

# BILATERAL ADRENALECTOMY: PAST, PRESENT AND FUTURE

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Bilateral adrenalectomy for Cushing's syndrome

*JAMA 1953 Oct 10;153(6):567*

- 701 references on Bilateral adrenalectomy over the last 60 years  
**(12/year)**

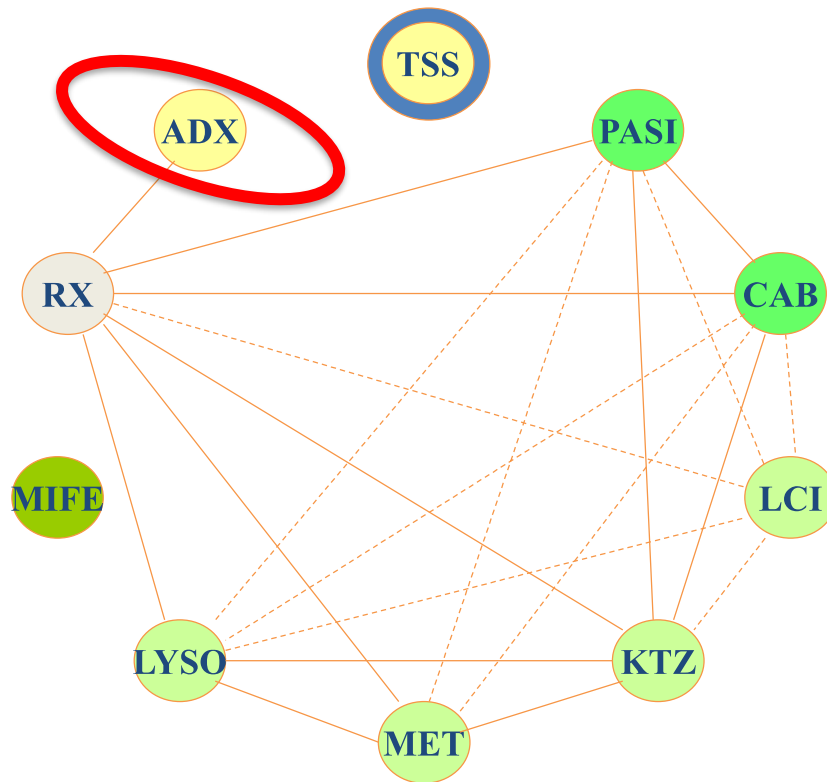
**Over the last 5 years**

- 2400 references for any kind of anticortisolic drug (480/year)
  - 90 references on Transsphenoidal surgery
  - 63 references on radiation techniques
  - 60 references on bilateral adrenalectomy

# **ACTH-DEPENDENT CUSHING'S SYNDROME**

# Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

B. M. K. Biller, A. B. Grossman, P. M. Stewart, S. Melmed, X. Bertagna, J. Bertherat, M. Buchfelder, A. Colao, A. R. Hermus, L. J. Hofland, A. Klibanski, A. Lacroix, J. R. Lindsay, J. Newell-Price, L. K. Nieman, S. Petersenn, N. Sonino, G. K. Stalla, B. Swearingen, M. L. Vance, J. A. H. Wass, and M. Boscaro



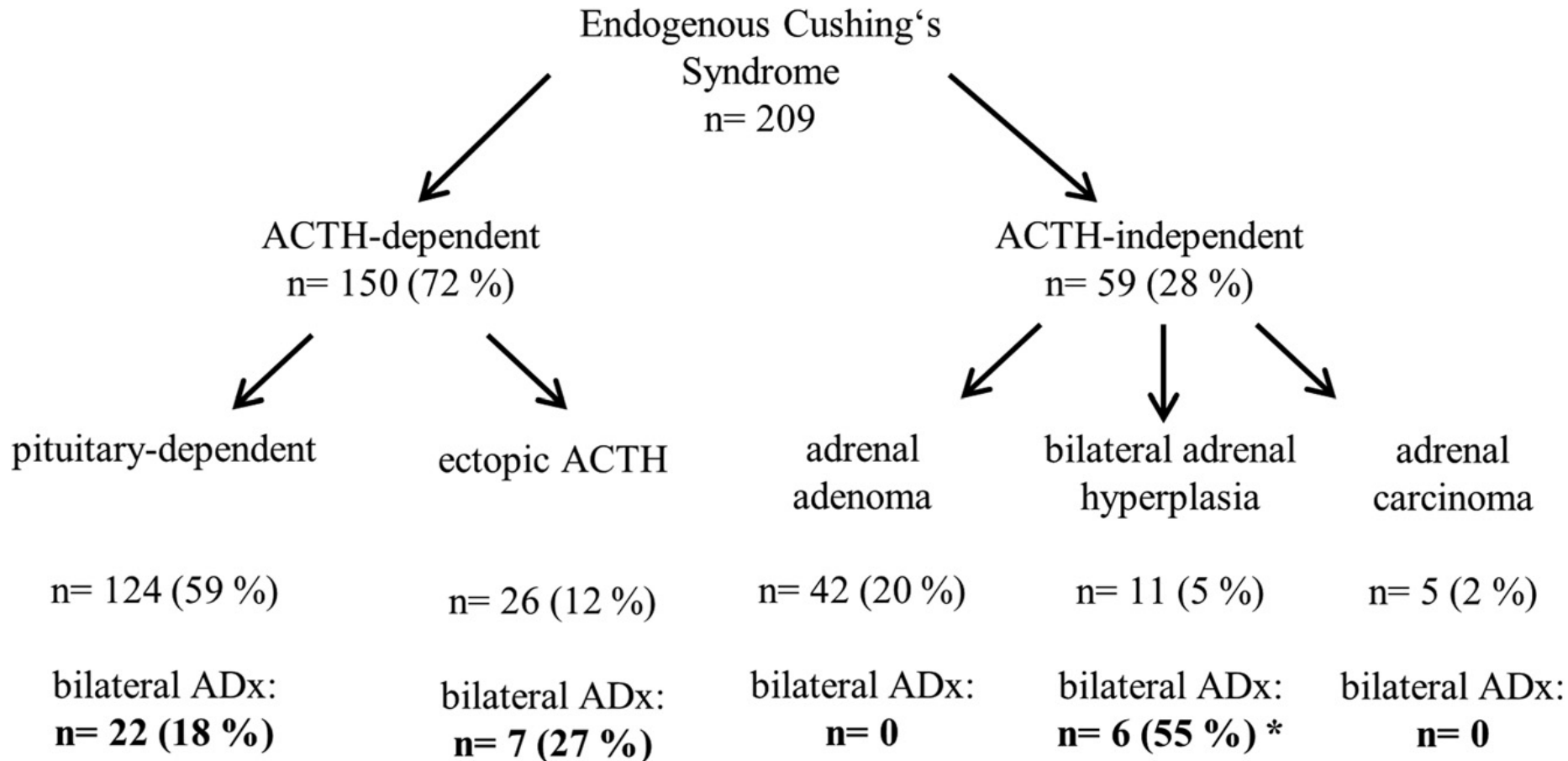
**Should bilateral adrenalectomy be only considered as a last-line treatment ?**

