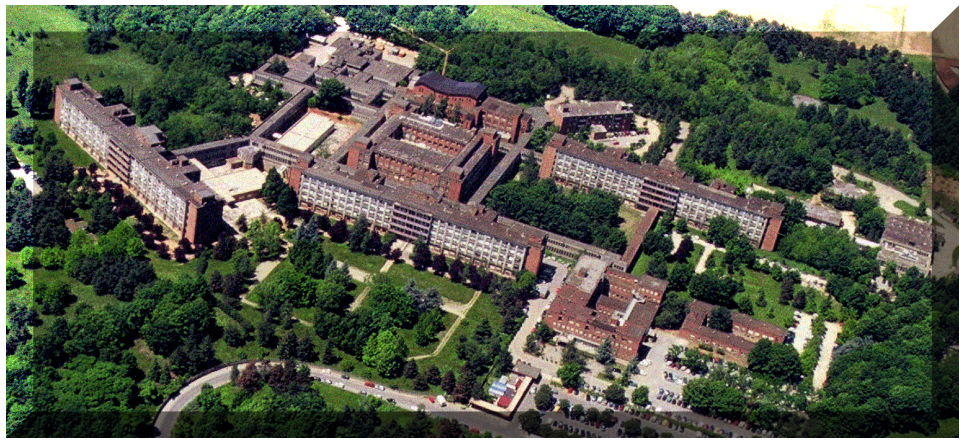
Il Carcinoma Surrenalico

Massimo Terzolo



Medicina Interna I
AOU San Luigi
Orbassano (TO)
Italy

AGENDA

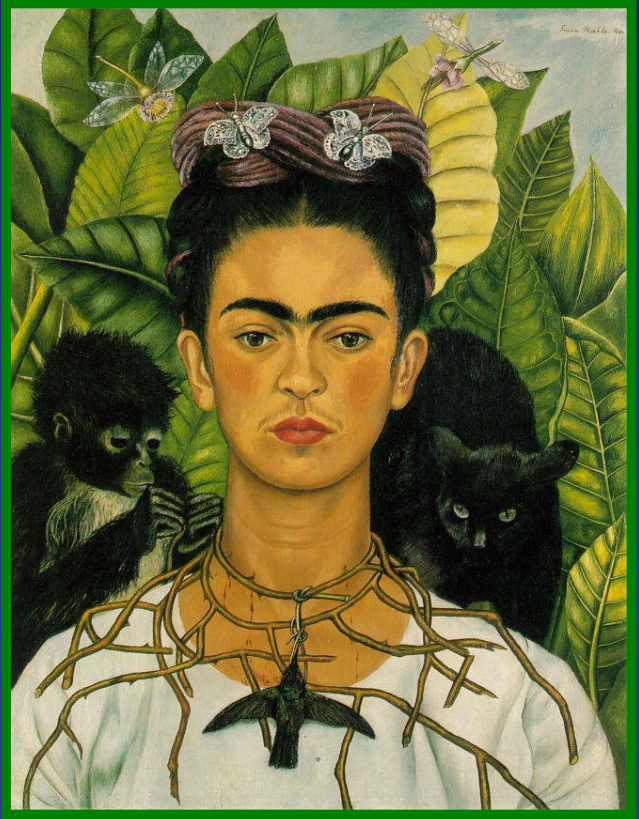
- DIAGNOSIS
- CLINICAL PRESENTATION
- IMPACT ON PROGNOSIS
- TREATMENT

DIAGNOSIS

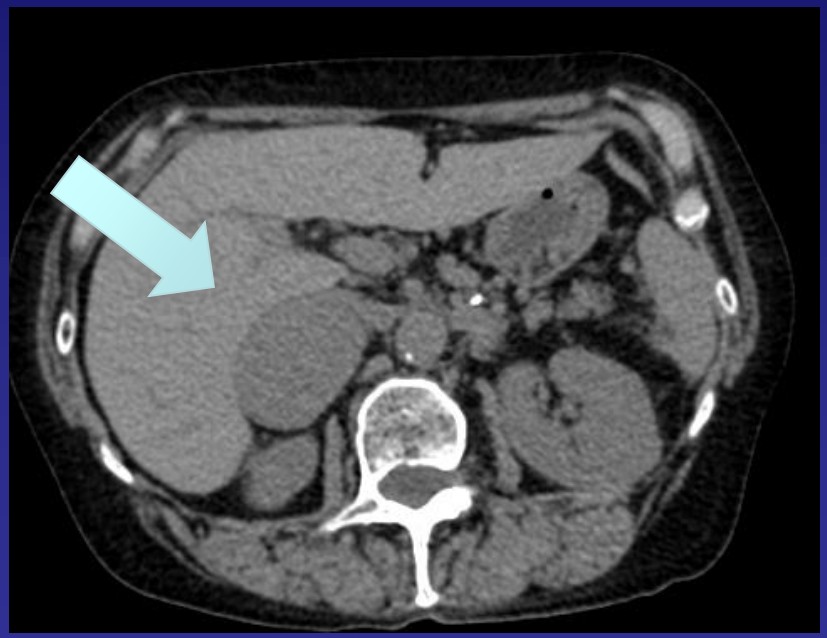
23-yr-old lady

October 2010, gynecologic consultation: amenorrhea, acne, hirsutism (F-G score 16), hair loss, weight gain, and pelvic pain.
FSH & LH 0.1 U/L, PRL 631 U/L, *Androstenedione 8.8 ng/mL*, TSH 0.9 mU/L; pelvic US normal
Diagnosis: PCO, Rx: EP

December 2010
Low-grade fever & nocturnal diaphoresis
Elevated ESR, CRP, WBC and LDH
Hematologic consultation: inflammatory syndrome
FSH & LH 0.1 U/L, PRL 1781 U/L,
Testosterone 6.7 ng/ml
EP continued



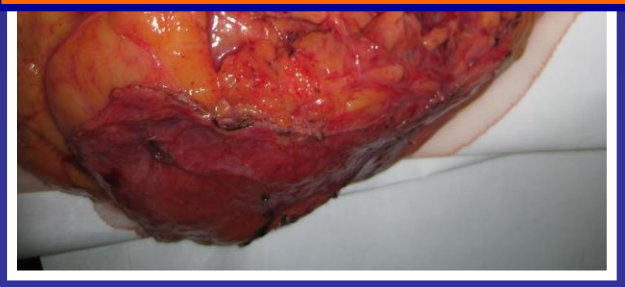
February 2011, endocrinological consultation
FSH 0.33 U/L, LH 0.2 U/L, PRL 18 ng/mL, *17-OHP 12.8 ng/mL*, *Androstenedione >11.4 ng/ml*, *DHEAS >1000 ng/mL*, *Testosterone 6.7 ng/mL*, cortisol 21.9 mcg/dL, ACTH 1 pg/mL,
WB-CT: right adrenal mass of 8 cm



