CHIRURGIA DEL MICRO E MACROADENOMA: EFFICACIA E COMPLICANZE

Paolo Marzullo

Napoli, 10-12 Aprile 2017
Centro Congressi Federico II - Via Partenope, 36

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin

J Clin Endocrinol Metab, August 2015

Predictors of surgical success

- Diagnostic tools
- Surgeon skills
- Tumor visualization
- Positive histology
- Remission criteria
- Length of follow-up
- Recurrences

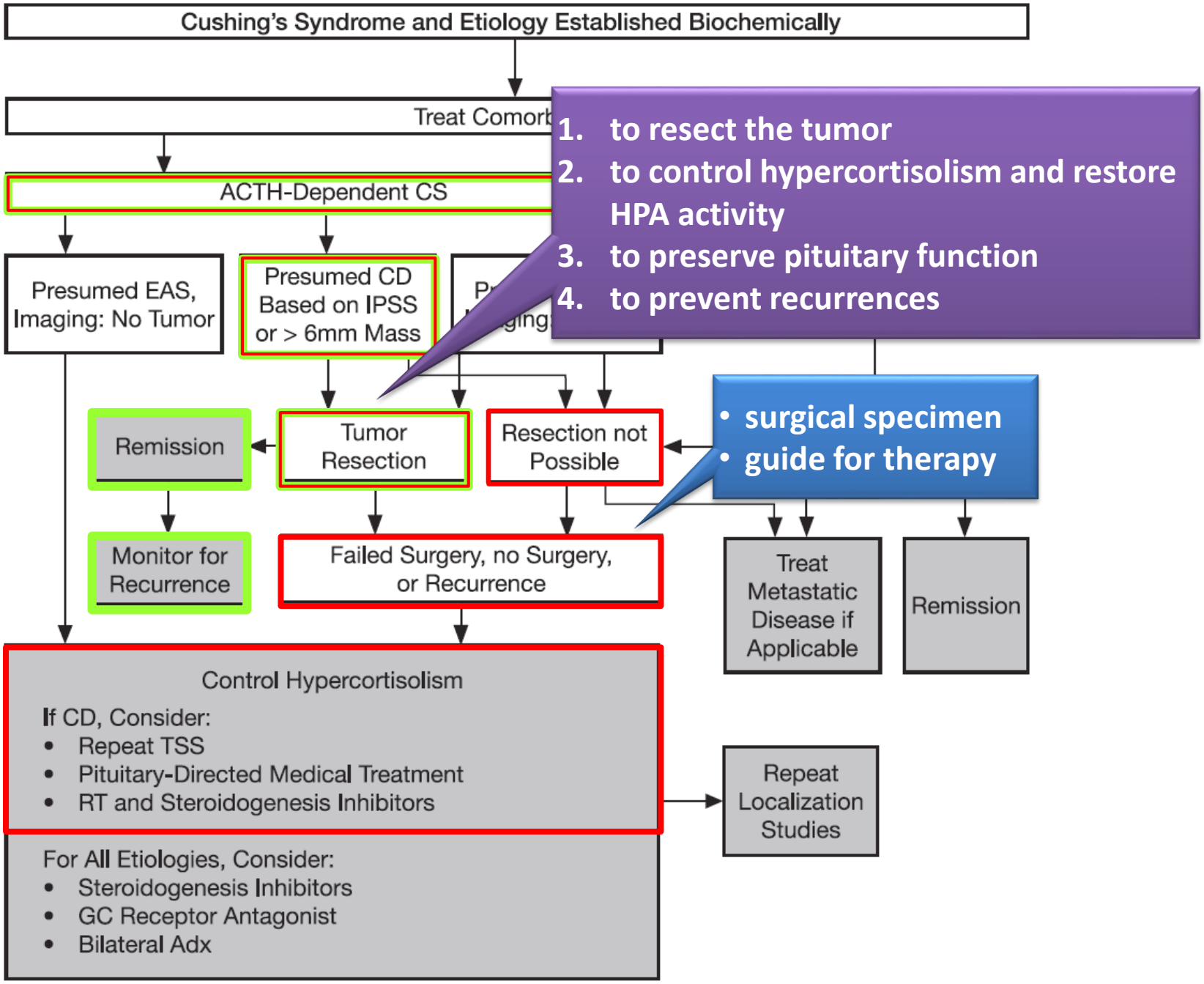
3.1 We recommend initial resection of primary lesion(s) underlying Cushing's disease (CD), ectopic and adrenal (cancer, adenoma, and bilateral disease) etiologies, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess (Figure 1). (1|⊕⊕⊕⊕)

3.1c We recommend transsphenoidal selective adenomectomy (TSS) by an experienced pituitary surgeon as the optimal treatment for CD in pediatric and adult patients. (1|⊕⊕⊕⊕)

3.1ci We recommend measuring serum sodium several times during the first 5–14 days after transsphenoidal surgery. (1|⊕⊕◯◯)

3.1cii We recommend assessing free T_4 and prolactin within 1–2 weeks of surgery, to evaluate for overt hypopituitarism. (1|⊕⊕◯◯)

3.1ciii We recommend obtaining a postoperative pituitary magnetic resonance imaging (MRI) scan within 1–3 months of successful TSS. (Ungraded best practice statement)


Cushing's Syndrome and Etiology Established Biochemically
Treat Comorb
ACTH-Dependent CS
Presumed EAS, Imaging: No Tumor
Presumed CD Based on IPSS or > 6mm Mass
1. to resect the tumor
2. to control hypercortisolism and restore HPA activity
3. to preserve pituitary function
4. to prevent recurrences
Remission
Tumor Resection
Resection not Possible
• surgical specimen
• guide for therapy
Monitor for Recurrence
Failed Surgery, no Surgery, or Recurrence
Treat Metastatic Disease if Applicable
Remission
Control Hypercortisolism
If CD, Consider:
• Repeat TSS
• Pituitary-Directed Medical Treatment
• RT and Steroidogenesis Inhibitors
Repeat Localization Studies
For All Etiologies, Consider:
• Steroidogenesis Inhibitors
• GC Receptor Antagonist
• Bilateral Adx

- Patients with Cushing's disease generally present with hypercortisolemia symptoms due to ACTH hypersecretion from the adenoma.

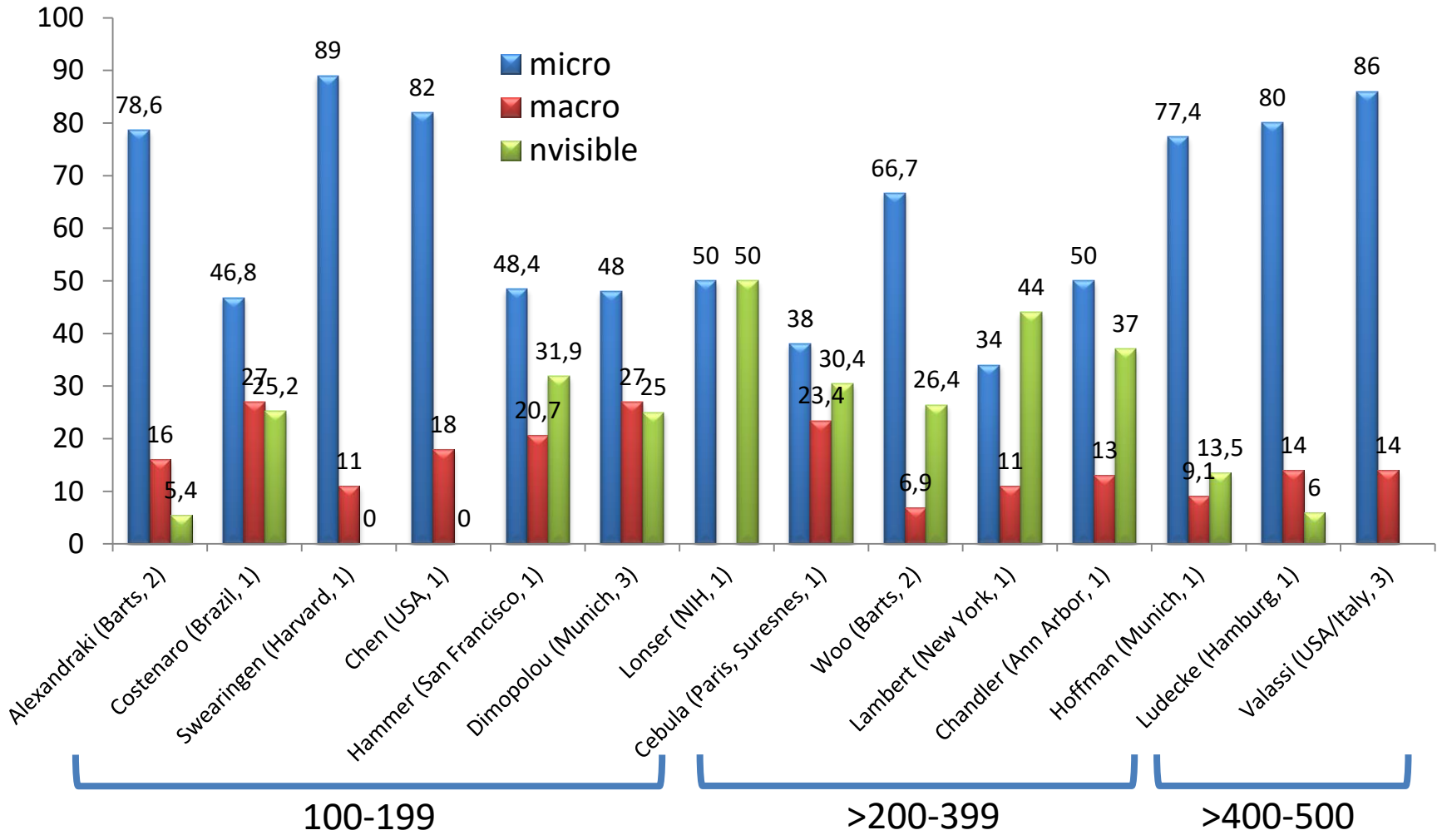
- Rather, symptoms attributable to pituitary adenoma size, such as headache or optic chiasm compression, are rare.

CD tumors are different compared to other pituitary tumors

In contrast to other functioning microadenomas, the tumors in CD are not round and well circumscribed; they are frequently binodular with small connections, sometimes of a diffuse growing pattern, and they are not always enclosed. Even if most adenomas are deliquescent, some of them present with a firm consistency and therefore can easily be misinterpreted as normal pituitary tissue.

Hoffman BM et al, J Neurosurg 2008

ACTH-sec. micro- and macroadenomas at MRI (surveys on >100 cases)



Preoperative adenoma finding rates by MRI

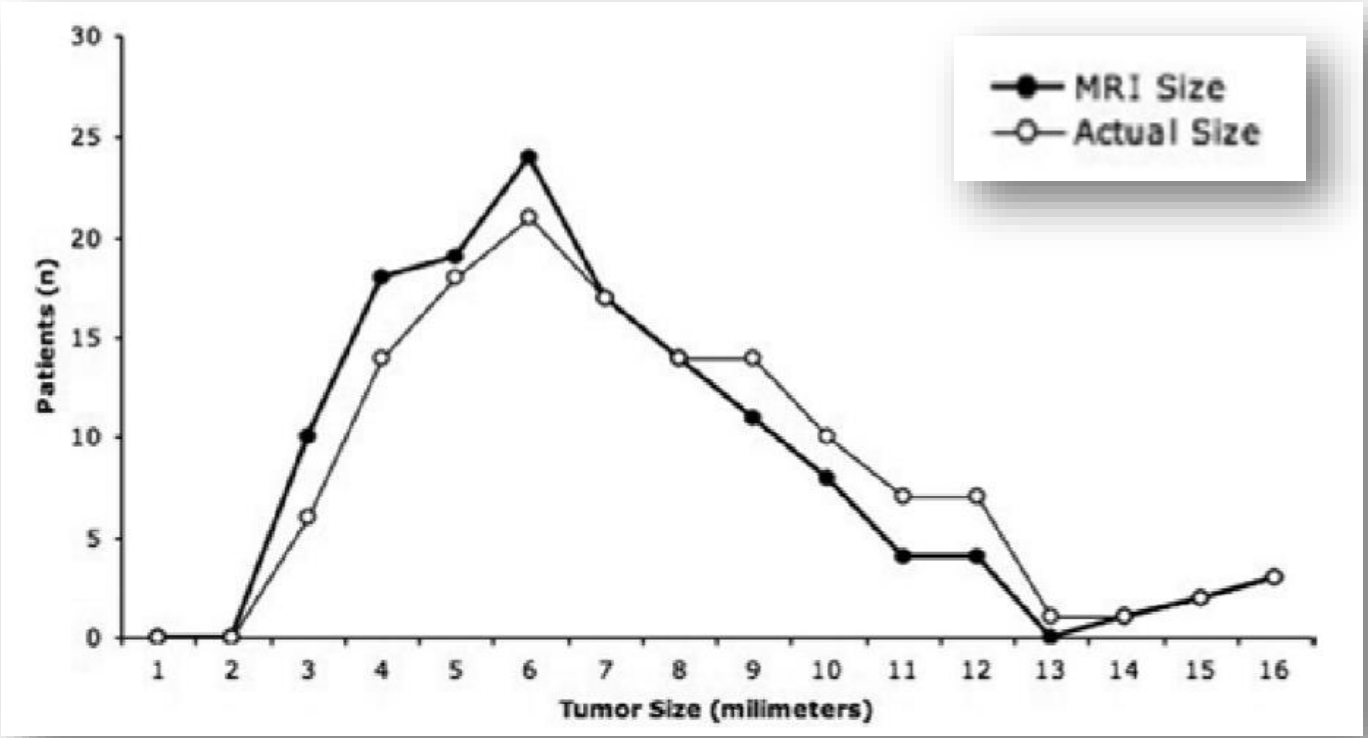
Table 1. Cushing's disease – preoperative adenoma finding rate by MR imaging in the literature (1993–2000)