**Figure 5.** Combined strategies: the "Cushinggame." TSS, transsphenoidal surgery; PASI, pasireotide; CAB, cabergoline; LCI, LCI699; KTZ, ketoconazole; MET, metyrapone; LYSO, Lysodren; MIFE, mifepristone; RX, radiotherapy; ADX, adrenalectomy.

*Biller, JCEM, 2008*

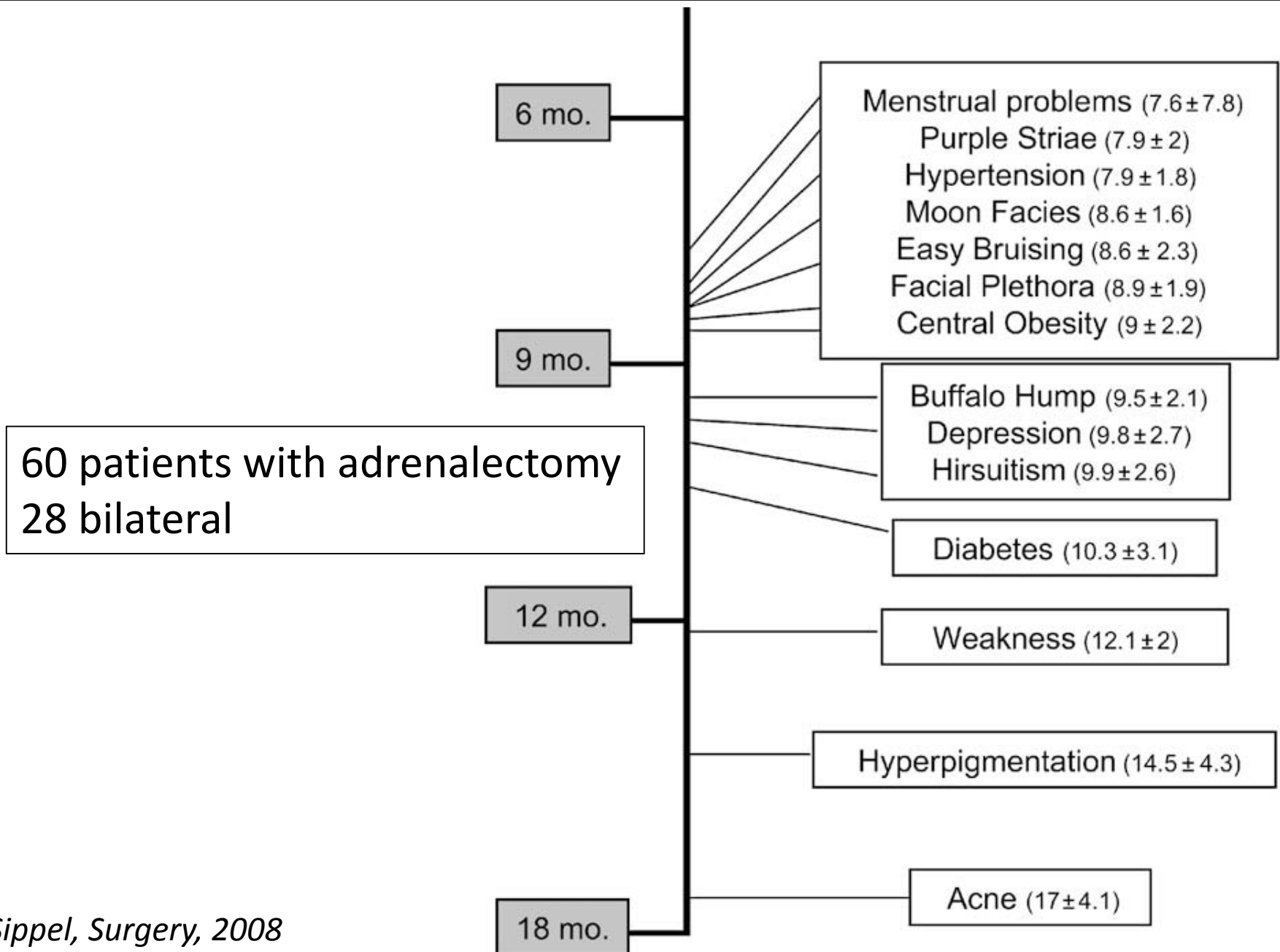
*Bertagna, JCEM, 2013*

# Outcome of Bilateral Adrenalectomy in Cushing's Syndrome: A Systematic Review



**21% PATIENTS WITH BILATERAL ADRENALECTOMY**

# SYMPTOMS REMISSION IN 7-18 MONTHS



# CUSHING COMPLICATIONS REMISSION

	<b>Before BADX</b>	<b>After BADX</b>	
	<i>n (%)</i>	<i>n (%)</i>	<b><i>P</i></b>
High blood pressure	31 (91)	25 (69)	0.023
Diabetes mellitus	14 (45)	6 (17)	0.011
Osteopenia or osteoporosis	27 (84)	30 (73)	0.251
Cushing's stigmata	34 (100)	8 (22)	0.000
Muscle weakness	21 (72)	11 (33)	0.002
Psychiatric morbidity	16 (53)	17 (47)	0.621
Menstrual irregularity <sup>a</sup>	14 (82)	4 (50)	0.093

# IMPROVED QUALITY OF LIFE IN 30-50% CASES

39 patients

**TABLE 5.** Postoperative Quality of Life

Characteristic	Value
Satisfaction with BLA [no. (%)]	
