Pituitary Tumours 2015: The Oxford experience

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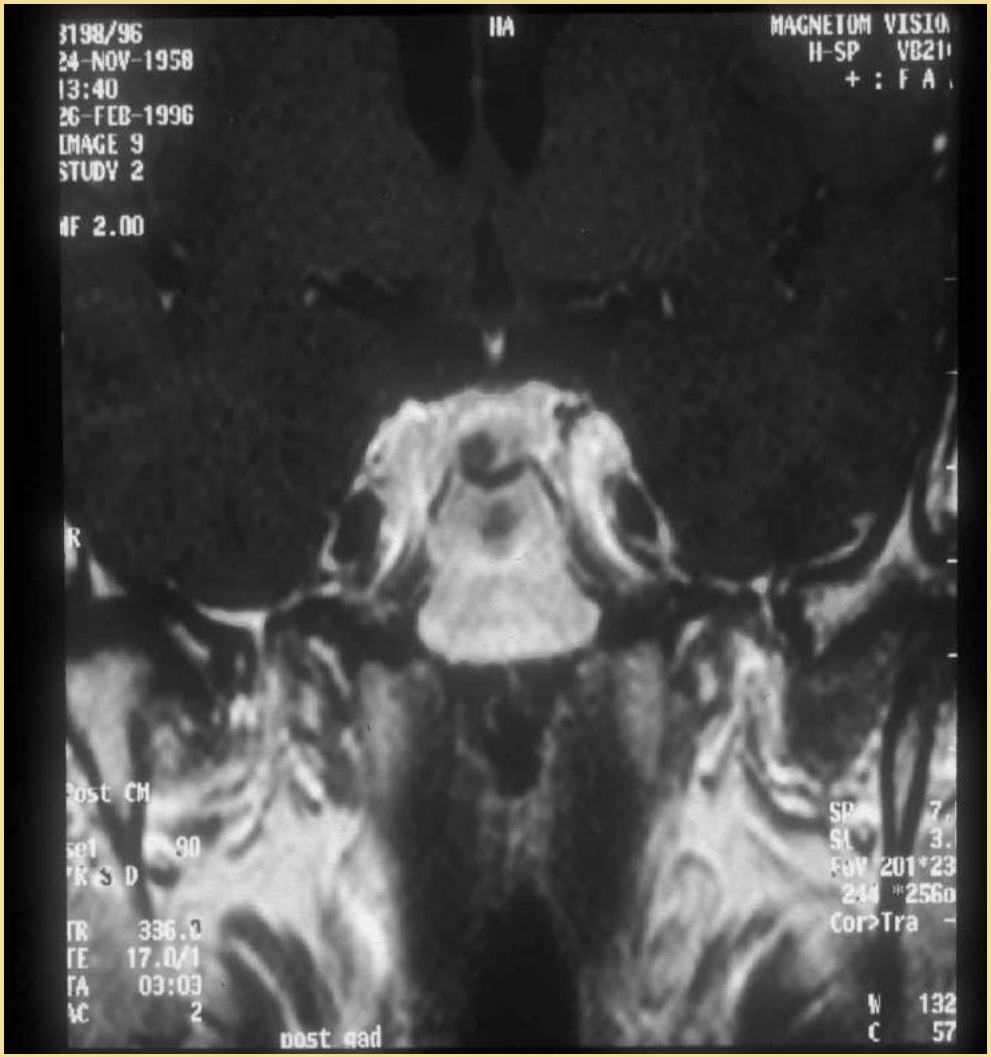
Caledonian Society for Endocrinology 2015 meeting
Friday 27th of November 2015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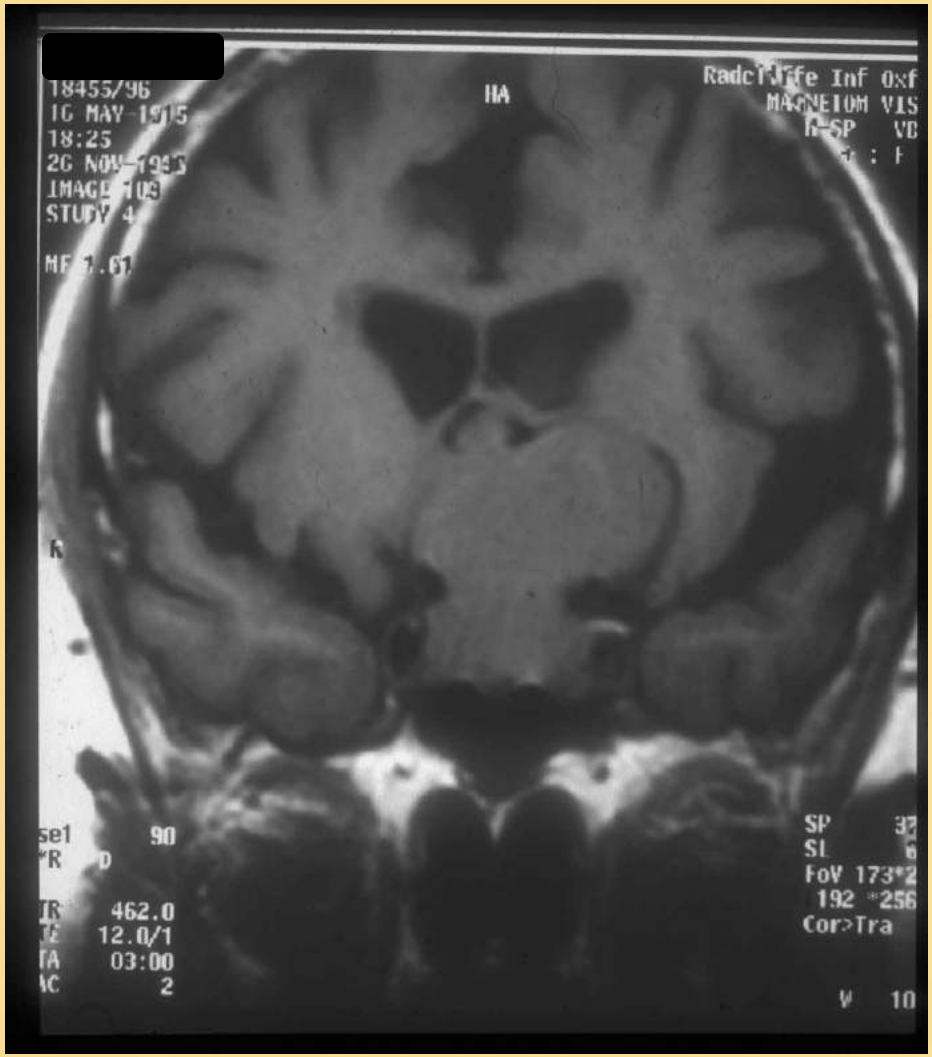
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Classification of Pituitary Tumours

FUNCTIONING

- prolactin
- growth hormone (GH)
- adrenocorticotrophic hormone(ACTH)

NON FUNCTIONING

VERY RARE:

- Thyroid stimulating hormone (TSH)
- Luteinising hormone (LH)
- Follicle stimulating hormone (FSH)

