

Ecocardiogramma: nei limiti

Ecografia addome: cisti ovarica, utero fibromatoso

Ecografia collo: normale

Polisonnografia: normale

Colonscopia: normale

2010: il punto della situazione

La terapia: che fare?

Terapia medica

Terapia chirurgica

Che fare?

La terapia

Terapia chirurgica

RIFIUTO

Terapia Farmacologica

Ernesto De Menis

Dipartimento Medicina Clinica 2

Ospedale Montebelluna - AULSS2 - Marca Trevigiana

ernesto.demenis@aulss2.veneto.it

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Ipsen/Pfizer/Novartis/Otsuka/Shire

Obiettivi e Target

1) Tumore

2) Ipersecrezione GH e IGF-I

3) Organi bersaglio

Dopaminergici

- Bromocriptina (os, LAR)
- Quinagolide
- Cabergolina

Analoghi somatostatina

Prima generazione

- -Octreotide (sc. LAR, orale)
- -Lanreotide (LR, Autogel)

Seconda Generazione

- -Pasireotide (sc, LAR)

Antagonisti GH

- Pegvisomant

Terapie combinate

DOPAMINERGICI: la storia

BACKGROUND

Liuzzi A., Chiodini PG., Botalla L., Cremascoli G., Silvestrini F.

Inihibitory effect of L-Dopa on GH release in acromegalic patients

J Clin Endocrinol Metabol 1972;35:941-943

Chiodini PG., Liuzzi A., Botalla L., Cremascoli G., Silvestrini F.

Inhibitory effect of dopaminergic stimulation on GH release in acromegaly

J Clin Endocrinol Metabol 1974;38:200-206

STUDI CLINICI

Chiodini PG., Liuzzi A., Botalla L., Oppizzi G., Muller EE., Silvestrini F.

Stable reduction of plasma growth hormone (hGH) levels during chronic administration of 2-Br-alpha-ergocryptine (CB-154) in acromegalic patients

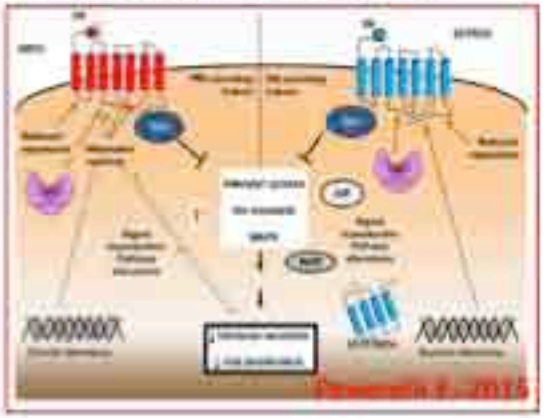
" In 7 acromegalic patients responsive to acute administration of a single dose of 2-Br-alpha-ergocryptine (CB-154) chronic CB-154 (10 mg orally for 30 days) was accompanied by a significant and stable reduction of GH.

In 5 unresponsive patients to acute administration, no appreciable variation in hGH levels was present after 30 days of treatment.

These results suggest that 2-Br-alpha-ergocryptine offers a new approach to the medical treatment of acromegaly" *J Clin Endocrinol Metabol 1975;40:705-708*

DOPAMINERGICI

Cabergolina: Off-label



SELETTIVITA' per D2R
EMIVITA PLASMATICA
EMIVITA TISSUTALE

EFFICACIA superiore
TOLLERABILITA' migliore
COMPLIANCE superiore

PRECAUZIONI GENERALI

Grave Insufficienza Epatica

Disturbi Neuropsichiatrici

Gravi Cardiopatie - Arteriopatie

Fistola liquorale

GASTROINTESTINALI
Nausea/Stipsi/Vomito

CARDIOVASCOLARI
Ipotensione ortostatica/Reazioni vaso-vagali/Stuffness nasale/Vasospasmo digitale/Aritmie/Infarto miocardico/ valvulopatie/Embolia polmonare

EFFETTI CNS
Cefalea/Vertigini/Testa leggera

NEUROPSICHICI
Insonnia/Sonnolenza/Confusione/ Alterazioni umore/Allucinazioni/Psicosi

VARI : Fibrosi

INIZIO TERAPIA

Basse dosi (0.25 mg)

Somministrazione serale

INCREMENTO DOSE

Graduale (0.25 mg week)

DOSE MASSIMALE

0.5 mg/die

DOPAMINERGICI

SECREZIONE ORMONALE

NORMALIZZAZIONE IGF-I

-Valori iniziali di GH/IGF-I

-Iperprolattinemia ?

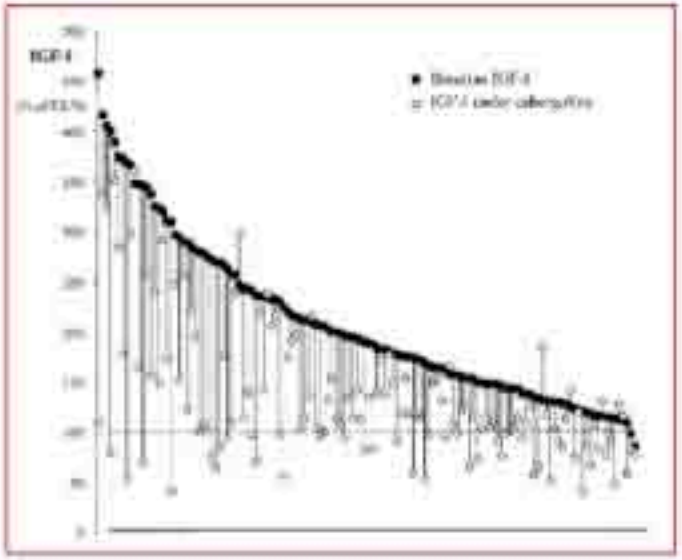
- Dose

-Espressione recettori D2

SHRINKAGE MASSA

IGF-I basale	Normale IGF-I
< 750 ng/mL	53%
>750 ng/mL	17%

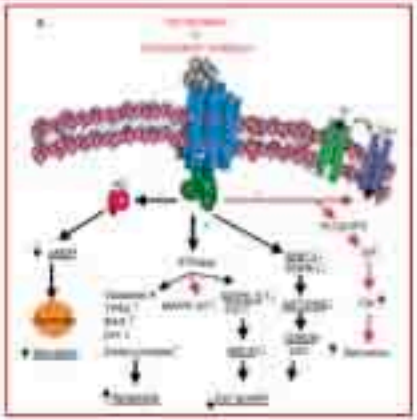
GH basale	Normale IGF-I
< 20 ng/mL	48%
>20 ng/mL	12%

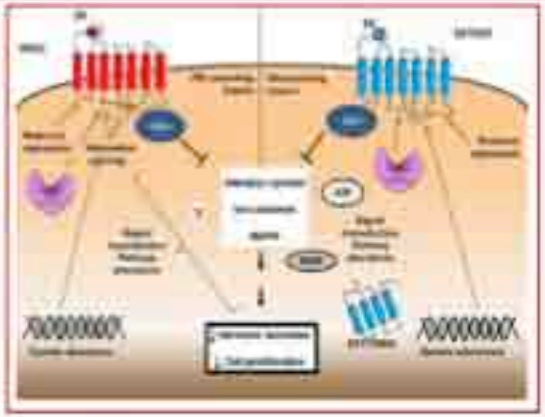


Sandret,, J Clin Endocrinol Metabol 2011

Abs, J Clin Endocrinol Metabol 1998

ANALOGHI SOMATOSTATINA (SSA)





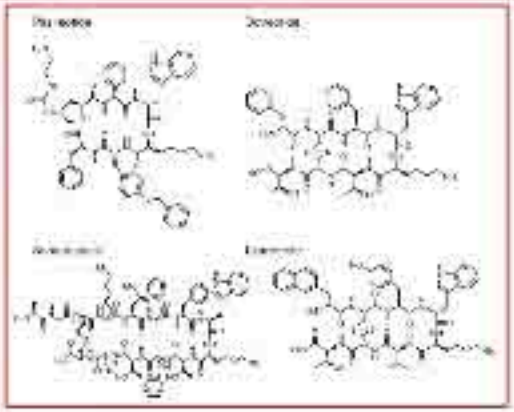


Table 1 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide, and lanreotide to the five human sst[1]

Compound	sst_1	sst_2	sst_3	sst_4	sst_5
Somatostatin (SRIF-14)	0.93 ± 0.12	0.15 ± 0.2	0.56 ± 0.17	1.50 ± 0.4	0.29 ± 0.04
Pasireotide	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	>1000	0.16 ± 0.01
Octreotide	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	>1000	6.3 ± 1.0
Lanreotide	180 ± 20	0.54 ± 0.08	14 ± 9	230 ± 40	17 ± 5

Octreotide sc

Octreotide LAR: 10-40 mg/28 giorni

Lanreotide SR

Lanreotide Autogel (ATG): 60-120 mg/28-42 giorni

ANALOGHI SOMATOSTATINA (SSA)

GESTIONE TERAPIA

Iniziare con dosi "basse" ed incremento in accordo a GH/IGF dopo 3 mesi

Iniziare con dosi "elevate" ed eventuale riduzione

- Maggiore tollerabilità agli effetti collaterali
- Maggiore rapidità efficacia

EFFETTI COLLATERALI

Locali: addominali (crampi, diarrea, distensione addominali. Malassorbimento), alopecia

Aritmie: bradicardia, QT

Calcolosi colecistica (asintomatica, complicata)

Metabolismo glucidico (ipoglicemia, peggioramento tolleranza glucidica)

ANALOGHI SOMATOSTATINA (SSA)

EFFICACIA CLINICA : SECREZIONE ORMONALE

Studi clinici

Predittività di risposta (risposta a breve termine)

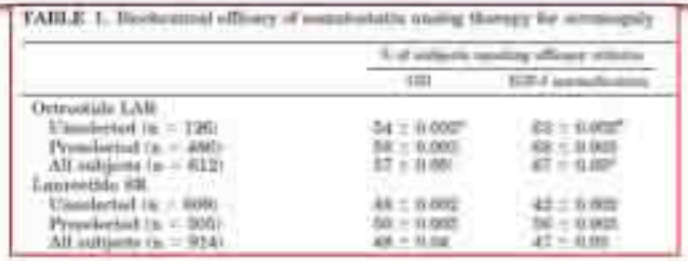
Dose/intervallo di somministrazione

Formulazione farmaceutica del farmaco

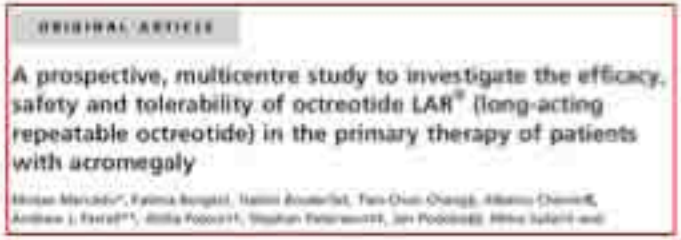
Durata della terapia

Criteri di risposta

- GH < 2.5 ng/ml o GH < 1.0 ng/ml
- IGF-I normale
- GH e IGF-I
- GH/IGF-I discordanze (40% dei pazienti)



JCEM 2005

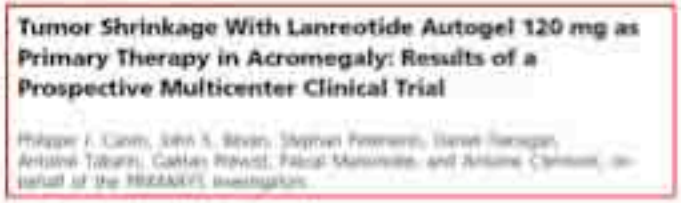


A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR® (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly

Clin End 2007

Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study

Clin End 2009



Tumor Shrinkage With Lanreotide Autogel 120 mg as Primary Therapy in Acromegaly: Results of a Prospective Multicenter Clinical Trial

JCEM 2014

ANALOGHI SOMATOSTATINA (SSA)

EFFICACIA CLINICA: RIDUZIONE MASSA (shrinkage)

50-70% hanno riduzione significativa di massa in primary therapy

Solo 1-3% aumento massa

JCEM 2005

ORIGINAL ARTICLE

A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR® (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly

Clin End 2007

Tumor Shrinkage With Lanreotide Autogel 120 mg as Primary Therapy in Acromegaly: Results of a Prospective Multicenter Clinical Trial

JCEM 2014

FATTORI PREDITTIVI DI RISPOSTA SSA

BASELINE

Età; Forme genetiche

Valori GH/IGF-I; Aspetto Radiologico

Test ad octreotide

DURANTE TERAPIA

Risposta a 3-6 mesi

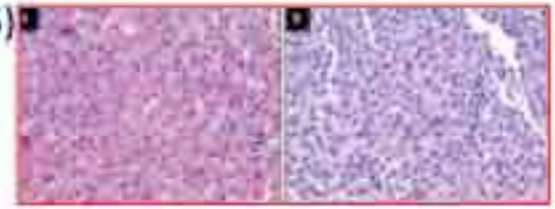
ISTOLOGIA

Sparsely/densely granulated

GSP mut/Espressione recettoriale (sstr2/sstr5)
forme tronche di sstr5/AIP/Ki67

PRECEDENTE INTERVENTO CHIRURGICO

secrezione, massa

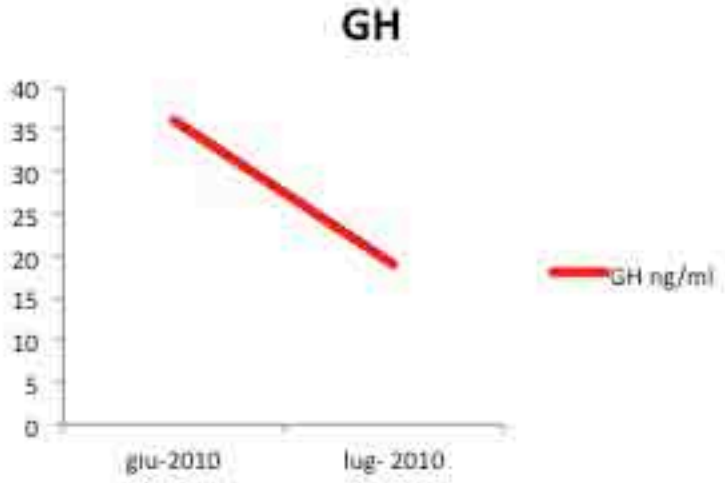


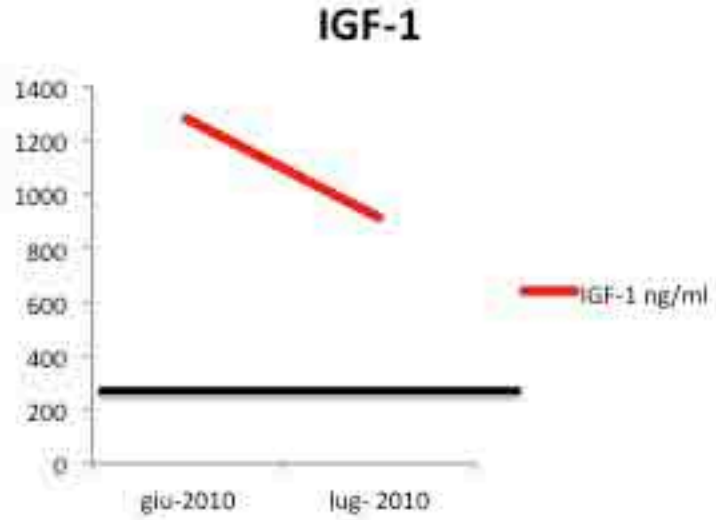
La terapia

Terapia chirurgica — RIFIUTO

Terapia medica — OCTREOTIDE LAR 30 MG/28 GG

Luglio: un mese di terapia medica





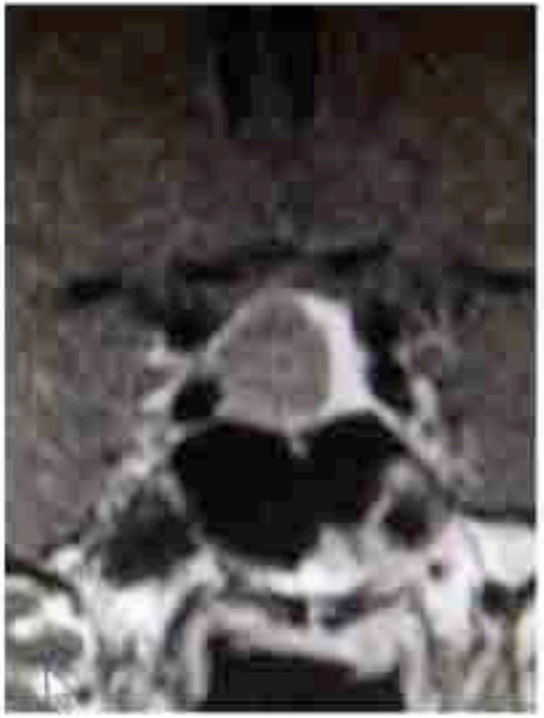
Continua terapia medica
Persiste il rifiuto all'intervento

Settembre 2010

Persistenza di cefalea

GH: 14 ng/ml

Modesta riduzione volumetrica



Che fare?

Aumento dose terapia medica?

Chirurgia?

Che fare?

Che fare?

Aumento dose terapia medica

Chirurgia

22 ottobre 2010: la chirurgia

Intervento complicato da prolasso del diaframma e sanguinamento a carico del seno cavernoso venoso (intervento terminato anzitempo)

EI: Adenoma ipofisario GH+, PRL e ACTH–

Ki67 5%, occasionali mitosi, p53 -

SPECIAL FEATURE
Clinical Practice Guideline

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Eduard R. Laws, Jr., Shlomo Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass

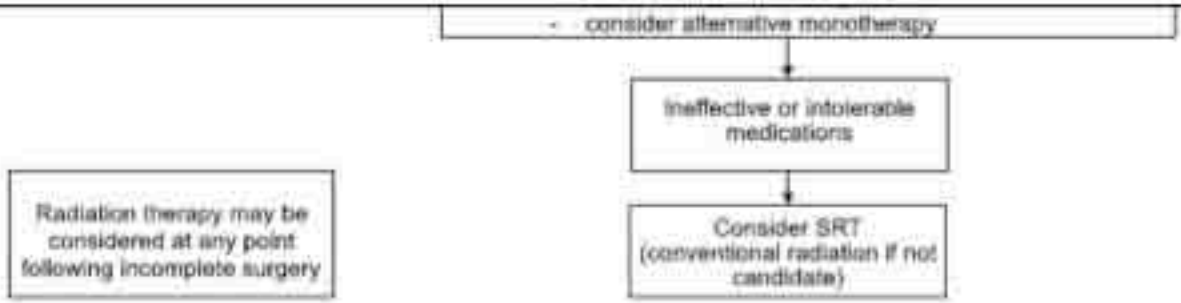
ITALIAN CHAPTER

3.0 Goals of management

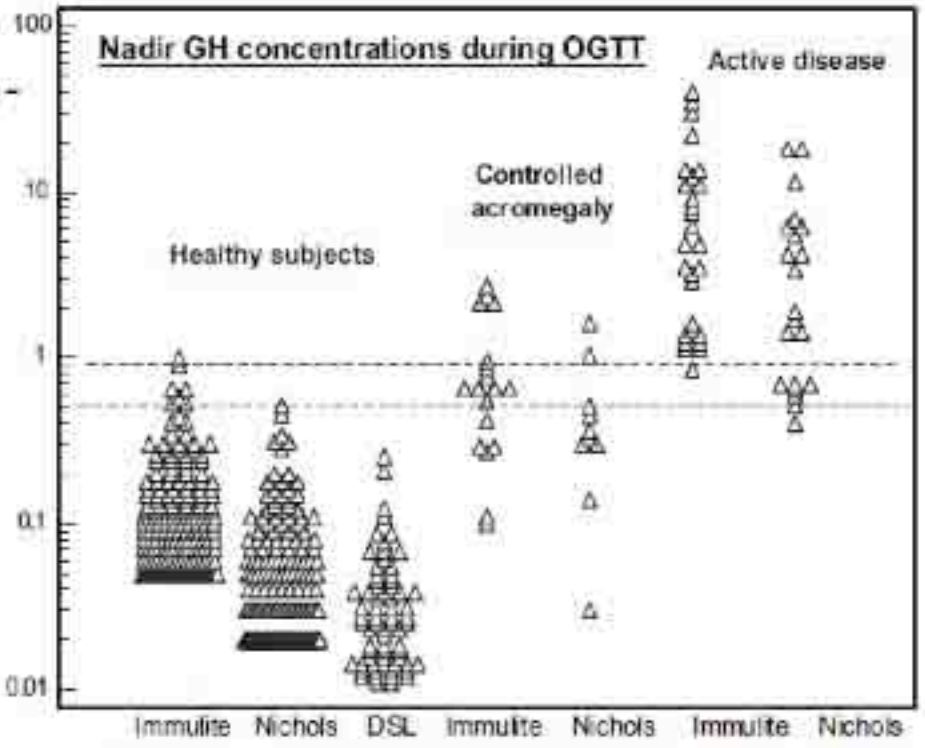
3.1 We suggest a biochemical target goal of an age-normalized serum IGF-1 value, which signifies control of acromegaly. (2|⊕⊕◯◯)

3.2 We suggest using a random GH < 1.0 μg/L as a therapeutic goal, as this correlates with control of acromegaly. (2|⊕◯◯◯)

3.3 We suggest maintaining the same GH and IGF-1 assay in the same patient throughout management. (2|⊕⊕◯◯)



The results obtained with the Immulite assay were, on average, 2.3 fold higher than those obtained with Nichols and 6-fold higher than those obtained with Diagnostic Systems Laboratories.



Different Cut-off limits

Immulite: 1 mcg/L

Nichols: 0.5 mcg/L

Nadir GH levels were significantly higher in females than in males (Immulite 2.2 *vs.* 0.73 mcg/liter and 0.16 mcg/liter *vs.* 0.08 mcg/liter, respectively).

Valutazione funzione ipofisaria residua

Thyrotropin deficiency

The biochemical diagnosis is suggested by low serum FT4 levels and inappropriately normal or low basal TSH levels

Gonadotropin deficiency

Women: Menstrual disturbances and amenorrhea with low serum estradiol concentration (<100 pmol/l) and normal or low concentrations of gonadotropins

Men: Central hypogonadism is characterized by low testosterone with low or normal LH and FSH serum concentrations, and impaired spermatogenesis.