Very satisfied	18 (50)
Satisfied	13 (36.1)
Neutral	1 (2.8)
Dissatisfied	1 (2.8)
Very dissatisfied [no. (%)]	3 (8.3)

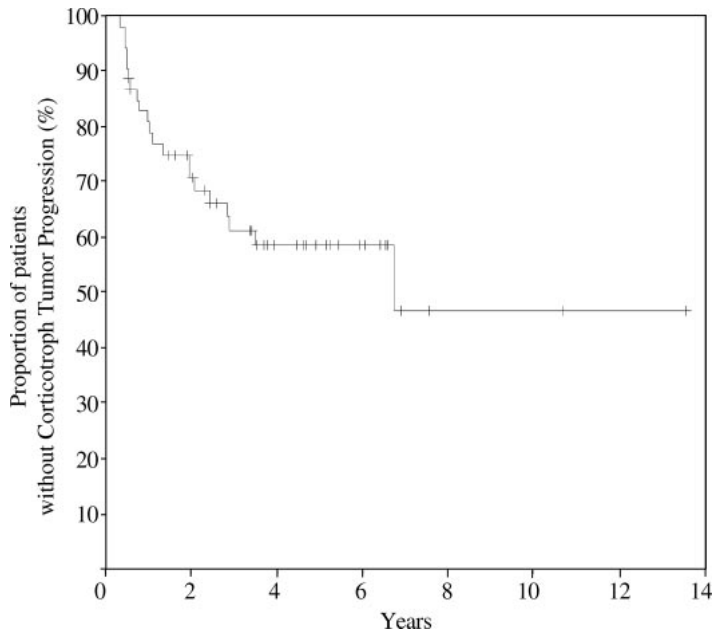
Instrument	Female BADX patients (n=20) compared with a healthy population (%)	Male BADX patients (n=6) compared with a healthy population (%)	Female patients with CD (n=52) <sup>a</sup> compared with a healthy population (%)	Male patients with CD (n=11) <sup>a</sup> compared with a healthy population (%)
SF-36 Physical functioning	50.0	16.7		
SF-36 Role-physical	60.0	0.0		
SF-36 Bodily pain	35.0	16.7		
SF-36 General health	40.0	16.7		
SF-36 Vitality	55.0	16.7		
SF-36 Social functioning	55.0	0.0		
SF-36 Role-emotional	45.0	16.7		
SF-36 Mental health	35.0	16.7		
Tuebingen CD-25 total score	45.0	16.7	90.4	45.5



# A LOW RISK OF SIDE EFFECTS IN EXPERIENCED HANDS ?

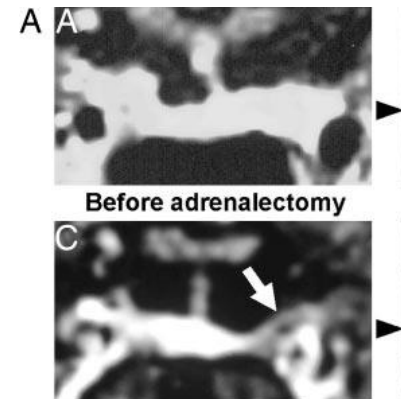
- Morbidity: 6-31%
- Mortality: 0-15%
  - In Cushing's disease: median < 1%
- « Recurrence »: 1-10%
- Thrombo-embolic events: 5/1000 patients-year  
(Place of anticortisolic presurgical treatment ?)

