Traitement des hypercortisolismes

Pr Antoine TABARIN

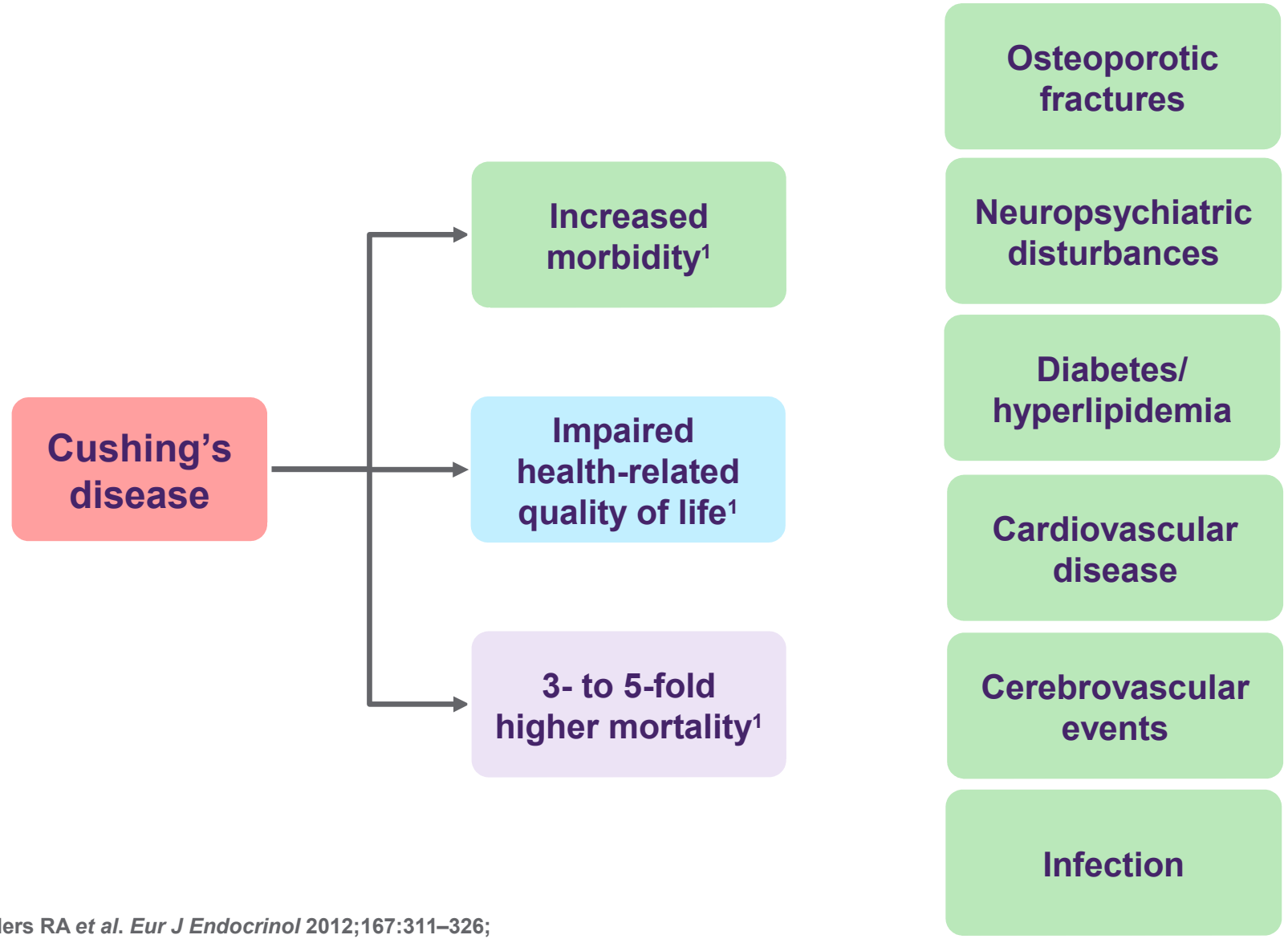
UNIVERSITÉ DE BORDEAUX

C·H·U
Hôpitaux de Bordeaux

Etapes du diagnostic de syndrome de Cushing

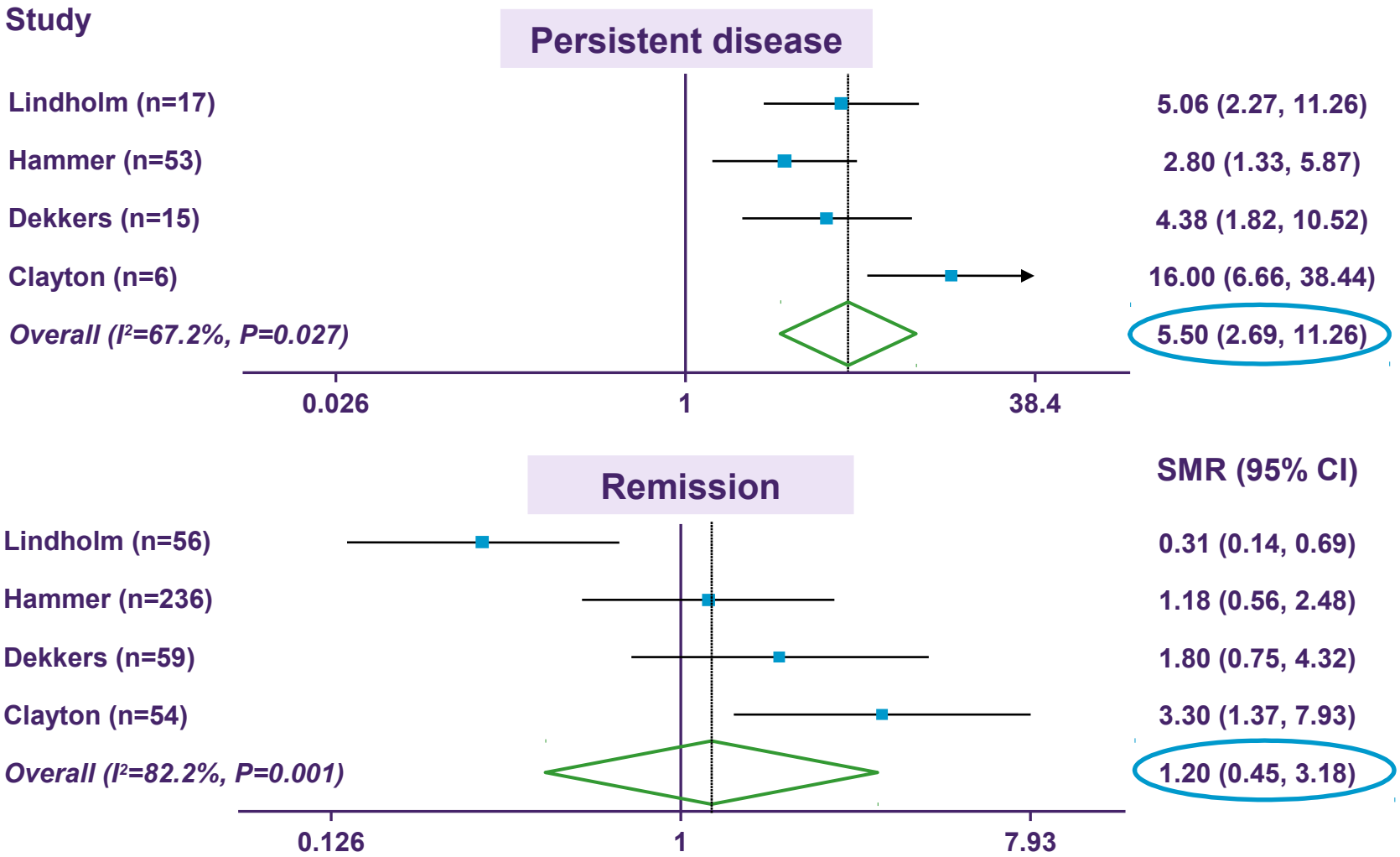
- Mettre en évidence l'hypercortisolisme chronique
- Etablir l'ACTH-dépendance du syndrome
- Mettre en évidence la tumeur à l'origine du syndrome

Consequences of Cushing's disease



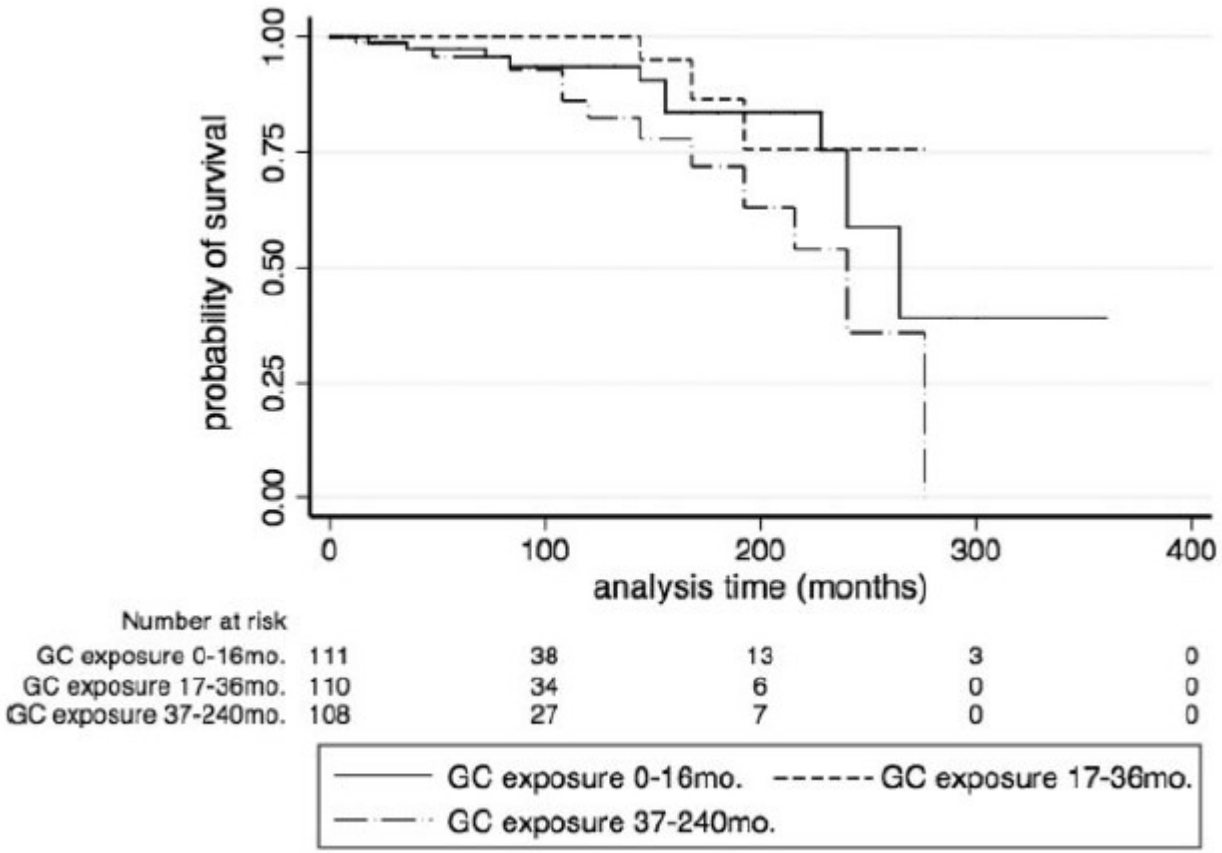
[1]Feelders RA *et al*. *Eur J Endocrinol* 2012;167:311–326;
[2]Etxabe J & Vazquez JA. *Clin Endocrinol (Oxf)* 1994;40:479–484

Patients with persistent Cushing's disease have higher rates of morbidity and mortality



