

# Perioperative management; criteria for cure and relapse



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# Disclosure

- ENDO 2016-8 Annual Meeting Steering Committee member
- ECE 2017-8 Program Organizing Committee
- Co-investigator (Ipsen, Novartis)
- Invited speaker (Novartis)
- Editor (Edimarks)

# Outline

- Perioperative management of :
  - Transsphenoidal surgery
  - Adrenalectomy
- Post-operative assessment of:
  - Cushing's disease
  - Adrenal Cushing

# Transsphenoidal surgery

## *Pre-operative anticortisolic treatment?*

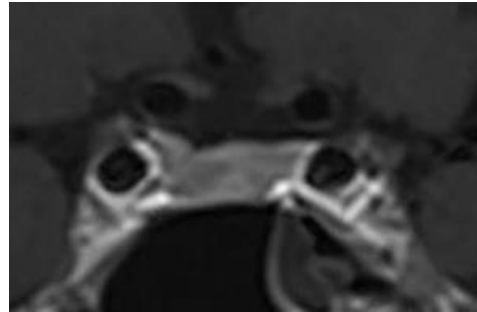
Mrs B, 58 yo

Severe Cushing's disease

**Femoral thrombosis**

→ 6 months of Metirapone

→ TSS: cortisol drops to 27 pmol/l



Antiplatelet ~~X~~  
Anticoagulation

Mrs M, 67 yo

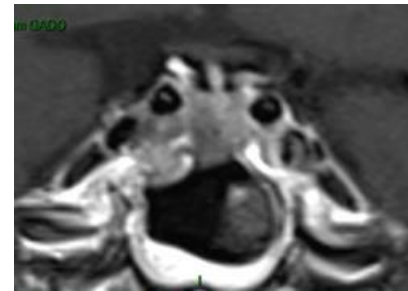
Cushing's disease

**70% stenosis of circumflex artery**

→ Uncoated stent + 4 weeks Clopidogrel & Aspirin

→ 2 months of Metirapone

→ Debulking TSS: Cortisoluria : 6N → 2N

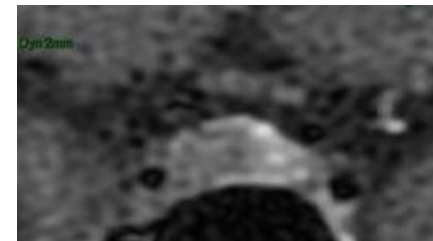


Mrs D, 38 yo

Severe Cushing's disease

→ (Ketoconazole+) Metirapone 4gr/day + Mitotane

→ Scheduled: Debulking TSS (+ radiotherapy if still severe)



Multidisciplinary management +++

# Transsphenoidal surgery

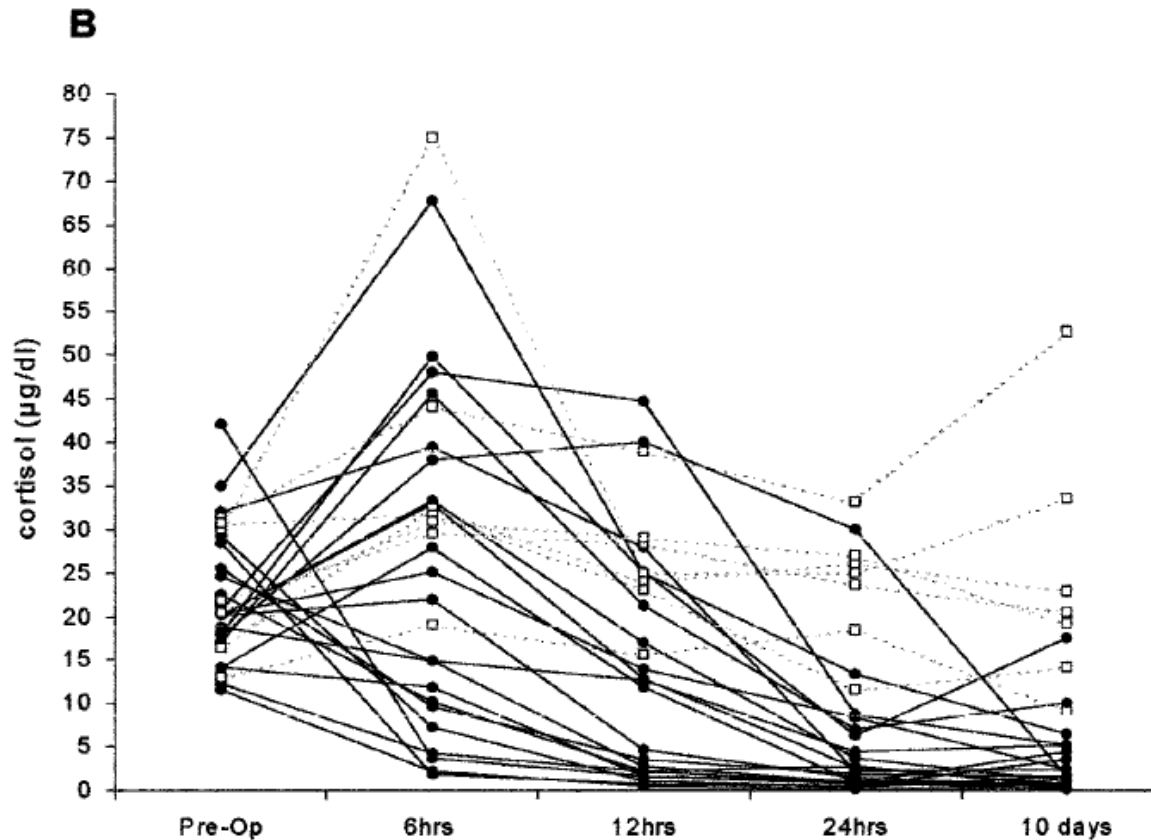
## *Pre-operative anticortisolic treatment?*

- Benefit for severe Cushing?
- Benefit for all Cushing?
- Risks?
  - No harm on the pituitary adenoma (*dixit Dr Gaillard!*)
  - Anticortisolic drugs side effects

# Transsphenoidal surgery

## *Per-operative glucocorticoid replacement?*

- During or after surgery?



# Transsphenoidal surgery

## *Post-operative management*

- Thrombosis prevention
  - Avoid anticoagulation  
*(compression stocking, early walk...)*
- Pituitary deficiency detection
  - Corticotroph deficiency
  - Other axes & Diabetes Insipidus

# Adrenal surgery

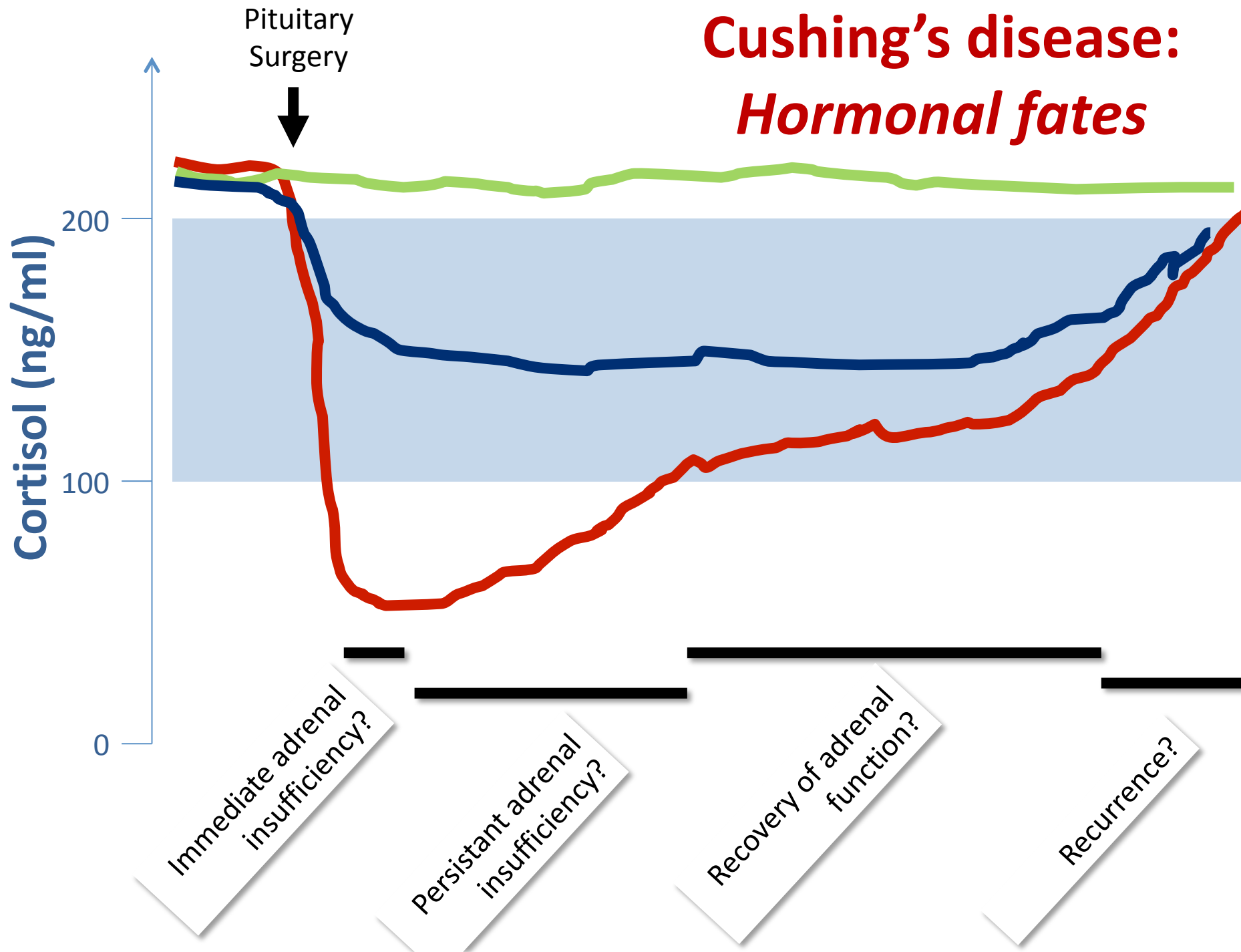
- Pre-operative preparation?
- Per-operative glucocorticoid supplementation
- Specific surgery procedures
- Post-operative management