Authors	Center	Year	No. of patients	Correct adenoma identification
Buchfelder et al. [3]	Erlangen, FRG	1993	41 (microadenomas)	21/41 (52%)
Magiakou et al. [35]	Bethesda, USA	1994	50 (children)	26/50 (52%)
Ram et al. [37]	Bethesda, USA	1995	18 (microadenomas)	8/18 (44%)
Knappe et al. [39]	Hamburg, FRG	1995	42 (children)	25/42 (59%)
Devoe et al. [40]	San Francisco, USA	1997	18 (children)	13/18 (72%)
Barrou et al. [41]	Paris, France	1997	54 (unselected)	42/54 (78%)
Watson et al. [42]	Bethesda, USA	1998	107 (microadenomas)	39/107 (36%)
Graham et al. [32]	Portland, USA	1999	58 (microadenomas)	29/58 (55%)
Kaltsas et al. [43]	London, GB	1999	69 (unselected)	50/69 (72%)
Semple et al. [44]	Charlottesville, USA	1999	105 (unselected)	87/105 (83%)
Kurosaki et al. [38]	Hamburg, FRG	2000	51 (microadenomas)	19/51 (37%)

Preoperative adenoma identification on MR imaging is associated with 18-fold higher odds of finding the adenoma at surgery and 4-fold higher chance of postresection biochemical remission

Ludecke DK et al, J Neuro-Oncol 2001
Lonser RR et al, J Neurosurg 2017

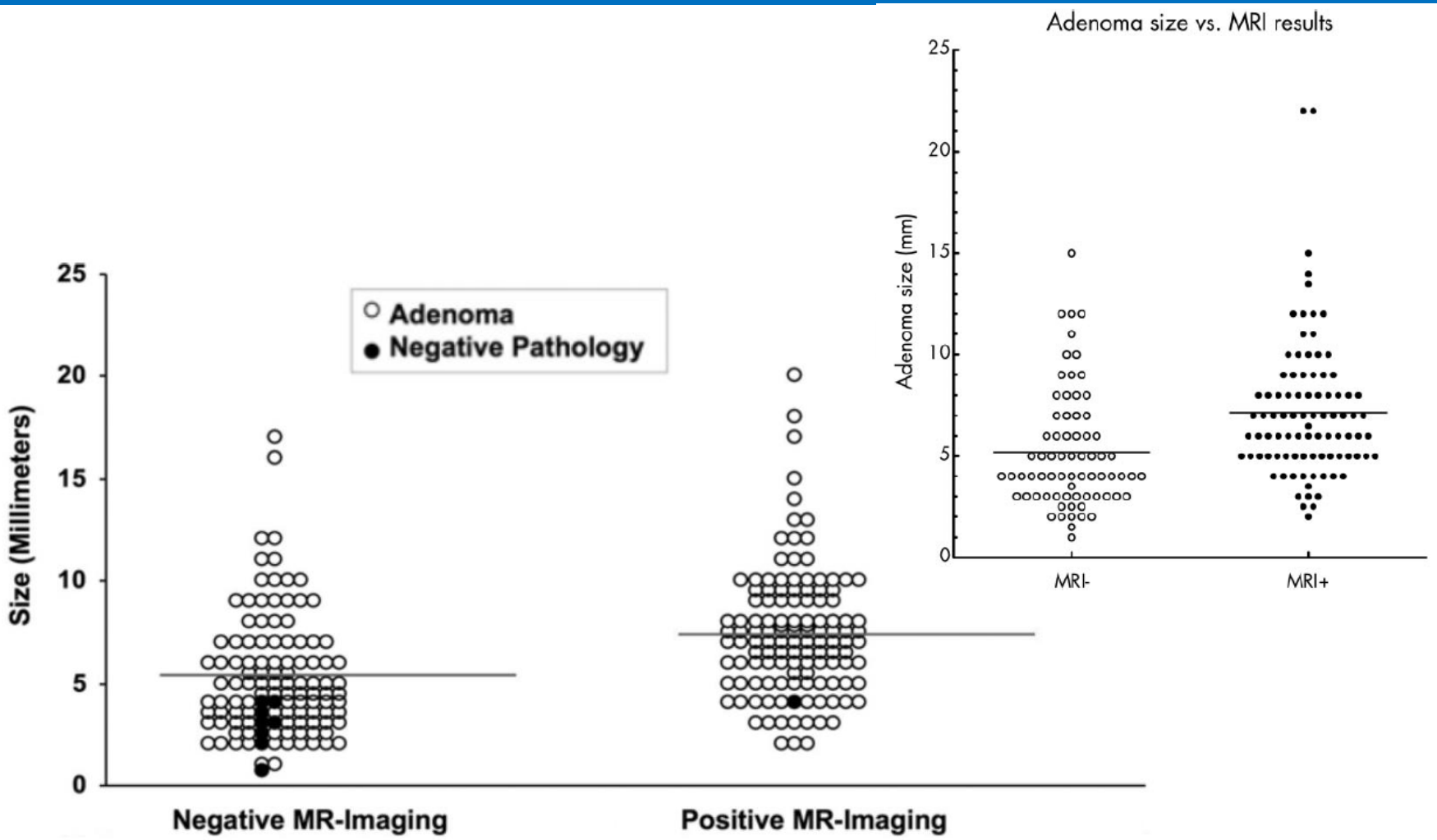
MRI measurement within 2 mm of the tumor size at surgery in most cases



There is an overall tendency to underestimate tumor size on MRI, probably related to the resection of the pseudocapsule.

Jagannathan J et al, J Neurosurg 2009

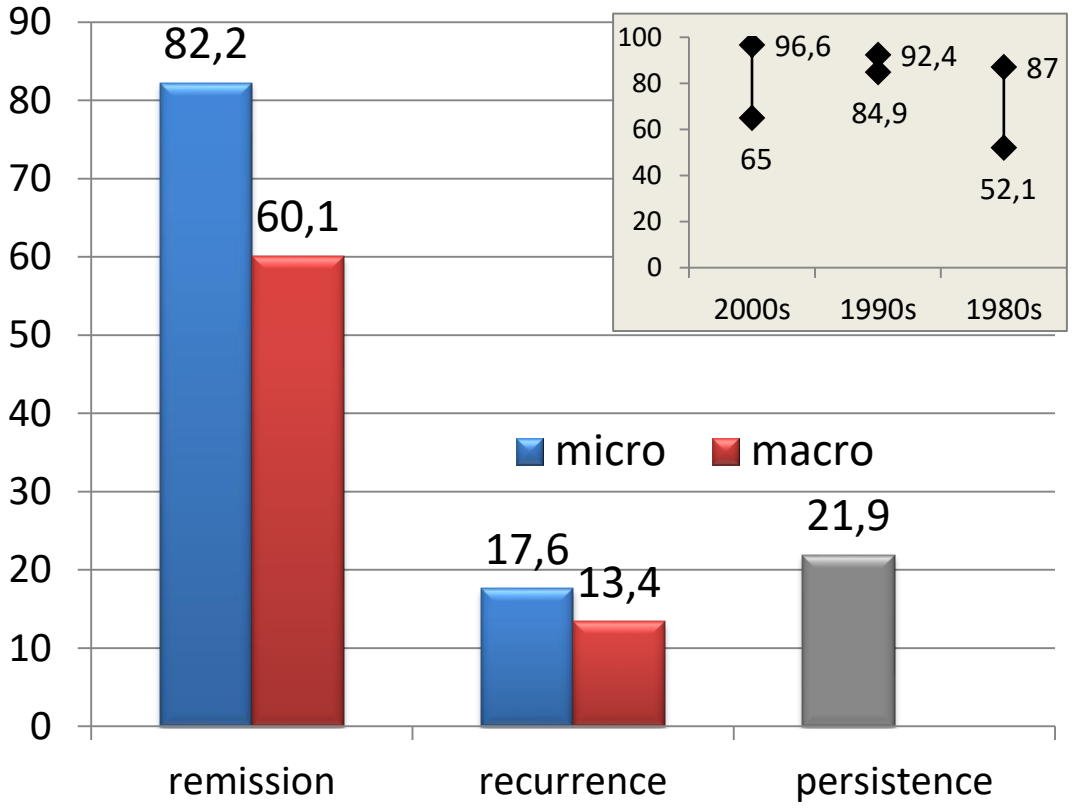
Size of adenomas at surgery in adult and pediatric patients with positive/negative MRI



Jagannthan J et al, J Neurosurg 2009
Lonser RR et al, JCEM 2013

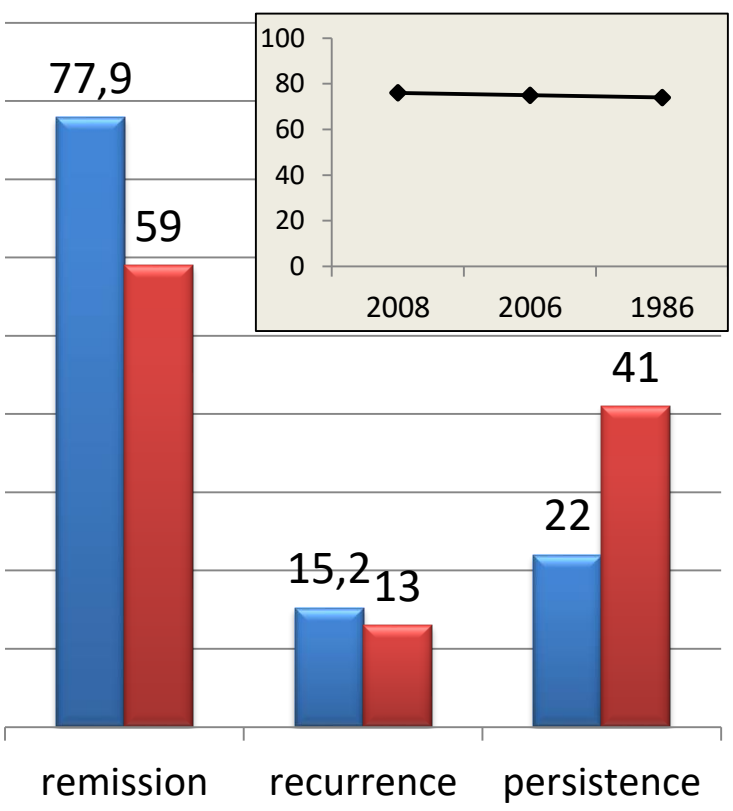
Remission rate is lower in macroadenoma than microadenoma

N=1774



Petersenn S et al, Eur J Endocrinol 2015

N= 526



Hoffman BM et al, J Neurosurg 2008

Surgical experience and Cushing's disease

In general, in a single neurosurgeon's series, a continuous improvement in normalization of the hypersecretory status for prolactin[50] and human growth hormone–producing[51] adenomas as well as a decrease of pituitary insufficiency following surgical treatment of nonfunctioning tumors[52] could be experienced and has been documented. On the contrary, during surgical treatment of pituitary-dependent CD, we did not observe this phenomenon.

