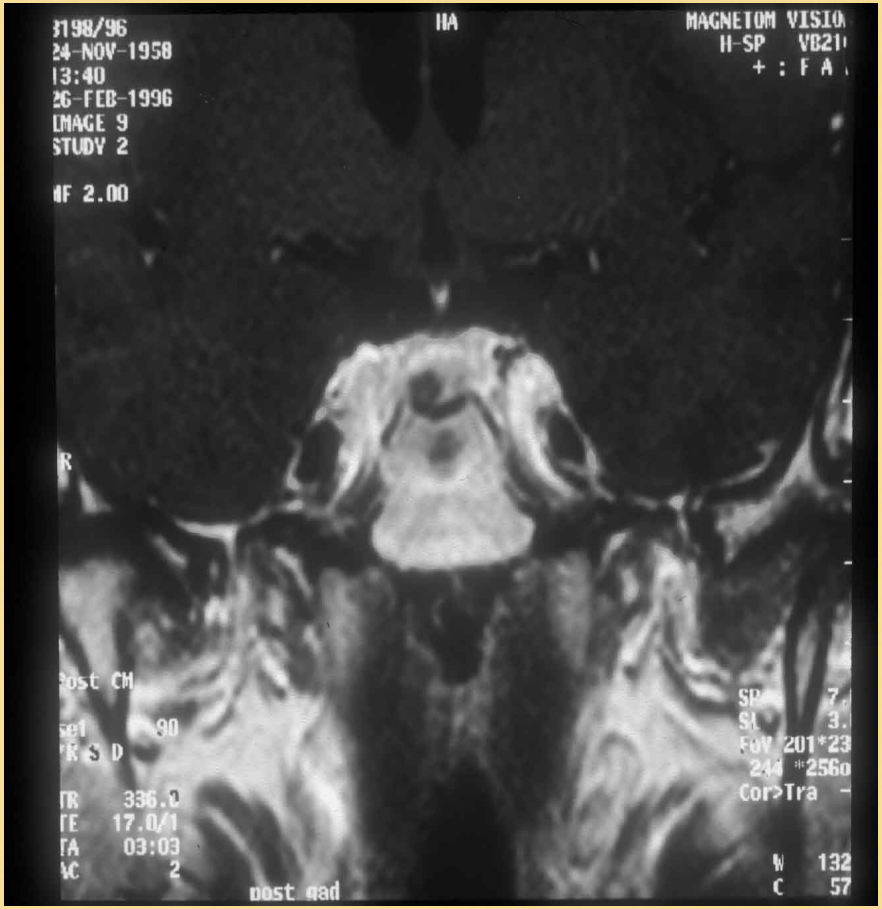
Relapse of pituitary adenomas after surgery

John Wass

University of Oxford, UK

Department of Endocrinology, Churchill Hospital, Oxford

7-10 November 2013, 6th Joint Meeting with AACE
American Association of Clinical Endocrinologists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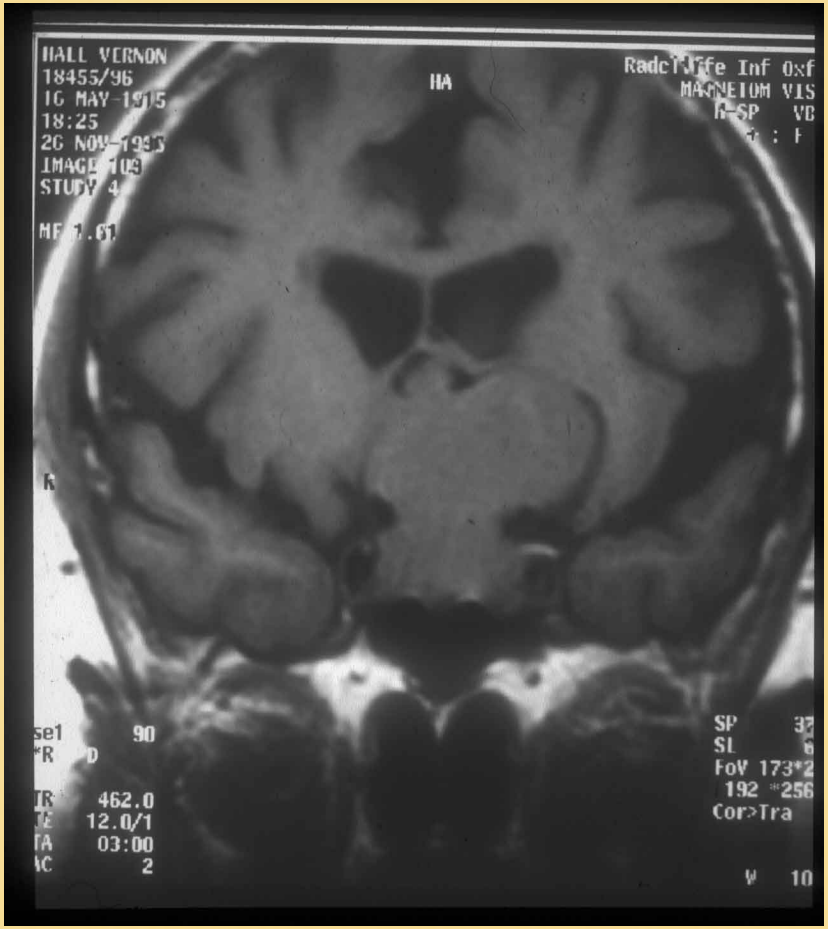
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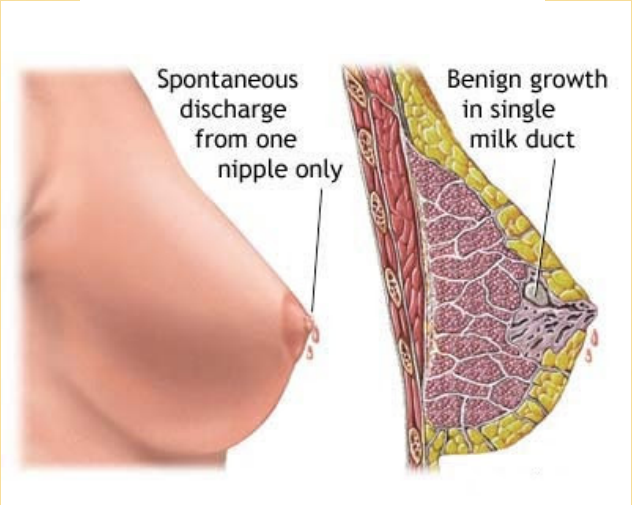
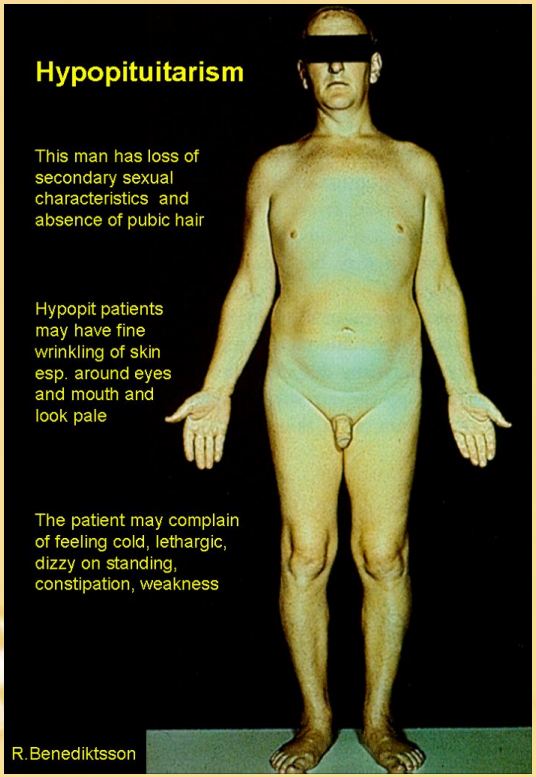
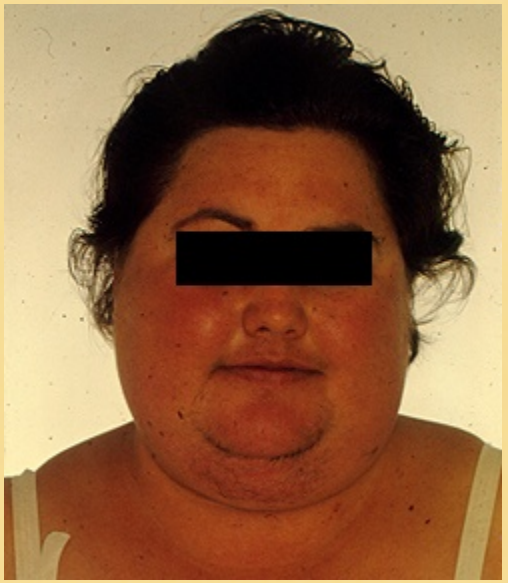
Galactorrhoea