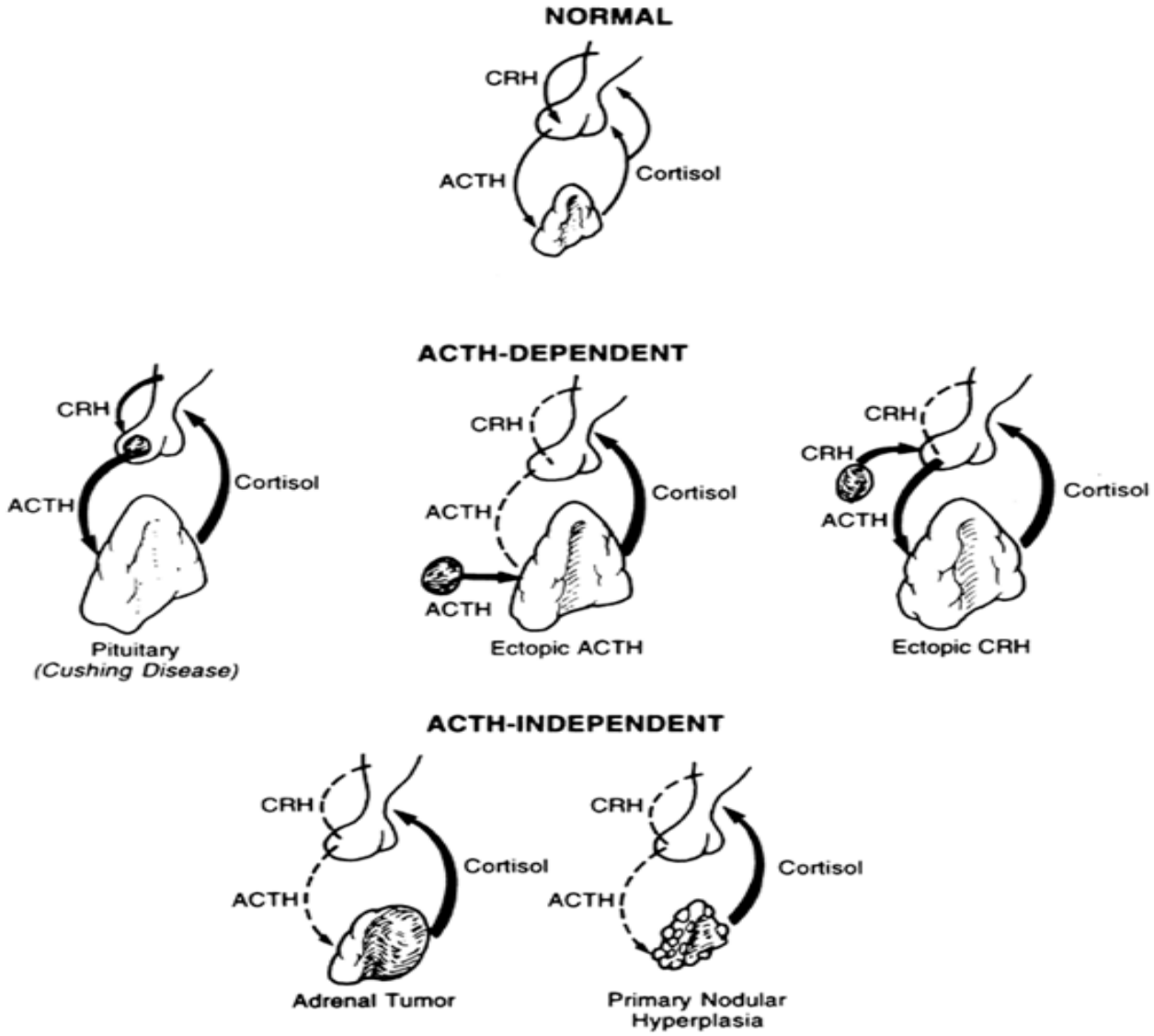
Clayton RN *et al. JCEM* 2011

Prognosis Factors in Cushing's Disease

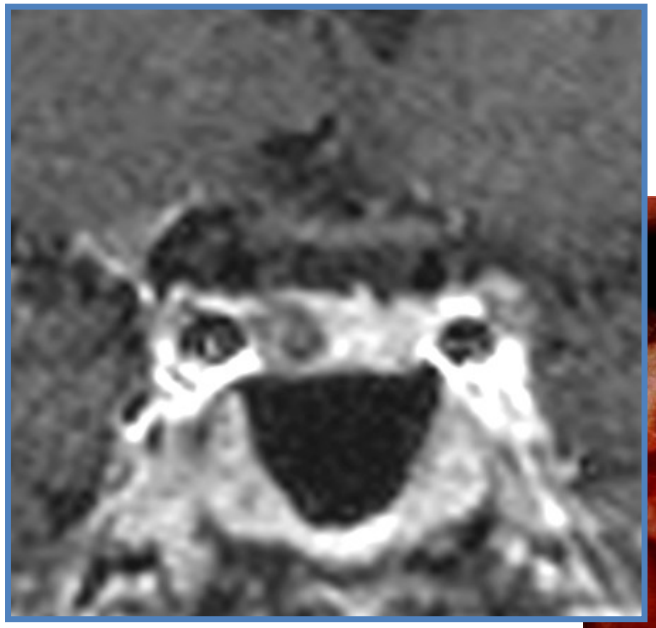


Lambert J et al. JCEM 2013

Etiologies du syndrome de Cushing

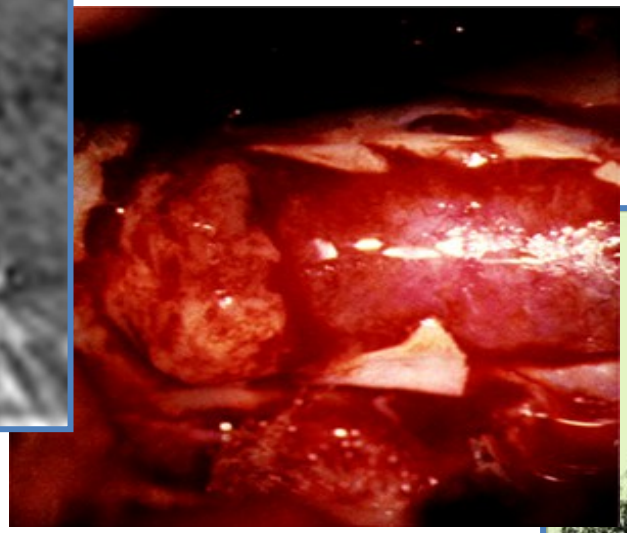


Le cas idéal…

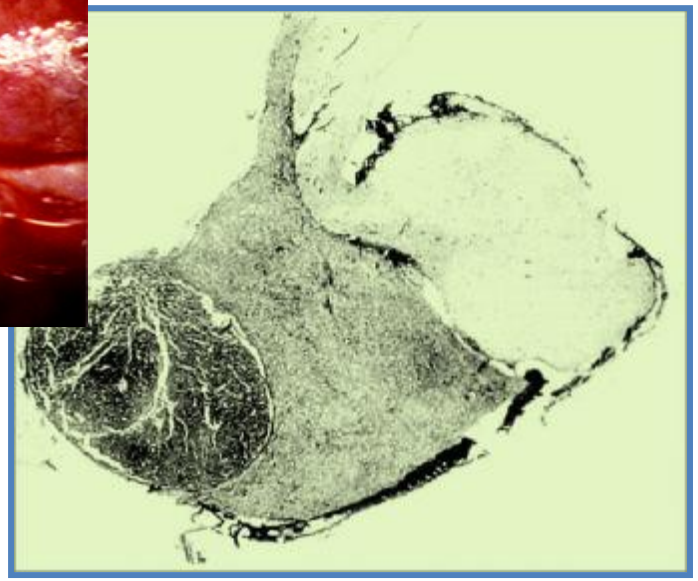


Microadenoma

‘Intra-operative’ visualization



Histological confirmation

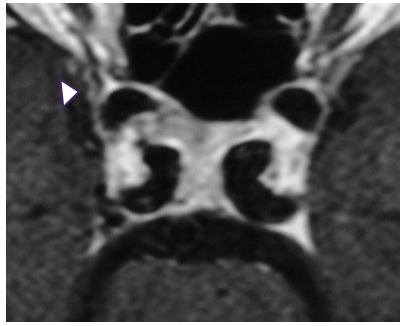


However, in real life….

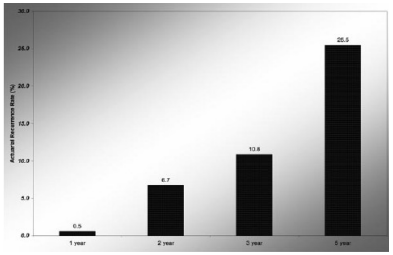
Not always feasible

Not always successful

- Initial success rate 60–90% in patients with a microadenoma
- Remission rates lower (<65%) in patients with a macroadenoma



Not always lasting



Patil et al., JCEM 2008

Traitement Etiologique du syndrome de Cushing

✓ ***Yes, but….Pas toujours possible :***

- **EAS occulte ou inopérable**

Ejaz 2011 (N = 43) : 67 % *Isidori 2006 (N = 40): 70%*
Ilias 2005 (N = 90): 54% *Aniszewski 2001(N = 106): 88%*

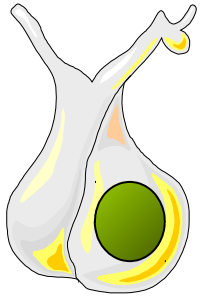
- **ACC non résequable en totalité (stade III et IV)**

Stade III et IV : Abiven 2006: 43 % *Fassnacht 2009 : 56%*

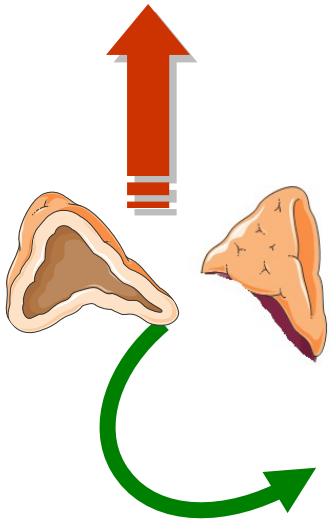
- **Morbidité de la chir transphénoïdale dans le contexte des hypercortisolismes intenses..**

Therapeutic Tools

- ✓ **Surgery**
- ✓ **Pituitary Radiotherapy**
- ✓ **Medical Targeting** (cabergoline, pasireotide)



- ✓ **Steroïdogenesis Inhibitors** (ketoconazole, metyrapone, LCI 699)
- ✓ **Bilat Adrenalectomy** op'DDD , Surgery



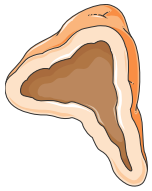
- ✓ **GR Inhibition** Mifepristone

Medical Treatment of Hypercortisolism

- ✓ **Rare Disease : very few evidence based data…**
  - Retrospective evaluations
  - Heterogeneous cohorts
  - Limited number of patients
  - Variable criteria of judgement

- ✓ **Lack of control group or reference treatment**

- ✓ **Possible « side effect »…**
  …..Adrenal Insufficiency

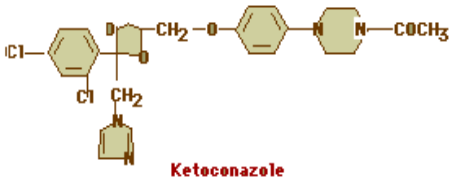


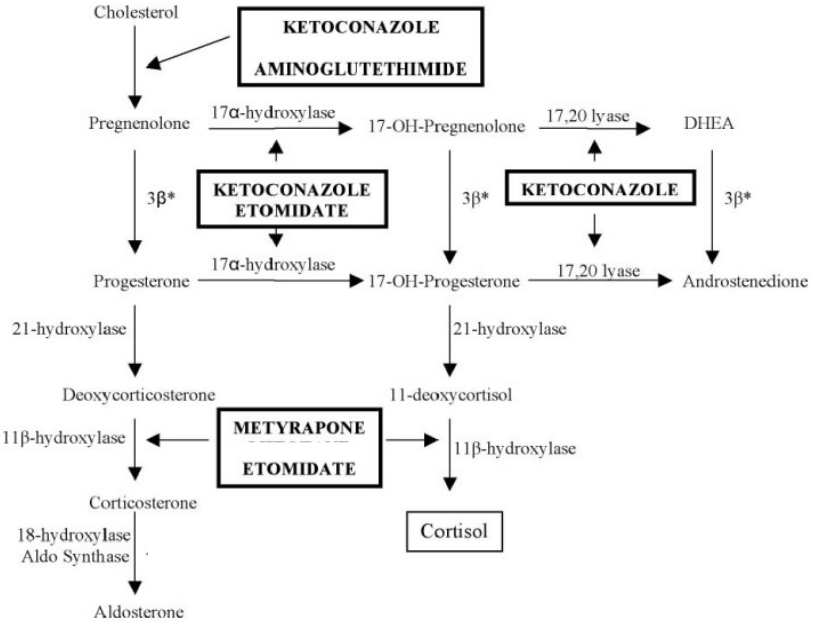
Medical Therapies Directed at the Adrenal Glands

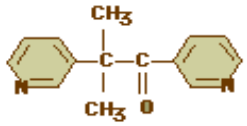
- Steroidogenesis Inhibitors
- Adrenolytic Drugs

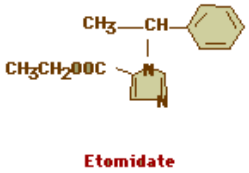
Steroido-genesis inhibitors

- Metyrapone, Ketoconazole, Etomidate, LCI699
- Rapid effect (hours to day)
- Do not restore circadian rhythm of cortisol
- Rare escape Phenomenon ?
- *Two Strategies : titration vs block and replace*



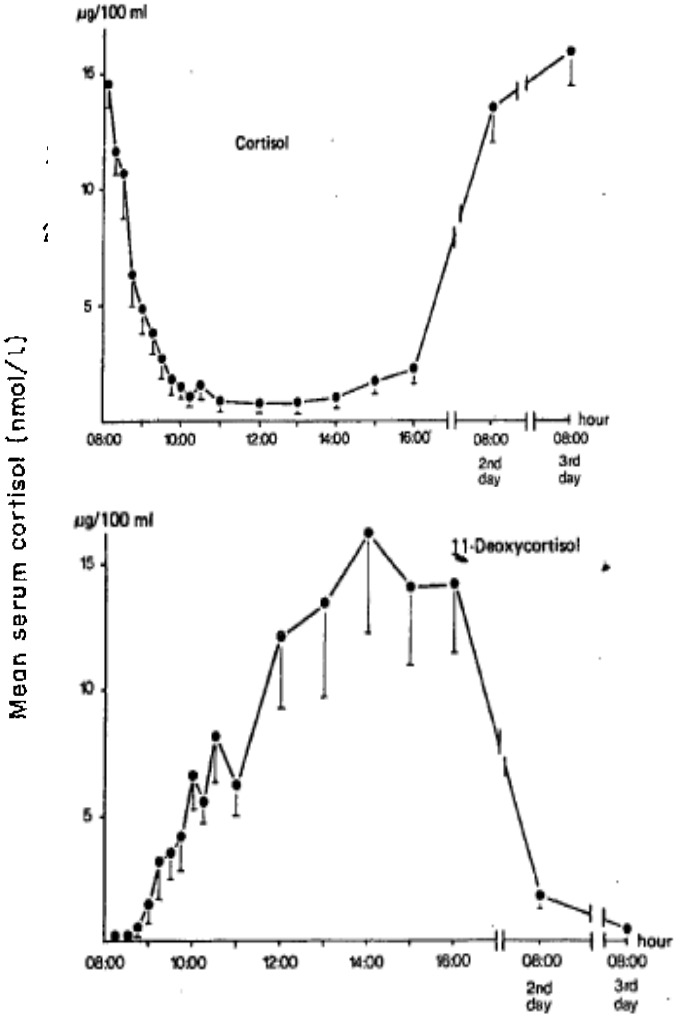






Metyrapone

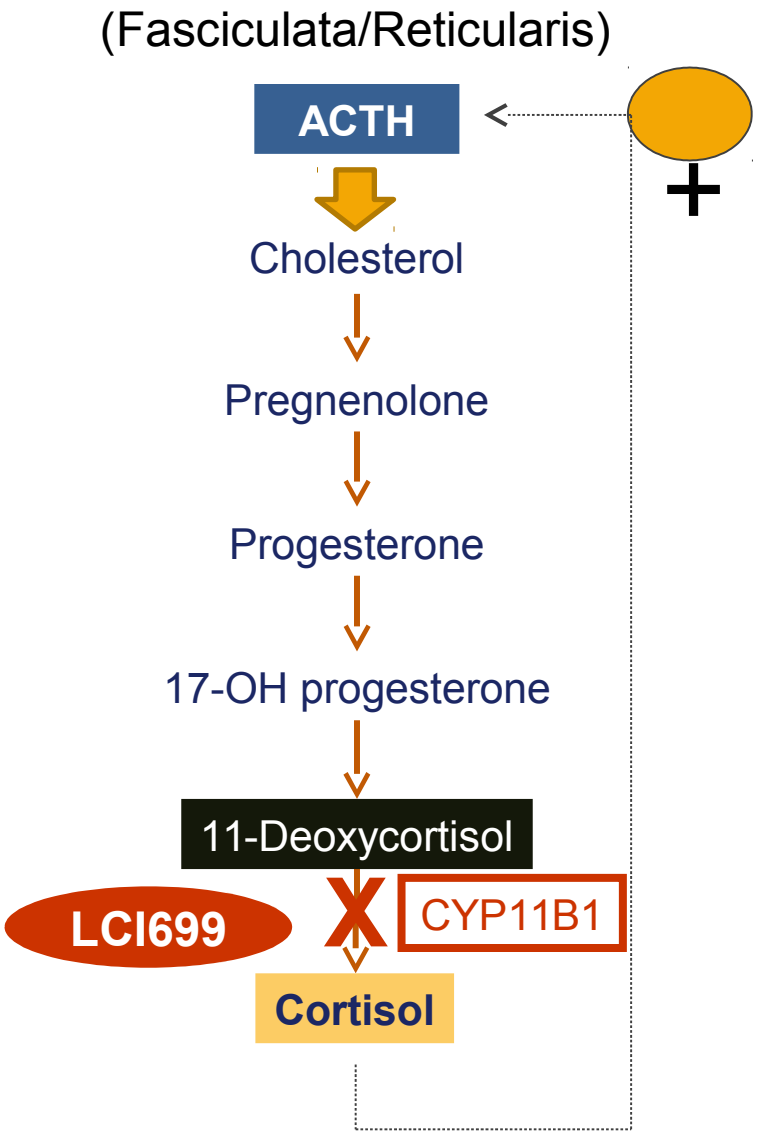
- 53 patients treated for 1-16 weeks
- Within 2 h decrease in cortisol levels
- 75 % controlled with 500 to 6000 mg/d (m = 2.25 mg/d)
- Side effects :
  - Hypokalemie / œdema 5-10%
  - Nausea / Abd dyscomfort: 13%
  - Acne 40%
- Assay interference with 11 deoxyF



