Sindrome di Cushing: quando e come la terapia medica

In quali casi iniziare il trattamento medico

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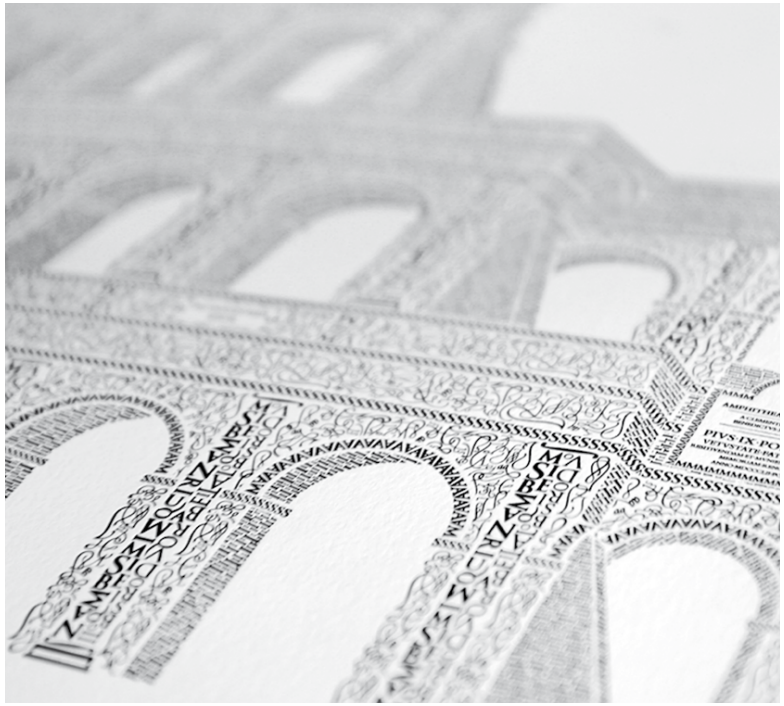

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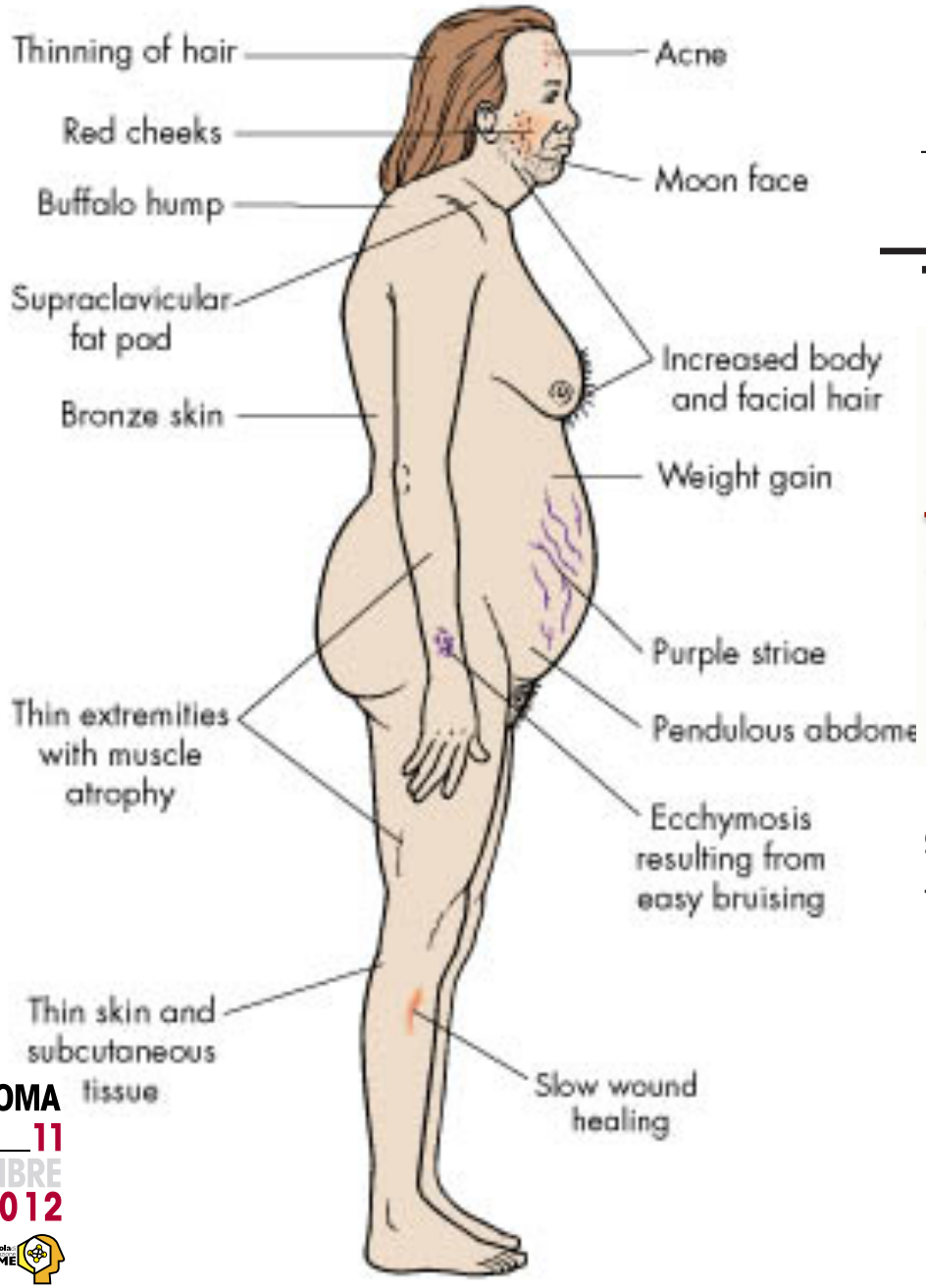
Perché l’esigenza di una terapia ?