## Nelson's syndrome



Incidence: 0-47% cases, median 21%

Main predictive factor:  
Rate of ACTH increase  
in the 1st year following  
surgery



# UNDERESTIMATED RISK OF ADRENAL CRISIS ?

423 patients **educated** for adrenal insufficiency

221 primary AI

202 secondary AI

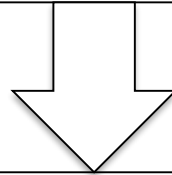
Prospective follow-up for 2 years

8.3 adrenal crises per 100 patients-year

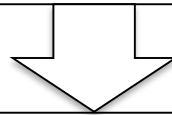
0.5 Adrenal crisis related **death** per 100 patients-year

# BILATERAL ADRENALECTOMY IN FEW WORDS

- Effective
- Relatively rapidly acting
- Low mortality
- The risk of Nelson's syndrome: probably not a major issue in the 21st century
- The risk of adrenal crisis: education to be kept on again and again



WHY NOT USING BILATERAL ADRENALECTOMY MORE FREQUENTLY ?

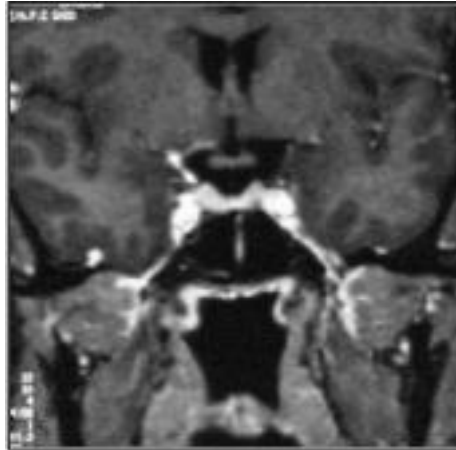


**Mean time diagnosis-bilateral adrenalectomy: 1.8-6 years**

# WHAT ARE THE THEORETICAL INDICATIONS OF BILATERAL ADRENALECTOMY IN ACTH DEPENDENT CUSHING'S SYNDROME ?



Severe Cushing's syndrome as a salvage therapy



Normal pituitary MRI



Failed surgery/radiation technique

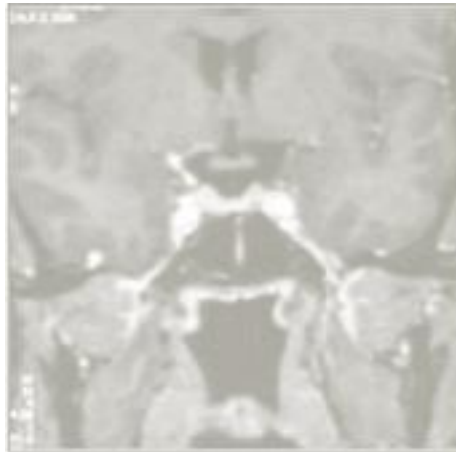
Or recurrence with normal MRI



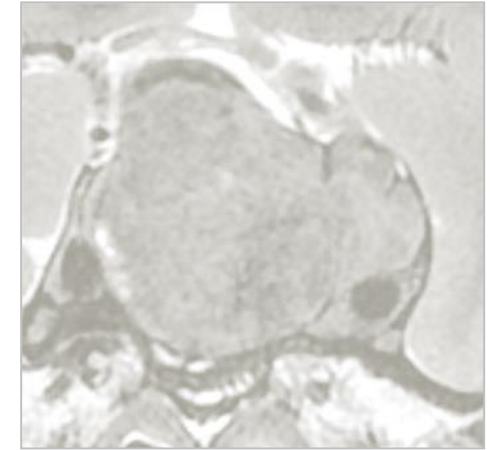
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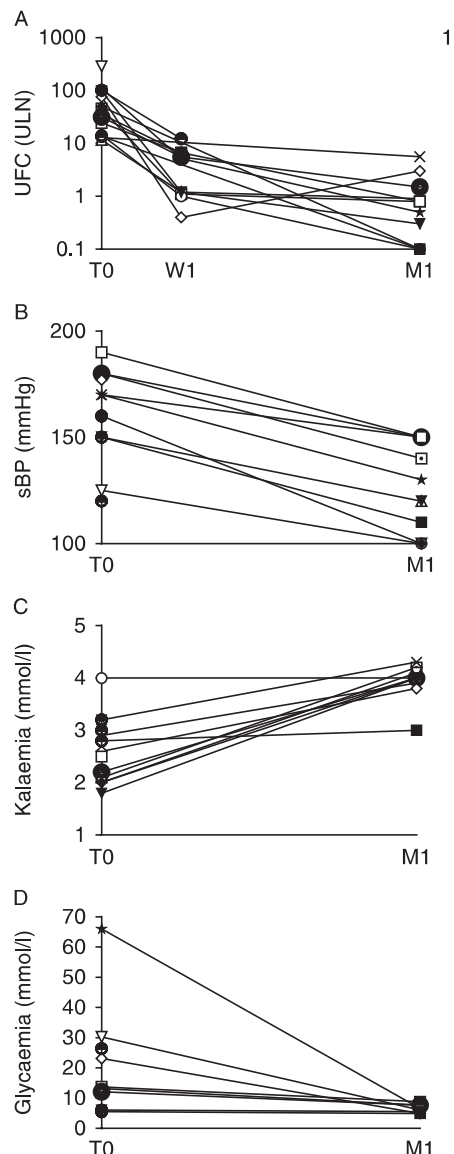
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# ASSOCIATION OF ANTICORTISOLIC DRUGS AS A SALVAGE THERAPY