# Outline

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- Post-operative hormonal assessment of:
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  - Adrenal Cushing

# Cushing's disease: *Hormonal fates*



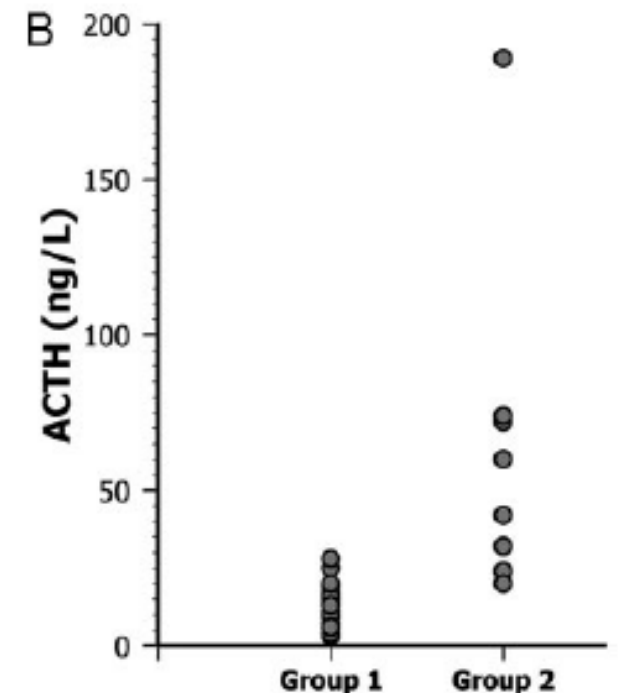
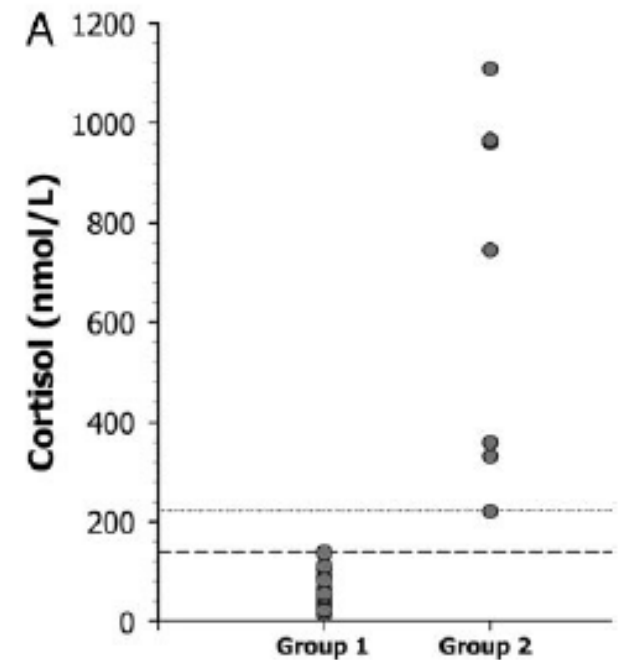
# Early plasma cortisol *Threshold?*

-Trainer et al, Clin Endo 1993

cut-off: < 50 nmol/l (20/48)  
0 recurrence at 4 yrs

-Esposito et al, JCEM 2006

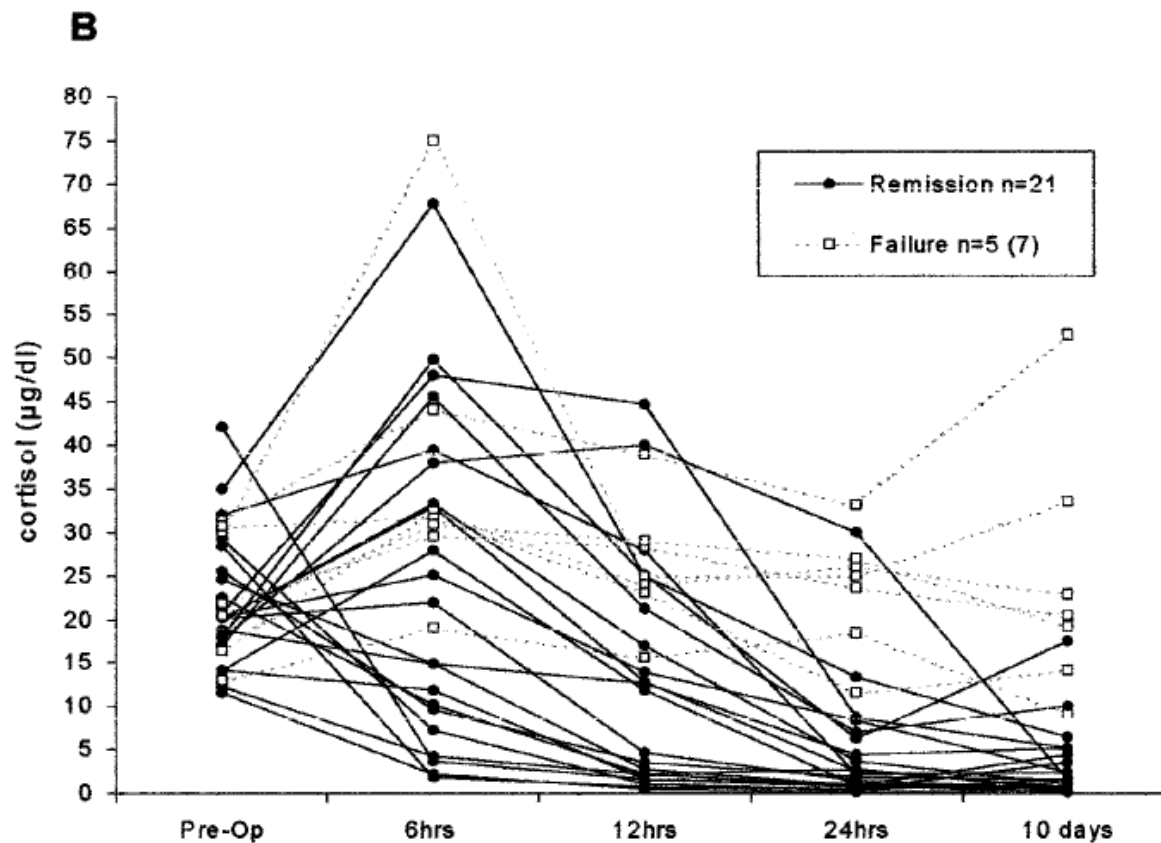
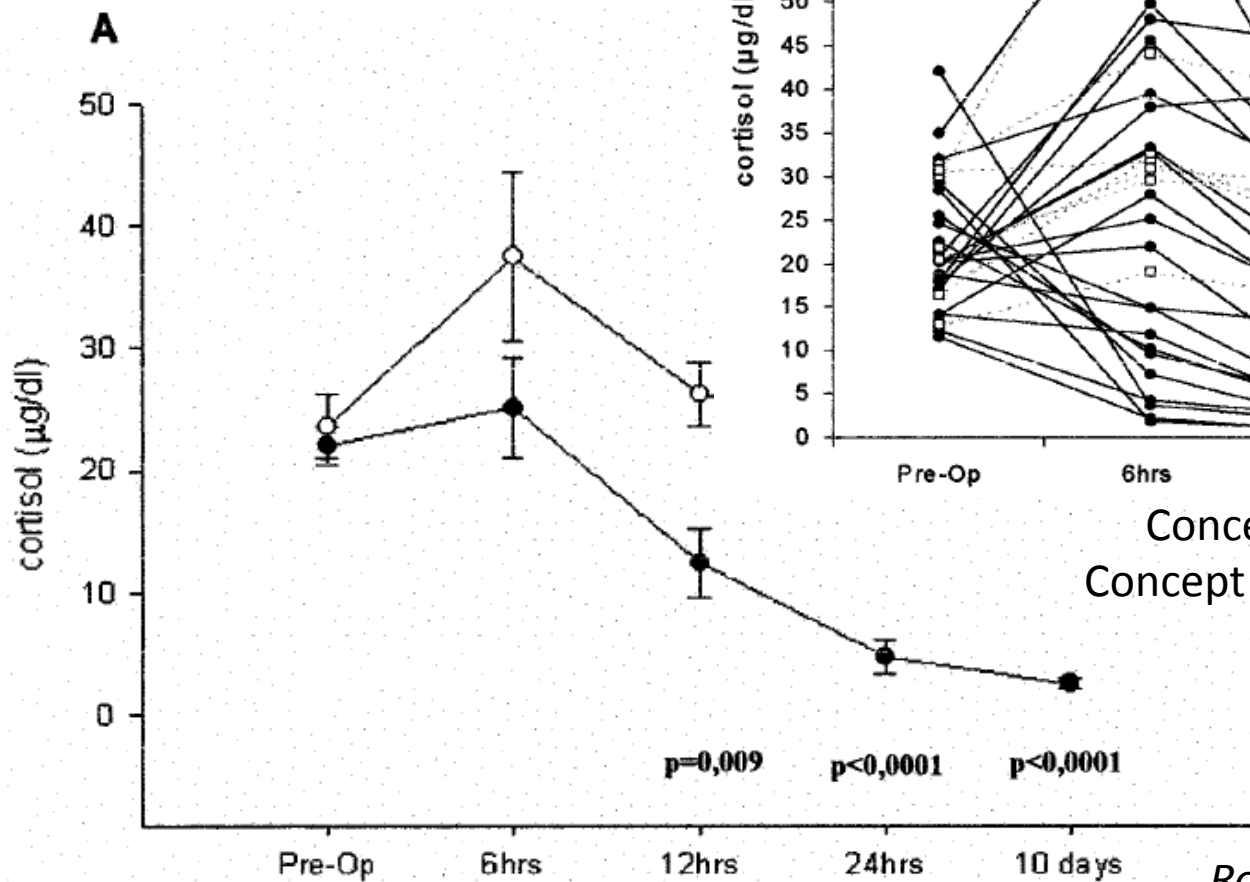
Cut-off : <140 nmol/l (31/40)  
0 recurrence at 3 yrs