Mortality in Cushing's syndrome: a systematic review and meta-analysis.

Hypercortisolemia and infection

Graversen D, Vestergaard P, Stochholm K, Gravholt CH, Jørgensen JO.

Eur J Intern Med. 2012 Apr;23(3):276-282.

Systemic or local im

Osteoporosis

Chi trattare ?

	Proportion	Female:male
Corticotropin-dependent		
Cushing's disease	70%	3·5:1·0
Ectopic corticotropin syndrome	10%	1:1
Unknown source of corticotropin*	5%	5:1
Corticotropin-independent		
Adrenal adenoma	10%	4:1
Adrenal carcinoma	5%	1:1
Macronodular hyperplasia	<2%	1:1
Primary pigmented nodular adrenal disease	<2%	1:1
McCune-Albright syndrome	<2%	1:1

*Patients might ultimately prove to have Cushing's disease.

Table 1: **Causes of Cushing's syndrome**

Newell-Price J et al. Lancet '06, 367: 1605-17

Quale terapia

The American Journal of Medicine (2005) 118, 1340-1346

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE ®

REVIEW

Evaluation and treatment of Cushing's syndrome

Lynnette K. Nieman, MD, Ioannis Ilias, MD, DSc

Selective surgical excision of tumors producing ACTH or cortisol is the optimal treatment of Cushing's syndrome because it spares normal adjacent structures, and effects immediate remission and eventual recovery of normal adrenal function.

Worldwide, transsphenoidal resection for Cushing's disease has immediate postoperative cure rates of 78% to 97%,[55-59] with the best results obtained for microadenomas that are visualized by experienced neurosurgeons. Because macroadenomas may invade dura or bone, remission rates are lower, 50% to 80%.[60]

Therapeutics and Clinical Risk Management

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REVIEW

Treatment of Cushing disease: overview and recent findings

Tatiana Mancini[1]
Teresa Porcelli[2]
Andrea Giustina[2]

Surgical treatment of CD

The first-line treatment of CD is the surgical removal of the pituitary tumor by transsphenoidal approach, performed by an experienced surgeon. Repeated TS may be undertaken if disease persists after initial surgery as soon as persistent disease is evident, but a delay of 4–6 weeks may be required to confirm the need for reoperation.[9] The transsphenoidal