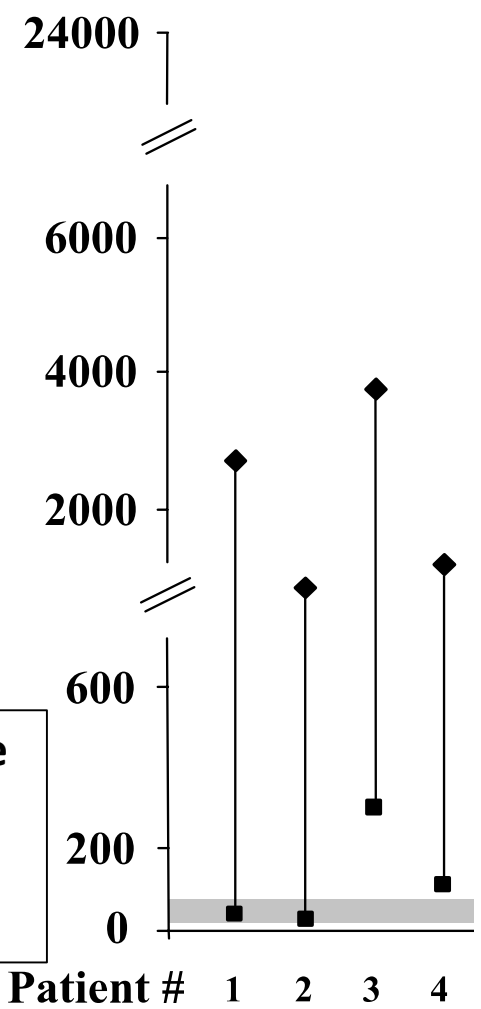


**Ketoconazole/Metyrapone**

- 14 patients with EAS
- **End of 1st week**  
Median UFC: 40 to 3.2 (EAS)
- **End of 1st month**  
UFC values normal in 73%
- Good tolerance

**Ketoconazole/Metyrapone/Mitotane**

- 4 patients with CD/EAS
- **Major UFC decrease between d1 and d3**



# MIFEPRISTONE AS A SALVAGE THERAPY

	Etiology	Sex/age	Previous treatments		Pre-mifepristone				
			Surgery	Anticortisolic drugs	Clin. signs	Psy. signs	Hypertension	HypoK	Diab.
13	EAS	M/55	N	Etomidate, metyrapone	+	-	-	+	+
14		F/43	N	Ketoconazole	+	+	+	+	+
15		F/38	Y	Ketoconazole	+	-	+	+	-
16	CD	M/45	Y	Ketoconazole	+	-	-	-	-
17		M/56	Y	Ketoconazole	+	-	-	-	-
18		F/50	N	None	+	+	-	+	-
19		F/45	N	None	+	-	-	-	-

**Very fast onset of action  
(48 hours)**

**7 PATIENTS**

**Doses: 600 - 1200 mg/d**

Clinical improvement **75%**

Psychiatric improvement **100%**

Worsening of Hypokaliemia **20%**

Adrenal Insufficiency **20%**

# ETOMIDATE AS A SALVAGE THERAPY

<b>Etomidate infusion rate options</b>	<b>Blockade</b>	<b>Target cortisol level</b>	<b>Biochemical monitoring</b>	<b>Other</b>
0.04–0.05 mg/kg per h = 2.5–3.0 mg/h	Partial	Titrate to serum cortisol 500–800 nmol/l in physiologically stressed patient, 150–300 nmol/l in non-physiologically stressed patient	Potassium level	Sedation scoring initially every 2 h then every 12 h after first 24 h
0.5–1.0 mg/h	Complete (will need steroid replacement)	< 150 nmol/l	Cortisol level Potassium level  Cortisol level	Sedation scoring initially every 2 h then every 12 h

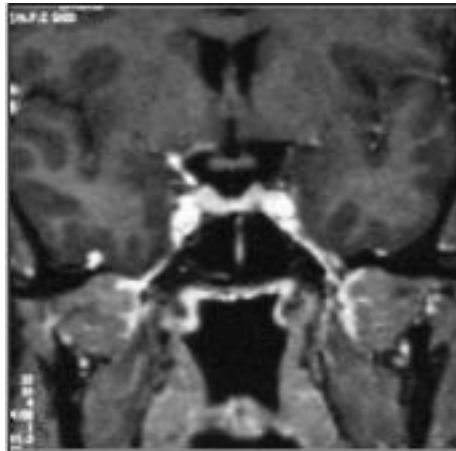
- 12 case reports of patients with Cushing's disease
- Intensive Care Unit



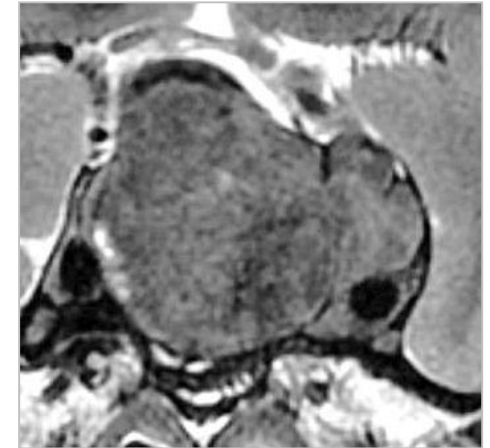
# WHAT ARE THE THEORETICAL INDICATIONS OF BILATERAL ADRENALECTOMY IN ACTH DEPENDENT CUSHING'S SYNDROME ?