Serum testosterone should be measured in the morning given its diurnal rhythmicity

SHBG

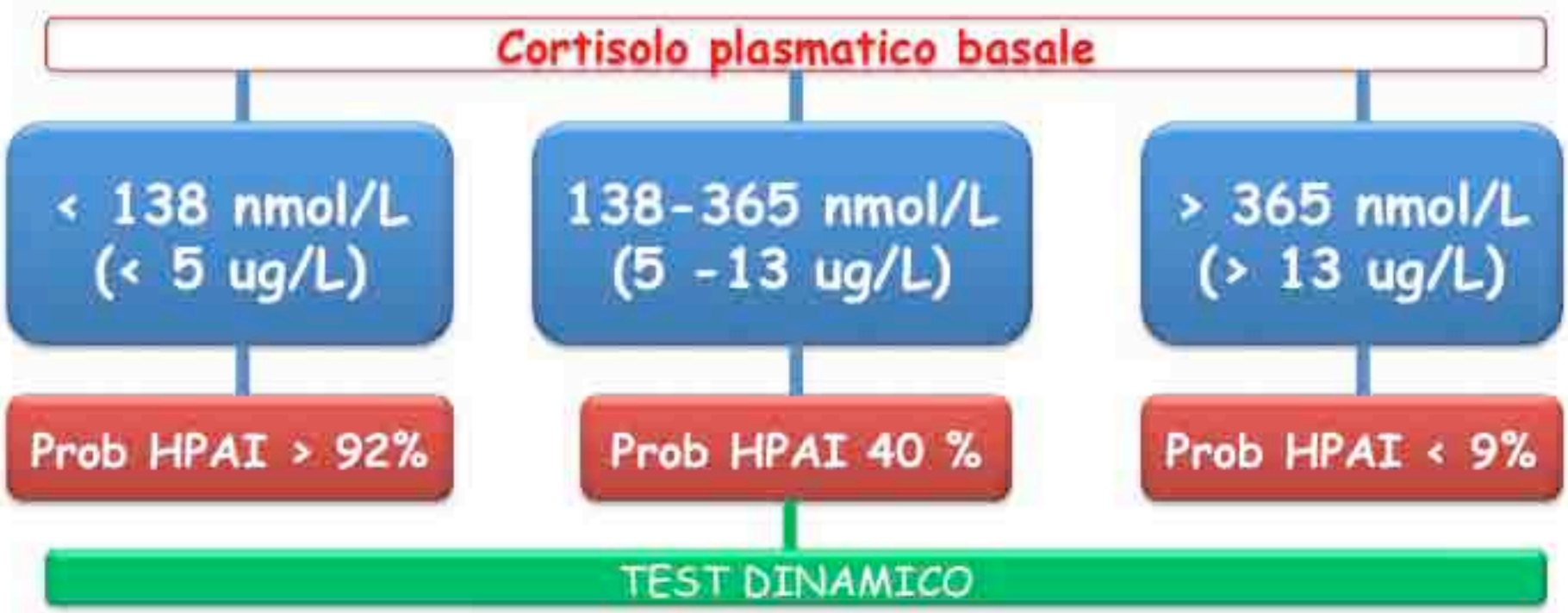
Diagnosi di iposurrenalismo centrale

- **ACTH:**
  - non affidabile per ampia sovrapposizione con soggetti normali
  - problemi di dosaggio per i valori bassi (kit, stabilità campione)

- **CORTISOLO LIBERO URINARIO:**
  - limitata utilità per sovrapposizione con soggetti normali
  - dosaggio poco affidabile per i valori bassi

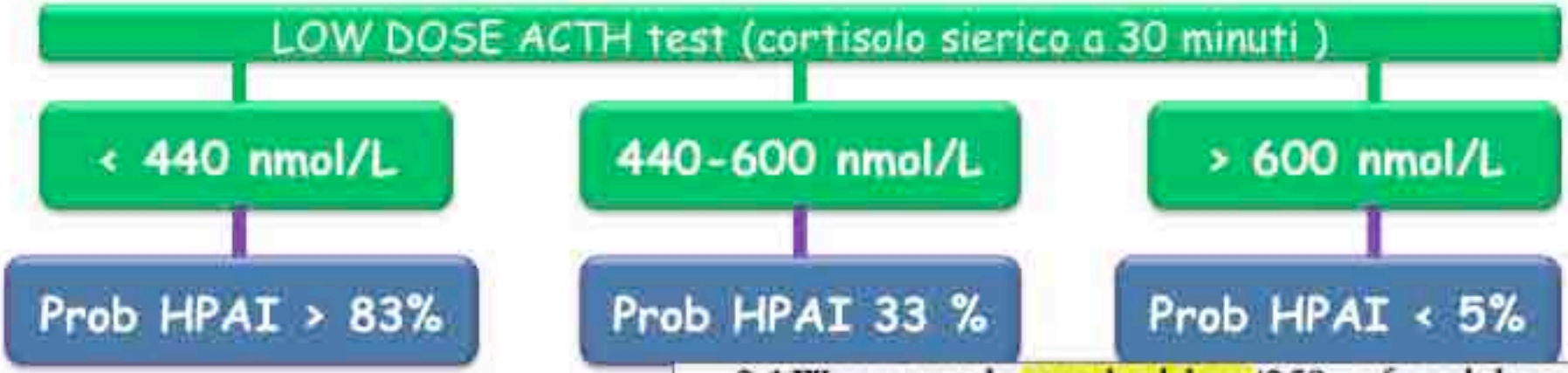
- **CORTISOLO PLASMATICO MATTUTINO:**
  possibile test di screening ma con limiti

Iposurrenalismo centrale



Kazlauskaite, JCEM 2008

Iposurrenalismo centrale



2.1 We suggest the standard dose (250 μg for adults and children ≥2 y of age, 15 μg/kg for infants, and 125 μg for children <2 y of age) iv corticotropin stimulation (30 or 60 min) test over other existing diagnostics tests to establish the diagnosis of adrenal insufficiency. Peak cortisol levels below 500 nmol/L (18 μg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency. (2|⊕⊕◯◯)

2.2 We suggest the low-dose (1 μg) corticotropin test for diagnosis of PAI only when the substance itself is in short supply. (2|⊕⊕◯◯)

2.3 If a corticotropin stimulation test is not feasible, we suggest using a morning cortisol <140 nmol/L (5 μg/dL) in combination with ACTH as a preliminary test suggestive of adrenal insufficiency (until confirmatory testing with corticotropin stimulation is available). (2|⊕◯◯◯)

Kazlauskaite, JCEM 2008

Stadiazione complicanze e follow-up

European Journal of Endocrinology (2012) 167 189–198 ISSN 0804-4643

CLINICAL STUDY

Predictors of morbidity and mortality in acromegaly: an Italian survey

M Arosio, G Reimondo[1], E Malchiodi[2], P Berchialla[3], A Borraccino[1], L De Marinis[4], R Pivonello[5], S Grottoli[6], M Losa[7], S Cannavò[8], F Minuto[9], M Montini[10], M Bondanelli[11], E De Menis[12], C Martini[13], G Angeletti[14], A Velardo[15], A Peri[16], M Faustini-Fustini[17], P Tita[18], F Pigliaru[19], G Borretta[20], C Scaroni[21], N Bazzoni[22], A Bianchi[4], M Appetecchia[23], F Cavagnini[24], G Lombardi[5], E Ghigo[6], P Beck-Peccoz[2], A Colao[5] and M Terzolo[1] for the Italian Study Group of Acromegaly*

95% CI: 1.34–2.70). Main causes of death were vascular diseases and malignancies with similar prevalence. A multivariate analysis showed that older age, higher GH at the last follow-up, higher IGF1 levels at diagnosis, malignancy, and radiotherapy were independent predictors of mortality.

Table 3 Predictors of mortality.

Variables	OR	95% CI	P value
Univariate model			
Age	3.55	2.42–5.21	<0.001
Male sex	1.06	0.63–1.79	NS
Macroadenoma	0.85	0.47–1.54	NS
Delay of diagnosis	1.23	0.95–1.63	NS
GH at diagnosis	1.02	1.00–1.04	NS
IGF1 at diagnosis (SDS)	1.12	1.00–1.25	0.05
GH at FU	1.03	1.00–1.05	0.05
IGF1 at FU (SDS)	0.99	0.82–1.21	NS
Malignancy	11.98	6.95–20.64	<0.001
Diabetes	1.09	1.02–3.51	0.04
Hypertension	2.29	1.37–3.83	0.002
Radiotherapy	2.35	1.36–4.09	0.002
Hypoadrenalism	0.51	0.07–3.79	NS
Hypogonadism	1.15	0.55–2.41	NS
No. of therapies	0.51	0.27–0.99	NS
Smoking	1.44	0.72–2.85	NS
Multivariate model			
Age	4.56	2.62–7.99	<0.001
IGF1 at diagnosis (SDS)	1.14	1.01–0.25	0.04
GH at FU	1.06	1.03–1.10	<0.001
Malignancy	7.26	3.54–14.86	<0.001
Diabetes	0.67	0.37–2.06	NS
Hypertension	0.81	0.40–1.65	NS
Radiotherapy	4.32	1.97–9.45	<0.001

	Number of patients (M/F)	Age at diagnosis mean (M/F)	Macro-adenomas (%)	Diabetes mellitus (%)	Hypertension (%)	Disease control (%)	SMR (95% CI)
(9)	419 (178/241)	47	–	–	–	46	1.26 (1.03–1.54)
(19)	1219 (478/741)	45	73	37.6	39.1	51	–
(13)	208 (125/83)	42	84	29.7	54.4	–	2.70 (2.10–3.50)
(11)	334 (161/173)	47.5 (45/48)	67	–	–	55	1.16 (0.85–1.54)
(20)	418 (213/205)	44 (42/46)	79	25.3	39.4	49	1.39 (0.96–2.03)
(21)	1485 (677/808)	44 (41/47)	79	–	–	–	–
Present study	1512 (624/888)	45 (43/47)	70	16	33	65	1.13 (0.87–1.46)

The full hormonal control of the disease, nowadays reached in the majority of patients with modern management, reduces greatly the disease-related mortality.

SPECIAL FEATURE
Clinical Practice Guideline

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Edward R. Laws, Jr, Sébastien Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass

2.0 Presentation and management of comorbidities and mortality risk

2.1 We suggest evaluating all patients presenting with acromegaly for associated comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnea. (2|⊕⊕◯◯)

2.2 We also recommend that such comorbidities be longitudinally monitored and rigorously managed. (Ungraded recommendation)

2.3 We suggest screening for colon neoplasia with colonoscopy at diagnosis. (2|⊕⊕◯◯)

2.4 We suggest a thyroid ultrasound if there is palpable thyroid nodularity. (2|⊕⊕◯◯)

2.5 We recommend assessing for hypopituitarism and replacing hormone deficits. (1|⊕⊕⊕◯)

Pituitary (2013) 16:294–302
DOI 10.1007/s11102-012-0420-x

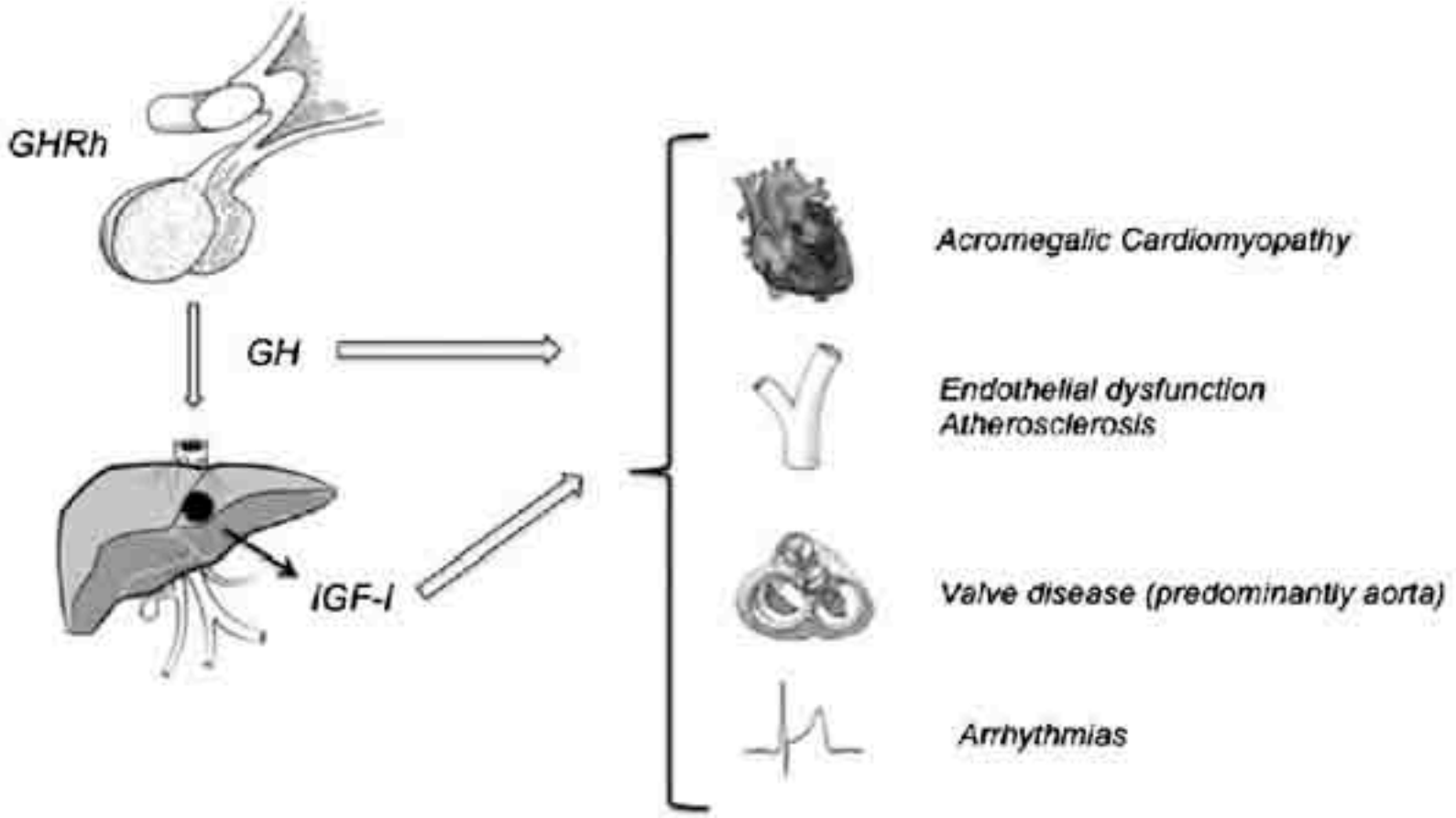
ITALIAN CHAPTER

A consensus on the diagnosis and treatment of acromegaly complications

S. Melmed · F. F. Casanueva · A. Klibanski · M. D. Bronstein · P. Chanson · S. W. Lamberts · C. J. Strasburger · J. A. H. Wass · A. Giustina

Diagnosis	During long-term follow-up
Blood pressure measurement	Every 6 months or when change of treatment (if hypertensive)
Echocardiography	Annually
ECG	Annually
Epworth scale or sleep study	Annually
Echo Doppler of peripheral arterial and venous system	Annually particularly in gigantism
OGTT	Fasting blood glucose every 6 months (particularly in uncontrolled disease and during SRL therapy), HbA_{1c} every 6 months if diabetes present
Total testosterone, SHBG and prolactin (males)	Annually (free testosterone when doubts in interpretation of total testosterone)
LH, FSH, 17β-estradiol and prolactin (females)	Annually (or when pregnancy is desired)
AcroQol	Annually
DEXA	Every 2 years if patient with osteopenia/osteoporosis
Thoracic and lumbar spine X-ray	Every 2–3 years if osteoporosis risk factors, kyphosis or symptoms
Colonoscopy	Every 10 years (more frequently if IGF-I remains persistently elevated or if abnormal colonoscopy or family history of colonic cancer)
Genetic screening for markers of familial acromegaly (if suspicion)	

Effetti del GH sul sistema CV



Mosca et al, Int J Cardiol 2013

Pituitary (2013) 16:391–402
DOI 10.1007/s11102-012-0420-x

ITALIAN CHAPTER

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Growth Hormone, Insulin-Like Growth Factors, and the Skeleton

Andrea Giustina, Gherardo Mazziotti, and Ernesto Canalis

Endocrine Reviews 29(5):535–559

doi: 10.1210/er.2007-0036

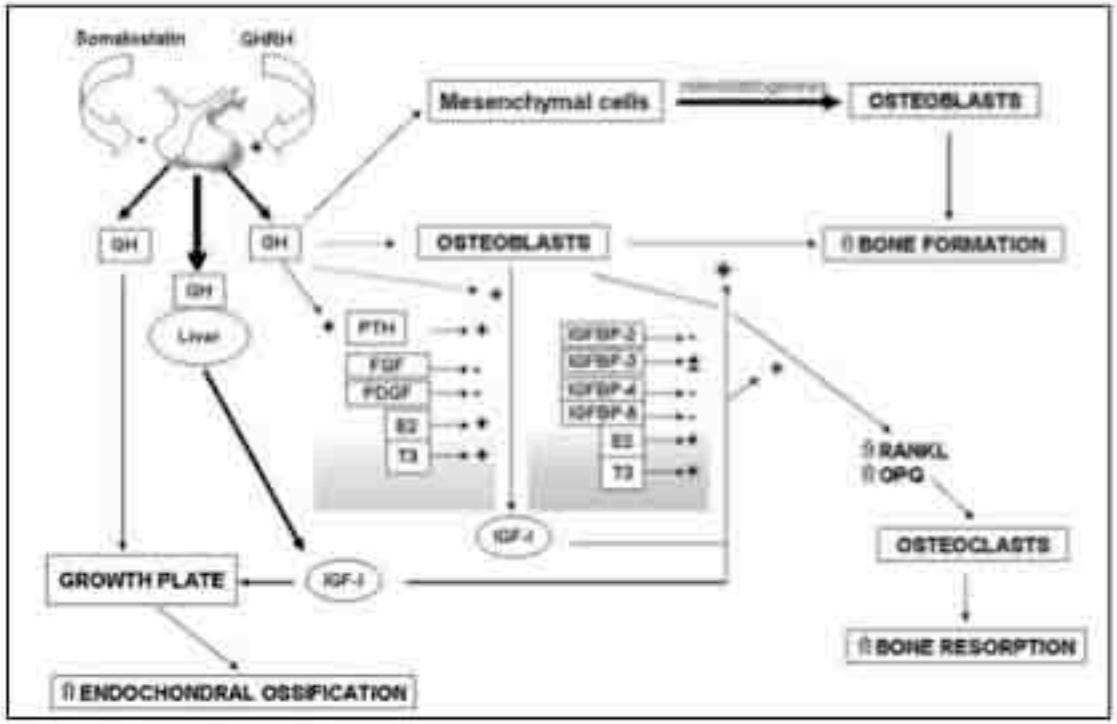

TABLE 1. Effects of GH on bone

Functions	Effects
Growth plate	
Replication of condrocytes	↑ ↑
Endochondral bone formation	↑ ↑
Bone remodeling unit	
Osteoblastogenesis	↑
Proliferation of osteoblasts	↑
Function of mature osteoblasts	↔ ↑
Production of osteoprotegerin	↑
Production of RANK-L	↔
Calcium metabolism	
Phosphate retention	↑

Effects of GH on bone. ↔ no effect; ↑ minor stimulating effect; ↑ ↑ major stimulating effect.

Progression of acromegalic arthropathy despite long-term biochemical control: a prospective, radiological study

K M J A Claessen[1], S R Ramautar[1], A M Pereira[1], J W A Smit[1], F Roelfsema[1], J A Romijn[1], H M Kroon[2], M Kloppenburg[3] and N R Biermasz[1]

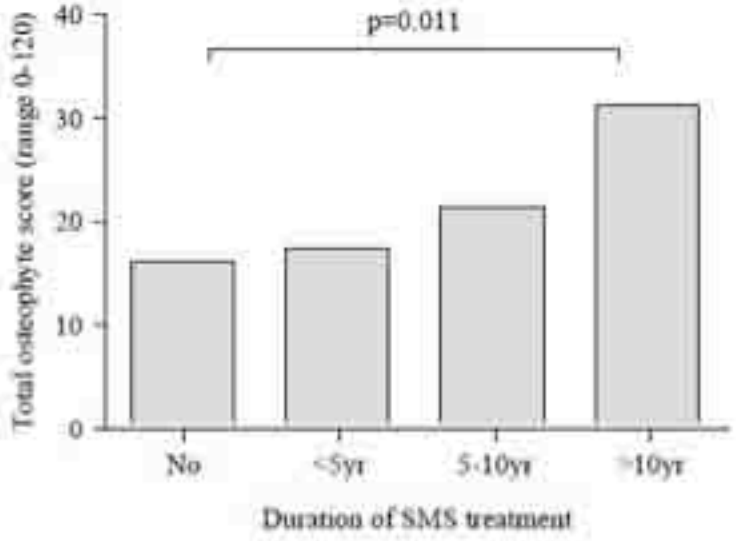

Figure 1 Dose–response relationship between duration of SMS therapy and severity of osteophytosis (at patient level), adjusted for age and baseline IGF1 s.d. levels.

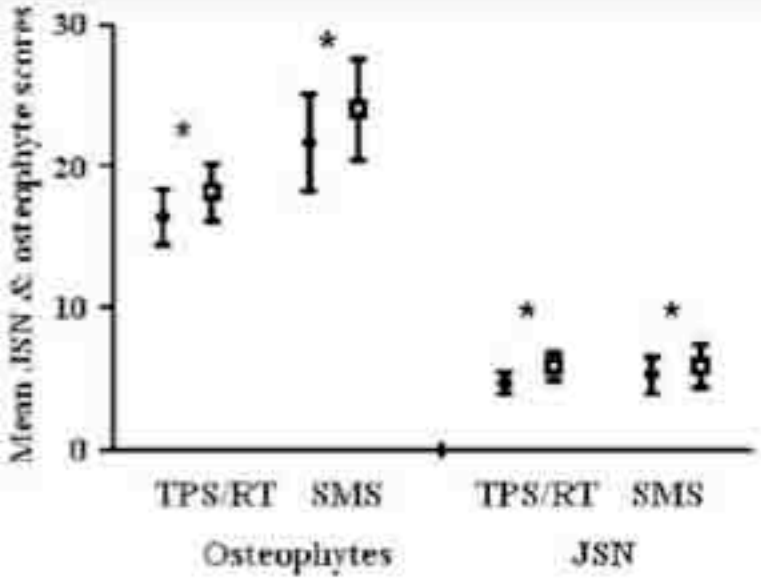

Figure 2 Mean osteophyte and JSN scores at baseline and follow-up, respectively, for acromegaly patients treated by surgery and/or radiotherapy vs patients treated by SMS analogs. Mean osteophyte and JSN scores (±s.e.m.) of both study visits were shown for patients treated by TPS and/or RT vs patients treated by SMS analogs. The left symbol (circle) of each pair represents the baseline OP/JSN score; the right one (square) represents the score after 2.6 years of additional follow-up. TPS, transsphenoidal surgery; RT, radiotherapy; SMS, somatostatin analogs; *$P<0.001$.

Printed in U.S.A.