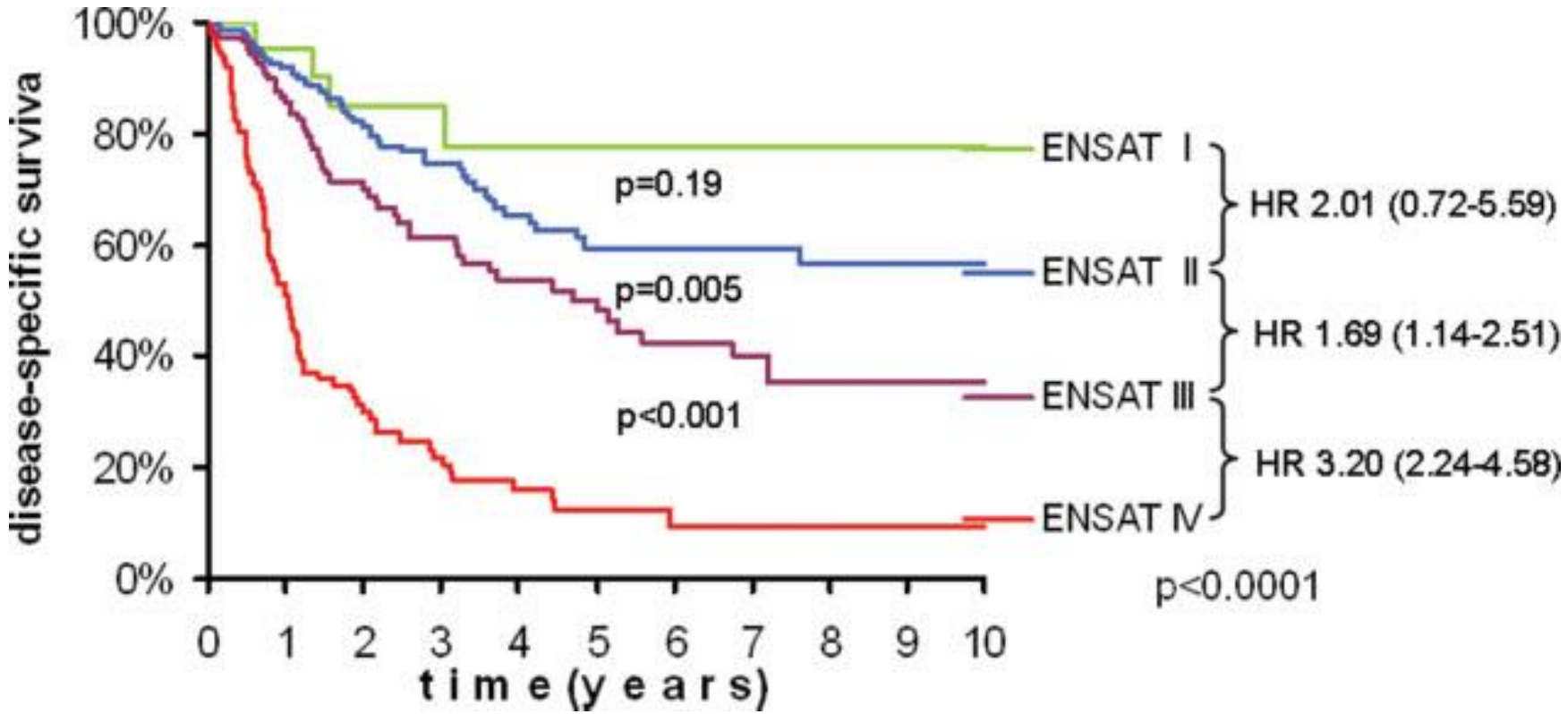
UFC: 568 mcg/24h
1-mg ODST: 35.8 mcg/dl

April 2011, open ADX.
Gross pathology: yellow-brown adrenal mass, size 9 cm, weight 672 g
Histology: Weiss 7, mitosis 14/50 HPF, Ki-67 20%

ACC is an unusual cause of hyperandrogenism and cortisol excess but should be promptly recognized !

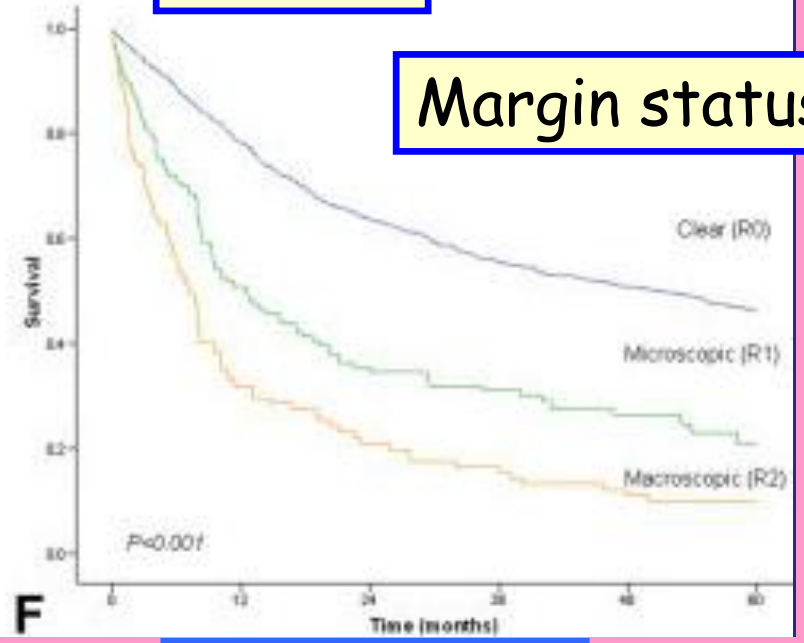


Disease-specific survival stratified according to the new 2008 ENS@T staging classification for ACC on 416 patients. ***Fassnacht et al., 2009***



n = 3482

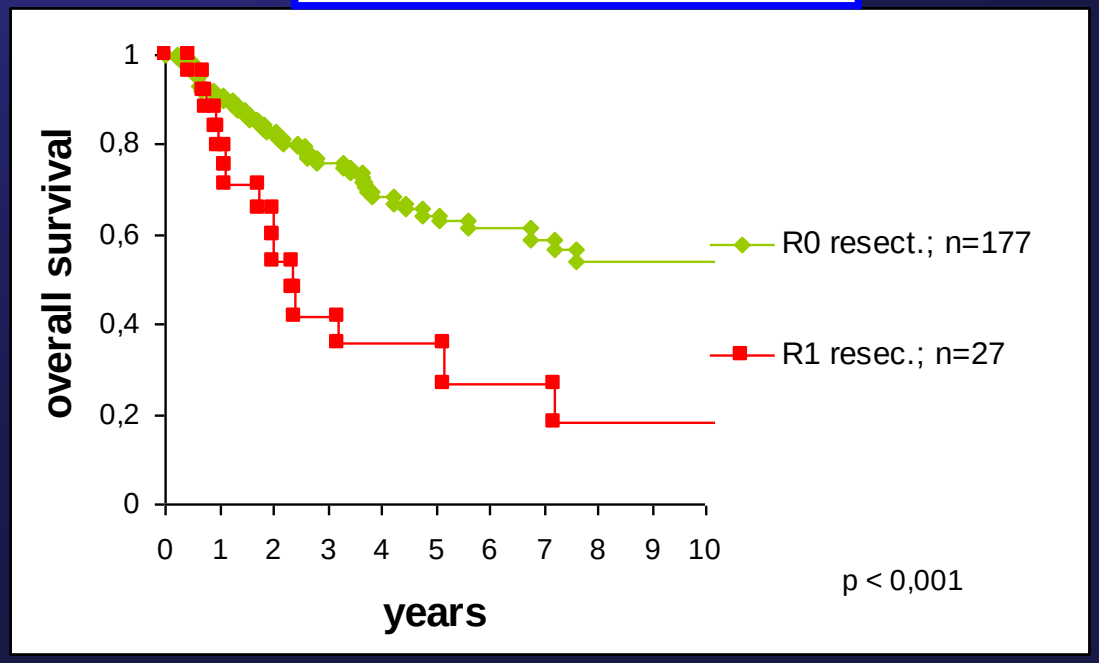
Margin status



Bilmoria et al., 2008

Successful primary surgery has a dominant role on disease-specific survival.

German ACC Registry, 2008



“SUSPICIOUS” CLINICAL FEATURES

- Cushing plus hyperandrogenism or feminization
- “PCO” occurring at unusual ages
- Cushing plus constitutive symptoms
- Cushing plus mass effect
- Rapidly progressive Cushing

TRAPS FOR THE UNWARY

- Missing Cushingoid features in a “PCO”
- Missing to recognize an atypical presentation of Cushing
- Missing to recognize cancer-related symptoms

DIAGNOSTIC APPROACH TO AN ADRENAL MASS

- Is the mass malignant?

- Does the mass have endocrine activity?
  - May prove adrenocortical origin (and exclude pheo!)
  - May suggest malignancy
  - May detect residual tumor or tumor recurrence after surgery
  - Prevent life-threatening adrenal insufficiency after surgery

ASSESSMENT OF SECRETORY ACTIVITY

M. Fassnacht et al, JEI 2004

Relevant endocrine activity is related to tumor size.

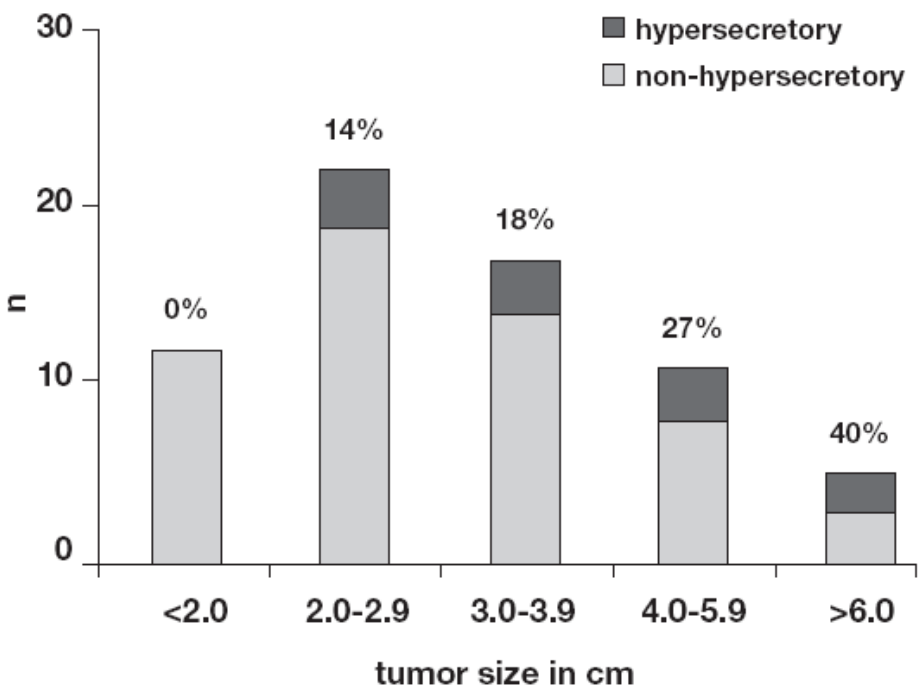


Fig. 1 - *Tumor size and endocrine activity in adrenal incidentalomas. Adapted from (ref. 108).*