# « Early » Plasma cortisol

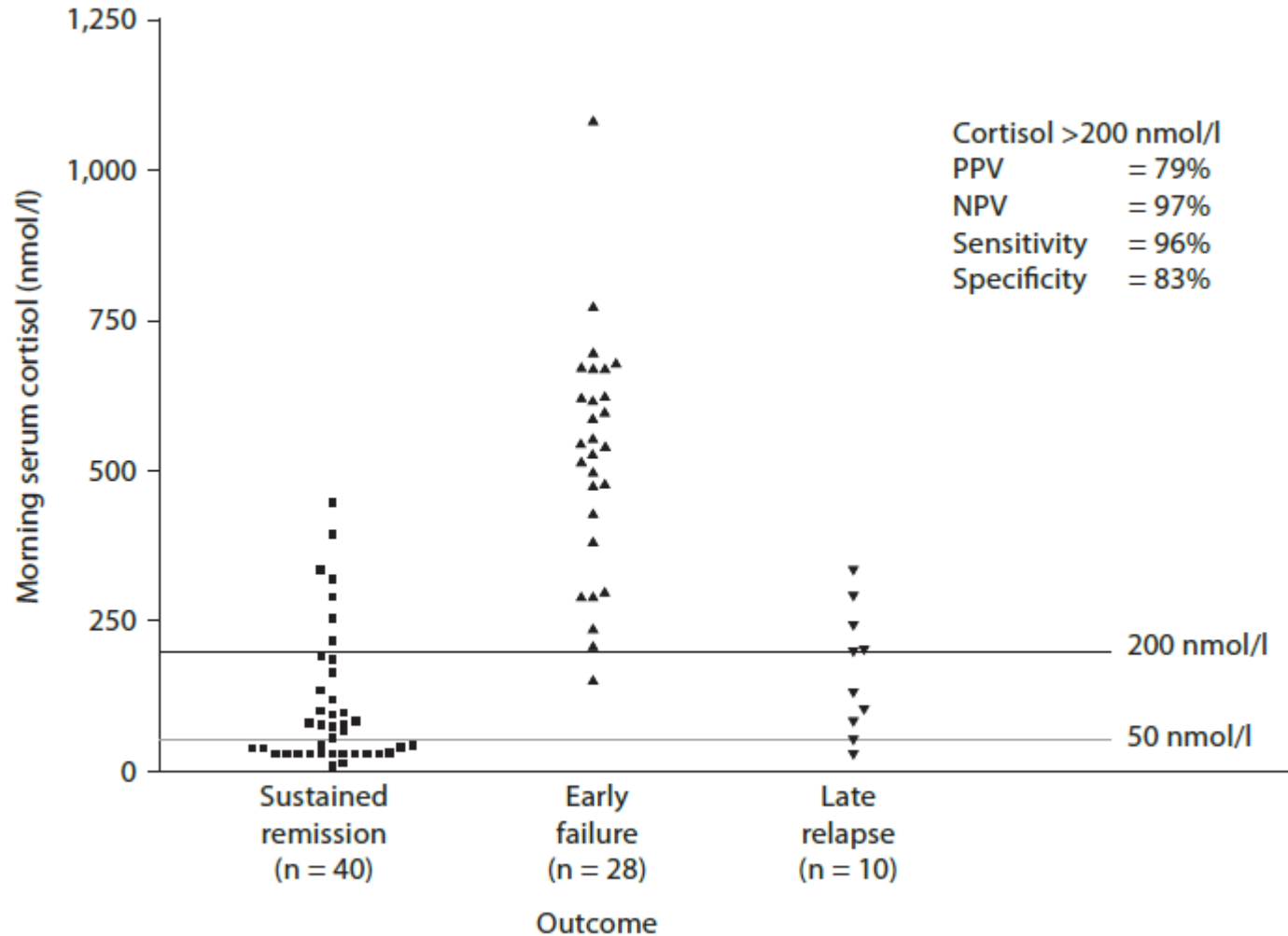
## When ?

Criteria for remission: Low cortisol & 1mg-dex suppression <30 ng/ml



Concept of « late » remission  
Concept of early recovery? (at D10)

# Early plasma cortisol... ...and long-term outcome



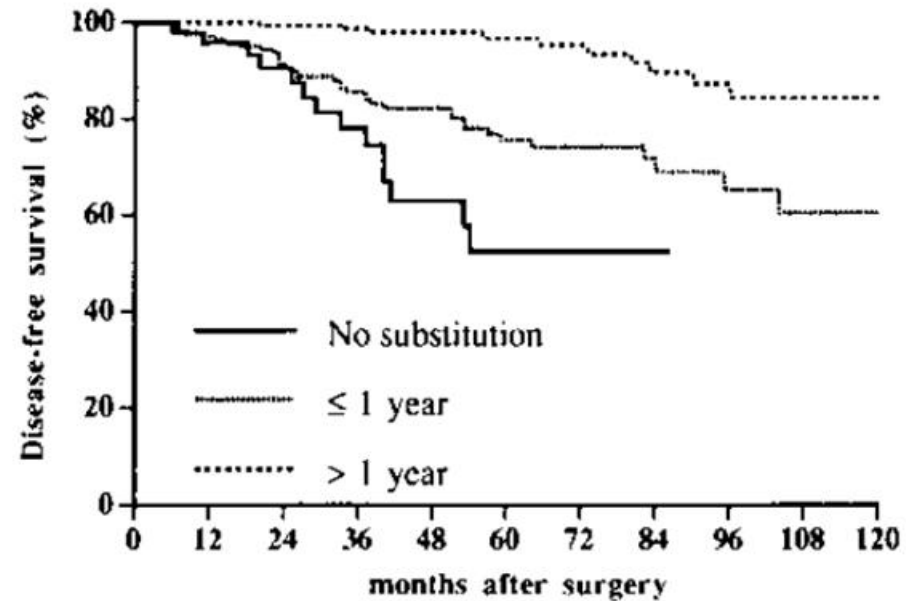
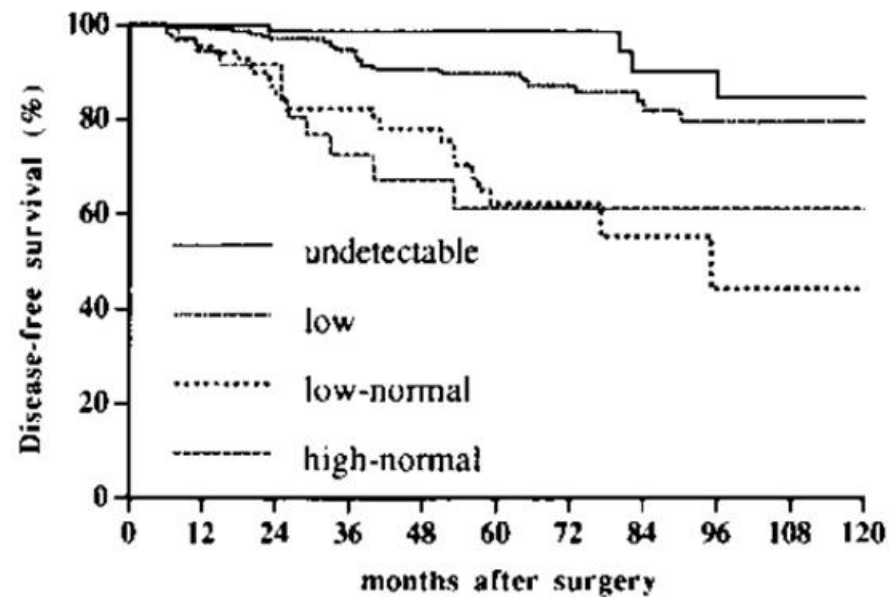
*Alwani et al, Neuroendocrinology 2010*