Schöneshöfer M et al, J Endocr Invest, 1980

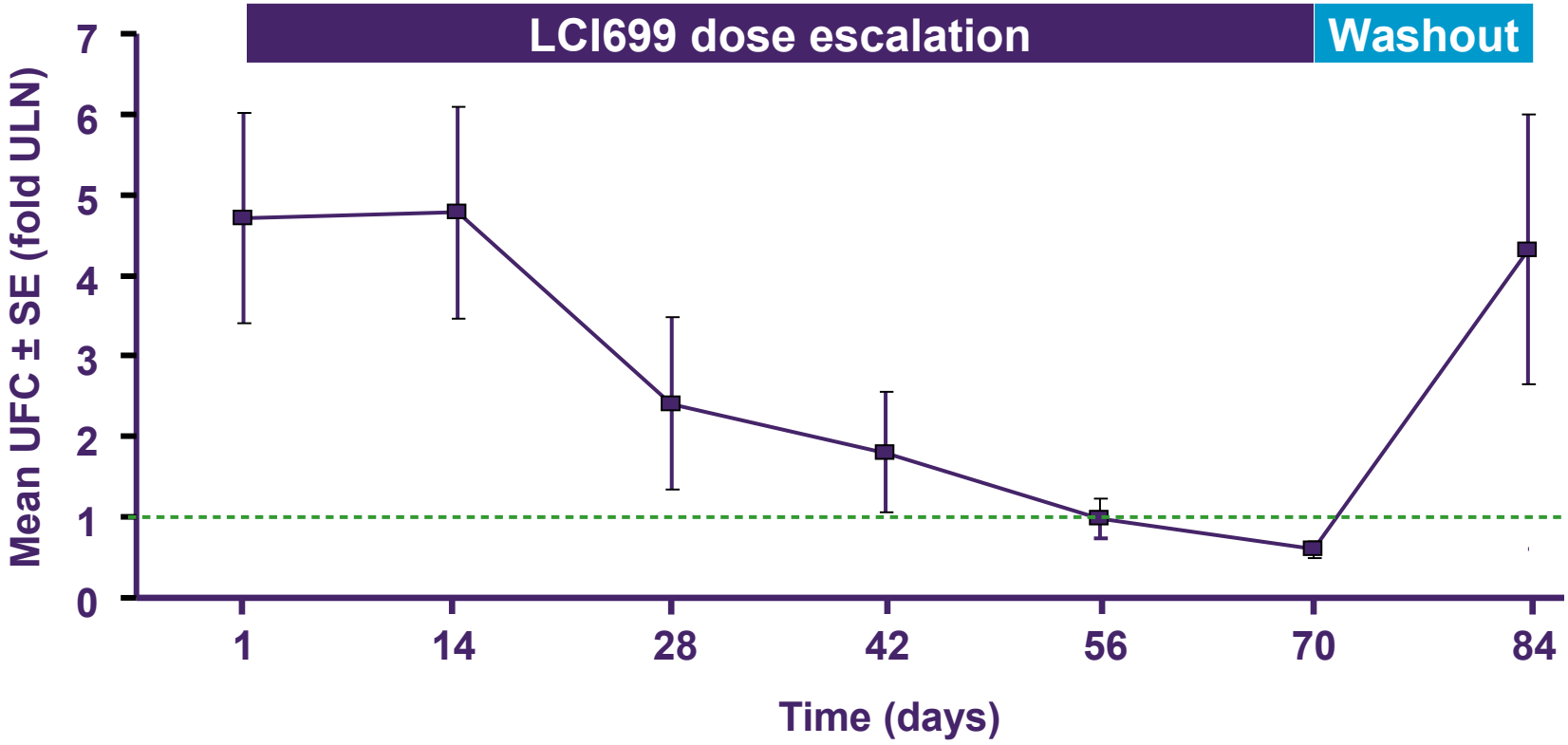
Verhelst et al. , Clin Endocrinol 1991

LCI699


(Fasciculata/Reticularis)
ACTH
+
Cholesterol
Pregnenolone
Progesterone
17-OH progesterone
11-Deoxycortisol
LCI699
CYP11B1
Cortisol

Mean UFC levels decreased during LCI699 treatment

- 11/12 (92%) had normal urinary cortisol at day 70
- Urinary cortisol normalized in all 12 patients at least once



Safety of LCI699

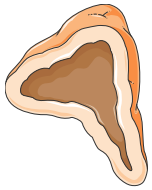
- All patients experienced at least one AE during treatment
  - Most AEs were mild to moderate on the short-term...

- **LCI699 is super-metyrapone : .**
  - **LCI699 is more potent than metyrapone (IC_{50} approximately 2.5 vs 7.5 n_M)**
  - **longer plasma half-life (approximately 4 vs 2 h), suggesting that twice daily dosing should suffice**

Ketoconazole

- French retrospective multicenter study reviewing data from 200 patients
- At the last follow-up, 49.3% of patients had normal UFC levels (25.6% had at least a 50% decrease)
- Median final dose of ketoconazole was 600 mg/d.
- 20% treated prior to surgery : 48.7% had normal UFC and 50% showed improvement of hypertension, hypokalemia, and diabetes
- 20.5% stopped the treatment due to intolerance. Major liver intolerance in 2.5% of patients. No fatal hepatitis was observed.

Castinetti F et al. JCEM 2014



Etomidate

European Journal of Endocrinology (2012) **167** 137–143

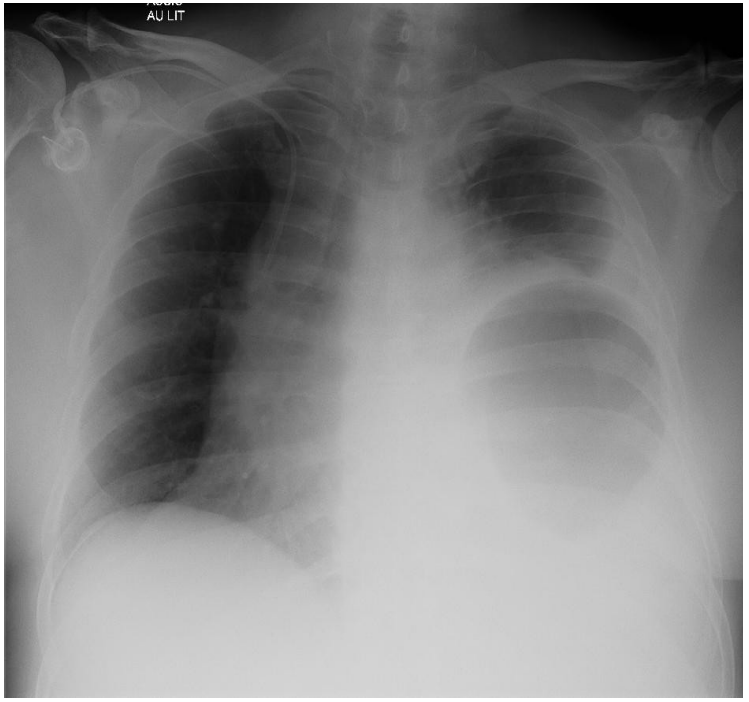
REVIEW

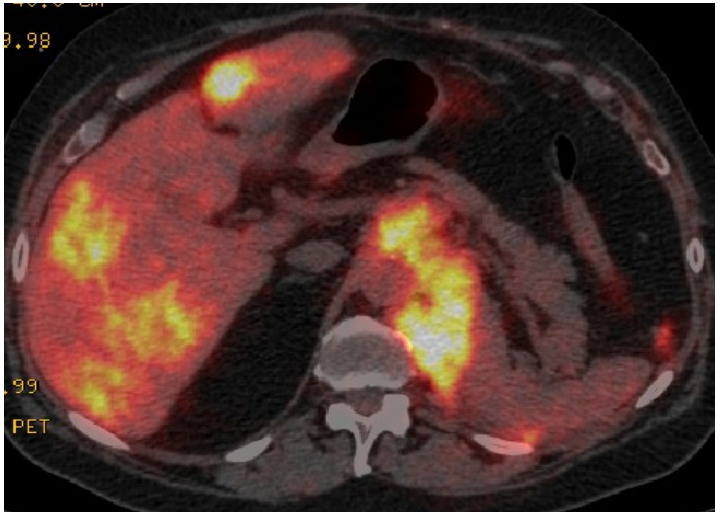
THERAPY IN ENDOCRINE DISEASE

Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review

Veronica A Preda[1,2], Jonathan Sen[1], Niki Karavitaki[1] and Ashley B Grossman[1]

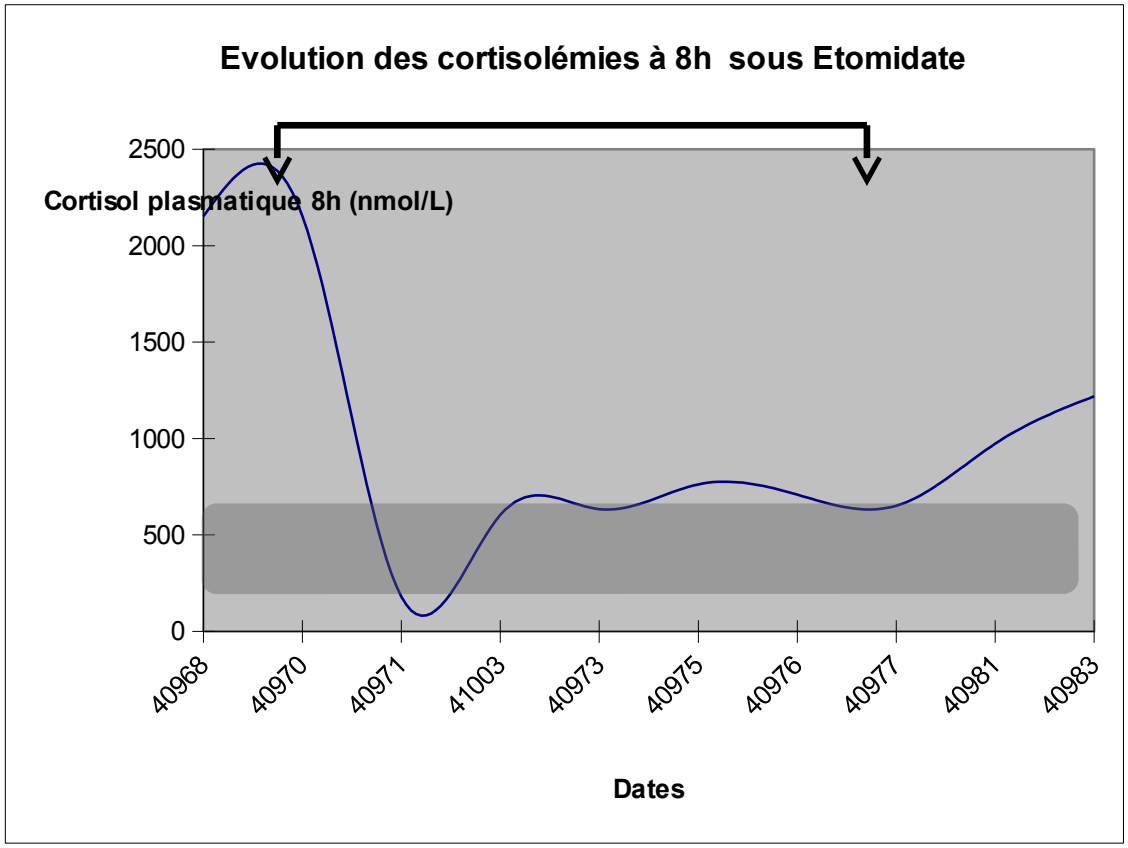
- ✓ **IV administration at subhypnotic doses 0.05 to 0.3 mg/kg/h *(2.5 to 3 mg/h)***
- ✓ **Delay ± 12h**
- ✓ **Titration or block and replace with hydrocortisone IV 0.5 - 1 mg/h**
- ✓ **ICU**

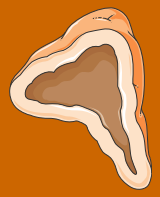




Nizoral 1200 mg/jour, Lysodren 6g/ jour, Metopirone 4000 mg /jour

- ✓ **Etomidate 0.1 mg/kg/h (8 mg/h)**
- ✓ **Hydrocortisone IV 3 mg/h**

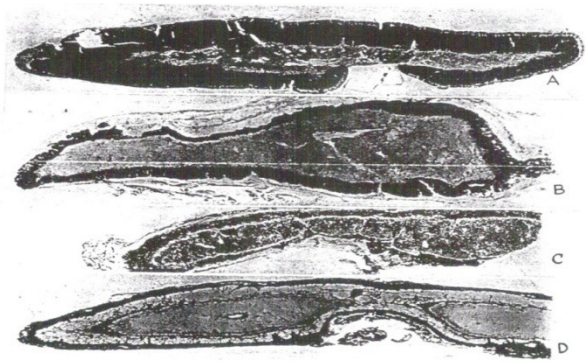




Adrenolytic Drugs

- Mitotane at “high” doses
- Destruction of Adrenal Cortex
- Results in adrenal Insufficiency
- Delayed Effect

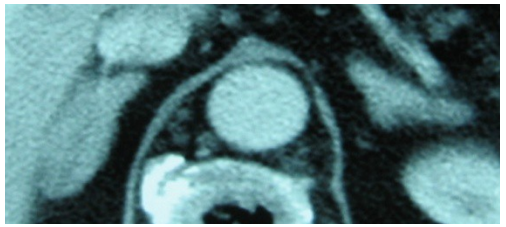
Dogs

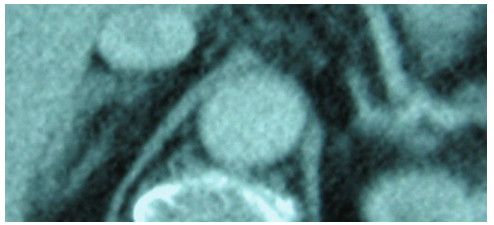


Before

After

Humans



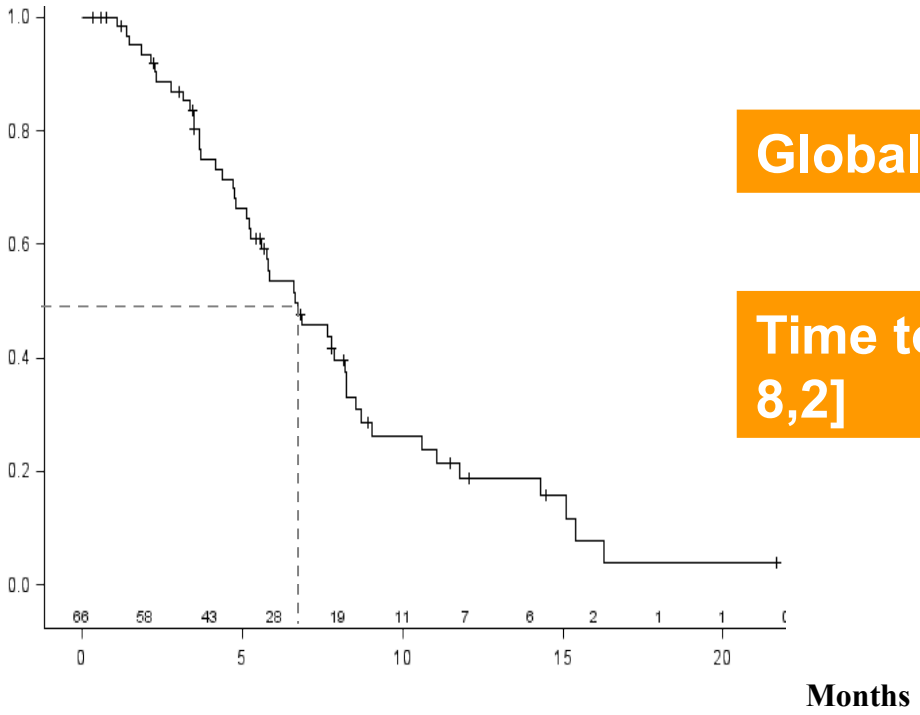


Nelson A, Woodard G. 1949, Arch. Path

Mitotane

- ✓ 76 patients treated with MITOTANE at Cochin Hospital (Paris)