Acromegaly



Cushing's Disease



Clinical Endocrinology (2010) 72, 377–382 doi: 10.1111/j.1365-2265.2009.03667.x

ORIGINAL ARTICLE

Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK)

Alberto Fernandez, Niki Karavitaki and John A. H. Wass

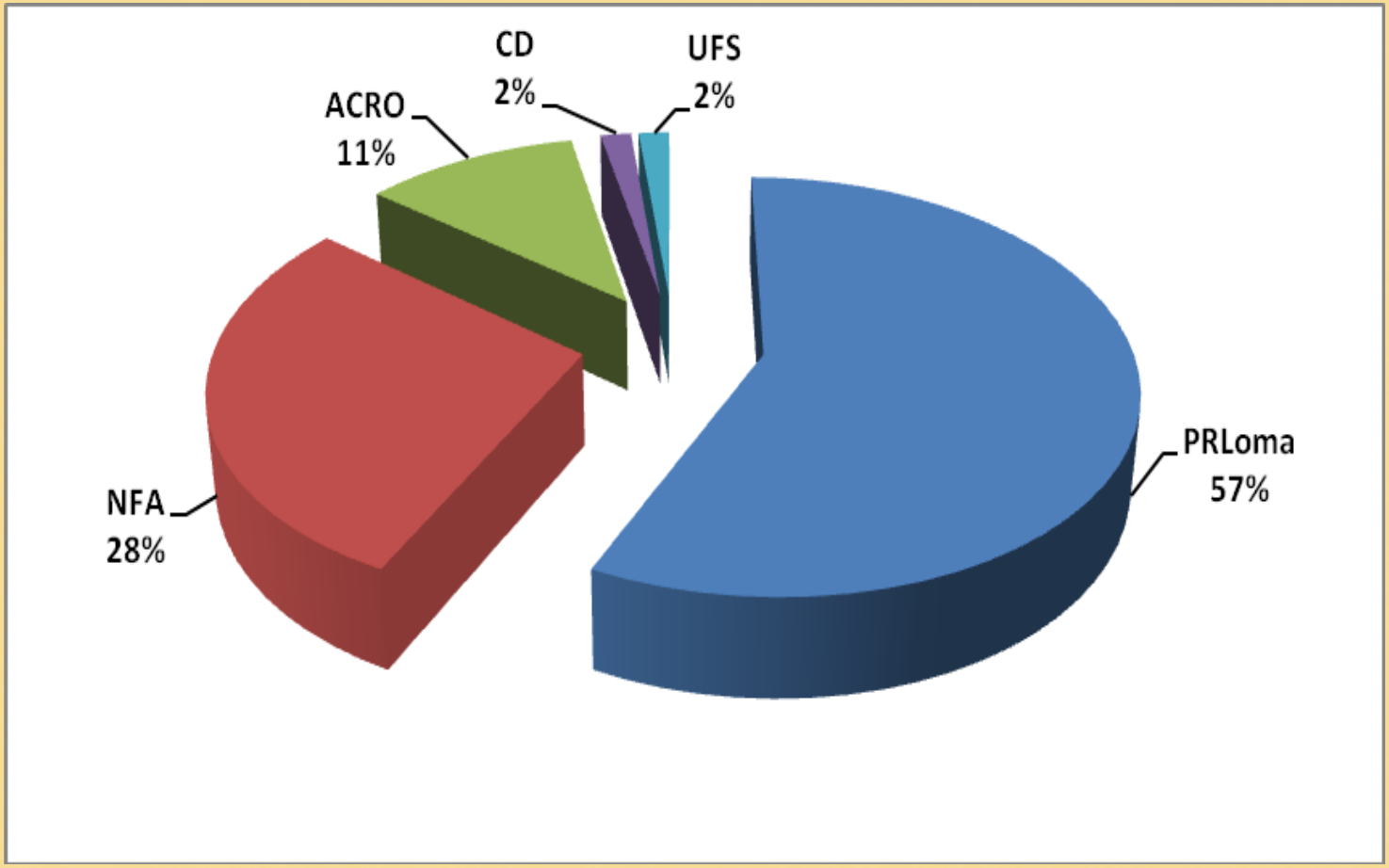
Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

81,449 inhabitants
91% of study population

	PRL	NFA	ACRO	CD	TOTAL
Total No.	37	18	7	1	64
Prevalence (1,000,000)	45.6	22.2	8.6	1.2	78.8
Duration of symptoms (yrs)	0.5-12	0-8	1.5-15	7	

Approximately 1 per 1,000 clinically significant pituitary adenomas

Distribution of pituitary adenomas subtypes



Prolactinoma

Treatment of choice cabergoline 0.25 – 3mg per week

No cardiac valve effects

Clinical Endocrinology (2009) 70, 104–108 doi: 10.1111/j.1365-2265.2008.03458.x

ORIGINAL ARTICLE

Valvular heart disease and the use of cabergoline for the treatment of prolactinoma

Neil Herring*, Cezary Szmigielski*, Harald Becher*, Niki Karavitaki† and John A. H. Wass†

*Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford University and †Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

Conclusions

We found no evidence of increased mitral valve tenting area/height, valvular thickening or significant regurgitation with the long term administration of the commonly used doses of cabergoline to treat prolactinoma.

Clinical Endocrinology (2011) 75, 819–824 doi: 10.1111/j.1365-2265.2011.04136.x

ORIGINAL ARTICLE

Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma

Thomas M. Barber*, Julia Kenkre*, Catherine Garnett*, Rebecca V. Scott*, James V. Byrne† and John A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, and †Department of Radiology, Churchill Hospital, Oxford OX3 7LJ, UK

Do Macroprolactinomas Recur after 3-5 Years Treatment?

Number of patients:15

Treated > 3 years (mean 7.5 years)

Prolactin suppressed to normal

Do Macroprolactinomas Recur a after 3-5 Years Treatment?

Recurrence of hyperprolactinaemia in 14 (93%)

Mean time to recurrence 8.8 months

Mean prolactin at baseline 28,246 mU/L

on treatment 144 mU/L

at recurrence 2,236 (411-12,847)

Do Macroprolactinomas Recur after 3-5 Years Treatment?

Most macroprolactinomas have a recurrence of hyperprolactinaemia

Clinical Endocrinology (2013) 79, 217–223 doi: 10.1111/cen.12124

ORIGINAL ARTICLE

Does hypopituitarism recover when macroprolactinomas are treated with cabergoline?

Niki Karavitaki*, Ruxandra Dobrescu*, James V. Byrne†, Ashley B. Grossman* and John A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital and †Department of Neuroradiology, John Radcliffe Hospital, Oxford, UK

Do patients with macroprolactinoma have an improvement in pituitary function?