Endocrine Reviews 26(6):830–848
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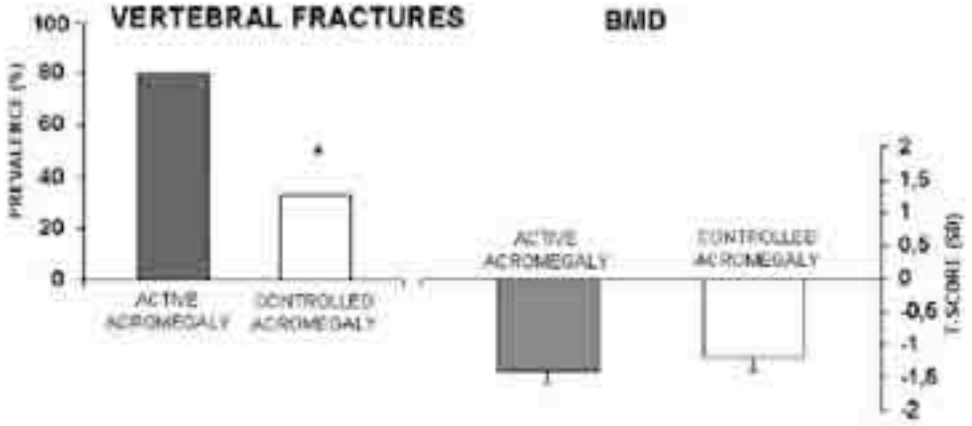
doi: 10.1210/er.2003-0030

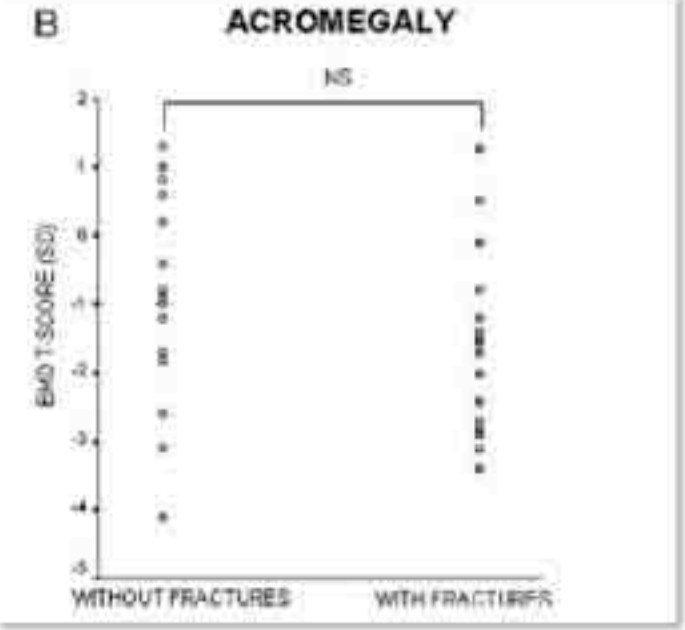
Growth Hormone, Insulin-Like Growth Factors, and the Skeleton

Andrea Giustina, Gherardo Mazziotti, and Ernesto Canalis

Department of Medical and Surgical Sciences (A.G., G.M.), Chair of Internal Medicine, University of Brescia, 25125 Brescia, Italy; Department of Research, Saint Francis Hospital and Medical Center (E.C.), Hartford, Connecticut 06105; and The University of Connecticut School of Medicine (E.C.), Farmington, Connecticut 06030

ITALIAN CHAPTER





Decreased BMD has been reported in acromegaly almost exclusively at the lumbar spine, a site rich in trabecular bone, whereas increases in BMD may be observed in the forearm, a site rich in cortical bone

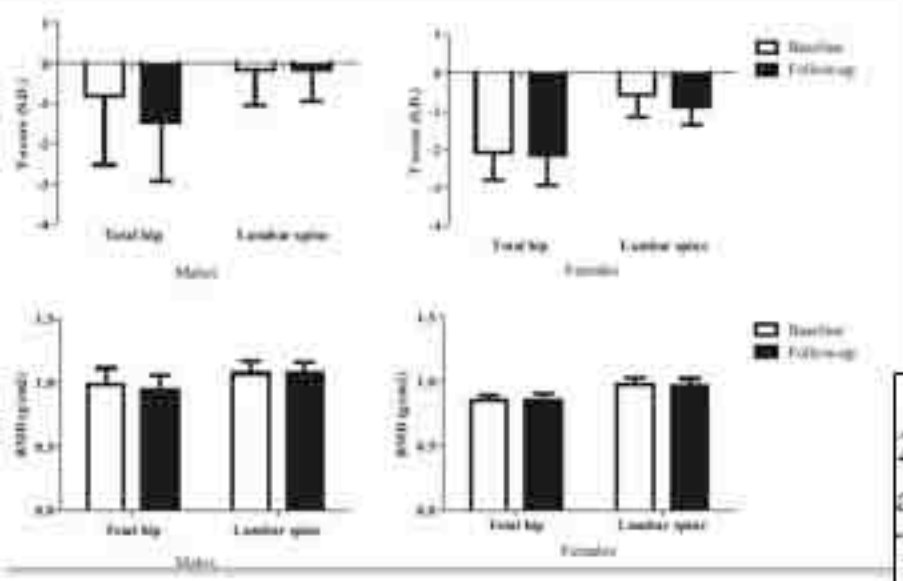
The occurrence of vertebral deformities in acromegaly correlates with the duration of the active disease and with serum levels of IGF-I, but not with BMD, and they are found in patients with normal or minimally decreased BMD

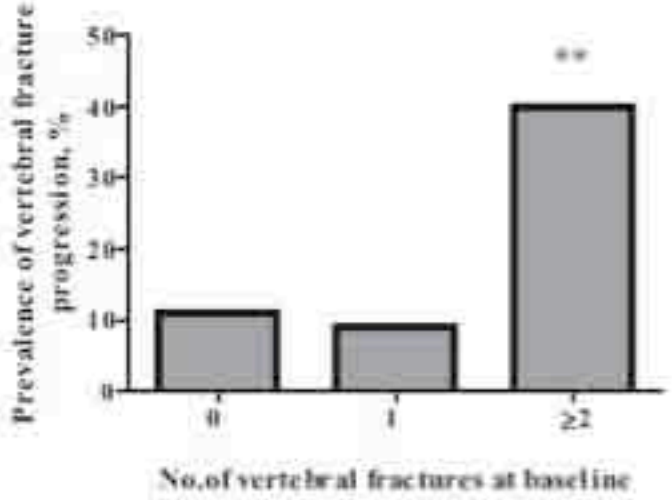
Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study

J Clin Endocrin Metab. First published ahead of print September 30, 2013

R.M.J.A. Claessen[1], H.M. Kroon[2], A.M. Pereira[1], N.M. Appelman-Dijkstra[1], M.I. Ventegan[3], M. Kloppenburg[4], N.A.T. Hamdy[1], N.R. Biermasz[1]

1 Dept. of Endocrinology & Metabolic Diseases and Center for Endocrine Tumours Leiden (LETC), 2 Radiology, 3 Neurosurgery, 4 Rheumatology, Leiden University Medical Center, Leiden, The Netherlands





In conclusion, we demonstrated that VFs progress in 20% of patients with long-term biochemically controlled acromegaly in the absence of osteoporosis or osteopenia. These data suggest persisting poor bone quality possibly related to long-term exposure to high circulating GH levels, although this also remains to be established. Based on our findings and the morbidity and mortality attached to VFs, we recommend the inclusion of VF assessment in the follow-up evaluation of acromegaly patients, also after establishment of biochemical remission, to allow timely therapeutic intervention to prevent further fractures. Fu-

Pituitary (2013) 16:391–402
DOI 10.1007/s11102-012-0420-x

ITALIAN CHAPTER

A consensus on the diagnosis and treatment of acromegaly complications

S. Melmed · F. F. Casanueva · A. Klibanski · M. D. Bronstein · P. Chanson · S. W. Lamberts · C. J. Strasburger · J. A. H. Wass · A. Giustina

Diagnosis	During long-term follow-up
Blood pressure measurement	Every 6 months or when change of treatment (if hypertensive)
Echocardiography	Annually
ECG	Annually
Epworth scale or sleep study	Annually
Echo Doppler of peripheral arterial and venous system	Annually particularly in gigantism
OGTT	Fasting blood glucose every 6 months (particularly in uncontrolled disease and during SRL therapy), HbA_{1c} every 6 months if diabetes present
Total testosterone, SHBG and prolactin (males)	Annually (free testosterone when doubts in interpretation of total testosterone)
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DEXA	Every 2 years if patient with osteopenia/osteoporosis
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Colonoscopy	Every 10 years (more frequently if IGF-1 remains persistently elevated or if abnormal colonoscopy or family history of colonic cancer)
Genetic screening for markers of familial acromegaly (if suspicion)	

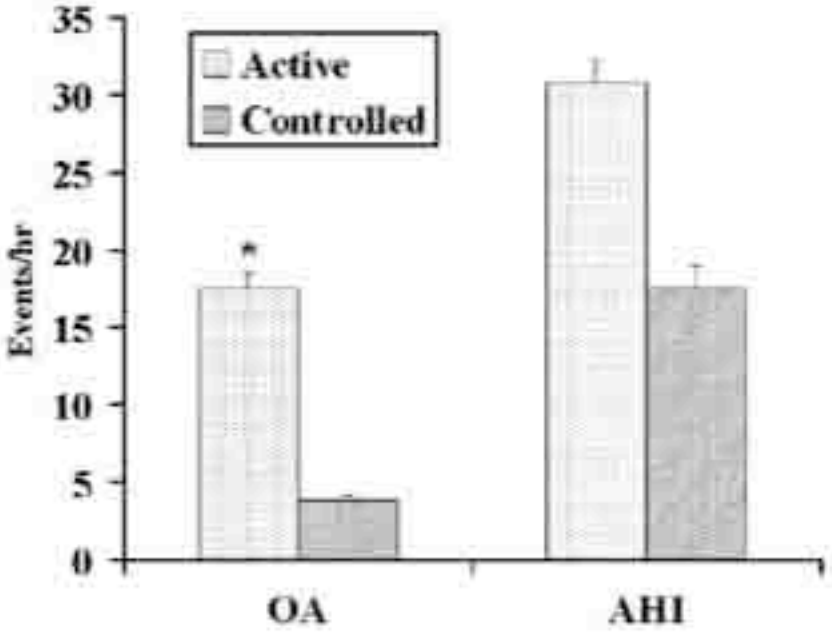
Nell'acromegalia...

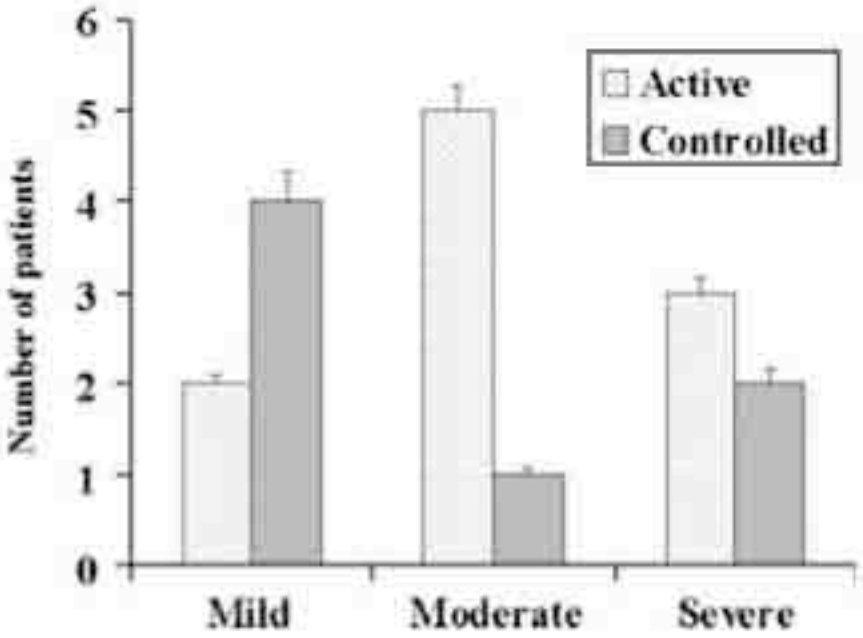
- presente nel 19-81% dei pazienti acromegalici

- cause:
  - fattori anatomici: edema...
  - obesità
  - ipotiroidismo
  - fattori neuromuscolari

Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease

Maria Vittoria Davi*, Luca Dalle Carbonare, Andrea Giustina[1], Marcello Ferrari, Anna Frigo, Vincenzo Lo Cascio and Giuseppe Francia





European Journal of Endocrinology (2008) **159** 533–540

Pituitary (2013) 16:391–402
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Genetic screening for markers of familial acromegaly (if suspicion)	

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ITALIAN CHAPTER

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 Cevenini, Fulvia Daffara, Ezio Gaia, Ennio Martino, Gaetano Lombardi, Alberto Angeli, and Annamaria Colao

TABLE 3. Colonoscopic findings in patients and controls analyzed by demographic and clinical data

Variable	Patients			Controls		
	No neoplasia (n = 170)	Neoplasia (n = 85)	P	No neoplasia (n = 197)	Neoplasia (n = 36)	P
Age (yr)	48.7 ± 12.6[a]	50.3 ± 12.8	NS	49.1 ± 11.8	56.7 ± 11.1	p = 0.001
Male gender	85 (50.0)[b]	30 (46.1)	NS	128 (64.9)	28 (77.8)	p = NS
Family history	5 (2.9)[b]	3 (4.6)	NS	3 (1.5)	1 (2.7)	p = NS
Disease duration (months)	127.3 ± 69.4[a]	150.0 ± 95.1	NS			
Disease activity	141 (82.9)[b]	53 (81.5)	NS			
IGF-I	100.5 ± 105.0[a]	92.4 ± 94.4	NS			

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

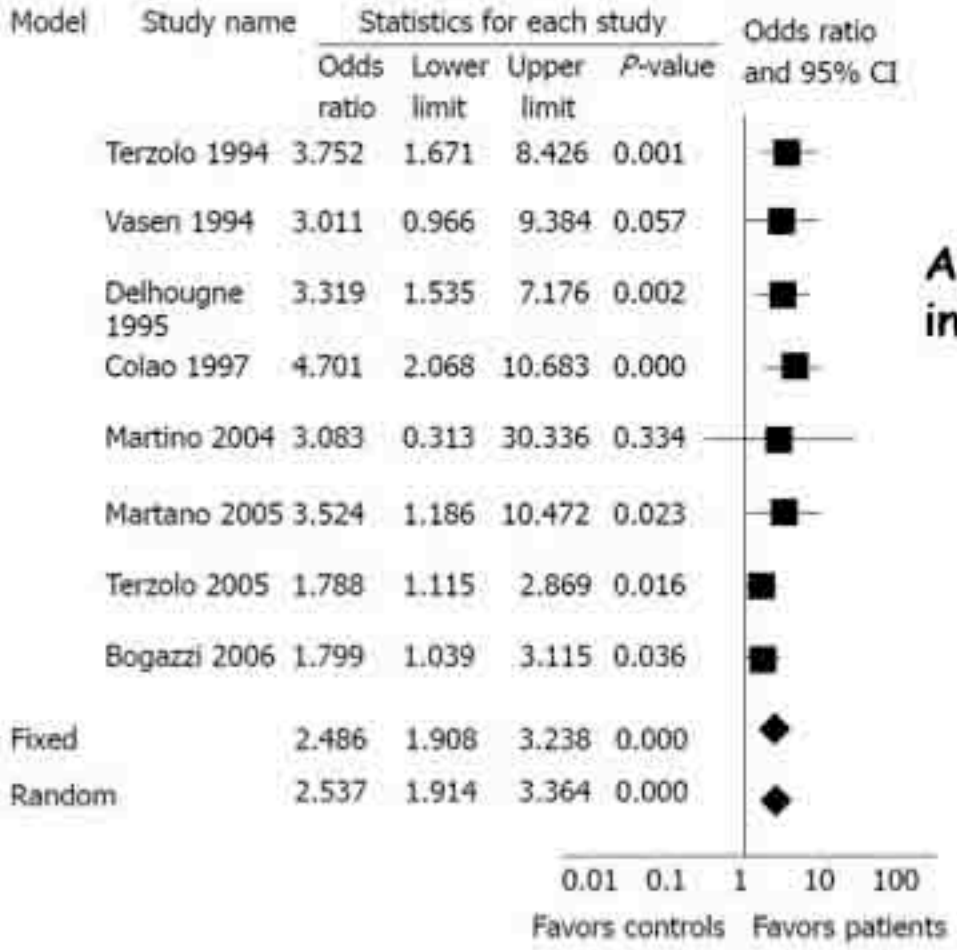
TABLE 6. Colonoscopic findings at the follow-up exam, analyzed by demographic and clinical data

Variable	Patients with new neoplasia (n = 20)	Patients without new neoplasia (n = 101)	P
Age (yr)	57.1 ± 12.0[a]	50.5 ± 12.7	0.03
Male gender	12 (60.0)[b]	48 (47.5)	NS
IGF-I	23.9 ± 67.9[a]	−8.9 ± 68.1	0.01
Previous neoplasia	18 (90)[b]	2 (1.9)	<0.0001

[a] Mean ± SD.

- Moderate increase in colon cancer risk
- Young age
- Severity of the disease potentially correlated with an increased colon cancer risk

Risk of colorectal neoplasm in patients with acromegaly: A meta-analysis



Acromegaly is associated with an increased risk of colorectal neoplasm

Linee guida AACE 2011

- Prima colonscopia → alla diagnosi
- Prima colonscopia negativa ed IGF-I nella norma → colonscopia ogni 10 anni
- Prima colonscopia positiva per polipi e/o IGF-I elevato → colonscopia ogni 5 anni

- LG Confermate dalla Pituitary Society (2013)

Katznelson et al, Endocrine Practice 2011

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Ecografia tiroidea?

Diagnosis	During long-term follow-up
Blood pressure measurement	Every 6 months or when change of treatment (if hypertensive)
Echocardiography	Annually
ECG	Annually
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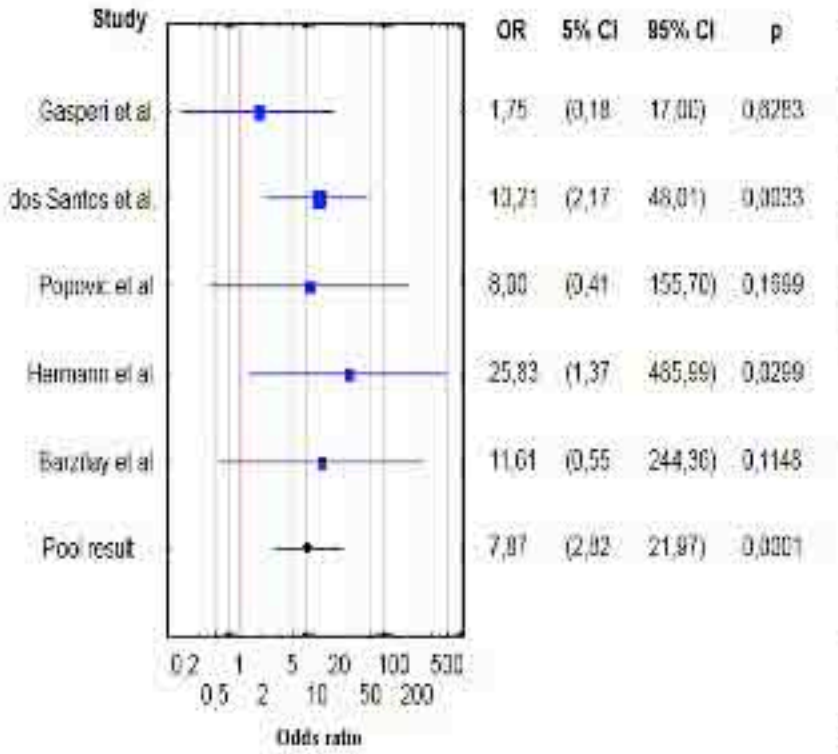
Genetic screening for markers of familial acromegaly (if suspicion)	

OPEN ACCESS Freely available online PLOS

Risk of Thyroid Nodular Disease and Thyroid Cancer in Patients with Acromegaly – Meta-Analysis and Systematic Review

Kosma Wolinski, Agata Czarnywojtek, Marek Ruchala*

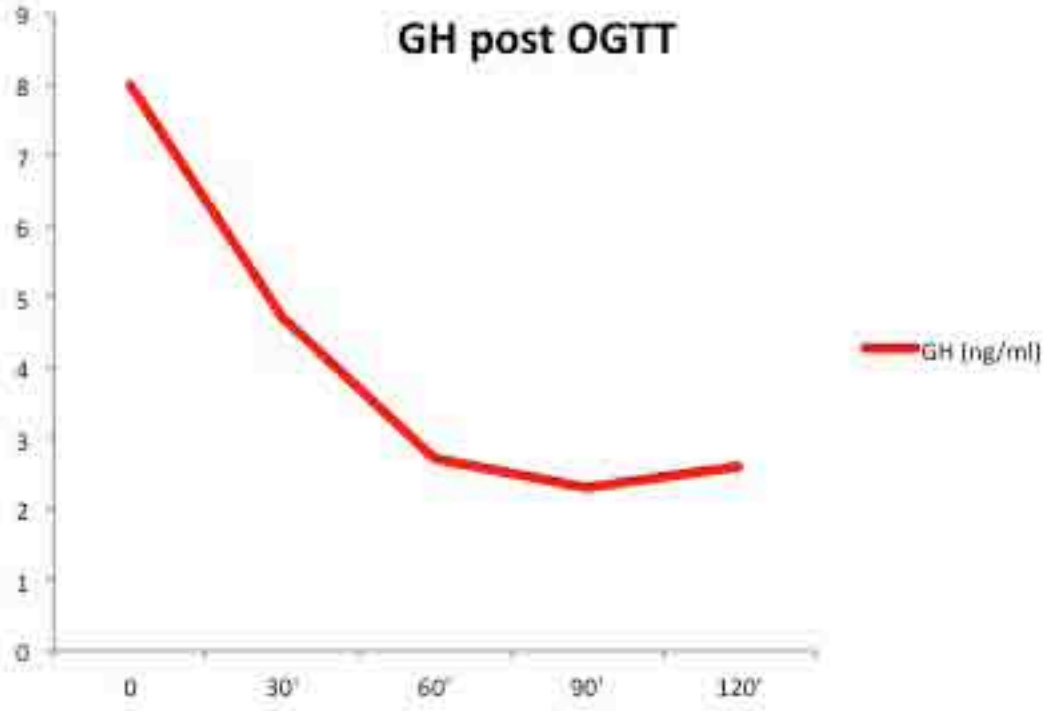


Thyroid nodular disease turned out to be significantly more frequent in patients with acromegaly than in control groups (OR = 3.6, RR= 2.1) and it seems to be a very common disorder in these patients (prevalence slightly below 60%).

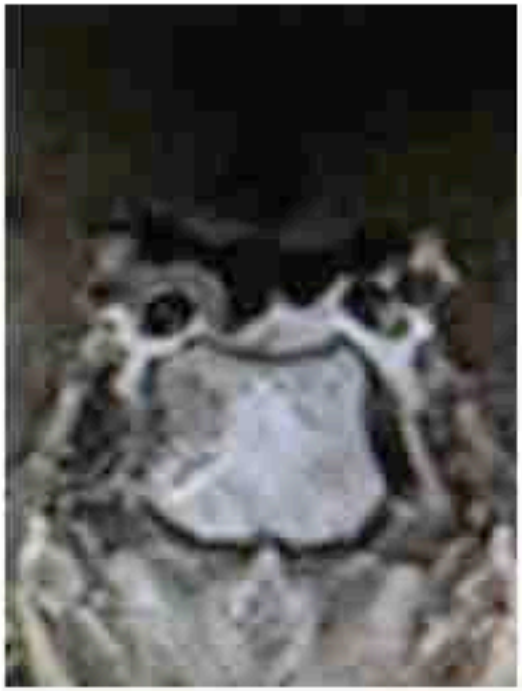
Thyroid cancer prevalence 5%

The risk of TC is elevated even more strongly than the risk of colon cancer (OR 7.9 vs. 4.4).

Rivalutazione Post-Chirurgica: gli ormoni



Rivalutazione Post-Chirurgica: RMN



RM: residuo adenomatoso che avvolge il seno cavernoso destro

Rivalutazione Post-Chirurgica: la clinica

CEFALEA: 2 vv/mese, a metà ciclo e in fase pre-mestruale, in regione frontale, a blocchi di 3 gg, intensità e caratteristiche diverse rispetto al pre-operatorio

FISIONOMIA normalizzata

PARESTESIE ridotte

RONCOPATIA nettamente diminuita

ASTENIA serale

PROSPETTIVA DI GRAVIDANZA

NESSUNA TERAPIA ANTI GH

Settembre 2011
Un anno dopo l'intervento

Flussi mestruali regolari
Un aborto spontaneo: anomalia cromosomica

Cefalea mensile, periodo pre-mestruale, peri-nasale
Fisionomia tornata normale

IGF-1 257% ULNR
GH 3,6 ng/ml (valore medio)

RM: invariata

Inizia Cabergolina 0.25 mg/die

Agosto 2011: la gravidanza

Dicembre 2011: gravidanza!