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

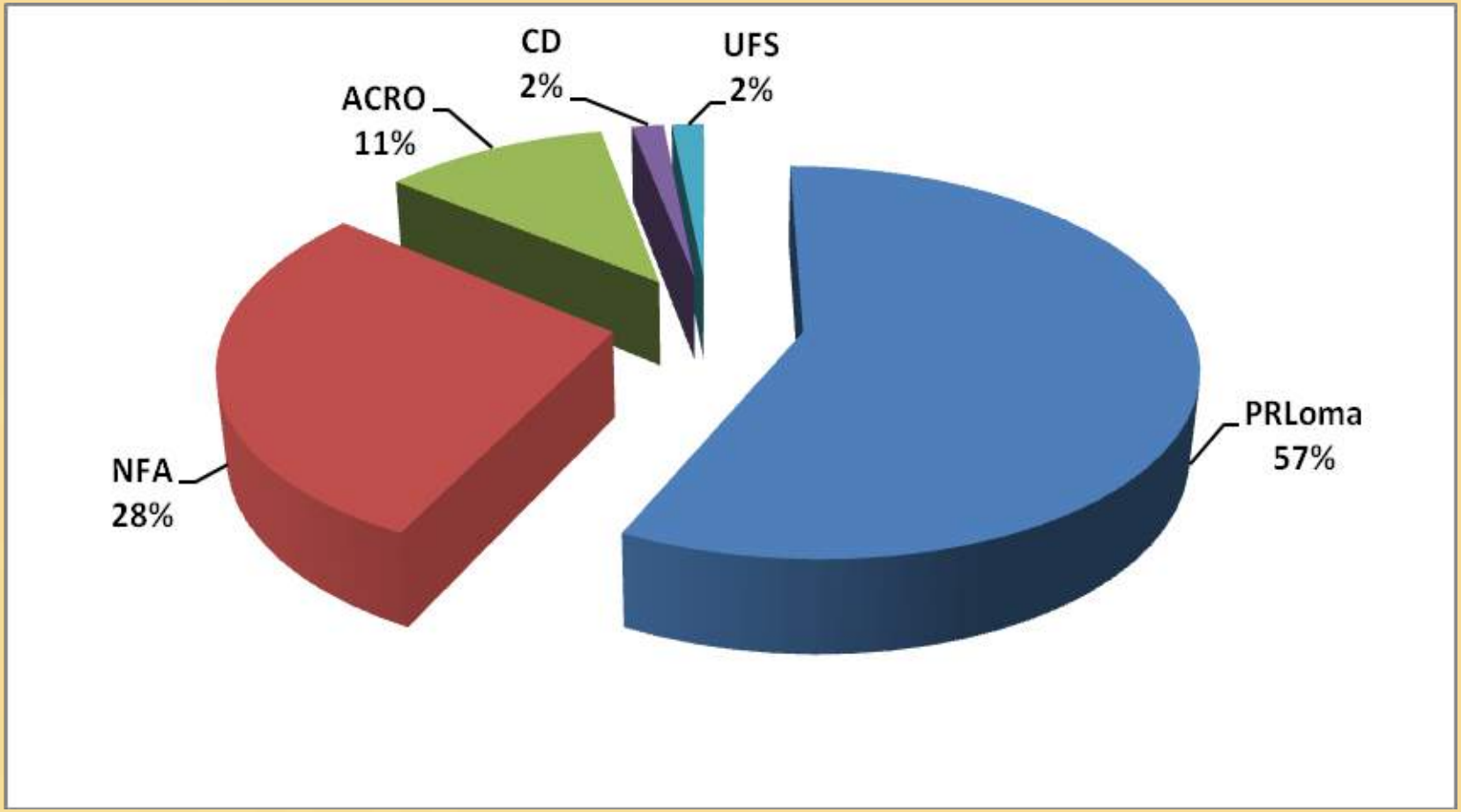
Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

81,449 Inhabitants
91% of study population

	PRL	NFA	ACRO	CD	TOTAL
Total No.	37	18	7	1	64
Prevalence (100,000)	45.6	22.2	8.6	1.2	78.8
Duration of symptoms (yrs)	0.5-12	0-8	1.5-15	7	

Prevalence 79/100,000

Distribution of pituitary adenomas subtypes



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

- All patients presenting to the Department of Endocrinology in Oxford between 1989-2005 with presumed NFA.

- Inclusion criteria:
  - imaging features suggestive of a pituitary adenoma,
  - no clinical and/or biochemical evidence of hormonal hypersecretion,
  - monitoring being the initial choice of management,
  - at least one repeat imaging during the follow-up period.

- Subjects presenting with acute apoplexy were excluded.

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)

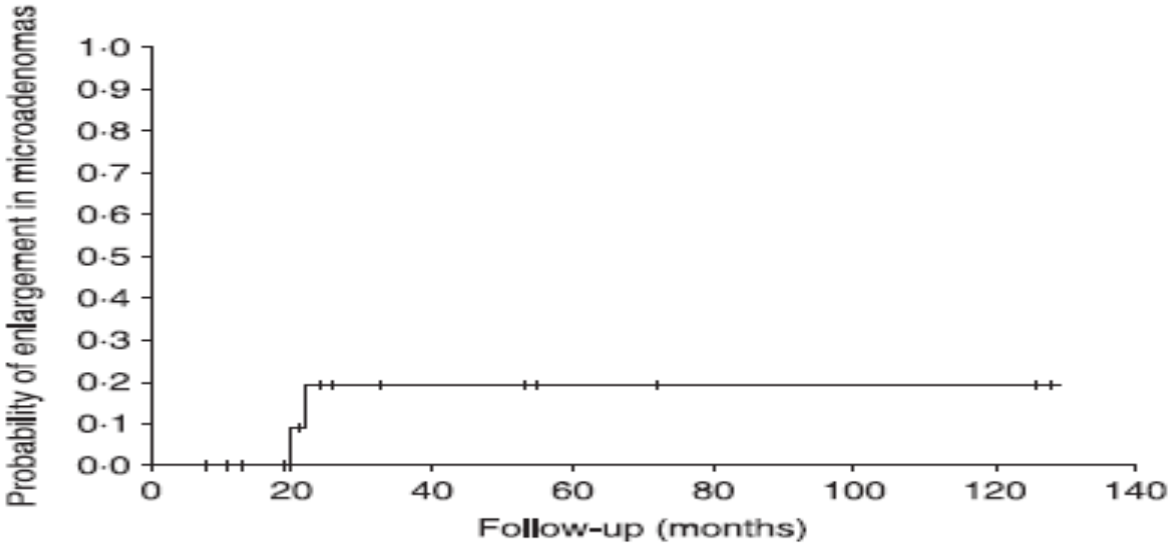


Fig. 2 Probability of tumour enlargement in patients with microadenoma during the follow-up period.