N=78

Follow-up: >8 years

# Early plasma cortisol

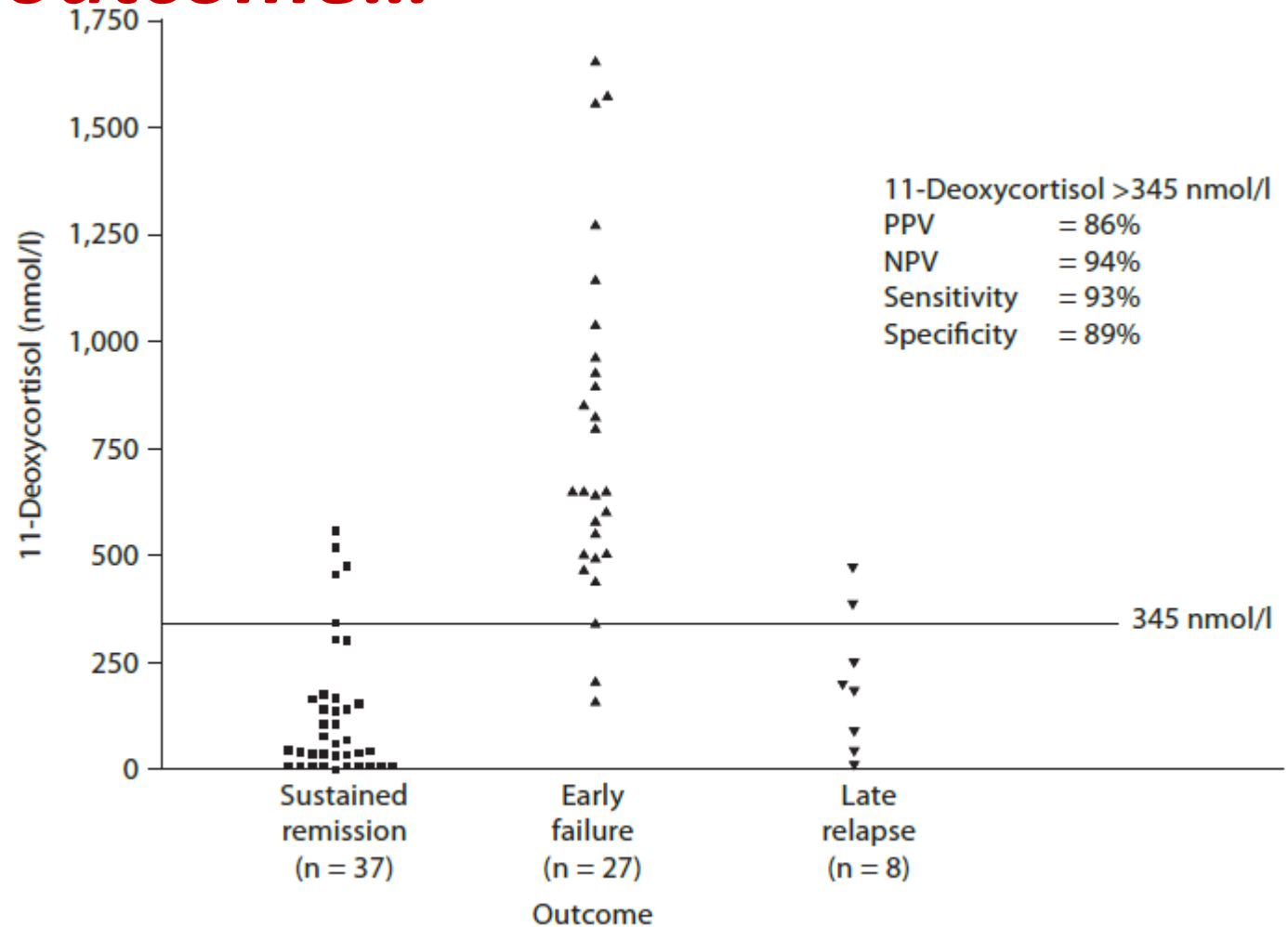
## *Duration of adrenal insufficiency*



Bochicchio et al, JCEM 1995

# Early 11-deoxy-cortisol after Metirapone

## *Long term outcome...*



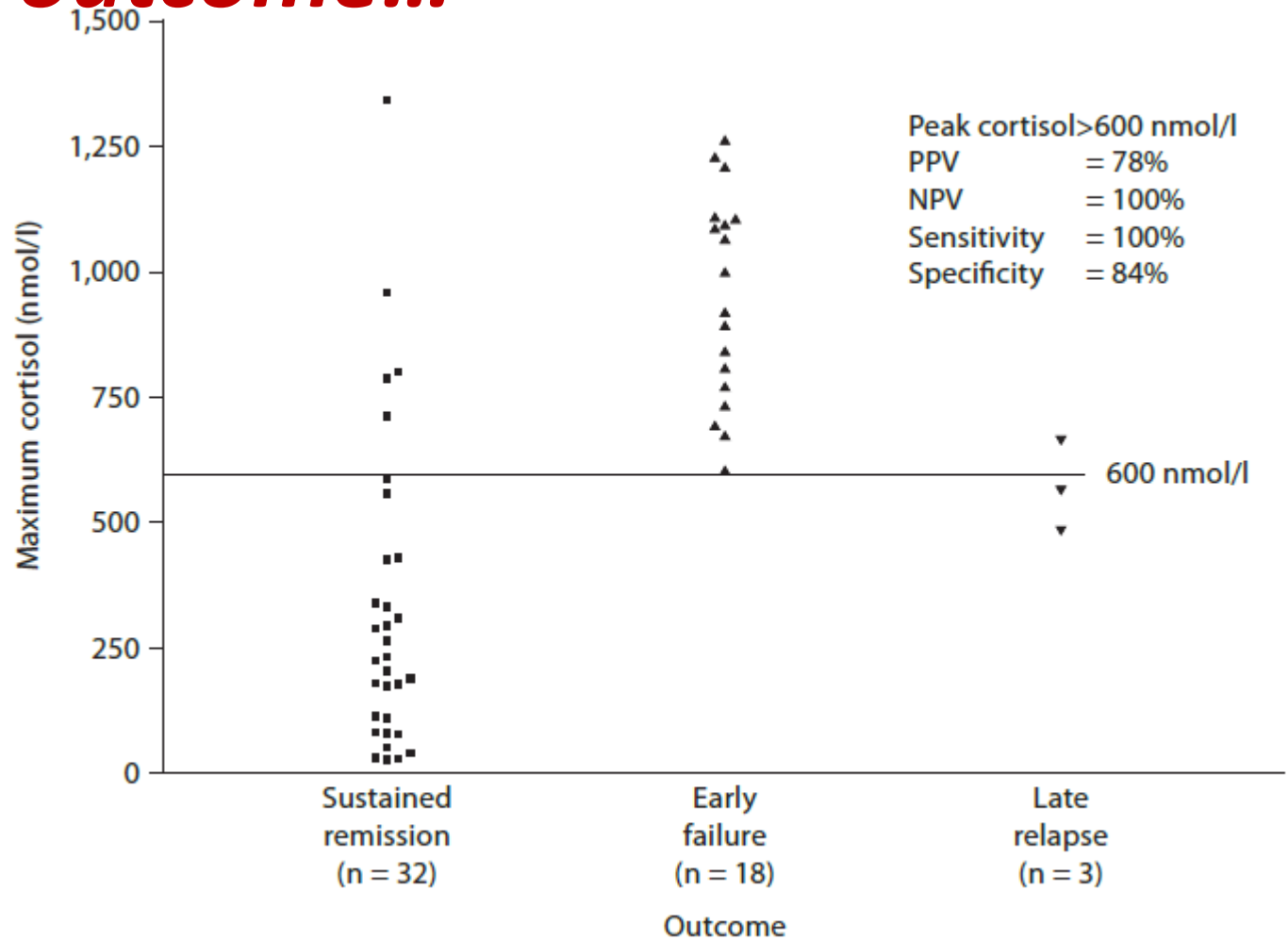
N=78

Follow-up: >8 years

