



Acromegalia não “controlada”: abordagem em longo prazo

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Declaração de Conflito de Interesse

De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e a Resolução RDC 96/2008 da Agência Nacional de Vigilância Sanitária declaro os seguintes conflitos de interesse para essa apresentação:

- *Palestrante: Novartis Biociências, Ipsen*
- *Pesquisa Clínica: Novartis Biociências*
- *Apoio Associação SEMPR Amigos: Novartis Biociências, Ipsen, Pfizer*

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Cesar Luiz Boguszewski, CRM-PR 11236



12th Acromegaly Consensus Conference
19-21 Junho, 2018 - Praga, República Tcheca



O que os resultados de consensos significam?

Primary
DOI: 10.1007/s11102-012-0420-4



Cortina D'Ampezzo

Outcomes in selected, related clinical conditions were also considered, and included pregnancy, familial acromegaly and invasive macroadenomas. The need for a new disease staging model was considered, and design of such a tool was proposed.

acromegaly consensus was published in March 2011, the Acromegaly Consensus Group that had produced these documents met to revise and update guidelines on acromegaly complications. The meeting was sponsored by the Pituitary Society and the European Neuroendocrinology



Versailles



Munich

Evidence/Consensus Process: Relevant assays, biochemical measures, clinical outcomes, and definition of disease control were discussed, based on the available published evidence, and the strength of consensus statements was rated.

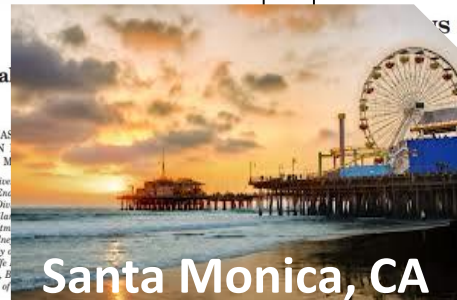
Conclusions: Criteria to define active acromegaly and disease control were agreed, and several significant changes were made to the 2000 guidelines. Appropriate methods of measuring and achieving disease control were summarized. *J Clin Endocrinol Metab* 95: 3141-3148, 2010



Paris



Vancouver



Santa Monica, CA



Londres

Conclusions: The group developed a consensus on the approach to managing acromegaly including appropriate roles for neurosurgery, medical therapy, and radiation therapy in the management of acromegaly.

ABSTRACT
In February 1999, a workshop was held in Cortina, Italy to develop a consensus defining the criteria for cure of acromegaly. The workshop was sponsored by the University of Brescia and hosted by the Italian

endocrinologists, neurosurgeons, and radiotherapists skilled in the management of acromegaly. This statement summarizes the consensus achieved in these discussions. *J Clin Endocrinol Metab* 88: 428-429, 2000.

For these reasons, the European Pituitary Society formed a joint and invited international experts to address the current status of both biochemical assessment and long-term monitoring in patients with acromegaly at a consensus conference held in Feldafing, Germany, in April 2003.

by RIAs. There is no simple conversion factor between the two types of assays, but it would appear that the target threshold may be lowered severalfold. Regardless of methodology, an optimal assay should

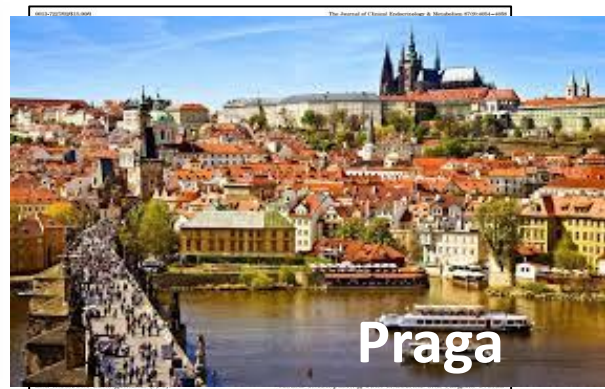


Sevilha



Nice/Monte Carlo

European Journal of Endocrinology 153: 737-740



Praga

Canadian consensus guidelines for the diagnosis and management of acromegaly
Ezzat *et al.*, Clin Invest Med 2006

**Treatment guidelines for acromegaly:
Report from Scandinavian Workshop on
the Treatment of Acromegaly**
Growth Horm IGF Res. 2001

**American Association of Clinical Endocrinologists
medical guidelines for clinical practice for the
diagnosis and treatment of acromegaly: 2011 update**
Katznelson *et al.*, Endocr Pract 2011

**Consensus of the Polish Society of Endocrinology.
Presurgical somatostatin analogs therapy in acromegaly**
Bolanowski *et al.*, Endokrynol Pol 2007

**Croatian Society of Endocrinology guidelines
for the diagnosis and treatment of acromegaly**
Kastelan *et al.*, Lijec Vjesn 2012

**Acromegaly: an endocrine society clinical
practice guideline.**
Katznelson *et al.*, J Clin Endocrinol Metab 2014

**Practical guidelines for diagnosis and treatment of
acromegaly. Grupo de Neuroendocrinología de la
Sociedad Española de Endocrinología y Nutrición.**
Cordido *et al.*, Endocrinol Nutr 2013

**Management of acromegaly in Latin America:
expert panel recommendations**
Barkan *et al.*, Pituitary. 2010

French consensus on the management of acromegaly
Chanson *et al.*, Ann Endocrinol (Paris) 2009

**Recommendations of Neuroendocrinology Department
from Brazilian Society of Endocrinology and Metabolism
for diagnosis and treatment of acromegaly in Brazil**
Vieira Neto *et al.*, Arq Bras Endocrinol Metabol. 2011

**AME Position Statement on clinical
management of acromegaly**
Cozzi *et al.*, J Endocrinol Invest 2009

**Expert consensus document:
A consensus on the medical treatment
of acromegaly.**
Giustina *et al.*, Nat Rev Endocrinol 2014

Opções de Tratamento na Acromegalia

- Controle Hormonal (normalizar IGF-1 e GH)
- Controle do tumor
- Preservação da Função Hipofisária
- Melhora da Qualidade de Vida
- Controle das comorbidades
- Normalização do Risco de Mortalidade (SMR)

