Pituitary Update 2009

ACROMEGALY

International standard
Cure rate
Overall 40 – 50%
Microadenomas 80-90%

Manchester surgical experience
Cure rate
Overall 17.8%
Microadenomas 38.8%
Macroadenomas 11.8%

Clinical Endocrinology (1998) 49, 653–657

The outcome of surgery for acromegaly: the ... specialist pituitary surgeon for ... hormone (GH) ...

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finally revised 22 April 1998; accepted 29 May 199...

Summary

OBJECTIVE Acromegaly is associated with ... life expectancy, while therapeutic 'cure' (d... achievement of GH levels <5 mU/l) is associ... normalization of life expectancy. Surgery ren... treatment of choice but in those in whom c... 'cure' is not achieved, radiotherapy and/or ... treatment are valuable treatment modalitie... chance of subsequent 'cure' with radiother... somatostatin analogue therapy is increased... post-operative GH level is reduced below 3... Using strict criteria for cure and a single ded... pituitary surgeon, two large European s... reported 'cure' rates of 42% and 56%. In the ... chester region, surgery for these patients has ... performed by a number of neurosurgeons, wit... specific designated pituitary surgeon dominating ... picture. We wished to examine the impact of ... surgical strategy on cure rates and the incidence ... a post-operative GH level below 30 mU/l.

DESIGN We reviewed the GH results between 19... and 1997 for every acromegalic who had been referred ... to the endocrine departments of the two Manchester ... hospitals responsible for the majority of pituitary ... disease referrals in Manchester and who had been ... subsequently referred for pituitary surgery.

PATIENTS AND MEASUREMENTS Seventy-three (33 ... male) patients had had GH status assessed before ... and after surgery by an OGTT or GH profile. The ...

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...reatly reduced, ...lity in these patients.

Acromegaly is uncommon, with an annual incidence in the UK of 3–4 cases per million and an estimated prevalence of 40–60 cases per million (Alexander *et al.*, 1980; Ritchie *et al.*, 1990). In the vast majority of patients it is caused by a pituitary tumour and is associated with a significantly shortened life span. This is primarily due, not to a direct effect from the tumour, but to cardiovascular, respiratory and cerebrovascular disease (Melmed *et al.*, 1995). Therapeutic 'cure' of acromegaly (defined by achievement of GH levels <5 mU/l) is associated

...ly was diagnosed ...

...1997. During this period 22·9% (8/35) of patients ...ved a mean GH level of <5 mU/l following surgery, ...% (10/34) achieved a nadir of <5 mU/l during an OGTT, ...45·6% (10/22) of patients with GH levels >30 mU/l ...eratively achieved GH levels <30 mU/l postoperatively. ...spite the suggestion of a trend of improved cure rate with ...there is no statistically significant difference between ...results.

...sion

...enoidal surgery remains the initial treatment of choice ...ts with acromegaly. Until a medical therapy is ...at provides tumour shrinkage, as well as control of ...nd good tolerability, it is likely to remain so. The ...und this strategy is based on the assumption that ...py is associated with a high expectation of 'cure', ...annot be achieved, a significant reduction in GH ...published to date suggest this is the case (Ross & ...Fahlbusch *et al.*, 1992; Sheaves *et al.*, 1996; ...996), with cure rates of between 33 and 81% ...able 2). However, the results in our study are ...mpressive, with the majority of patients ...H levels postoperatively.

...postoperative 'cure' of acromegaly is a ...have analysed data from this study in a ...ys to allow a more accurate comparison ...ly published studies.

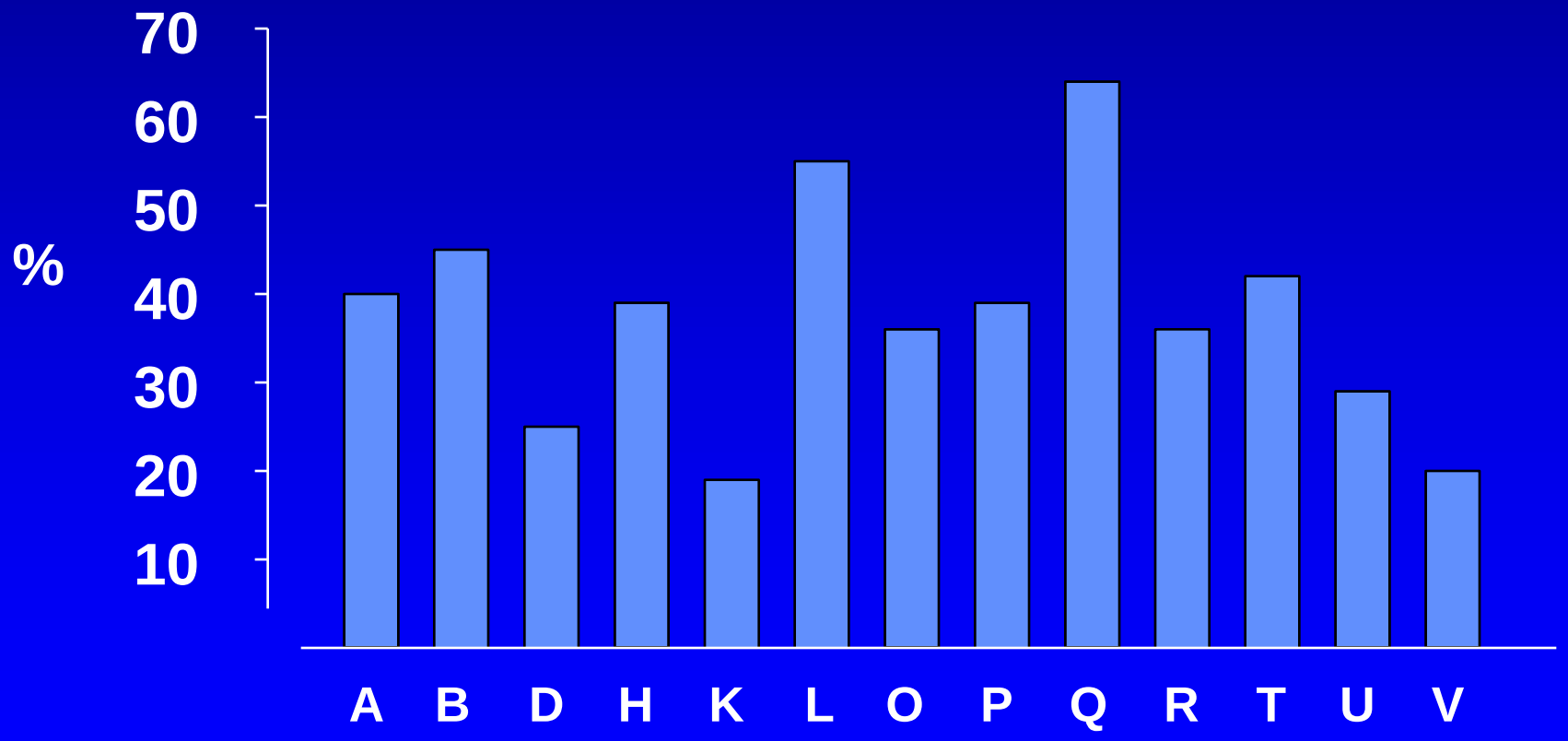
...ohort was compared to that of Sheaves ...h this latter group used a different ...serum GH level during a 4-pount day ...work of Dobrashian *et al.* (1993) ...ble. Cure rates for our group as a ...roadenomas and for macroadeno- ...comparable groups in the cohort ...f note, however, that the number ...g macroadenomas is large in ...p, implying that the expected ...g surgery would be lower.