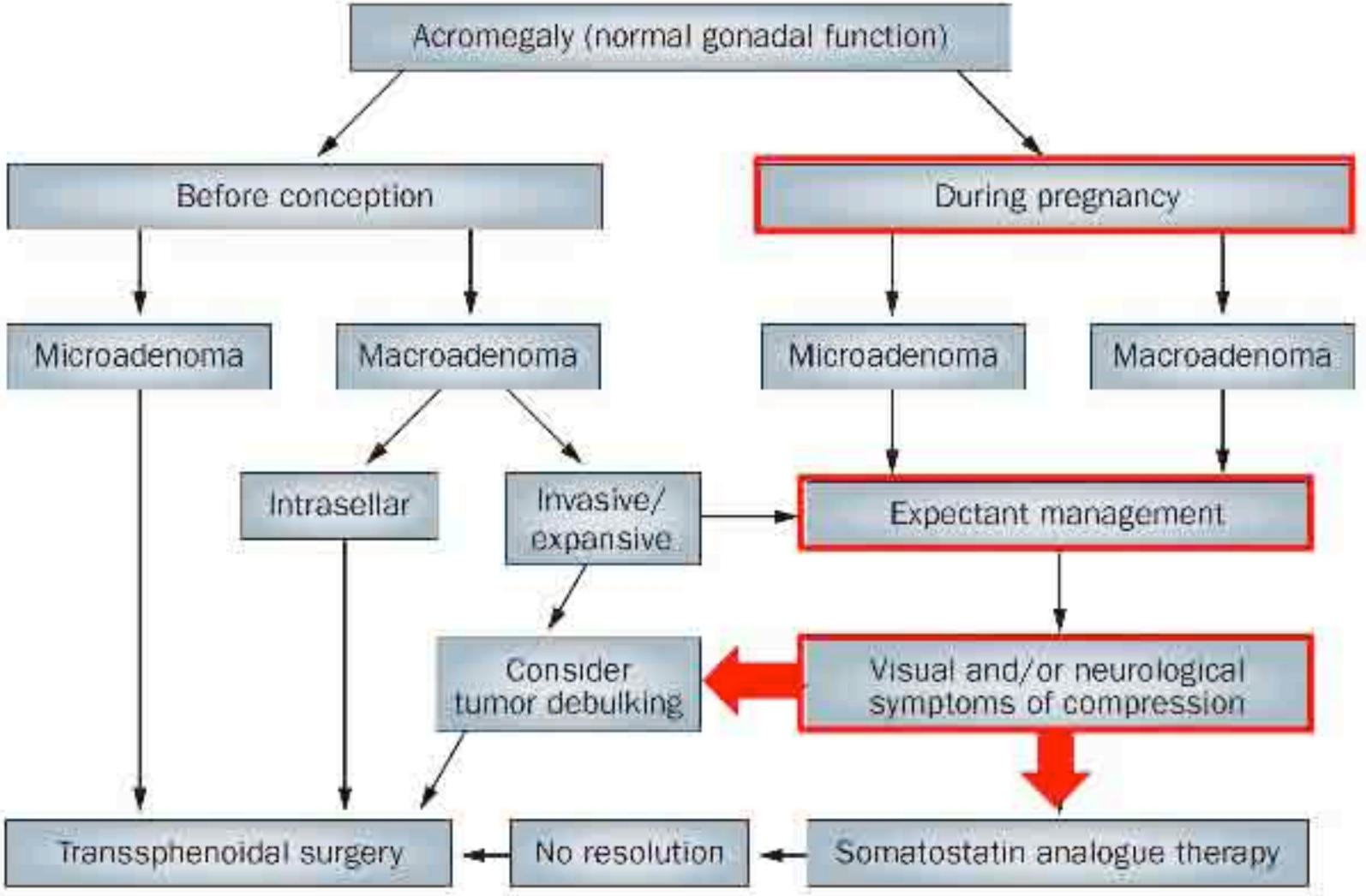
Stop cabergolina

Agosto 2011: la gravidanza

Acromegalia e gravidanza: follow-up, frequenza rivalutazione, terapia

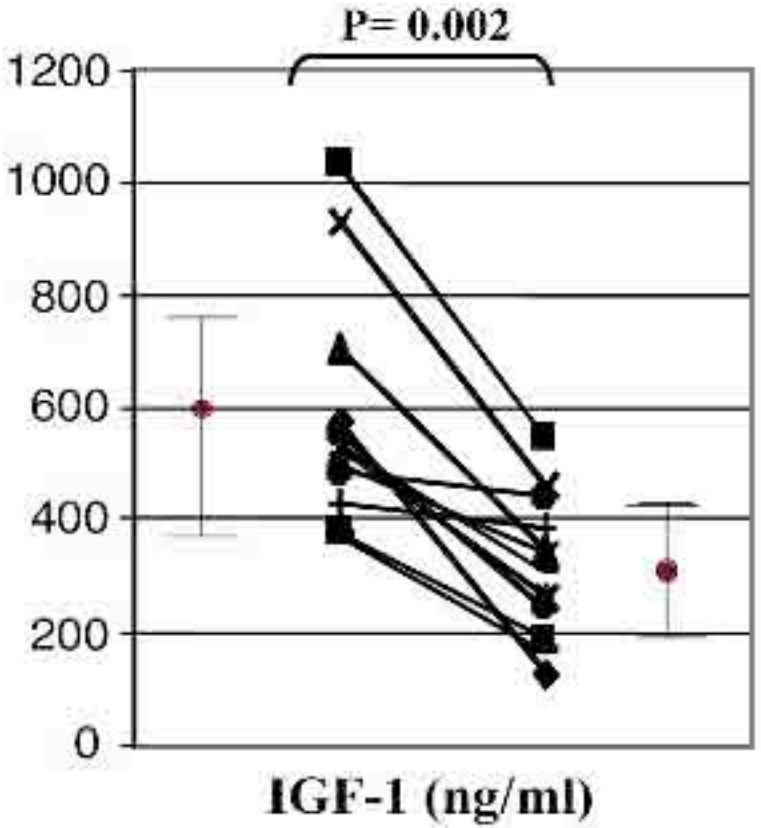
Pietro Maffei,
Clinica Medica 3^, Azienda Ospedaliera Padova
pietromaffei@libero.it
pietro.maffei@aopd.veneto.it

Management

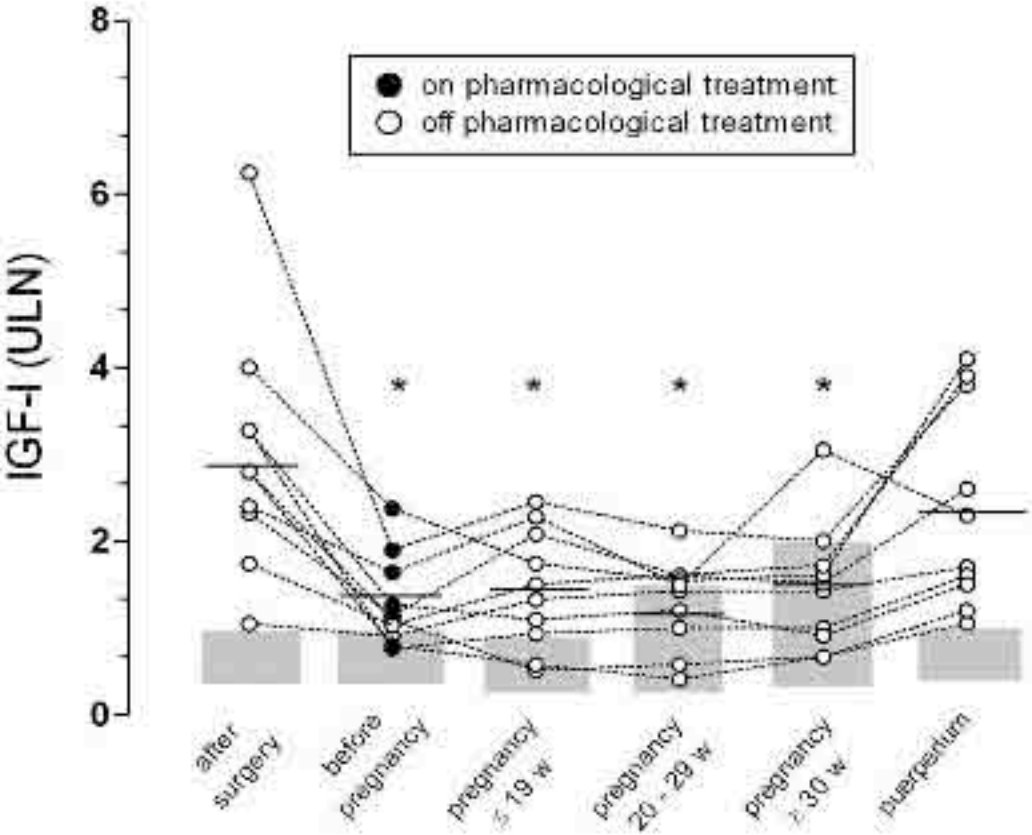


Bronstein M et al, Nat Rev Endocrinol, 2011

IGF-I in gravidanza



Caron et al, JCEM 2010



Abucham et al, EJE 2017

Terapia medica in gravidanza

	DA	SSA	PEG
Categoria (FDA)	B	B-C	B
Teratogenicità	NO	NO	NO
Passaggio Placenta	SI ?	SI	NO
Passaggio Feto	SI ?	SI	NO ?
Attività nel feto	SI ?	NO ?	?
Passaggio Latte	na	SI	NO ?
Off-label	SI	SI	SI

Management della terapia: Durante la gravidanza

- ✓ STOP terapia medica
- ✓ CV basale (se manca un precedente)
- ✓ Funzione ipofisaria
- ✓ Micro/MACRO adenoma
  - Valutazione clinica (sintomi di espansione)
  - Ripetere CV soprattutto se Macroadenoma
- ✓ Sintomi di espansione (cefalea, visus, NC)
  - CV + RMN senza mdc (evitare 1° trimestre) (R92 – AACE)
  - Terapia chirurgica
  - Terapia medica (SSA)

Management della terapia: Dopo la gravidanza

- ✓ Dosaggio GH e IGF-I e funzione ipofisaria
- ✓ Riprendere terapia medica
- ✓ Opzione chirurgica per guarigione
- ✓ RMN:
  - Non necessaria nell'immediato post-parto
  - Passaggio del gadolinio nel latte → feto
  - Evitare allattamento nelle ore successive
  - Eventualmente senza gadolinio
- ✓ Allattamento:
  - Non controindicato
  - SSA e PEG non attivi per via orale

La gravidanza

	3 MESI	6 MESI
IGF-1 (%ULNR)	128%	117%
GH (ng/ml), media	7.3	3.8

Gravidanza normodecorsa, non complicazioni
Regressione cefalea in gravidanza
4 settembre 2012 TC
Allattamento

Il post-partum

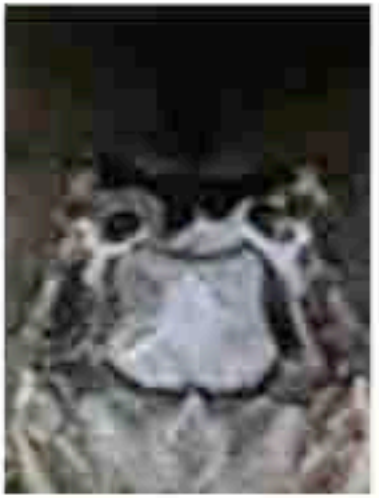
Ripresa di FM tre mesi dopo il parto

Ripresa di cefalea: ogni 2 gg, di forte intensità, persistente e resistente a terapia analgesica

IGF-1: 376%

GHm 4.2 ng/ml

RM: invariata



Ripresa di Terapia con SSA OCT 30/28 gg → non modifiche quadro ormonale

2013: che fare?

Alte dosi di analoghi somatostatina

Pegvisomant

Pegvisomant + analogo somatostatina

Altro (Radioterapia?)

ANALOGHI SOMATOSTATINA (SSA)

RESISTENZA *(Colao End Rev 2011)*

Biochimica

Massa

Durata Terapia (12 mesi)

Dosi

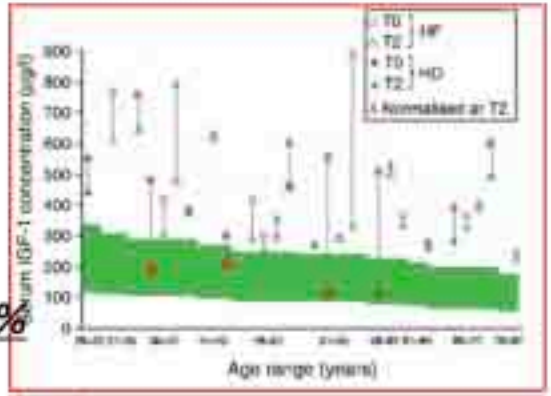
TABLE 8. Definition of response to 12 month treatment of SA at therapeutic dosages in acromegaly

Full response	Control of GH and IGF-I levels and >20% tumor shrinkage in patients treated first-line Control of GH and IGF-I levels and >20% tumor shrinkage or stabilization of tumor remnant in patients treated second-line or in those with no tumor on magnetic resonance imaging at baseline
Partial response	Significant decrease (>50%) of GH and/or IGF-I levels with no achievement of control and/or >20% tumor shrinkage in patients treated first-line or second-line
Poor response or resistance	Nonsignificant decrease of GH and IGF-I levels with no achievement of control and no tumor shrinkage in patients treated first line or increase in tumor size in any patient

"ALTE DOSI

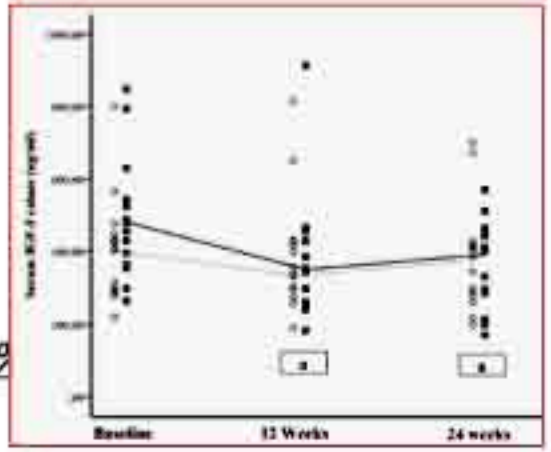
Giustina et al. EJE 2009

OCT-LAR
30/21 gg
60/28 gg
Normalizzazione IGF-I *36%*
(solo HD)



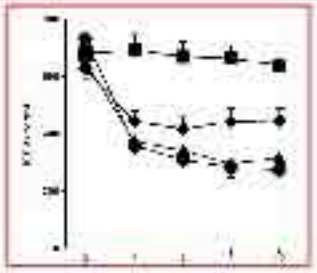
Giustina et al. JCEM 2017

LAN-ATG
120/21 gg
180/28 gg
Normalizzazione IGF-I *27%*



ANTAGONISTI RECETTORIALI GH (PEGVISOMANT)

EFFICACIA: normalizzazione IGF-I



Trial clinici registrativi: rapida risposta, normalizzazione fino a 90% pazienti

Real life (AcroStudy): risposta un po' più lenta, normalizzazione 70%

EFFICACIA: parametri clinici

Sintomi-segni

PASQ/AcroQoL

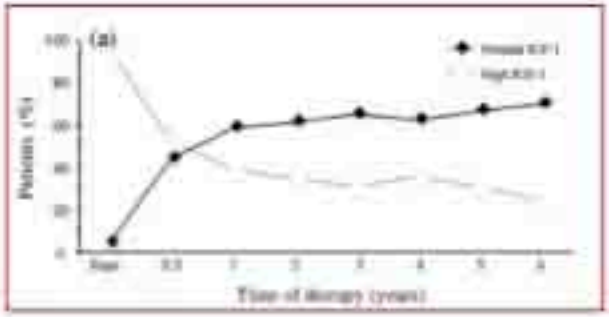
Metabolismo glucidico

Cardiovascolare

ORIGINAL ARTICLE

ACROSTUDY: the Italian experience

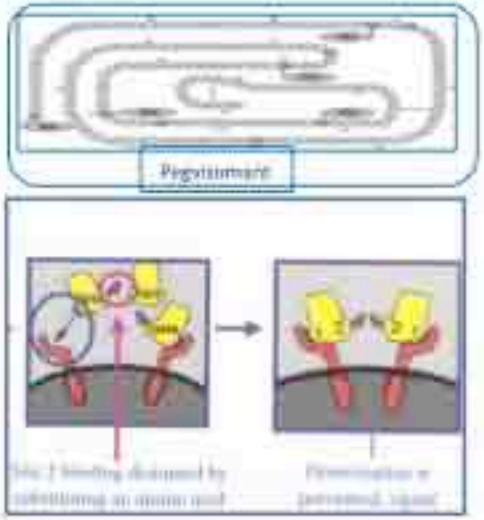
S. Gasperi · P. Maffei · F. Bugari · S. Camarà · A. Colao · E. Ghigo · R. Gomez · E. Graziano · M. Mastrobattista · P. Jonsson · L. De Martin



FATTORI PREDITTIVI DI DOSE

Peso corporeo; valori di GH/IGF-I, sesso; radioterapia;

ANTAGONISTI RECETTORIALI GH (PEGVISOMANT)



INDICAZIONI

Malattia non controllata

- dopo S/RT

- resistente-intollerante SSA

GESTIONE TERAPIA

(Loading dose) Dose iniziale di 10 mg/die

Titolazione progressiva (4-6 settimane) fino a 30 mg/die

MONITORAGGIO

IGF-I (NO GH)

Transaminasi, glicemia; RMN

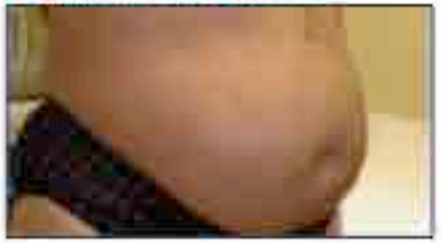
EFFETTI COLLATERALI

Locali: lipoipertrofia

Epatici: incremento transaminasi →SSA

Diabetico: →ipoglicemia

Aumento massa tumorale ?



TERAPIE COMBINATE

RAZIONALE

Efficacia biochimica/massa

Compliance

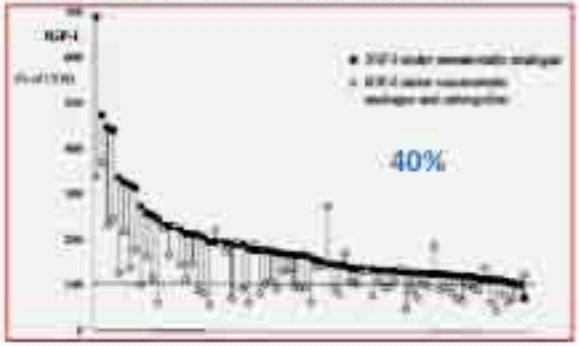
Miglioramento clinico

(QoL, m. glucidico ?)

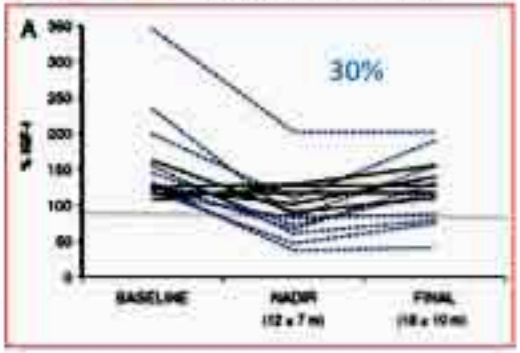
Costi

Acrostudy Italy

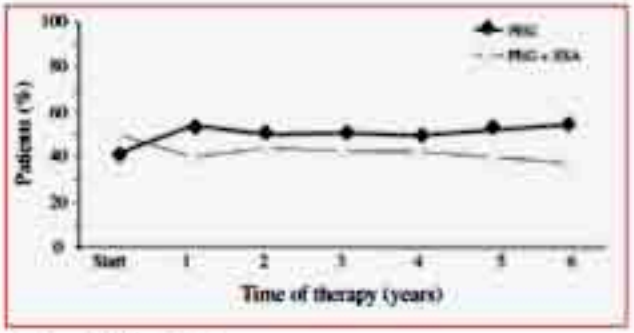
DA+SSA *Sandret, JCEM 2011*



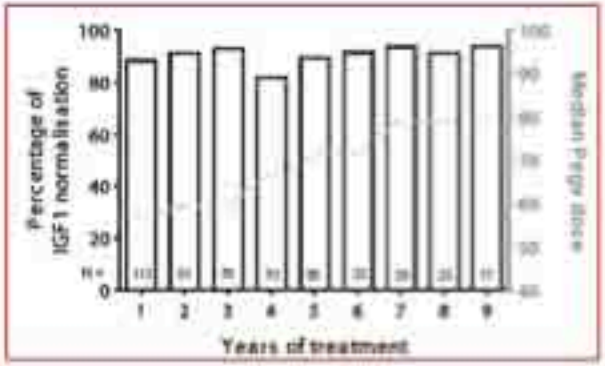
DA+PEG *Bernabeu, P 2012*



PEG+SSA



Grottoli E 2014



Neggers JCEM 2014

2013: che fare?