- **Cirurgia Transesfenoidal**

- **Medicamentos**

- **I – Análogos da Somatostatina**

- *Lanreotide*

- *Octreotide*
- *Pasireotide*

- **II – Agonistas Dopaminérgicos**

- *Cabergolina*

- **III – Antagonista do receptor do GH**

- *Pegvisomanto*

- *IV – Off label*

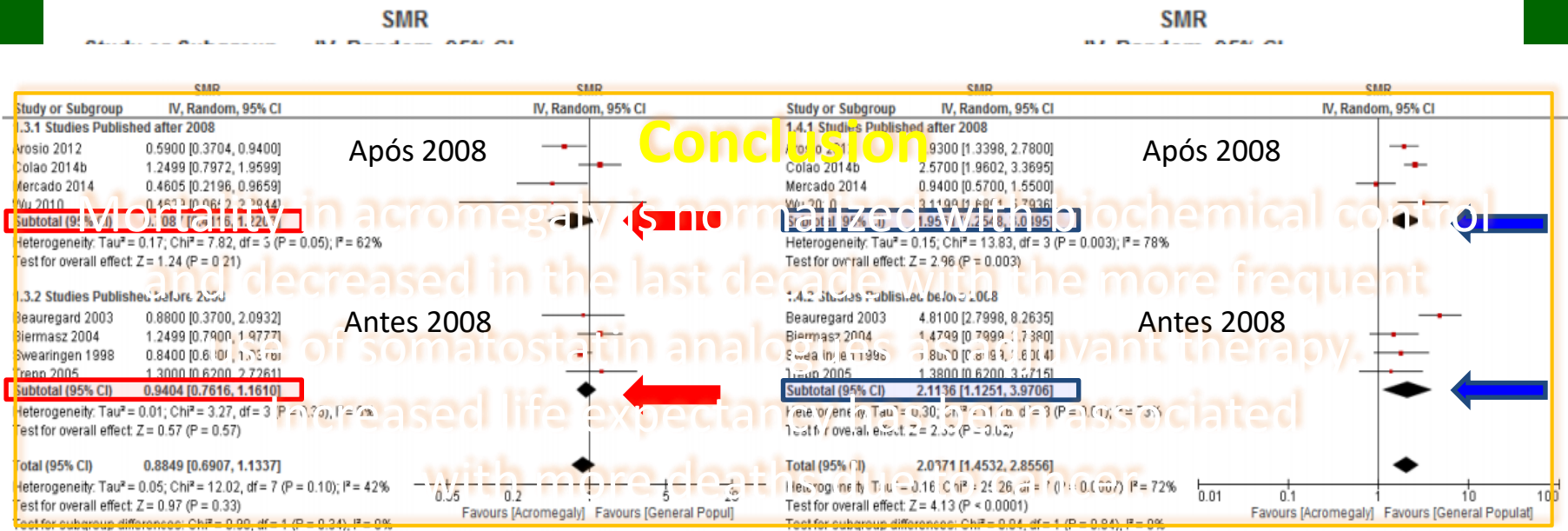
- **Radioterapia**



Mortalidade na Acromegalia

Bolfi F, Neves AF, Boguszewski CL, Nunes-Nogueira VS. Eur J Endocrinol 2018

Mortality in Acromegaly decreased in the last decade: A Systematic Review and Meta-Analysis



Doença Controlada

Test for overall effect: Z = 4.01 (P < 0.00001)

Total (95% CI) 1.34 [0.97, 1.84]

Heterogeneity: Tau² = 0.22; Chi² = 114.76, df = 9 (P < 0.00001); I² = 92%

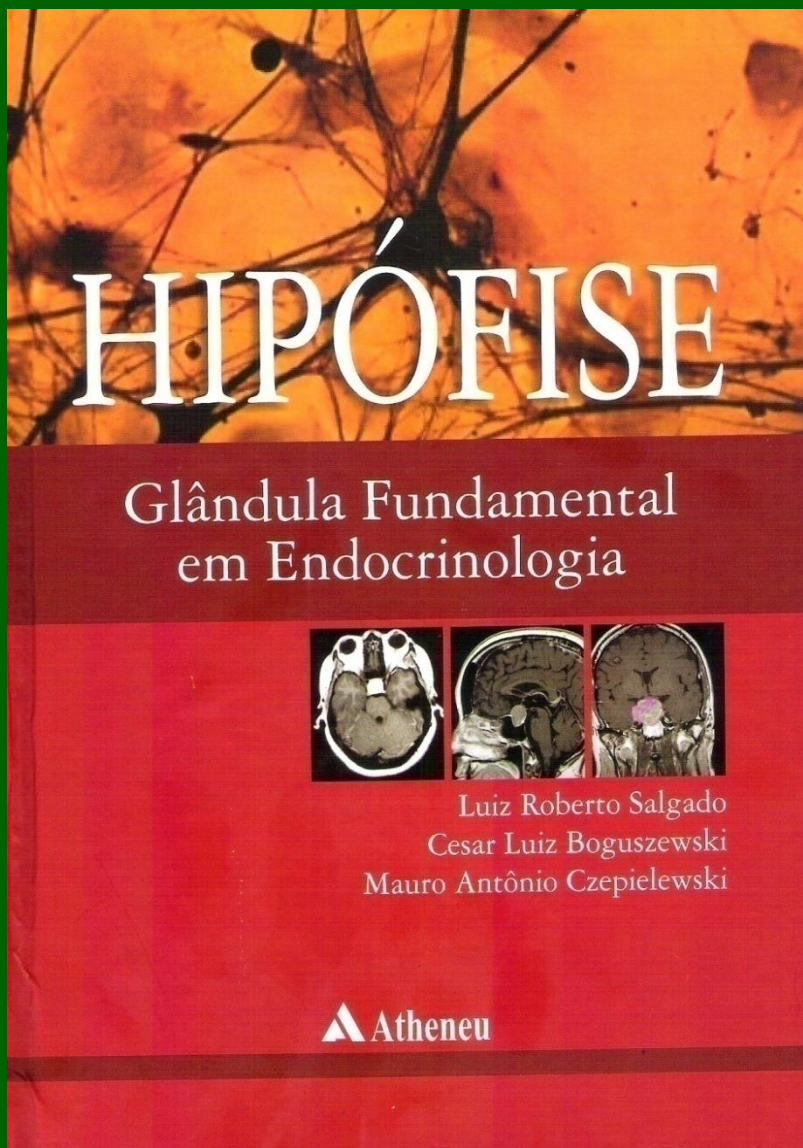
Test for overall effect: Z = 1.80 (P = 0.07)

Test for subgroup differences: Chi² = 17.72, df = 1 (P < 0.0001); I² = 94.4%

Doença Não Controlada

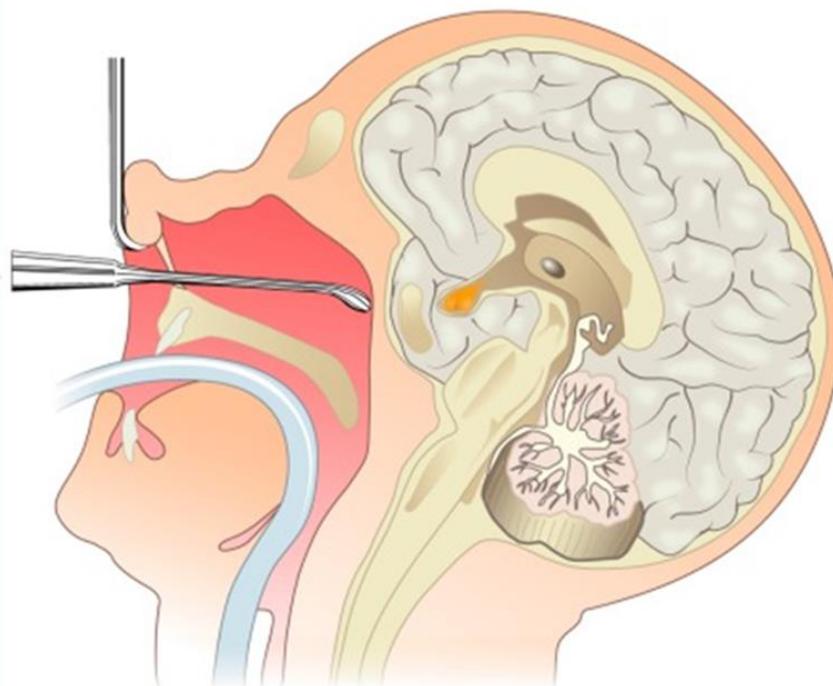


Opções de Tratamento na da Acromegalia



- Cirurgia Transesfenoidal
- **Medicamentos**
 - I – Analógos da Somatostatina
 - Lanreotide*
 - Octreotide*
 - Pasireotide*
 - II – Agonistas Dopaminérgicos
 - Cabergolina*
 - III – Antagonista do receptor do GH
 - Pegvisomanto*
 - IV – *Off label*
- **Radioterapia**