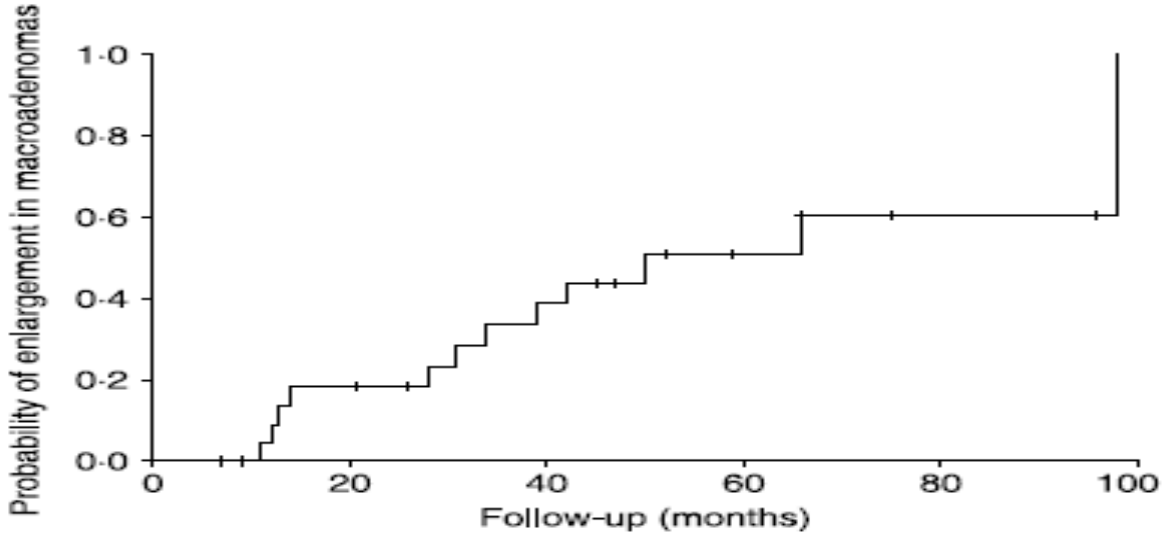


Fig. 3 Probability of tumour enlargement in patients with macroadenoma during the follow-up period.

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*

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NFA recurrence rates after classical pituitary apoplexy

32 patients

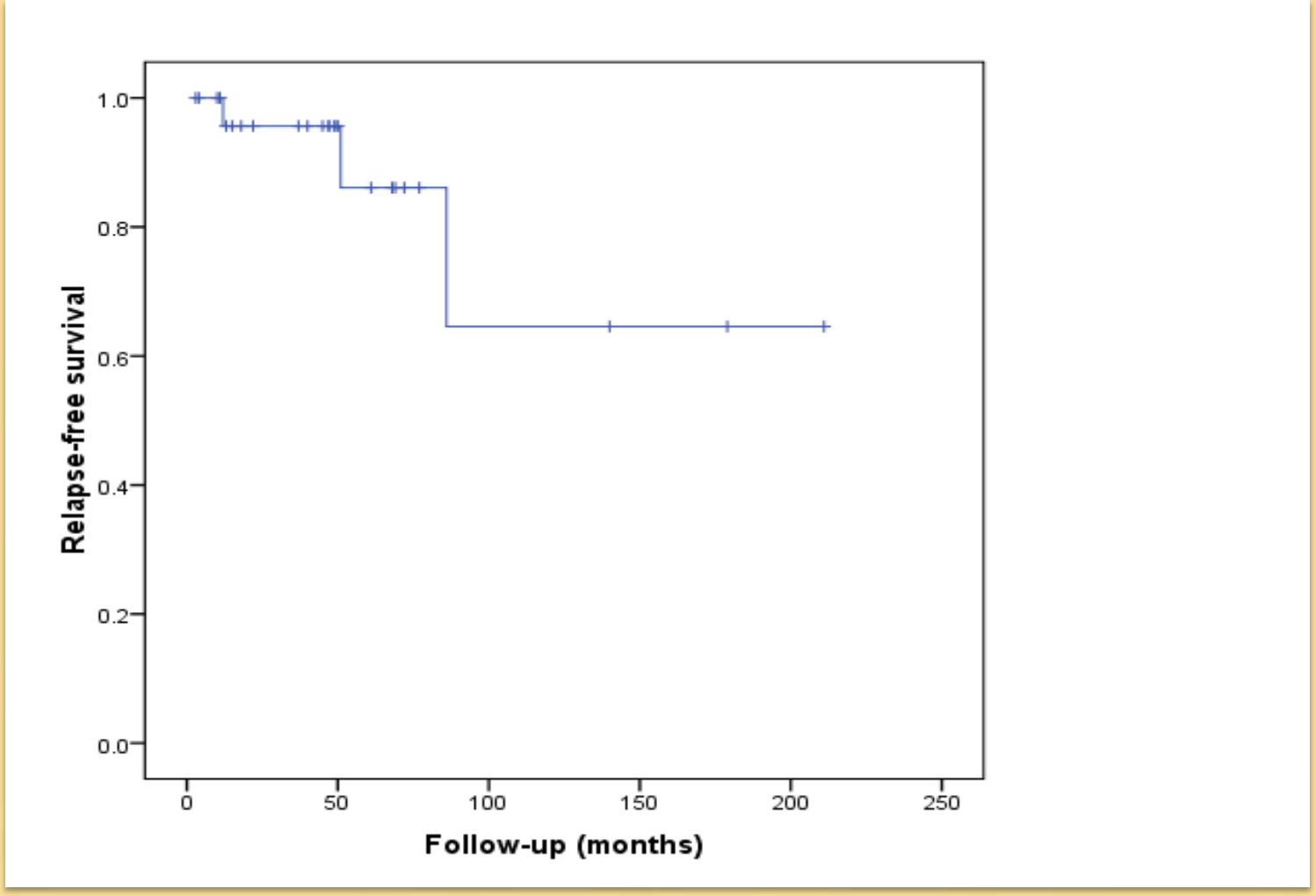
mean age 58.5 years (29-85)

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)



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)