*Alwani et al, Neuroendocrinology 2010*

# Cortisol after CRH

## *Long term outcome...*



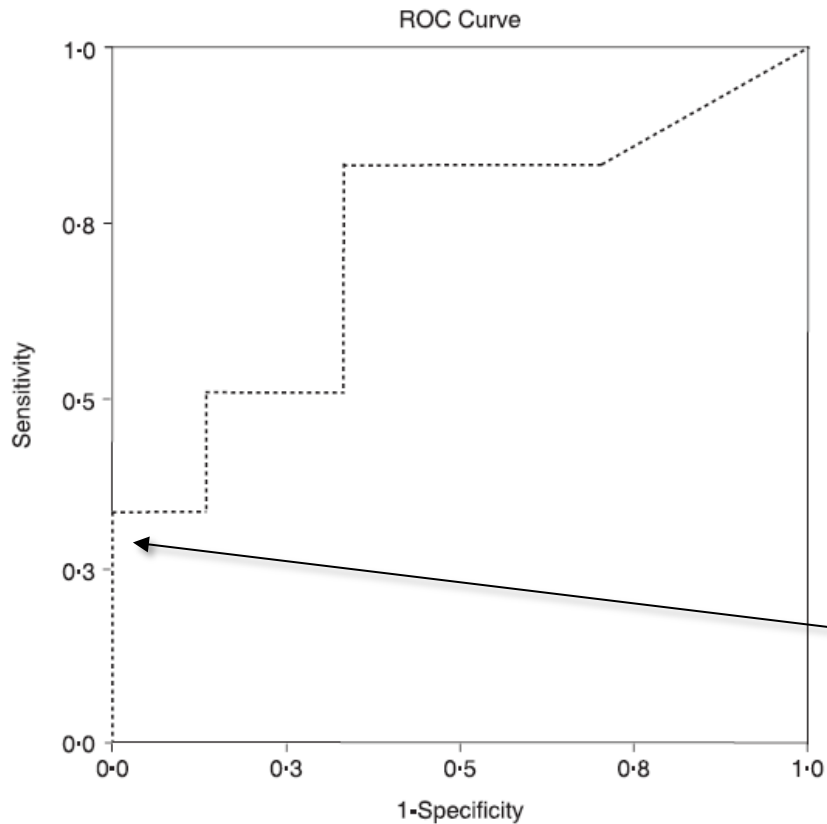
N=78

Follow-up: >8 ans

*Alwani et al, Neuroendocrinology 2010*



# Cortisol after Desmopressin

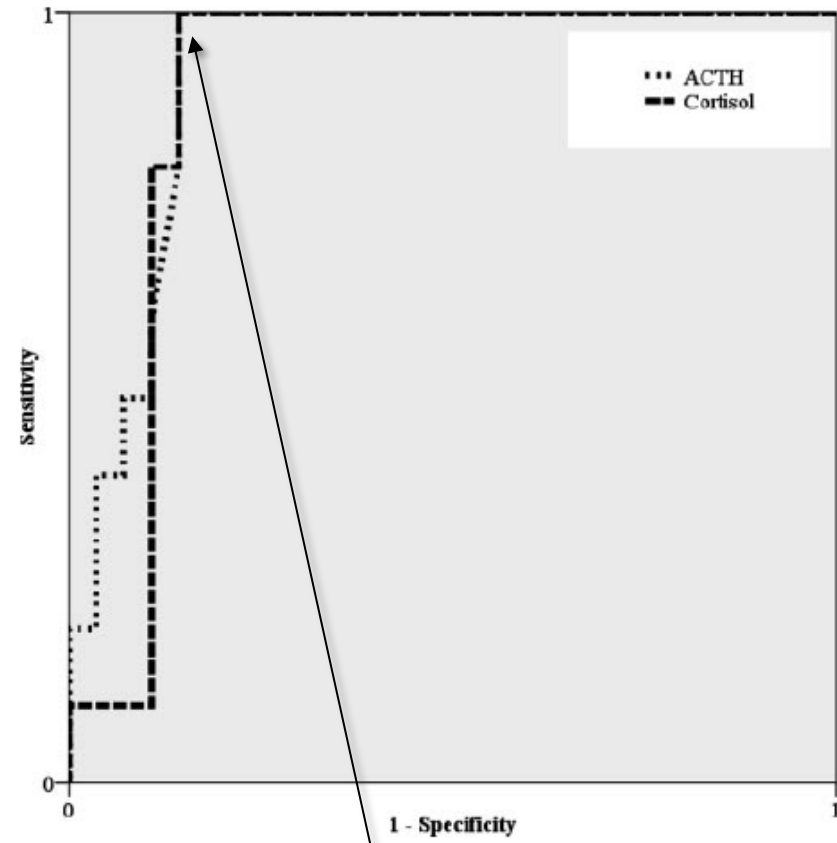
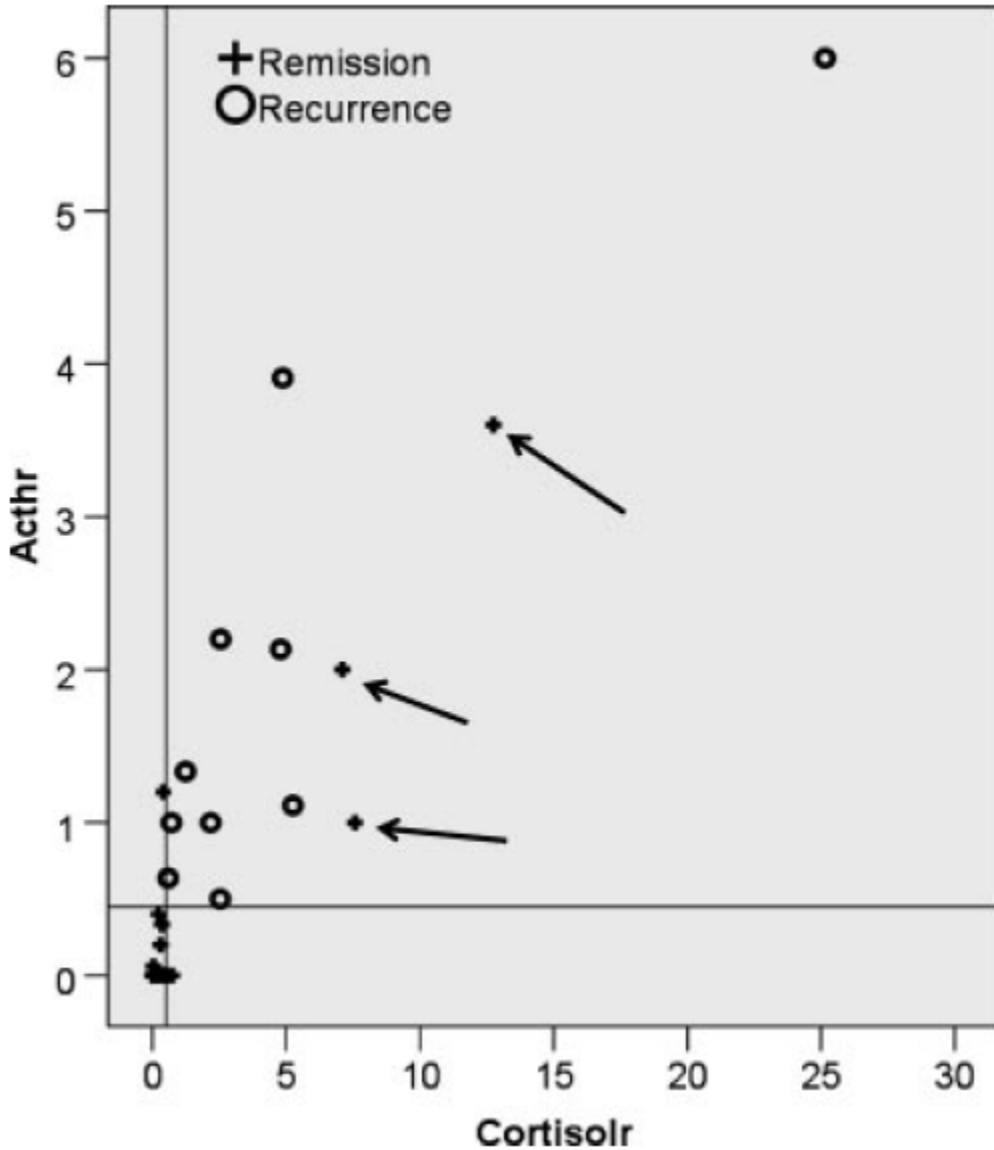