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Or recurrence with normal MRI



# BALANCING THE RISKS AND BENEFITS OF TRANSSPHEOIDAL SURGERY AND THE SIDE EFFECTS OF BILATERAL ADRENALECTOMY

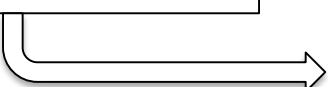
**Pituitary MRI modifies the efficacy of transsphenoidal surgery**



YES	NO
<i>Bochichio D et al. 1995</i>	<i>Salenave S et al. 2004</i>
<i>Barrou Z et al. 1997</i>	<i>Testa RM et al. 2007</i>
<i>Rees DA et al. 2002</i>	<i>Jehle et al. 2008</i>
<i>Rollin G et al. 2007</i>	<i>Hofmann BM et al. 2008</i>
<i>Witek et al. 2012</i>	<i>Alwani RA et al. 2010</i>
<i>Yamada et al. 2012</i>	<i>Sun et al. 2012</i>
	<i>Starke et al. 2013</i>

**REMISSION RATE: 65-98% / RECURRENCE RATE: 2-30%**

**Pituitary MRI modifies the rate of side effects**

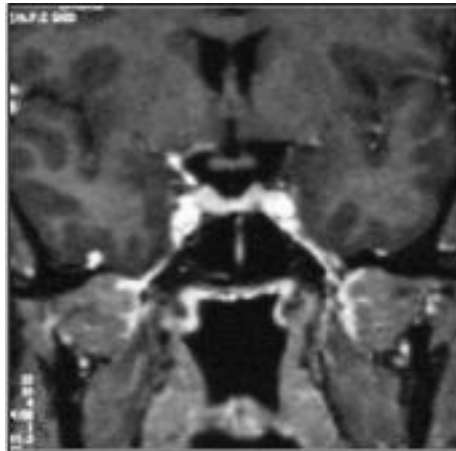


Surgery	<i>n</i>	Remission	Hypopituitarism
Total hypophysectomy	24	18 (75%)	21 (88%)
Hemihypophysectomy	15	13 (87%)	5 (33%)
Selective adenomectomy	14	10 (71%)	2 (14%)