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

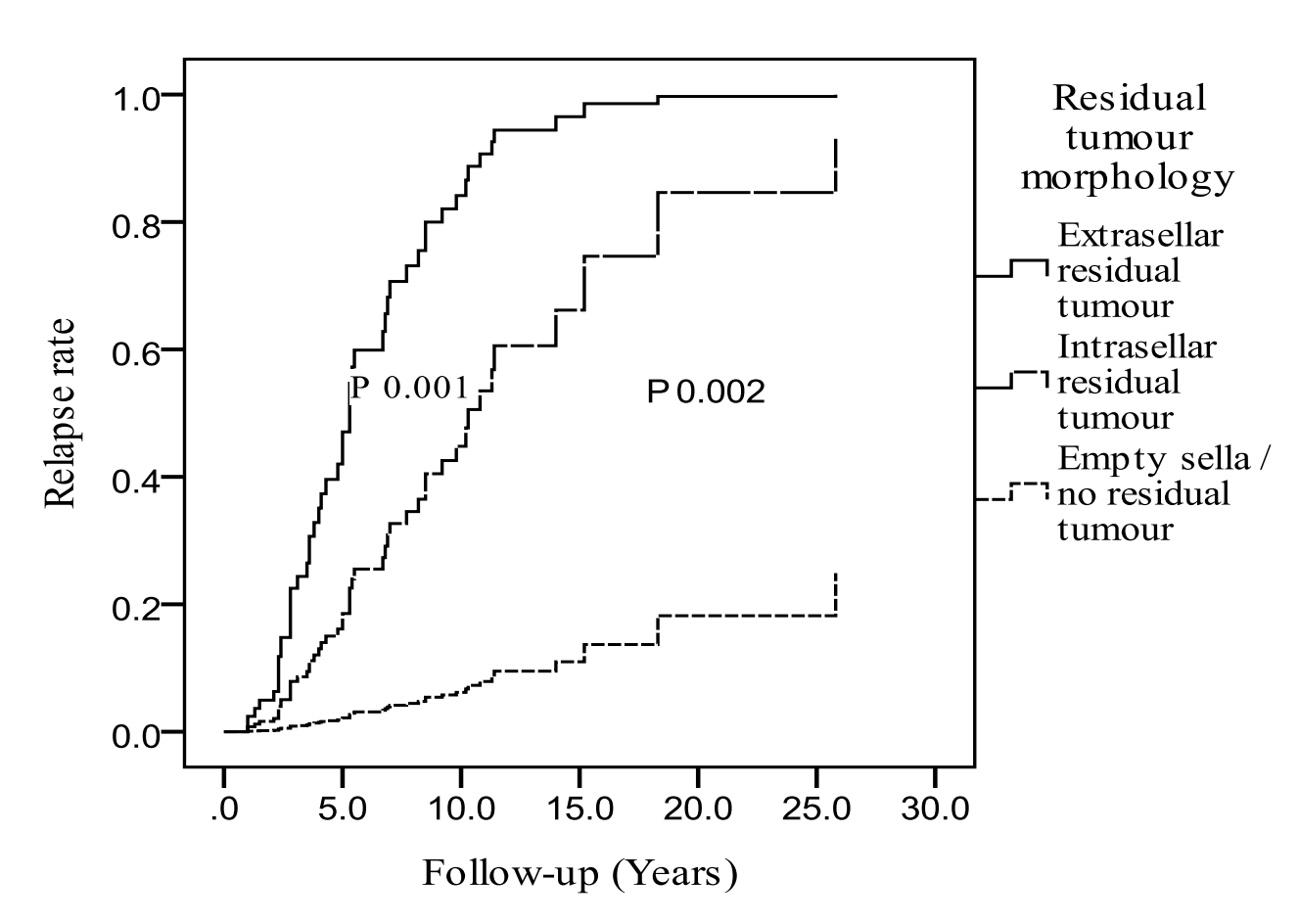
- 155 patients (94M)
- 29 followed > 10 years
- Mean follow up 6.1 years (median 4.3 – range 1-25.8)
- Regrowth 34.8%

  20.4% relapse > 10 years

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.



FOLLOW UP ALGORHITHM for NFAs

Operation (Euthyroid ± steroid cover)

Reassess post operatively @ 6 weeks All axes even if hypopituitarism pre-op

Synacthen + ITT + basals

-T3 peri-operative

-12% recovery

3 months post op scan

Little residual tumour

+ no cavernous sinus tumour

↓

Annual MRI pituitary

- 5 years

- then 2 yearly

Residual tumour

+ cavernous sinus involvement

↓

Adjuvant external beam pituitary irradiation

↓

Annual pituitary function tests + visual fields

Indications for considering post operative radiotherapy

Residual tumour post operatively in cavernous sinus

Difficult resection with firm/hard tumour

Side effects

- hpopituitarism
- late tumour development (2%)
- ? Memory problems
- cerebrovascular disease

Aggressive pituitary tumours: the role of temozolomide and the assessment of MGMT status

Ann I. McCormack[*,†], John A. H. Wass[†] and Ashley B. Grossman[‡]

Eur J Clin Invest 2011; 41 (10): 1133–1148

Temozolomide use in Pituitary Tumours

Since 2006

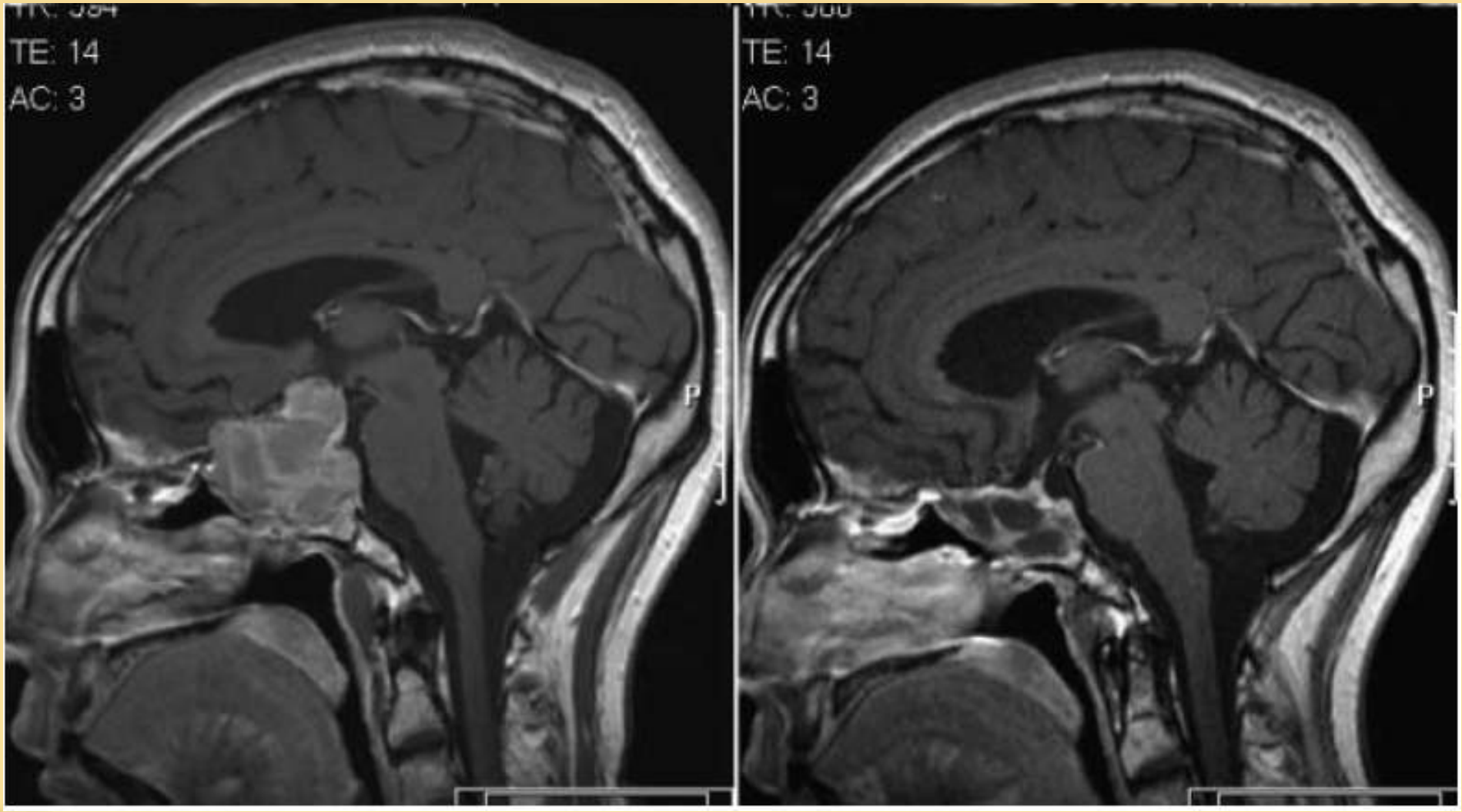
First chemotherapeutic agent to be successful