c.o. : delta cortisol > 193 nmol/l

*Rohmanoli et al, Clin Endocr 2008*

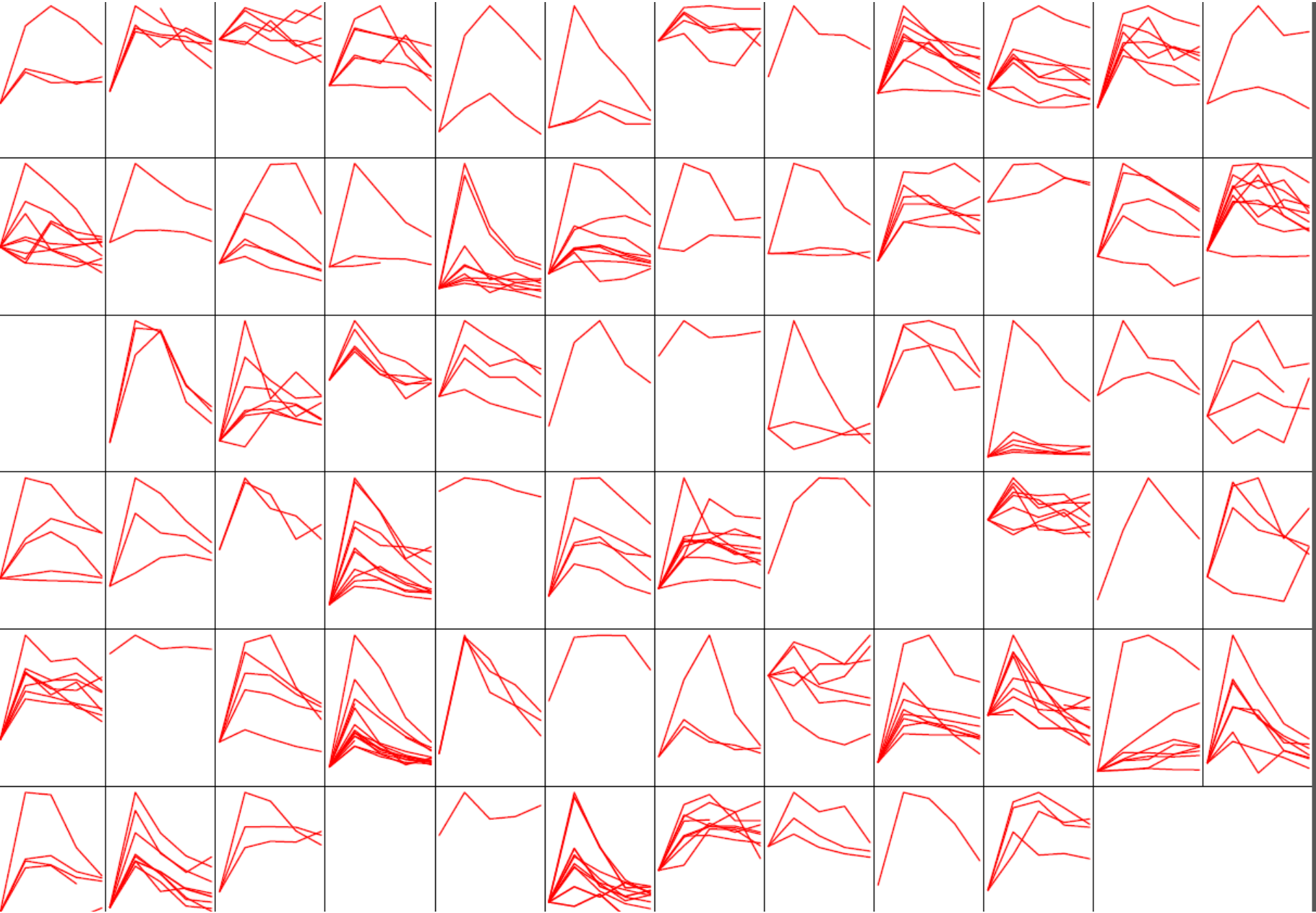
N=41 patients in remission

# Desmopressin + dexamethasone suppression



c.o. : delta cortisol & delta ACTH >50%

N=38



# Cortisol cycle

## *During adrenal insufficiency*

Mrs L., 46 yo. ans

2 years after pituitary surgery

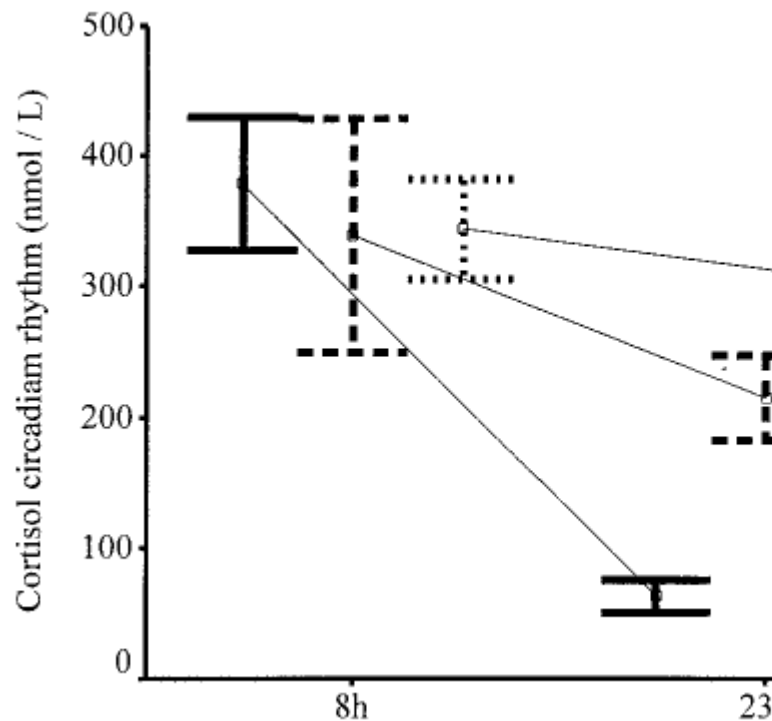
	08h	12h	16h	20h	24h	04h	
Plasma cortisol	21	36	37	28	41	27	ng/ml

Cortisol low but flat cycle:

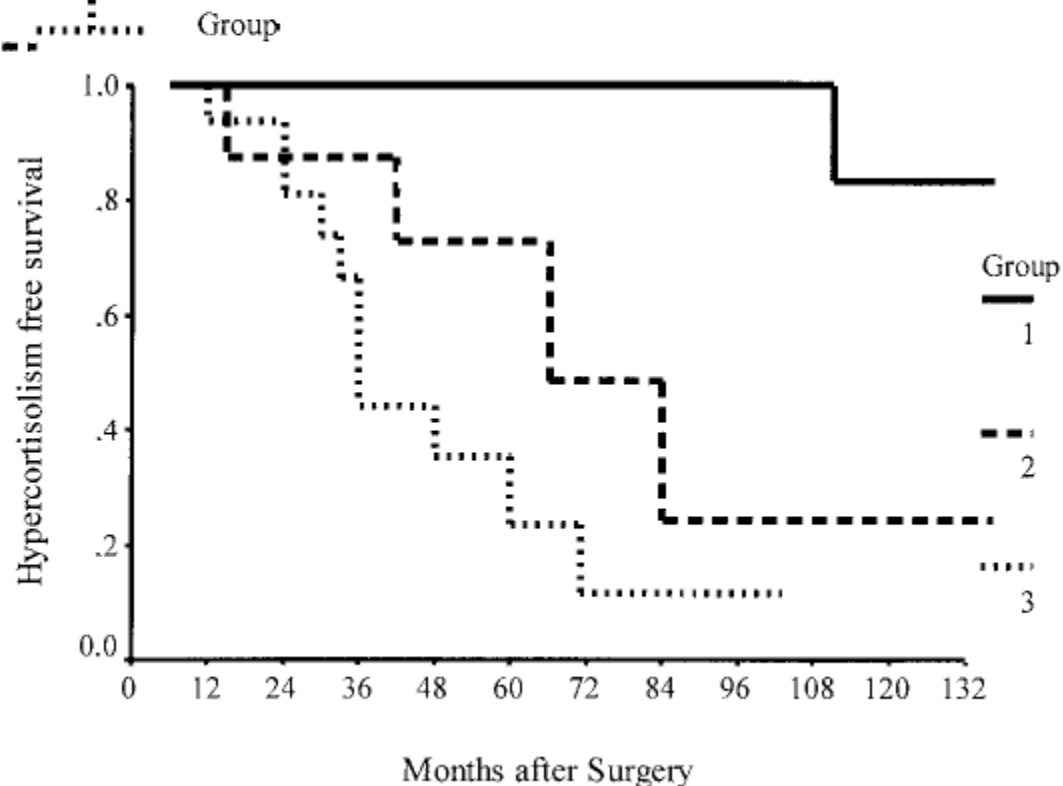
- Persistent adrenal insufficiency?
- Low autonomous secretion?

# Cortisol cycle

## After recovery of adrenal function



Gpe 1: normal cortisol cycle  
 (Insufficiency then eucortisolism)  
 Gpe 2: abnormal cortisol cycle  
 (Insufficiency then eucortisolism)  
 Gpe 3: No insufficiency