Persistent hypercortisolism

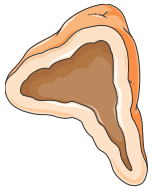


Global remission rate: 72%

Time to remission: 6,7 mo [5,2-8,2]

- ✓ Median dose : 2.7 ± 1.2 g / d
- ✓ Mitotane level over 8,5 mg/l: 100 % remission

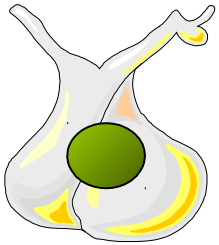
Baudry et al. , EJE 2012



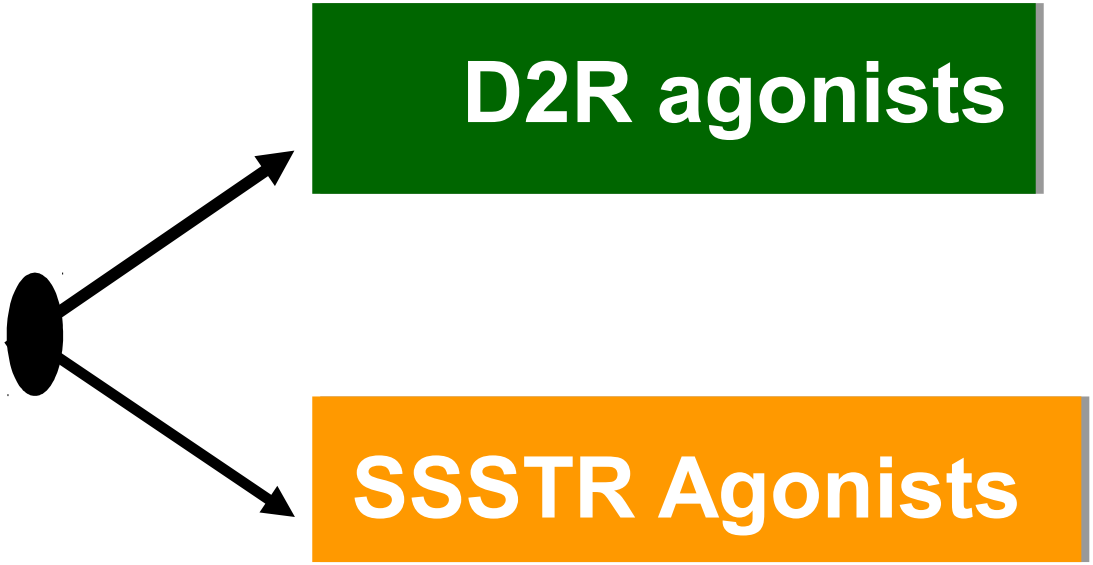
Mitotane : Tolerance

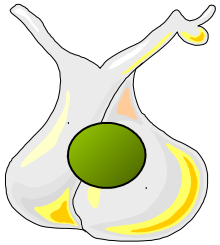
	Mild intolerance	Intolerance leading to Mitotane discontinuation
Gastro-intestinal signs	**36 (47%)**	**5 (7%)**
Increased transaminases :	**13 (17%)**	**1 (1%)**
>ULN	11	
>3x ULN	2	
Increased GGT :	**36 (47%)**	
>3xULN	24	
>5xULN	12	
Neurologic signs	**23 (30%)**	**6 (9%)**
Lipid disorders:	**54 (71%)**	
LDL cholesterol > 3.35 mmol/l	15 (20%)	
LDL cholesterol > 5.16 mmol/l	19 (25%)	
Triglycerides > 2.28 mmol/l	25 (34%)	

Baudry et al. , EJE 2012

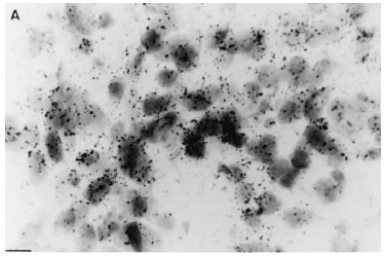


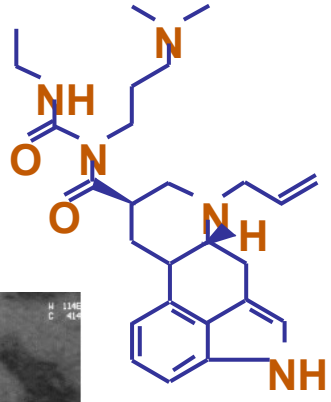
Tumor-Directed Medical Therapies





Tumor-Directed Medical Therapies





Cabergoline

Petrossians et al. Eur J Endocrinol 2009

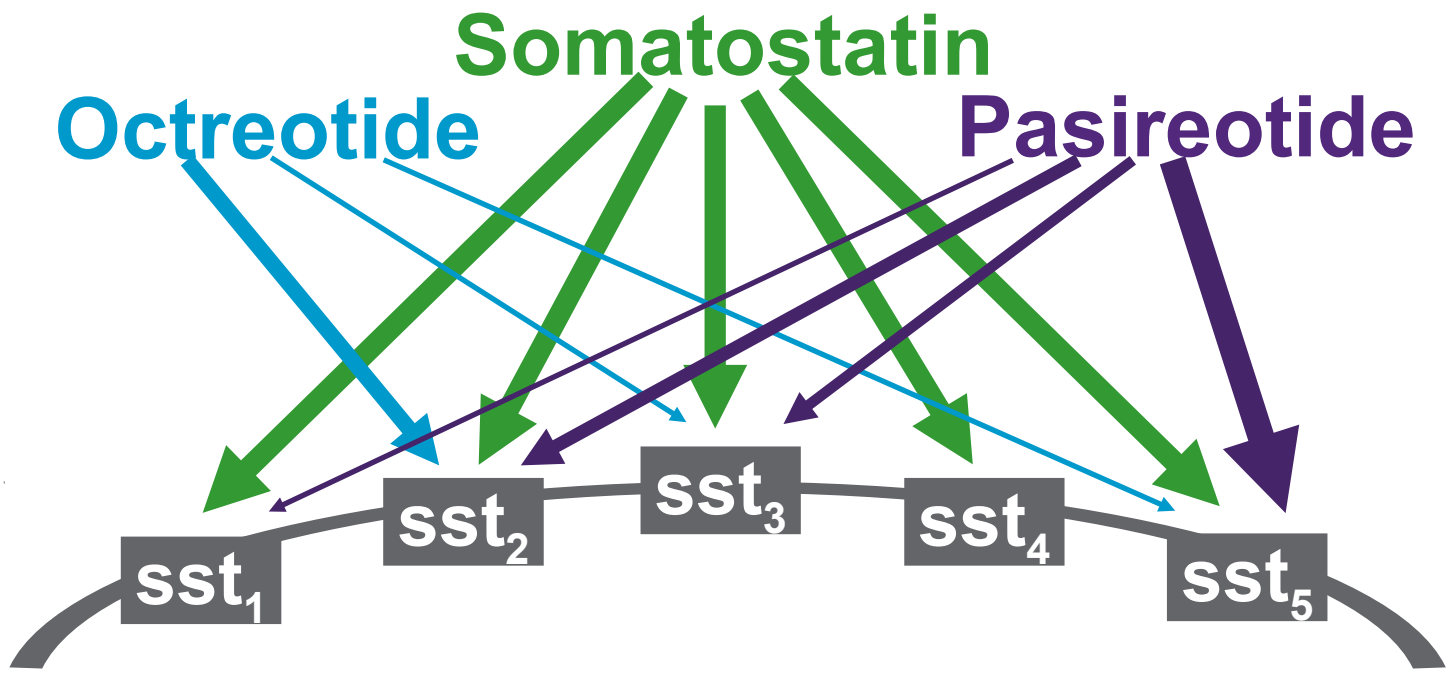
to ttt

ntrol in 25 to 40 % of patients

Mean doses : 2.1 and 3.5 mg / w (0.5 to 7.0)

Pivonello R et al. J Clin Endocrinol Metab 2009
Vilar L et al. Pituitary 2010
Godbout A et al. Eur J Endocrinol 2010

Tumor-Directed Medical Therapies



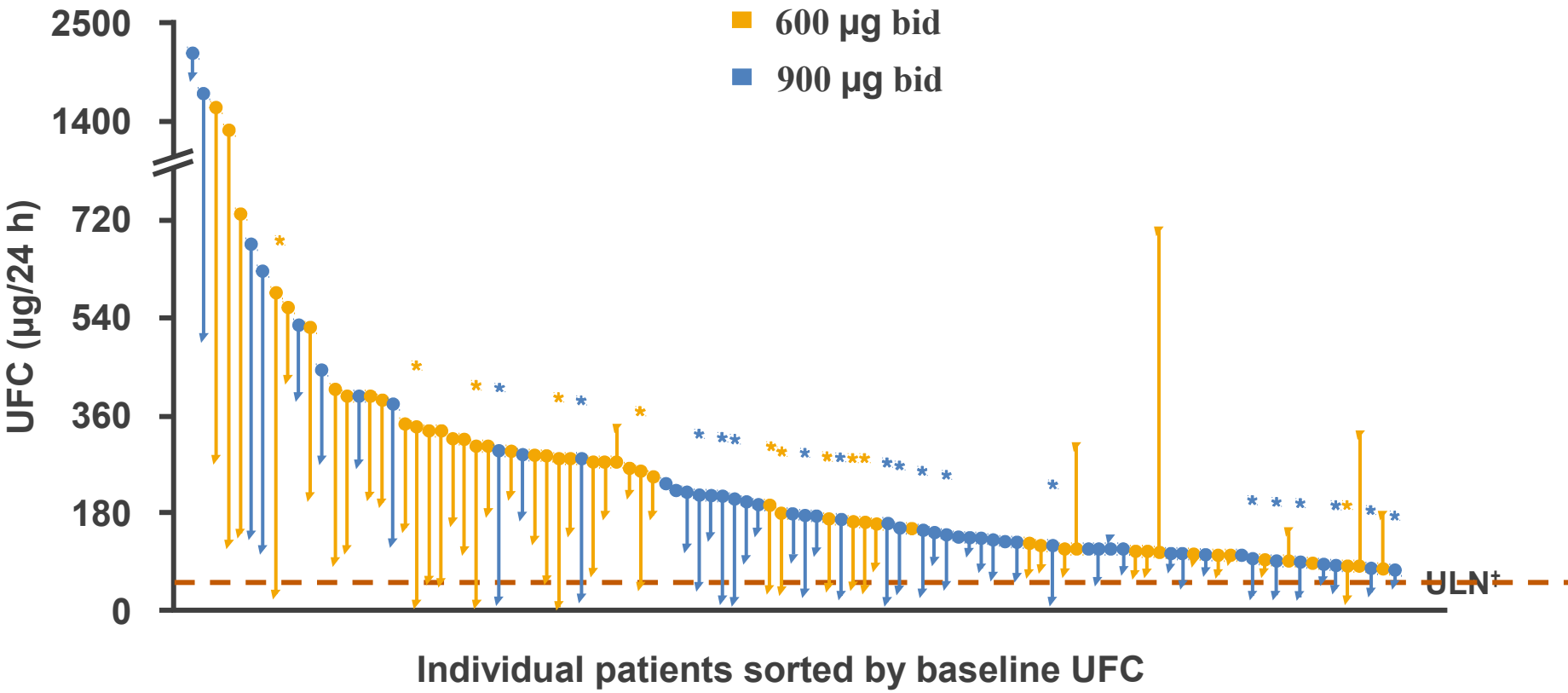
Phase III pasireotide study

- ✓ 162 patients with previous surgery (79%) and/or medical treatment (48%) but no radiotherapy in previous 10 y
- ✓ Randomization to 600 or 900 µg bid.