Hoffman BM et al, J Neurosurg 2008

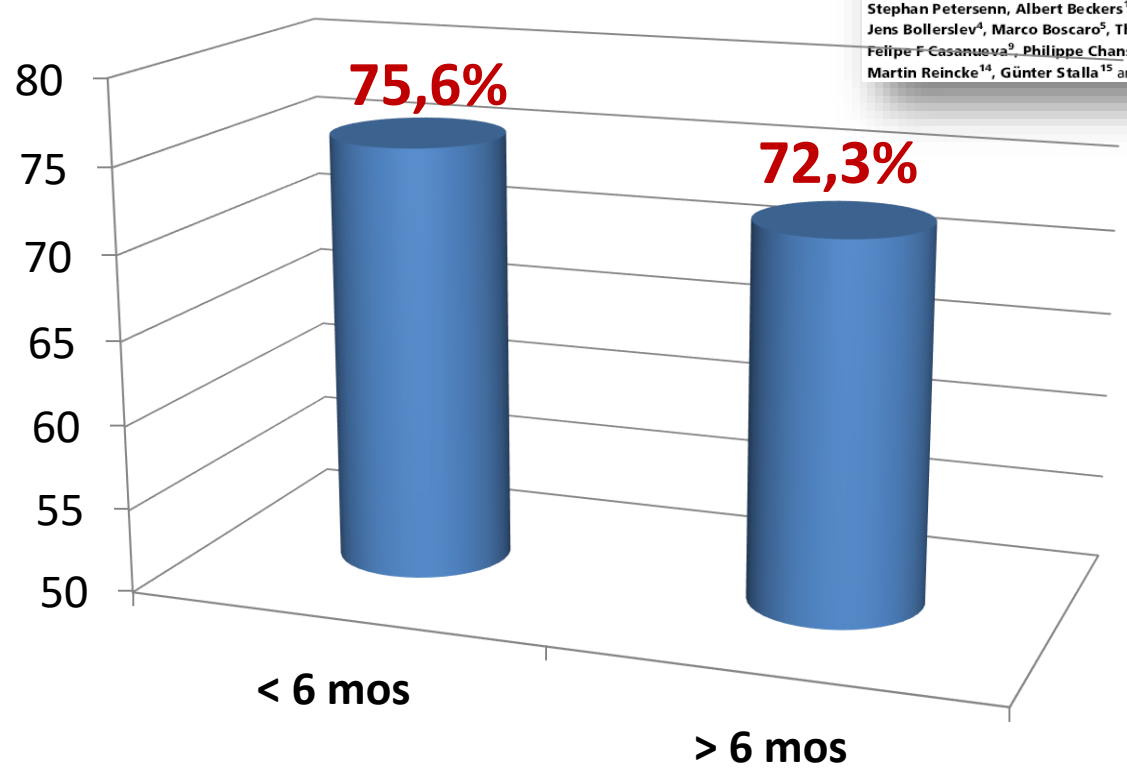
The predictive role for early remission vs late remission on definitive outcome

THERAPY OF ENDOCRINE DISEASE

Outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence

Stephan Petersenn, Albert Beckers[1], Diego Ferone[2], Aart van der Lely[3], Jens Bollerslev[4], Marco Boscaro[5], Thierry Brue[6,7], Paolo Bruzzi[8], Felipe F Casanueva[9], Philippe Chanson[10,11,12], Annamaria Colao[13], Martin Reincke[14], Günter Stalla[15] and Stelios Tsagarakis[16]

Cumulative remission data



Remission and recurrence after surgical tumor resection

4.1 We suggest an individualized management approach based on whether the postoperative serum cortisol values categorize the patient's condition as hypocortisolism, hypercortisolism, or eucortisolism. (Ungraded best practice statement)

4.2 We recommend additional treatments in patients with persistent overt hypercortisolism. (1|⊕⊕⊕⊕)

4.3 We recommend measuring late-night salivary or serum cortisol in patients with eucortisolism after TSS, including those cases where eucortisolism was established by medical treatment before surgery. (1|⊕⊕◯◯)

4.4 We recommend using tests to screen for hypercortisolism to assess for recurrence in patients with ACTH-dependent CS. (1|⊕⊕⊕◯)

How to assess long-term remission of CD after TTS

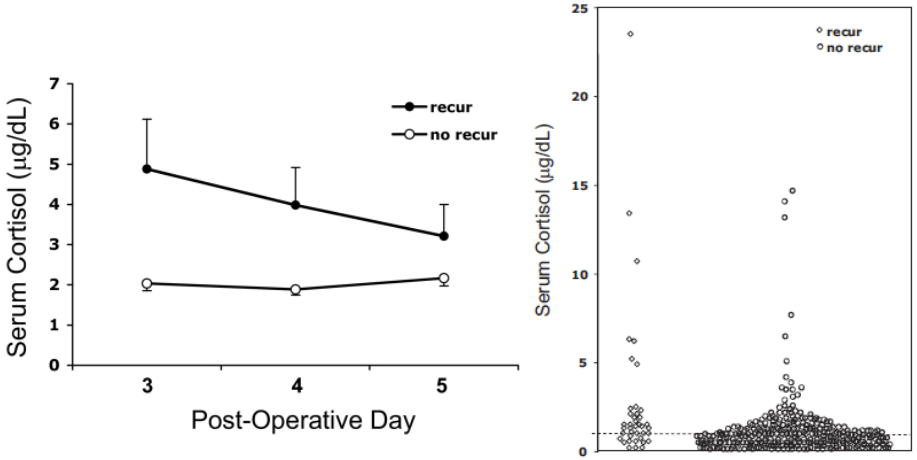
- **Non-provocative tests:**
  - morning cortisol on Day 1-3 or day 5-10 (cutoff <5, <2, <1 mcg/L);
  - Late night serum cortisol;
  - Late night salivary cortisol;
  - ACTH (<5 pg/mL);
  - UFC (<20 mcg/24 h)

- **Provocative tests:**
  - overnight LDDST and CRH test.

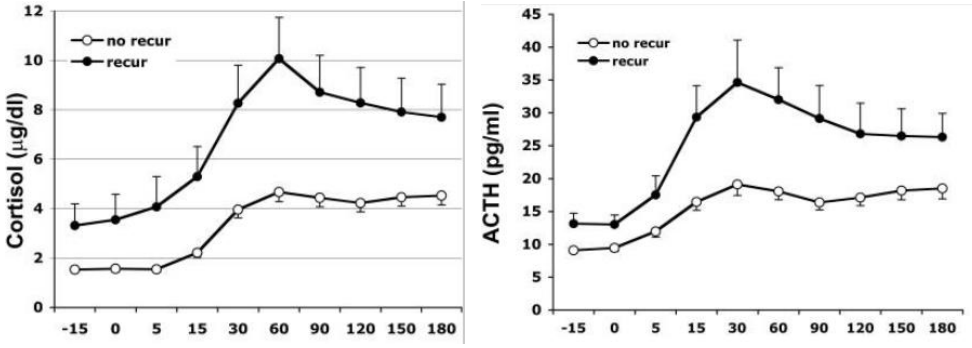
Early postoperative predictors of sustained remission (N=418)

- Cortisol <5 µg/dl predicts remission
- Cortisol <1-2 µg/dl is highly predictive for sustained remission
- Fewer patients achieved a cortisol nadir <2 µg/dl (87%) than <5 µg/dl (98%)
- Recurrence rates were similar if:
  - <1 µg/dl: 7.5%
  - <2 µg/dl: 9.5%
  - <5 µg/dl: 10.4%

Morning cortisol

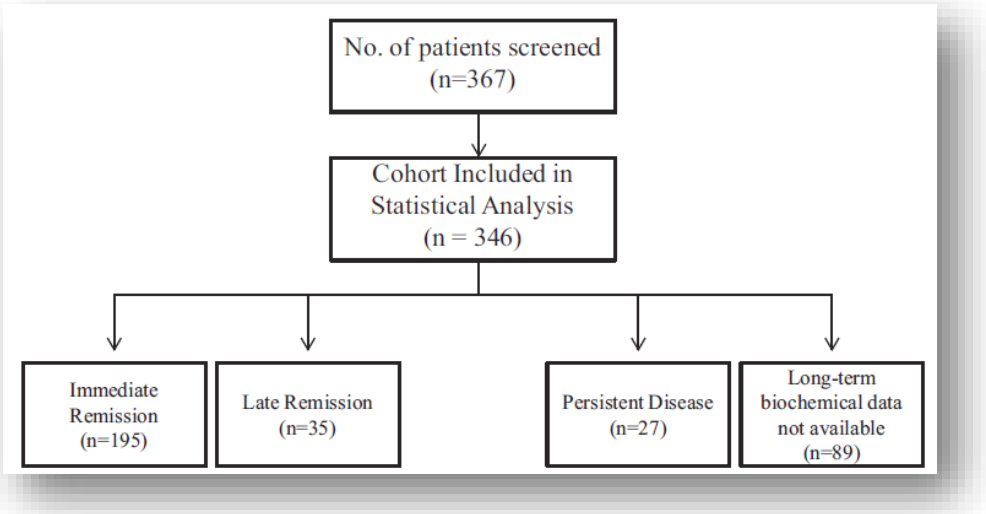


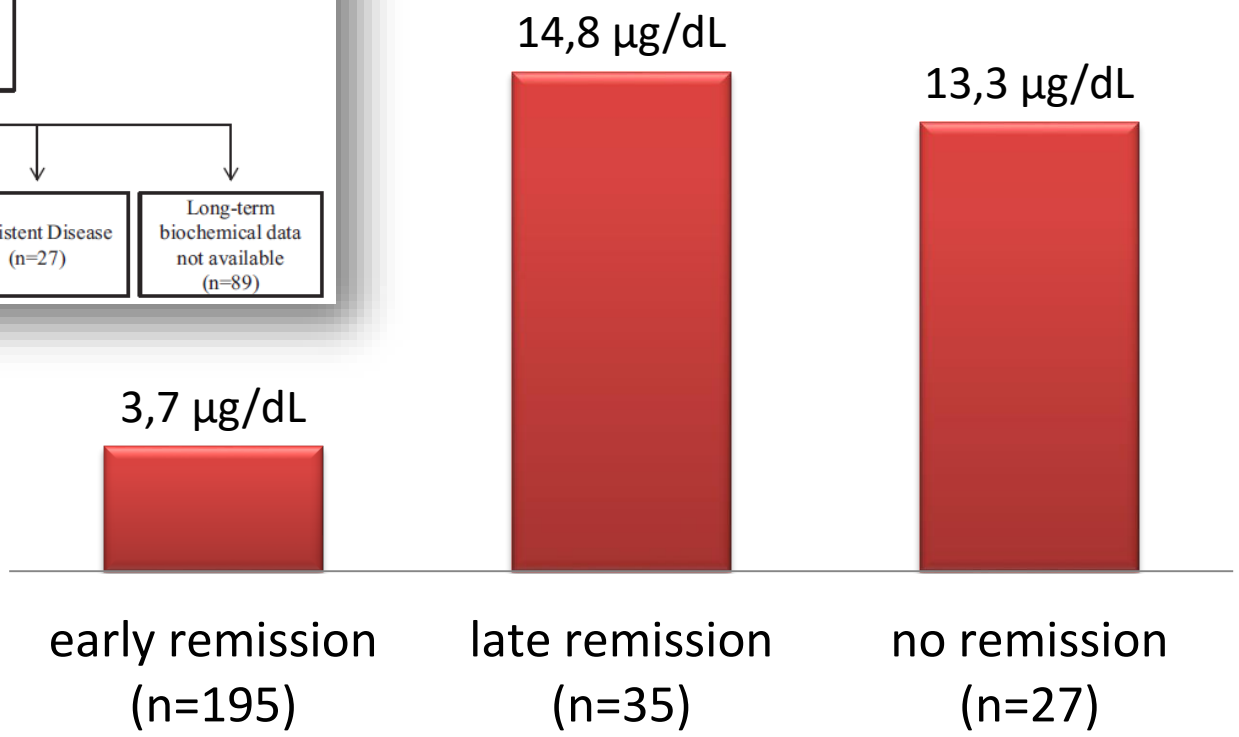
CRH test



Lindsay JR et al, J Clin Endocrinol Metab 2011

Late surgical remission, defined by cortisol concentrations <5 µg/dL (N=346)