Maximal response - 10-12 months

Complete hormonal normalisation 50%

Maximum 80% reduction in tumour size

Response may continue for up to 3 years after drug



European Journal of Endocrinology (2009) **161** 631–637

Temozolomide

(McCormack et al, Eur. J. Clin. Invest. 2011 41 1133)

Oral alkylating agent

Treatment of pituitary tumours – overall 24/60 (response 60%)

Prolactinomas	73%
ACTH secreting (including Nelsons)	60%
Non-functioning	40%

Response evident first 3 months

Temozolomide

The Future

Controlled trials - multicentre

- dose regimen ? Duration

Dual therapies + Bevacizumab (anti VEGF a/b)

Long-term data collection on temozolomide (so far only 13)

markers of aggressive behaviour in tumours

TREATMENT ALGORHYTHMS
for
AGGRESSIVE PITUITARY ADENOMAS

Surgery

Assessment of mitotic index
Ki 67
p53
(PTTG)

Post op scan @ 3 months
cavernous sinus invasion
and/or residual tumour

Follow up scans

Consider Radiotherapy
(consider dopamine agonists, SMS analogues)

Further surgery (experienced surgeon)

Temozolomide

MGMT status
Assess at 3 months
Continue at least for 1 year

Experimental therapy

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

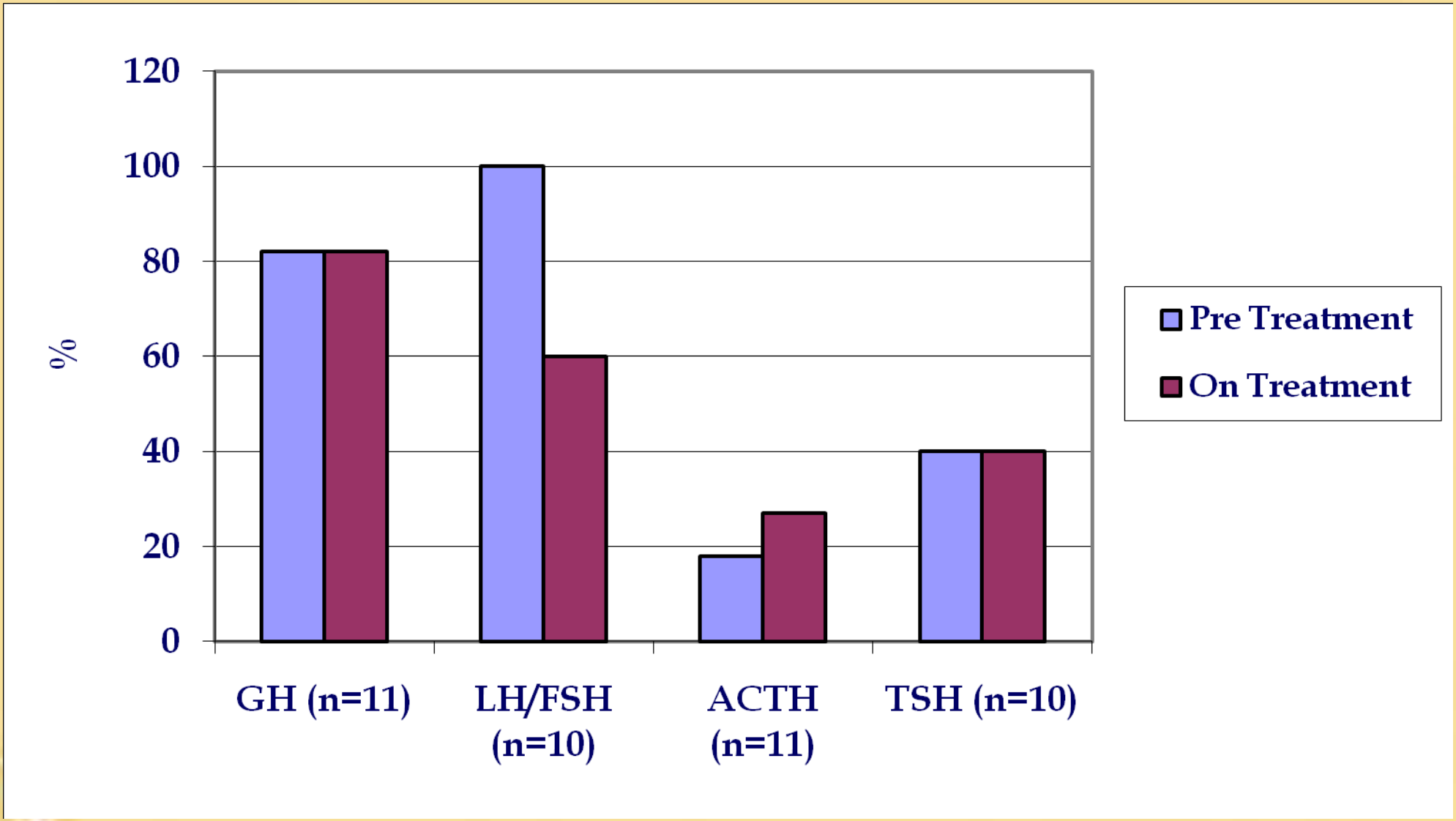
All achieved normal prolactin

All had significant tumour shrinkage

All had pituitary function assessed yearly

(insulin/glucagon test and basal bloods)

Hormone deficits



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. Byrnet 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)