Primary efficacy endpoint :
Normalization of UFC without dose up-titration at 6 months

Colao AM et al. NEJM 2012

Change in UFC from baseline to month 6



Median percentage UFC change from baseline was –47.9% in both groups

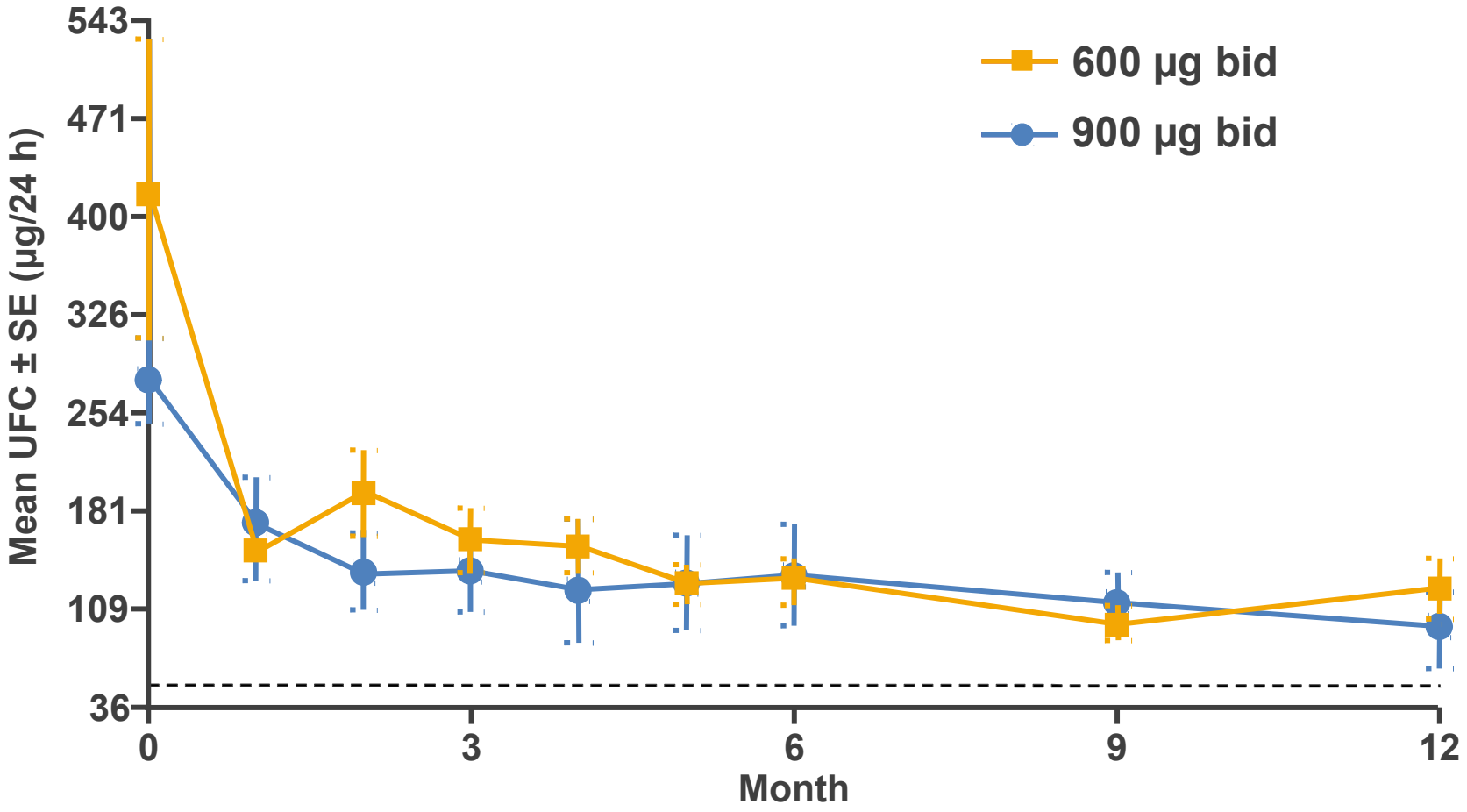
Colao AM et al. NEJM 2012

Primary Efficacy Results

	600 µg x 2/j (n=82)	900 µg x 2/j (n=80)	Overall (n=162)
6 months			
*Reponse, n (%)	12 (14.6)	21 (26.3)	33 (20.4)
[95% CI]	[7.0, 22.3]	[16.6, 35.9]	[14.2, 26.6]

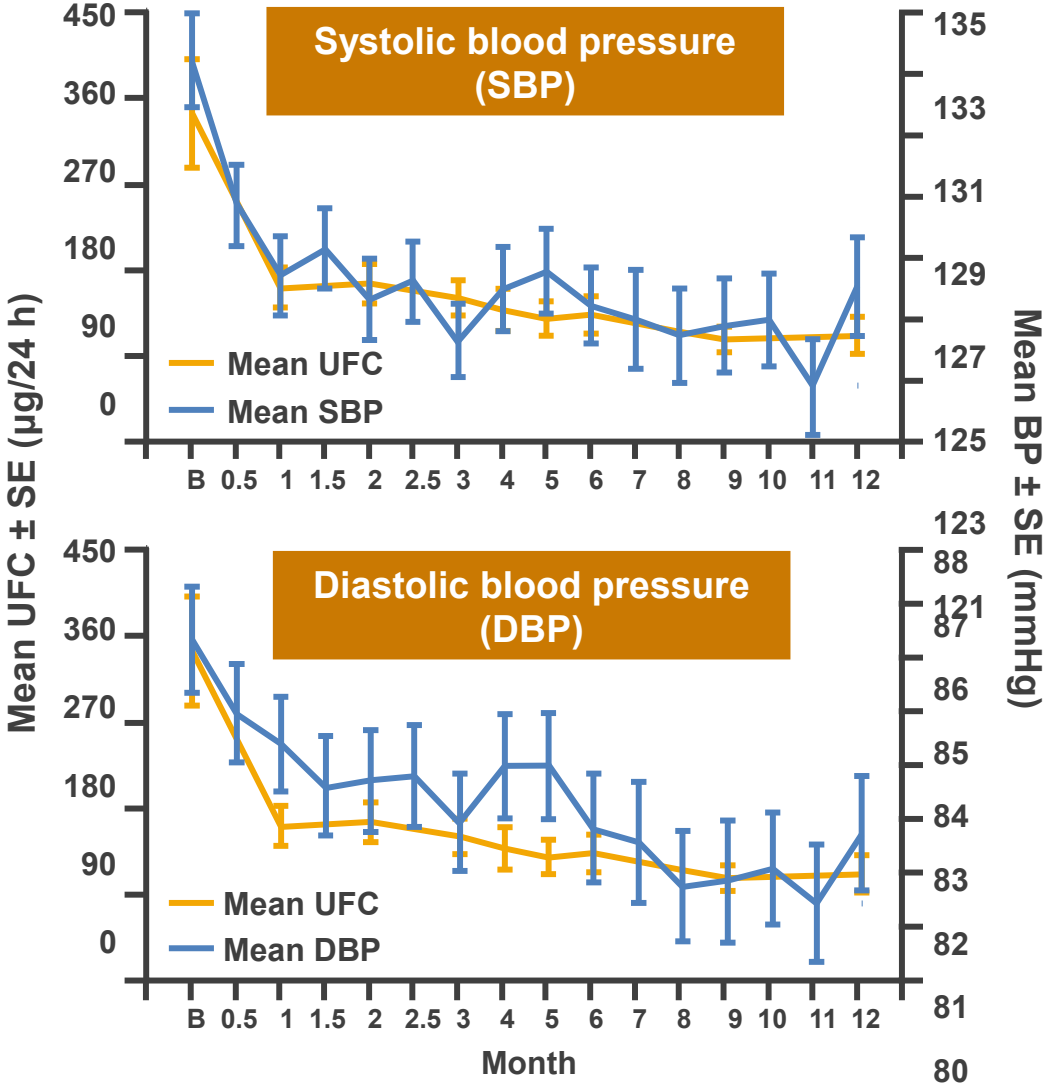
Colao AM et al. NEJM 2012

Mean UFC over time



Within 2 months, non responders can be identified

Clinical Syndrome



At month 12 :

SBP –6.1 mmHg
(95% CI: –9.8, –2.4)

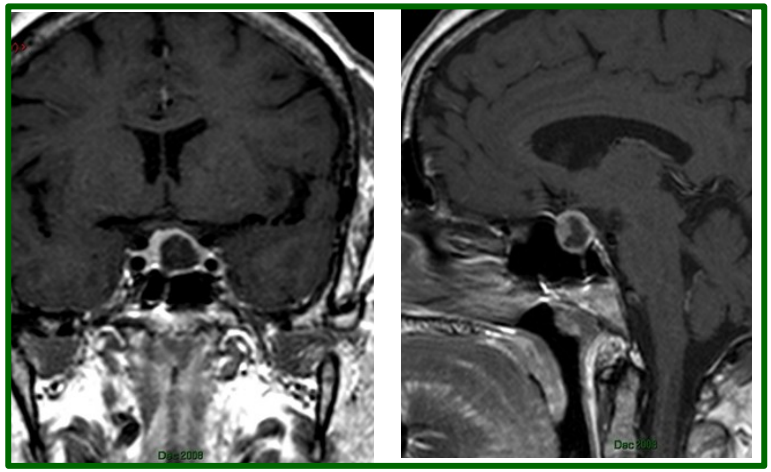
DBP –3.7 mmHg
(95% CI: –6.2, –1.2)

Colao AM et al. NEJM 2012

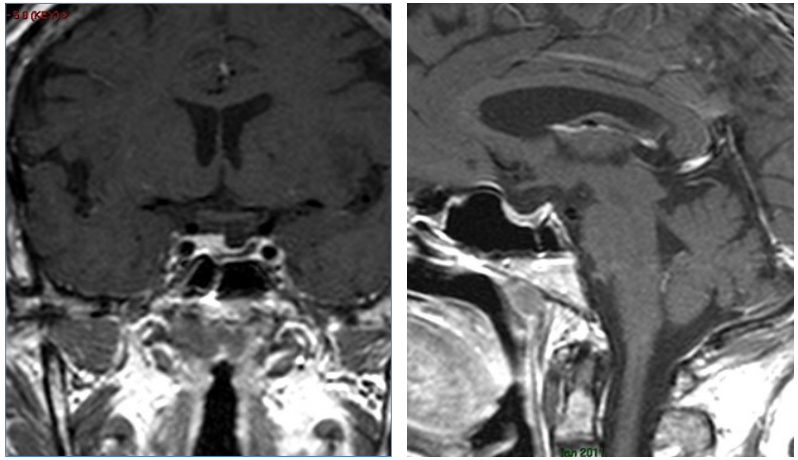
Adenoma Shrinkage

- 46 % patients had measurable pituitary tumors

- At M12 :
  - 9.1 % (- 46.3 to 28) in 600 µg group
  - 43.8 % (- 68 to - 19) in 900 µg group



Baseline

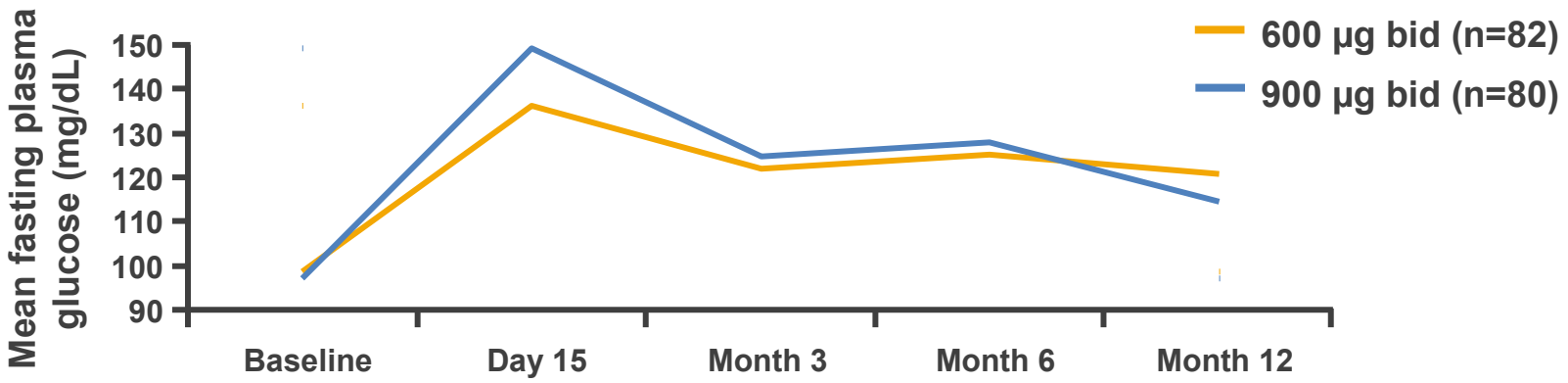


After pasireotide

Courtesy of Dr Ilan Shimon

Safety

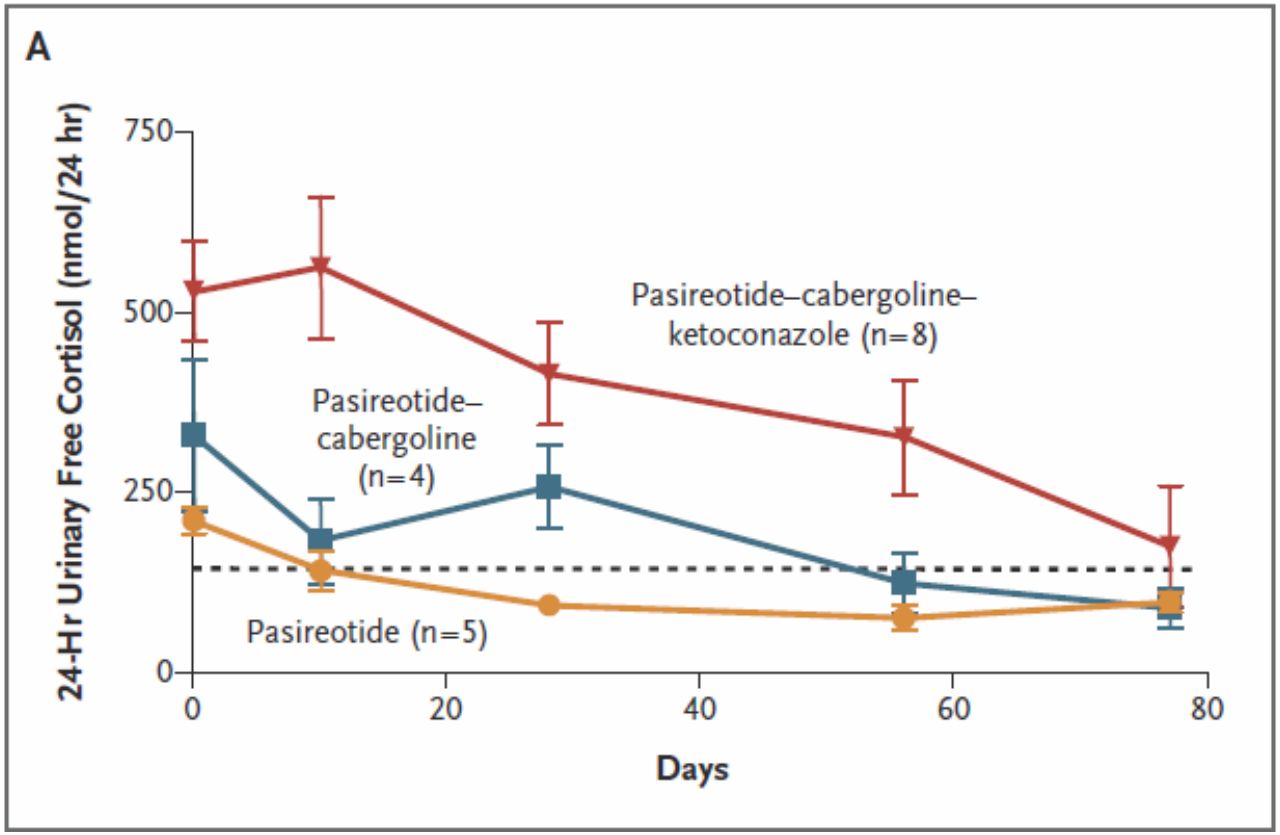
73% of patients had an hyperglycemia-related AE



- **Pre-existing diabetes or IGT increases the risk of hyperglycemia AE**

- **Risk among normoglycemic patients :**
  - **glucose-intolerance: 43%**
  - **diabetes : 34%**
  - **need for medical treatment in 45%**