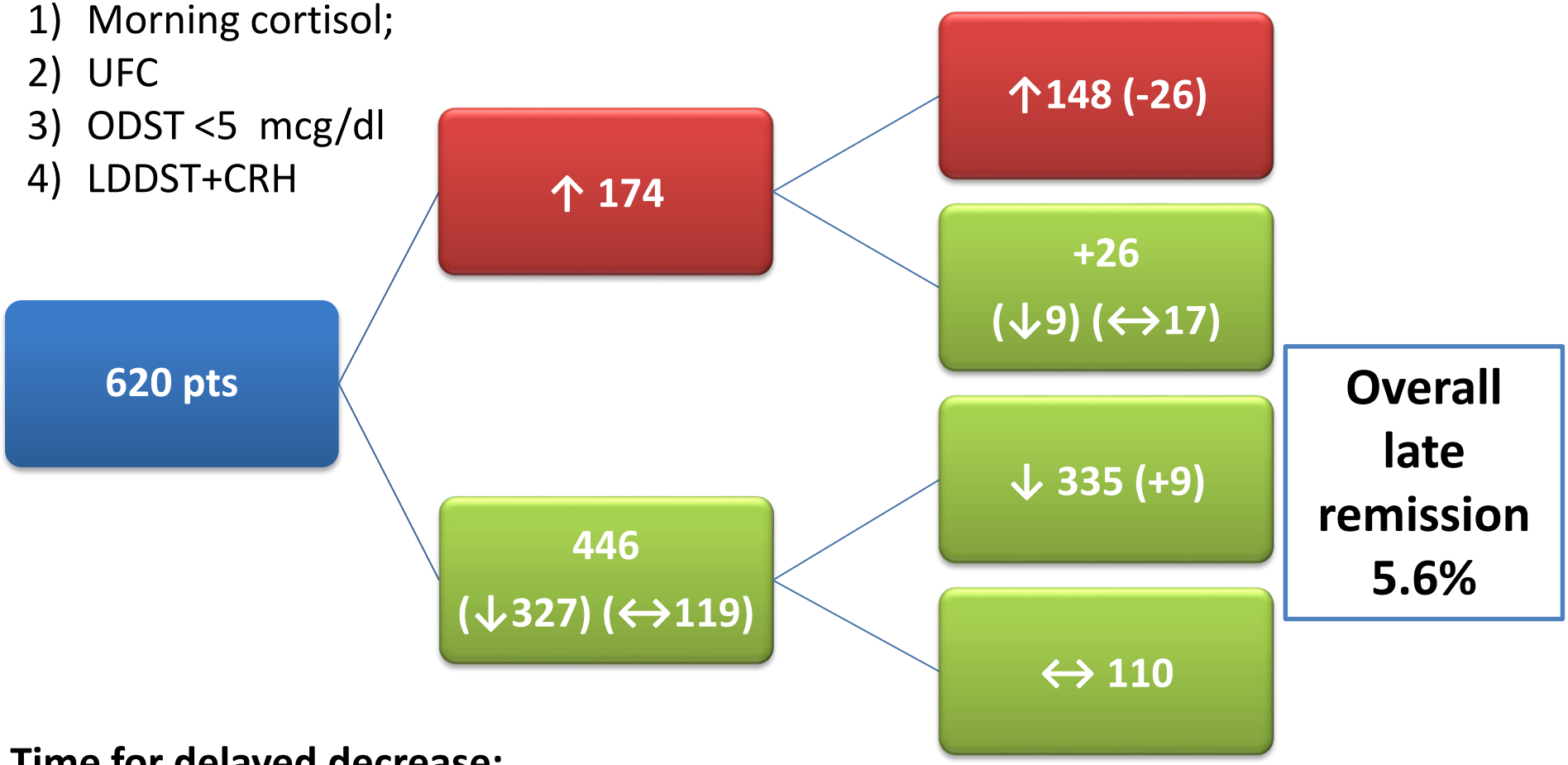


Lambert JK et al, J Clin Endocronol Metab 2013

Delayed remission after TSS in CD patients

Criteria for recurrence, 2 among:

1) Morning cortisol;
2) UFC
3) ODST <5 mcg/dl
4) LDDST+CRH

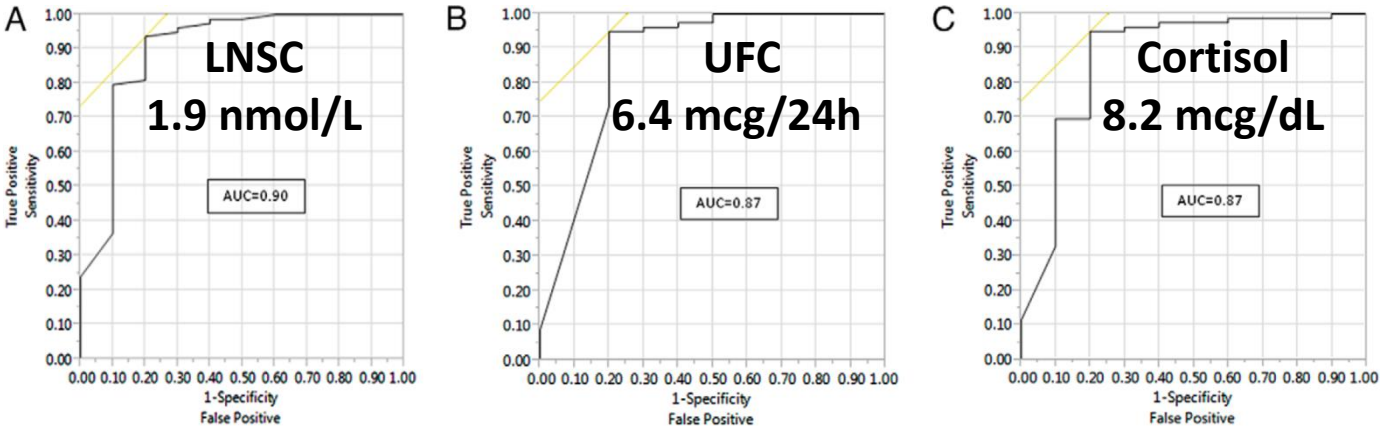


Time for delayed decrease:
median 9 d; range 4–180 d

Valassi E et al, Clin Endocrinol Metab 2010

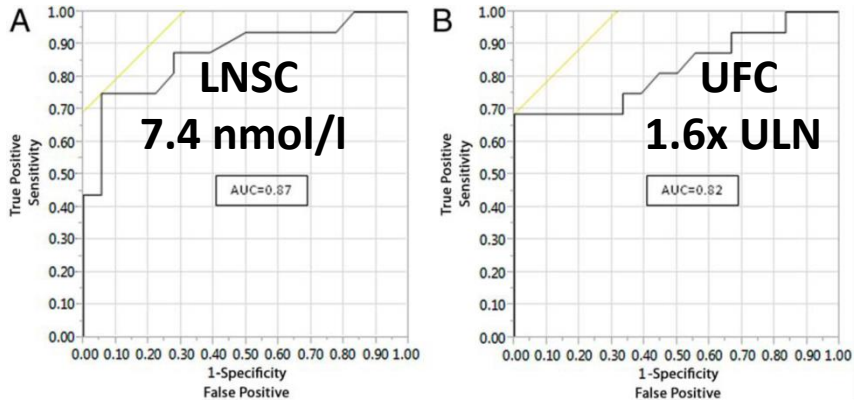
Late-night salivary cortisol for remission and recurrence in Cushing's disease (N=224)

<3 mos remission



Remission in 89% of 89 pts with LNSC data

>12 mos recurrence



Remission with LNSC:
94% sensitivity; 80% specificity

Remission with UFC or cortisol:
95% sensitivity; 80% specificity

Recurrence with LNSC:
75% sensitivity and 95% specificity

Recurrence with UFC:
68% sensitivity; 100% specificity

Amlashi FG et al J Clin Endocrinol Metab. 2015

Factors influencing incomplete tumor removal

Removal of incidental adenomas rather than the corticotroph tumor(s)

Mistakenly assuming an adenoma was found, resulting in the removal of a site that appears abnormal at surgery, but that proves to be normal gland on histological inspection;

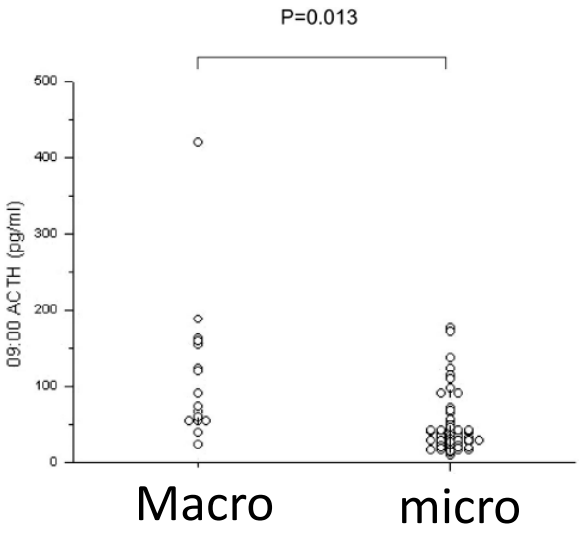
Incomplete removal of an ACTH-secreting adenoma contained within the pituitary;

Invasive ACTH-secreting adenoma that was not recognized or incompletely removed at surgery can result in lack of biochemical remission

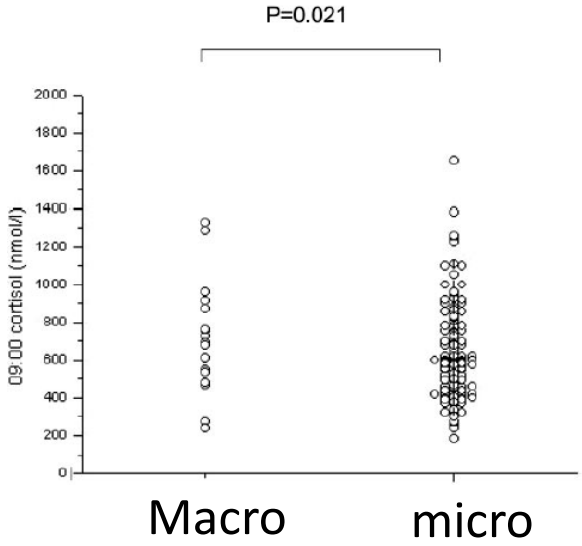
R. R. Lonser, L. Nieman, and E. H. Oldfield. J Neurosurg 2017