11 Patients (10 M 1 F) aged mean 38 (17-56)

9 Followed for 3 years; 2 for 2 years

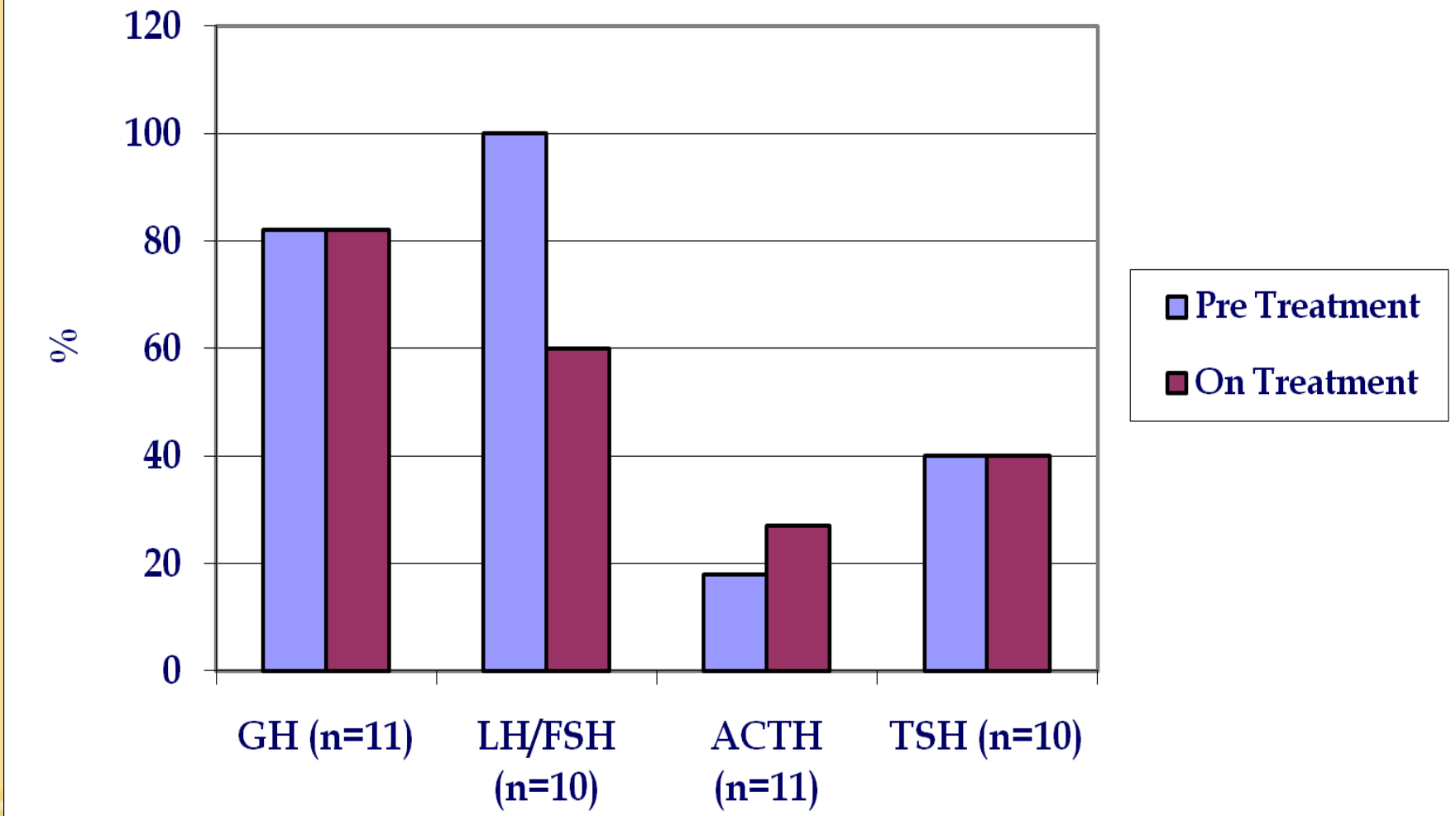
All achieved normal prolactin

All had significant tumour shrinkage

All had pituitary function assessed yearly

(insulin/glucagon test and basal bloods)

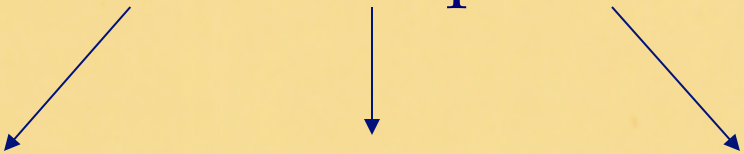
Hormone deficits



Trans-sphenoidal Surgery for Microprolactinoma: an acceptable alternative to dopamine agonists?

Turner *et al*. 1999, **140**, 43-47

Microprolactinoma 32 female patients



Intolerant 31% Resistant 9% Intolerant & Resistant 12.5%

Trans-sphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists?

Turner *et al.*, 1999, 140, 43-47

25 (79%) cured (normal post op prolactin)

Follow up 6 years (2 months to 16 years)

1 (4%) recurrence @ 12 years

28.6% GH deficient

8.0% diabetes insipidus

Macroprolactinoma

Pre-treatment — Prolactin (off drugs)
MRI
Anterior pituitary function
Visual fields

Warn about CSF rhinorrhoea

Start cabergoline — 0.5 mg weekly/
0.5 mg increments weekly or more rapidly if field defects

Measure prolactin at each increment

Fields at one month

Scan at 3 months

8% resistant 5% intolerant

1) Other dopamine agonist 2) Radiotherapy 3) Surgery

Stop therapy at 5 years if prolactin normal
MRI small tumour not touching chiasm

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(10):3829–3835

doi: 10.1210/jc.2007-0373

Nonsurgical Cerebrospinal Fluid Rhinorrhea in Invasive Macroprolactinoma: Incidence, Radiological, and Clinicopathological Features

S. G. I. Suliman,* A. Gurlek,* J. V. Byrne, N. Sullivan, G. Thanabalasingham, S. Cudlip, O. Ansorge, and J. A. H. Wass

Non Surgical CSF Rhinorrhoea

- 114 patients
  - macroprolactinoma
- Incidence of CSF rhinorrhoea
- Factors predicting leakage
- Makers of invasiveness

Non Surgical CSF Rhinorrhoea

8.7%

2.6% spontaneous

6.1% d.a induced

Male preponderance 9.1% (p 0.008)

Dopamine agonist resistance higher in csf rhinorrhoea

30% vs. 5% (p 0.003)

Not related to baseline prolactin level

rate of prolactin decline

tumour volume at diagnosis

Clinical Endocrinology (2007) 67, 938–943 doi: 10.1111/j.1365-2265.2007.02990.x

ORIGINAL ARTICLE

What is the natural history of nonoperated nonfunctioning pituitary adenomas?

N. Karavitaki*, K. Collison*, J. Halliday*, J. V. Byrne†, P. Price‡, S. Cudlip§ and J. A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK, †Department of Neuroradiology, John Radcliffe Hospital, Oxford, UK, ‡Department of Diabetology and Endocrinology, The Great Western Hospital, Swindon, UK and §Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK

- *Series of patients systematically assessing the outcome of NFAs not treated by surgery or radiotherapy during long follow-up periods are limited.*

- *Aim: investigate the outcome of a series of consecutive patients with presumed NFA (micro- or macroadenoma) not offered treatment at initial presentation (for a number of reasons) and to identify possible factors predicting subsequent increase in the tumour size.*

Table 3. Outcome of follow-up imaging

	Total tumours	Microadenomas	Macroadenomas
Mean follow-up, months (range)	42 (8–128)	41 (8–128)	43 (9–98)
Increase in size, *n* (%)	14/40 (35)	2/16 (12·5)	12/24 (50)
Mean time of detection, months (range)	34·3 (11–98)	21 (20–22)	36·5 (11–98)
Stable, *n* (%)	21/40 (52·5)	13/16 (81·3)	8/24 (33·3)
Decrease in size, *n* (%)	5/40 (12·5)	1/16 (6·3)	4/24 (16·7)
Mean time of detection, months (range)	24·6 (7–46)	19 (–)	26 (7–46)

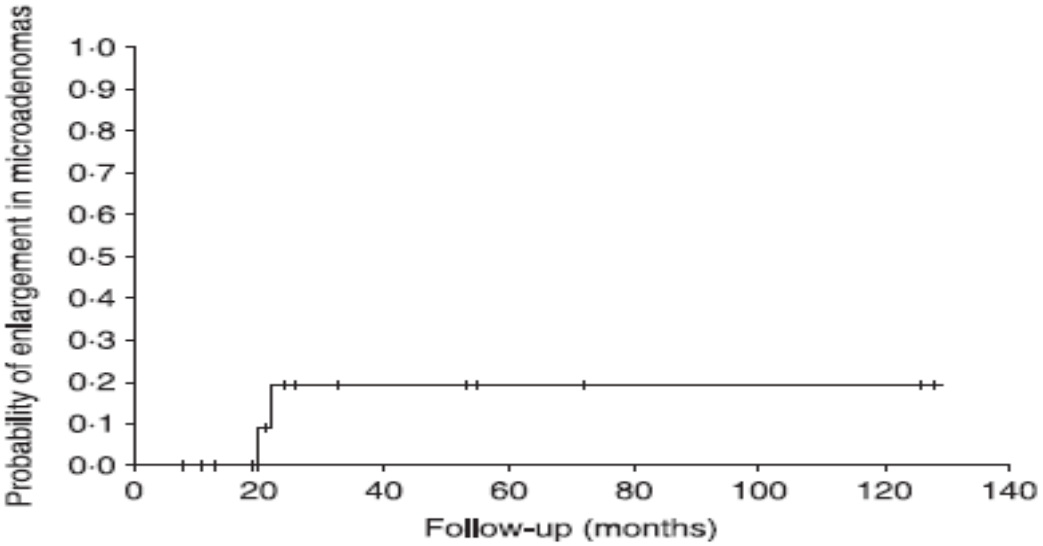


Fig. 2 Probability of tumour enlargement in patients with microadenoma during the follow-up period.