- ✓ In general, baseline hormonal evaluation is of limited help in predicting malignancy.
- ✓ In patients with adrenal hypersecretion, a short history and rapid progression of symptoms are suspicious for a malignant tumor.
- ✓ The following hormones are supposed to have some predictive value for the presence of a malignant lesion provided their levels are clearly elevated:

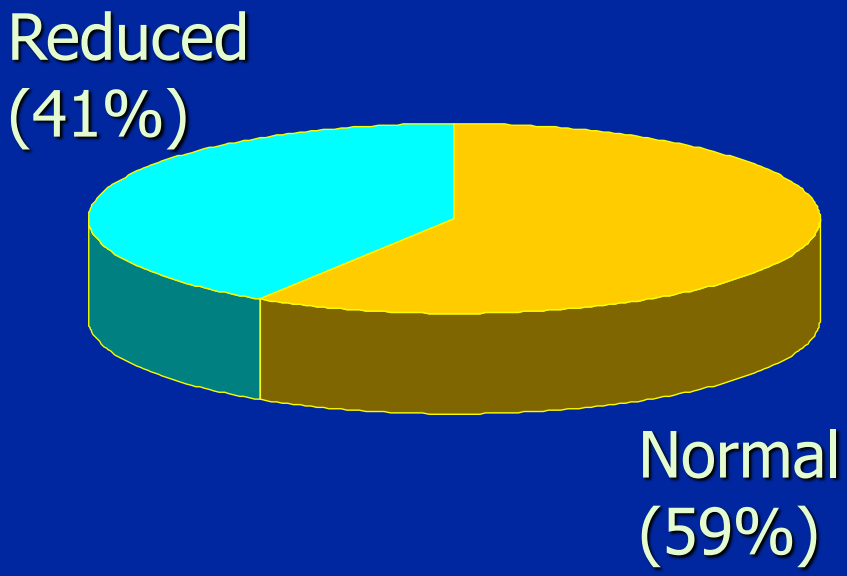
  -serum DHEAS

  -serum estradiol in males or in post-menopausal women

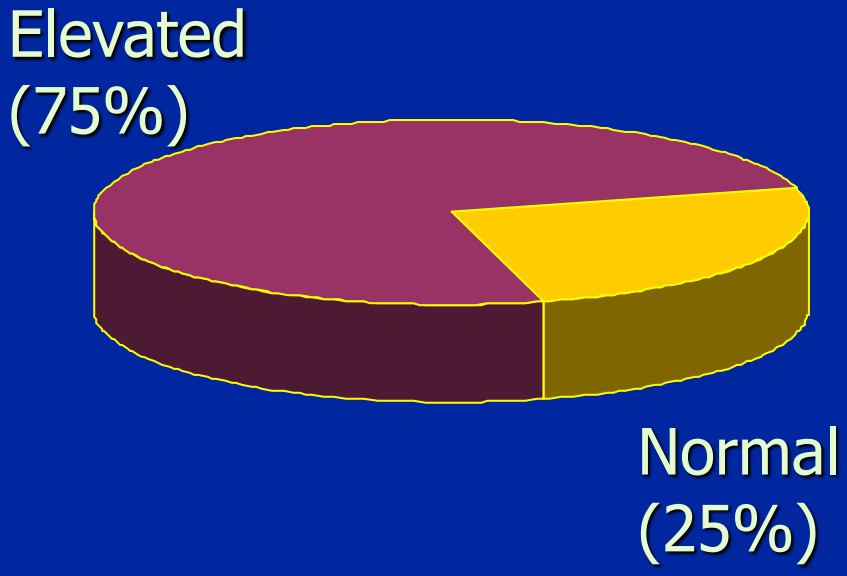
DHEAS and Adrenal Masses

Age	Men (n. 142) *DHEAS (µg/dl)*	Women (n. 214) *DHEAS (µg/dl)*
< 40	106 - 505	70 - 430
40-60	80 - 420	60 - 276
>60	21 - 388	10 - 216