Macroadenoma as one end of a spectrum of tumor autonomy

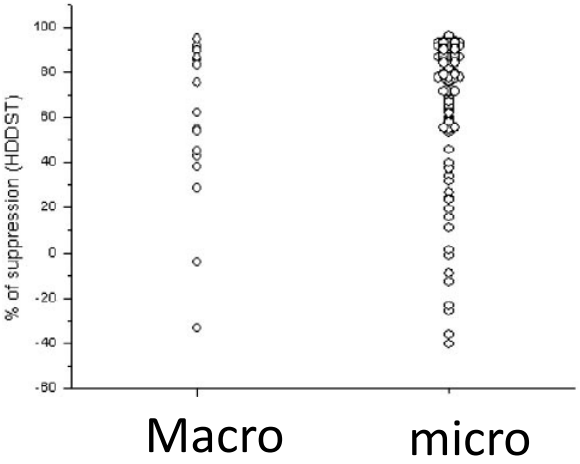
significantly higher ACTH



significantly higher cortisol



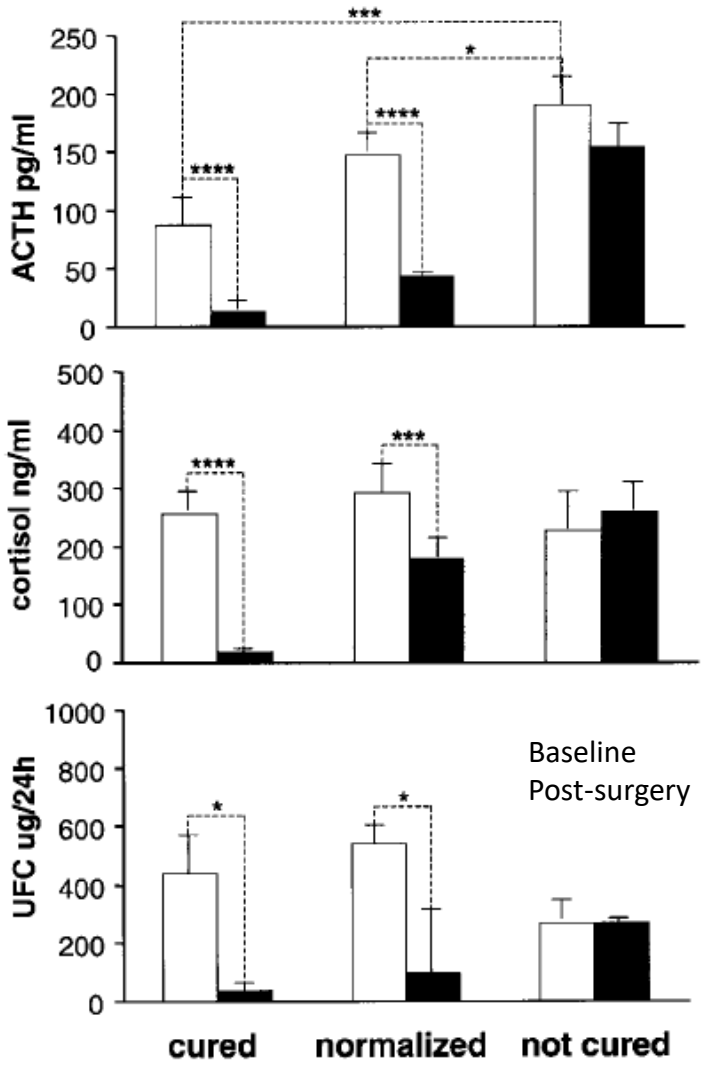
relative resistance to dexamethasone



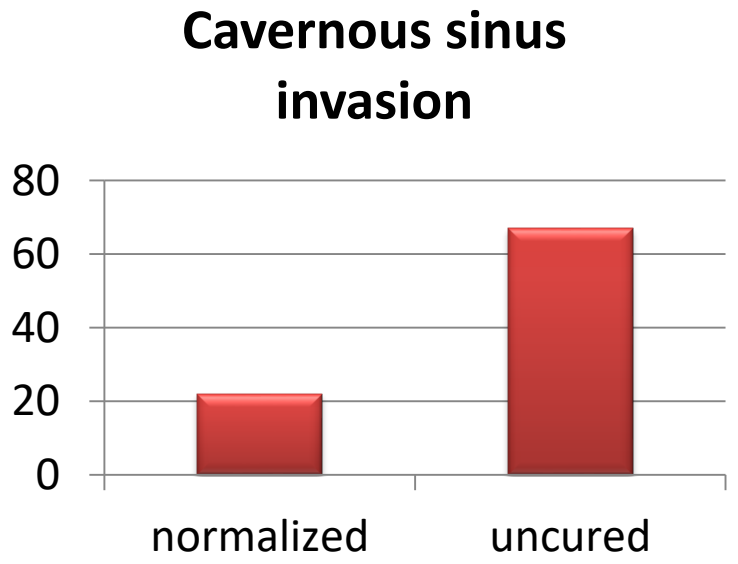
"These tumors have a distinct profile compared with microadenomas"

Woo SY et al, J Clin Endocrinol Metab 2005

Surgical outcome of macroadenomas is related to hormones and anatomy



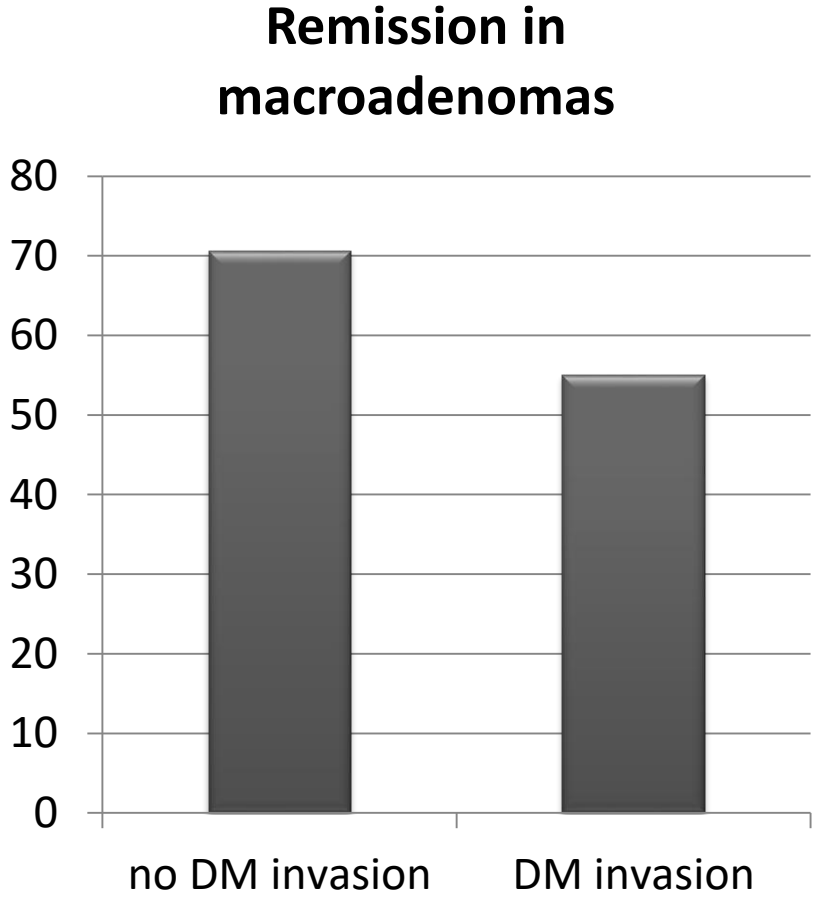
"…reduced ACTH bioactivity, impaired sensitivity to CRH, insensitivity to dexamethasone, growth and invasiveness of the tumor could be an index of a low degree of differentiation and could explain a poor prognosis".



Cannavo' S et al. Eur J Endocrinol 2003

Residual tumor is a highly possible reason for relapses

- Most relapses can be attributable to microscopic residual left at the adenoma margin or unrecognized microscopic dural invasion along the wall of the cavernous sinus (initially unrecognized.



Dalla Piazza RF et al Pituitary 2015

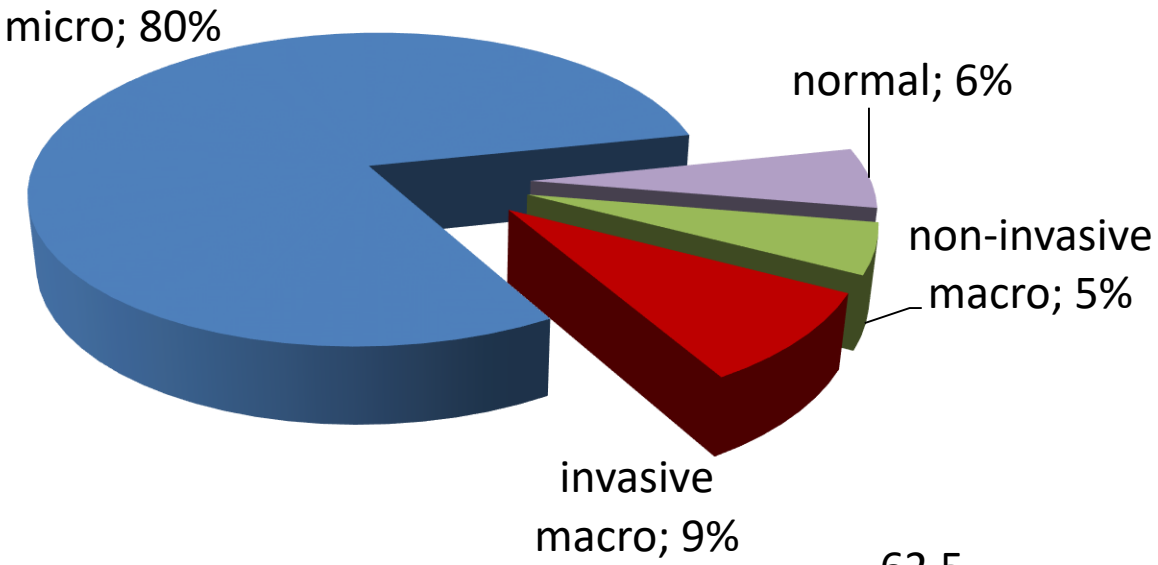
De Tommasi C et al J Neurosurg 2005

Tumor grade: relationship of adenoma to sella and sphenoid sinuses (n=289)

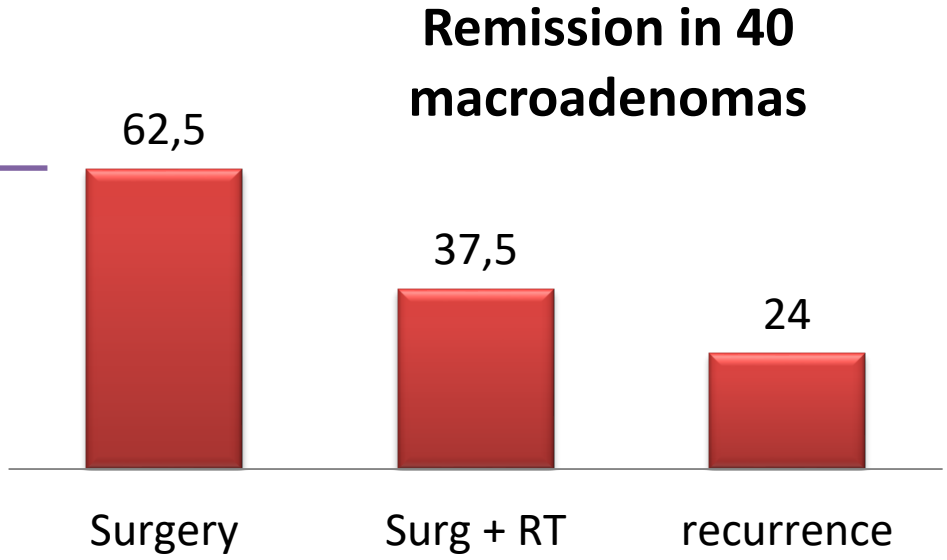
Grade	Invasion	n	Initial remission no. (%)	Persistent disease no. (%)
Grade I	Micro, IS	140	121 (86)	19 (14)
Grade II	Macro, IS	52	43 (83)	9 (17)
Grade III	Sellar perforation	8	5 (63)	3 (38)
Grade IV	Sellar destruction	0	0	0
Grade V	Metastases	0	0	0

Hammer G et al, J Clin endocrinol Metab 2004

Distribution (%) of ACTH-secreting adenomas by size and invasion criteria (N=472)