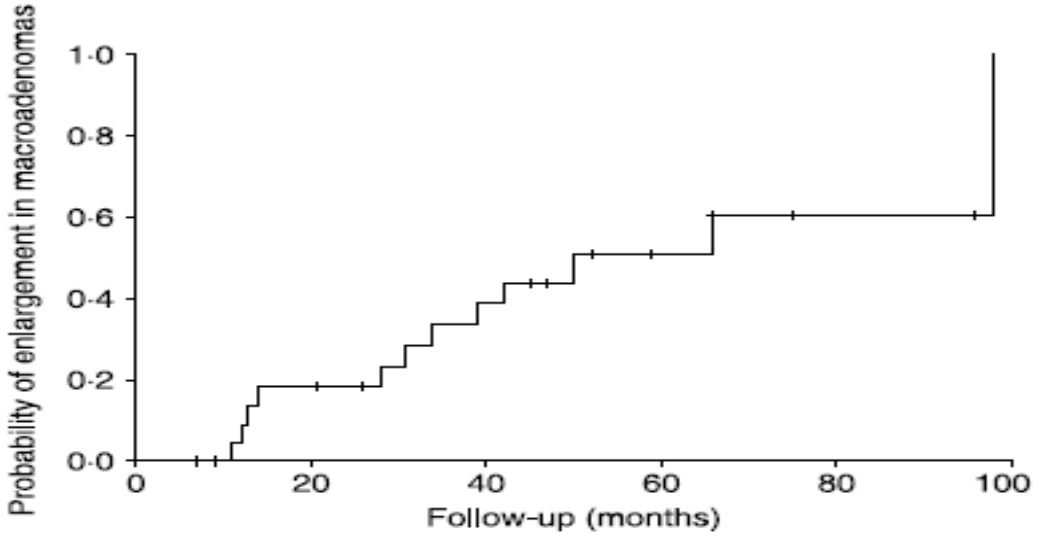


Fig. 3 Probability of tumour enlargement in patients with macroadenoma during the follow-up period.

Clinical Endocrinology (2006) 65, 524–529 doi: 10.1111/j.1365-2265.2006.0

ORIGINAL ARTICLE

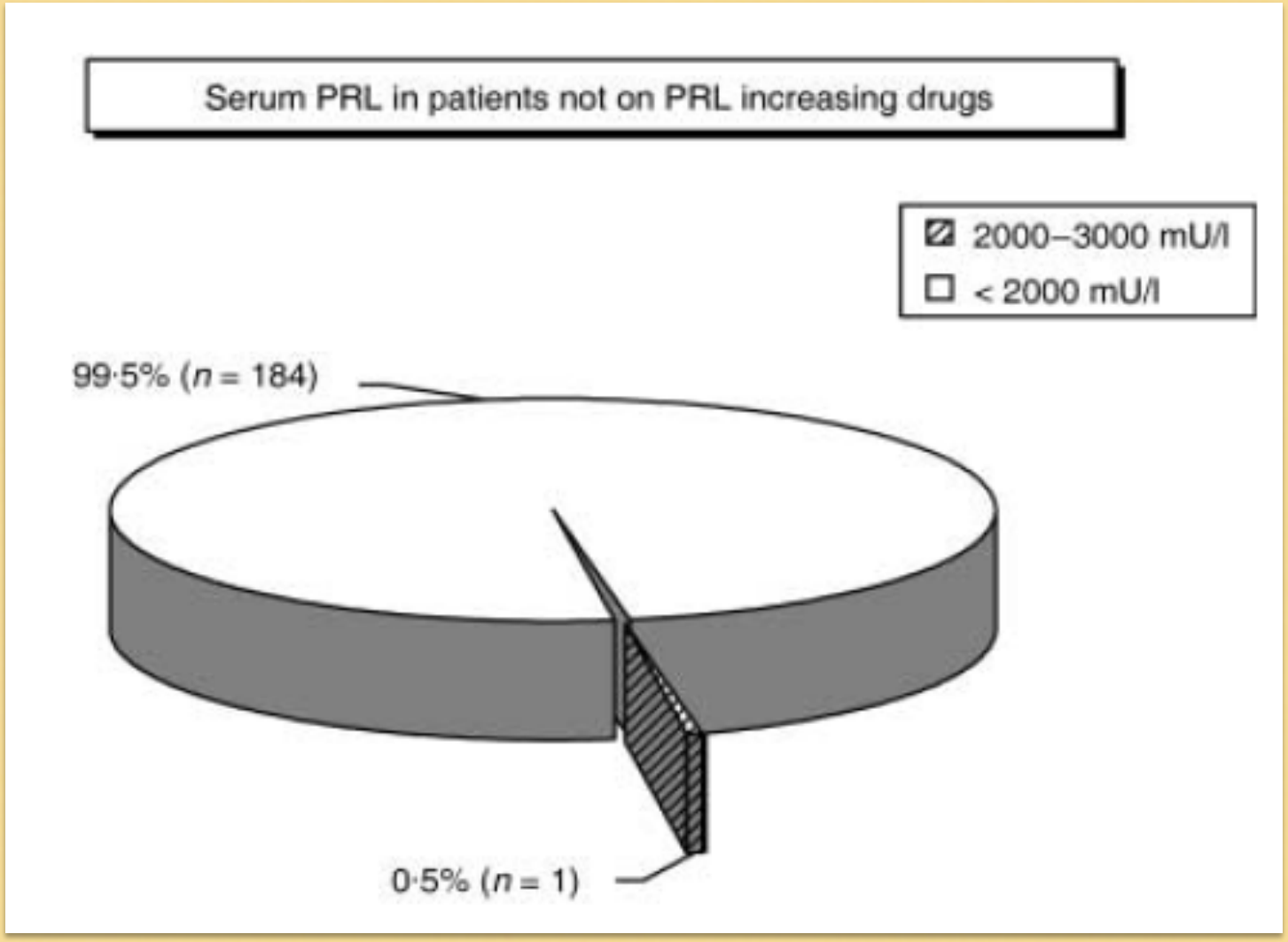
Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma

Niki Karavitaki* Gaya Thanabalasingham* Helena C. A. Shore* Raluca Trifanescu* Olaf Ansorge† Niki Meston‡ Helen E. Turner* and John A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, †Neuropathology Department, Radcliffe Infirmary and ‡Department of Chemical Pathology, John Radcliffe Hospital, Oxford, UK

Disconnection Hyperprolactinaemia

226 patients	55 years (18-88)	
	verified non functioning adenomas	
	41 patients on prolactin elevating drugs	
All	Median prolactin	386 mU/L (16-3257)
No drugs		363 mU/L (16-2565)
Serum prolactin < 2000 mU/L		98.7% (all)
		99.5% (no drugs)


Serum PRL in patients not on PRL increasing drugs
2000–3000 mU/l
< 2000 mU/l
99·5% (n = 184)
0·5% (n = 1)

European Journal of Endocrinology (2011) 165 739–744 ISSN 0804-4643

CLINICAL STUDY

Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma?