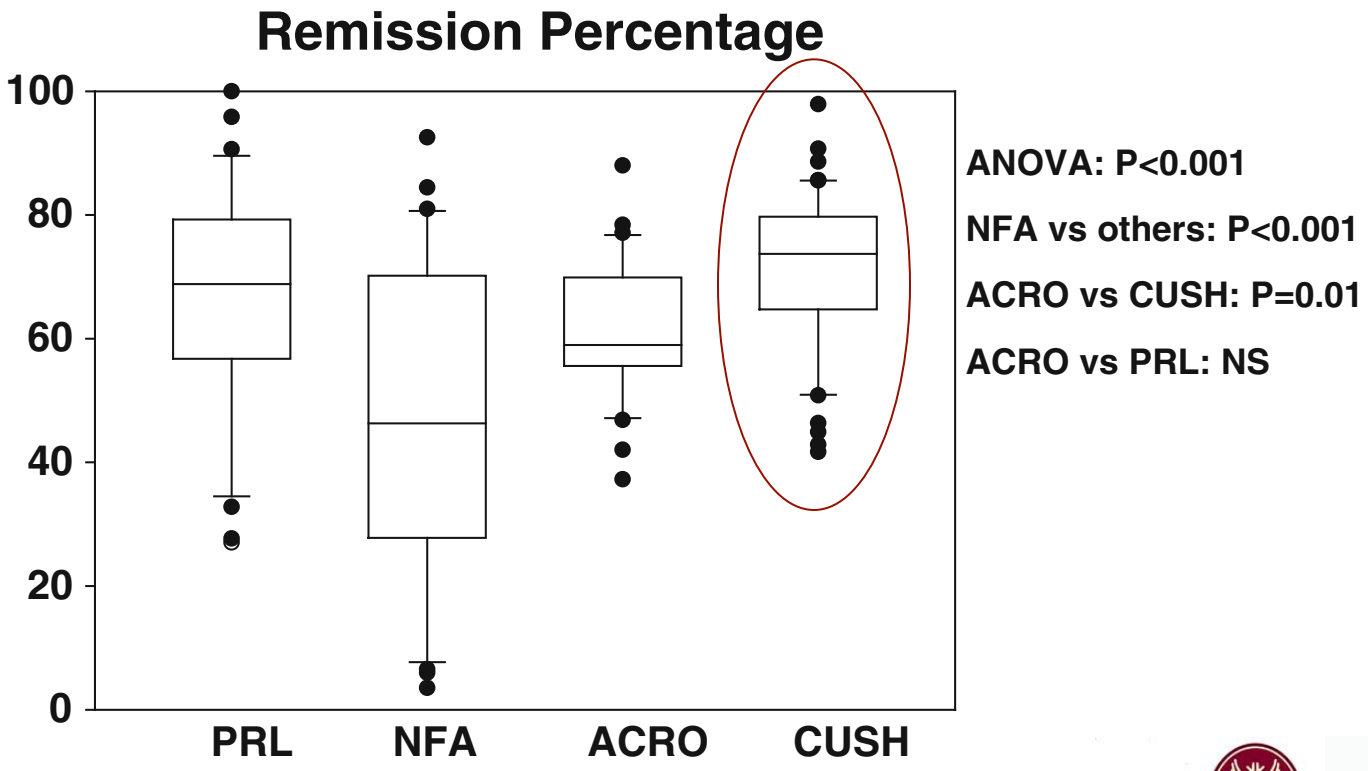
Efficacy

Remission rates in patients with microadenoma are in the range of 65%–90%. The recurrence rates are 5%–10% at 5 years and 10%–20% at 10 years. In patients with macroadenoma, remission rates are lower (<65% in most series), and recurrence also occurs sooner than i
with microadenoma (mean of 16 months vs 49 mon