...had GH status assessed pre- and post- ...%) had macroadenomas and 18 (24·7%) ...patients (5·5%) insufficient data were ...adenoma. The mean (SEM) GH level ...94·1 mU/l (11·5), 58·3 mU/l (15·1) in ...nomas, and 104·9 mU/l (14·9) in patients

...ce Ltd, *Clinical Endocrinology*, **49**, 658–657

	Definition of cure	
OGTT	Nadir <5 mU/l during OGTT	GH levels reduced to mean <30 mU/l during OGTT
1		
(73)	23·6% (17/72)	51·9% (27/52)
(8)	58·8% (10/17)	81·8% (9/11)
(1)	13·7% (7/51)	43·2% (16/37)

British National Acromegaly Database
Percentage of patients achieving a normal IGF-I in different surgical centres



Complications of pituitary surgery

	# of operations		
Complication	**<200**	**200-500**	**>500**
Anaesthetic complications	3.5	1.9	0.9*
Carotid artery injury	1.4	0.6	0.4*
CNS injury	1.6	0.6	0.4*
Haemorrhage	2.8	4.0	0.8*
Loss			5*
Opht			4*
Men			5#
Nasal septum perforation	7.6	4.6	3.3*
Post-operative epistaxis	4.3	1.7	0.4*
Post-operative sinusitis	9.6	6.0	3.6*
Hypopituitarism	20.6	14.9	7.2*
DI	19.0	NA	7.6*
Death	1.2	0.6	0.2*

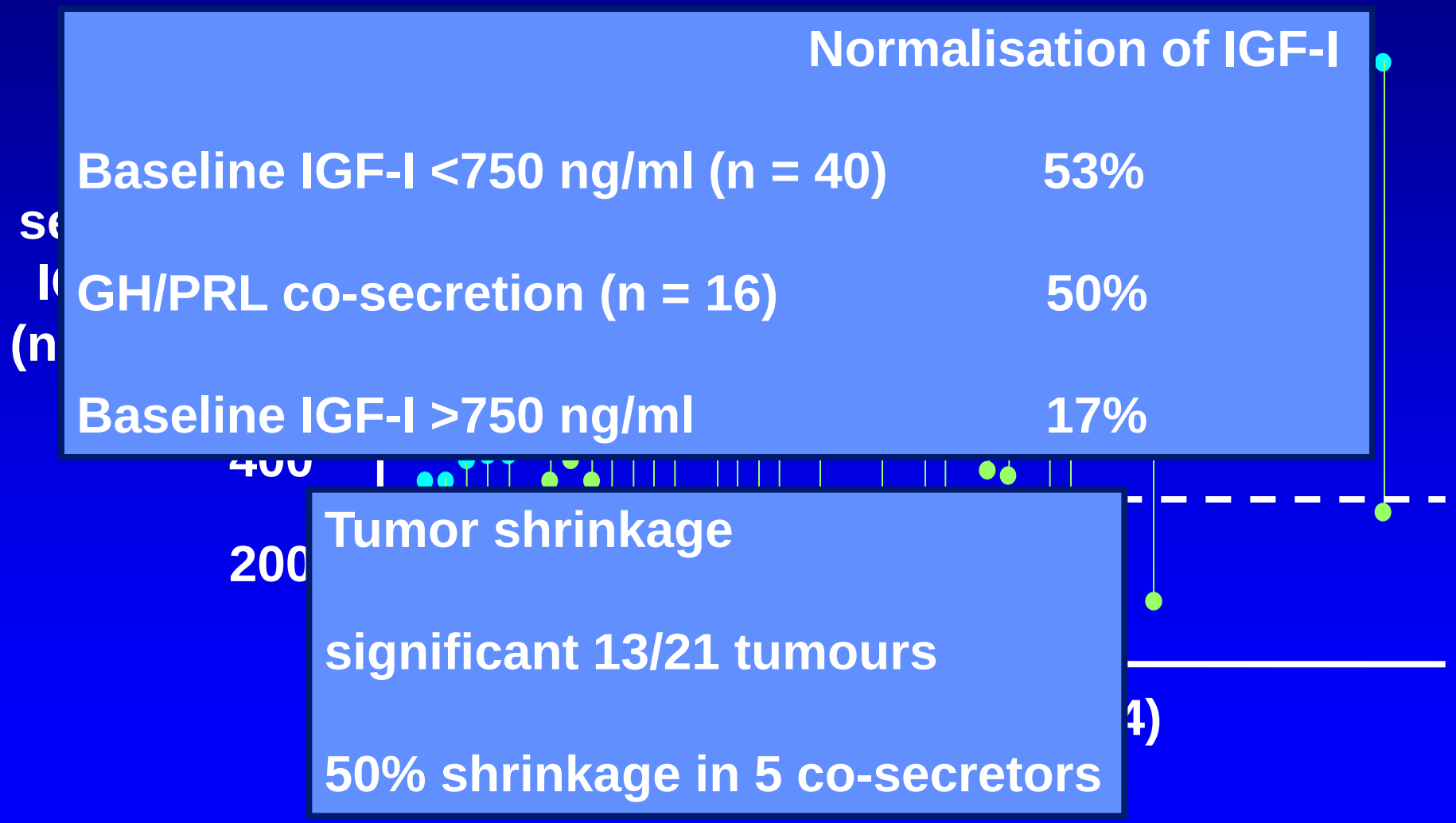
Transsphenoidal surgery requires dedicated surgeons

* P<0.001

#P<0.05

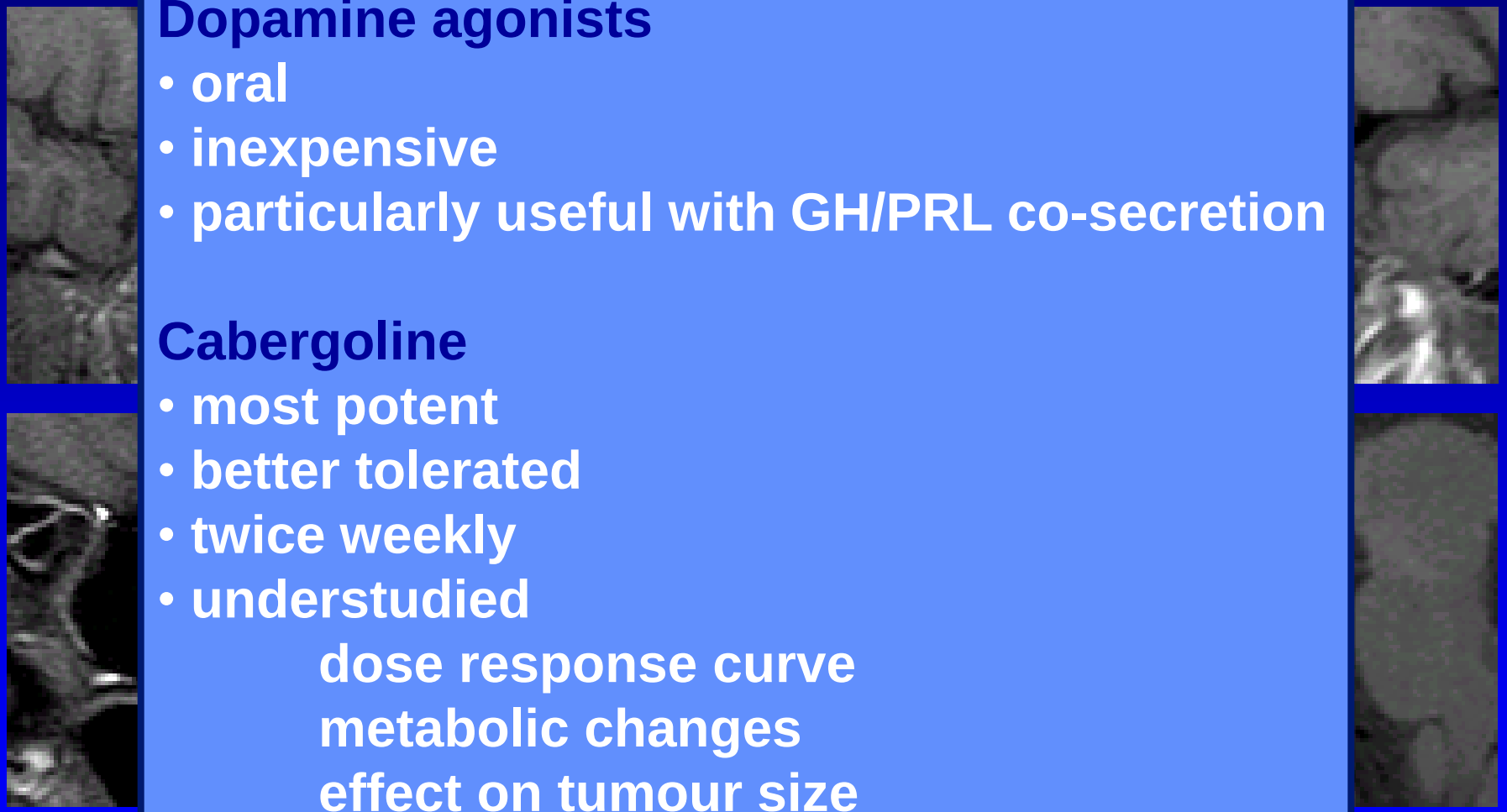
Ciric Neurosurgery 1997;40:225

Normalisation (<300 ng/ml) of IGF-I by cabergoline (3.5 mg/week) in 39% of 64 patients with acromegaly