Raghava Reddy, Simon Cudlip[1], James V Byrne[2], Niki Karavitaki and John A H Wass

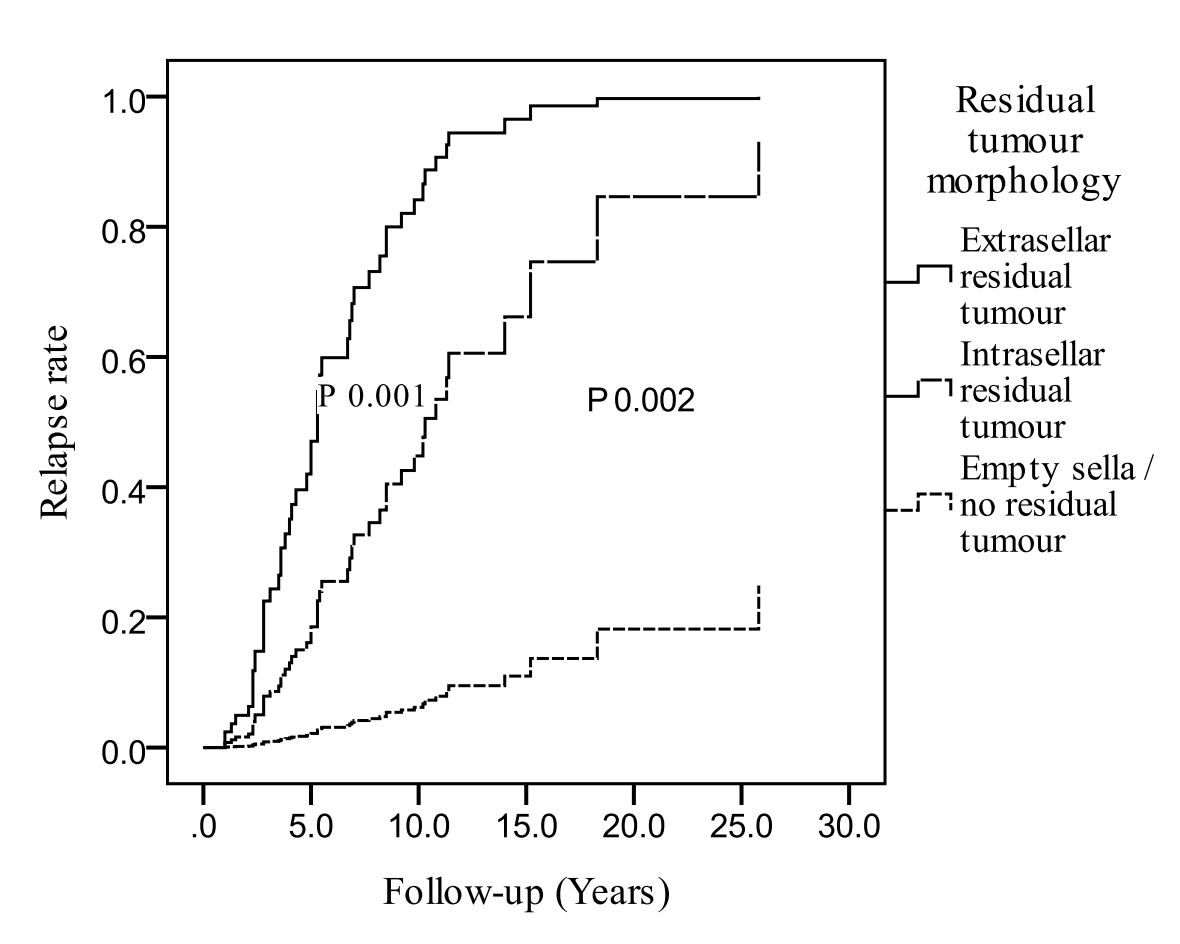
Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford, Oxford OX3 7LJ, UK, Departments of [1]Neurosurgery and [2]Neuroradiology, The John Radcliffe Hospital, Oxford, UK

(Correspondence should be addressed to J A H Wass; Email: john.wass@noc.nhs.uk)

Table 2: Re-growth rates detected by 1, 5 and 10 years in the 3 groups based on postoperative imaging details.

	No residual tumour (A)	*Intrasellar residual (B)*	*Extrasellar residual (C)*
At 1 year	*0%*	*1.5%*	*4.2%*
At 5 years	*0%*	*20%*	*53%*
At 10 years	*6%*	*53%*	*80%*
P Value			
Vs A	-	*0.001*	*<0.001*
Vs B	*0.001*	-	*<0.001*
Vs C	*<0.001*	*<0.001*	-

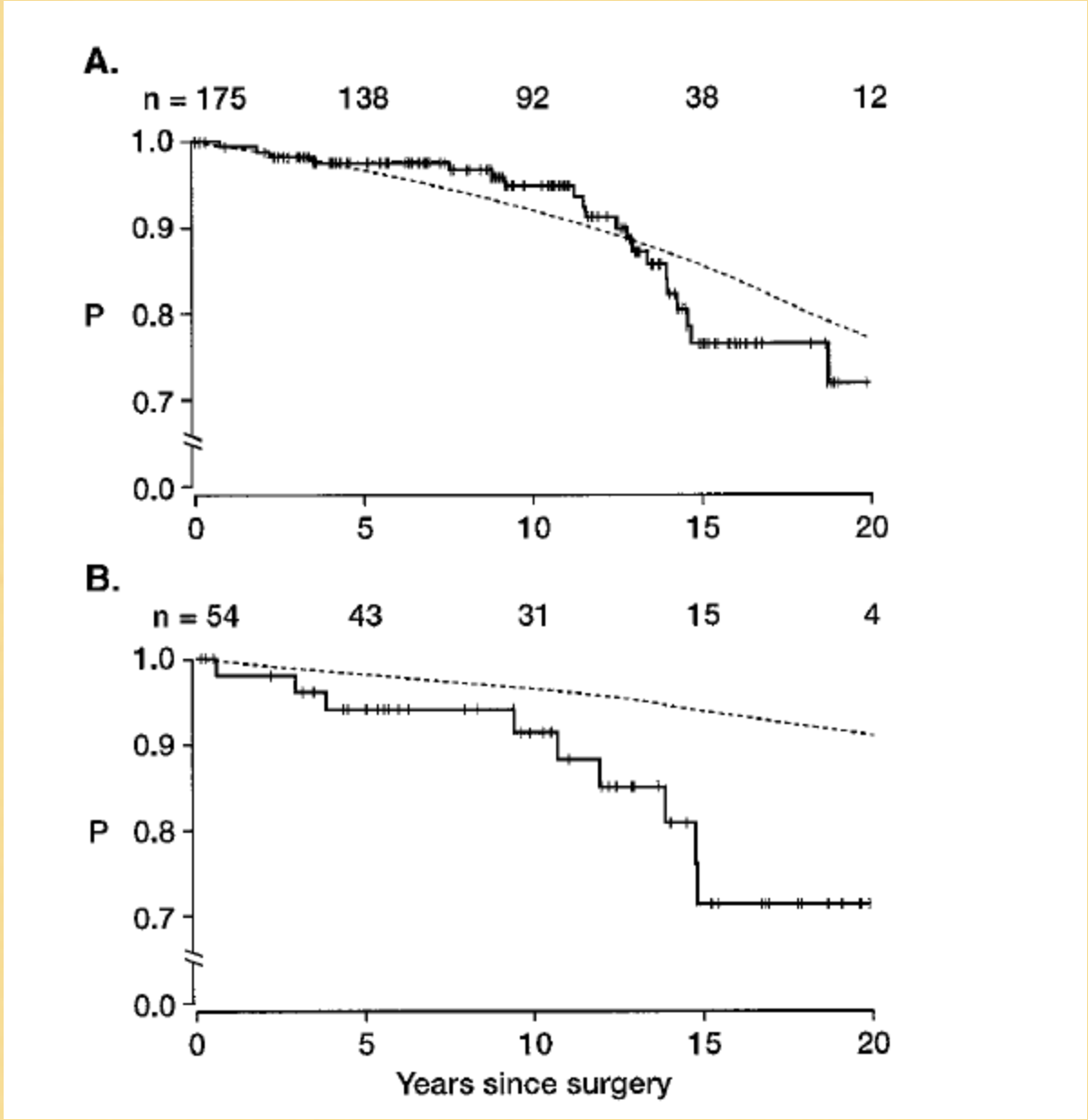
Figure 1: Relapse rate according to postoperative scan classification.