Alte dosi analoghi somatostatina

Terapia combinata con cabergolina

Pegvisomant

Pegvisomant + analogo somatostatina

Radioterapia

La terapia medica

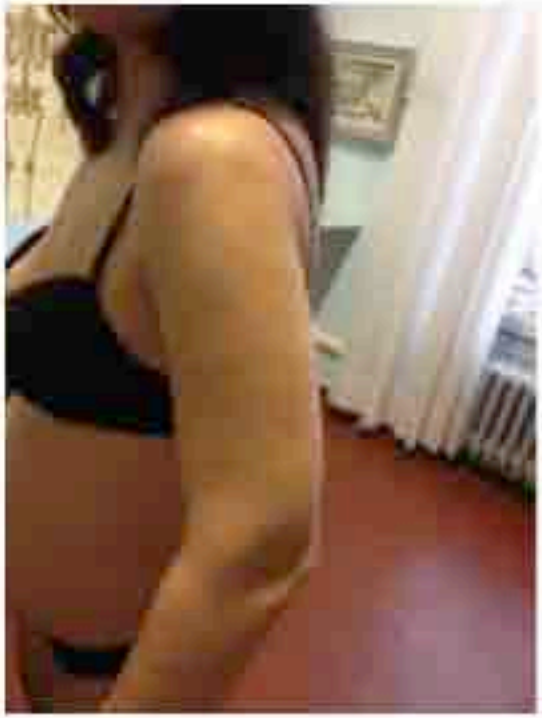
OCTREOTIDE 30 mg/28 GG + PEGVISOMANT 10 mg/die

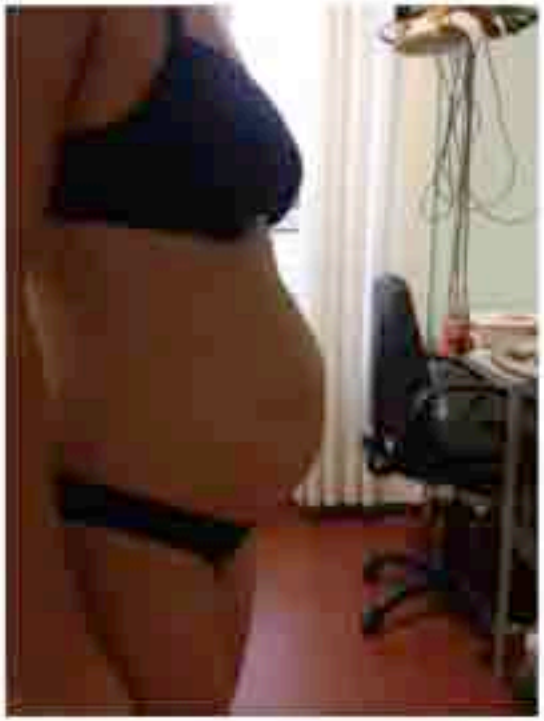
IGF-1 90% ULNR

Clinica:

Cefalea persistente, peri-orbitaria, 2 vv/mese

La terapia medica: gli effetti collaterali





STOP PEGVISOMANT

IGF-1: 215%

La terapia medica

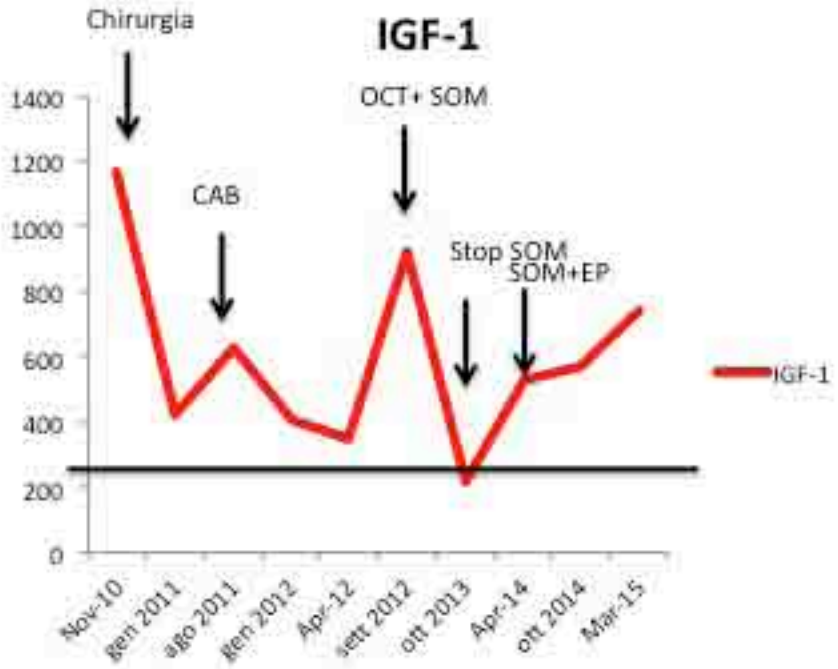
OCTREOTIDE 30 mg/28 GG + ESTROPROGESTINICO

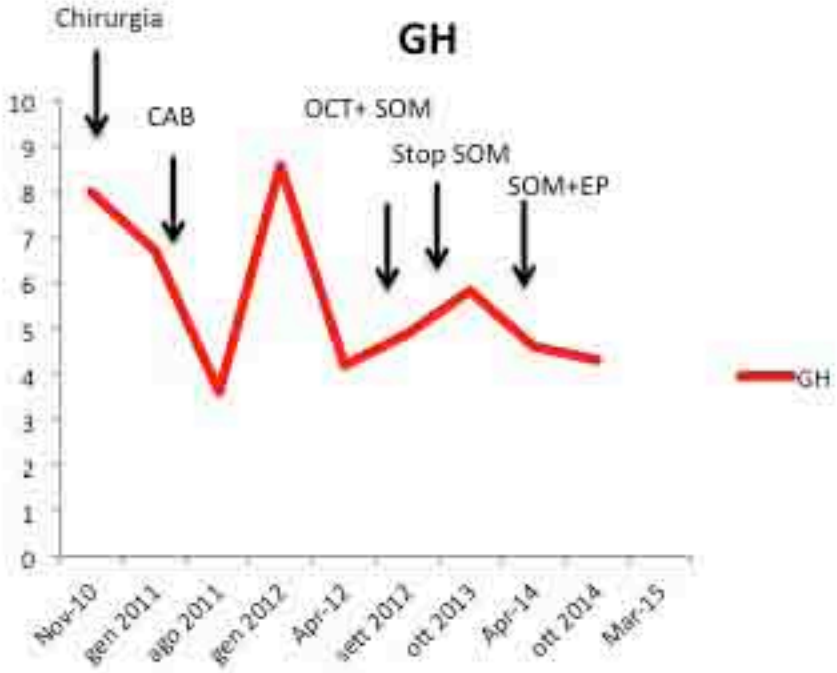
Secrezione: IGF-1 217%
GH 4,6 ng/ml

Clinica: ipertensione
peggioramento cefalea

Stop OCTREOTIDE ed ESTROPROGESTINICO

Strategia terapeutica





I casi difficili

M. Losa - Rep. Neurochirurgia

Rep. Neurochirurgia – IRCCS San Raffaele

Milano

I casi difficili: la radioterapia

- Tipi di radioterapia
- Risultati della radioterapia
- Effetti collaterali
- Ruolo della radioterapia
- Temozolomide nei casi “ultradifficili”

Tipi di radioterapia

Il timore nei confronti della terapia radiante origina dai risultati dei trattamenti effettuati negli anni '60-'80.

Tuttavia, la metodologia radiante si è evoluta negli ultimi decenni, permettendo dei trattamenti circoscritti al bersaglio biologico.

Tipi di radioterapia

DOSE FRAZIONATA

Convenzionale

Conformazionale
(IMRT, tomoterapia)

DOSE UNICA

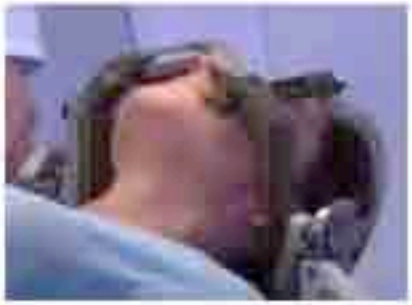
Leksell Gamma Knife

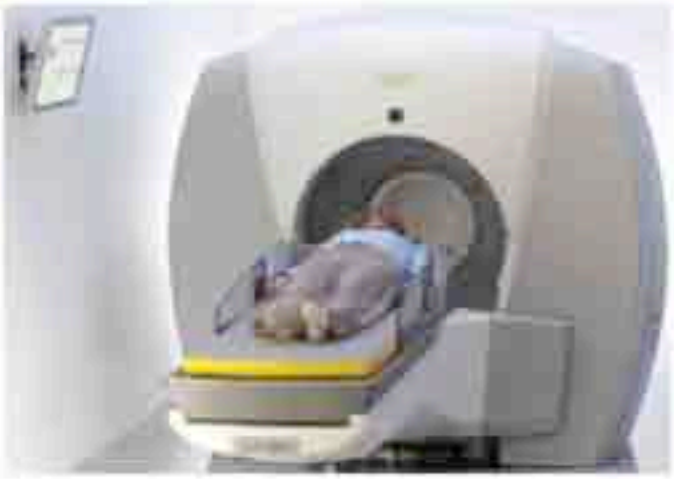
Cyber Knife

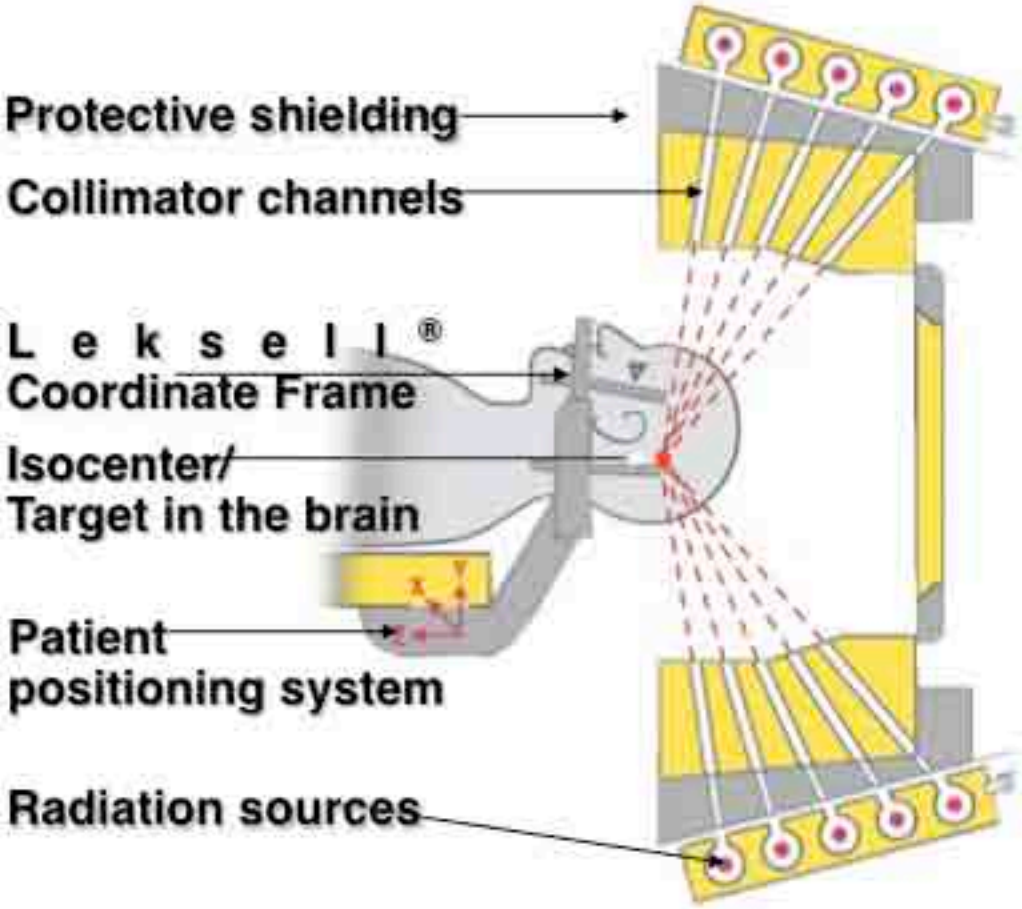
Proton beam

LINEAC

Tipi di radioterapia: Gamma Knife







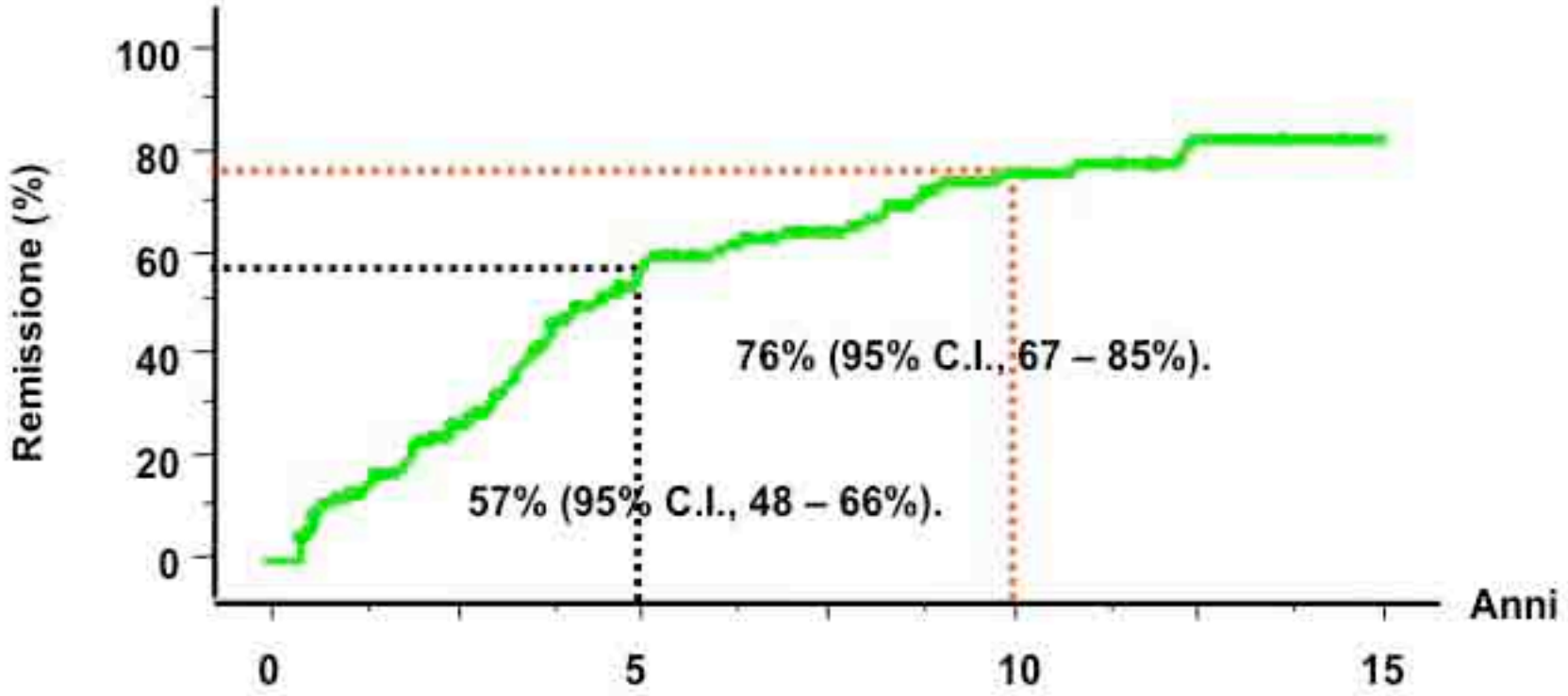
Risultati della Gamma Knife

Autore	No. pts.	Isodose 50% (Gy)	F.U. (mediana)	Remissione
Castinetti et al. JCEM '05	82	26	49	17%
Jezkova et al. Clin End '06	96	35	54	52%
Pollock et al. J Neuros '07	46	20	63	50%
Losa et al. JCEM '08	83	23	69	60%
Jagannathan et al. Neuros '08	95	22	49	53%
Ronchi et al. Clin End '09	35	20	114	49%
Liu et al. Neuro-onc '12	40	21	72	48%
Lee et al. JCEM '14	136	25	61	67%

Fattori prognostici della Gamma Knife

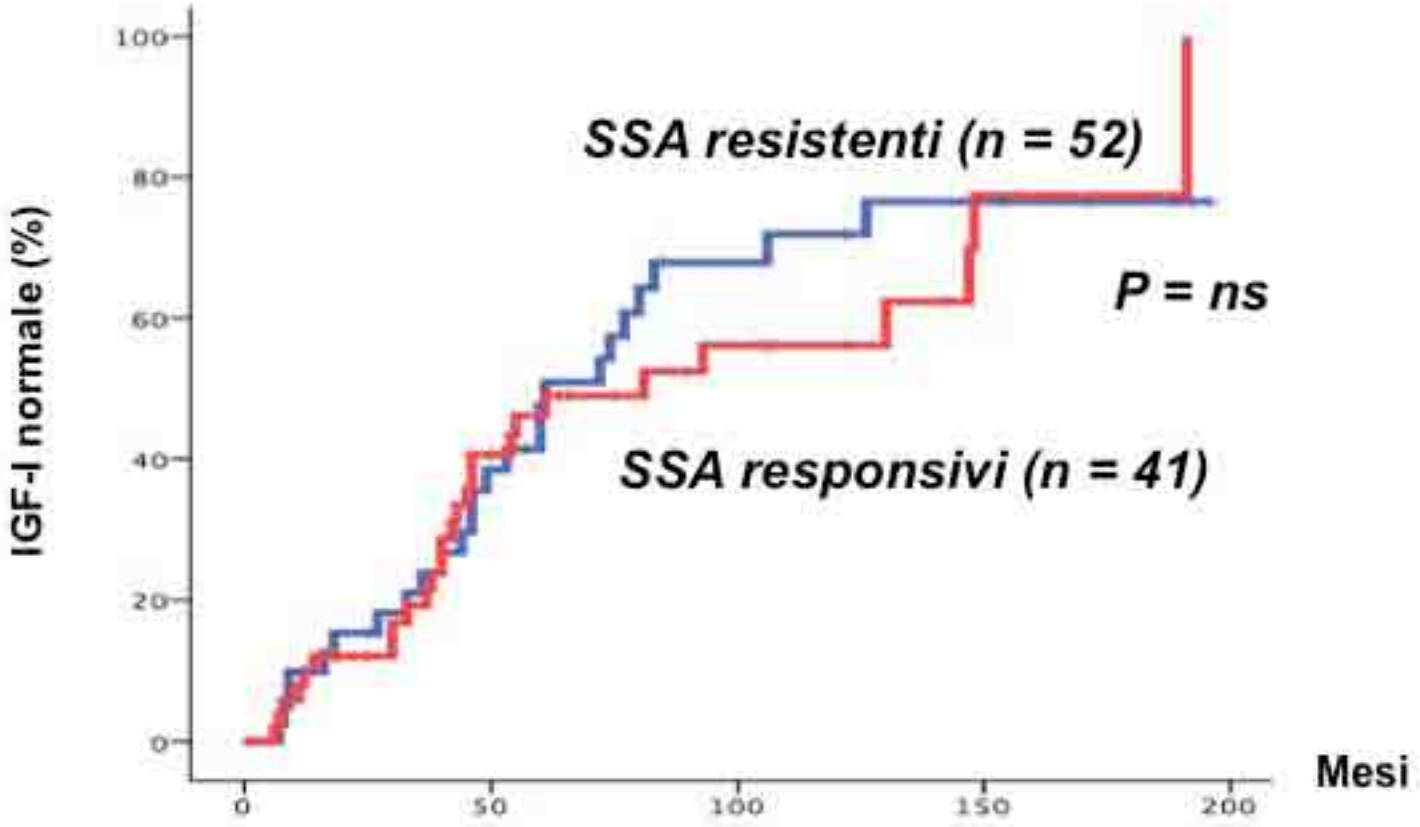
Autore, anno	Età	GH pre GK	IGF-I pre GK	Dose Gy	Dimensioni	Pretrattmento con SSA
Castinetti et al. JCEM '05	-	+	-	-	NR	-
Jezkova et al. Clin End '06	NR	+	+	NR	-	NR
Pollock et al. J Neuros '07	-	-	+	-	-	+
Losa et al. JCEM '08	-	+	+	-	-	-
Jagannathan et al. Neuros '08	NR	NR	-	-	-	+
Ronchi et al. Clin End '09	-	+	-	-	-	-
Lee et al. JCEM '14	-	-	+	+	-	-

Risultati della Gamma Knife



A rischio	144	69	14
Remissione	0	42	84

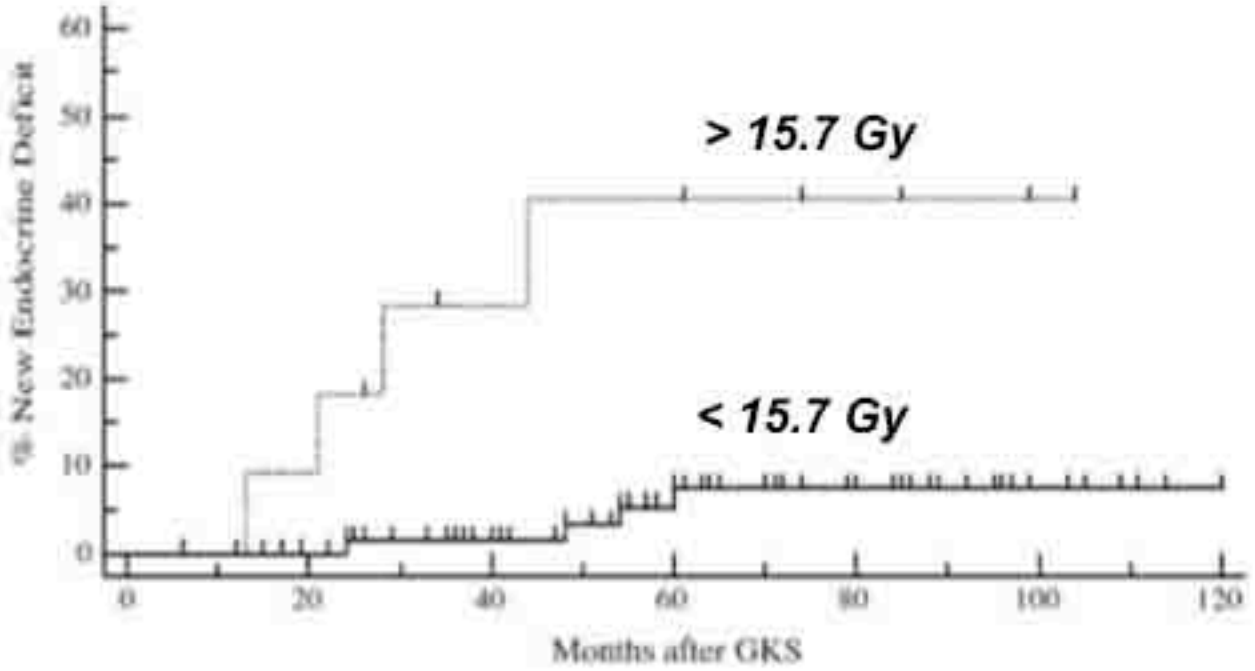
Risultati della Gamma Knife



Effetti collaterali della Gamma Knife

Autore, anno	No. pazienti	Radionecrosi	Difetto visivo	Diplopia
Castinetti et al. JCEM '05	83	0%	1%	0%
Vik-Mo et al. Eur J End '07	53	0%	4%	0%
Pollock et al. J Neuros '07	46	2%	0%	0%
Losa et al. JCEM '08	83	0%	0%	0%
Ronchi et al. Clin End '09	35	0%	0%	0%
Liu et al. J Neuroonc '12	40	0%	0%	0%
Lee et al. JCEM '14	136	1%	3%	1%