Abs JCEM 1998:83;374

The effect of cabergoline on a GH-secreting adenoma



Dopamine agonists

- oral
- inexpensive
- particularly useful with GH/PRL co-secretion

Cabergoline

- most potent
- better tolerated
- twice weekly
- understudied
  - dose response curve
  - metabolic changes
  - effect on tumour size
  - combination therapy

0 s

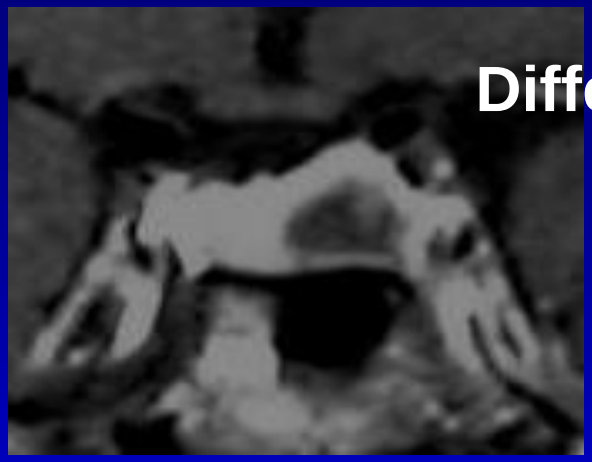
Courtesy of Michael Rickels & Peter Snyder

Pre-Treatment GH and Outcome in Acromegalics on Somatostatin Analogs

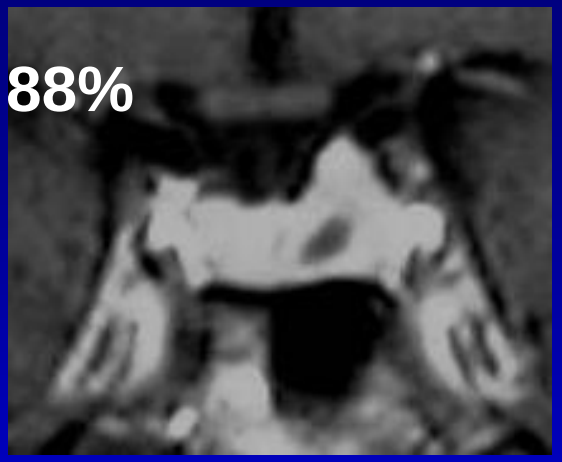
Pre-Treatment GH (ng/ml)	Remission Rate % (GH <1.7ng/ml)
1.7 -3.3	60
3.3 - 6.7	48
6.7 -10.0	54
10.0 - 20.0	31
20.0 - 33.3	19
>33.3	14