Potential new treatments of non-functioning pituitary adenomas

Dopamine agonists

Somatostatin analogues



Abosch et al, JCEM 1998; 83: 3411-3418

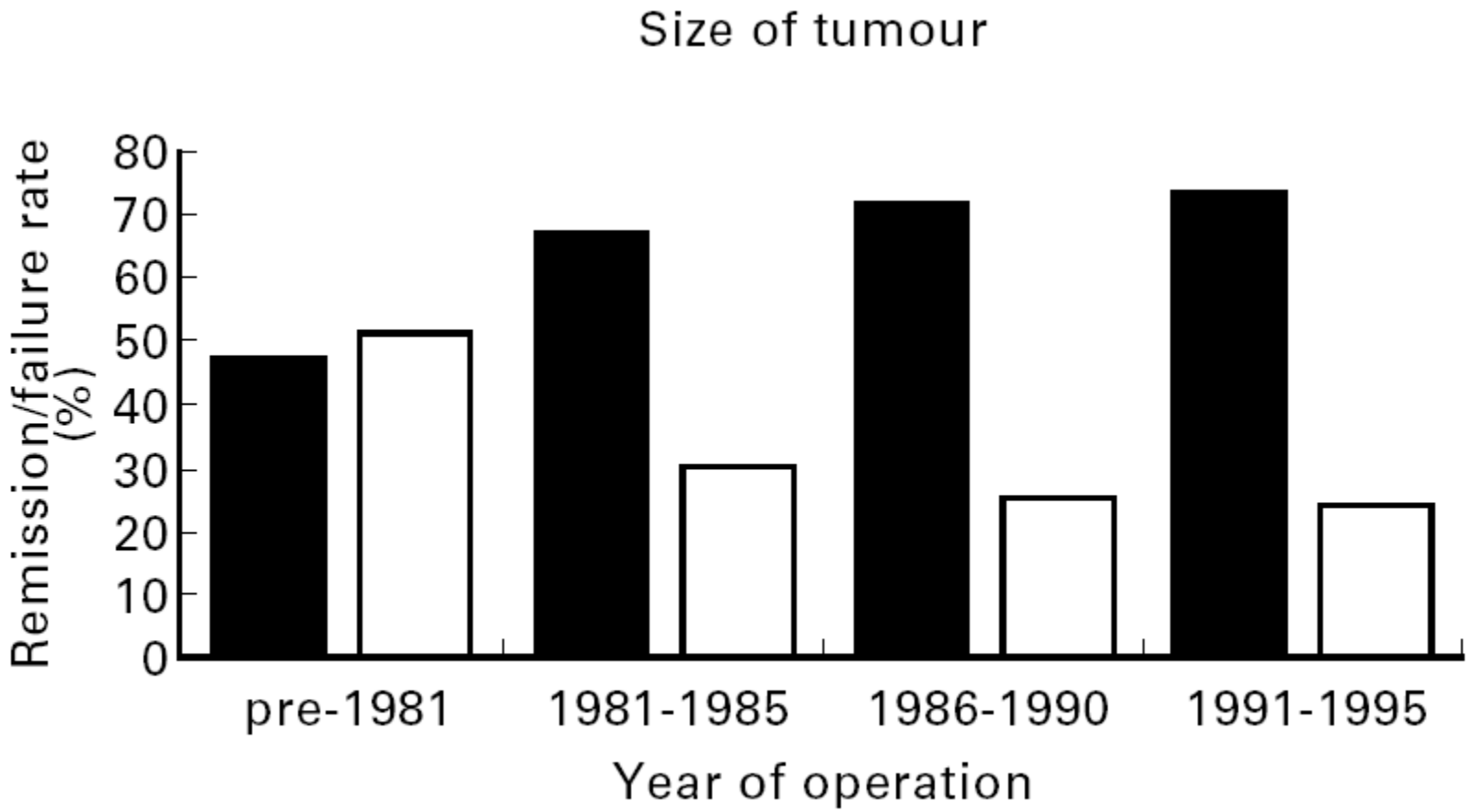


Fig. 2 Success and failure rates with time of surgery. ■ Remission; □ Failure.

Ahmed S, Elsheikh M, Page RCL, Adams CBT, Wass JAH. Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. ***Clinical Endocrinology*** **1999; 50, 561-567**

Clinical Endocrinology (2013)

doi: 10.1111/cen.12207

ORIGINAL ARTICLE

Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists

Trevor A. Howlett, Debbie Willis, Gillian Walker, John A.H. Wass, Peter J. Trainer and the UK Acromegaly Register Study Group (UKAR-3)*

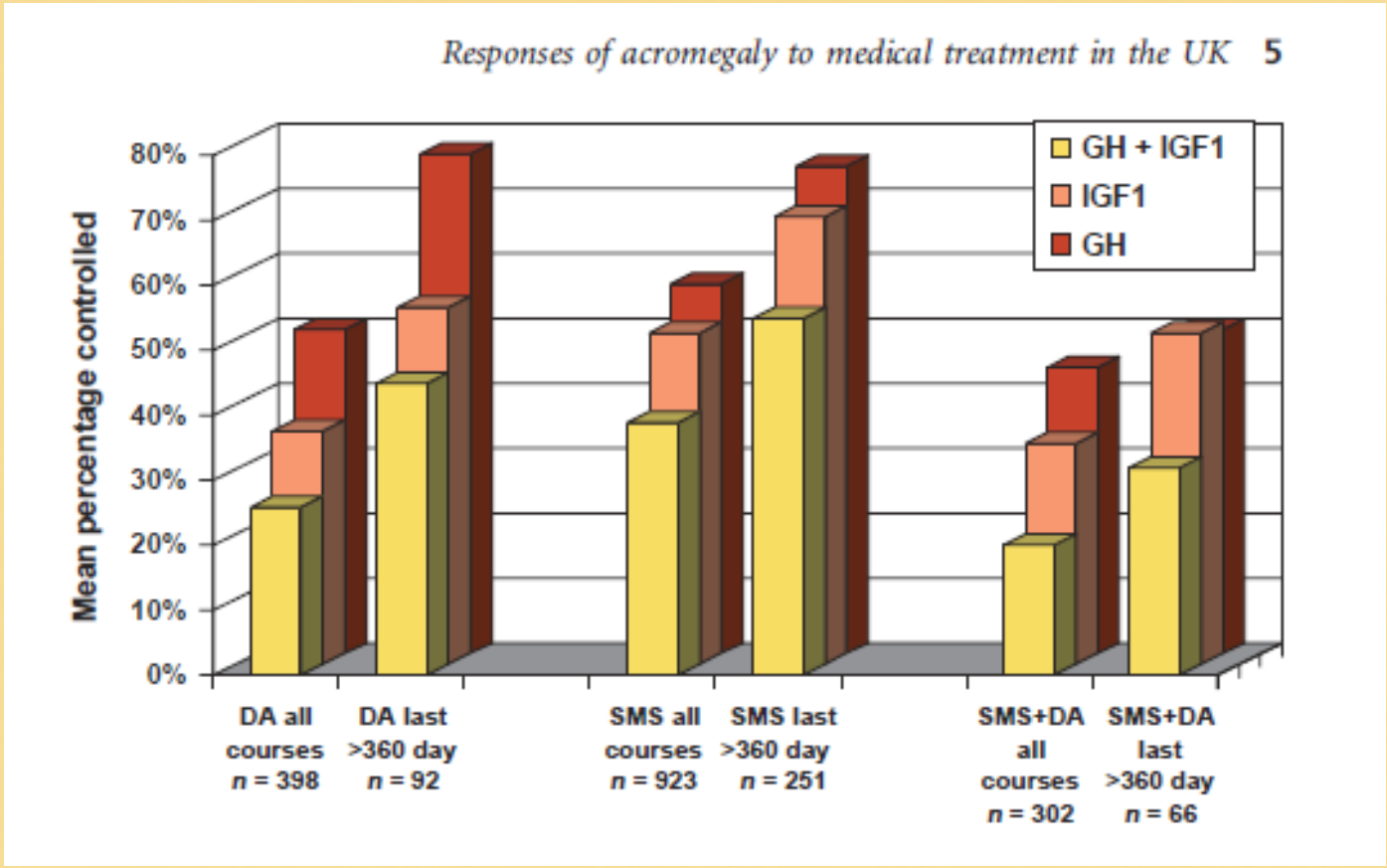
UK Acromegaly Register, Society for Endocrinology, Bristol, UK

GH levels and GH and IGF1 control in individual patients at latest value on and off medical treatment, stratified by the last era of observations