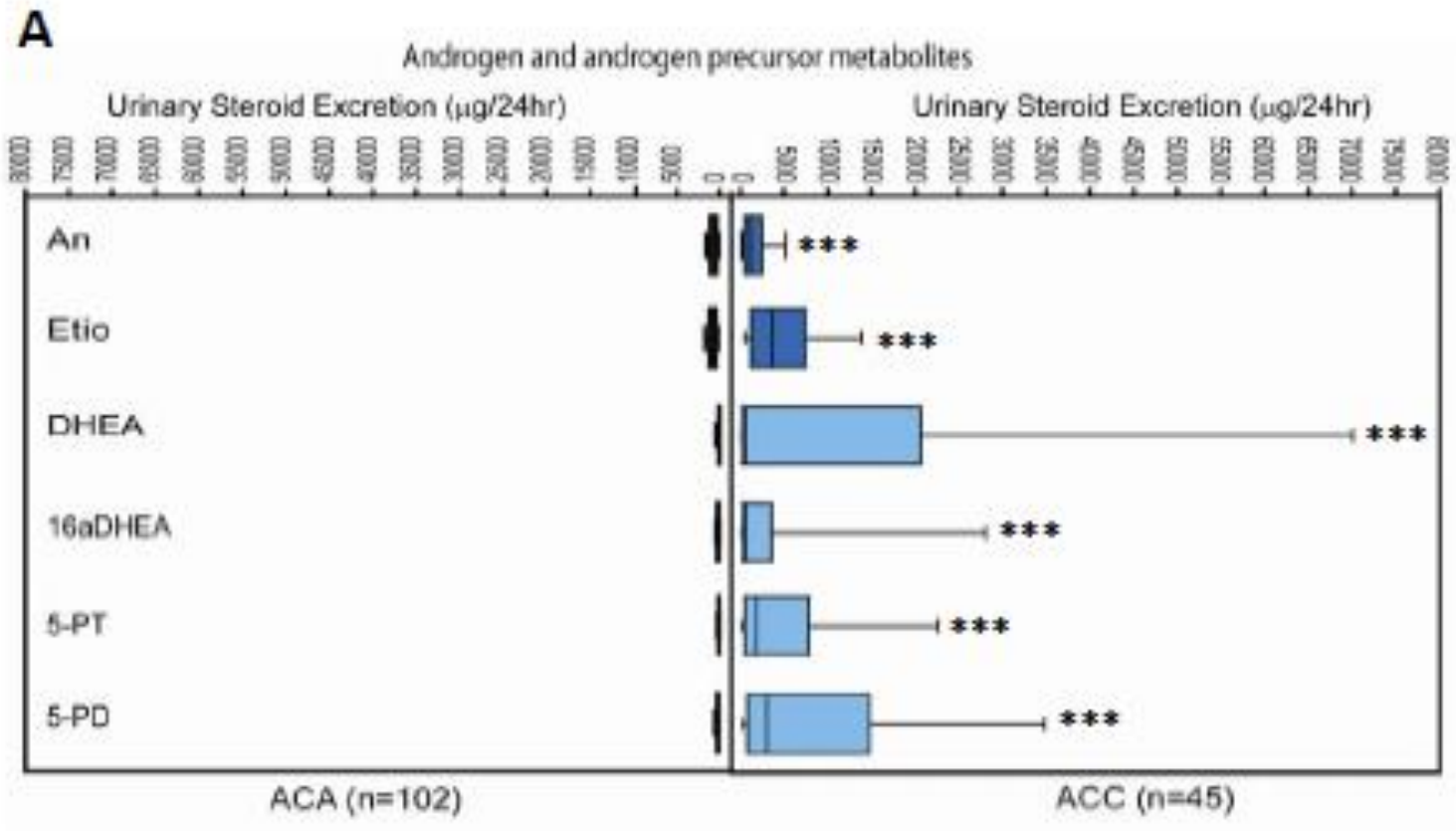
Benign masses



Malignant masses



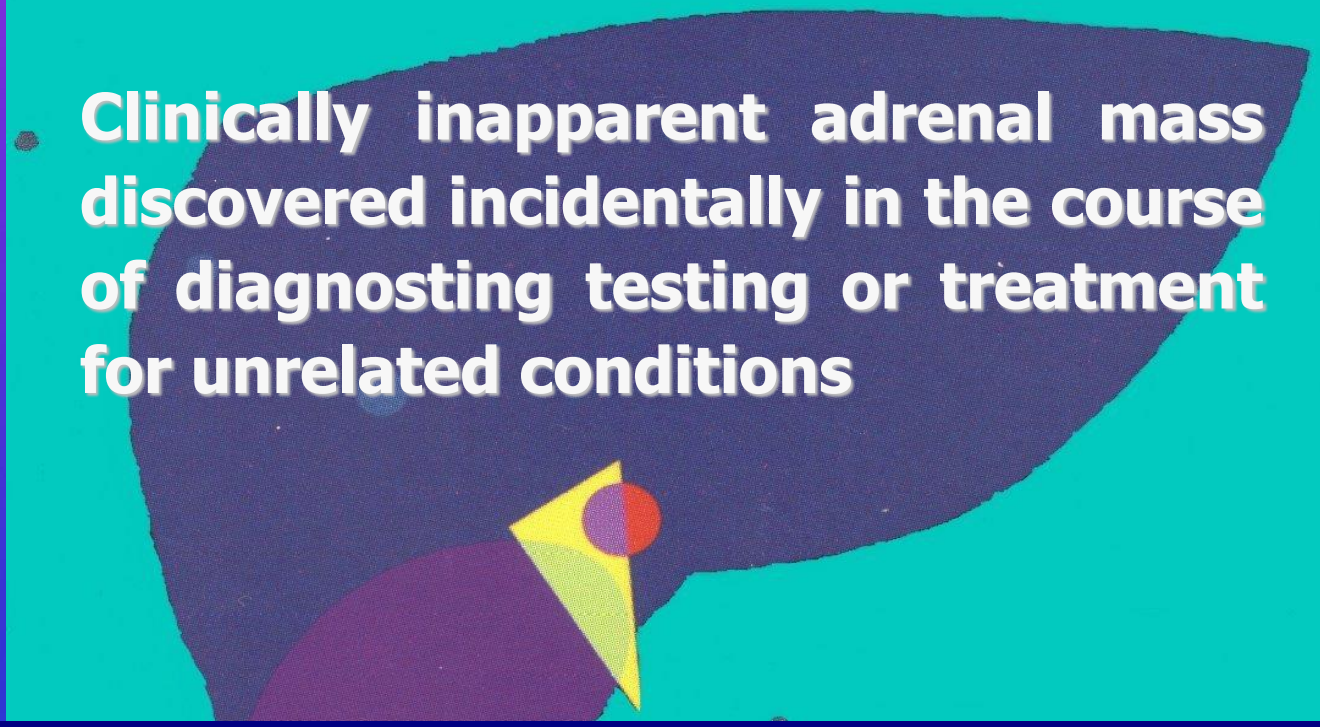
Terzolo et al, EJE 2003



Arlt et al. 2011

INCIDENTALOMA

- Clinically inapparent adrenal mass discovered incidentally in the course of diagnosting testing or treatment for unrelated conditions

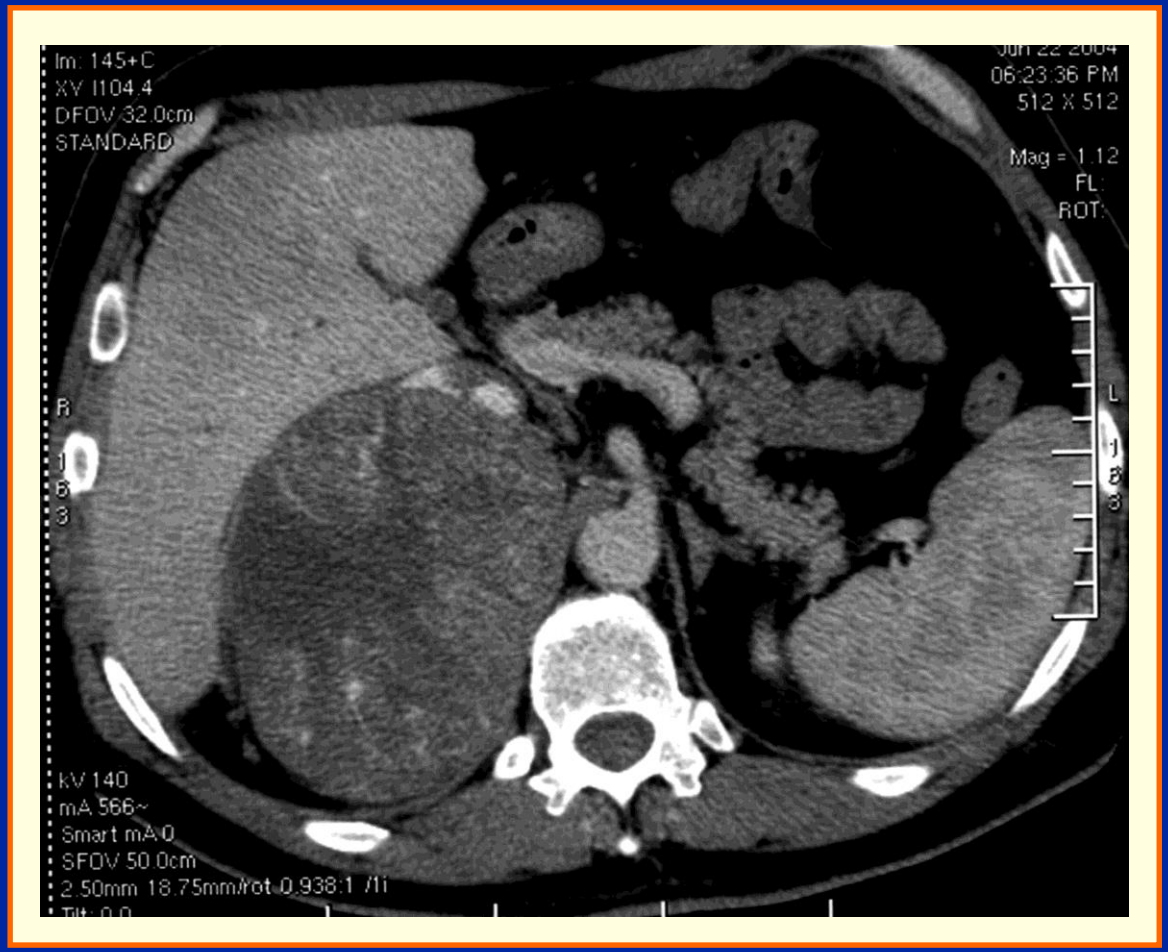


Adrenal-Incidentaloma-Detected-Serendipitously: the new endocrine epidemic.

***Griffing JCE&M* 1994**

IMAGING

COMPUTED TOMOGRAPHY



A thin-collimation CT is the imaging method of choice for adrenal masses and for differentiation of benign from malignant lesions

RECOMMENDED HORMONAL WORK-UP IN PATIENTS WITH SUSPECTED ACC

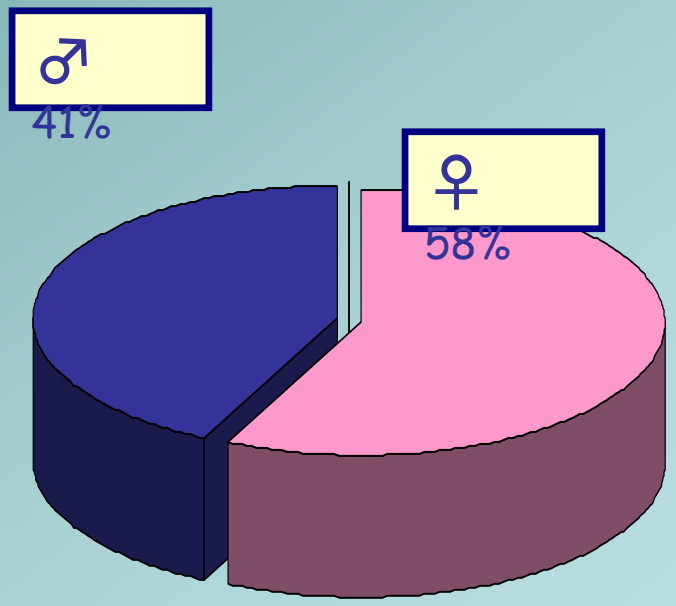
Glucocorticoid excess (minimum 3 out of 4 tests)	• 1 mg DST • 24 hour UFC • basal serum cortisol • basal plasma ACTH
Sexual steroids and steroid precursors	•Serum DHEA-S •Serum 17-OHP •Serum androstenedione •Serum testosterone •Serum 17-beta-estradiol (only in men and postmenopausal women)
Mineralocorticoid excess	•Serum potassium •Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalemia)
Exclusion of a pheochromocytoma	24 hour urinary catecholamines or fractionated metanephrines Plasma meta- and normetanephrines