Pituitary (2012) 15:71–83
DOI 10.1007/s11102-011-0347-7

Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis

Ferdinand Roelfsema · Nienke R. Biermasz · Alberto M. Pereira



Inconvenienti della terapia

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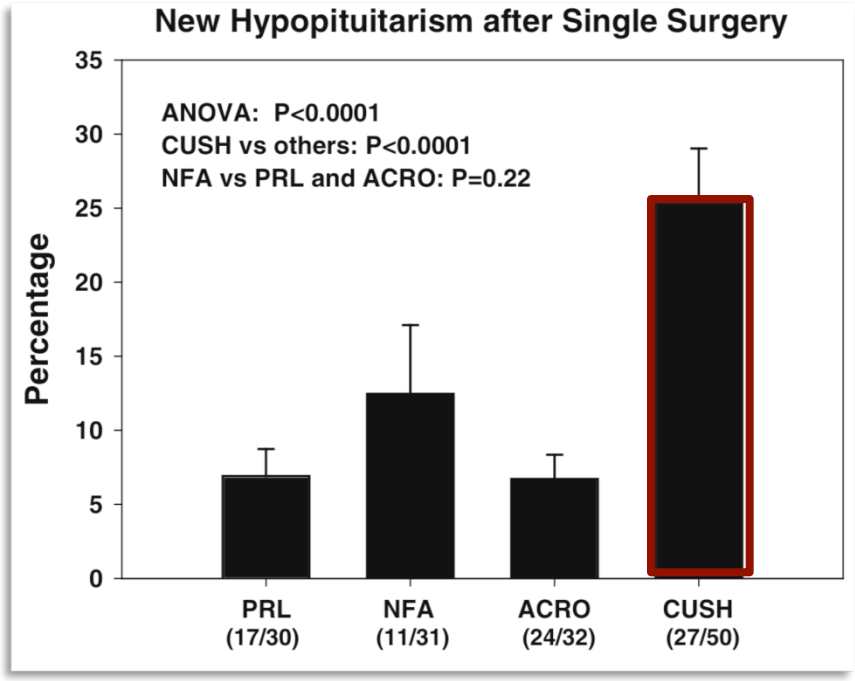
ipopituitarismo



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The Journal of Clinical Endocrinology & Metabolism 91(10):3746–3753

doi: 10.1210/jc.2006-0997

CLINICAL REVIEW: Cushing's Syndrome: Important Issues in Diagnosis and Management

James W. Findling and Hershel Raff

recidiva

Question 5: What Are Approaches to the Patient with Cushing's Disease Who Has Had Unsuccessful Pituitary Surgery or in Whom Cushing's Disease Has Recurred?

The most important treatment recommendation that an endocrinologist makes to a patient with Cushing's disease is referral to a neurosurgeon with extensive experience in operating on patients with corticotroph microadenomas. Even under the best circumstances, remission rates after transsphenoidal pituitary microsurgery range from 42 to 86% (70).

Furthermore, even in patients who clearly have a clinical and biochemical remission (preceded by secondary adrenal insufficiency), there is a recurrence rate of 5–25% (70). Consequently, there are many patients with Cushing's disease who either fail initial pituitary surgery or have a recurrence.

Outcome of Cushing's Disease following Transsphenoidal Surgery in a Single Center over 20 Years

Hassan-Smith ZK, Sherlock M, Reulen RC, Arlt W, Ayuk J, Toogood AA, Cooper MS, Johnson AP, Stewart PM

JCEM '12 97: 1194-1201

Results: Three outcome groups were identified: cure, 72% (52 of 72); persistent disease, 17% (12 of 72); and disease recurrence, 11% (eight of 72). Overall, the standardized mortality ratio was 3.17 [95% confidence interval (CI), 1.70–5.43], whereas in the cure group it was 2.47 (95% CI, 0.80–5.77), and it was 4.12 (95% CI, 1.12–10.54) for disease recurrence/persistent disease groups.

Conclusions: Mortality is increased in CD and may be higher in patients with persistent/recurrent disease compared to patients cured after initial treatment.

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Ferdinand Roelfsema · Nienke R. Biermasz · Alberto M. Pereira

recidiva

Over the last four decades the preferred treatment of choice of pituitary adenomas has been transsphenoidal surgery, although primary medical treatment is currently used in most patients with prolactinoma and in selected patients with acromegaly [1–4]. The obvious advantage of surgery is the quick relief of signs and symptoms, and the arrest of permanent damage to organ systems caused by the hormonal excess. Recurrence of a pituitary adenoma after apparent cure is well recognized.