Combination Therapy

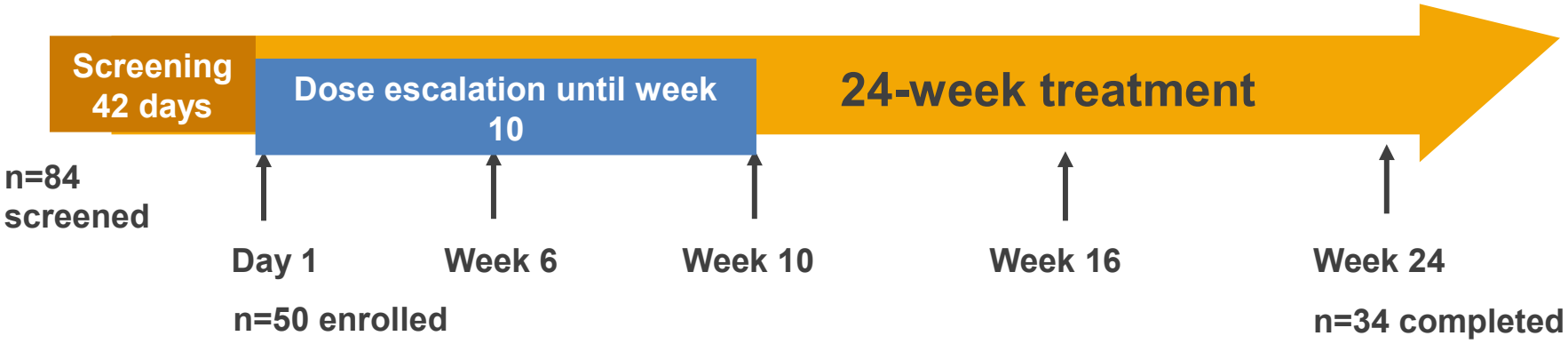


Feldeers R *et al. NEJM* 2010

GR

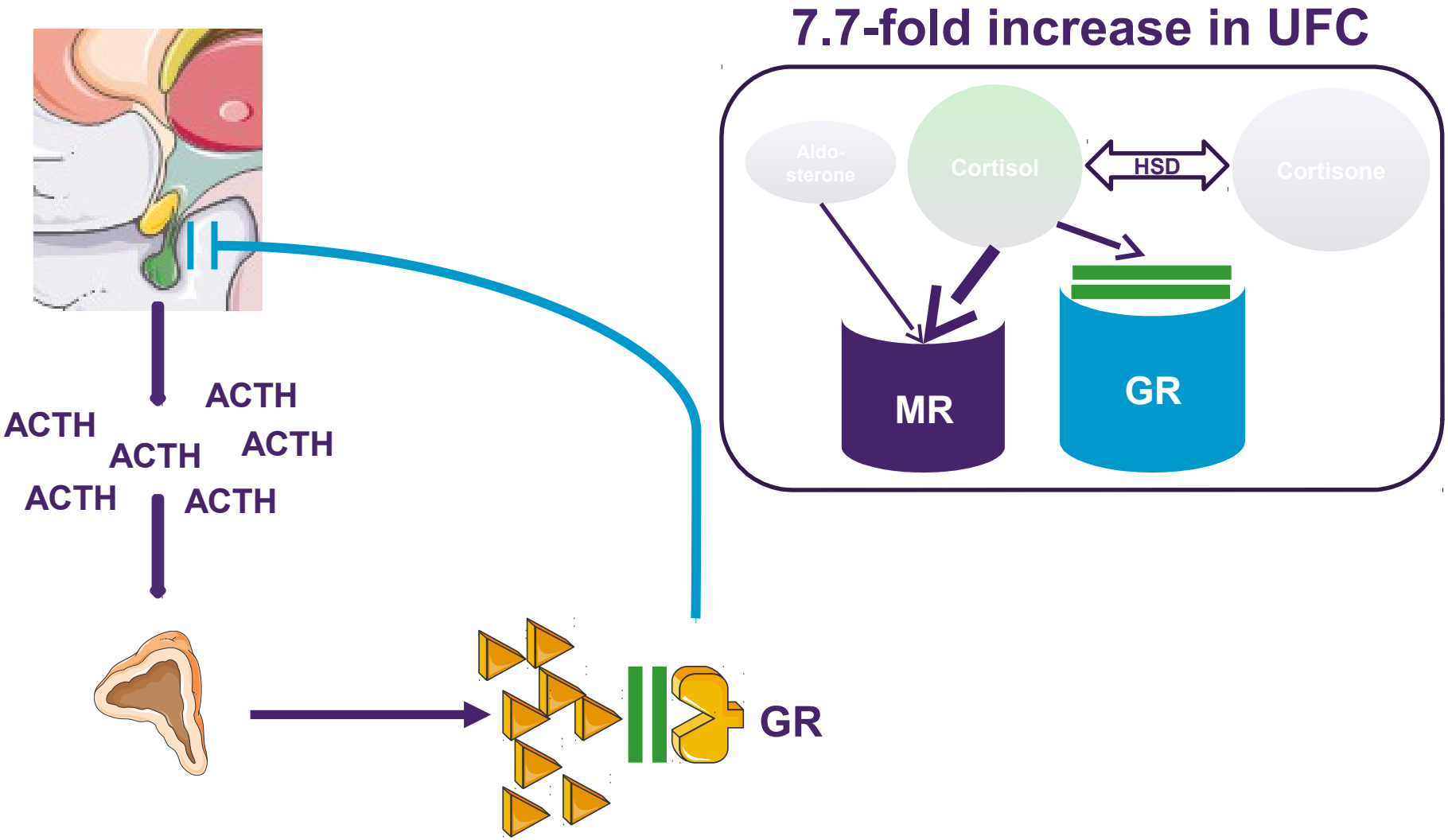
Mifepristone

- Glucocorticoid receptor (GR) antagonist blocks the action of cortisol by binding to the GR-II (cortisol) receptor
- Rare Reports In Cushing's disease (*Castinetti et al, EJE, 2009*)
- In Phase III open study as a treatment for Cushing's syndrome



Fleseriu M *et al. JCEM* 2012

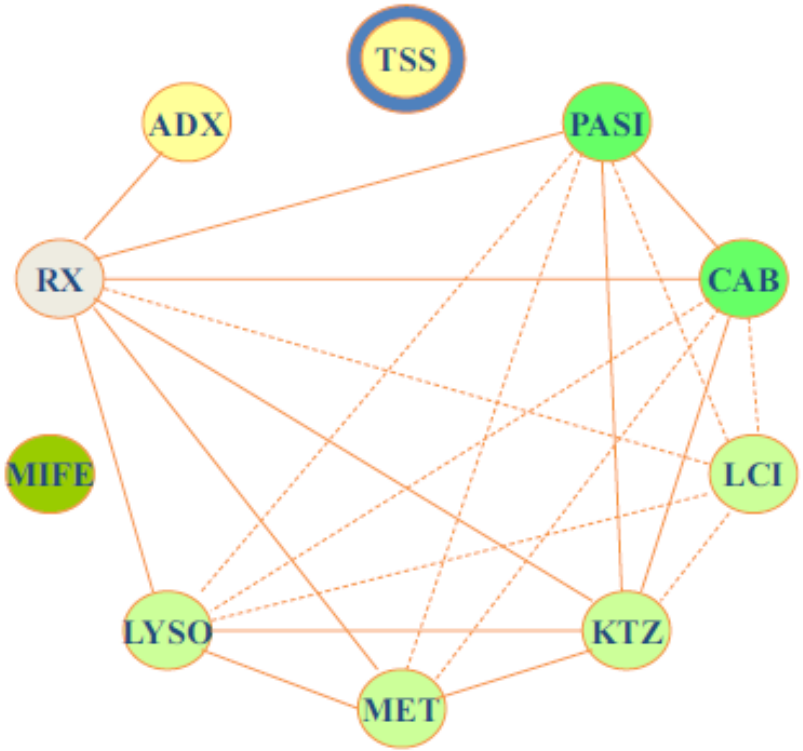
Mechanism of action and consequences of mifepristone therapy



HSD, 11β-hydroxysteroid dehydrogenase;
MR, mineralocorticoid receptor

Medical treatment in Cushing's disease

Which drug ? The impossible algorithm…



Criteria of choice

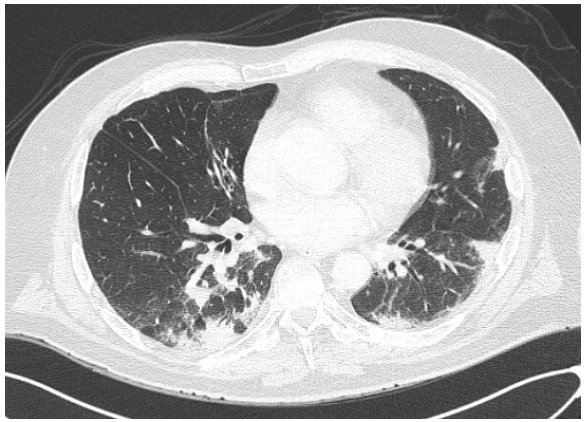
Efficacy
Tolerance
Cost
Individual patient factors
Availability

Cushing sévères
Complications à court terme

✓ **Complications**

- **Métaboliques (hyperglycémie, hypokaliémie)**
- **Infectieuses**
- **Cardiovasculaires (HTA maligne, OAP)**
- **Thrombo-emboliques**
- **Psychiatriques (délire, agitation)**
- **Osseuses (fractures multiples, tassements)**
- **Décubitus (escarres)**
- **Perforations d'organe creux**

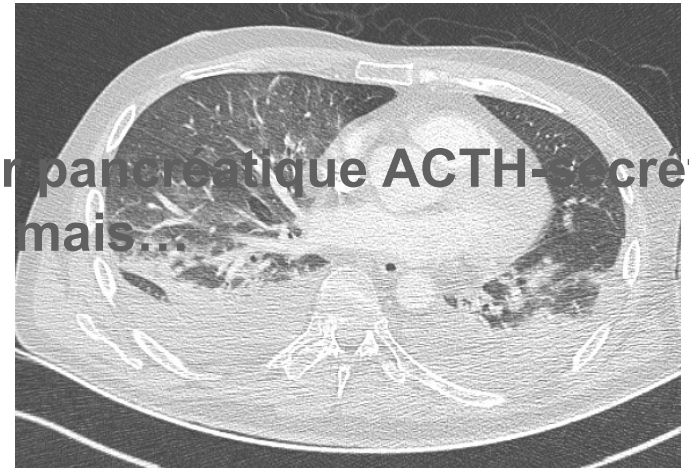
Complications infectieuses

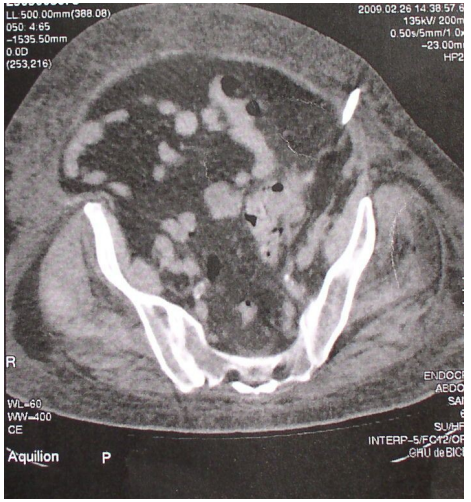


Pneumocytose + Embolie Pulmonaire

Tumeur primitive occulte…

Tumeur pancréatique ACTH-sécrétante
Visible mais…





- **Mauvais pronostic des CPC associés à un Cushing paranéo**

  Nagy-Mignotte H et al. J Thor Oncol 2014

- **Mauvais pronostic des ACC secrétants du cortisol**

  Abiven et al. JCEM 2006

  Berruti et al. Endocr rel Cancer 2005

Cushing grave
Attitude pragmatique

- ✓ **Ne pas perdre de temps à l'enquête étiologique**
  - **Bilan endocrinien de « base »**
  - **Pas de freinage à la Dex….**
  - **Imagerie orientée (TDM AP, IRM hypo)**

- ✓ **Evaluer rapidement les complications et la gravité (réa ?)**

- ✓ **Débuter les traitements symptomatiques**

Cushing grave
Attitude pragmatique

Héparine IV

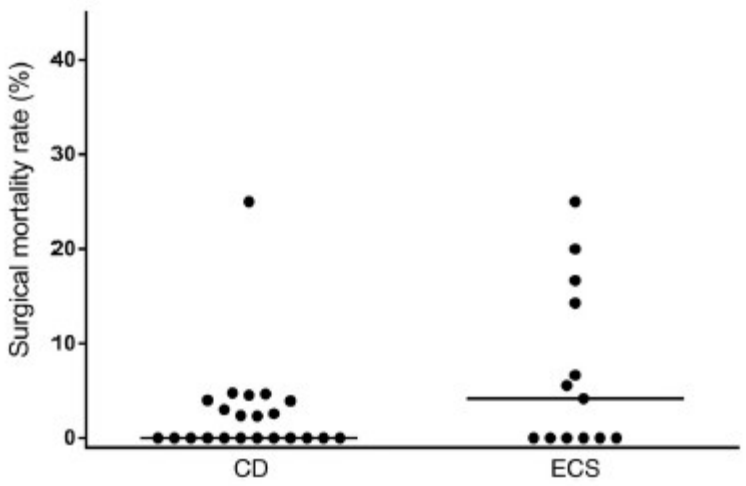
Antibiothérapie IV

Dérivés nitrés IV

Insulinothérapie IV

Soludactone IV

Potassium IV



- ✓ **Mortalité post -opératoire (CV et infections) plus élevée**
- ✓ **Pas de réduction avec voie laparoscopique**

Ritzel et al. JCEM 2013

Dans les séries récentes « positives » les patients ont été préparés par inhibiteurs de la stéroidogénèse

Alberda et al. Surg Endos 2012

Chow et al Clin Endocrinol 2008

Sauvetage des Cushing graves par inhibiteurs de la steroidog

- ✓ **Etude Rétrospective des patients avec Cushing sévère (Clinique + CLU > 5x N)**
- ✓ **14 EAS** (*3 bronchial, 3 pancreatic and 2 thymic carcinoids; 2 metastatic neuroendocrine carcinomas of unknown origin, 2 small-cell lung carcinomas, 1 MTC, and 1 occult tumour)*
- ✓ **8 ACC**
- ✓ **Traitement *de sauvetage* symptomatique par association de metyrapone et ketoconazole**

Sauvetage des Cushing graves par inhibiteurs de la steroidogenese

- ✓ **96% avec HTA sévère, 88% avec hypokaliemie sévère et 75% avec diabete**

- ✓ **60% ont une autre complication severe du Cushing (psy, infection, phlebite ou embolie pulmonaire, fractures, sarcopenie).**

- ✓ **Etude à 1 semaine et 1 mois**
  - **Hormonologie**
  - **End Points Cliniques :**
    - **Pression Artérielle et Traitements**
    - **Glycémie et Traitements**
    - **Kaliémie et Traitements**

Sauvetage des Cushing graves par inhibiteurs de la steroidogenese

Baseline : 40 x ULN

W1 : 3.2 x ULN (50% N)

M1 : 0.5 x ULN (73% N)