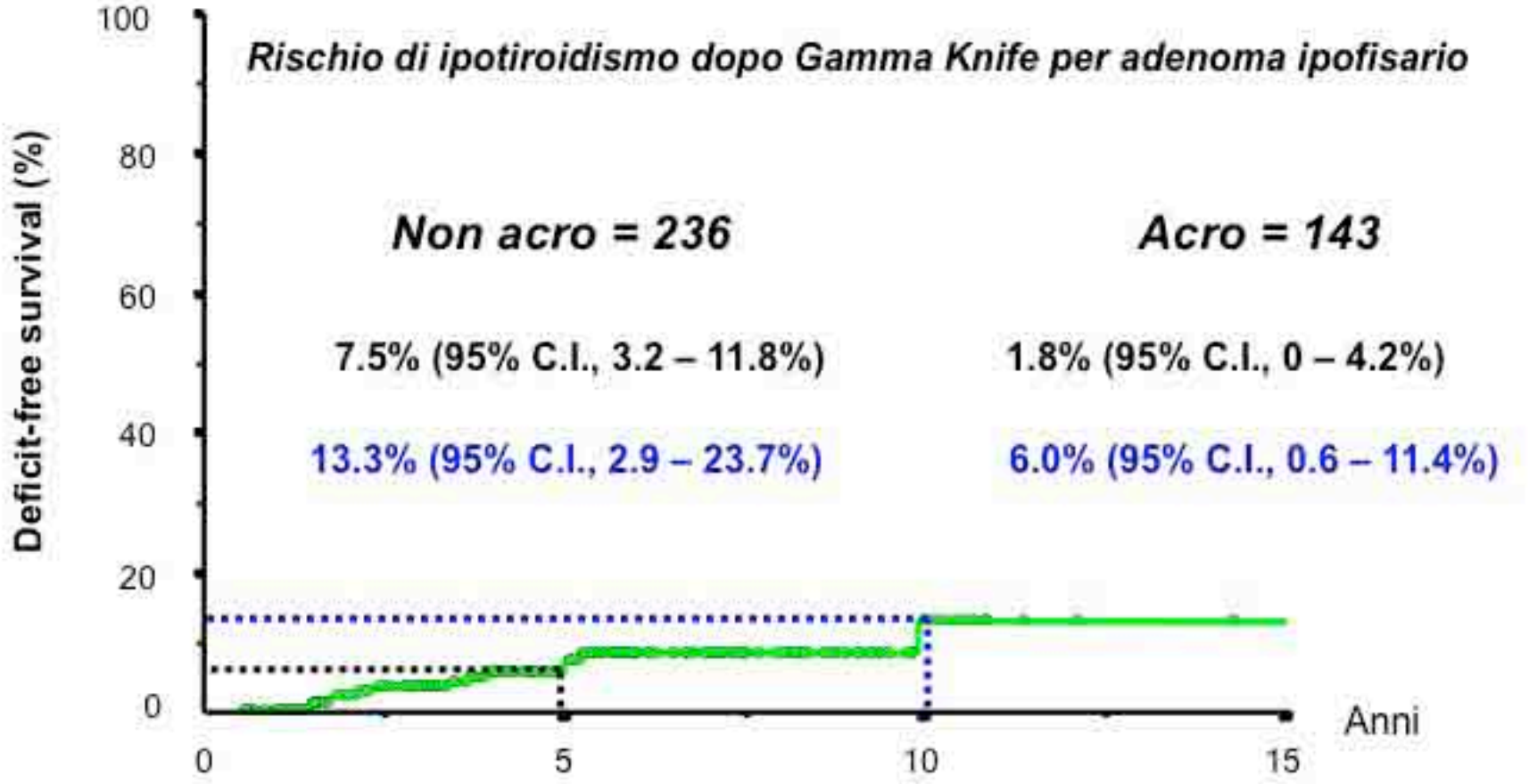
Effetti collaterali della Gamma Knife



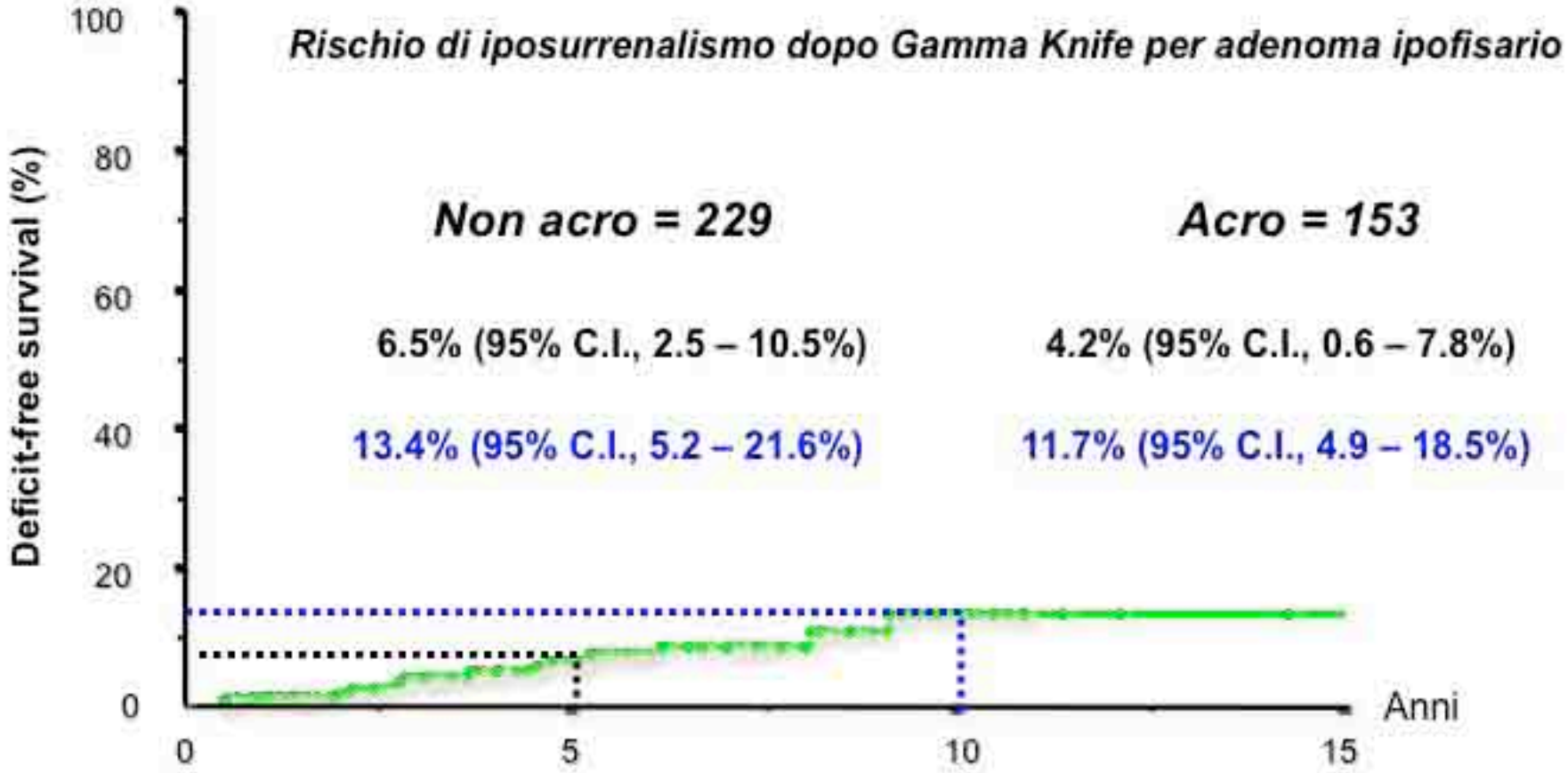
Mean dose to the pituitary/stalk was a strong independent predictor of pituitary deficiency

From Sicignano et al., Radiother Oncol. 104:119-124, 2012

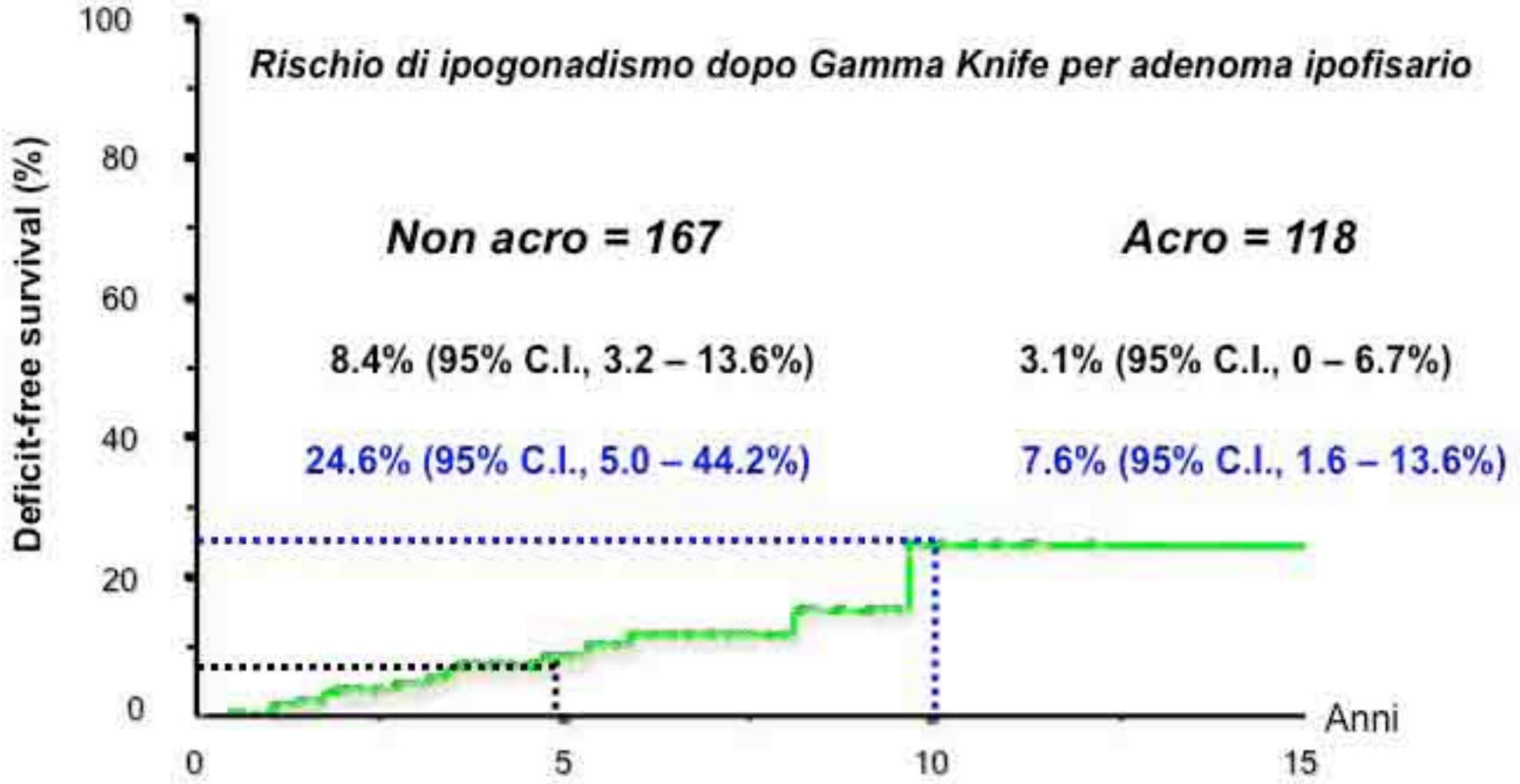
Effetti collaterali della Gamma Knife



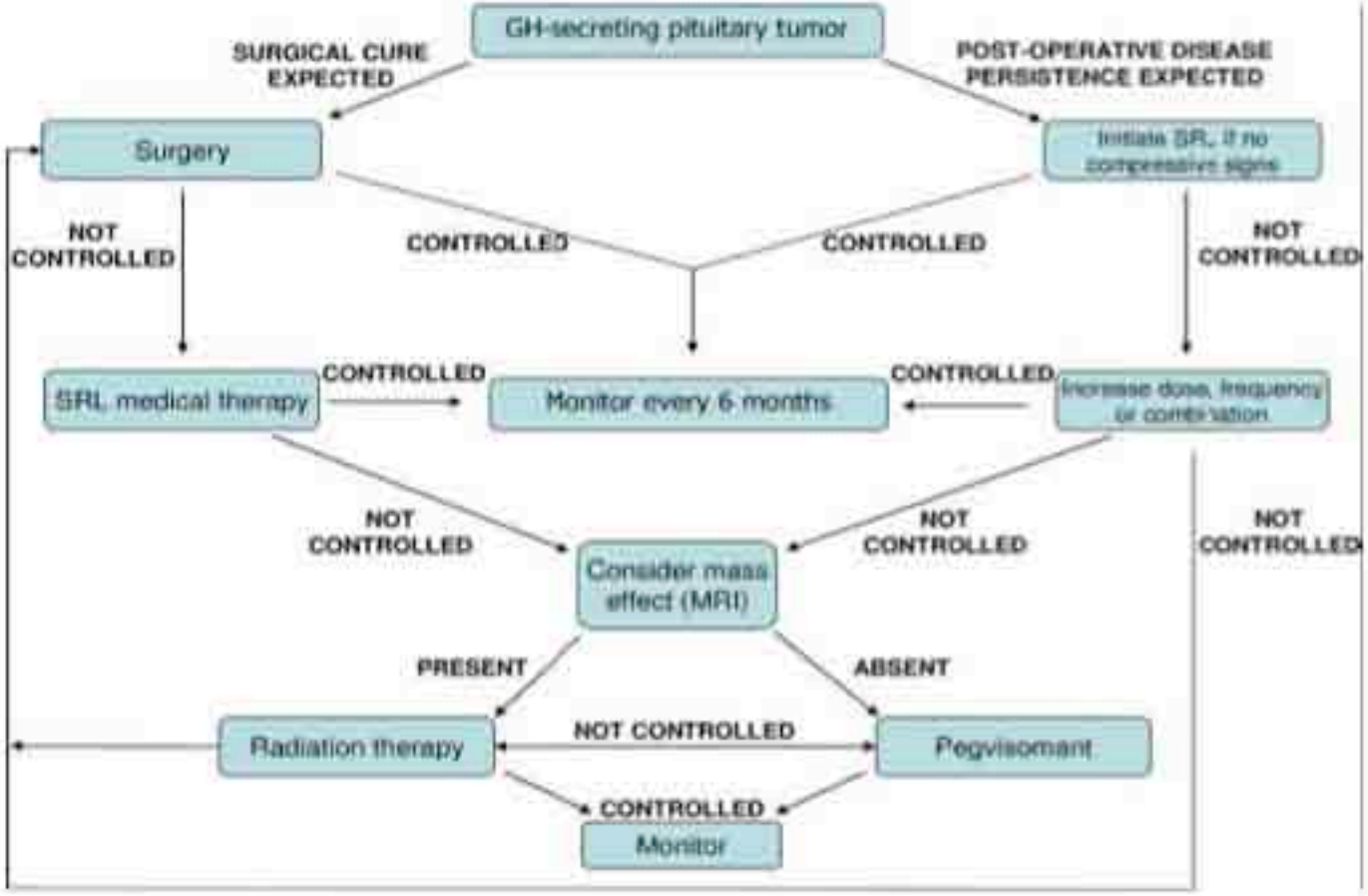
Effetti collaterali della Gamma Knife



Effetti collaterali della Gamma Knife



Ruolo della radioterapia



From Melmed et al., JCEM 94:1509-1517, 2009

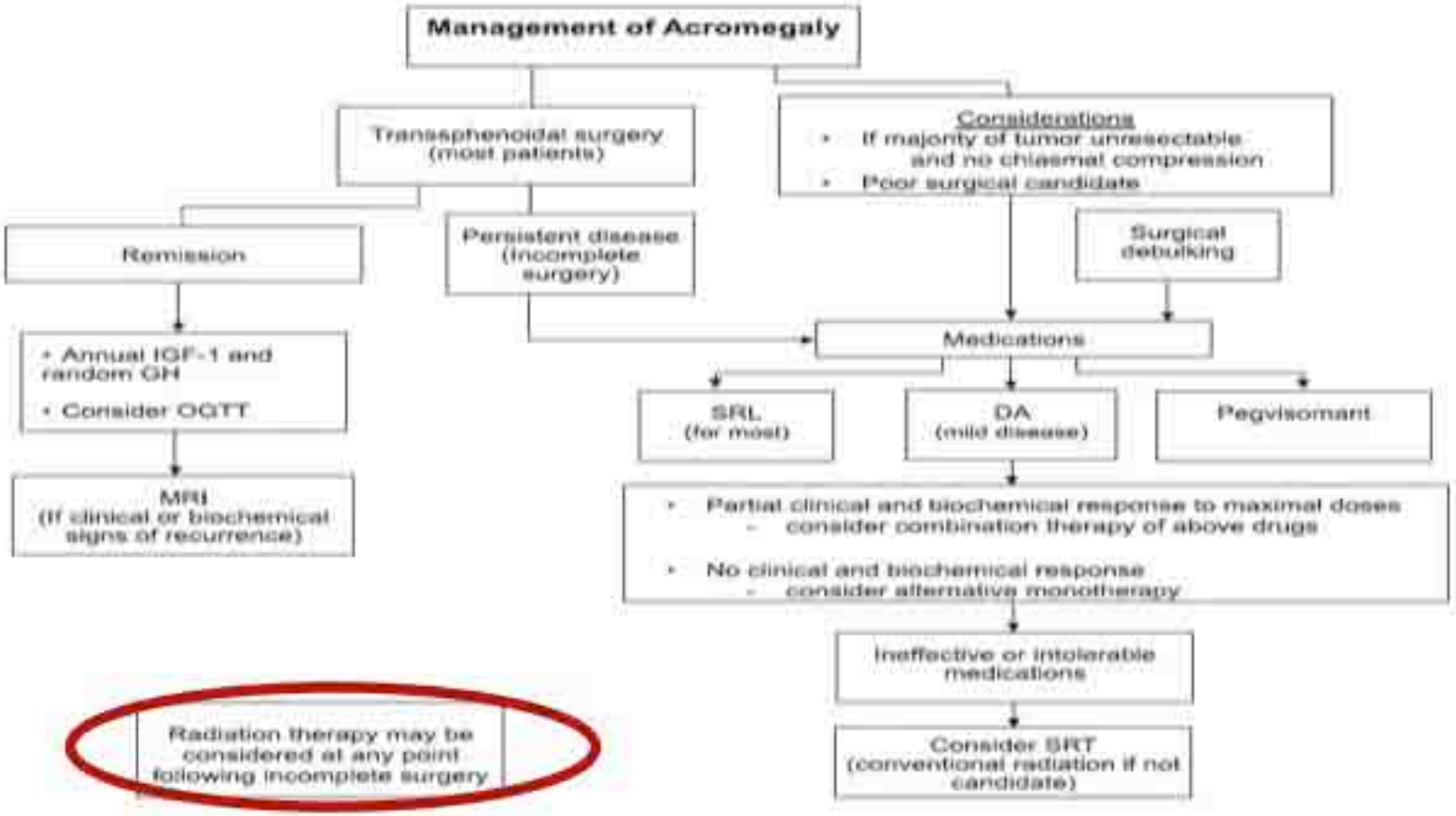
III° livello

Ruolo della radioterapia: i costi

Treatment	Efficacy	Duration of treatment	Lifetime cost ($)
TNS surgery	80%	1 time	39,311
Radiosurgery	45%	1 time	56,356
Octreotide (24 mg/4 wk)	60%	38.3 yrs	1,667,052
Lanreotide (103 mg/4 wk)	60%	38.3 yrs	1,578,567
PEG (20 mg/day)	80%	38.3 yrs	2,620,833
SA + PEG (120mg + 60 mg/wk)	95%	38.3 yrs	2,573,339

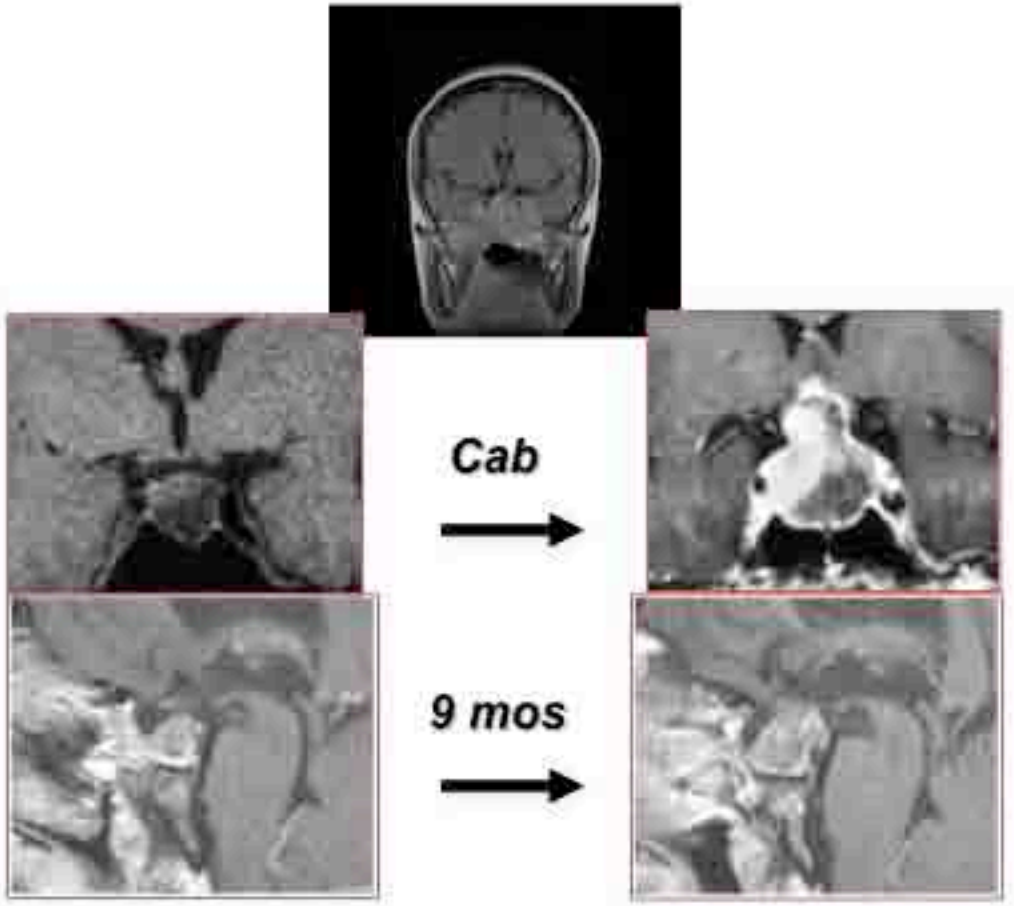
From Marko et al., J Neurosug, 117:522-538, 2012

Ruolo della radioterapia: linee guida E.S. 2014



Ruolo della Temozolomide

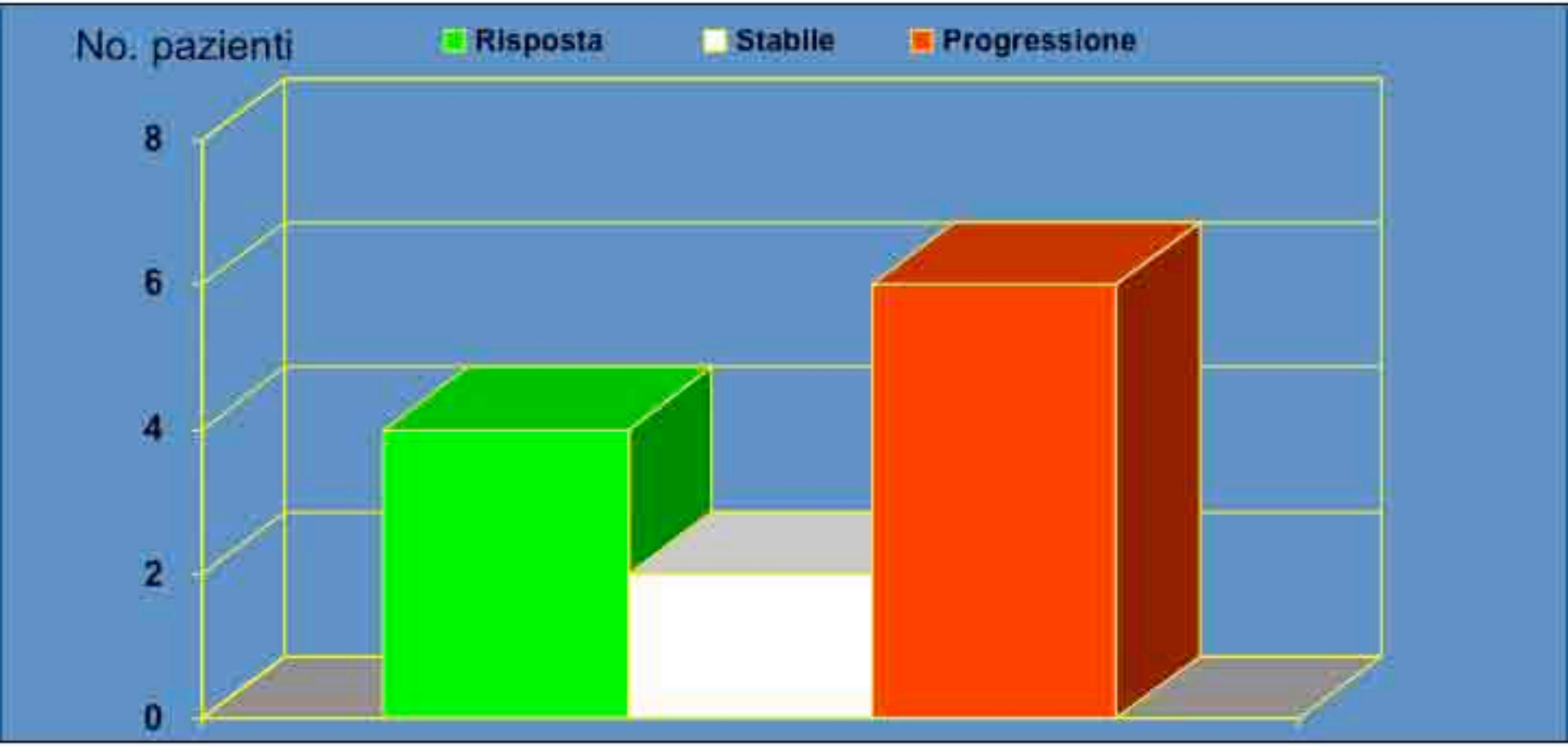
- Invasivo
- \+
- Resistente
- \+
- Crescita rapida