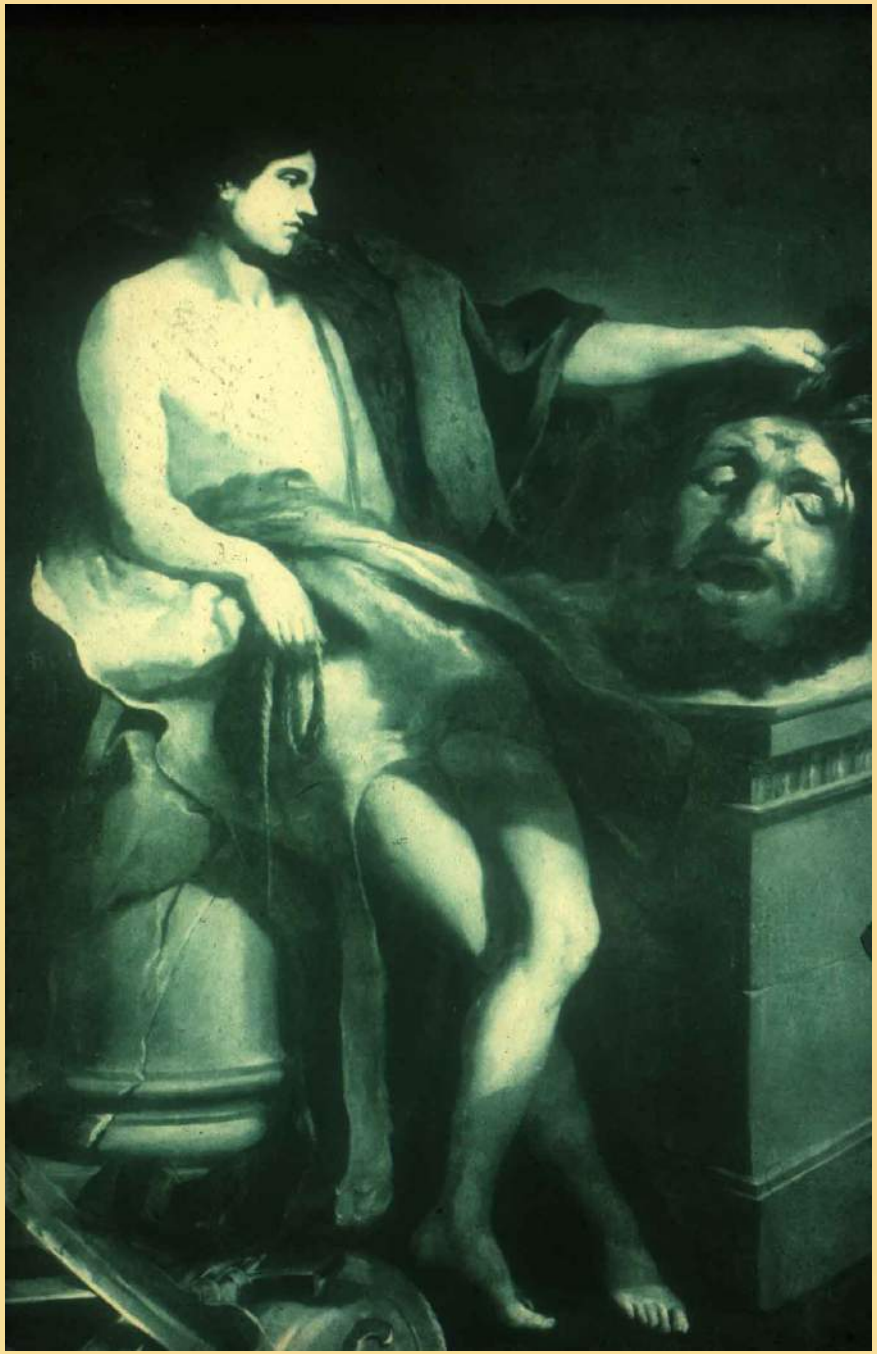
Prolactin suppressed to normal

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)



Clinical Features due to:

Growth hormone over secretion

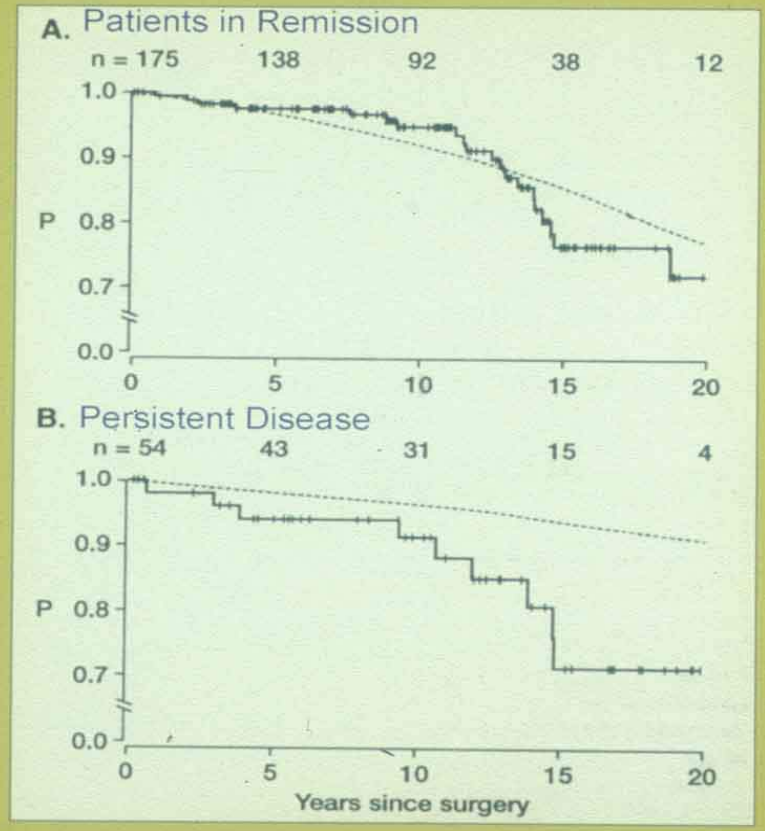
- **Clinical effects**
  e.g. enlarged hands and feet
- **Metabolic effects**
  e.g. diabetes mellitus

Pituitary tumour

- **Local effects**
  e.g. visual field defects
- **Endocrine effects**
  e.g. hypopituitarism

Mortality in Acromegaly

(Abosch et al JCEM 1998)