# WHAT ARE THE THEORETICAL INDICATIONS OF BILATERAL ADRENALECTOMY IN ACTH DEPENDENT CUSHING'S SYNDROME ?



Severe Cushing's syndrome as a salvage therapy



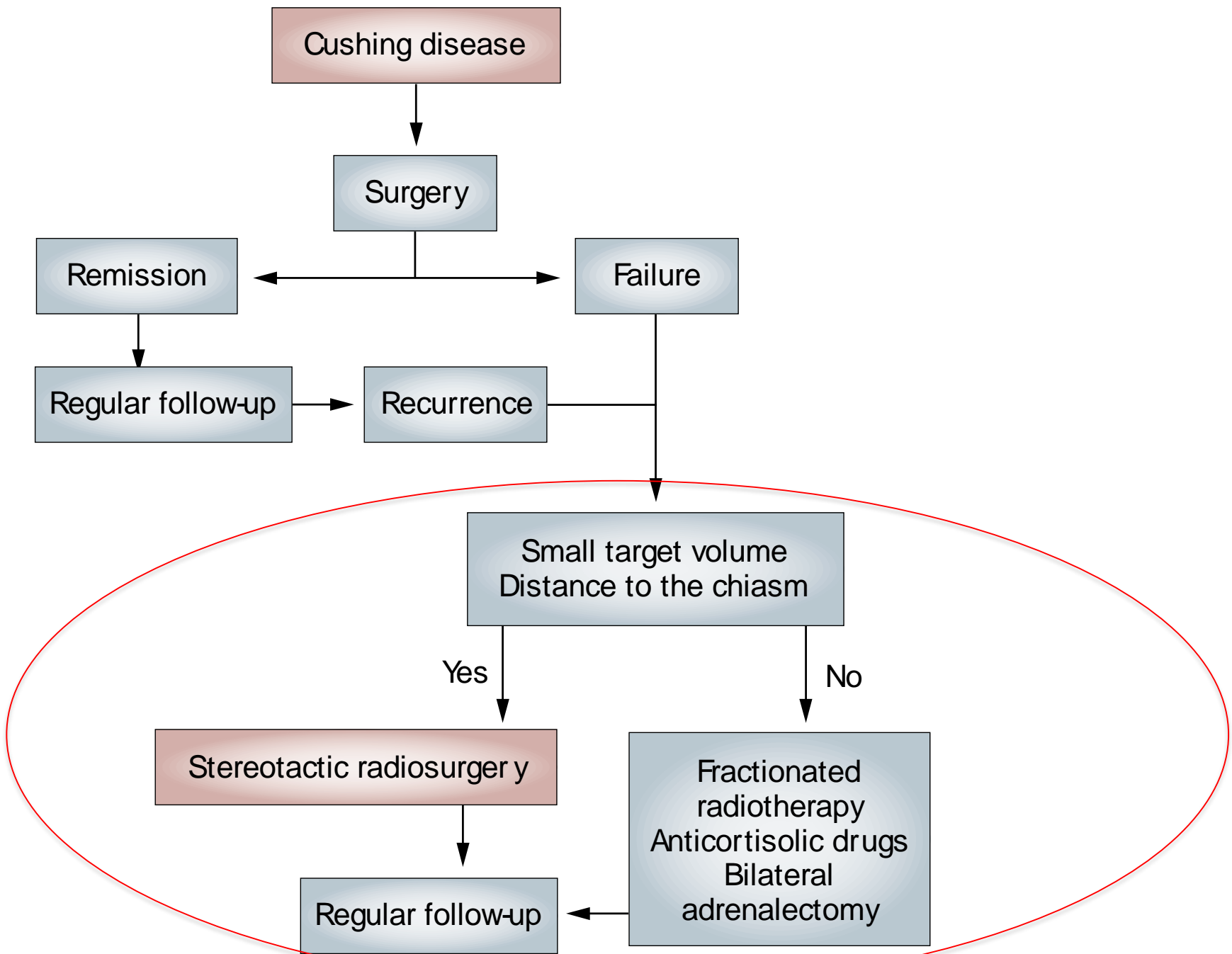
Normal pituitary MRI



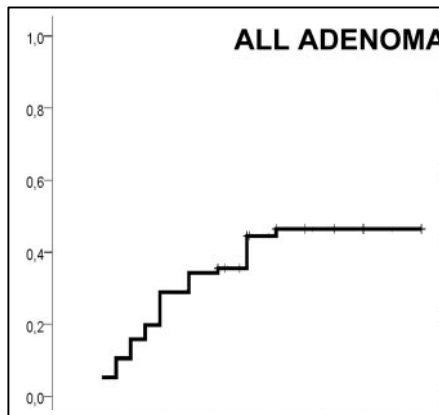
Failed surgery/radiation technique

Or recurrence with normal MRI





# BALANCING THE RISKS AND BENEFITS OF RADIATION TECHNIQUES AND THE SIDE EFFECTS OF BILATERAL ADRENALECTOMY



50-80% remission  
Mean time to remission: 24-60 months

2ary Tumors

Cognitive impairment

Optic neuritis

Increased risk of stroke

Hypopituitarism

Oculomotor nerve palsy

Results of Gamma Knife surgery for Cushing's disease

Clinical article

JASON P. SHEEHAN, M.D., PH.D.,<sup>1,3</sup> ZHIYUAN XU, M.D.,<sup>1</sup> DAVID J. SALVETTI, M.D.,<sup>1</sup>  
PAUL J. SCHMITT, M.D.,<sup>1</sup> AND MARY LEE VANCE, M.D.<sup>2</sup>

Departments of <sup>1</sup>Neurological Surgery and <sup>3</sup>Radiation Oncology; and <sup>2</sup>Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia

96 patients

Mean f/up 48 months (12-210)

70% remission at last f/up

**Recurrence in 15 patients (15,6%)**

**Mean time: 38 months (5-121)**

# BALANCING THE RISKS AND BENEFITS OF LONG-TERM USE OF KETOCONAZOLE AND THE SIDE EFFECTS OF BILATERAL ADRENALECTOMY

**51 patients treated > 24 months  
(mean: 108 months)**

**UFC normalized in 33 patients (65%)  
UFC decreased > 50% in 12 patients**

	Frequency	Mean dose (mg/d)
<b>Liver enzyme increase</b>	30 (15.8%)	772+/-305
<b>Adrenal insufficiency</b>	10 (5.4%)	700+/-256