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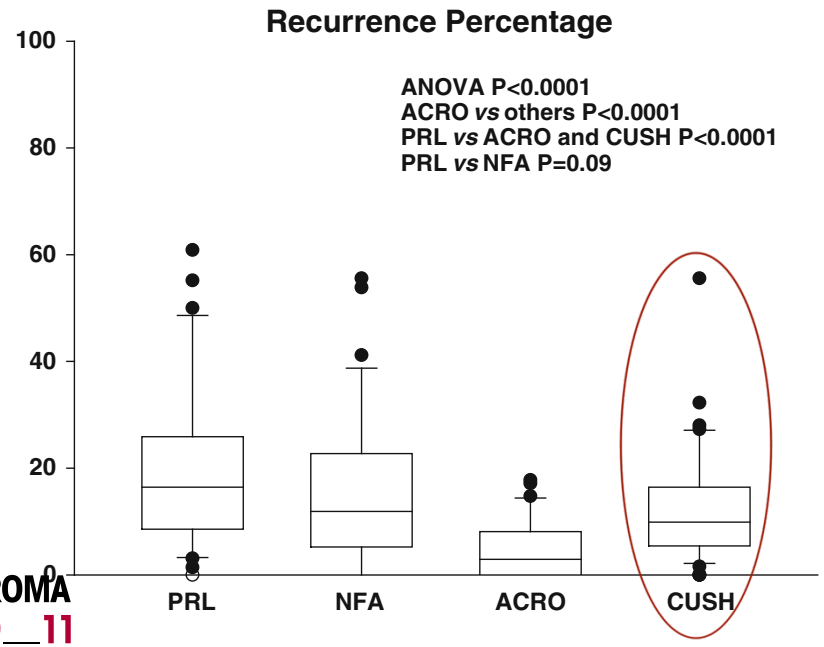

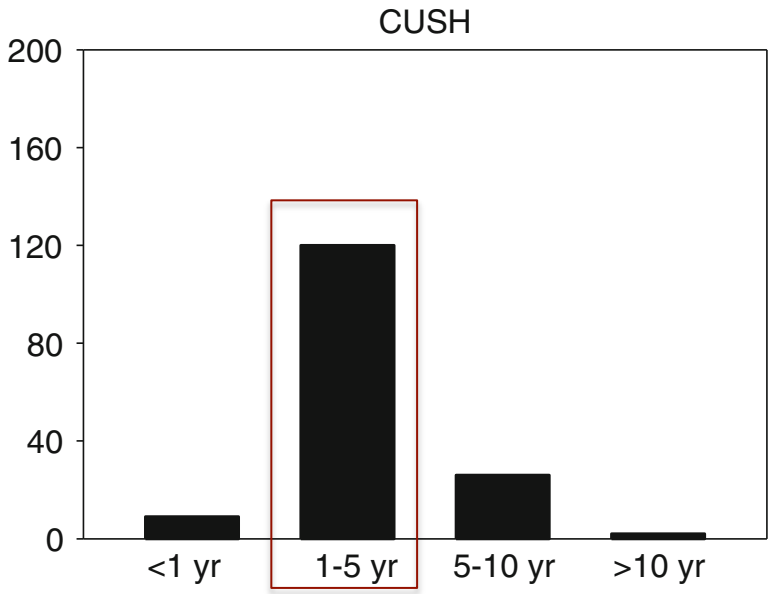

Surgical Management and Outcomes in Patients with Cushing Disease with Negative Pituitary Magnetic Resonance Imaging

Yamada S, Fukuhara N, Nishioka H, Takeshita A, Inoshita N, Ito J, Takeuchi Y

World Neurosurgery '12, 77: 525-532

imaging negativo

When the pituitary origin of adrenocorticotropic hormone secretion is established by IPSS in patients with normal MRI findings, we recommend TSS as the first-line treatment for CD, although chance of surgical cure (50% in this series) is lower than that of MRI-visible microadenomas. In contrast, other therapeutic options must be considered in patients with negative MRI and IPSS findings.