Resultados do Tratamento Cirúrgico na Acromegalia



Cirurgia Transesfenoidal

- **54 pacientes (30 H:24 M)**
todos operados pela mesma
equipe cirúrgica (2001-2011)
Idade: 41.5 ± 12.3 anos
- **91% macroadenomas**
- **Doença Controlada (DC):**
sem tratamento adicional
Doença Não Controlada (DNC):
tratamento adjuvante
- **Curto-prazo (3 meses)**
61% DC, 39% DNC
- **Longo-prazo (>12 meses)**
51,8% DC, 48,2% DNC



Cunha MLV. Resultados da cirurgia transesfenoidal realizada por uma única equipe neurocirúrgica no tratamento da acromegalia: comparação entre diferentes critérios bioquímicos na análise da remissão da doença. 2015

Reoperação na Acromegalia Não Controlada

Almeida et al, J Neurosurg. 2017

Características Clínicas

Characteristic	First-Time Surgery	Reoperation	p Value
Age, yrs	49.1 ± 15.7	34.3 ± 12.8	0.007*
Sex			0.29
Female	21 (60%)	4 (36.4%)	
Male	14 (40%)	7 (63.6%)	
Preop GH, µg/L	25.6 ± 36.8	7.7 ± 13.1	0.04*
Preop IGF-I, µg/L	737 ± 340	745 ± 375	0.94
Preop hormonal deficits	3 (9.1%)	3 (27.2%)	0.31
Tumor size	16.9 ± 11.9	14.8 ± 10.0	0.574
Microadenomas	13 (37.1%)	5 (45.5%)	0.73
Macroadenomas	22 (62.9%)	6 (54.5%)	
Knosp classification			0.468
Grade 0	3 (8.6%)	1 (9.1%)	
Grade I	14 (40%)	4 (36.4%)	
Grade II	8 (22.9%)	1 (9.1%)	
Grade IIIA	2 (5.7%)	1 (9.1%)	
Grade IIIB	3 (8.6%)	1 (9.1%)	
Grade IV	5 (14.3%)	3 (27.3%)	
CS invasion	10 (28.6%)	5 (45.5%)	0.46

Preditores de Sucesso

Variable	Controlled Disease	Active Disease	p Value
First-time surgery (n = 35)	25 (71.4%)	10 (28.6%)	
Age, yrs	52.4 ± 15.3	39.9 ± 13.4	0.03*
Sex	10 M/15 F	4 M/6 F	0.678
Preop GH, µg/L	16.9 ± 25.5	57.7 ± 55.0	0.01*
Preop IGF-I, µg/L	657 ± 300	1021 ± 340	0.01*
Tumor size, mm	11.6 ± 4.23	31.1 ± 12.8	0.001*
Microadenomas	12	1	0.055
Macroadenomas	13	9	
CS invasion	2	8	0.001*
Reoperation (n = 11)	7 (63.6%)	4 (36.3%)	
Age, yrs	35.5 ± 14.2	32.7 ± 9.17	0.77
Sex	4 M/3 F	3 M/1 F	0.53
Preop GH, µg/L	3.72 ± 2.98	23.8 ± 21.9	0.18
Preop IGF-I, µg/L	694 ± 379	867 ± 414	0.66
Tumor size, mm	12.1 ± 8.8	19.5 ± 11.7	0.26
Microadenomas	4	1	0.54
Macroadenomas	3	3	
CS invasion	1	4	0.01*

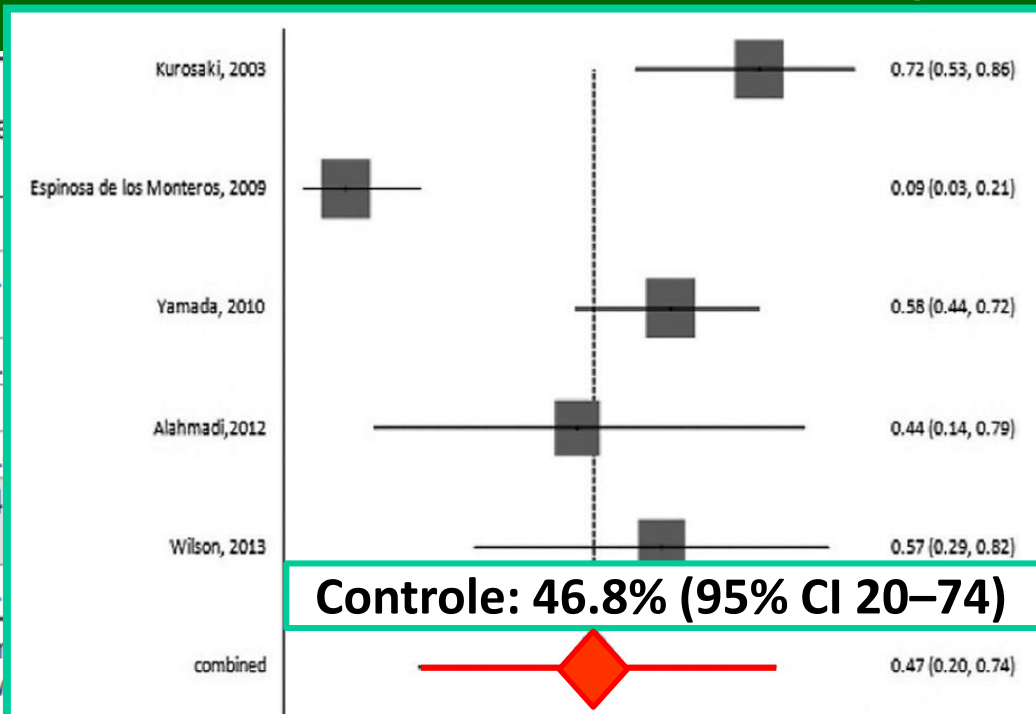
Reoperação na Acromegalia Não Controlada

Almeida et al, J Neurosurg. 2017

Meta-análise Resultados Cirúrgicos

Authors & Year	No. of Pts	Me
Kurosaki et al., 2003	32	43
Espinosa de los Monteros et al., 2009	53	38
Yamada et al., 2010	53	41
Alahmadi et al., 2012	9	50
Wilson et al., 2013	14	41
Total	161	4
Current series	11	34