Courtesy of John Wass and British acromegaly database

Tumor shrinkage with LAR as primary therapy

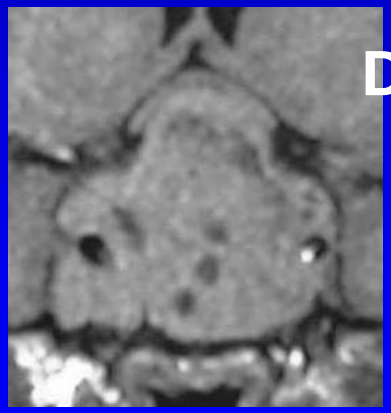


Difference 88%

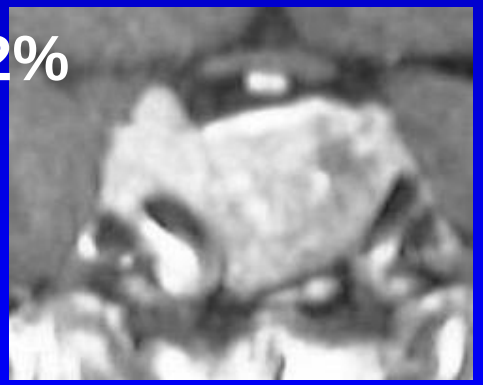


Baseline 552 mm3

24 weeks 63 mm3



Difference 52%

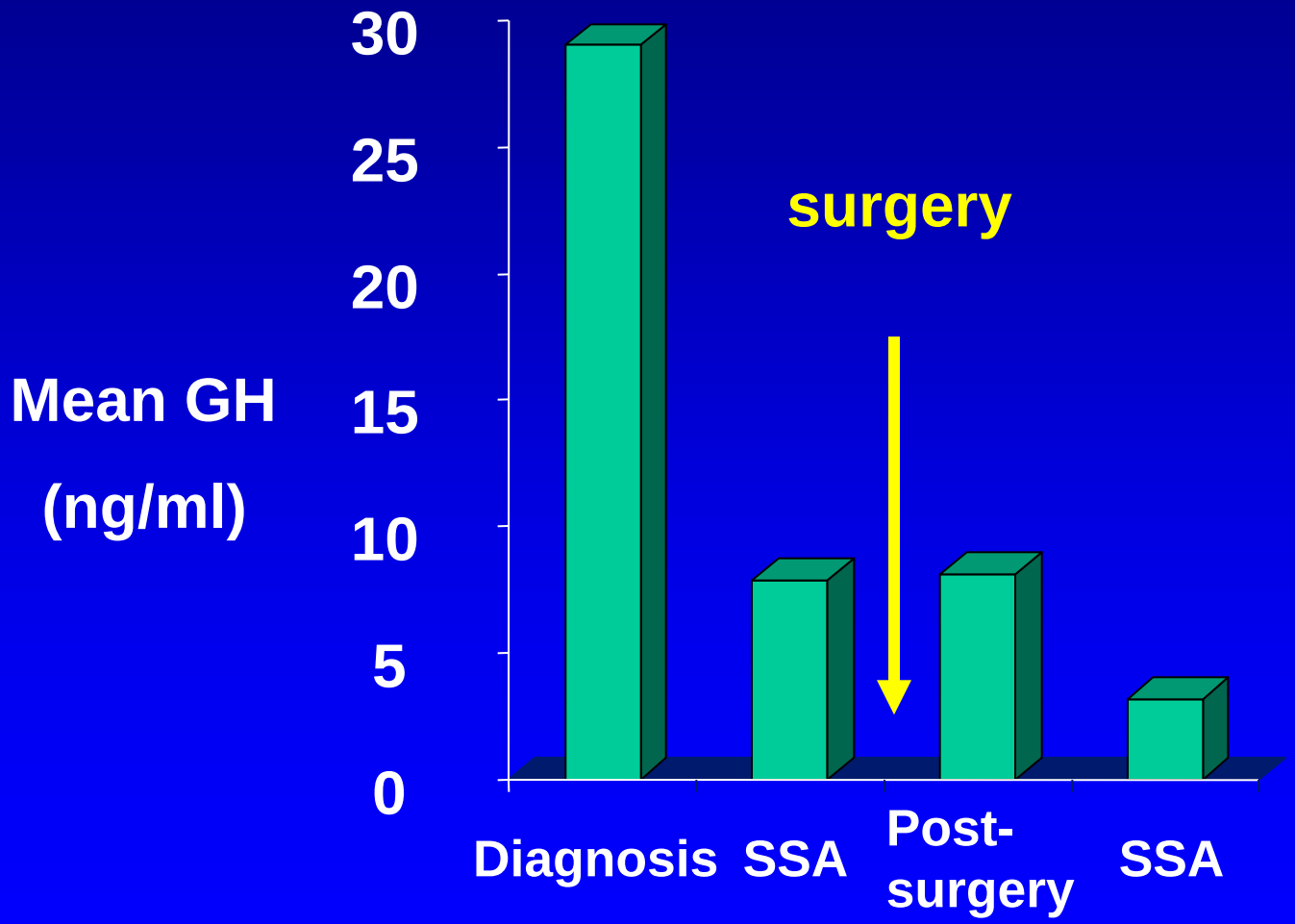


Baseline 61733mm^3

24 weeks 29537 mm^3

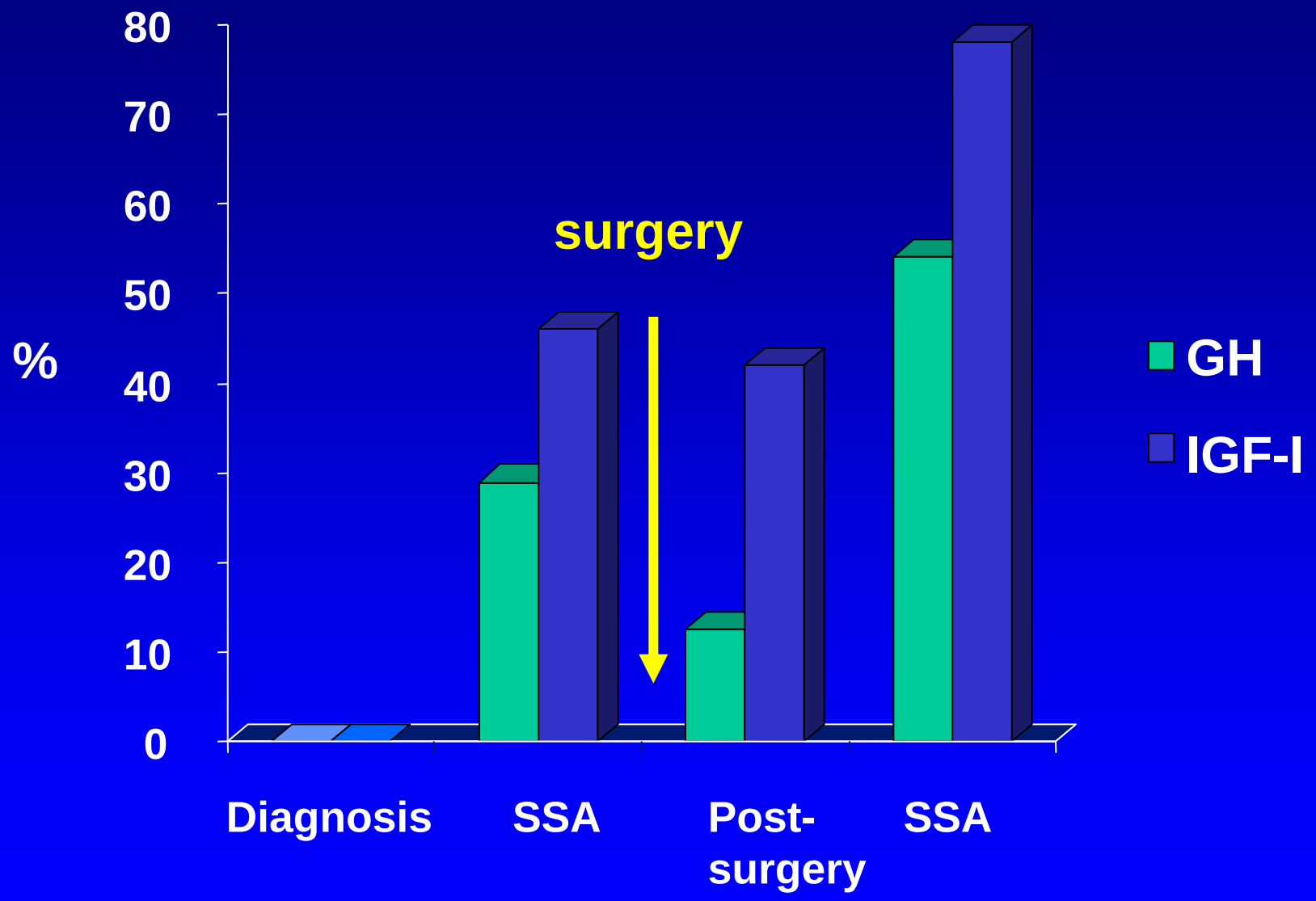
Bevan JCEM 2002:87;4554

GH response to therapy in newly diagnosed patients with acromegaly



Courtesy of Albert Beckers

Patients achieving therapeutic goals

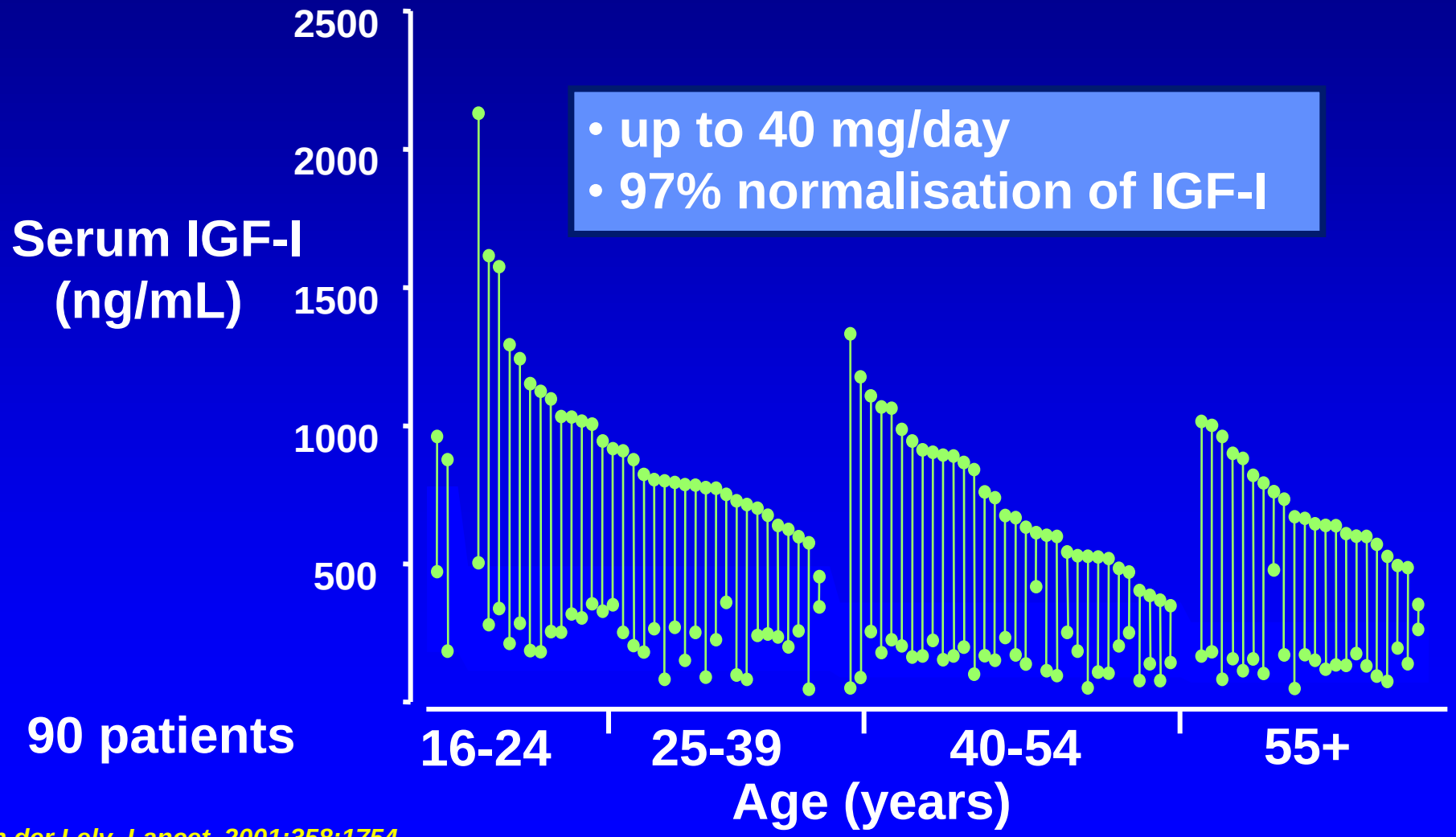


Courtesy of Albert Beckers

Somatostatin Analogs

- Injection every 3-6 weeks
- Expensive
- Tumor shrinkage
- Achieve biochemical “cure” in majority of acromegalics
- GI Symptoms
- Gall stones
- Adverse effect on carbohydrate metabolism