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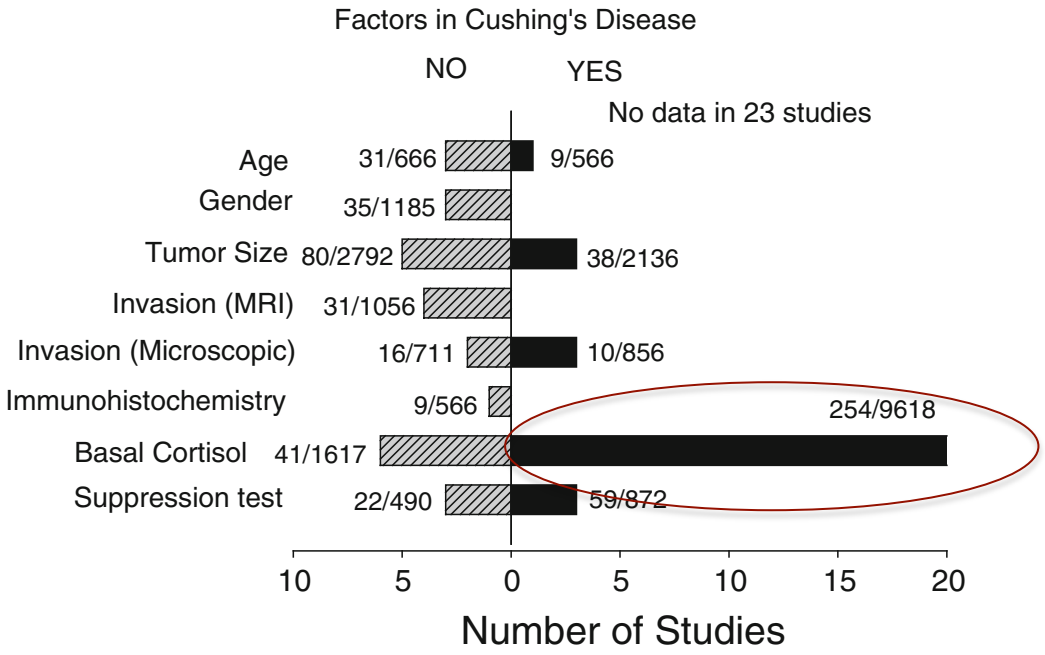

fattori predittivi

ROMA 9__11 NOVEMBRE 2012

Table 3 Reported outcomes of surgery and radiotherapy in patients with CD.

Treatment option	Control/remission	Incidence of complications and adverse effects	Comments
TSS (in patients with microadenomas)	Remission: 73–100% (37, 82, 83, 84) Recurrence: 5–13% (37, 83)	Hypopituitarism: 34% (84) CSF leak: 1.8–13% (83, 84) DI: 5–57% (83, 84)	TSS induces remission in about 80% of patients (minimum of 6 months' follow-up), the remission rate ranged from 73 to 100% and the recurrence rate from 5 to 13%
TSS (in patients with macroadenoma)	Remission: 65–100% (37, 82, 84) Recurrence: 18–36% (37, 87)	DI: 19% (84) Hypopituitarism: 24% (84) CSF leak: 14% (84)	Results from studies highlighting the differences of outcome by size of adenoma are equivocal
Repeat surgery	Remission: 61–73% (88, 89) Recurrence: 9–13% (88, 89)	Hypopituitarism: 50% (88) Pan-hypopituitarism: 7% (89)	The odds of failure for repeat TSS is 3.7-fold greater vs initial TSS (89) Can be successful when residual tumor is detectable on MRI (88)
Conventional radiotherapy	Remission: 49–83% (89, 92, 93, 117) Probability of remission as a function of follow-up time: 100% (2 years), 82% (5 years), 72% (7 years), 65% (10 years) (118) Recurrence: 0–11% (93, 117)	DI: 3% (93) Hypopituitarism: 3–21% (93, 117) Central hypopituitarism: 20% (93) i) Prevalence increases to 77% 10 years after irradiation (119) ii) Leads to reduced life expectancy, mainly caused by cardiovascular diseases (120) iii) Increases risk for vascular mortality by 50% (120)	Average (mean or median) time to normalization usually 6–36 months (92, 93, 94) Remission usually occurs during first 2 years after irradiation (118)
SRS, GKRS	Remission: 43–66% (94, 121, 122, 123)	Pan-hypopituitarism: 7.5% (94) Quadrantanopsia: 2% (123)	Remission usually occurs within the first 2 years following radiotherapy (123)
Adrenalectomy	95–100% (95, 96, 97, 98)	Operative mortality: 0–3.6% (95, 96, 97, 124, 125, 126) Life-long glucocorticoid and mineralocorticoid replacement therapy, osteoporotic fractures Nelson's syndrome (NS): i) Expanding pituitary tumor; absence of negative feedback on corticotroph tumor cells by high cortisol levels ii) Progressive cutaneous hyperpigmentation iii) Risk of developing NS after BA is relatively high: 8–46% (117, 127) iv) Presentation time varies from 0.5 to 24 years postoperatively; prophylactic RT of the sellar region after BA may prevent development	The proportion of patients presenting corticotroph tumor progression reached 39% and plateaued at 47% after 7 years (124)

BA, bilateral adrenalectomy; CSF, cerebrospinal fluid; DI, diabetes insipidus; GKRS, gamma knife radiosurgery; NS, Nelson's syndrome; RT, radiotherap
SRS, stereotaxic radiosurgery.