Endo = endoscopy; FU = follow-up; n = number of patients
* The 2000 guidelines are also known



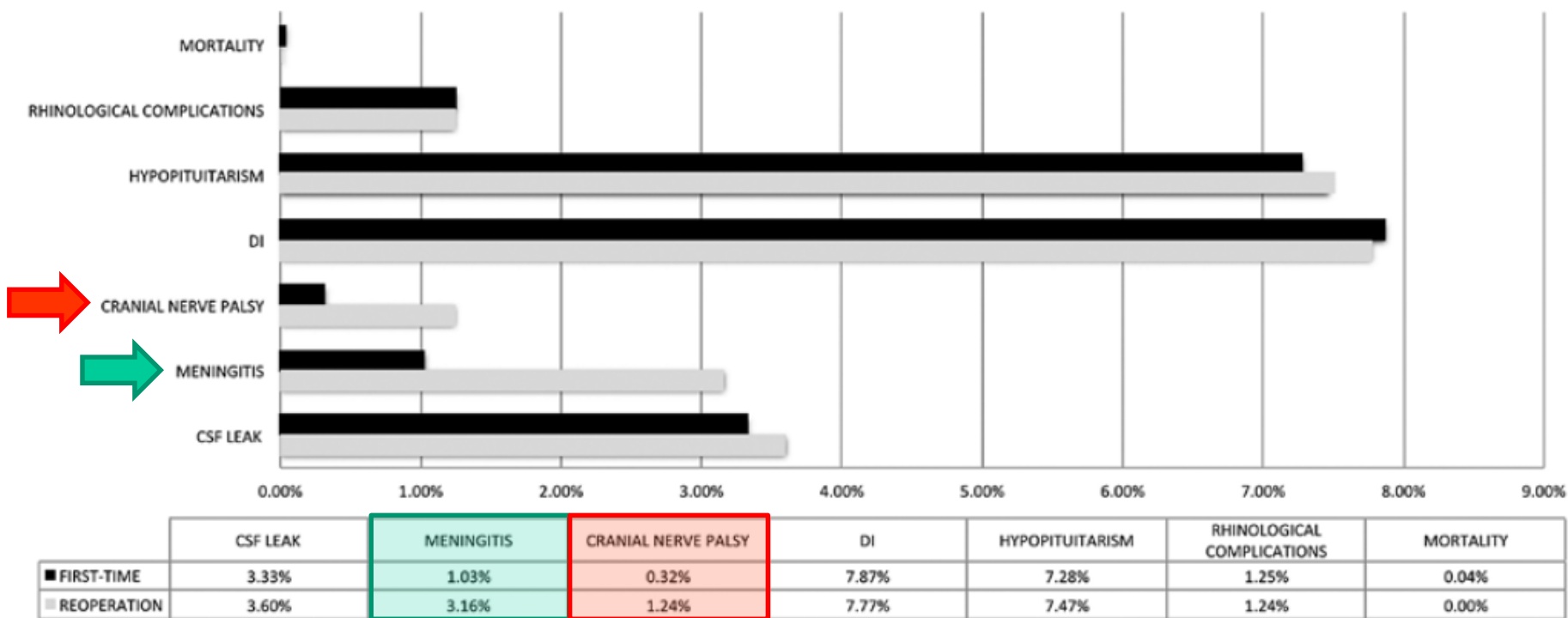
	CS Invasion (%)	FU (mos)
Thomas	6 (18.7%)	48
	12 (23%)	NA
	25 (47.1%)	56 (12-144)
	4 (44%)	21 (3-64)
	NA	NA
	47 (32%)	53.7 (3-144)
	5 (45.4%)	70 (6-150)

	Primeira Cirurgia (%)	Reoperação (%)
Microadenoma	77,7 (95% CI 68-85)	73,6 (95% CI 32-98)
Macroadenoma	54,3 (95% CI 45-62)	27,5 (95% CI 5-57)*
Invasão Seio Cavernoso	38,5 (95% CI 27-50)	14,7 (95% CI 4-29)*

Reoperação na Acromegalia Não Controlada

Almeida et al, J Neurosurg. 2017

Complicações Cirúrgicas



Análogos da Somatostatina na Acromegalia Não Controlada

Kasuki, Wildemberg & Gadelha, Eur J Endocrinol 2017

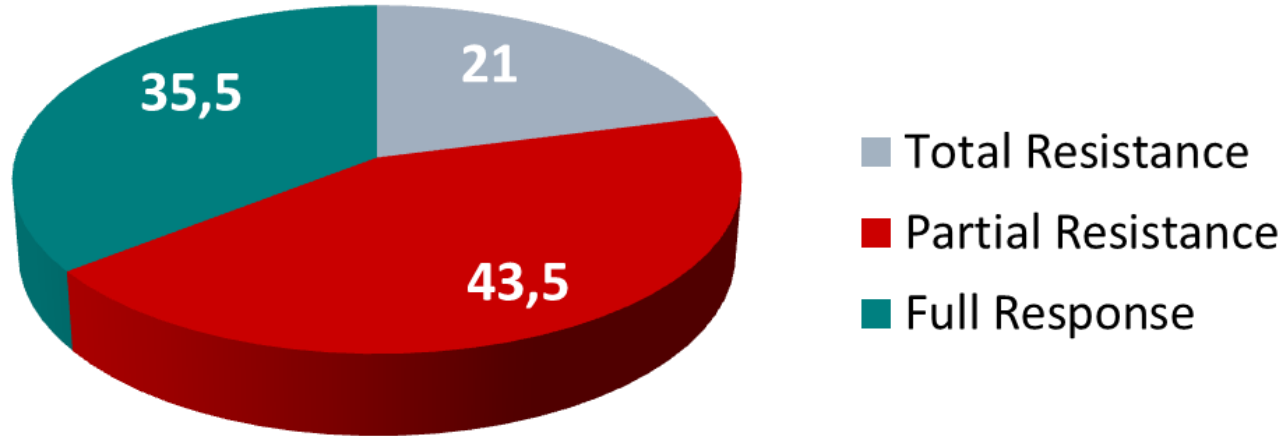
Três modelos de resposta bioquímica (dosagens de GH & IGF-I)

- (1) Acromegalia controlada (“full responders”): 30%**
GH < 1.0 µg/L e IGF-I normal (ajustado para idade)
- (2) Acromegalia parcialmente controlada (“partial responders”): 45–50%**
Redução dos níveis de GH e/ou IGF-I ≥ 50% em relação aos valores pré-tratamento, mas sem normalização
- (3) Acromegalia não controlada (“no or poor responders”): 20–25%**
Redução dos níveis de GH e IGF-I < 50% em relação aos valores pré-tratamento

Análogos da Somatostatina na Acromegalia Não Controlada

Biochemical Response (%)

n= 62 (33 women; 29 men)



■ *Total Resistance: < 50% decrease of GH and/or IGF-1 levels*

■ *Partial Resistance: $\geq 50\%$ decrease in GH and/or IGF-1 without normalization*