IGF-I at baseline and after 12 months of pegvisomant



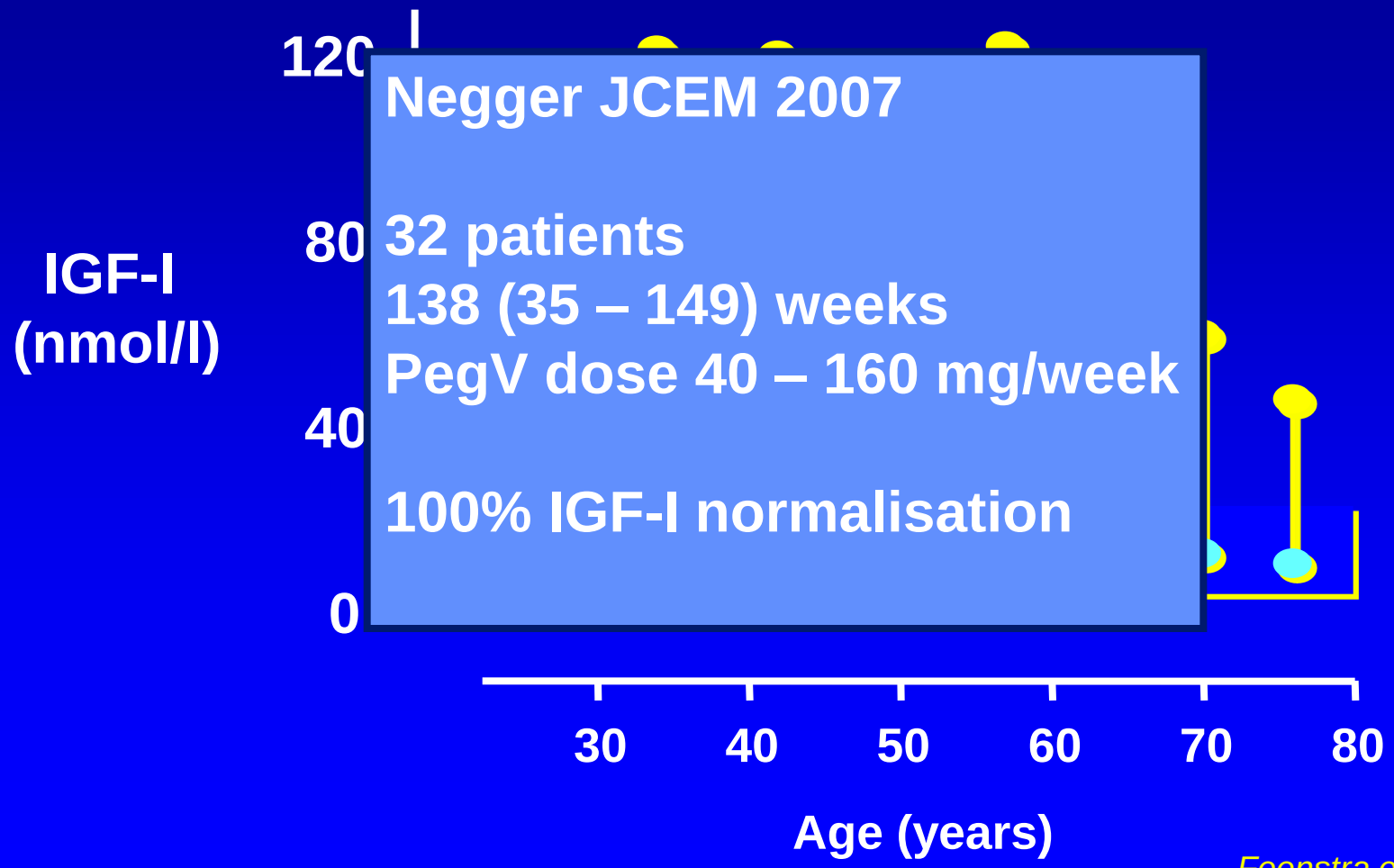
van der Lely Lancet 2001:358;1754

Pegvisomant

- Daily injection
- Novel therapy
- Very expensive
- Achieve normal IGF-1 level in over 95% but GH level actually rises
- Abnormalities of liver function
- Tumor size?
- Beneficial effect on carbohydrate metabolism

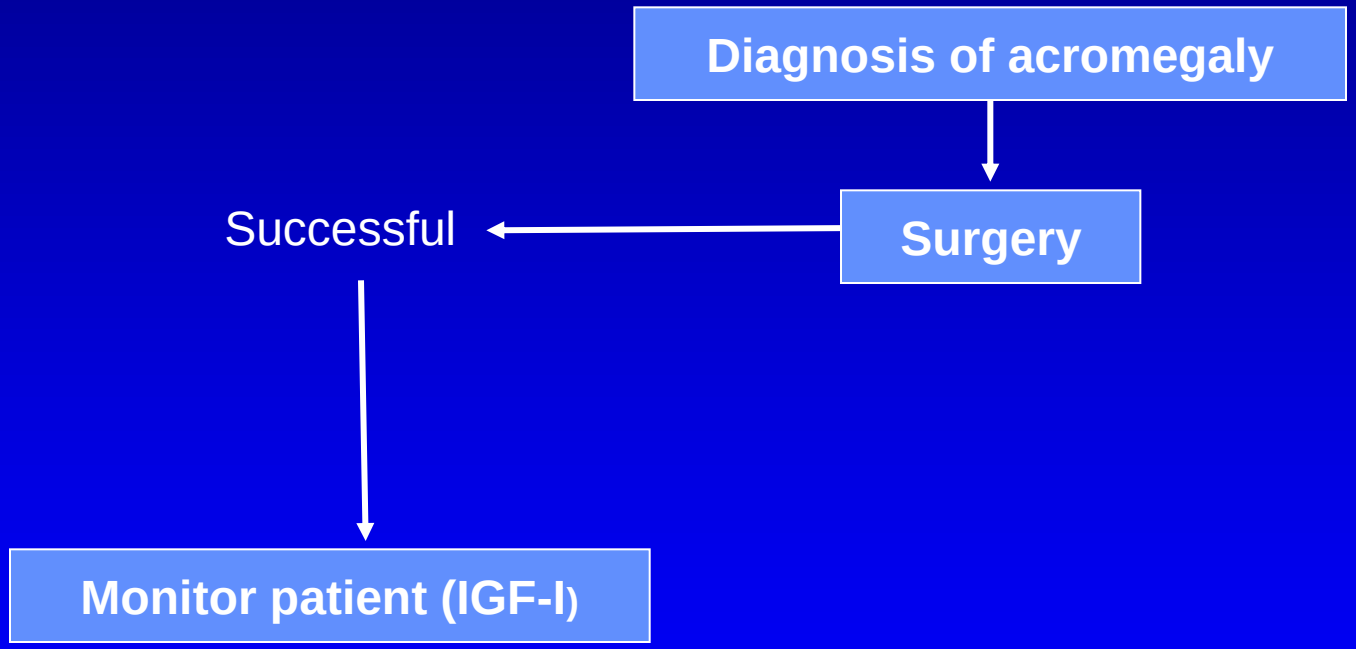
IGF-I in 19 patients with acromegaly treated with a SMS analog and pegvisomant