CLINICAL PRESENTATION

SAN LUIGI SERIES 246 PATIENTS FROM 1995 TO 2011

MEDIAN AGE AT DIAGNOSIS: 45, 5-73 yrs

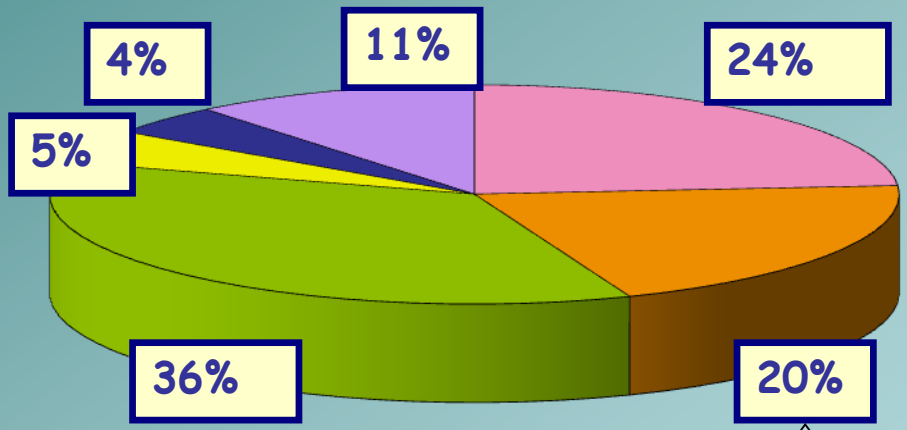
143 F, M 103



MEDIAN ACC SIZE: 11, 2-25 cm
MEDIAN WEISS SCORE: 6, 3-9
MEDIAN Ki67% VALUE: 20, 1-87

24% WERE ADRENAL INCIDENTALOMAS

COCHIN SERIES, 202 patients



NON FUNCTIONING (48), 24%

OTHER SECRETIONS (9), 4%

VIRILIZATION (10), 5%

CUSHING and VIRILIZATION (72), 36%

CUSHING (41), 20%

CUSHING and OTHERS STEROID (22), 11%

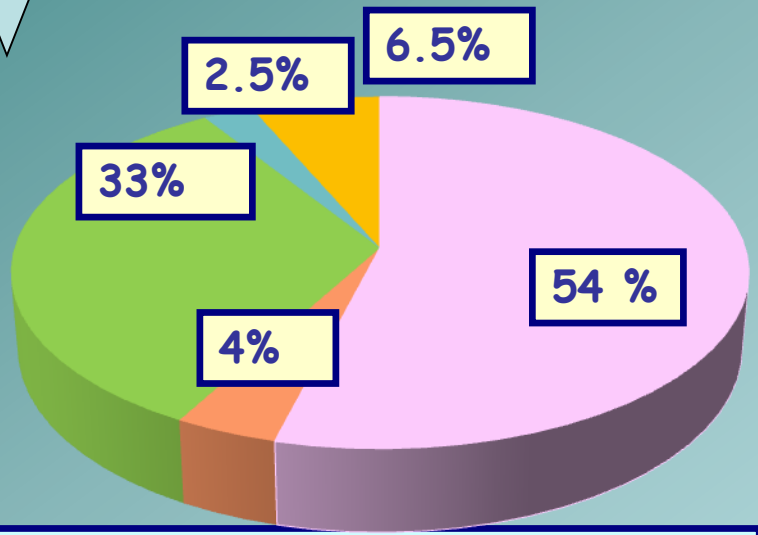
CUSHING ± VIRILIZATION (82), 33%

ESTROGEN (4), 2.5%

VIRILIZATION (16), 6.5%

NON FUNCTIONING (133), 54%

ALDOSTERONE (11), 4%



SAN LUIGI SERIES 246 patients

Impact on prognosis

Clinical and Biological Features in the Prognosis of Adrenocortical Cancer: Poor Outcome of Cortisol-Secreting Tumors in a Series of 202 Consecutive Patients

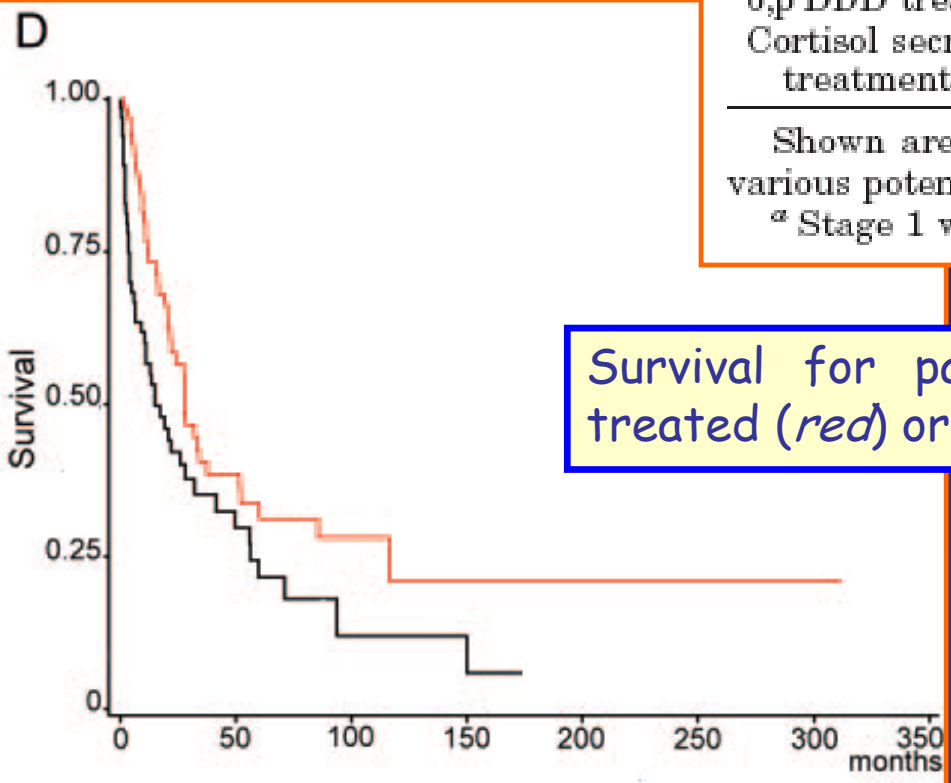
Gwenaelle Abiven, Joel Coste, Lionel Groussin, Philippe Anract, Frédérique Tissier, Paul Legmann, Bertrand Dousset, Xavier Bertagna, and Jérôme Bertherat

TABLE 4. Final prognostic model

	HR	95% CI of HR	*P*
Age	1.03	1.02–1.05	<0.0001
Stage 2[a]	1.93	0.85–4.39	0.12
Stage 3[a]	4.42	1.91–10.22	0.0005
Stage 4[a]	7.93	3.36–18.72	<0.0001
Cortisol secretion	3.94	2.22–6.99	<0.0001
o,p'DDD treatment	1.29	0.60–2.78	0.51
Cortisol secretion × o,p'DDD treatment interaction	0.40	0.17–0.95	0.04

Shown are the results of a multivariate analysis of survival for various potential prognostic factors. CI, Confidence interval.

[a] Stage 1 was taken as the reference category.



Survival for patients with cortisol-secreting ACC treated (*red*) or not treated (*black*) with o,p'DDD (D)