■ *Full Response: $\text{GH} \leq 1 \text{ ng/mL}$ and normal IGF-1*

Análogos da Somatostatina na Acromegalia Não Controlada

Giustina et al. A consensus on the medical treatment of acromegaly. Nat Rev Endocrinol 2014

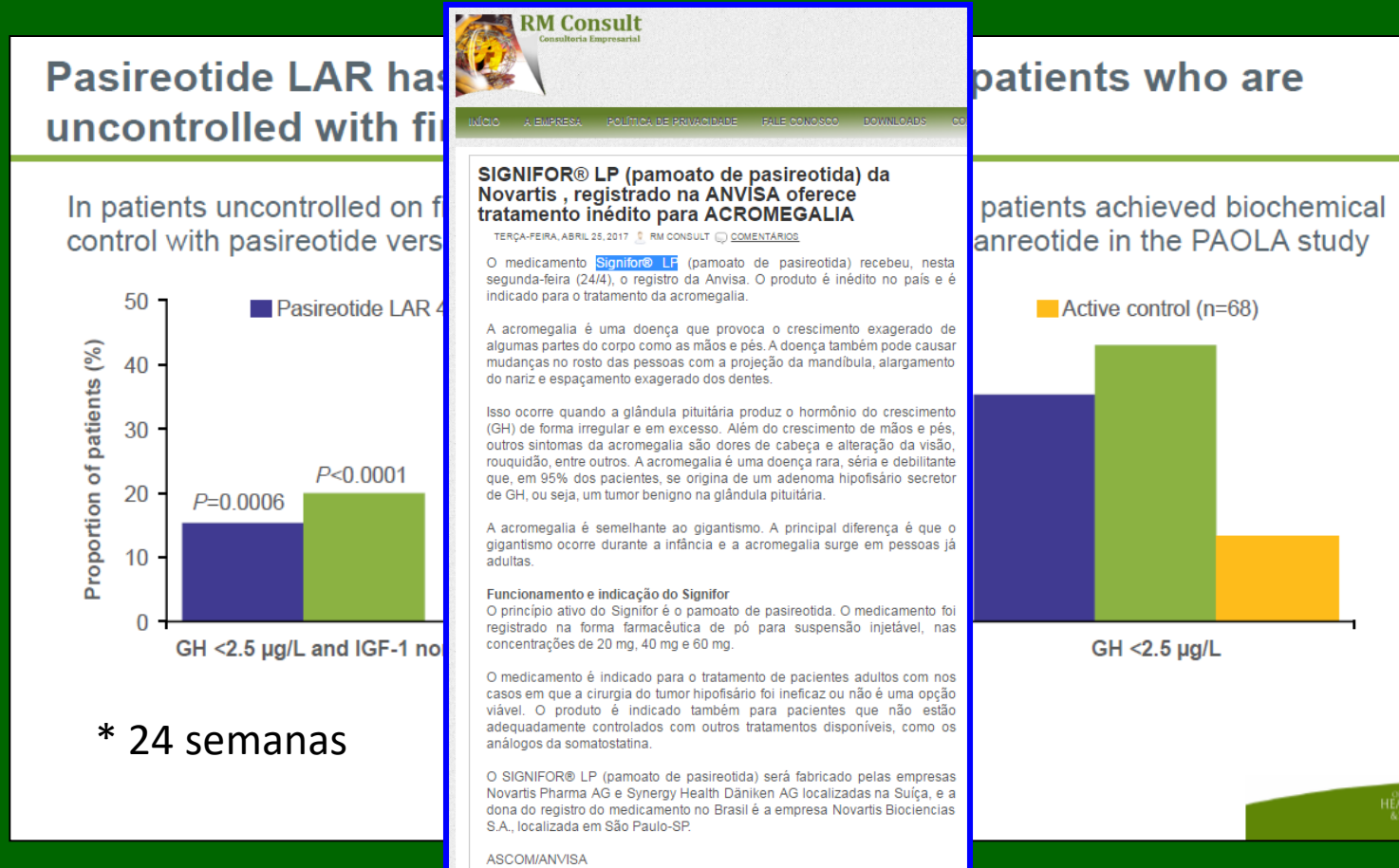
“Long-acting **lanreotide and octreotide** formulations target primarily the somatostatin receptor subtype 2 and have similar efficacy”

“Tumour shrinkage is commonly observed with long-acting **lanreotide and octreotide** therapy concordant with a reduction in GH secretion”

tumor volume can be difficult to evaluate after surgery due to the irregularity of the tumor remnant and the presence of postoperative changes

Análogos da Somatostatina na Acromegalia Não Controlada

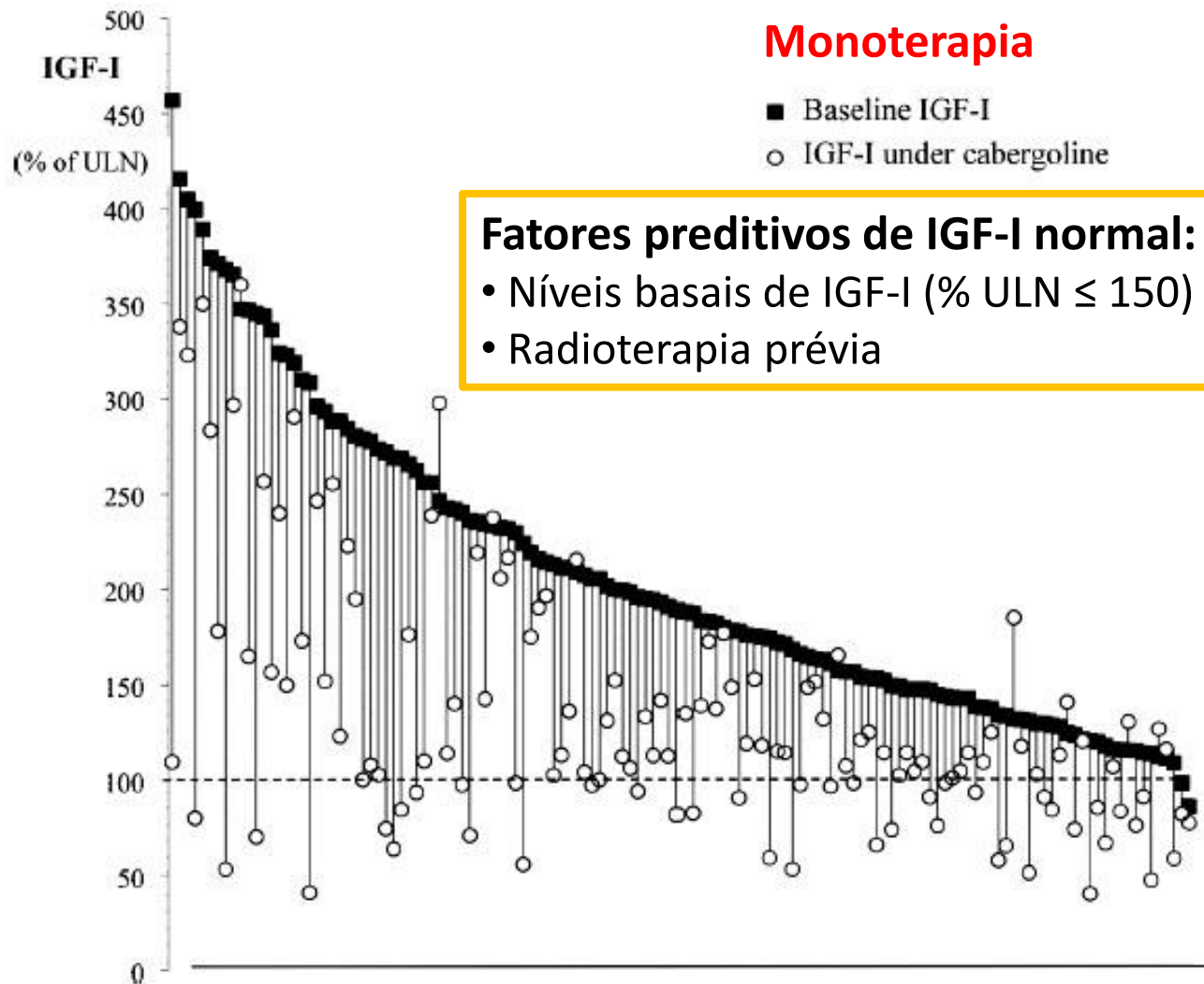
Gadelha et al., Lancet Diab Endocrinol 2014