UK Acromegaly Register 2012

Control of IGF_1 and GH in the cohort

	Controlled	Non controlled
GH (n=164)	57%	38%
IGF_1 (n=145)	55%	30%

GH = 2 µg/L

IGF_1 = the normal range

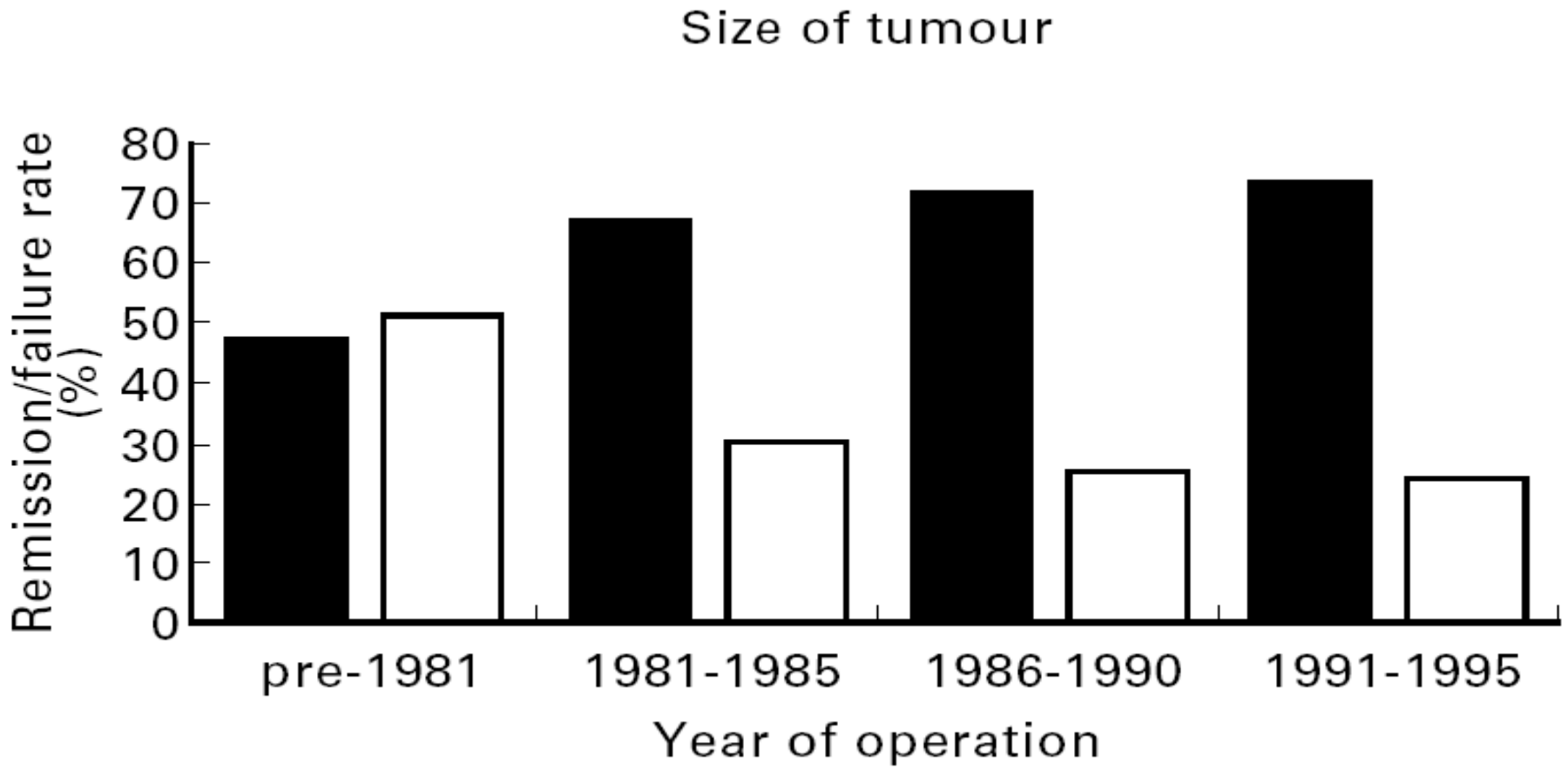


Fig. 2 Success and failure rates with time of surgery. ■ Remission; □ Failure.

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

Pre-Treatment GH and Outcome in Acromegalics on Somatostatin Analogues

Pre-Treatment GH mU/L	Cure Rate %
5-10	60
10-20	48
20-30	54
30-60	31
60-100	19
>100	14

Acromegaly
Prospective study of GH macroadenomas in Oxford
- Is surgical debulking worthwhile?

Protocol

29 patients (12M) with acromegaly and macroadenoma
1 DNA, 1 lost of follow-up

27 patients (11M) - studied prospectively - completed the study

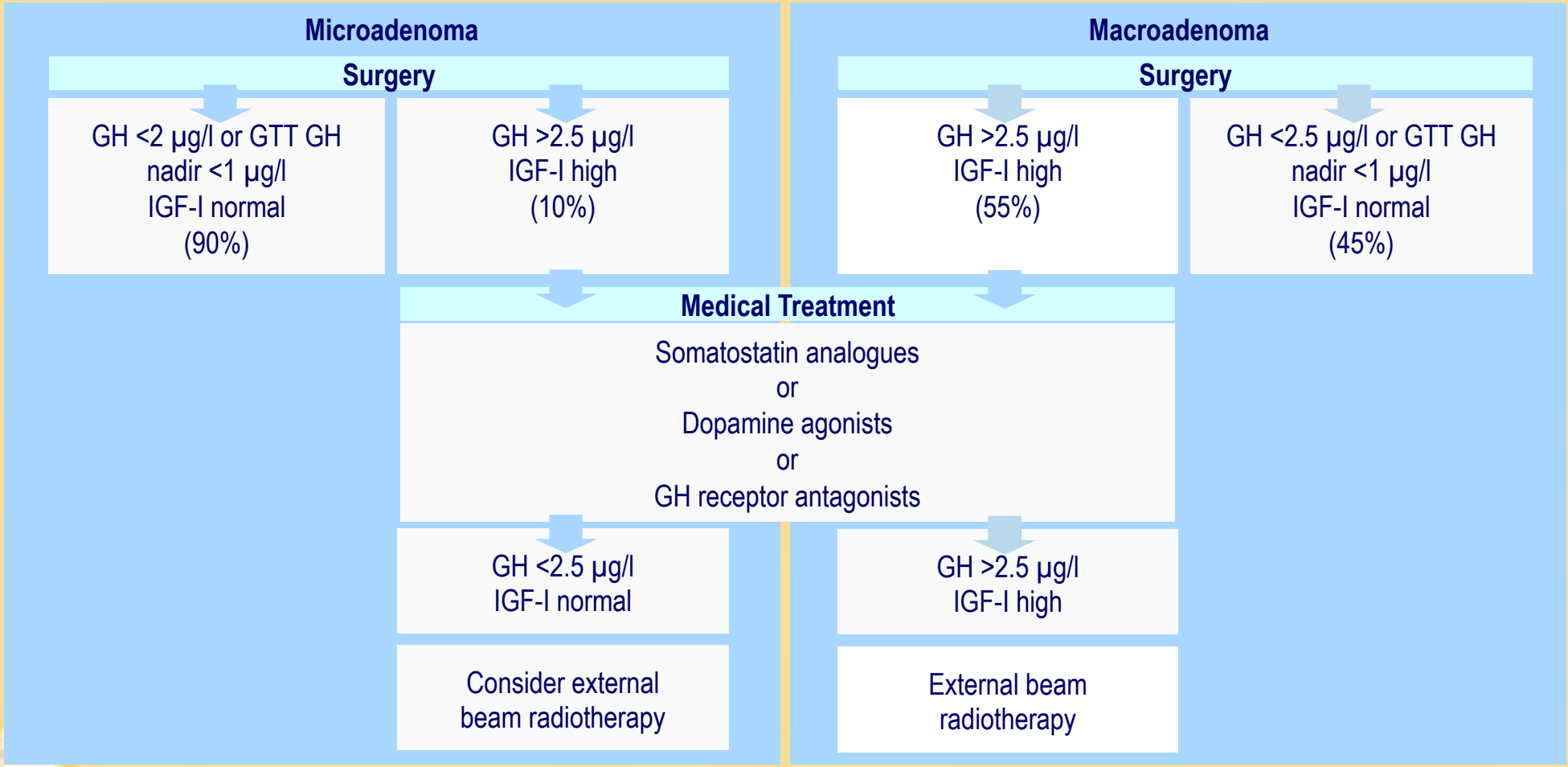
1. Treated with lanreotide 2 weekly preoperatively for 16 weeks.
2. Reassessed at 8 weeks – if necessary (GH >5 mU/L) lanreotide increased to weekly.
3. Surgery.
4. 4 months post surgery – reassessed.
5. If GH > 5 mU/L retreated with lanreotide as preoperatively.

Prospective study of GH macroadenomas in Oxford - Is surgical debulking worthwhile?

Pre and post operation lanreotide comparison in uncured patients

Pt	Pre op + lanreotide GH (mU/L)	Post op + lanreotide GH (mU/L)
9	12	8
13	19	3
17	36	4
21	17	5
27	183	53
29	20	17

Treatment Paradigms in Acromegaly



From Wass, Lamberts & Melmed in *Handbook of Acromegaly*, edited by John Wass. Bristol: BioScientifica

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

0163-769X/06/$20.00/0
Printed in U.S.A.