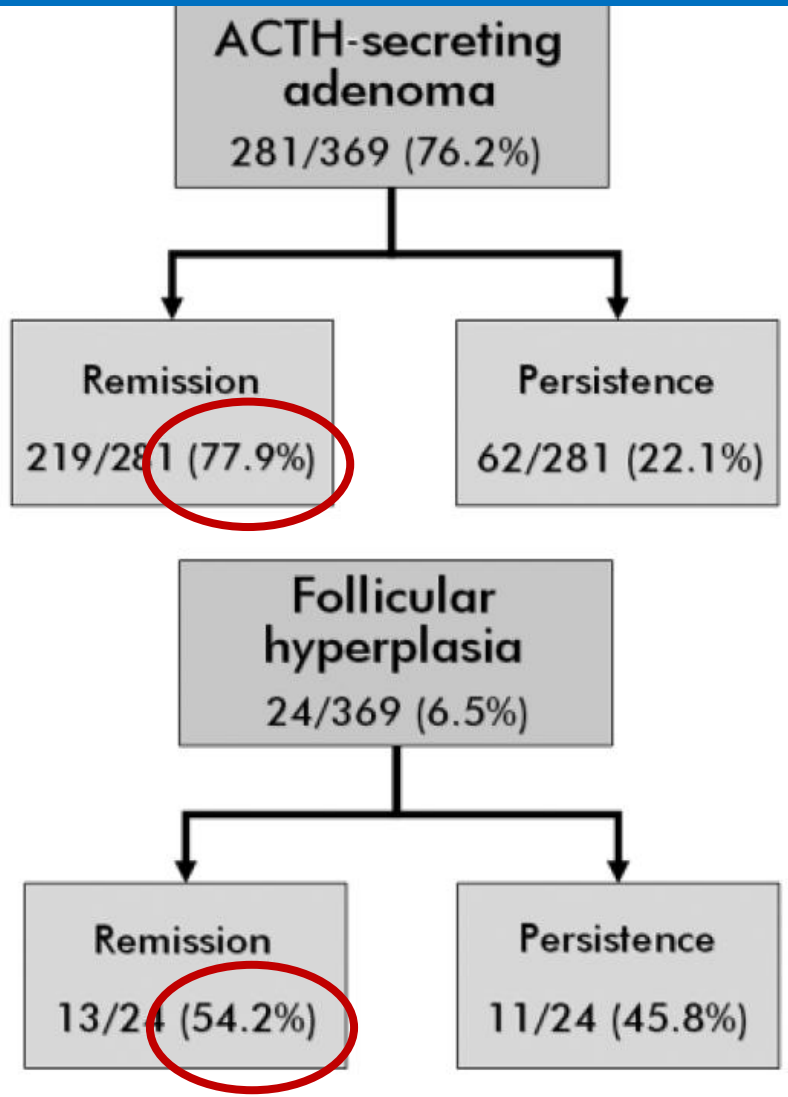


Only 22% of cavernous sinus wall invasion cases in CD are accurately detected by MR imaging

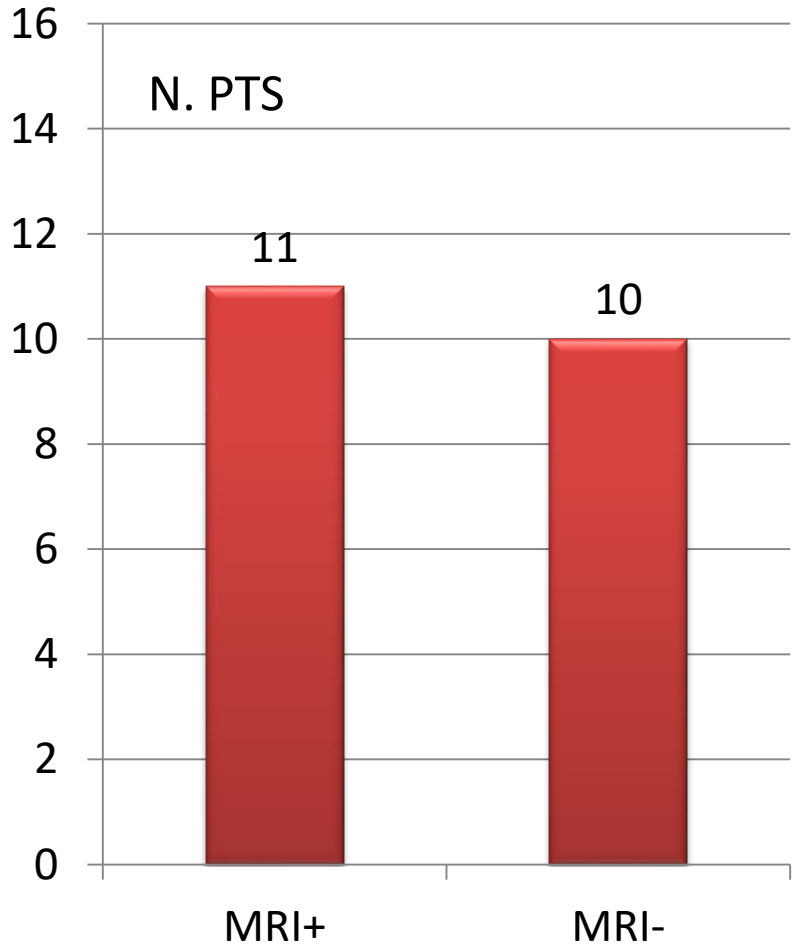


Ludecke DK et al, J Neuro-Oncol 2001
Lonser RR et al, J Neurosurg 2012

Correlation of surgical results with histopathological findings (N=369)

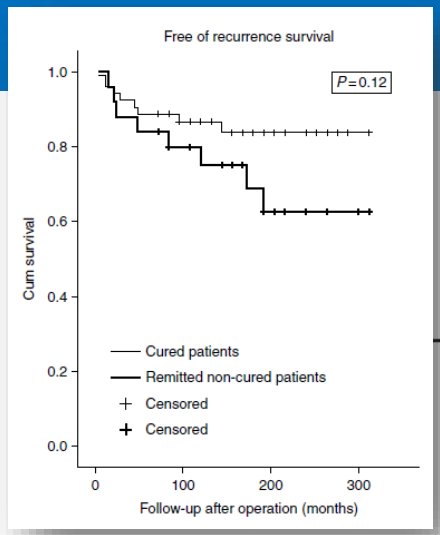


Hofmann BM et al, J neurosurg 2008



Chandler WF et al, Neurosurgery 2016

Factors associated with remission and recurrence (N=131)

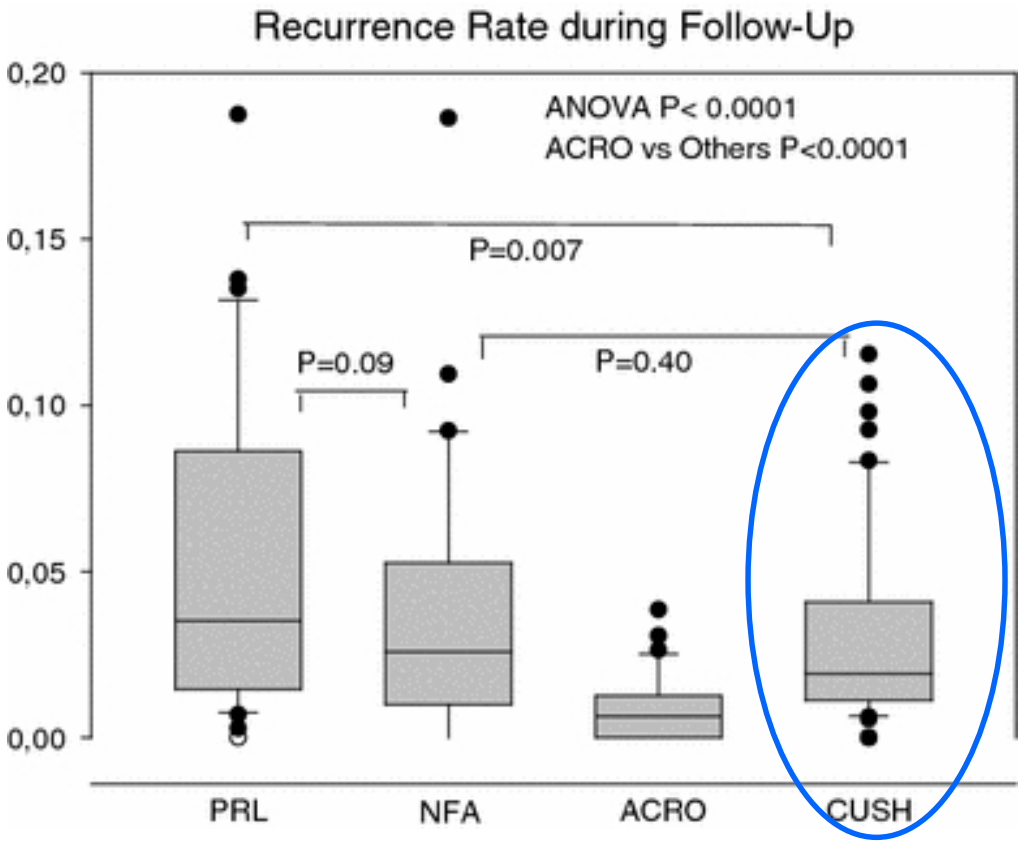


	Univariate logistic regression analysis	
	OR (95% CI)	*P*
Factors associated with a positive surgical outcome		
Macroadenoma presence[a]	0.28 (0.106–0.7379)	0.01
Gender[b]	2.692 (1.132–6.406)	0.025
Positive histology[a]	3.048 (1.353–6.869)	0.007
Factors associated with recurrence rates		
Extension of surgery[c]	0.214 (0.053–0.855)	0.029
Time of recovery HPA axis	0.926 (0.872–0.982)	0.011
Positive histology[a]	4.25 (0.893–20.233)	0.069

[a]Yes, 1 and no, 0.
[b]Female, 1 and male, 0.
[c]1, Adenomectomy; 2, hemi–hypophysectomy and 3, total hypophysectomy.

Alexandraki KI et al, Eur J Endocrinol 2013

Recurrence rate in patients treated by TTS: the atypical behavior of ACTH-sec. adenomas



Roefsema F et al, Pituitary 2012

Recurrence rate is not significantly influenced by the type of postsurgical assessment

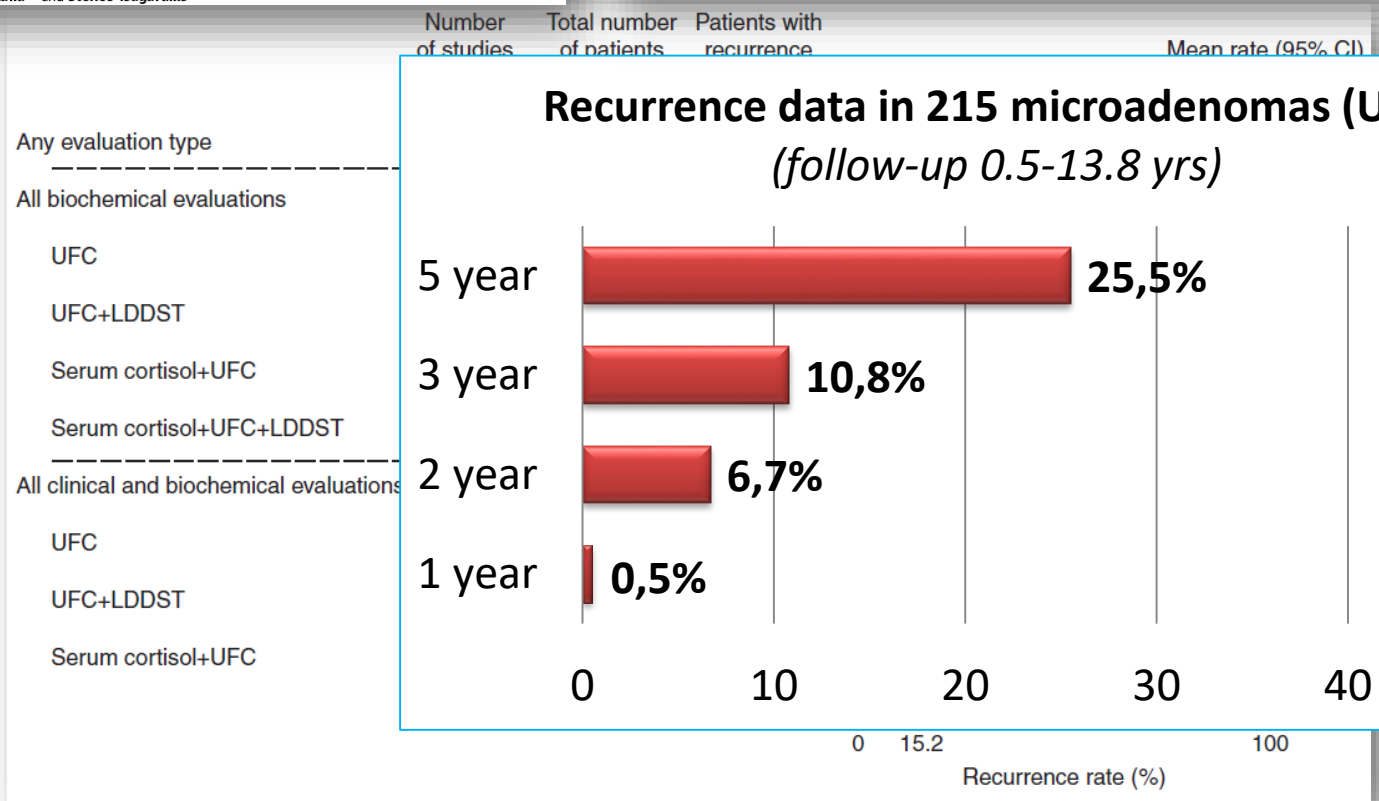
THERAPY OF ENDOCRINE DISEASE

Outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence

Stephan Petersenn, Albert Beckers[1], Diego Ferone[2], Aart van der Lely[3], Jens Bollerslev[4], Marco Boscaro[5], Thierry Brue[6,7], Paolo Bruzzi[8], Felipe F Casanueva[9], Philippe Chanson[10,11,12], Annamaria Colao[13], Martin Reincke[14], Günter Stalla[15] and Stelios Tsagarakis[16]

Late Recurrences of Cushing's Disease after Initial Successful Transsphenoidal Surgery

Chirag G. Patil, Daniel M. Prevedello, Shivanand P. Lad, Mary Lee Vance, Michael O. Thorner, Laurence Katznelson, and Edward R. Laws, Jr.