- Eficácia: 20% dos resistentes a octreotide or lanreotide
- Segurança: hiperglicemia (diabetes) mais intensa e frequente

Cabergolina na Acromegalia Não Controlada

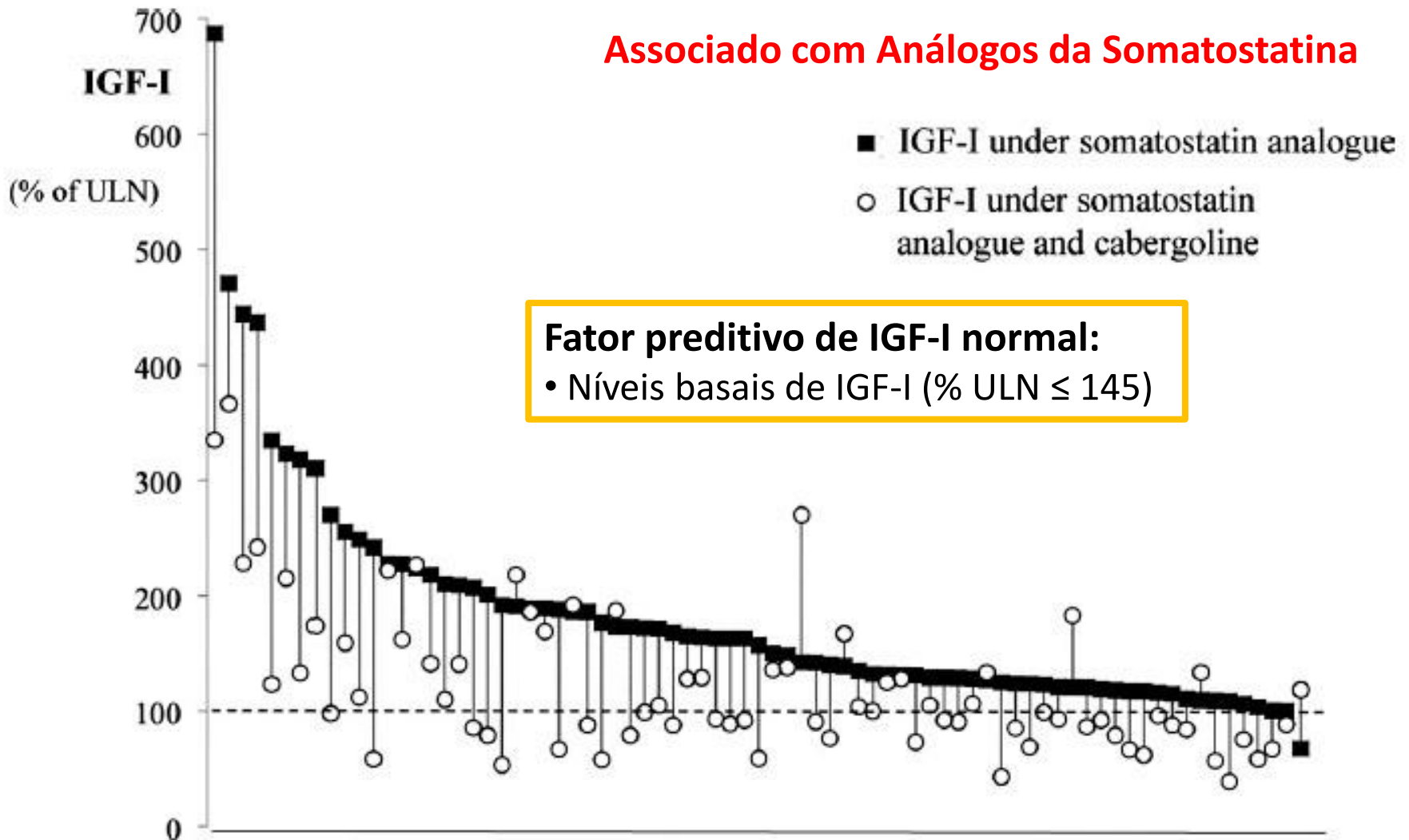
Sandret, Maison and Chanson, *J Clin Endocrinol Metab* 2011



E CABERGOLINA		
	IGF-I normal (%)	GH < 2.5 (%)
	34	48
	50	0
	NA	20
	0	0
	100	100
	57	57
	22	22
	33	33
	79	79
	73	73
	43	43