- during high-dose long-acting monthly i.m. SRIF analog therapy



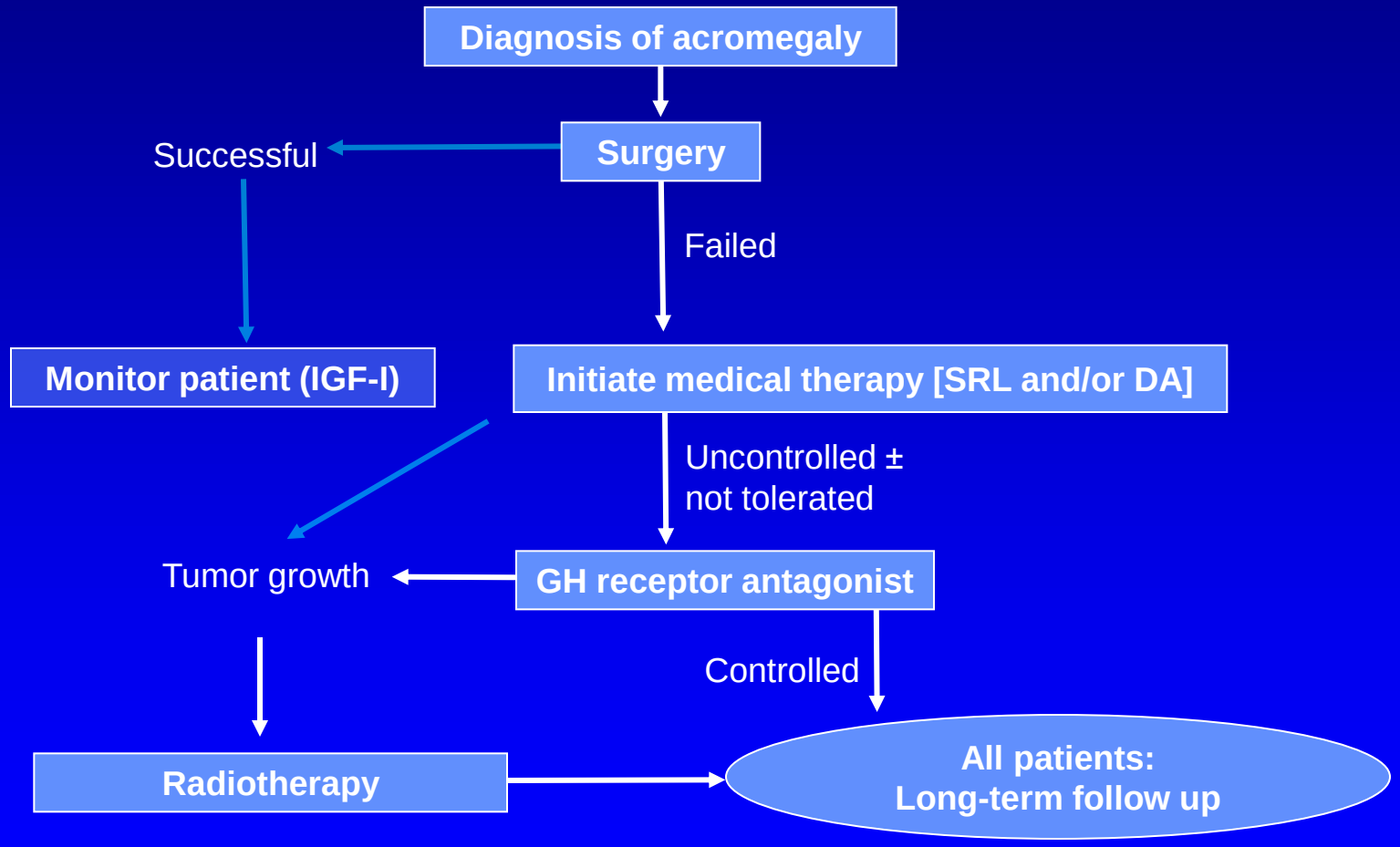
Feenstra et al. Lancet 05

Treatment Algorithm



Adapted from Clemmons JCEM 2003;88:4759

Treatment Algorithm



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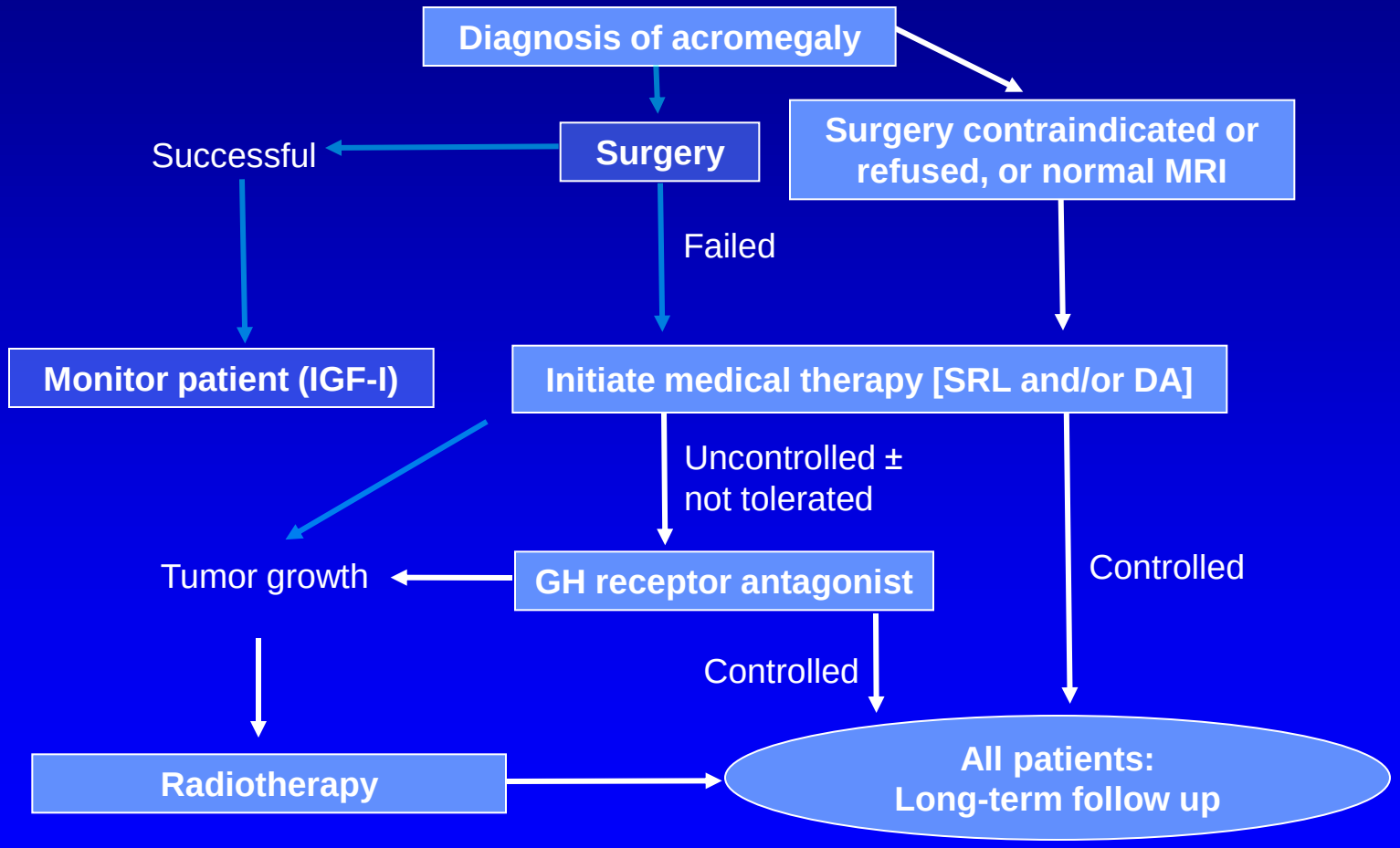
Treatment Algorithm



Adapted from Clemmons JCEM 2003;88:4759

Prolactinoma

200 patients with hyperprolactinaemia undergoing cabergoline withdrawal

- **Prospective observational study**

Recurrence rate of HPL after 5 years of cabergoline withdrawal

NTHPL	MICROS	MACROS
24%	32.6%	43.3%

MRI evidence of tumour regrowth not found in any patient

(Colao et al 2003)

Prolactinoma

Patients showing small remnant tumours on MRI at treatment withdrawal with either macros or micros at diagnosis, had a higher estimated recurrence rate after 5 years than those without evident tumour

- **Best predictor of persistent HPL**

- **Nadir value of maximal tumour diameter during cabergoline treatment**

(Colao et al 2003)

Prolactin

Clinical Problem

Interpretation of raised prolactin level in presence of pituitary macroadenoma

- **Prolactinoma vs NFPA?**

  - Prolactin level > 2000 mU/l
  = Prolactinoma (98.7% certainty)

  226 patients
  histological confirmation

- **“Hook” effect**

(Karavitaki et al 2006)

Cushing's Disease

Effectiveness of chronic treatment with cabergoline in patients unsuccessfully treated by surgery

- **20 patients with CD after unsuccessful surgery**
- **Cabergoline at initial dose 1mg/week, monthly increase until UFC normalised or maximal dose 7mg/week achieved**

(Pivanello et al 2009)

Cushing's Disease

Results

- **Short-term treatment (3 months)**
  - 75% (15) were responsive; among these, normalisation of UFC was maintained in 10, but treatment escape in 5 patients after 6-18 months

- **Among 10 long-term responsive patients**
  - 8 followed for 2 years
  2 cabergoline withdrawal for intolerance

- **Sustained control of cortisol hypersecretion at maximum cabergoline dose range 1-7mg/week (median 3.5) without significant side-effects in 8 of 20 patients**

(Pivanello et al 2009)

Assessing the HPA axis in patients with pituitary disease; a UK survey

Reynolds et al, CE 2006

How is ACTHⒹdiagnosed?