Endocrine Reviews 27(4):371–397

doi: 10.1210/er.2006-0002

Craniopharyngiomas

Niki Karavitaki, Simon Cudlip, Christopher B. T. Adams, and John A. H. Wass

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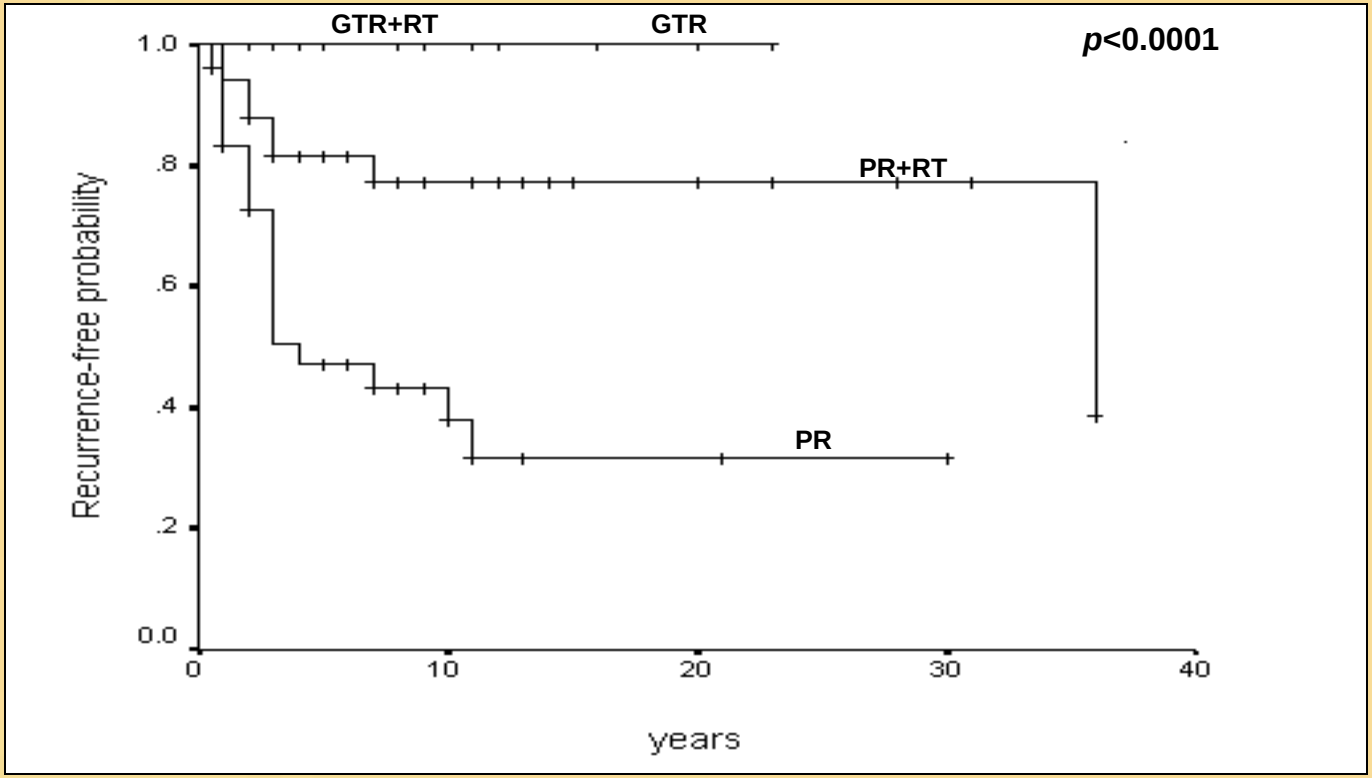
Recurrence-free probability



	GTR	GTR+RT	PR	PR+RT
10-yrs	100%	100%	38%	77%

Median time of 1st recurrence: 2.5 yrs in both groups (0.5-36).

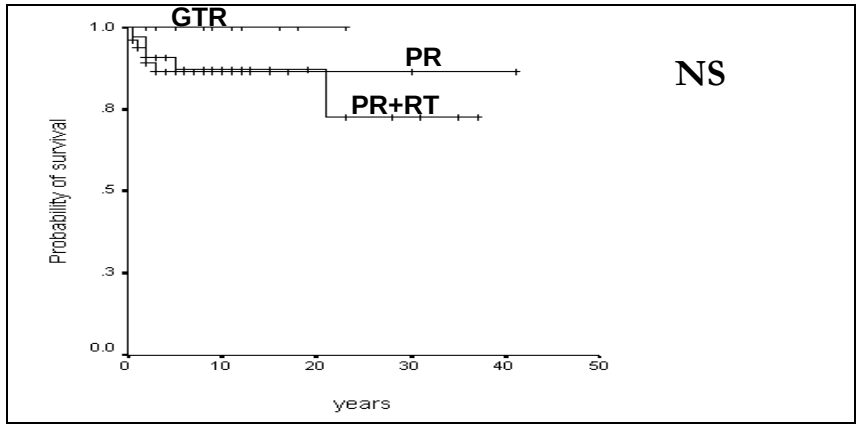
Karavitaki *et al.*, 2005

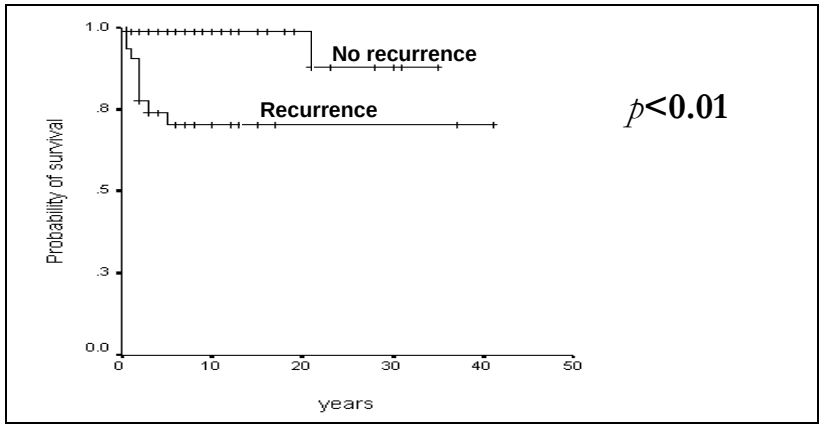
Long-term mortality

- **Mortality rates 3-6 times higher than of the general population (tumour-related, cardio-/cerebrovascular, respiratory).**

Bulow *et al.,* **1998; Pereira** *et al.,* **2005; Tomlinson** *et al.,* **2001**

- **10-yrs survival: 83-93%**





Rajan *et al.,* **1993; Hetelekides** *et al.,* **1993; Fahlbusch** *et al.,* **1999; Van Effentere & Boch, 2002; Karavitaki** *et al.,* **2005**

Clinical Endocrinology (2012) 76, 151–160 doi: 10.1111/j.1365-2265.2011.04235.x

REVIEW ARTICLE

Rathke's cleft cysts

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Rathke's cleft cysts

- Relapse 0 – 33%
- At last assessment

Major visual field defects	19% (6/31)
FSH/LH deficiency	53% (17/32)
ACTH deficiency	42% (14/33)
TSH deficiency	52% (17/33)
On Desmopressin	45% (15/33)