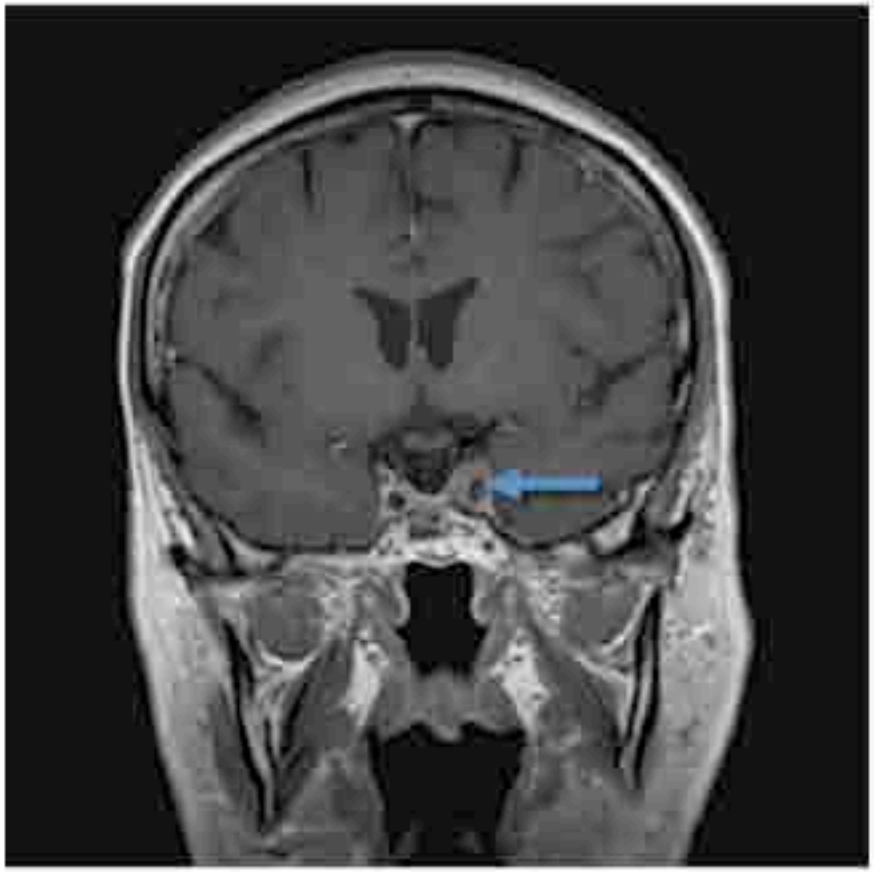
Ruolo della Temozolomide

Autore, anno	Sesso	Etá	No. Interventi	Altre terapie	Risposta TMZ
McCormack, 2009	M	48	5	RT, SSA, DA	No
Morin, 2012	M	22	2	RT,SSA, Peg	No
Battise, 2013	M	47	2	RT, SSA	No
Ceccato, 2015	F	39	1	SSA	No
Bengtsson, 2015	F	31	4	RT, SSA	Yes
Bengtsson, 2015	M	33	2	DA, SSA	Yes
Bengtsson, 2015	M	46	6	SSA, Peg	No
Bengtsson, 2015	F	40	4	DA	Yes
Bengtsson, 2015	F	49	1	DA, SSA	Yes
Bruno, 2015	F	34	2	DA, SSA	No
Losa, 2016	F	38	10	RT, SSA	Stabile
Losa, 2016	F	55	4	RT, SSA	Stabile

Ruolo della Temozolomide



Conclusioni



GAMMA KNIFE NEGLI ADENOMI IPOFISARI: SELEZIONARE IL PAZIENTE GIUSTO!

Take home message

NON SCORDATE L'OPZIONE RADIANTE. E' EFFICACE ED HA UNA

DISCRETA SICUREZZA ANCHE NEL LUNGO TERMINE.

Ottobre 2015: radiochirurgia

GAMMA KNIFE: 22 Gy, isodose prescrizione 50%, volume 0.4 cm^3

	3 MESI	6 MESI	12 MESI
IGF-1 % ULNR	195%	220%	195%
GH ng/ml	5.6	4	2.5

RM 3 e 12 mesi post GK: dimensioni del residuo invariate

2016: Che fare?

Wait and see

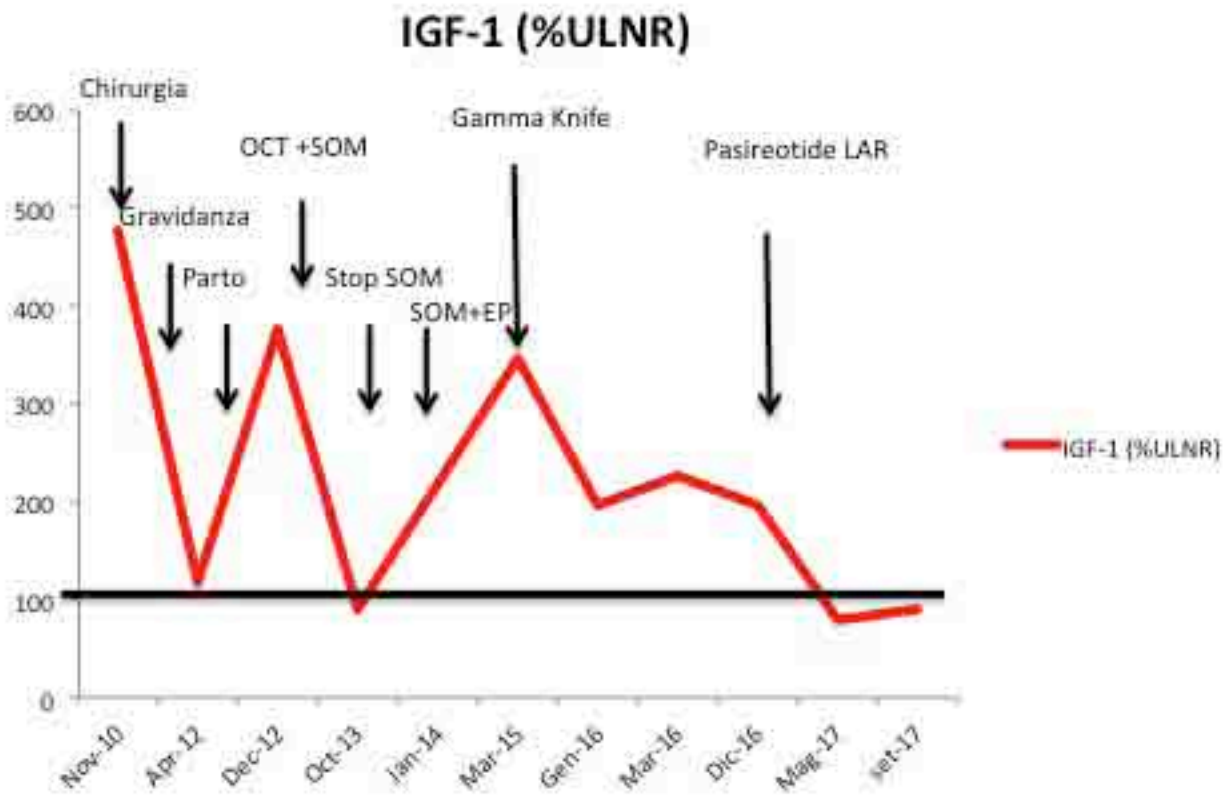
Altre opzioni

2016:Che fare?

Wait and see

Altre opzioni

Pasireotide LAR



Settembre 2017

Pasireotide LAR 40mg/28 gg

GH 0,5 ng/ml. IGF-1 80% ULNR

Trattamento ben tollerato

Cefalea: controllata da terapia medica

RM: stabilità del residuo

Assetto glicemico normale (HbA1C 39 mmol/mol, <42)

Strategia terapeutica

Maria Rosaria Ambrosio

Sezione di Endocrinologia e
Medicina Interna
Dipartimento di Scienze Mediche
Università degli Studi di Ferrara
e.mail:mbrmrs@unife.it

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

NESSUNO

Acromegalia: gestione clinica

Strategia

- Settore dell'arte militare che predispone le linee generali di condotta nelle varie operazioni di guerra, al fine di arrivare alla vittoria nel modo più rapido e meno dispendioso

- Capacità di raggiungere obiettivi importanti predisponendo, nel lungo termine e con lungimiranza, i mezzi atti a tale scopo

- Nei giochi, serie di mosse studiate per vincere l'avversario

Dizionario Treccani

Acromegalia: gestione clinica

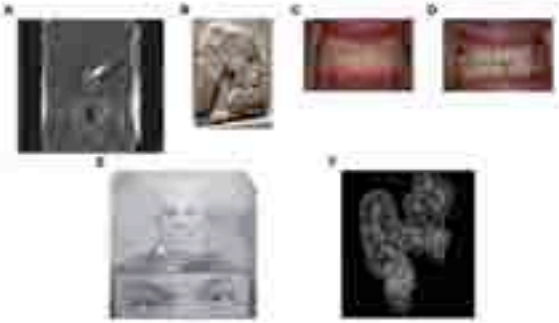
Therapeutic strategies

approaches to treatment based on principles of organization

Strategia terapeutica ➔ qualità e sicurezza nella scelta più idonea
dipendono in primo luogo dallo stato delle conoscenze scientifiche
e quindi delle conoscenze in possesso dell'operatore sanitario

Strategia terapeutica

THERAPEUTIC END-POINTS



- normalization of GH hypersecretion and IGF-1 values
- control of tumor growth
- relief of compressive effects on CNS and vascular structures, if present
- preservation or restoration of pituitary hormone reserve function
- treatment of comorbidities and normalization of mortality rates

Strategia terapeutica

Approccio "prova ed errore" con opzioni aggiuntive di trattamento fornite quando la malattia non è controllata

NORME REGOLATORIE

DESIDERATA DEI PAZIENTI

Katznelson L et al., J Clin Endocrinol Metab 2014;99:33

Strategia terapeutica

Donna 42 aa Giugno 2010

Caratteristiche clinic[illegible] ormonali di acromegalia
Voluminoso adenom[illegible]
iniziale invasione se[illegible]
a contatto con le vie[illegible]

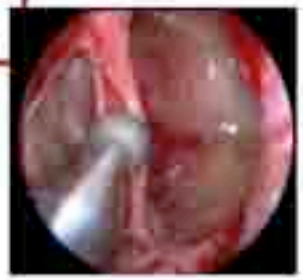
CHIRURGIA

PERCHE' ?

Cefalea persistente, frontale, quotidiana

Strategia terapeutica

Acromegaly: An Endocrine Society Clinical Practice Guideline



Outcomes of surgical management

With experienced pituitary surgeons, microscopic or endoscopic trans sphenoidal microsurgery results in an initial remission rate >85% for microadenomas and 40– 50% for macroadenomas

Cavernous sinus invasion indicates tumor that is likely surgically unresectable

Five-year disease recurrence rates range from 2 to 8%

Katznelson L et al. J Clin Endocrinol Metab, 2014, 99(11):3933–3951

Strategia terapeutica

Neurosurgical Treatment of Acromegaly

Buchfelder M & Schlaffer SM Pituitary 2017

Expert neurosurgical centers with a high degree of focus on pituitary diseases reach normalization rates between 75 and 90% in growth hormone-secreting pituitary microadenomas and some 45–70% in pituitary macroadenomas

The surgical results depend on tumor-related factors
- Size
- Extension
- Presence or absence of invasion
- Magnitude of IGF-1 and GH oversecretion

Surgical debulking of pituitary adenomas improves responsiveness to octreotide lar in the treatment of acromegaly

Fahlbusch R et al Pituitary 2017

Pituitary surgery alone was more effective than primary medical treatment ($p = 0.006$), and the combination of surgery followed by medical therapy was even more effective ($p < 0.0001$)
Subjects treated with medical therapy after surgical debulking had a significant improvement in response rate compared to matched subjects treated with primary medical therapy

Strategia terapeutica

Acromegaly: An Endocrine Society Clinical Practice Guideline

Preoperative medical therapy
We suggest against the routine use of preoperative medical therapy to improve biochemical control after surgery (2|⊕⊕OO)

For patients with severe pharyngeal thickness and sleep apnea, or high-output heart failure, we suggest medical therapy with somatostatin receptor ligands (SRLs) preoperatively to reduce surgical risk from severe comorbidities. (2| ⊕OOO)

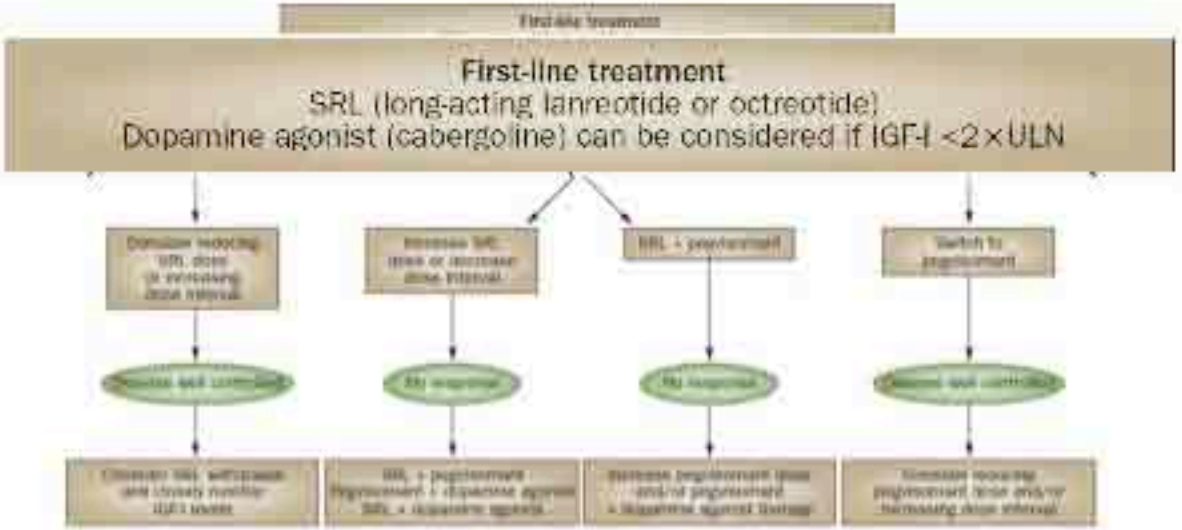
Katznelson L et al., J Clin Endocrinol Metab 2014,99:33

Strategia terapeutica

MA

RIFIUTA→TERAPIA CHIRURGICA

TERAPIA MEDICA
QUALE ?



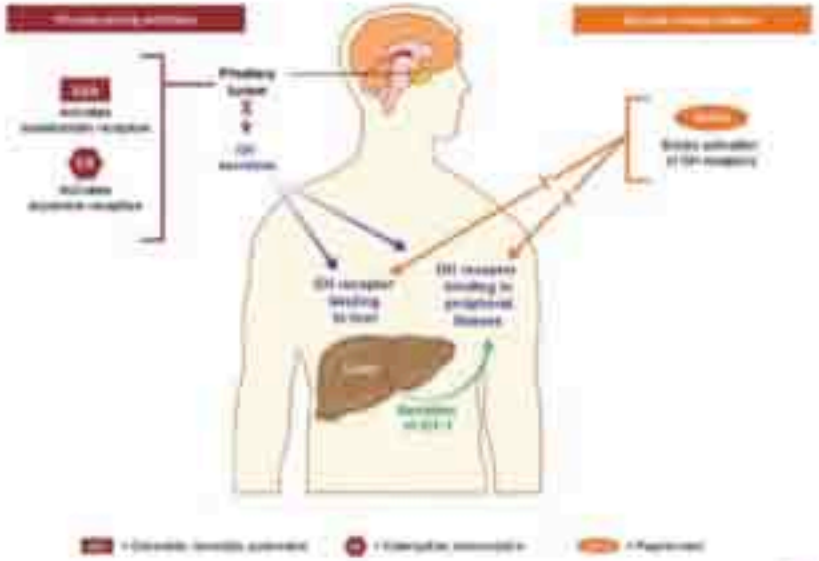
Giustina, A. *et al.* Nat. Rev. Endocrinol. **10**, 243–248 (2014)

Strategia terapeutica

«First generation» somatostatin analogs

octreotide LAR and lanreotide ATG
provided
biochemical control to 50 to 70%
of patients with active acromegaly
and
tumor shrinkage was observed in 40 to 90%

Classes of medical therapies for the treatment of patients with acromegaly



Shanik MH Endocr Pract 2016;22

Strategia terapeutica

HEADACHE

The resolution of headache after surgery or GH control is not always achieved

- Short-acting octreotide can reduce headache in 75–80 % of patients with acromegaly
- The use of slow-release monthly octreotide has been shown to reduce this symptom after the sixth injection
- Prospective trials of lanreotide therapy have also shown a significant reduction in headache in addition to the other symptoms of acromegaly

Some of these treatments, however, can have a deleterious effect on patients, for example dependency, and possibly rebound headaches

Abreu A et al Pituitary 2016; 19:448

Strategia terapeutica

- MACROADENOMA INVASIVO
- CEFALEA PERSISTENTE
- PARZIALE RESISTENZA ORMONALE

Strategia terapeutica

Resistance to somatostatin analogues

Definition of response to 12-month treatment of SA at therapeutic dosages in acromegaly	
Full response	Control of GH and IGF-I levels and >20% tumor shrinkage in patients treated first-line Control of GH and IGF-I levels and >20% tumor shrinkage or stabilization of tumor remnant in patients treated second-line or in those with no tumor on magnetic resonance imaging at baseline
Partial response	Significant decrease (>50%) of GH and/or IGF-I levels with no achievement of control and/or >20% tumor shrinkage in patients treated first-line or second-line
Poor response or resistance	Nonsignificant decrease of GH and IGF-I levels with no achievement of control and no tumor shrinkage in patients treated first-line or increase in tumor size in any patient

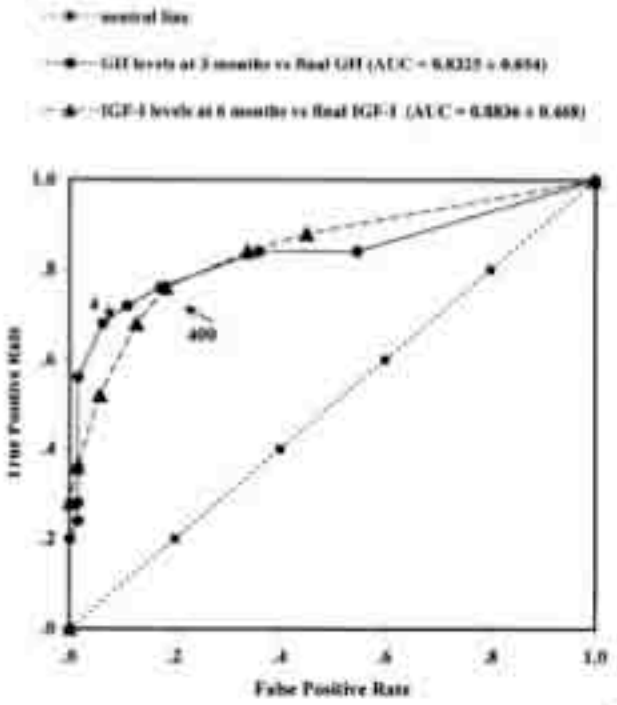
Colao et al. Endocrine Reviews, April 2011, 32:247

Strategia terapeutica

Resistance to somatostatin analogues

Four-Year Treatment with Octreotide-Long-Acting Repeatable in 110 Acromegalic Patients: Predictive Value of Short-Term Results?

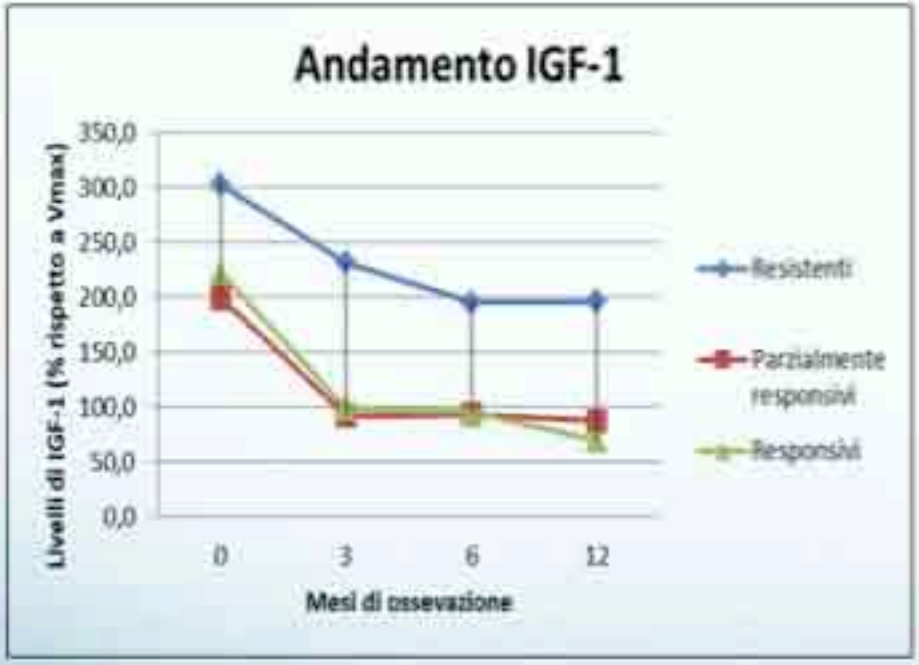
Patients attaining safe GH and normal IGF-I had GH levels below 5 µg/liter after 3 months and IGF-I levels below 550 µg/liter after 6 months

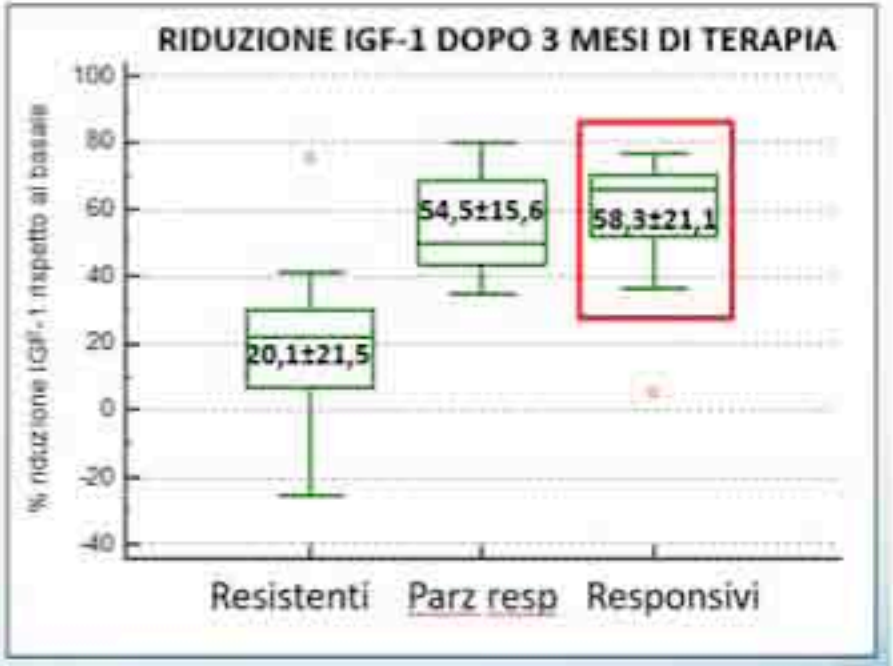


Cozzi R et al J Clin Endocrinol Metab 2003;88; 3090

Strategia terapeutica

Resistance to somatostatin analogues





La riduzione ≥ 50% dei livelli di IGF-1 dopo 3 mesi di terapia è predittiva di una buona risposta a lungo termine

Dati personali

Strategia terapeutica

PROSPETTIVA DI GRAVIDANZA

Cosa prevedono le linee guida?