- UK SoE Survey
  598 Clinical Members
  81 Respondents

ITT	9.00am Cortisol (>400 nmol/L)
SST	No Tests (NoT)
Glucagon	

Reynolds et al, Clin End (2006)

	ITT	SST	NoT	Glucagon	9C
Definitive testing of HPA Axis Post- Surgery	31%	44%	-	2.5%	2.5%
Long term Assessment					
XRT	7%	65%	-	4%	18%
Non – XRT	9%	36%	29%	-	18%

Reynolds et al, Clin End (2006)

SST

93.8% - 250 µg

4.7% - 1µg

IV vs IM – (50-50)

Interpretation of Results

- 67% - 30 min cortisol
- 17% - 60 min cortisol
- 7 % - increment cortisol
- 9% - combinations

Reynolds et al, Clin End (2006)

Interpretation of Results

SST

- Adequate peak cortisol response 250 – 650 nmol/l
- Peak cortisol >550nmol/l at 30 min (51%)

ITT

- Adequate peak cortisol response 400 – 600 nmol/l
- Peak cortisol > 550nmol/l (47%)

Reynolds et al, Clin End (2006)

Glucorticoid Replacement

If patients symptomless but had failed chosen test of HPA axis

- 28% - still treated with glucocorticoid replacement
- 38% - retested before treatment
- 24% - recommended glucocorticoid cover when unwell or ‘stressed’
- 6% recommend patient carry steroid card
- 4% - individual basis

Reynolds et al, Clin End (2006)

Glucocorticoid replacement

Hydrocortisone

- 20mg/day (56%)
- 67% - 10/5/5
- Higher doses by 25%
- Lower doses by 13%

General Trends

- More SST – Less ITT
- Lower replacement doses of HC

Reynolds et al, Clin End (2006)

Partial ACTH Ⓓ - Glucorticoid replacement

10 males – partial ACTH Ⓓ

- Base line plasma cortisol > 200nmol/l
- Peak stimulated cortisol<500nmol/l

10 matched controls

Cross-over randomised protocol – HC

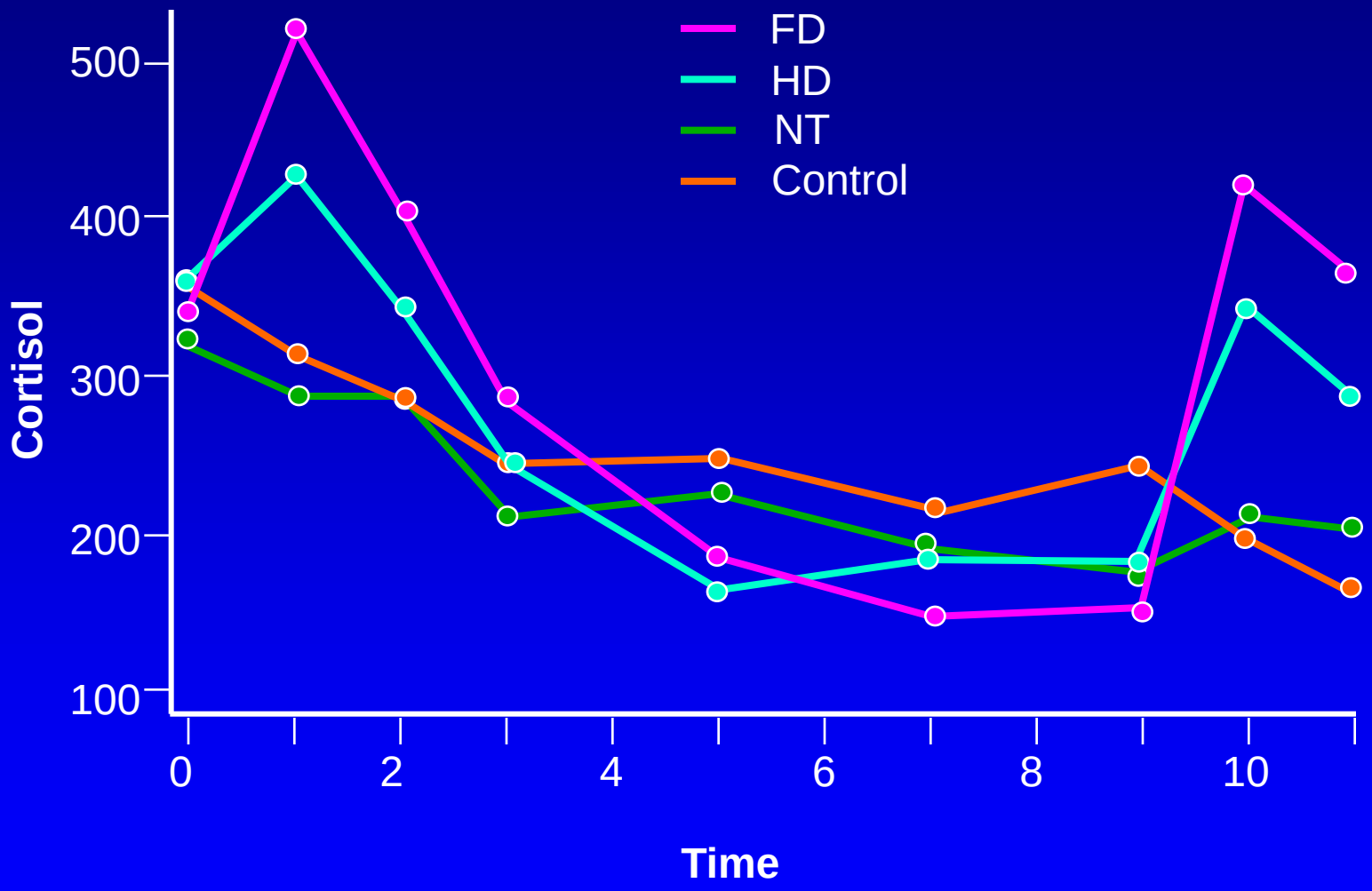
10mgs BD vs 5 mgs BD vs no treatment

Agha et al Clin End.2004

	Pts, n=10	Controls, n=10	P-value
Age (years)	43.9±10.8	38.9±12.2	0.34
BMI (kg/m^2)	31.1±4.5	30.8±4.3	0.88
CBG (mg/l)	41.7±7.1	44.9±4.6	0.25
Baseline cortisol	273.9±61.8	357.3±84.4	0.021
Peak stimulated cortisol	432.9±58.9		

Results presented as mean±SD. BMI, body mass index; CBG, corticosteroid-binding globulin

Agha et al 2004



Agha et al 2004

Partial ACTH deficiency

10 patients with pituitary disease

- **Suboptimal peak cortisol response (350-500nmol/l) to ITT**
- **Daily cortisol production rate (CPR) by isotope dilution using GCMS and 24 hour UFC**

Paisley et al (2009)

Partial ACTH deficiency

Results

- **Peak cortisol - 473.5 (366-494) nmol/l**
- **Strong positive correction (r = 0.75) between peak cortisol and CPR**
- **CPR (mg/day) was within reference range in all patients**
- **Wide range found for 24 hour UFC**
  - no correlation between UFC with either peak cortisol or CPR

Paisley et al 2009

Adult GHD Patients to be considered for GH replacement?

1. All
2. Based on biological endpoints
3. Based on GH/IGF-1 status

Partial GHD in Adults

- Definition
- Clinical Impact
- Pituitary/Biochemical Phenotype

Manchester, Naples

Partial GHD

- Group Research?
- Individual Diagnosis?

  - visceral fat mass

Conclusions

1. GH secretion is a continuum
2. Treat all GHD adults?

Biological Endpoints

Quality of Life

- Prevalence
- GH/IGF-1 status
- Mechanism
- Partial GHD
- RPCT

Biological Endpoints

Vascular Mortality

- Confounding variables
- 10 year study
- Risk factors
  - How many?
  - Clustering?

Skeletal Health

- Limited age range

Conclusion

No single biological endpoint cuts it!