Cabergolina na Acromegalia Não Controlada

Sandret, Maison and Chanson, J Clin Endocrinol Metab 2011



Pegvisomanto na Acromegalia Não Controlada

van der Lely et al., J Clin Endocrinol Metab 2012

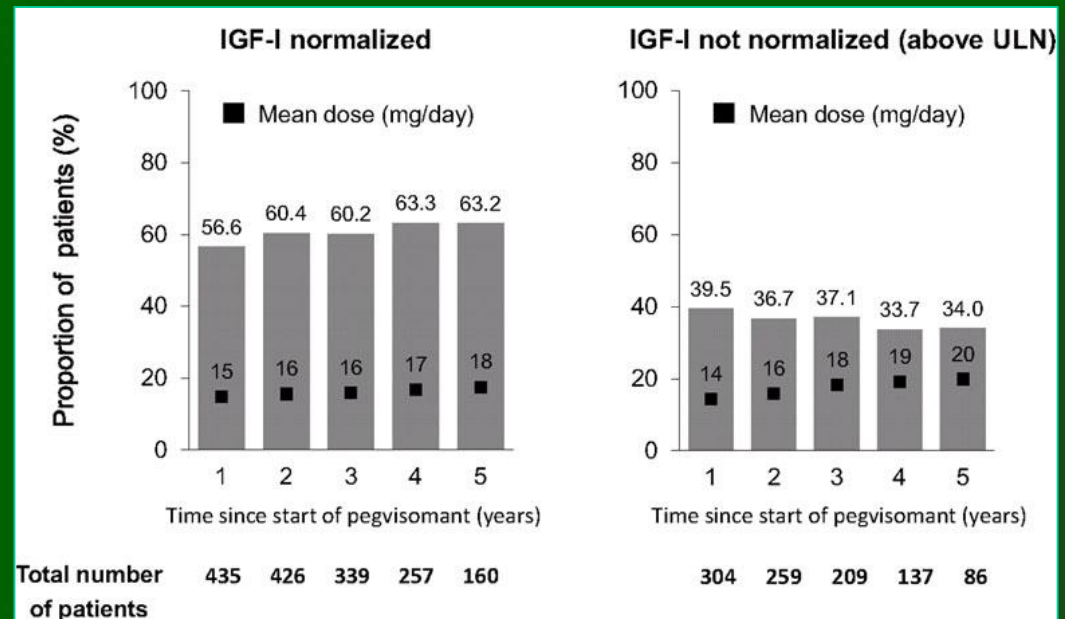
ACROSTUDY (N = 1288) Após 5 anos de terapia

Eficácia:

- Dose média diária: 18 mg
- **IGF-I normal: 63.2%**

Segurança:

- Evento adverso sério: 26 (2%)
- Crescimento tumoral (n=936): 3.2%
- Reações no local da injeção: 28 (2.2%)
- Elevação de transaminases (> 3 vezes ULN): 30 (2.5%)
- Insuficiência hepática ou morte: 0%



Pegvisomanto na Acromegalia Não Controlada

Franck et al., Eur J Endocrinol 2017

Fatores preditivos da dose de resposta ao pegvisomanto

Monoterapia

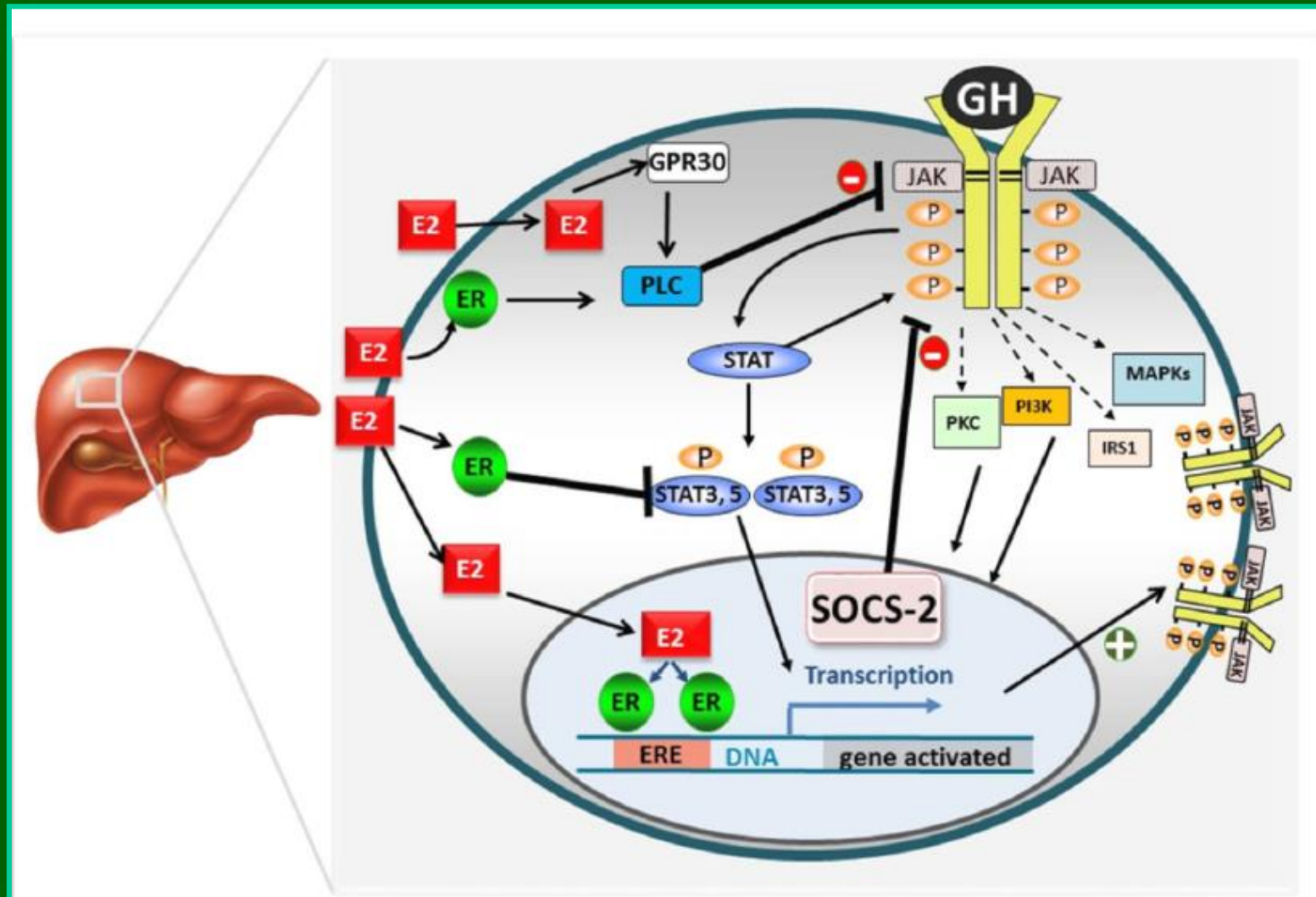
Peso do paciente

Associado com AS

Peso do paciente
Altura do paciente
Idade do paciente
Níveis de IGF-I

Estrogênio e SERMs na Acromegalia Não Controlada

Duarte, Jallad & Bronstein. *Endocrine* 2016



Estrogênio na Acromegalia Não Controlada

Duarte, Jallad & Bronstein. *Endocrine* 2016

Estudo	Mulheres (N)	Droga	Tempo (meses)	Terapia Concomitante	Média Redução IGF-I (%)
Cozzi 2003	4 idade reprodutiva 4 hipogonadismo ou pós-menopausa	Pílula trifásica Etinilestradiol 30-40-30 µg/dia Desogestrel 50-70-100 mg/dia	6	3 off 3 AS 2 AS+CAB	45
Vallette 2010	4 idade reprodutiva 1 hipogonadismo 6 pós-menopausa	Etinilestradiol 20 µg Levonorgestrel 100 µg	37,2	4 off 7 AS	57
Shimon 2012	3 idade reprodutiva 1 pós-menopausa	Contraceptivo oral Adesivo transdérmico	ND	1 off 2 AS 1 PEG	34 - 68*

Off: sem medicação para acromegalia; AS: Análogo da Somatostatina; CAB: Cabergolina; PEG: pegvisomanto; NA: não disponível