Strategia terapeutica

Acromegaly: An Endocrine Society Clinical Practice Guideline

Pregnancy

We suggest discontinuing long-acting SRL formulations and pegvisomant approximately 2 months before attempts to conceive, with use of short-acting octreotide as necessary until conception. (2|⊕⊕OO)

During pregnancy, we recommend that acromegaly medical therapy be withheld and administered only for tumor and headache control. (1| ⊕⊕OO)

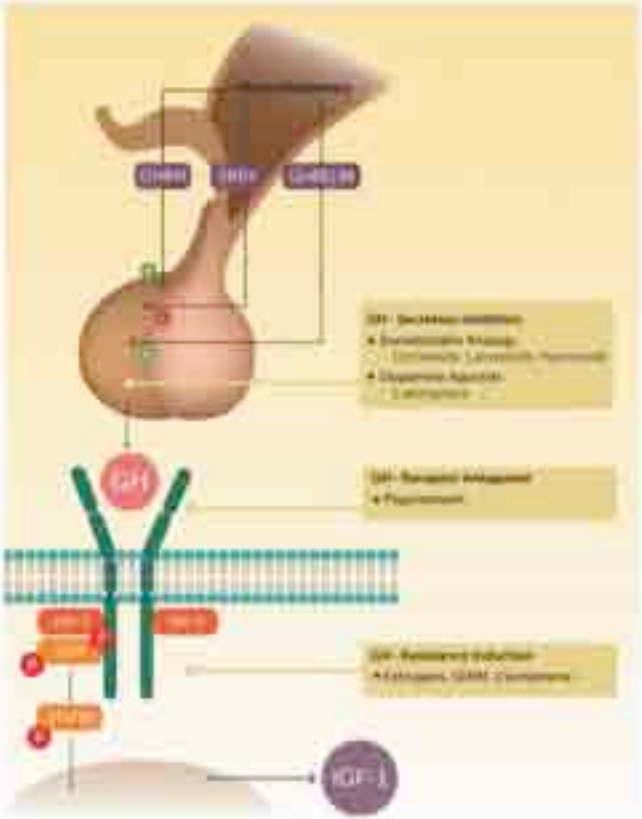
During pregnancy, we suggest serial visual field testing in patients with macroadenomas. (2| ⊕⊕⊕O)

We suggest against monitoring GH and/or IGF-1 levels during pregnancy. (2| ⊕⊕⊕O)

Katznelson L et al., J Clin Endocrinol Metab 2014;99:33

Strategia terapeutica

Estrogens and selective estrogen receptor modulators in acromegaly



Estrogens and selective estrogen receptor modulators in acromegaly

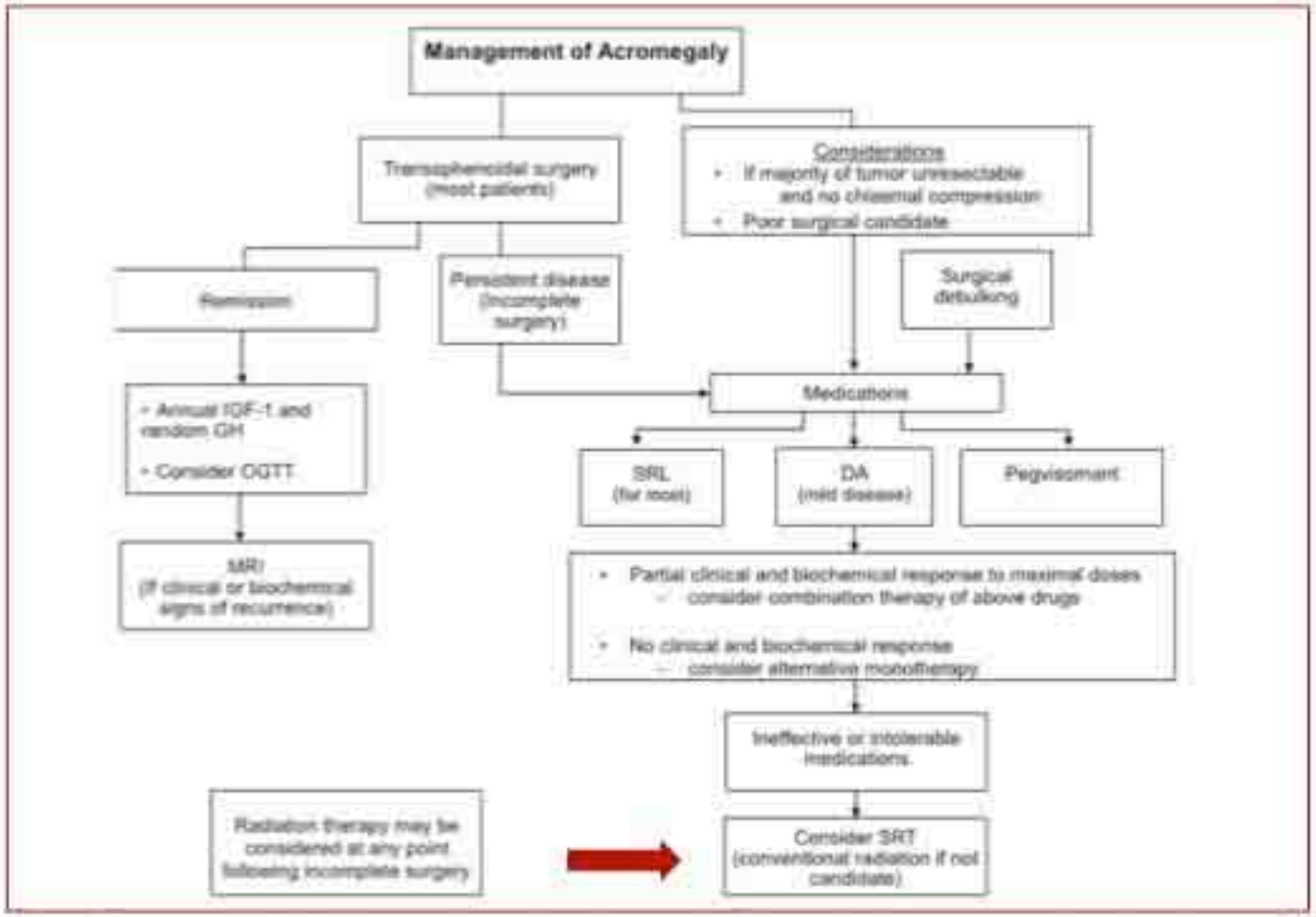
Main studies assessing estrogen and SERMs on acromegaly

Study	Patients	Drug used	Duration of the study (months)	Patients on drugs for acromegaly	Mean IGF reduction (%)
Cozzi et al. [64]	6 men 13 women	Tamoxifen 20–40 mg/day	2 months	19 off	29
Adamazo et al. [67]	13 women (postmenopausal)	Raloxifen 60 mg/day	6 months	9 off 1 Cab 3 Oct LAR	35
Cozzi et al. [63]	3 women (reproductive age) 4 women (hypogonadism or postmenopausal)	Triphasic pill (etinyl-estradiol 30-40-30 mcg/day and desogestrel 50-70-100 mg/day)	6 months	3 off 3 Oct-Lar 7 Oct-LAR + Cab	15
Dimaraki et al. [68]	8 men	Raloxifen 60 mg per os/day	5 weeks	6 off 2 Oct-LAR	6
Vallette et al. [61]	6 women (reproductive age) 1 woman (hypogonadism) 6 women (postmenopausal)	Ethinylestradiol 20 µg, Levonorgestrel 100 µg	3.1 years	4 off 7 Oct LAR	37
Shimon et al. [62]	3 women (reproductive age) 1 woman (postmenopausal)	Oral contraceptives (transdermal ones)	Not reported	1 off 2 Oct-LAR 1 Peg	31 to 98) Mean not reported
Ballili et al. [66]	15 men 2 women (postmenopausal)	Tamoxifen 20–40 mg/day	4 months	12 off 1 Oct-LAR + Peg 1 Cab 1 Oct-LAR	12
Duarte et al. [69]	16 men	Clomiphene 50 mg/day	3 months	1 Oct-LAR 7 Oct-LAR + Cab 8 Cab	11

Legend: off without medications for acromegaly, *Oct-LAR* Octreotide long-acting release, *Cab* Cabergoline.

Duarte FH et al Endocrine 2016

Strategia terapeutica



Katznelson L et al., J Clin Endocrinol Metab 2014;99:33

Strategia terapeutica

L'AIFA con la Determina 29 aprile 2016,

pubblicata sulla G.U. n. 115 del 18.05.2016, in vigore dal 19 maggio 2016,
ha definito il regime di rimborsabilità, di fornitura ed il prezzo di vendita del medicinale

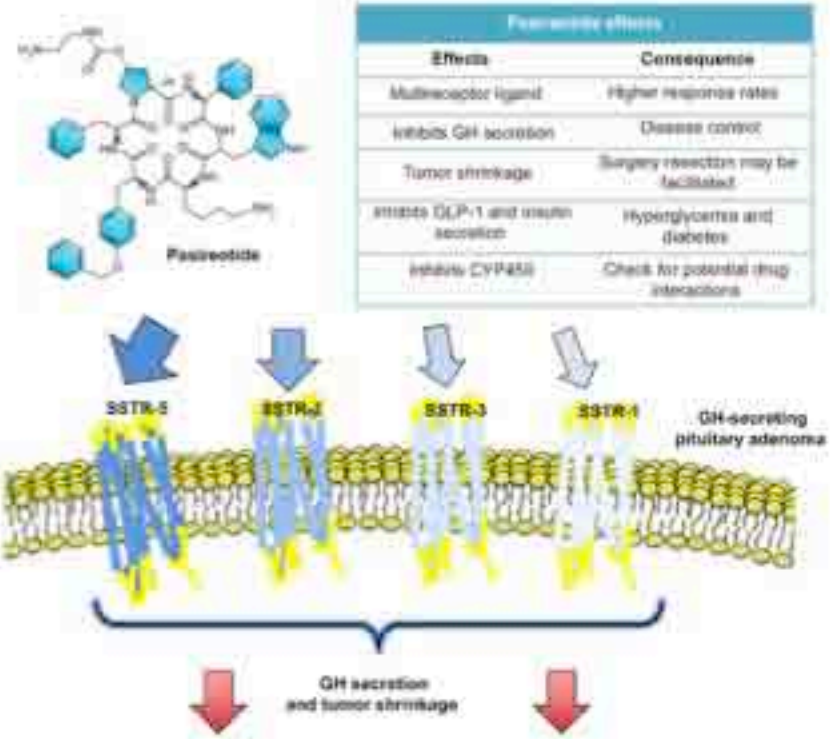
Signifor® (pasireotide)

INDICAZIONE

trattamento di pazienti adulti con acromegalia
per i quali l'intervento chirurgico
non è indicato o non è stato risolutivo
e che non sono adeguatamente controllati con il trattamento
con un altro analogo della somatostatina

Strategia terapeutica

Pasireotide: a novel treatment for patients with acromegaly



Cuevas-Ramos D & Fleseriu M Drug Design, Development and Therapy 2016:10 227

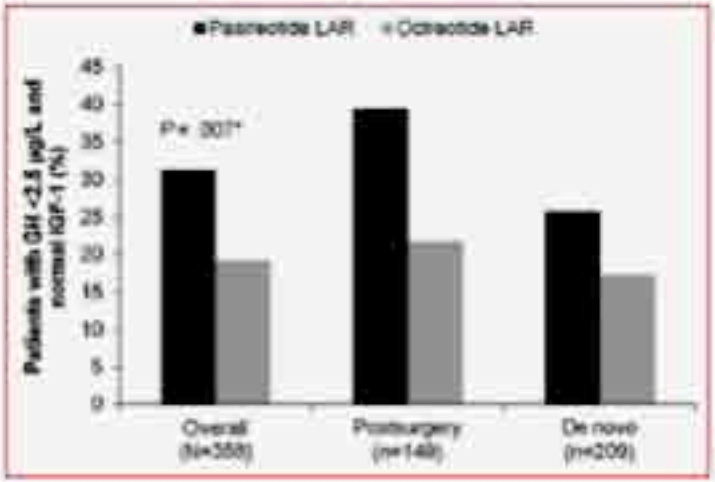
ANALOGHI SOMATOSTATINA
PASIREOTIDE

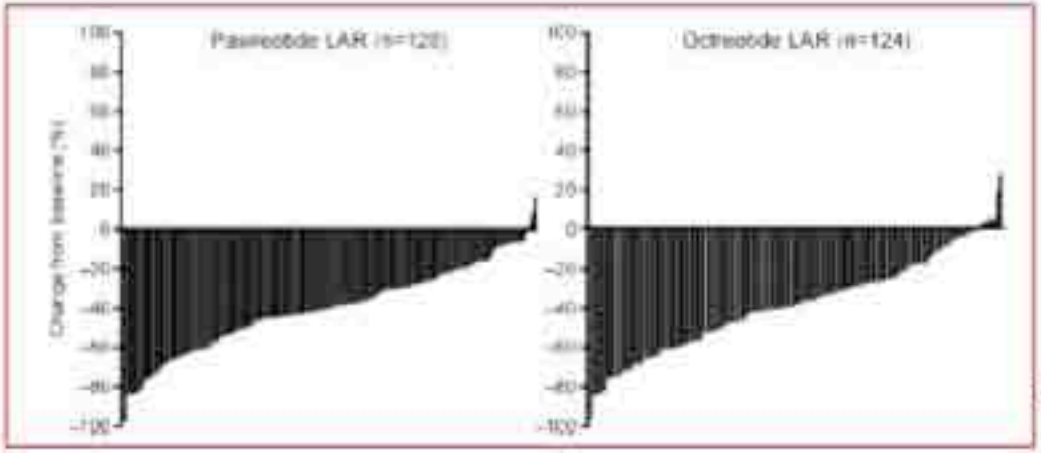
Pasireotide Versus Octreotide in Acromegaly: A Head-to-Head Superiority Study *JCEM 2014*

A. Colao, M. D. Bronstein, P. Freda, F. Gu, C.-C. Shen, M. Gadelha, M. Fleseriu, A. J. van der Lely, A. J. Farrall, K. Hermosillo Reséndiz, M. Ruffin, Y. Chen, and M. Sheppard*, on behalf of the Pasireotide C2305 Study Group

OCT LAR 182 pts: 20 mg→ 30 mg/28
PAS LAR 176 pts: 40 mg→ 60 mg/28

12 MESI





EFE 2017

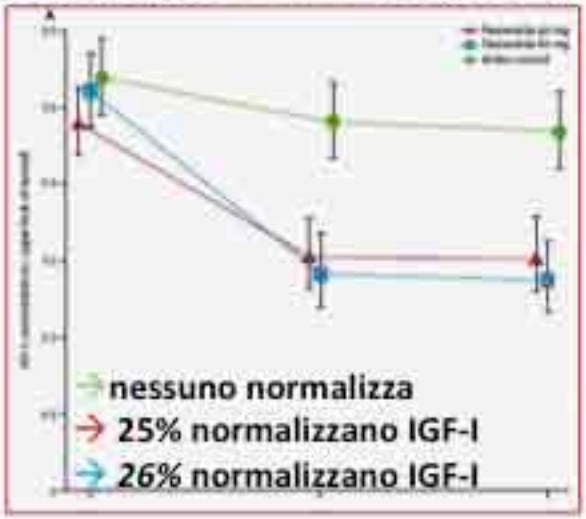
EFFETTI COLLATERALI Stessi degli SSA classici - Aumento rischio alterazioni glicemiche

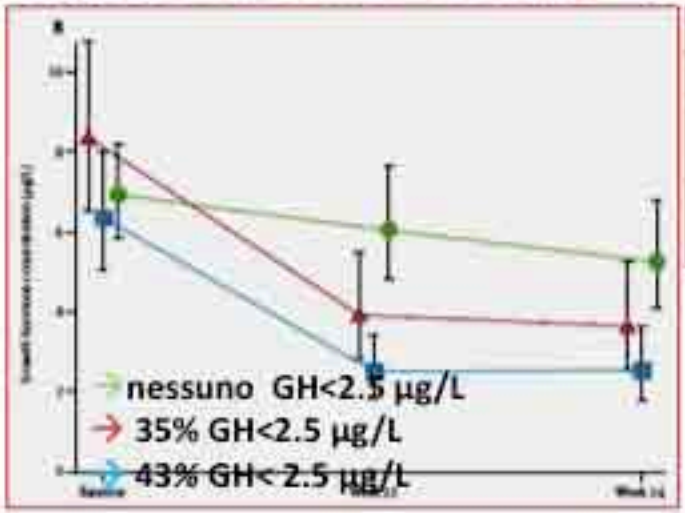
ANALOGHI SOMATOSTATINA
PASIREOTIDE

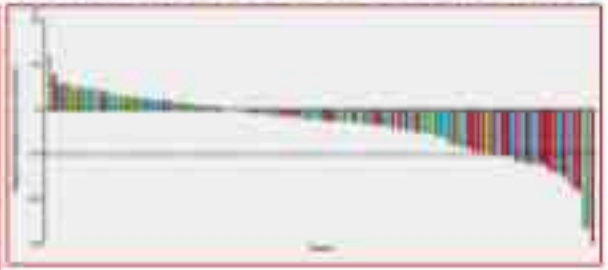
Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial

Gadelha
Lancet Diab End 2014

Pz. non controllati dopo 6 mesi di OCT LAR (30mg) - LAN ATG (120mg)
Continuano stessa terapia - Passano a Pasireotide LAR 40mg - Passano a Pasireotide LAR 60mg







Riduzione tumorale >25%
- 1.5%
- 18.5%
- 10.8%

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Strategia terapeutica

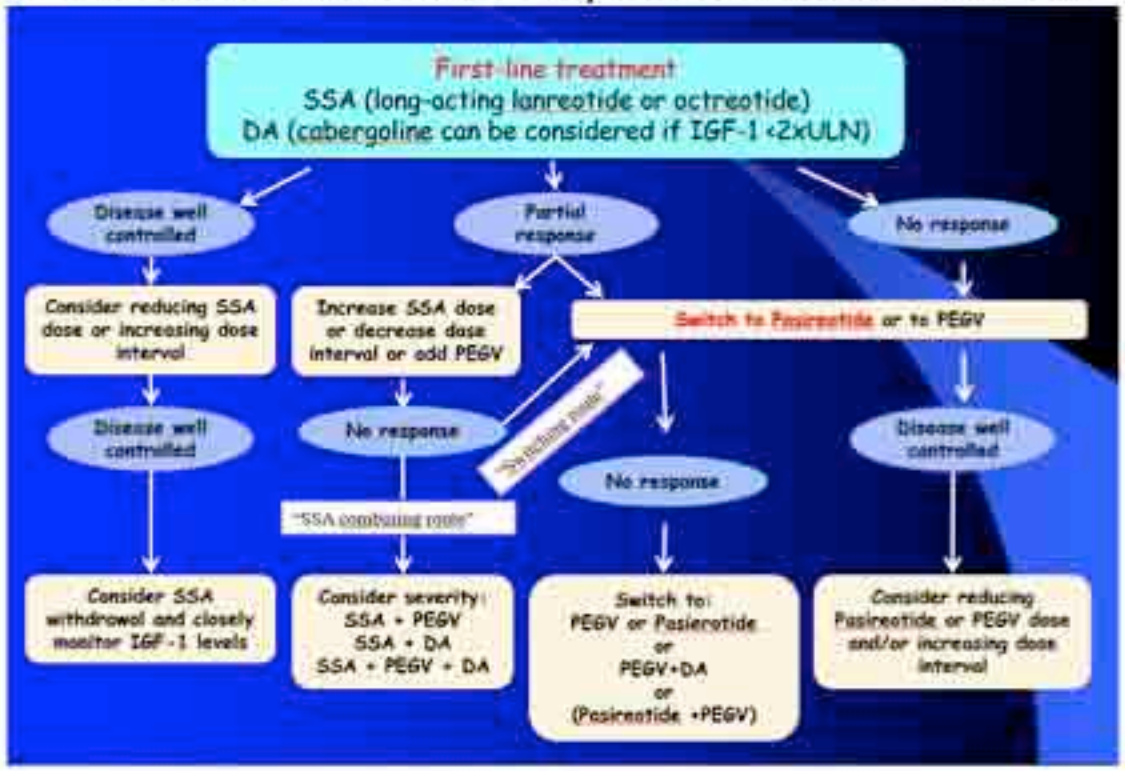
PASIREOTIDE

Quale posto
nell' ARMAMENTARIO
TERAPEUTICO?

Strategia terapeutica

Algorithm for the medical management of acromegaly after surgery or as primary treatment strategy when surgery is inappropriate

Pasireotide: Place in therapeutic armamentarium



Modified from Giustina A et al. *Nat Rev Endocrinol* 2014;10:243–248

Strategia terapeutica

Trattamento
dell'acromegalia

TERAPIA
PERSONALIZZATA

Bondanelli Marta
Franceschetti Paola
Lupo Sabrina
Rossi Roberta

Zatelli Maria Chiara

Bruni Stefania

Thanks for the attention

Damiani Luca
D'Ercole Francesca
Gagliardi Irene
Mella Alessandro
Mungari Roberta
Tarquini Mario

Sezione di Endocrinologia e Medicina Interna
Dipartimento di Scienze Mediche
Università degli Studi di Ferrara
Maria Rosaria Ambrosio mbrmrs@unife.it
Ambulatorio delle Patologie Ipofisarie
0532 236519

Ettore degli Uberti

THM

Renato Cozzi

SC Endocrinologia

ASST Grande Ospedale Metropolitano Niguarda

renato.cozzi@ospedaleniguarda.it

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Italfarmaco, Ipsen, Novartis

Quadro clinico alla diagnosi

- disordini mestruali
- cambio aspetto fisico e/o crescita parti acrali
- cefalea
- parestesie/tunnel carpale

- Comorbilità (sindrome acromegalica):
  - ricerca
  - controllo periodico
  - trattamento rigoroso

Diagnosi biochimica

- IGF-1 esame più sensibile per ipersecrezione di GH
- Valori di IGF-1 età-dipendenti
- Quando e se dosare ancora il GH
- Quale cut-off di GH con i metodi ultrasensibili
- I dosaggi di GH/IGF-1 producono valori eterogenei
- I risultati dei diversi laboratori non possono essere paragonati tra di loro

Terapia medica

- Ampia disponibilità di farmaci anti-GH
- Sartorializzazione terapeutica
- Recente disponibilità di Pasireotide LAR
- Quale posto nella strategia terapeutica
- Come controllare la sua tossicità

Casi difficili

- Definizione:
  - malattia aggressiva
  - casi non normalizzati dalla chirurgia?
  - pazienti resistenti ai farmaci?
- Obiettivi del trattamento: normalizzazione di GH/IGF-1 e controllo volume tumorale:
  - «cura definitiva»: radioterapia. Pro e contro
  - controllo farmacologico della malattia. Pro e contro

Strategia terapeutica

- Linee guida
- Desiderio dei pazienti
- Norme regolatorie
- Gravidanza
- Personalizzazione della terapia