Il problema è risolto ?

European Journal of Endocrinology (2012) **167** 311–326 ISSN 0804-4643

REVIEW
MANAGEMENT OF ENDOCRINE DISEASE

The burden of Cushing's disease: clinical and health-related quality of life aspects

R A Feelders, S J Pulgar[1], A Kempel[2] and A M Pereira[3]

Table 2 Comorbidities, prevalence at diagnosis, and reversibility in patients with CD.

Morbidity	Prevalence at diagnosis	Reversibility
Hypertension	55–85% (12, 14, 22, 53)	18-Year follow-up: posttreatment 24% (12/49); diagnosis 55% (27/49) (14) After 5 years' cortisol normalization: CD 40% (6/15); BMI-matched controls 20% (6/30) (3) After 1 year's cortisol normalization, hypertension was reversed in 44% (12) Less than 2 years after successful remission, 75% had normalized BP (55)
IGT	21–64% (12, 14, 22, 53)	18-Year follow-up: posttreatment 4% (2/49); diagnosis 24% (12/49) (14) After 5 years' cortisol normalization: CD 27% (4/15); BMI-matched controls 27% (8/30) (3)
Diabetes mellitus	20–47% (12, 14, 22, 53)	18-Year follow-up: posttreatment 18% (9/49); diagnosis 39% (19/49) (14) After 5 years' cortisol normalization: CD 33% (5/15); BMI-matched controls 7% (2/30) (3) After 1 year's cortisol normalization, diabetes was reversed in 40% of patients (12)
Overweight (BMI 25–30 kg/m^2)	21–48% (12, 22, 53)	After 5 years' cortisol normalization: CD 33% (5/15); sex- and age-matched controls 20% (6/30) (3)
Obesity (BMI > 30 kg/m^2)	32–41% (12, 22, 53)	After 5 years' cortisol normalization: CD 40% (6/15); 0 in controls (3) After 1 year's cortisol normalization, 38% were no longer obese (12)
Dyslipidemia	38–71%[a] (22, 53)	After 5 years' cortisol normalization, the prevalence was 27% (3)

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Persistence of Increased Cardiovascular Risk in Patients with Cushing's Disease after Five Years of Successful Cure

ANNAMARIA COLAO, ROSARIO PIVONELLO, STEFANO SPIEZIA, ANTONGIULIO FAGGIANO, DIEGO FERONE, MARIAGIOVANNA FILIPPELLA, PAOLO MARZULLO, GAETANA CERBONE, MARCELLO SICILIANI, AND GAETANO LOMBARDI

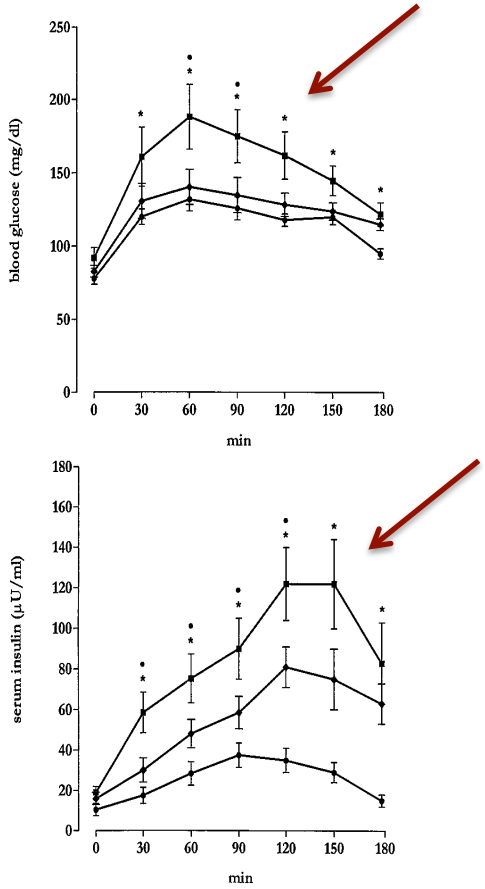

FIG. 1. Blood glucose and serum insulin responses to oral glucose tolerance test in patients cured of Cushing's disease (■), sex- and age-matched controls (●), and BMI-matched controls (♦). *, $P < 0.05$ compared to sex- and age-matched controls; ●, $P < 0.05$ compared to BMI-matched controls.