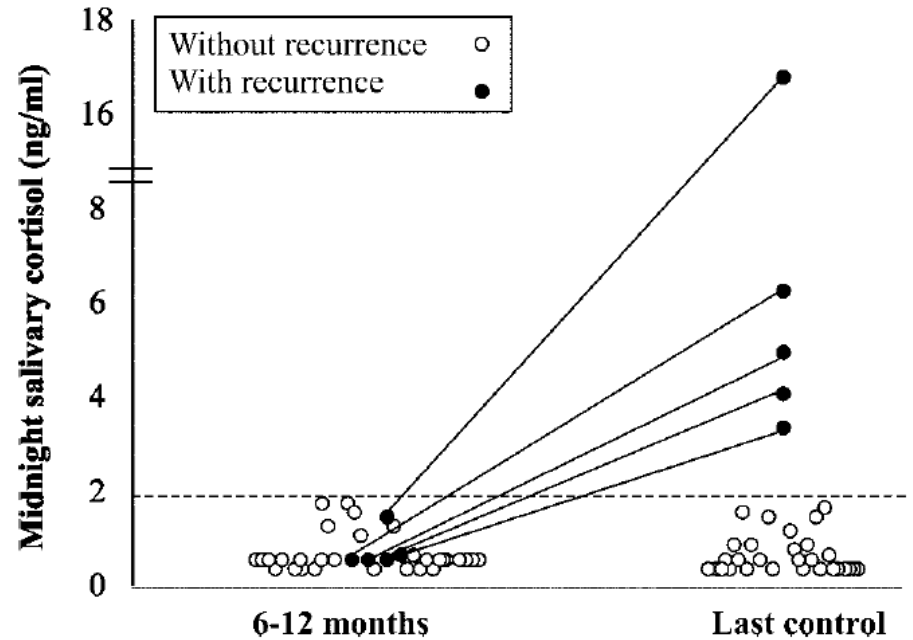
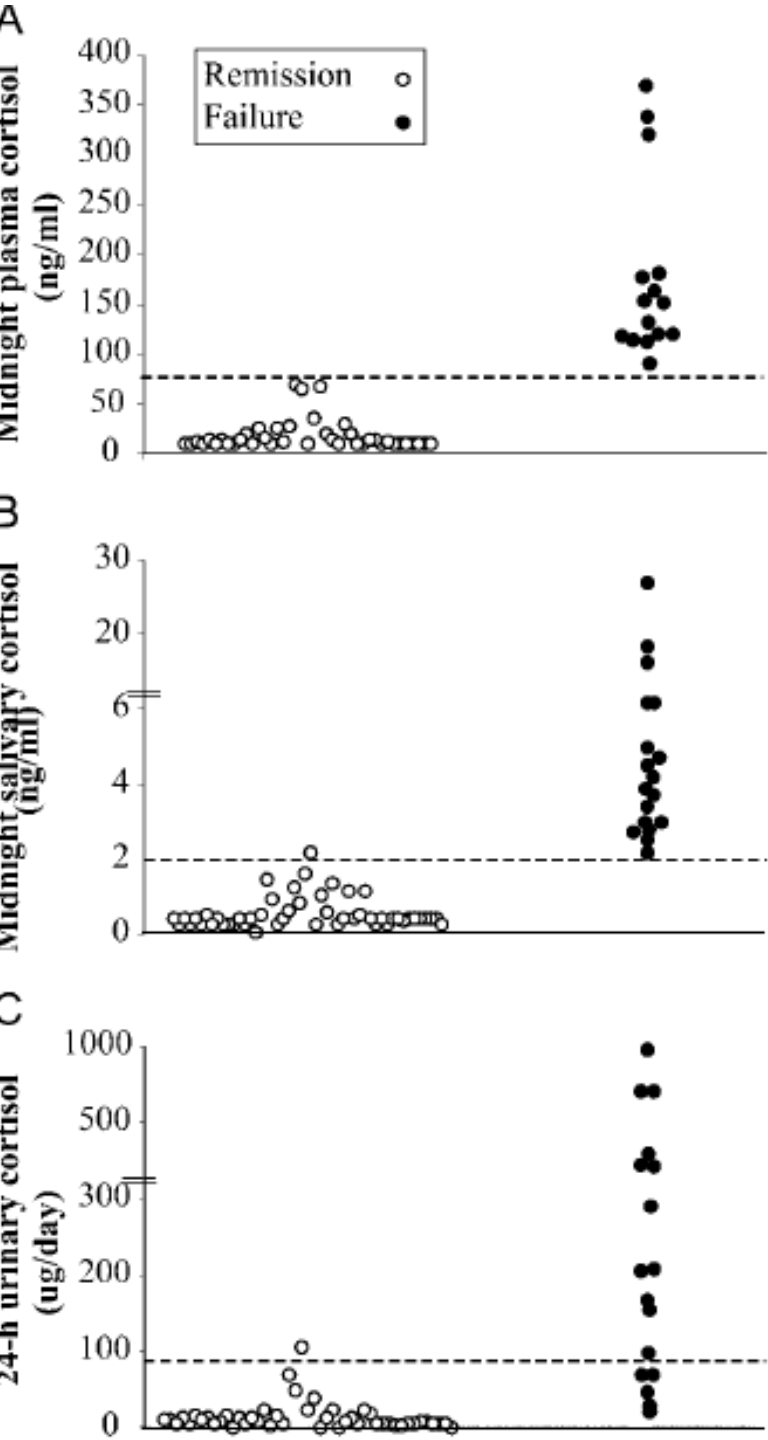


# Cortisol cycle

## Midnight salivary cortisol

Within 6 months after TSS

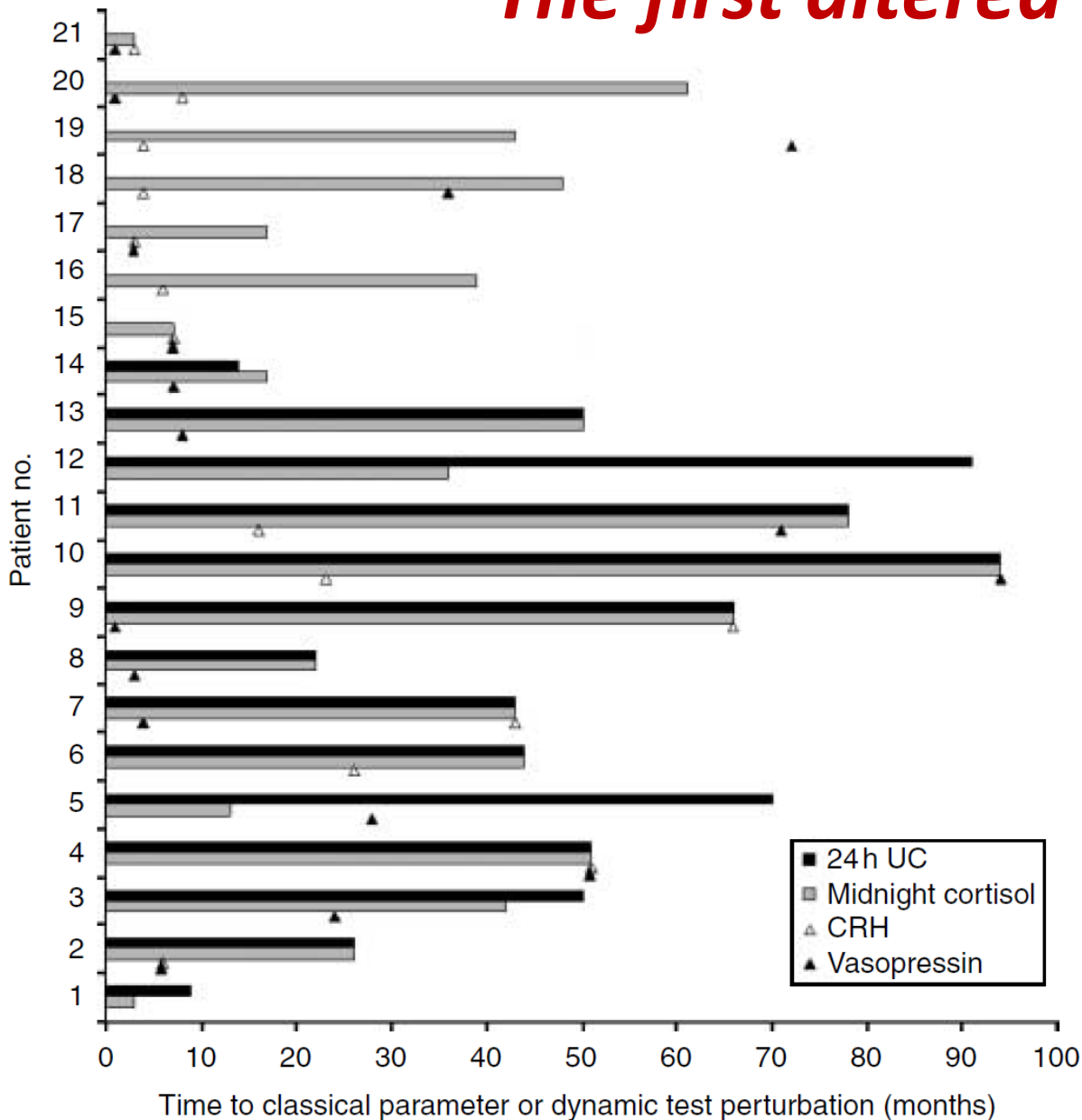
N=68



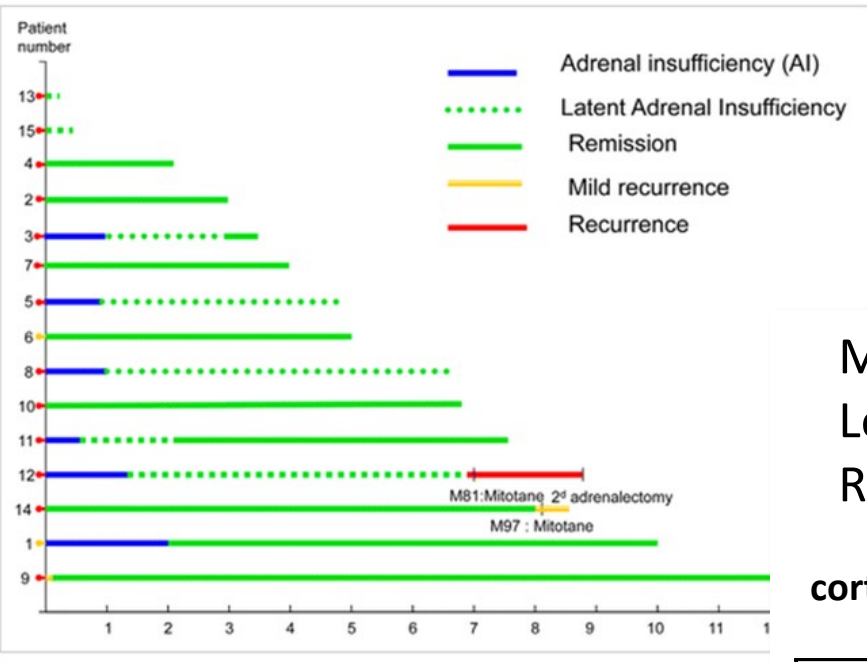
*Carasco et al, JCEM 2008*

# Recurrence of Cushing's disease

## *The first altered test*



# Surgical Treatment: Unilateral Adrenalectomy



M P, 54 yo

Left adrenalectomy in 2000.