Abiven et al., 2006

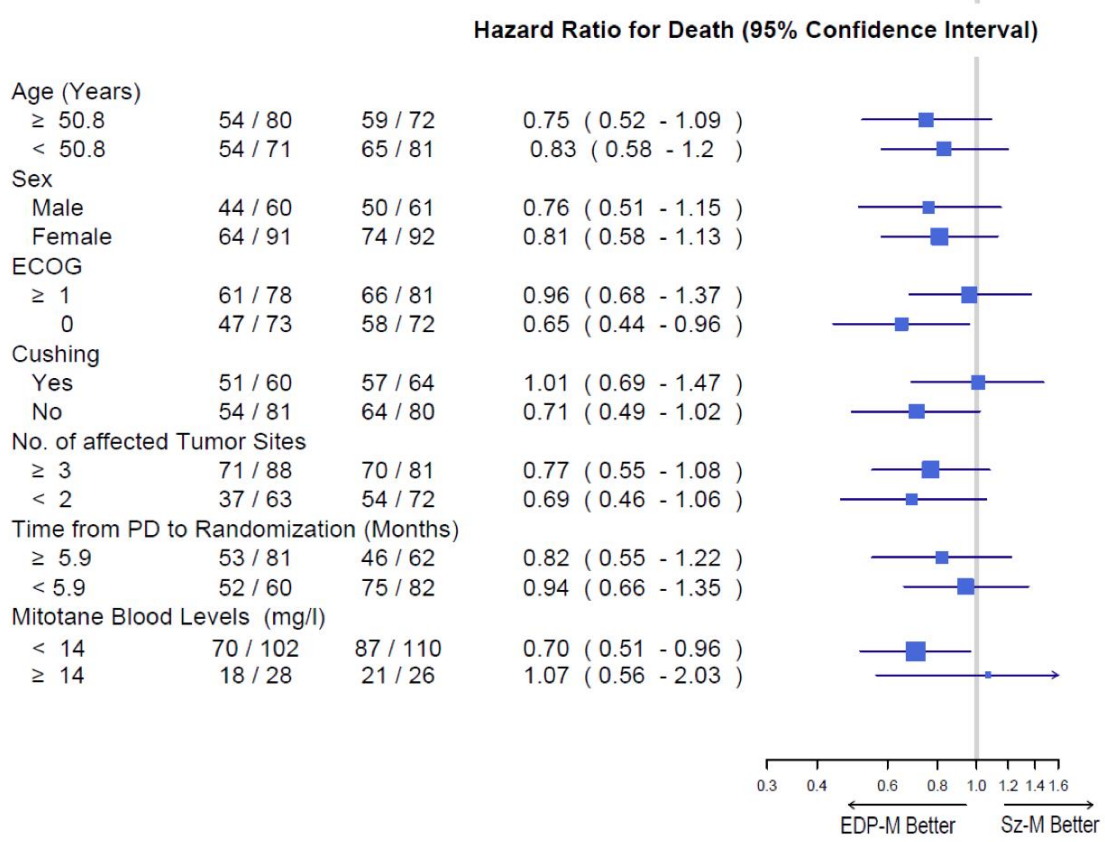
INDEPENDENT PROGNOSTIC FACTORS

Variables	Overall survival		
	Hazard Risk	95% Coefficient Interval	*P*
DFS (⩽2y vz >2y)	0.300	0.124–0.729	< 0.02
Multiple disease sites vz 1 site	1.767	0.907–3.443	= 0.09
PS (0 vz 1 vz 2–3)	1.228	0.800–1.885	= 0.35
Functional status (Cortisol ± androgens vz non functioning vz androgen)	0.641	0.422–0.973	< 0.04

Berruti et al., 2005

FIRM-ACT

B



Supplementary Figure S1. **Forest Plot of the Treatment Effect on Progression-free (A) and Overall Survival (B).**
The sizes of the squares are proportional to the number of events in each subgroup. Horizontal lines represent 95% confidence intervals. The position of the square represents the point estimate of the treatment effect. The cutoff for the variables age, ECOG, time from PD to randomization was chosen to target the median value. The mitotane blood level cutoff of 14 mg/l is based on previous publications.[8,9,24]
PD denotes primary diagnosis.

Table 3. Prognostic Factors for Overall Survival, According to Univariate and Multivariate Analyses.

Variable	Univariate Analysis			Multivariate Analysis*		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age†	0.98	0.96–1.00	0.05	0.98	0.96–1.00	0.02
Sex‡	0.90	0.55–1.47	0.68	0.78	0.46–1.33	0.36
Tumor stage			0.26			0.29
I	1			1		
II	3.81	0.93–15.68		3.68	0.90–15.23	
III	4.47	1.03–19.86		4.22	0.97–18.43	
IV	3.54	0.65–19.85		4.40	0.79–24.58	
Secreting tumor§	1.32	0.78–2.24	0.30			
Weiss score¶	1.04	0.57–1.89	0.89			
Study group						
Mitotane group	1		0.05	1		0.03
Control group 1	2.28	1.17–4.46		2.47	1.26–4.85	
Control group 2	1.73	0.89–3.39		1.96	1.00–3.87	

Terzolo et al., 2007

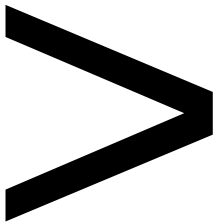
Retrospective study on 524 patients who underwent R0 surgery

No association between cortisol secretion and sex

No association between cortisol secretion and stage

Inverse relationship between cortisol secretion and age

SEX		
	female	321 (61.2%)
	male	203 (38.7%)
STAGE		
	1-2	336 (64.1%)
	3-4	188 (35.9%)
SECRETORY STATUS		
No secretion		247 (47.1%)
Cortisol		150 (28.7%)
Cortisol and androgens		43 (8.3%)
Cortisol and mineralocorticoids		4 (0.8%)
Cortisol and estrogen		2 (0.4%)
Cortisol and androgen and mineralocorticoids		3 (0.6%)
Mineralocorticoids		7 (1.3%)
Androgens		58 (11.1%)
Estrogens		9 (1.7%)



38.6%

Cortisol secretion is associated with a worse pronosis

Multivariate analysis on 524 patients

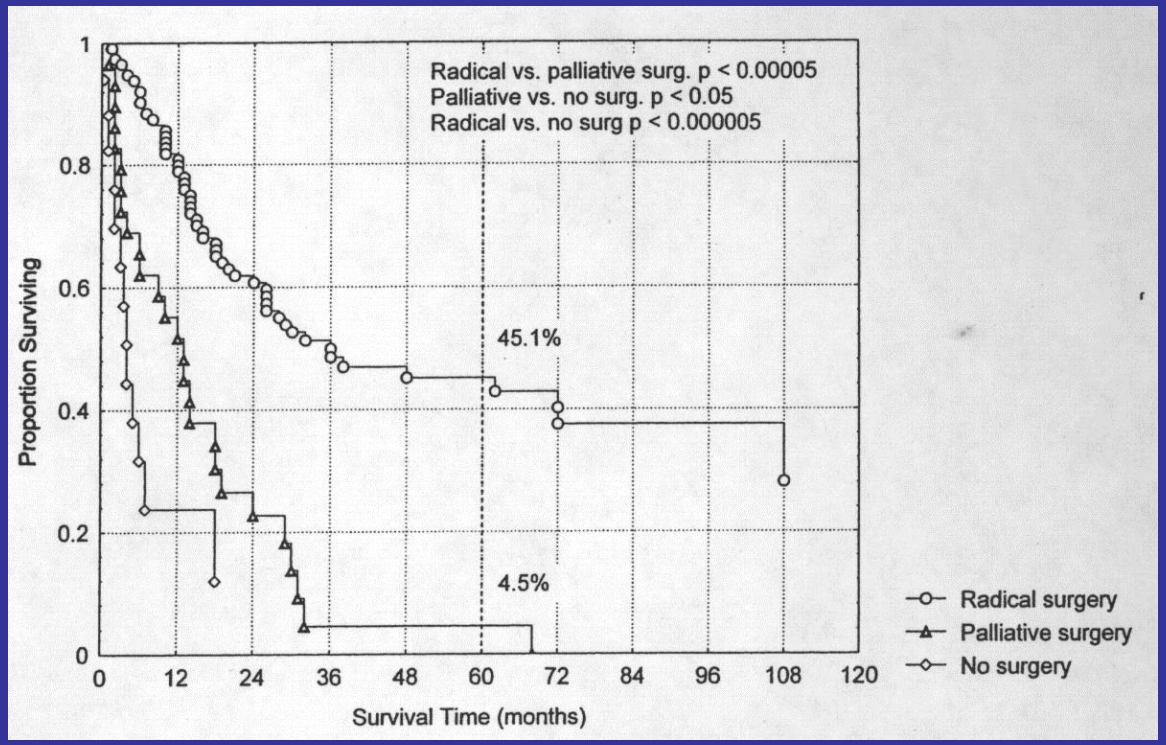
No. 524	DISEASE FREE SURVIVAL			OVERALL SURVIVAL		
	HR	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
Cortisol secretion	1,274	1,022-1,589	0,031	1,426	1,075-1,891	0,014
Sex	0,990	0,794-1,233	0,926	1,261	0,954-1,666	0,104
Age	1,076	0,941-1,231	0,283	1,203	1,016-1,426	0,032
Stage	1,356	1,184-1,553	0,000	1,791	1,506-2,128	0,000

TREATMENT

Benefit of tumor debulking when complete surgical excision is impossible

Tumor debulking may help to control hormone hypersecretion and in individual cases may increase the efficacy of subsequent therapies (*Allolio et al., 2003*).