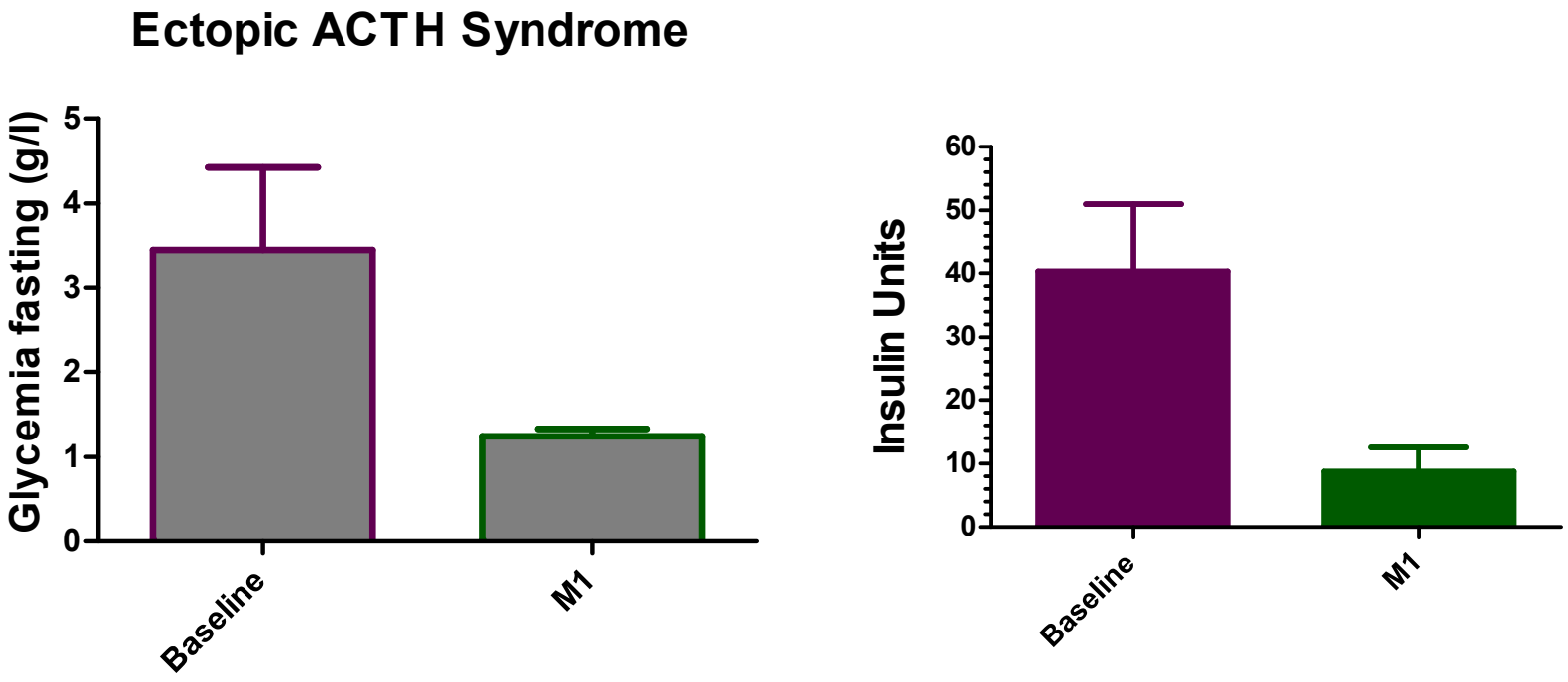
Baseline : 16 x ULN

W1 : 1.0 x ULN (75% N)

M1 : 1.0 x ULN (86% N)

Corcuff et al, EJE 2015

Sauvetage des Cushing graves par inhibiteurs de la steroidogenese



Corcuff et al, EJE 2015

Sauvetage des Cushing graves par inhibiteurs de la steroidogenese

Evolution de la Daily Drug Dosage des traitements
Anti HTA : 2.0 ± 0.3 à 1.0 ± 0.3

Corcuff et al, EJE 2015

Sauvetage des Cushing graves par inhibiteurs de la steroidogenese

Evolution de la supplémentation en K+ : 3.0 à 1.2 g/J
Evolution de la spironolactone : 114 à 69 mg/J

Corcuff et al, EJE 2015

Sauvetage des Cushing graves par inhibiteurs de la steroidogenese

✓ Tolerance

- Elevation des transaminase chez 2 patients necessitant arret du ketoconazole
- 11 patients ont des nausées (grade I ou II)
- Introduction de l'hydrocortisone chez 4 (15%) patients

✓ Adaptation des doses

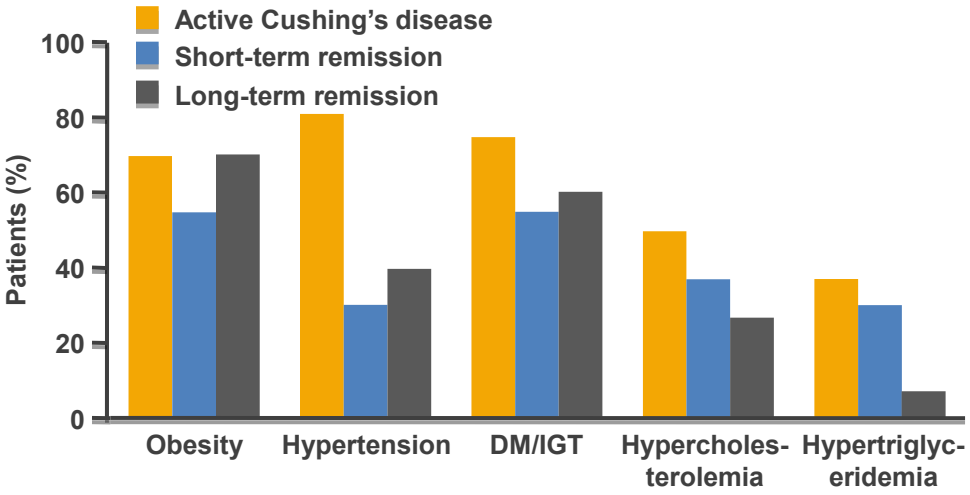
	Metyrap JO (mg)	Metyrap M1 (mg)	Keto JO (mg)	Keto M1 (mg)
EAS	2125	2150	900	800
ACC	1750	2625	1000	1000

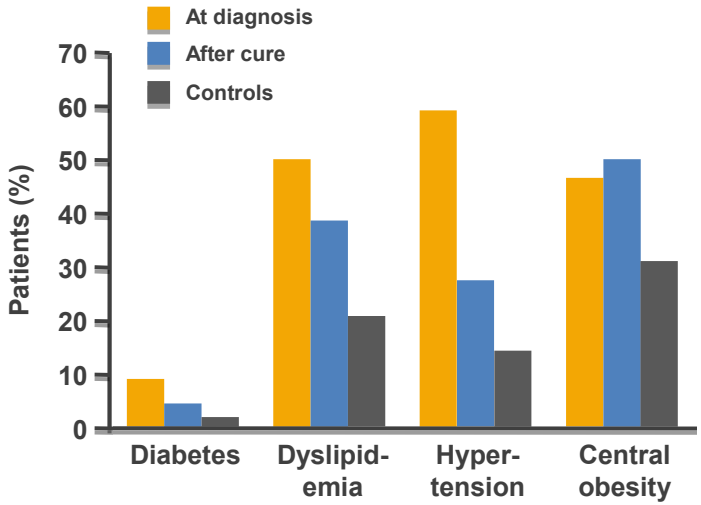
Conclusions

- ✓ **Association d'inhibiteurs de la steroidogénèse**
  - ✓ **Rapidité d'action**
  - ✓ **Efficacité dans > 70% des cas**
  - ✓ **Bonne tolérance**
  - ✓ **Permet de sortir de la « zone rouge » rapidement**
  - ✓ **Renforce le rôle de l'endocrinologue dans la prise en charge pluridisciplinaire carcinologique**

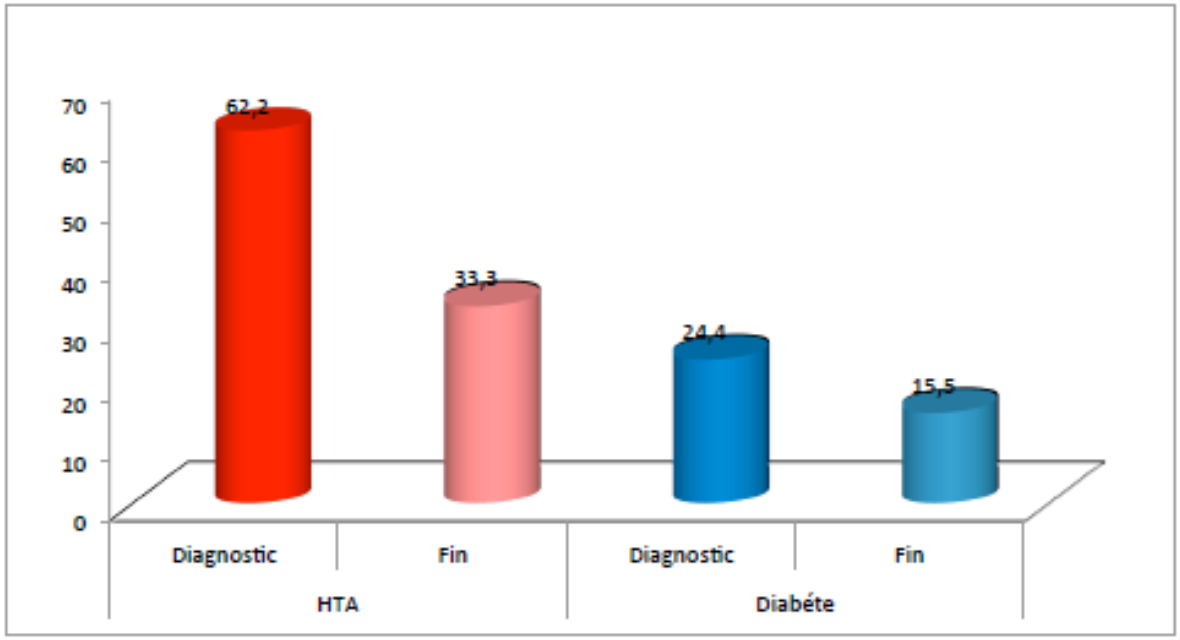
- ✓ **Débuter à 1000 mg ketoconazole + 2000 – 2500 mg metyrapone**
- ✓ **Contrôle Cortisol plasmatique et urinaire avec methode adaptée sous 3 – 5 jours**

Metabolic disease may persist after biochemical cure of hypercortisolism



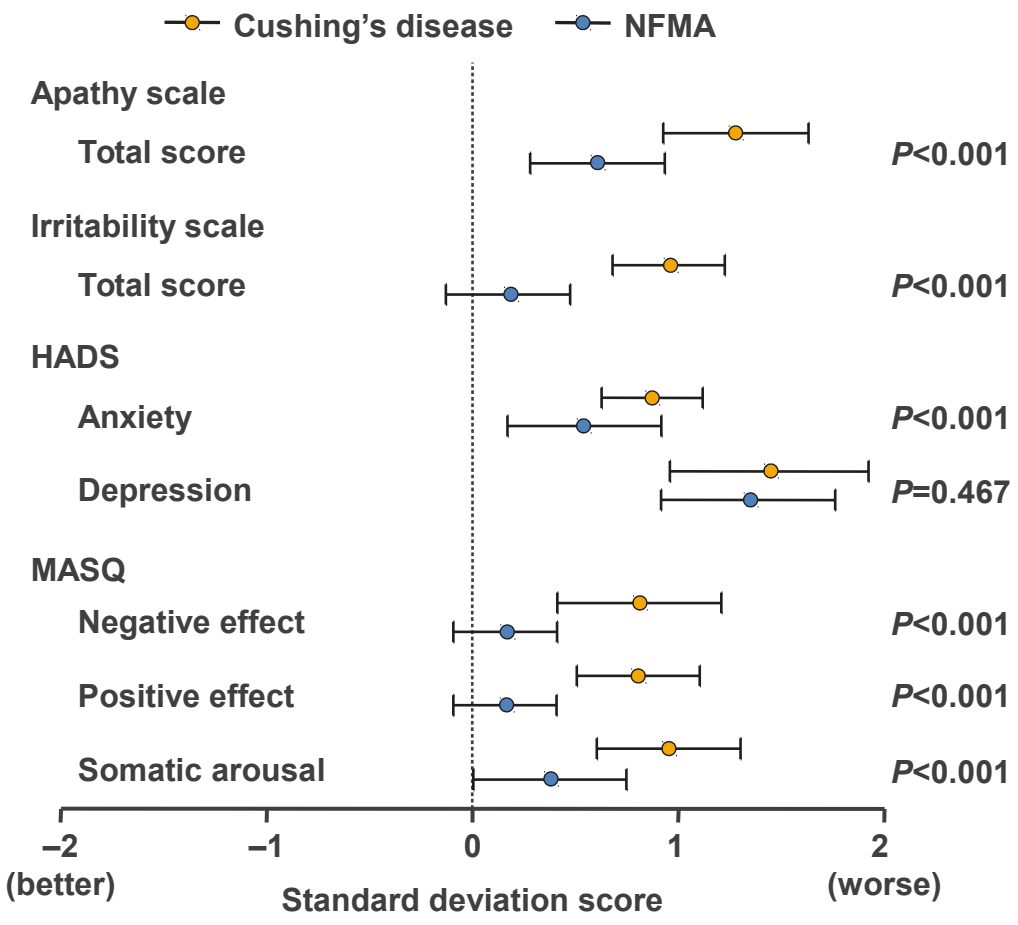


Pivonello R et al. Endocrinol Metab Clin North Am 2005
Barahona MJ et al. Front Horm Res 2010

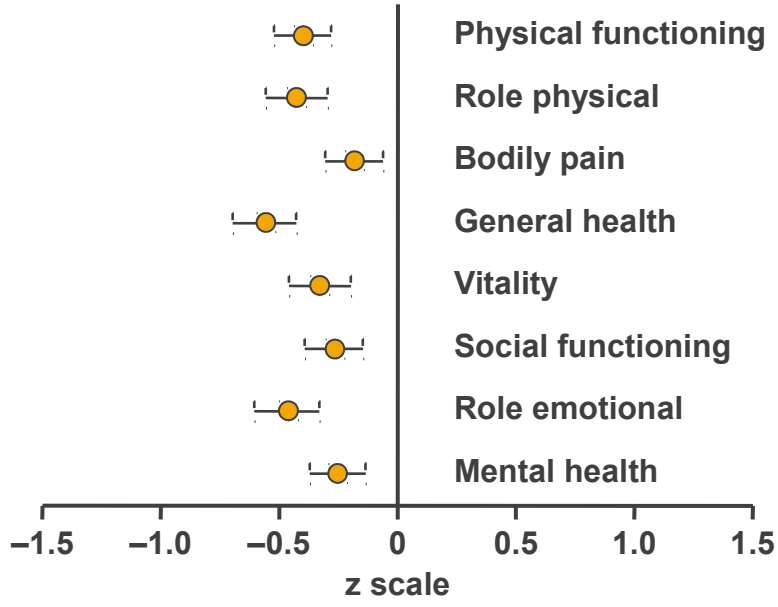


A Prevot – Thèse de Médecine 2013
102 patients avec maladie de Cushing - 2002-2012

After effects of Cushing's disease: Cognition/psychology



From Tiemensma (2011)