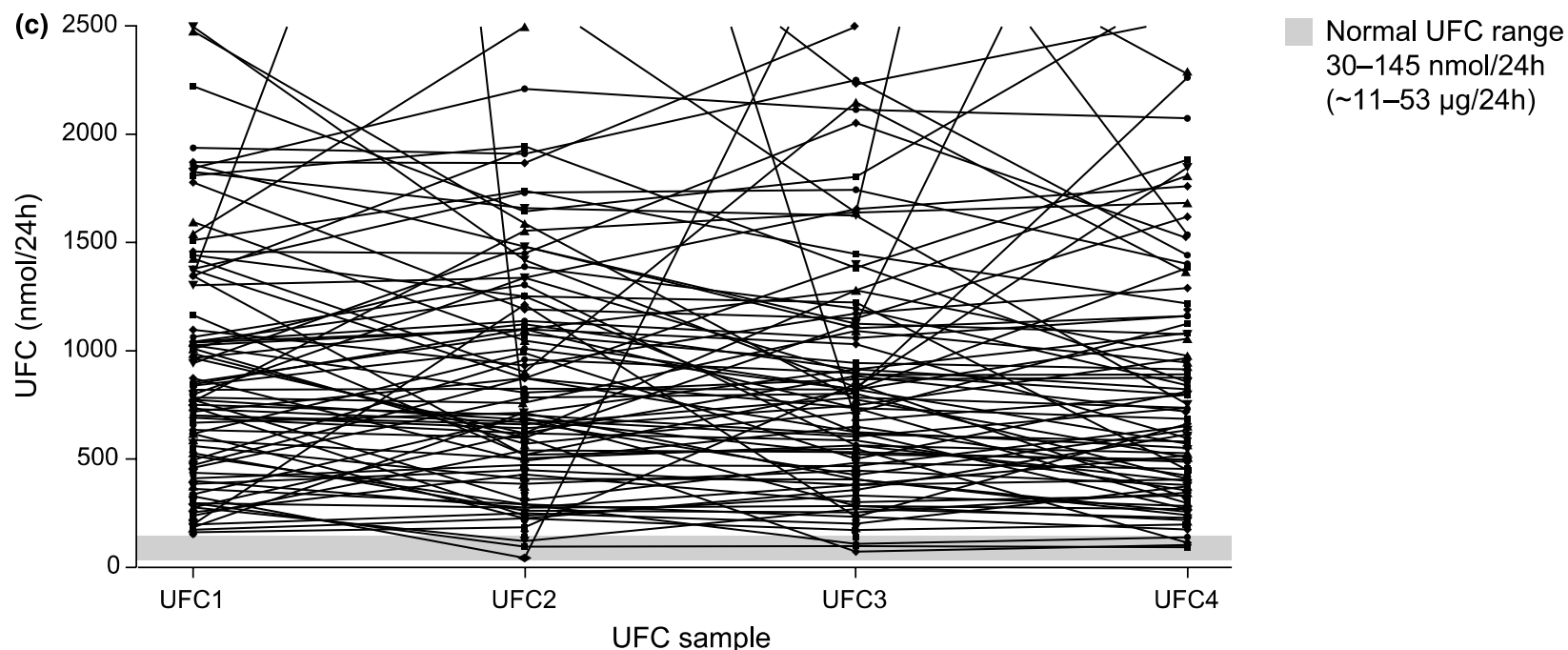
# THE « LONG-TERM » TREATMENT WITH ANTICORTISOLIC DRUGS

	Efficacy	Long-term specific side effects	Escape
<b>Ketoconazole</b>	50%	-	7%
<b>Metyrapone</b>	83%	-	Not evaluated
<b>Mifepristone</b>	?	Endometrial hyperplasia	Not evaluated
<b>Mitotane</b>	71%	Adrenal insufficiency ?	Very low if threshold obtained
<b>Pasireotide</b>	30%	-	Not evaluated
<b>Cabergoline</b>	20-40%	Valvular disease ?	20%

**NO CURE !!!**

*Castinetti, JCEM, 2014; Newell Price, unpublished; Fleseriu, JCEM, 2012; Baudry, EJE, 2012; Colao, NEJM, 2012; Pivonello, JCEM, 2009*

# THE URINARY FREE CORTISOL ISSUE



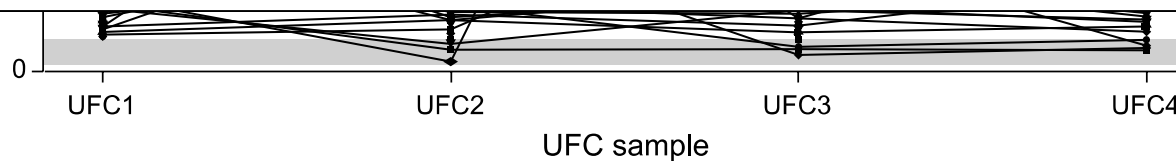
**Conclusions** There is intrapatient variability of approximately 50% in 24-h UFC measurements, which is relevant to targets set to estimate any treatment effect. Analysing more than two 24-h collection periods in individual patients does not result in a relevant decrease in variability. Interestingly, UFC levels did not correlate with hypercortisolism severity.



# THE URINARY FREE CORTISOL ISSUE



## EUCORTISOLISM OR SUBCLINICAL CUSHING ?



**Conclusions** There is intrapatient variability of approximately 50% in 24-h UFC measurements, which is relevant to targets set to estimate any treatment effect. Analysing more than two 24-h collection periods in individual patients does not result in a relevant decrease in variability. Interestingly, UFC levels did not correlate with hypercortisolism severity.

# BILATERAL ADRENALECTOMY IN ACTH DEPENDENT CUSHING'S SYNDROME

- Effective
- Relatively rapidly acting
- Low mortality
- The risk of Nelson's syndrome: probably not a major issue in the 21st century
- The risk of adrenal crisis: education to be kept on again and again

# BILATERAL ADRENALECTOMY IN ACTH DEPENDENT CUSHING'S SYNDROME

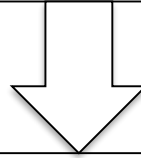
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## Indications in the 21st century

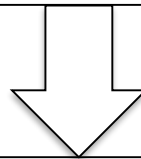
- **As a salvage therapy:** anticortisolic associations possible, to be kept in mind depending on the possibility of definite cure vs improving before bilateral adrenalectomy
- **In negative MRI:** probably no place for bilateral adrenalectomy
- **In surgery failure, recurrence or vs radiation techniques:** probably as a second line treatment only after testing anticortisolic drugs, and being sure that these drugs are not effective

# **ACTH-INDEPENDENT CUSHING'S SYNDROME (BAH)**

10 years: 279 adrenalectomies performed



11 for BAH had unilateral adrenalectomy  
All of them had biological Cushing's syndrome



**1 year post-surgery: No failure...**  
- 4 corticotroph deficiency  
- 7 normal glucocorticoid function

**16 patients** with bilateral macronodular adrenal hyperplasia and CS  
- 10 active Cushing; 5 subclinical Cushing; 1 cyclical Cushing  
**12 patients** with unilateral adrenalectomy

**3 in remission**  
Mean Follow-up: 106 months

**8 recurrences**  
Mean Follow-up: 93 months  
(Min 24; Max 264 months)  
  
Including 3 with subclinical  
still under surveillance

**1 persistent disease**  
Controlateral adrenalectomy 6 months later

# UNI/BILATERAL ADRENALECTOMY IN ACTH INDEPENDENT BILATERAL ADRENAL HYPERPLASIA

## Unilateral adrenalectomy

- Rapidly acting
- Low mortality
- Requires a prolonged follow-up, as the recurrence is **HIGHLY LIKELY** in the 10 following years after surgery
- Patients can be corticoid dependent for a while

## Unanswered questions

- **Which adrenal to remove ?**
  - Size criteria
  - Iodocholesterol scintigraphy uptake ?
- **Can we predict the outcome ?**
- **Is there really a place for bilateral adrenalectomy in such patients as 1st line? Probably not...**

## Endocrinology

T. Brue  
I. Morange  
M. Philippon  
F. Albarel  
M. Sahnoun



## Neurosurgery

H. Dufour  
J. Regis  
**Endocrine surgery**  
F. Sebag  
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