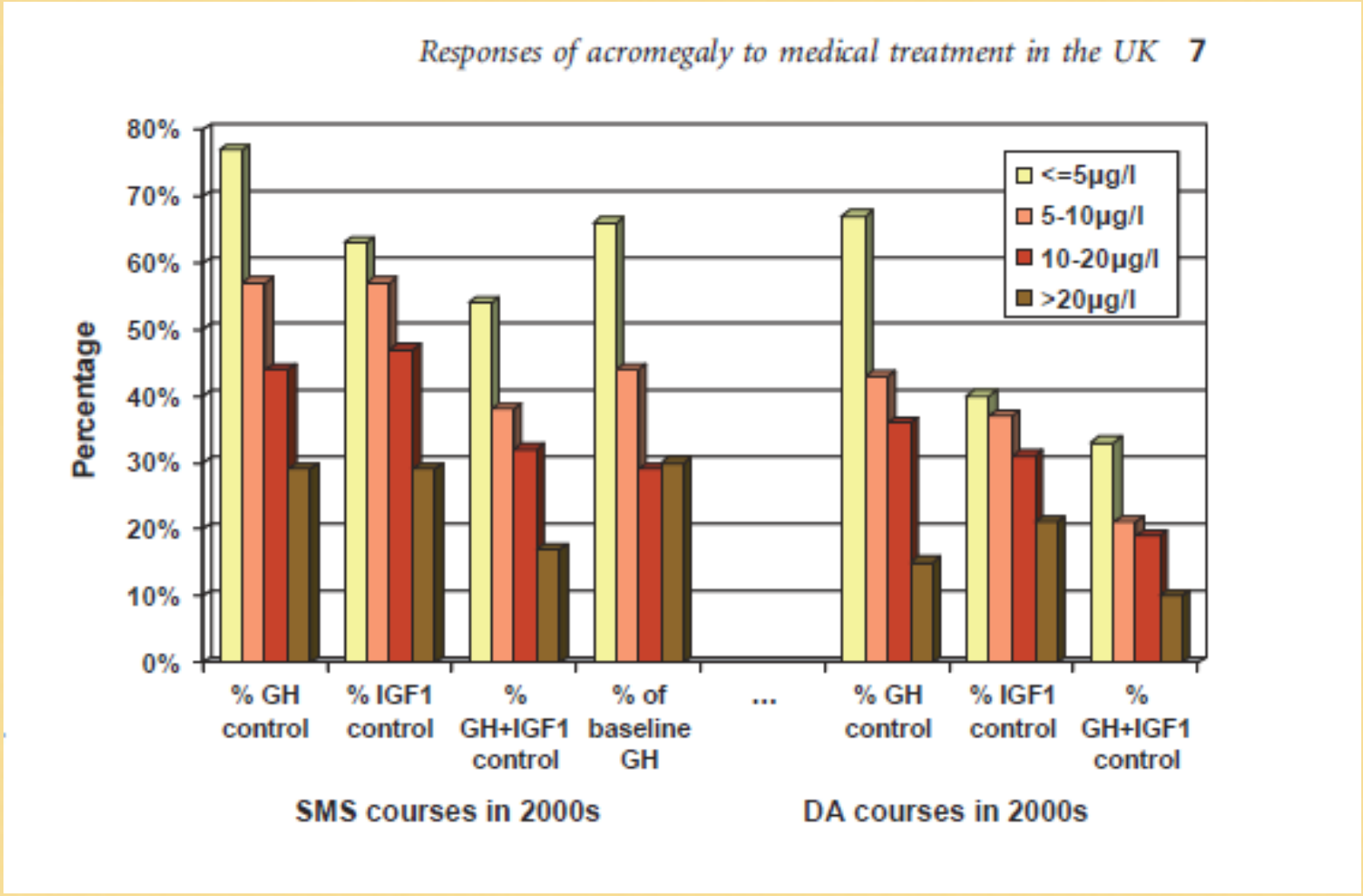
Howlett et al, Clinical End. 2013

	last era of observation		
	pre- 1990	*1990s*	*2000s*
Mean of last GH value – on RX	*15.1*	*12.5*	*4.5*
Latest values whether On or Off GH controlled	*38%*	*56%*	*71%*

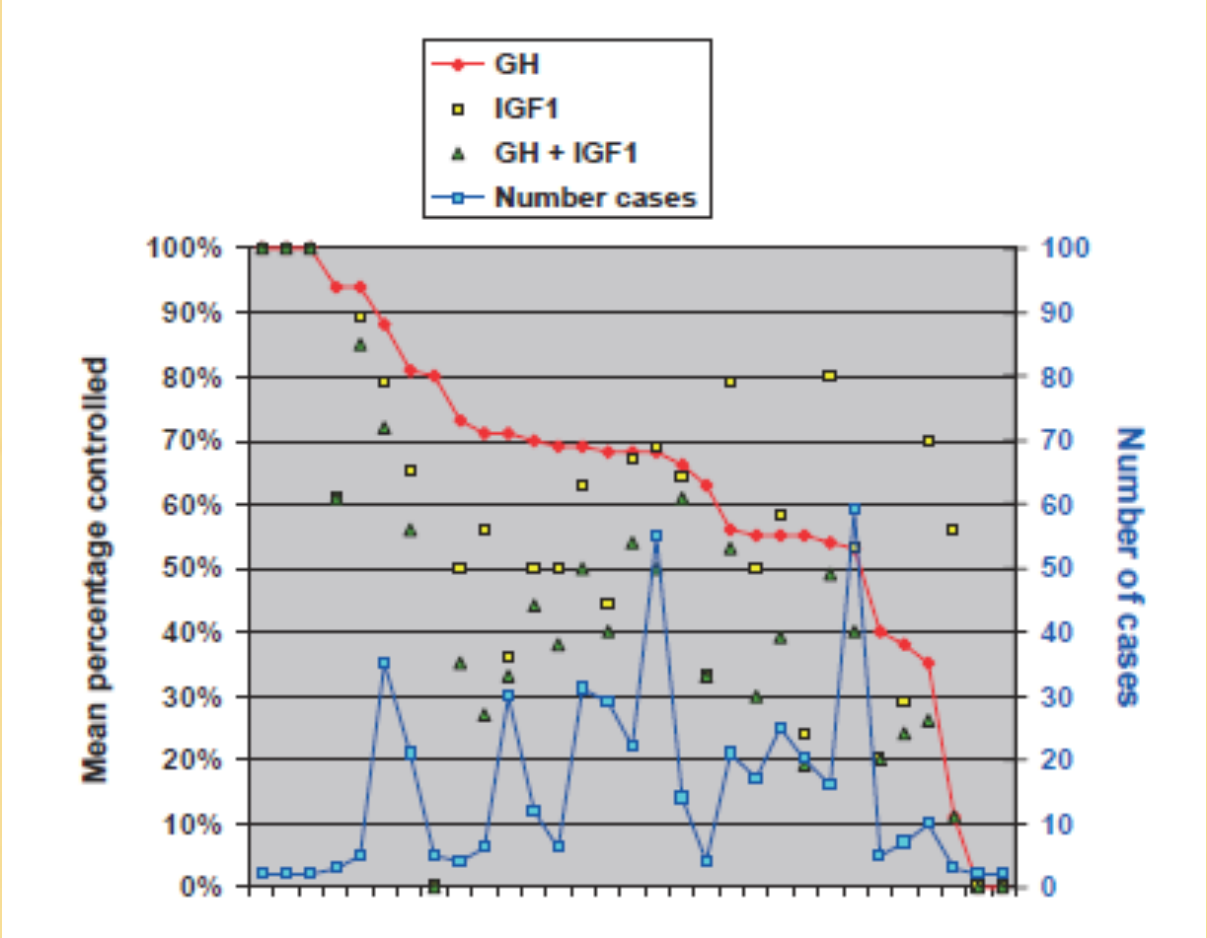
Responses of GH and IGF1 to treatment with somatostatin analogues (SMS) and dopamine agonists (DA) in treatment courses during the 2000s



Control of GH and IGF1 by dopamine agonists (DA) and somatostatin analogues (SMS) in 2000s, stratified by the precourse GH



Comparison of biochemical control of acromegaly in different UK centres and number of cases in each centre



Pituitary Surgery Results - Oxford

	Acromegaly	Prolactinoma	Cushing's
Cure rate (microadenoma)	90-100%	79%	63%
Recurrence rate	5.7% @ 4.4 yr.	4.0% @ 5.0 yr.	11.5% @ 3.3 yr.
TSH deficiency (Post-op)	5.0%	0%	25.8%

Ahmed et al 1999, Turner et al 2000, Yap et al 2002

Medical treatment of resistant acromegaly.