Remaining right adrenal is growing (4cm)

cortisol (F)	08h	12h	16h	20h	24h	04h	unités
F plasma	206	183	151	141	160	139	nmol/l
F saliva	7.80	6.92	5.49	5.26	5.66	5.40	nmol/l

*Debillon et al, JCEM 2015*

*Imohl et al, 2002*

*Lamas et al, 2002*

*Sato et al, 2006*

*Lacobene et al, 2008*

*Mazzuco et al, 2009*

*Albiger et al, 2015*

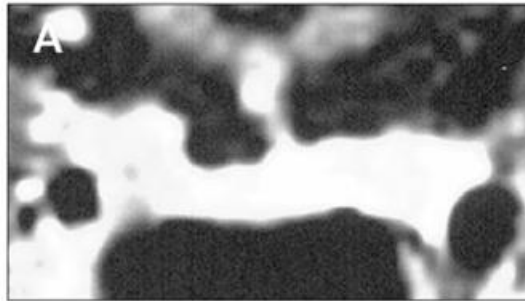
-> for mild hypercortisolism  
and asymmetric forms



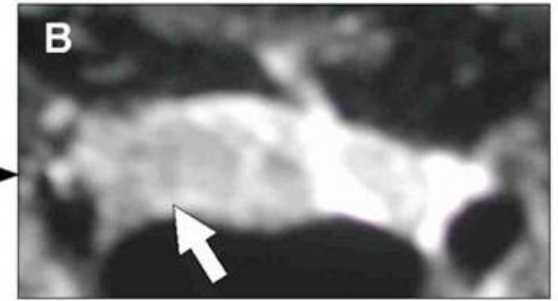
# Management of Nelson's syndrome

- MRI+++ (CTP)
- CTPS?

Figure 1A:



Before adrenalectomy



After adrenalectomy

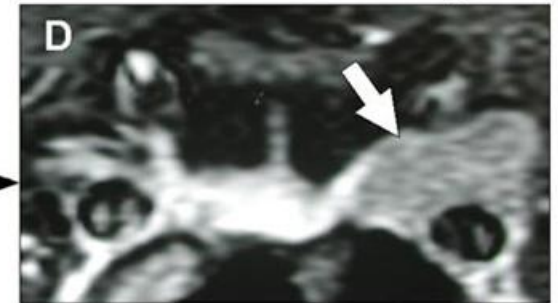
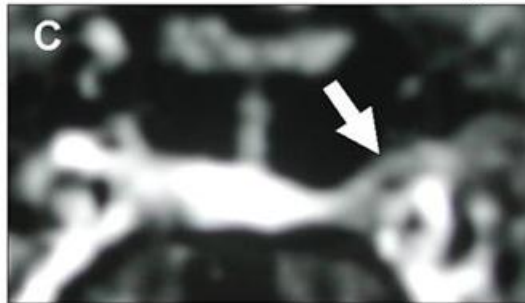
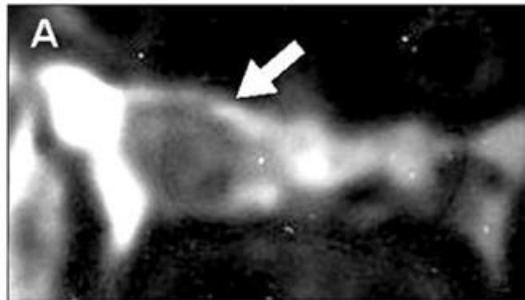
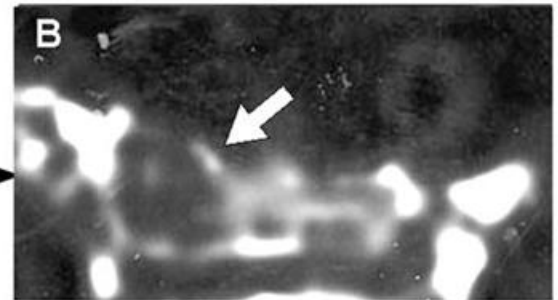


Figure 1B:

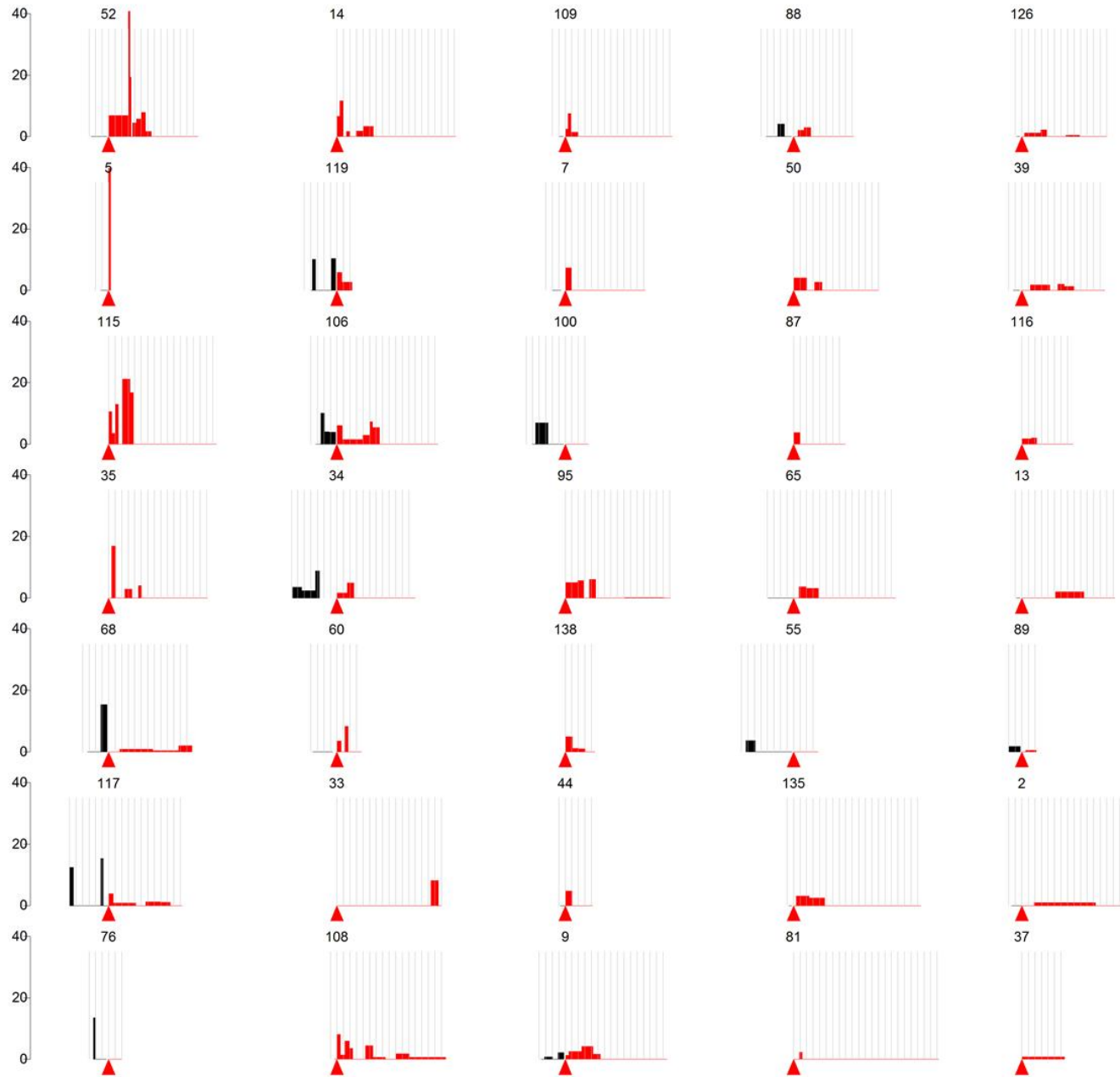


Before adrenalectomy



After adrenalectomy





*Bessière, Moutel, Assié unpublished*

# Conclusion

- Peri-operative management of Cushing patients:
  - a multidisciplinary task
  - for expert centers
- Low cortisol after pituitary surgery :
  - Is the best proof of remission!
  - But does not warrant recurrence-free evolution
  - life-long surveillance
- Recurrence: the challenge of « small Cushings »
  - For detection
  - For management

**Thank you !**

**Genomics & Signaling  
of Endocrine Tumors Team**

***Cochin Hospital***

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