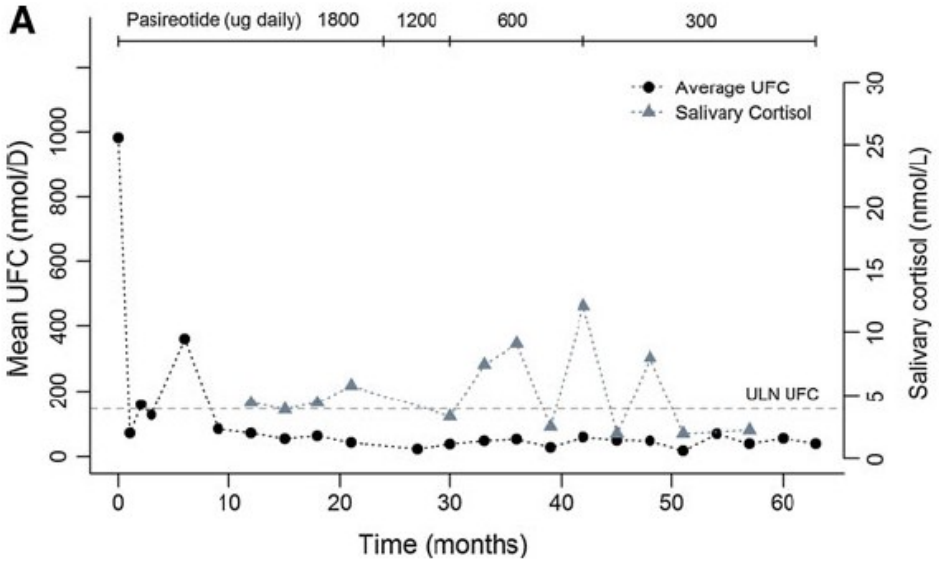


From Lindsay (2006)

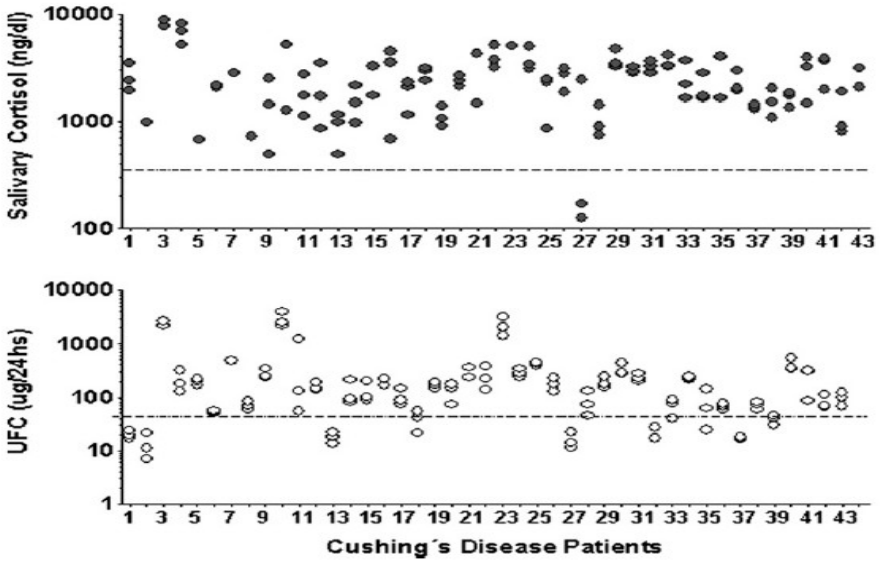
Tiemensma J *et al. J Clin Endocrinol Metab* 2011;96:964–971;
Lindsay JR *et al. J Clin Endocrinol Metab* 2006;91:447–453

Merci pour votre attention

What is “control” of hypercortisolism ?

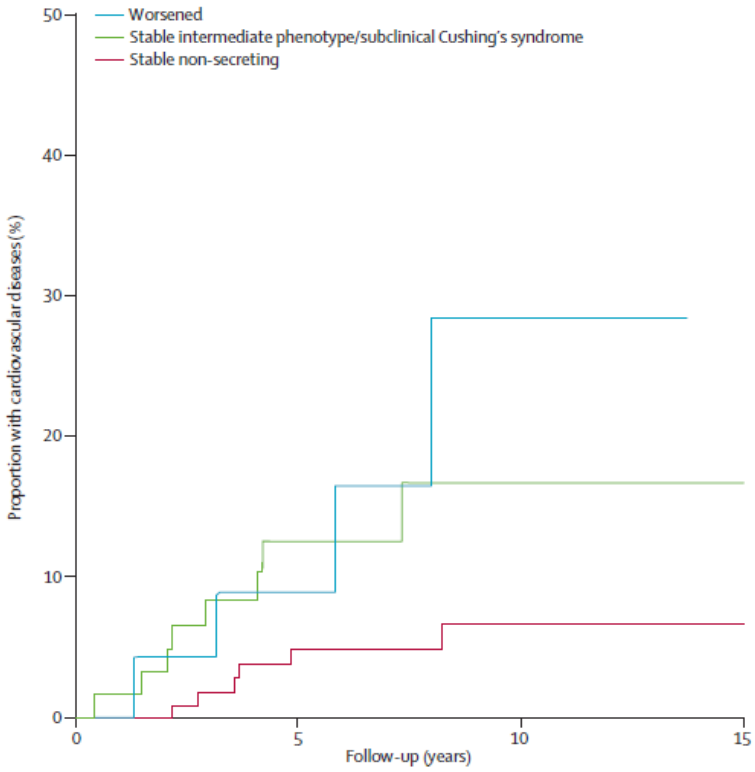


MacKenzie et al. Pituitary 2014

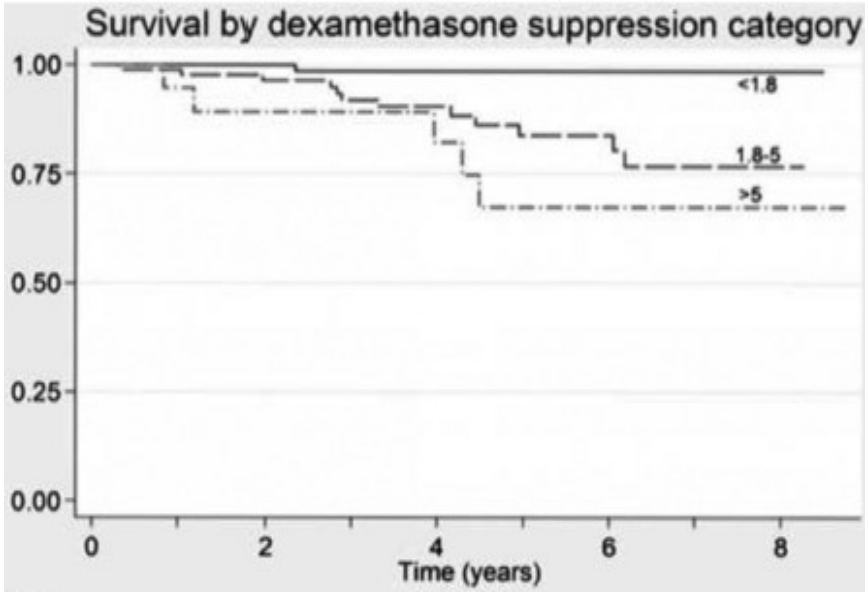


Elias PC et al. JCEM 2014

Consequences of cortisol-secreting incidentalomas



Di Dalmazi et al. Lancet 2014



Debono et al. JCEM 2014

Factors associated with remission

- **Established Factors**
  - **Macroadenoma vs microadenoma**
  - **First *vs* second surgery**
  - **Histological identification of ACTH-secreting adenoma**
- **Suspected Factors**
  - **Experience of the surgeon**
- **Debatable Factors**
  - **Visible adenoma at MRI**

Do patients with non-visible adenomas have lower surgical success rates?

Study	Success rate in patients with visible microadenomas (%)	Success rate in patients with non-visible adenomas (%)
Bochiccio et al. 1995	*87*	*74*
Barrou et al. 1997	*93*	*58*
Rees et al. 2002		
Salenave *et al*. 2		
Testa *et al*. 2007		
Jehle *et al*. 2008		
Sun et al. 2012	86	87
Yamada et al. 2012	*98*	*50*
Swearingen et al. unpublished	95	89

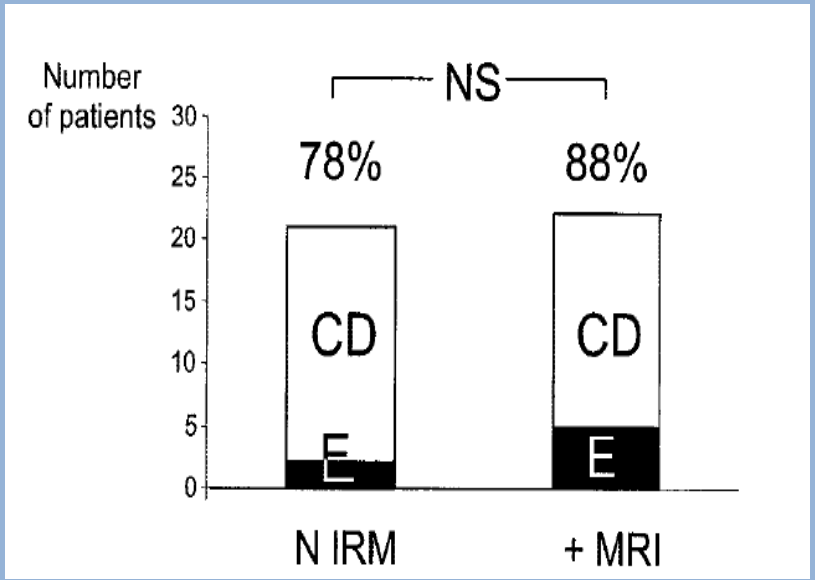
Visible adenomas: 75–100%
Non-visible adenomas: 50–89%

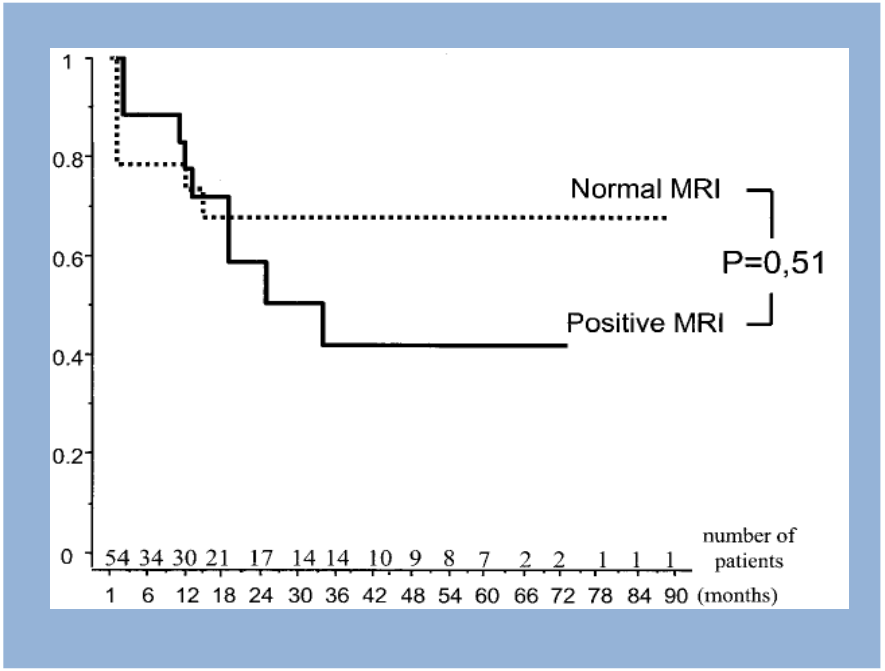
Surgical Strategy in MRI negative patients

- **54 adult patients**
- **All with positive C:P ACTH gradient during IPSS**
- **Similar Surgical Procedure** :
  - Meticulous Exploration
  - Selective adenomectomy when possible
  - Subtotal hypophysectomy if negative exploration

Salenave et al., JCEM 2004

Localising the corticotroph adenoma
MRI vs Surgical Strategy





Early Post-Op evaluation

Last evaluation (median 21 m.)

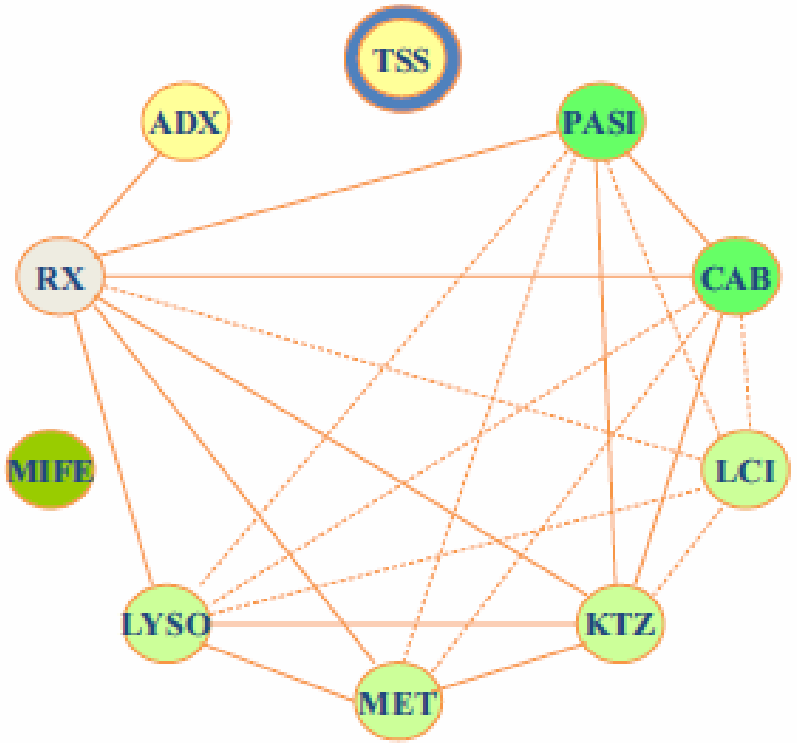
Salenave et al., JCEM 2004

Performance of the Surgeon *vs* MRI

- ✓ **Wind JJ et al. JCEM 2013**
  - 498 patients
  - **Identification of an adenoma in 96% of patients**
- ✓ **Hammer GD et al. JCEM 2004**
  - 289 patients
  - **Identification of an adenoma in 80% of patients**
- ✓ **Hofmann BD et al. J Neurosurg 2008**
  - 496 patients
  - **Identification of an adenoma in 87% of patients**

Treatment	Efficiency	Adverse Effects	Comments
Ketoconazole	Hours - 50%	Severe in < 5% 20% intolerance	Preferred in women over metyrapone
Metyrapone	Hours - 75%	GI Side effects Hirsutism	Spe UFC monitoring Preferred in men over ketoconazole
Mitotane	Slow (6 mo) – 75%	Numerous 30% intolerance	Prolonged chemical adrenalectomy
Pasireotide	Weeks – 25%	Frequent (75%) hyperglycemia	Approved
Cabergoline	Weeks -30% ?	Mild ? Secondary escape	Few data
Mifepristone	Rapid – 40-60 % ?	Numerous	Approved USA Difficulty to monitor
Pituitary RXT	Years - 70%	Hypopituitarism	fractionated vs radiosurgery ?
Bilat Adrenalectomy	Hours > 95%	Life Long steroid s Growth of PA (40%)	Decreased mortality nowadays

The « Cushing Game »



Criteria of Choice :

- Availability
- Rapidity of effects
- Effectiveness
- Sex
- Side effects
- Duration of treatment
- Cost

Bertagna et al. JCEM 2013