SOM230 (Pasireotide) improves growth hormone and IGF1 outcome.

Monitoring

Annual monitoring of
- GH - g.t.t.<1, basal <1.8ng/L
- IGF_1 - normal

+/- MRI pituitary

Cardiovascular
- blood pressure
- echo

Carbohydrate metabolism

Rheumatology

Colonoscopy/mammography/PSA

New drugs for acromegaly

Oral octreotide

SOM 230 (pasireotide)

GH secretion inhibitors

Causes of Cushing's syndrome

- Pseudo-Cushing's syndrome:
  - Alcoholism <1%
  - Severe depression 1%
- ACTH-dependent:
  - Pituitary adenoma 68% (Cushing's disease)
  - Ectopic ACTH syndrome 12%
  - Ectopic CRH secretion < 1%
- ACTH independent:
  - Adrenal adenoma 10%
  - Adrenal carcinoma 8%
  - nodular (macro or micro) hyperplasia 1%
  - Carney complex
- Exogenous steroids including skin creams e.g., clobetasol

Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit.

Yap et al, Clin Endocrinol (Oxf). 2002 Jan;56(1):25-31

Retrospective analysis of 97 patients:

followed for a mean of 92 months
(six months to 29 years)

Remission rate with an undetectable cortisol 68.5%

11.5% recurrence at 36 months

Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment.

Van de Pas et al, Clin End. 2013; 78:481-8

10 x increased risk of thromboembolism in Cushing's

Increased production of pro-coagulant factors

Impaired fibrinolytic activity

? Thromboprophylaxis after surgery

A 12 Month Phase 2 Study of Pasireotide in Cushing's disease

Colao et al, NEJM 2012: 366; 914-24

Double blind study 162 patients with Cushing's disease

Subcutaneous pasireotide – 600mcg
800mcg

Aim normal urinary cortisol

A 12 Month Phase 2 Study of Pasireotide in Cushing's disease

Colao et al, NEJM 2012: 366; 914-24

12 out of 82	600 mcg
21 out of 80	900 mcg

Achieved a normal urinary cortisol

A 12 Month Phase 2 Study of Pasireotide in Cushing's disease

Colao et al, NEJM 2012: 366; 914-24

Hyperglycaemic events 118 out of 162

European Journal of Endocrinology (2013) **169** 715–723 ISSN 0804-4643

CLINICAL STUDY

Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up

G Ntali, A Asimakopoulou[1], T Siamatras, J Komninos, D Vassiliadi[1], M Tzanela[1], S Tsagarakis[1], A B Grossman, J A H Wass and N Karavitaki

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK and [1]Department of Endocrinology, 'Evangelismos' General Hospital, Athens, Greece

(Correspondence should be addressed to N Karavitaki; Email: niki.karavitaki@ouh.nhs.uk)

Long term survival and cause of death in Cushing's syndrome

Two large tertiary centres

? Variables predicting mortality

480 subjects

311 Cushing's disease

74 adrenal Cushing's

33 Ectopic ACTH

Cushing's disease

ten year survival 95.3%

71% of deaths due to cardiovascular disease or sepsis

Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up

Ntali et al, EJE, 2013; 169: 715-723

SMRs high 9.3 (95% confidence intervals 6.2-13.4)

Ectopic ACTH 77.6% five years survival

Mortality effected even after successful cure

Pituitary apoplexy in non-functioning pituitary adenomas: long term follow up is important because of significant numbers of tumour recurrences

A. Pal*, C. Capatina*, A.P. Tenreiro*, P.D. Guardiola*, J.V. Byrne†, S. Cudlip‡, N. Karavitaki* and J.A.H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford; †Department of Neuroradiology, The John Radcliffe Hospital, Oxford; ‡Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK

NFA recurrence rates after classical pituitary apoplexy

32 patients

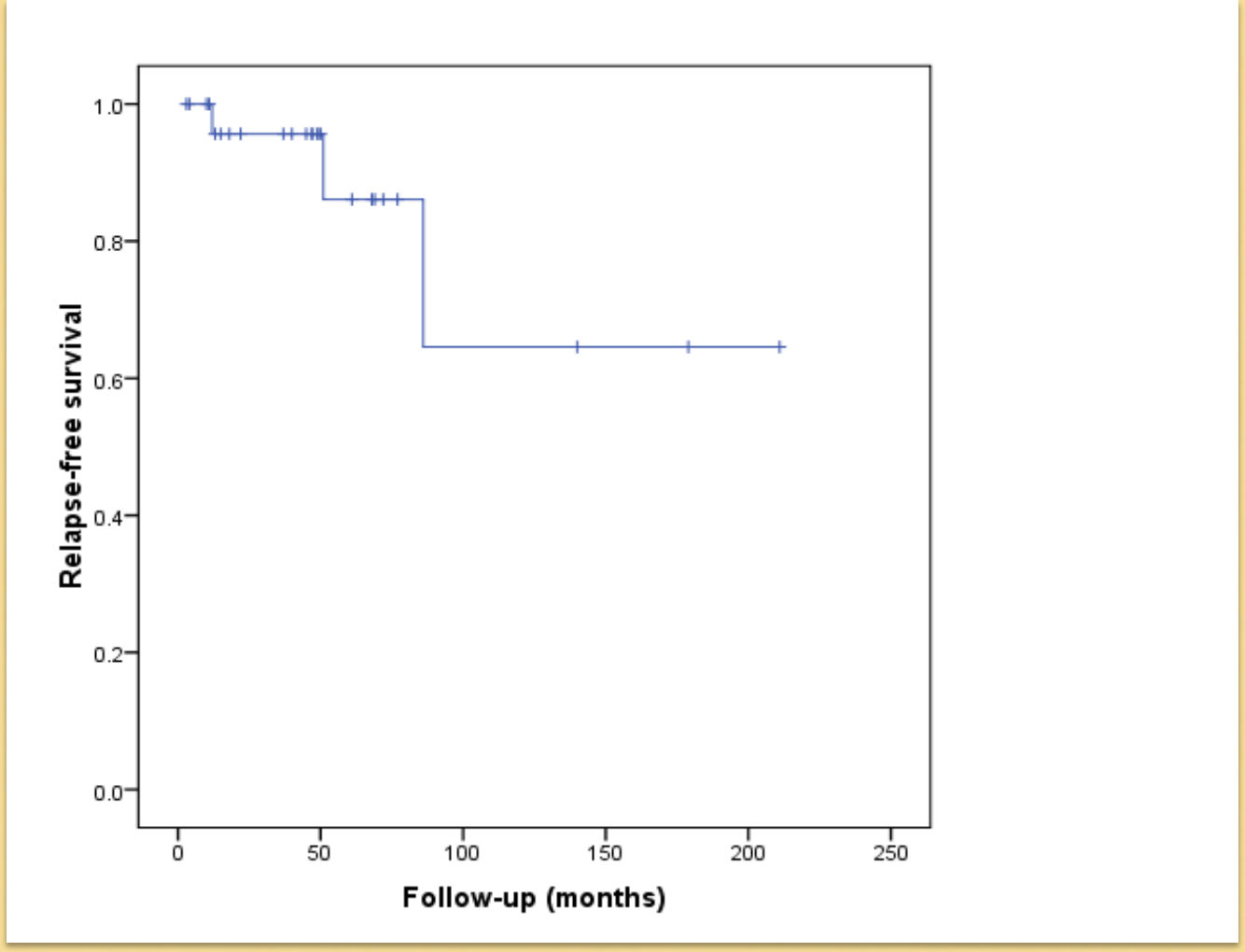
mean age 58.5 years (29-85)

mean follow up 65 months (3-211)

5 given adjuvant radiotherapy

3 (11.1%) patients relapsed at a mean 51 months

Relapse Free Survival After Classical Pituitary Apoplexy (NFAs)



FUTURE TREATMENTS OF PITUITARY TUMOURS

1. Genesis of pituitary tumours: PTTG, Angiogenesis, AIP gene
2. Replacement therapy: DHEA?
3. Surgery: Fewer expert centres, endoscopy
4. Drugs: selective Somatostatin receptor antagonists, Pegvisomant and oral octreotide
5. Radiotherapy: Gamma knife
6. Pituitary tumour gene therapy