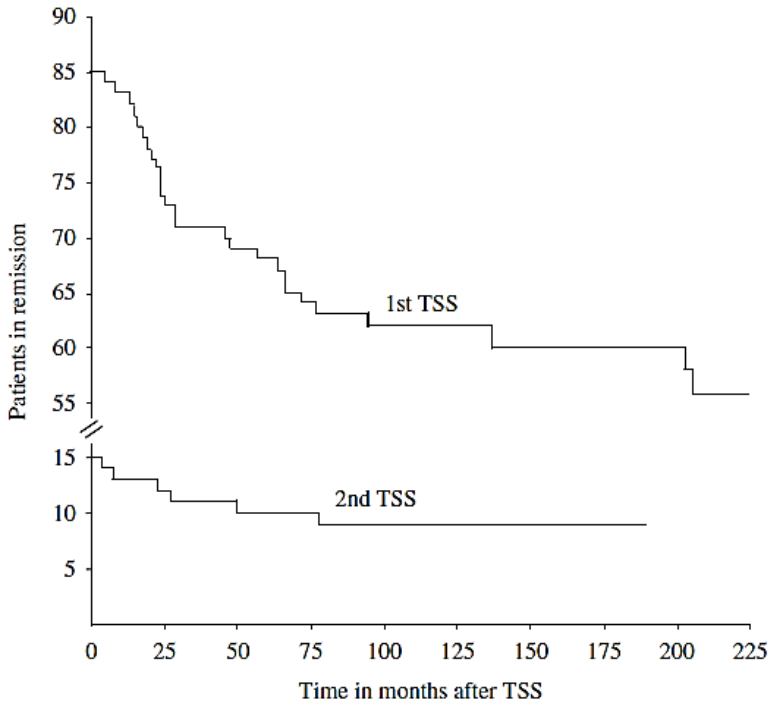
Recurrence data in 215 microadenomas (UFC)

(follow-up 0.5-13.8 yrs)

Long-term remission and recurrence rates after first and second TTS for CD (N=120)

- Recurrence rate after successful second TSS was 40% (40% of micro, 75% of macro and 17% of no visible adenoma).
- Time to recurrence after second TSS was shorter than after first TTS.
- Neither postoperative hypocortisolism nor its longer duration prevented patients from disease recurrence.

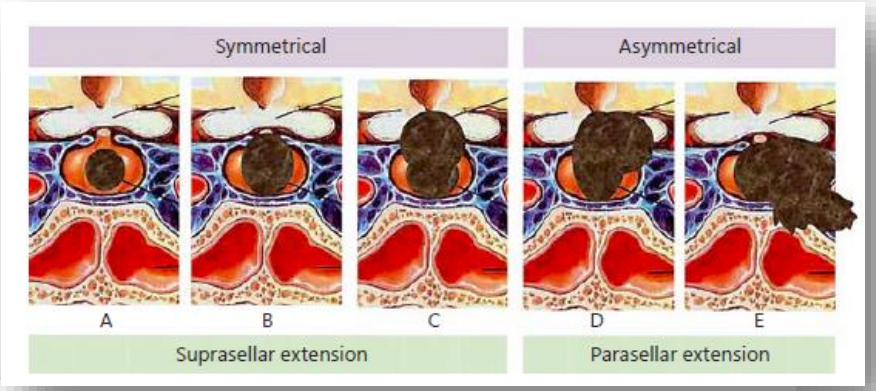
	Macroadenoma	Microadenoma
First TSS		
Remission		
Disease persistence		
Recurrence		
Mean time to recurrence ±s.d. (months)		
Second TSS		
Remission		
Disease persistence		
Recurrence		
Mean time to recurrence ±s.d. (months)		
Final outcome		
Remission		
Disease persistence		



Dimopoulou C et al, Eur J Endocrinol 2014

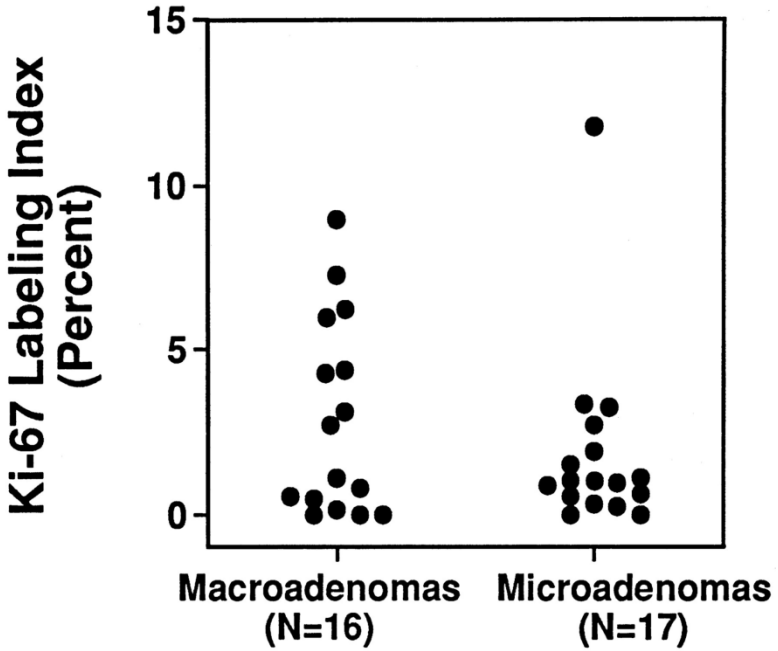
Aggressive Pituitary Tumors

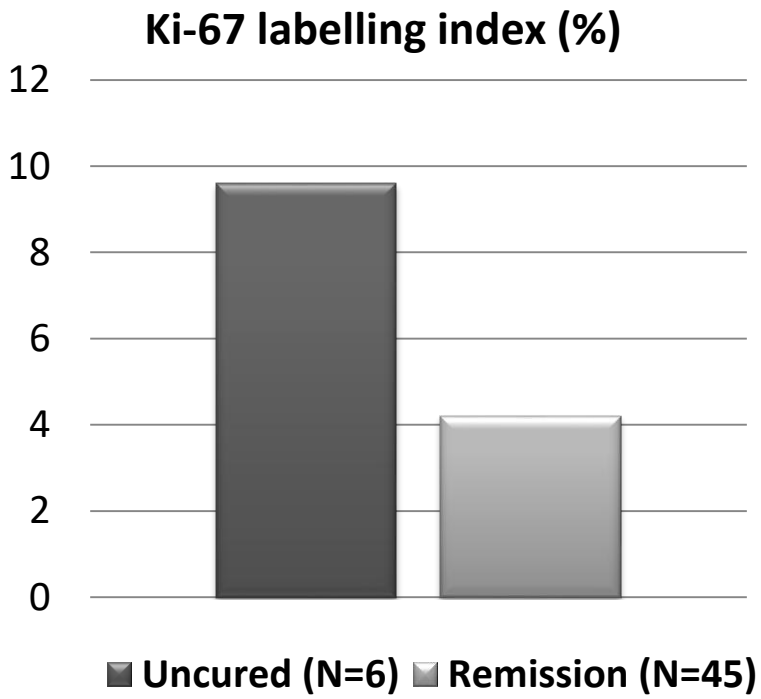
Eleftherios Chatzellis Krystallenia I. Alexandraki Ioannis I. Androulakis
Gregory Kaltsas



Histological	Novel biological markers
Histological subtype	Genomic imbalance (11q allelic loss)
Crooke's cell adenomas	DNA aneuploidy
Sparsely granulated somatotroph adenomas	MYO5A
Densely granulated lactotroph adenomas	Germline mutations associated with MEN1, MEN4, Carney complex, FIPA and SDH
Acidophil stem cell adenomas	Micro-RNAs
Thyrotroph adenomas	p27
Sparsely granulated corticotroph adenomas	Senescence markers (p16, p21, β-galactosidase)
Silent subtype 3 adenomas	PTTG
Null cell adenomas	HEPN-1
Ki67 LI	Growth factors (EGF, VEGF) and their receptors (EGFR, VEGFR)
p53	FGF-2 and ptd-FGFR4
Multimodal classification system (invasion, proliferation markers)	MMPs
	NCAM
	Galectin-3

Degree of proliferative activity differs between micro- and macroadenomas in CD





Katznelson L et al. J Clin Endocrinol Metab 1998

Losa M et al. Am J Pathol 2000

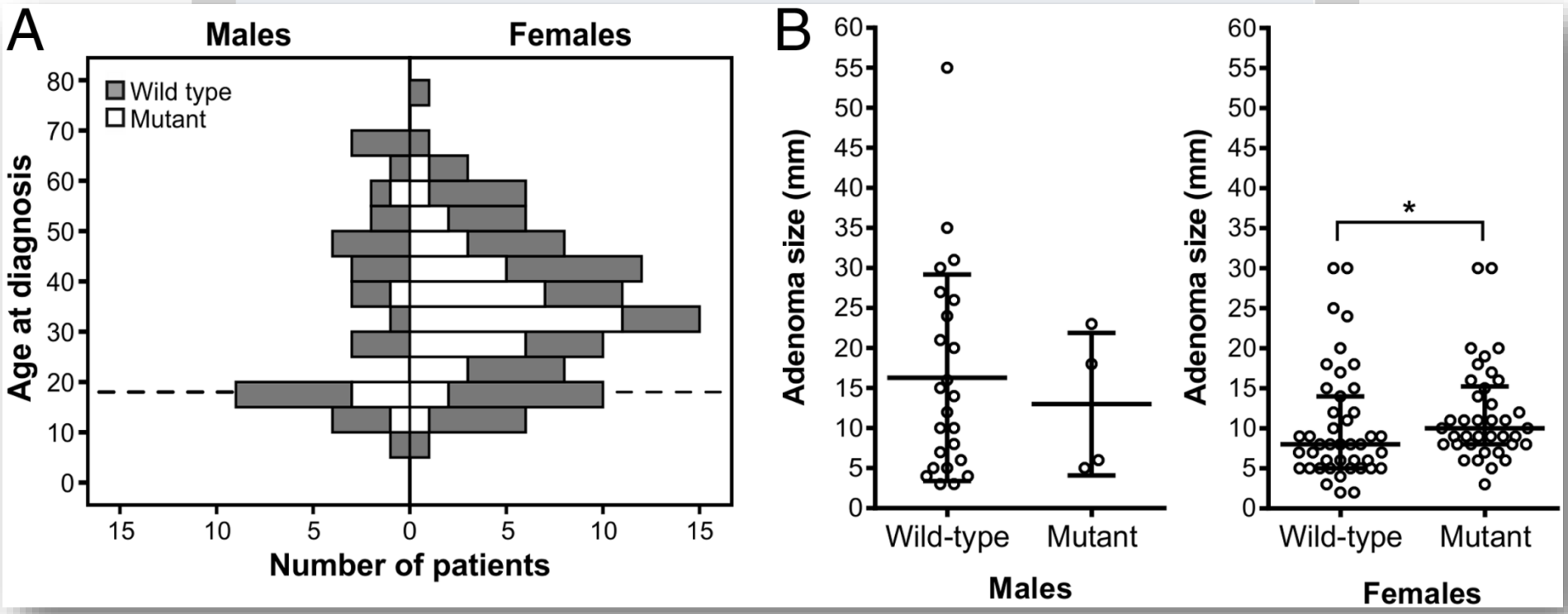
Minichromosome maintenance 7 (MCM7), a marker of aggressiveness