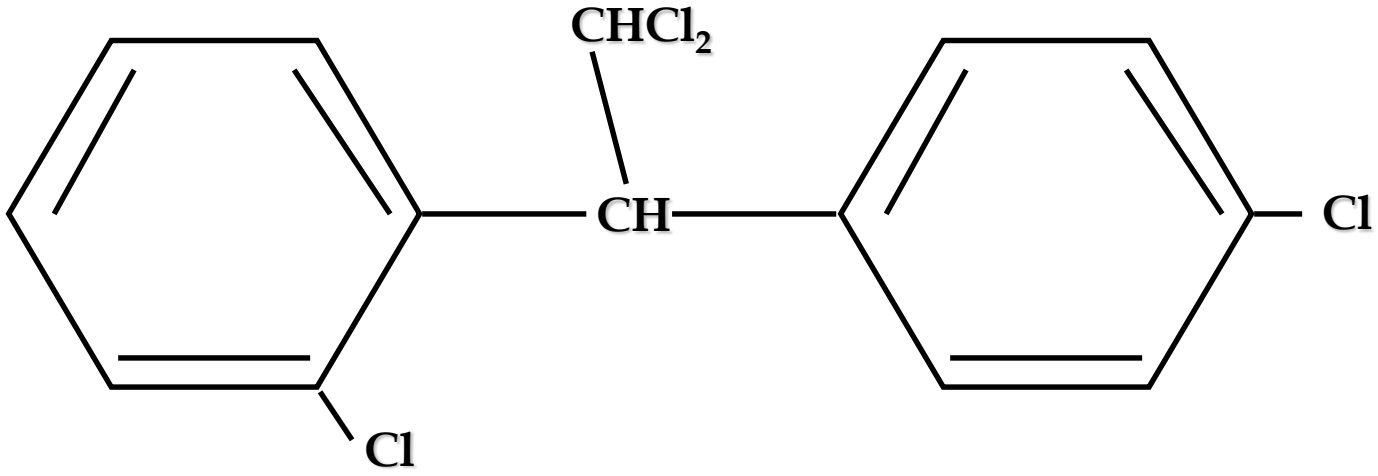
Extensive surgery carries the risk to accelerate cancer dissemination post-operatively (*Icard et al., 1997*).

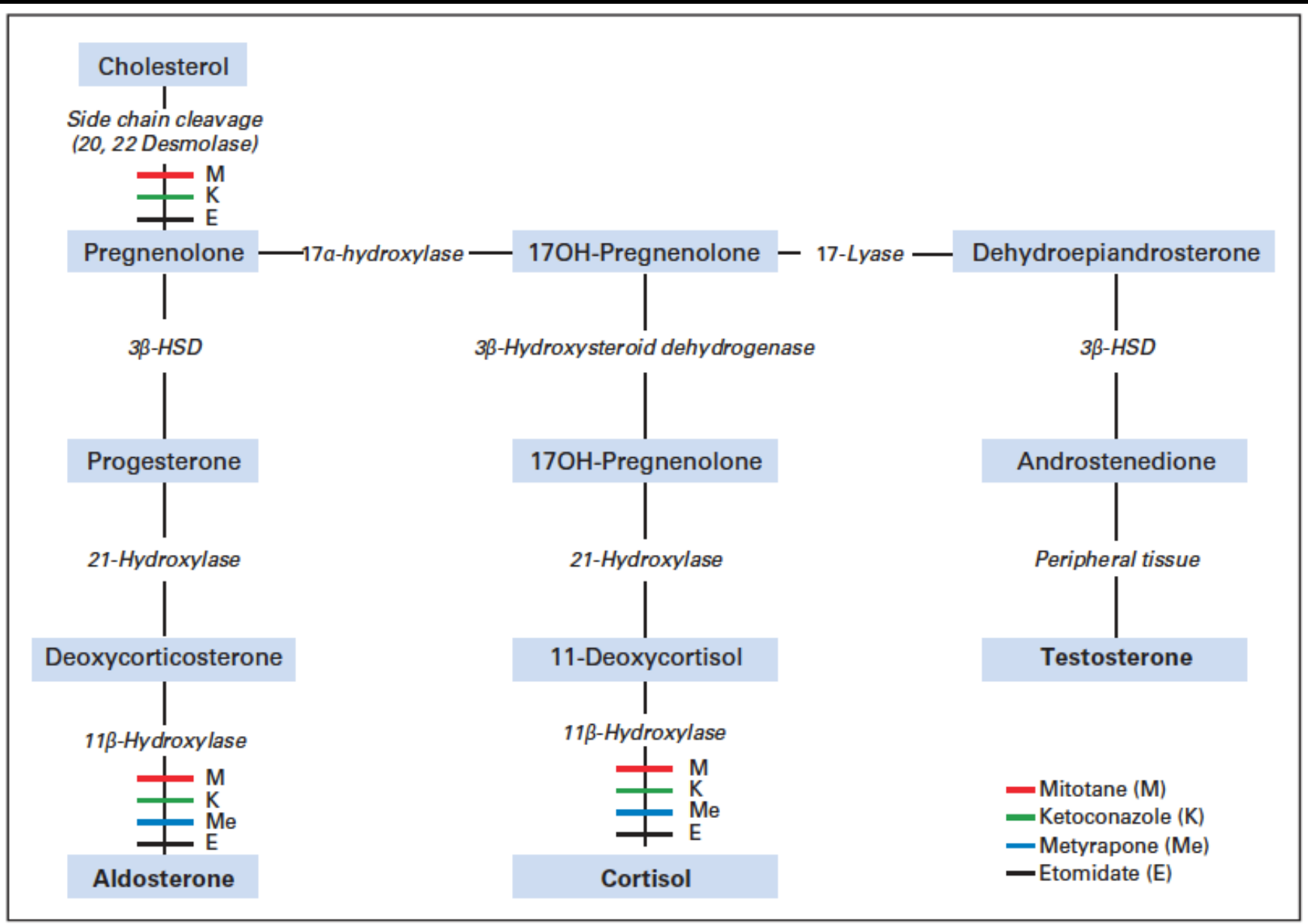


Bellantone et al., 1997

MITOTANE

1,1 - dicloro - 2 - (o - clorofenil) - 2 - (p - clorofenil) - etano




Cholesterol
Side chain cleavage
(20, 22 Desmolase)
M
K
E
Pregnenolone
17α-hydroxylase
17OH-Pregnenolone
17-Lyase
Dehydroepiandrosterone
3β-HSD
3β-Hydroxysteroid dehydrogenase
3β-HSD
Progesterone
17OH-Pregnenolone
Androstenedione
21-Hydroxylase
21-Hydroxylase
Peripheral tissue
Deoxycorticosterone
11-Deoxycortisol
Testosterone
11β-Hydroxylase
11β-Hydroxylase
M
K
Me
E
M
K
Me
E
Aldosterone
Cortisol
Mitotane (M)
Ketoconazole (K)
Metyrapone (Me)
Etomidate (E)

MITOTANE

Difficulties in appraising the evidence

Early studies antedate the era of modern imaging techniques.

Many studies are case reports or small case series and mitotane was often combined with other cytotoxic agents.

Reports of the results of the first studies must be interpreted with care because often any evidence of tumor shrinkage and improvement of steroid secretion was interpreted as tumor regression.

In many studies reporting a positive effect of mitotane, the responses have usually been short-lived; thus, it has been difficult to document a survival advantage.

For example, although Lubitz et al. (1973) found a 61% objective remission rate, the median overall survival was only 5 months.

MITOTANE

Studies assessing response with standard criteria

Author; study type	Dosage g/die	Patients n.	Response n., (%)	Duration months
Henley, 83; retrospective	NR	24	6 PRs (25)	3-24
Venkatesh, 89; retrospective	NR	72	21 PRs (29)	NA
Luton, 90; retrospective	3-20	37	5 PRs (13)	5-25
Decker, 91; prospective	6	36	2 CRs, 6 PRs (22)	3-82
Pommier, 92; retrospective	NA	29	7 PRs (24)	NA
Haak, 94; retrospective	4-8	55	8 CRs, 7 PRs (27)	2-190
Barzon, 97; retrospective	4-8	11	2 PRs (18)	40-64
Williamson, 99; II line	4-10	16	2 PRs (13)	NA
Baudin, 01; prospective	6-12	13	1 CR, 3 PRs (33)	10-48

SD: stable disease
CR: complete response
PR: partial response

NA: not available
NR: not retrieved

TREATMENT EFFICACY IN CONTROLLING CUSHING DUE TO ACC

- Hormonal response was observed only in the minority of cases who had complete objective response to MITOTANE MONOTHERAPY (*Baudin et al., 2001*)
- Hormonal response was observed in 66.7% of cases and 38.1% had a complete response to EDP + MITOTANE (*Berruti et al., 2005*)
- Control of hormone production is not possible in most patients with rapid tumor growth. However, an aggressive management occasionally is successful in achieving partial or -rarely- complete inhibition of hormone production (Veytsman et al., 2009)

MANAGEMENT OF CUSHING DUE TO ACC

- Treatment of the hormonal excess should not be delayed with the expectation that chemotherapy will reduce the tumor burden and improve symptoms.
- Instead, an aggressive medical approach to the management of excess hormone secretion by using steroidogenesis inhibitors singly or in combination should be adopted, even as chemotherapy is administered.
- Mitotane, the cornerstone of any strategy, should be started as soon as a diagnosis has been made and should be used in all patients at the highest tolerable dose.
- A therapeutic level will not be reached for several months, so that other agents must be initiated concurrently, especially if the symptoms are severe.