** Variação de resposta; redução média não relatada no estudo*

SERMs na Acromegalia Não Controlada

Duarte, Jallad & Bronstein. *Endocrine* 2016

Estudo	Pacientes (N)	Droga	Tempo (meses)	Terapia Concomitante	Média Redução IGF-I (%)
Cozzi 1997	6 homens 13 mulheres	Tamoxifeno 20-40 mg/dia	2	19 off	29
Attanazio 2003	13 pós-menopausa	Raloxifeno 60 mg/dia	6	9 off 1 CAB 3 AS	35
Dimaraki 2004	8 homens	Raloxifeno 120 mg/dia	1	6 off 2 AS	16
Balili 2014	15 homens 2 pós-menopausa	Tamoxifeno 20-40 mg/dia	4	14 off 1 AS+PEG 1 CAB 1 AS	17
Duarte 2015	16 homens	Clomifeno 50 mg/dia	3	4 AS 7 AS+CAB 5 CAB	41

Off: sem medicação para acromegalia; AS: análogo das Somatostatina; CAB: cabergolina; PEG: pegvisomanto

Tratamento Combinado na Acromegalia Não Controlada

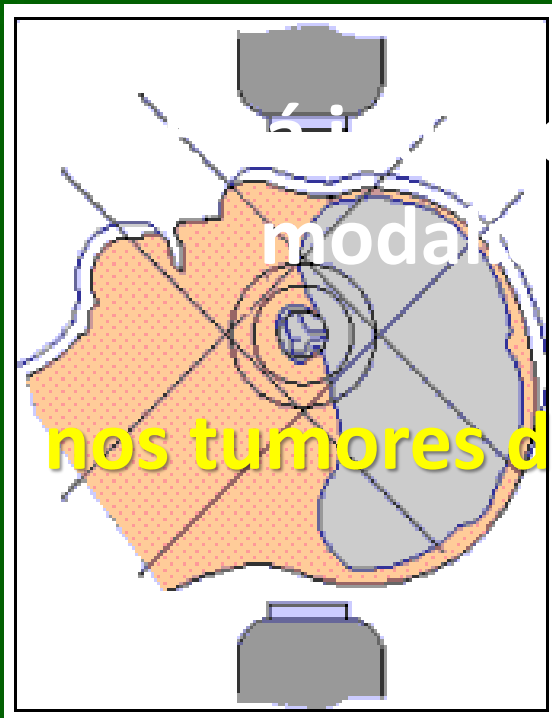
- Análogos da Somatostatina + Cabergolina
- Análogos da Somatostatina + Pegvisomanto
- Pegvisomanto + Cabergolina

“Estrogênios & SERMs”

Radioterapia na Acromegalia Acromegalia Não Controlada

Vieira Neto et al., Arq Bras Endocrinol Metab 2011

Melmed et al., J Clin Endocrinol Metab 2009

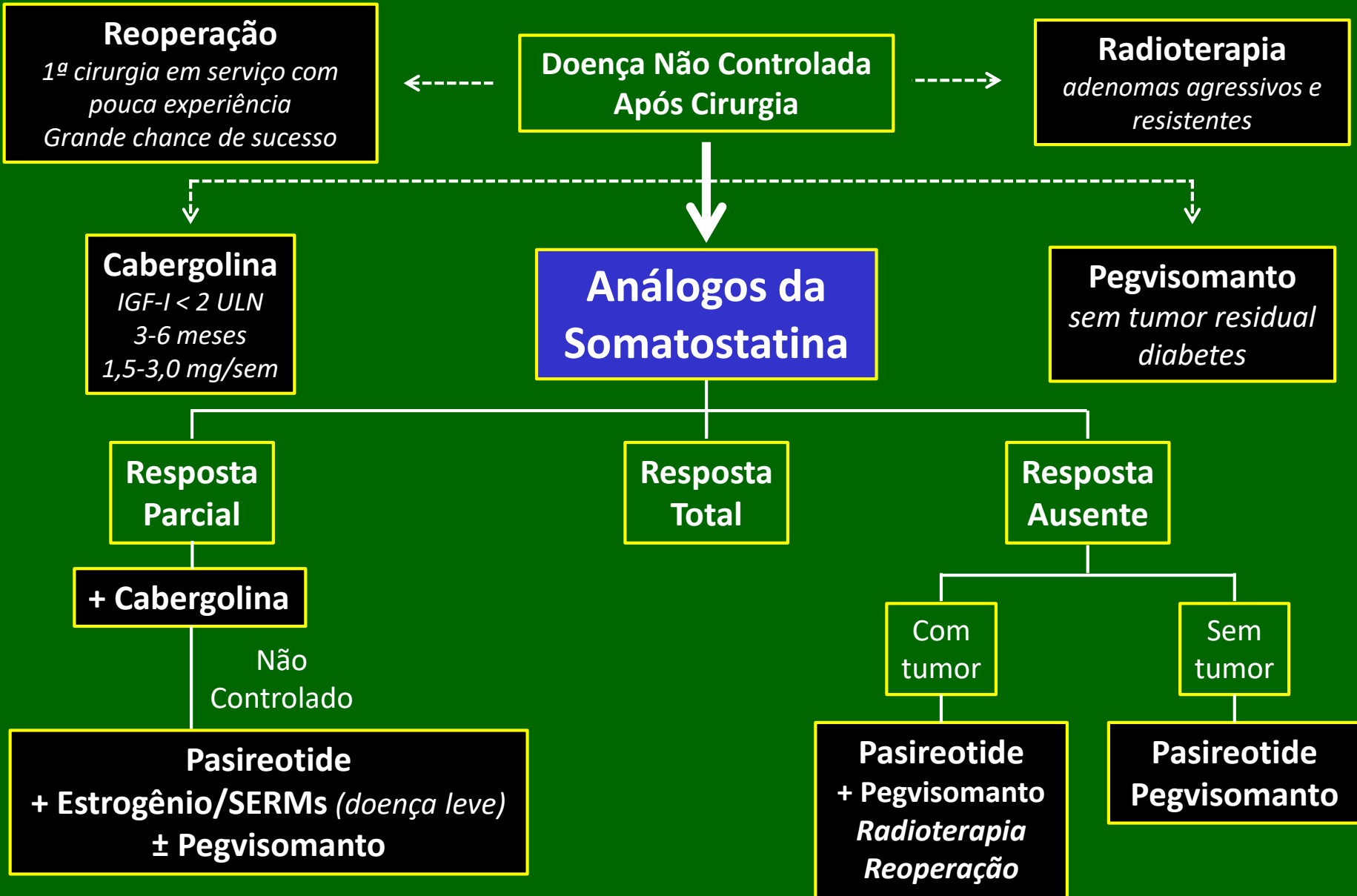


Convenção vs Estereotáxica
da nos casos em que as outras
moda ades terapêuticas falharam

e, especialmente,
nos tumores de comportamento mais agressivo

- Efetiva em 30-60% dos casos
- Resposta demorada (até 15 anos)
- Causa hipopituitarismo (~ 60%)
- Aumenta mortalidade ?

Algoritmo do Tratamento da Acromegalia Não Controlada



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... e a vocês pela atenção !