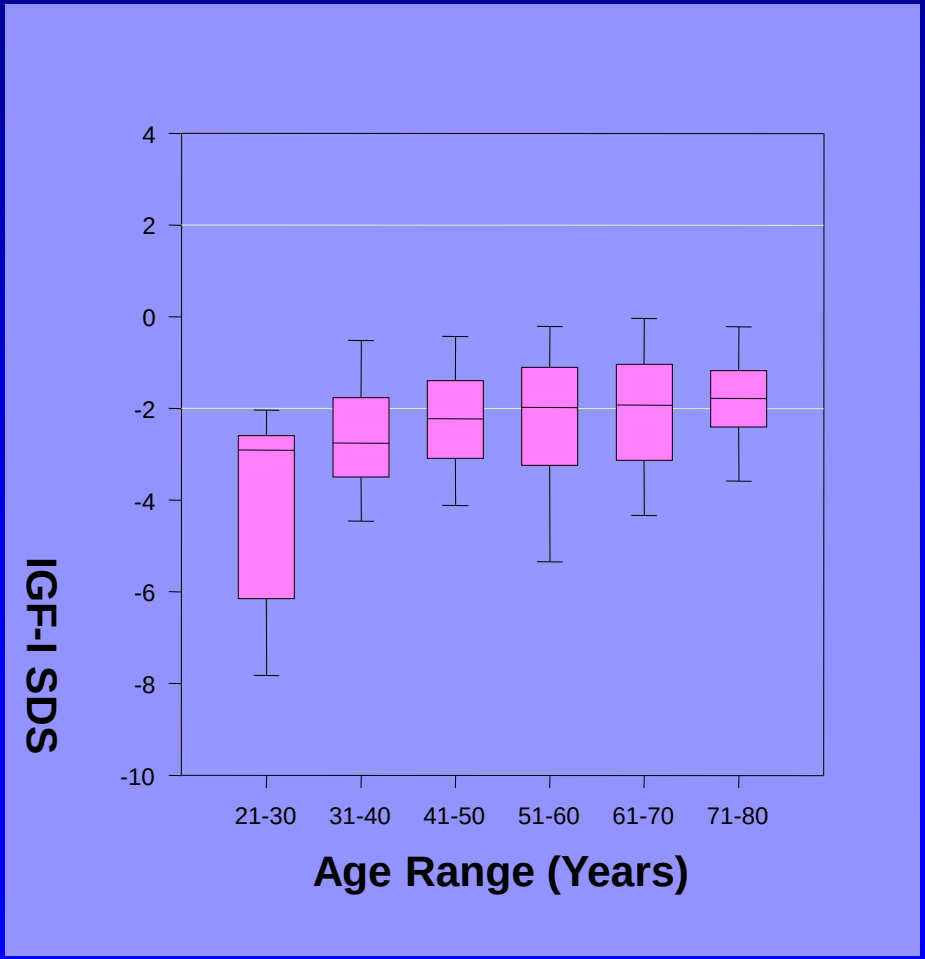
Patients and Methods

- Baseline IGF-I measurements from;

  - 376 females (median age 48, range 21 to 77 years) and - 434 males (median age 52, range 21 to 80 years)
- The cohort was stratified into six gender based age ranges
- IGF-I & IGF-I SDS were determined for each group

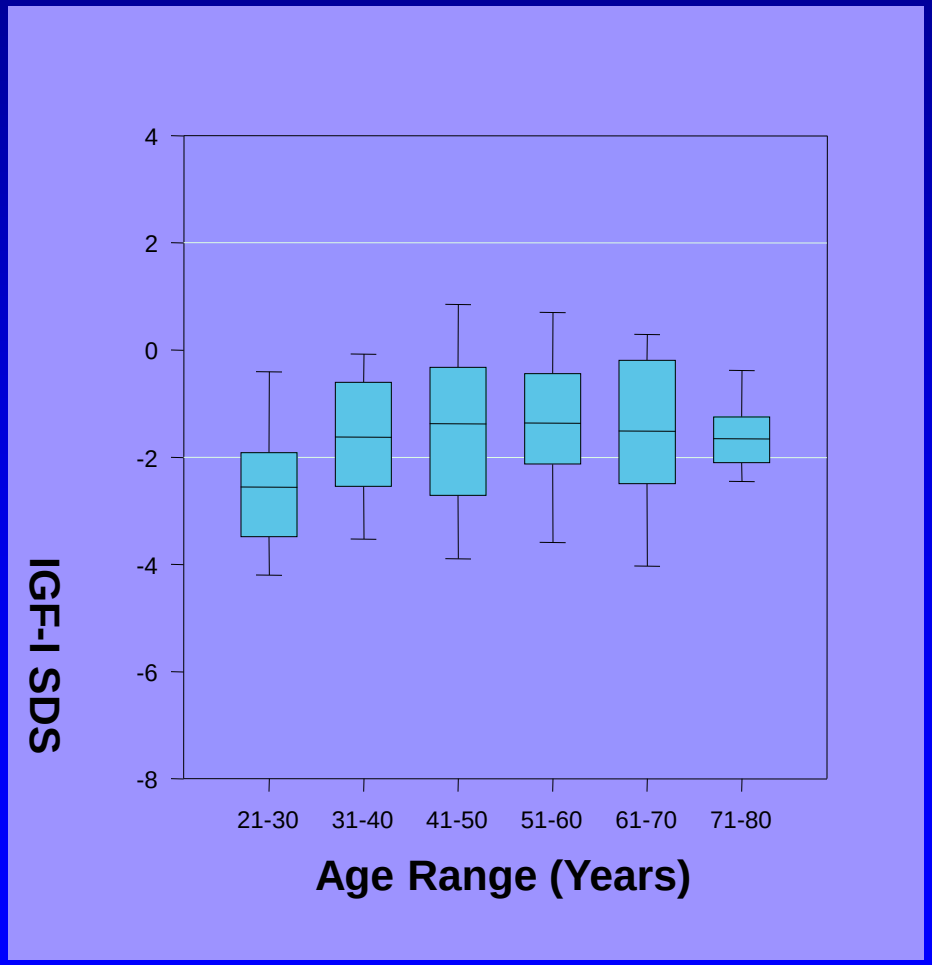
Mukherjee et al (2003)

Box and whisker plots representing IGF-I SDS in females with AO-GHD



Mukherjee et al (2003)

Box and whisker plots representing IGF-I SDS in males with AO-GHD



Mukherjee et al (2003)

Clinical Implication of Residual GH response to provocative testing in Adults with severe GHD

KIMS database

- Peak GH<3ng/ml to ITT
- IGF-1 status in 1098 patents who fulfilled criteria

Results

- Multivariate analysis – most important single predictor of GH peak to ITT was extent of HP dysfunction
- GH peak
  - positively related to IGF-1 level

Brabant et al (2007)

Conclusion

- GHD adults with pathologically low IFG-1 are more severely GHD than those with normal IGF-1

Implication

- What does this mean for
  - Health Economist?
  - Endocrinologist?

Long-acting GH preparation in patients with GHD

Open-label randomised study

- 135 patents – 32 weeks
- Depot GH vs Daily GH vs no treatment
- Dose GH titrated to maintain IGF-1 within age-adjusted normal range

Hoffman et al (2005)

Adverse events

1- death - "Adrenal crisis"
- On Depot GH

Two other serious and three non-serious cases of "adrenal crisis or insufficiency"

- 3 cases on daily GH vs 3 cases – depot GH
- All had ACTH deficiency and were on glucocorticoid replacement

Hoffman et al (2002)

Risk of Cortisol deficiency on GH replacement

- Ignorance – glucocorticoid dosage not ↑ during intercurrent illness
- Influence of Gh-IGF-1 axis on II β HSD driving cortisol-cortisone shuttle in favour of "cortisone"
- GH ↓ Cortisol-B-G

At Risk

- Steroid card/Emergency Pack
- Borderline ACTHⒹ not receiving glucocorticoid replacement

(Giavoli et al,2004)

- Sub-optimal glucocorticoid replacement

GH replacement and thyroid function in adult GHD patients

66 adult GHD patients

- 17 euthyroid/49 hypothyroid on T4
- 6 month GH replacement study – 2 dose regimes
- Normalisation of IGF-1 in 67% patients – independent of GH dose
- Significant ↓in FT4 and reverse T3 levels
- No change in TSH, FT3, thyroxine BG levels

Porretti et al (2002)

Porretti et al (2002)

- 8/17 euthyroid subjects and 9/49 central hypothyroid patients showed FT4 levels below normal range at end of study despite adequate substitution at baseline.

  Altogether 17/66 patients worsened thyroid function

* Monitor thyroid – function carefully

New Themes

- Drug delivery
  Hydrocortisone
  GH
- Copeptin
- Aryl Hydrocarbon Receptor Interacting Protein Gene