Veytsman et al., 2009

Mitotane, Metyrapone, and Ketoconazole Combination Therapy as an Alternative to Rescue Adrenalectomy for Severe ACTH-Dependent Cushing's Syndrome

Peter Kamenický, Céline Droumaguet, Sylvie Salenave, Anne Blanchard, Christel Jublanc, Jean-François Gautier, Sylvie Brailly-Tabard, Sophie Leboulleux, Martin Schlumberger, Eric Baudin, Philippe Chanson, and Jacques Young

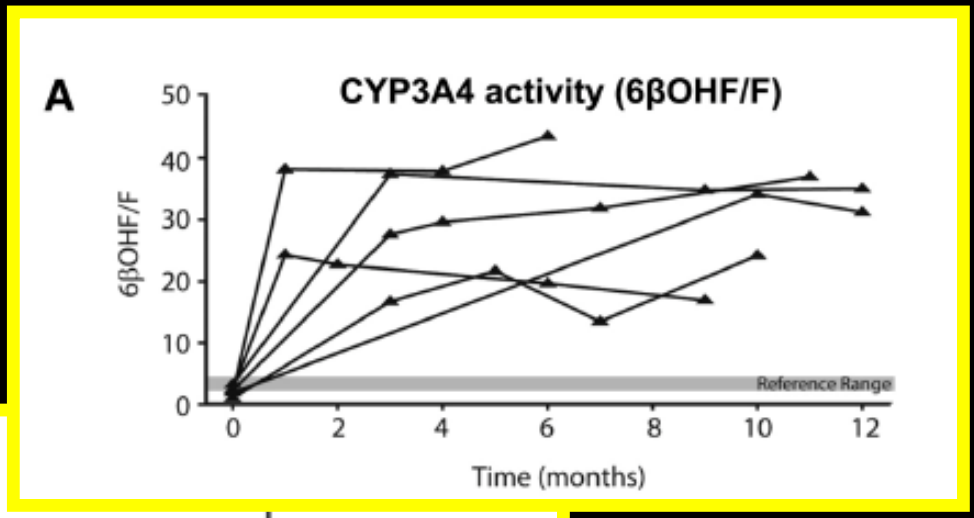
TABLE 1. Baseline clinical and hormonal parameters

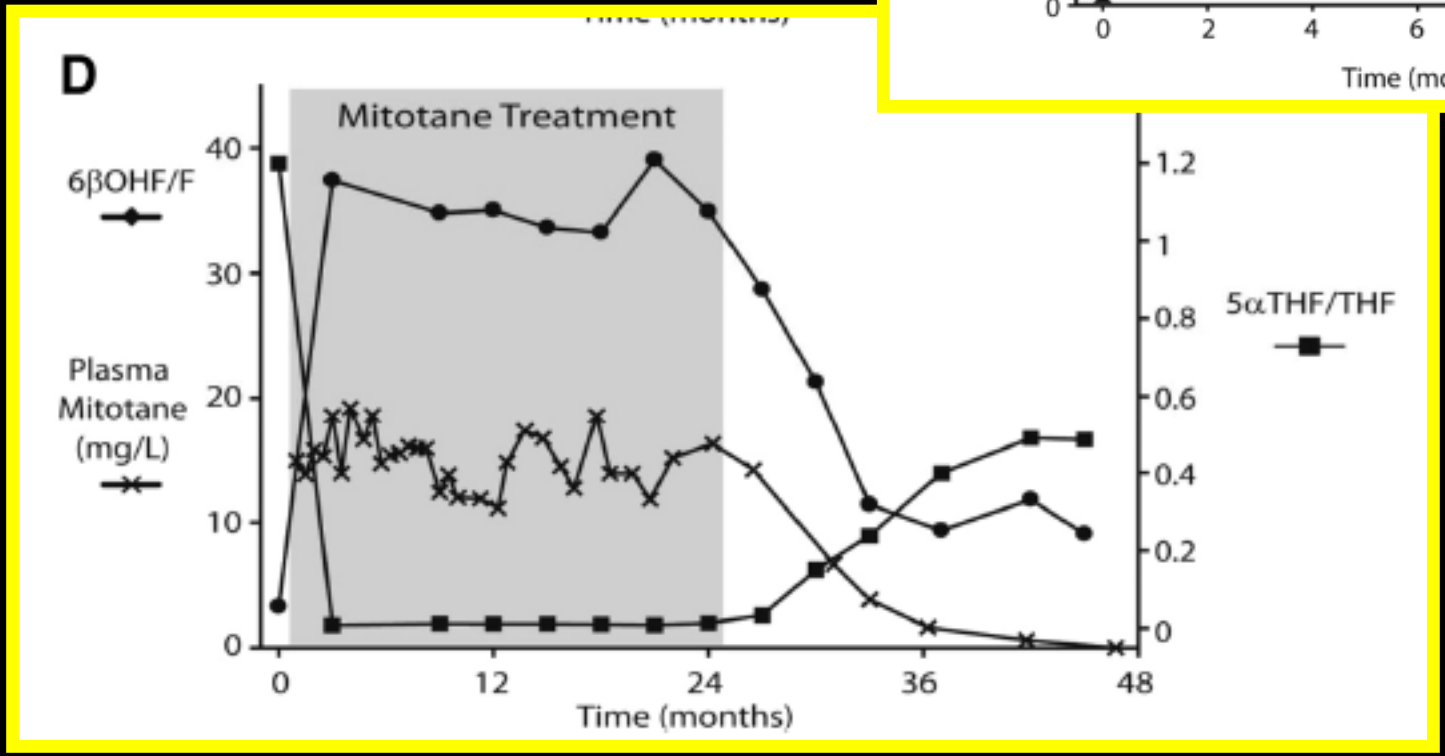
Toxicity may be problematic when using high doses of mitotane plus other steroid inhibitors and cytotoxic agents concomitantly

11	39/F	22605	653	2.4	Ketoacidosis, pneumonia, herpes zoster

Combination therapy (median doses): metyrapone 3.0 g/d (range 3.0–4.5), ketoconazole 800 mg/d (range 400-1200), and mitotane 3.0 g/d (range 3.0 –5.0).

How to monitor mitotane treatment?





Update on Mifepristone: patients with ACC

Table 2 Efficacy and adverse events of mifepristone in the 20 patients of the series.

				During mifepristone treatment						
	Etiology	Dose initial/final	Duration (months)	Clin. signs	Psy. signs	Hypertension	HypoK	Diab.	Adr. Ins.	Reason for cessation of mifepristone treatment
1	ACC	1000/1000	6	↓	↓	↓	↔	↓		Death (tumor progression)
2		400/400	2.5	↓	–	↔	↑	–		Death (tumor progression)
3		400/600	3	↓	–	↓	↑	–		Death (tumor progression)
4		400/600	3	↓	–	↓	↑	↔		Death (tumor progression)
5		400/2000	1	↔	–	–	↑	–		No significant benefit
6		600/600	2	↔	–	↔	–	–	↑	No significant benefit
7		600/1200	1	↓	–	↓	↑	↔	↑	Death (tumor progression)
8		400/1200	2	↔	–	↔	↑	–		Death (tumor progression)
9		400/600	3	↓	–	–	–	–		Ongoing treatment
10		200/600	2	↓	–	–	–	–		Tumor progression
11		200/400	1.5	↓	–	–	–	–		Death (tumor progression)
12		600/600	0.25	↔	↔	–	↑	↔		Uncontrolled hypokalemia, cessation after 1 week of treatment

Etiology: ACC, adrenocortical carcinoma; CD, Cushing's disease; BAH, bilateral adrenal hyperplasia; EAS, ectopic ACTH secretion. Dose: mg/day. In the column « during mifepristone treatment, ↔ when the criterion was unchanged, ↑ if the criterion appeared or was worsened during the treatment, – if the criterion was still absent, ↓ if the criterion decreased or disappeared with the treatment; Adr. Ins., clinical signs during the treatment were evocative of adrenal insufficiency (+), or no sign of adrenal insufficiency was present (–); note that patients 2, and 14 presented severe fatigue during the treatment.

- In 8 out of 12 pts (66%) rapid improvement of signs and symptoms;
- All patients with psychosis improved early;
- In 4 out of 7 hypertensive pts (57%) reduction of BP;
- In 1 out of 4 pts (25%) insulin treatment was discontinued;
- In 58.3% of pts occurrence of hypokalemia.

IN SUMMARY…

- The diagnosis of Cushing may offer the opportunity to detect ACC at an early stage
- The diagnosis of Cushing identifies patients at worse prognosis
- The diagnosis of Cushing in patients with advanced disease allows recognition and prevention - treatment of potential comorbidities (i.e. sepsis, thromboembolism, electrolyte alterations..etc)