Variables	n	MCM7 LI[a]	P[b]
Age			
≤40	48	16.54[c] ± 2.08	
>40	49	13.51 ± 2.06	0.1
Sex			
Female	59	15.57 ± 1.89	
Male	38	14.13 ± 2.35	0.04
Dimension			
Microadenoma	23	16.04 ± 3.03	
Macroadenoma	74	14.69 ± 1.69	0.7
Hormonal type			
LH–FSH	10	10.70 ± 4.40	
ACTH	23	22.61 ± 2.90	
GH	12	18.01 ± 4.02	
PRL	29	12.69 ± 2.58	
Non-secreting	23	10.65 ± 2.90	0.04

	MCM7 LI		
	Non-invasive	Invasive	P[a]
ACTH	14.8 ± 2.8 (17)[b]	44.8 ± 4.8 (6)	0.0023
GH	11.2 ± 6.1 (8)	31.7 ± 8.7 (4)	0.23
NSA[c]	8.6 ± 3.6 (9)	12.0 ± 2.9 (14)	0.34
PRL	13.4 ± 2.3 (20)	11.0 ± 3.5 (9)	0.30
FSH/LH	8.3 ± 7.1 (3)	11.7 ± 4.6 (7)	0.90

Coli A, et al. Eur J Endocrinol 2016

Mutations in ubiquitin-specific protease (UBS)-8 gene in patients with CD



Reincke M et al , Nat Genet 2015

Perez-Rivas LG et al, J Clin Endocrinol Metab 2015

Clinical outcomes of surgery for ACTH-sec pituitary adenoma

Predictors of Mortality and Long-term Outcomes in Treated Cushing's Disease: A Study of 346 Patients

Jessica K. Lambert, Levana Goldberg, Sofia Fayngold, Jane Kostadinov, Kalmon D. Post, and Eliza B. Geer

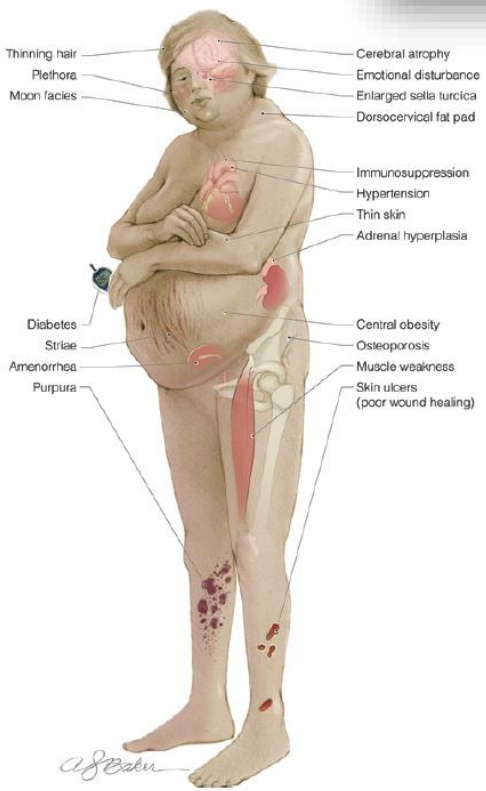
Characteristic	Total Cohort (n = 346)
Age at diagnosis, y[a]	39.9 (7–77)
Female:male[b]	265:81 (77%)
Duration of follow-up[a]	6.3 y (1 mo to 30 y)
Duration of GC exposure, mo[c,d]	40 (2 mo to 20 y)
Comorbidities[b]	
Hypertension	248 (72%)
Diabetes	95 (27%)
Depression	76 (22%)
Psychosis	6 (2%)
Osteoporosis	67 (19%)
Coronary artery disease	14 (4%)
Cerebrovascular accident	4 (1%)
Dyslipidemia	55 (16%)
MRI findings[b,e]	
Microadenoma	117 (34%)
Macroadenoma	39 (11%)
No visible adenoma	87 (25%)
Inhomogeneous pituitary[f]	67 (19%)
BIPSS[b]	160 (46%)
Preoperative ACTH, pg/mL[a]	84.2 (8–1000)
Preoperative UFC, μg/24 h[c]	269.5 (18.1–8097)
Preoperative hemoglobin A1c[b,g]	7.9 (4.6–19.6)
Preoperative systolic BP, mm Hg[b,h]	146 (96–220)
Preoperative diastolic BP, mm Hg[b,h]	89 (53–150)
Preoperative BMI, kg/m^2[b,i]	31.5 (17–51.6)
Preoperative low-density lipoprotein, mg/dL[b,j]	130.8 (60–352)
Preoperative triglycerides, mg/dL[b,k]	167 (40–1243)

Endocrine
DOI 10.1007/s12020-016-0984-8

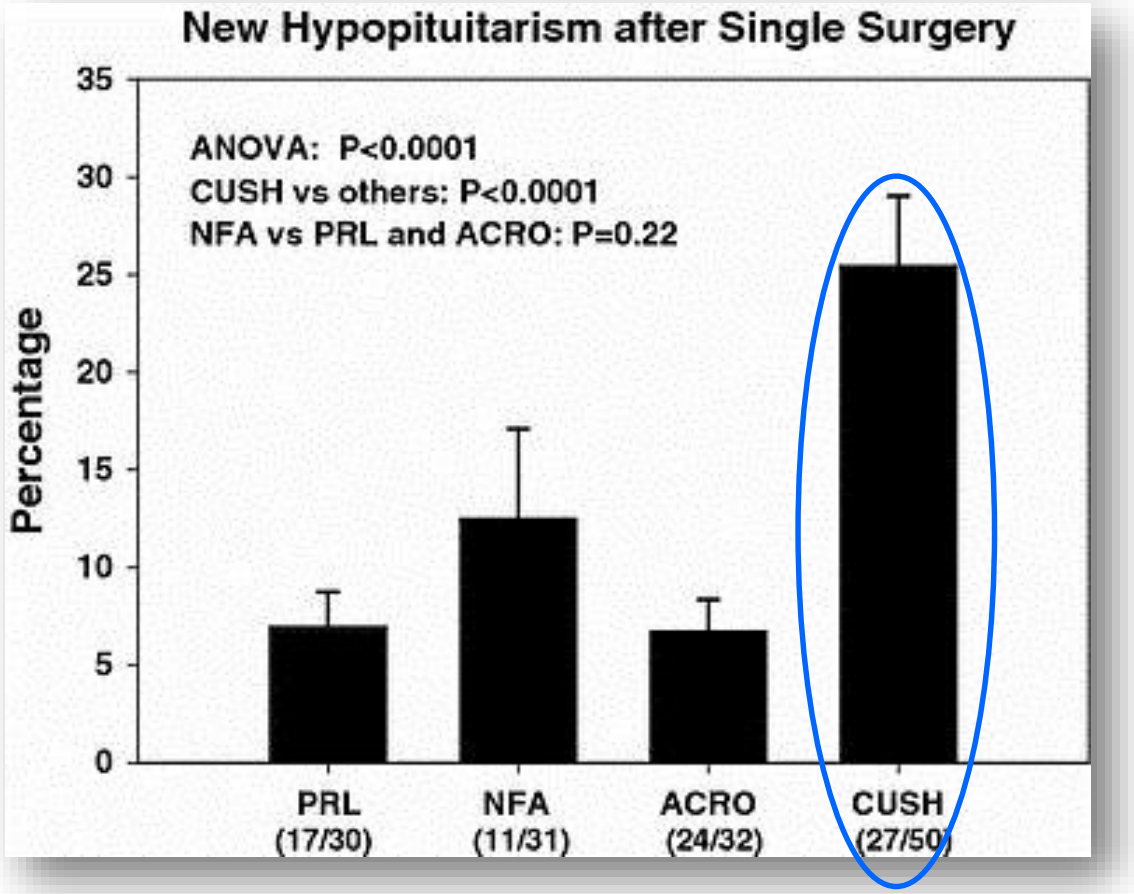
REVIEW

Cushing's disease: the burden of illness

Rosario Pivonello[1] · Maria Cristina De Martino[1] · Monica De Leo[1] · Chiara Simeoli[1] · Annamaria Colao[1]



The incidence of new hypopituitarism after single TTS is increased in ACTH-sec. tumors



Roefsema F et al, Pituitary 2012

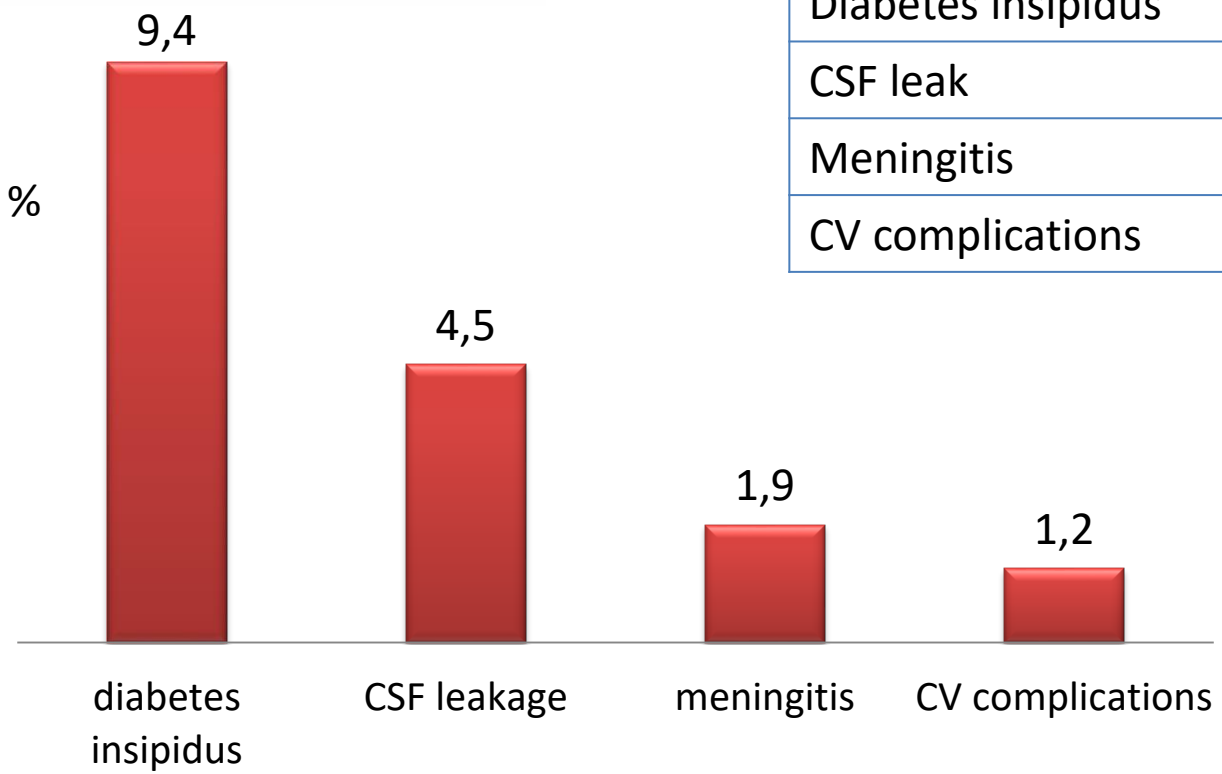
Complications of microsurgery for ACTH-sec pituitary adenomas

THERAPY OF ENDOCRINE DISEASE

Outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence

Stephan Petersenn, Albert Beckers[1], Diego Ferone[2], Aart van der Lely[3], Jens Bollerslev[4], Marco Boscaro[5], Thierry Brue[6,7], Paolo Bruzzi[8], Felipe F Casanueva[9], Philippe Chanson[10,11,12], Annamaria Colao[13], Martin Reincke[14], Günter Stalla[15] and Stelios Tsagarakis[16]

Correlation with surgical experience	r	p
Hypopit	-0.29	ns
Diabetes insipidus	-0.54	<0.05
CSF leak	-0.74	<0.001
Meningitis	-0.54	<0.05
CV complications	-0.51	ns



Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years

Bernd Markus Hofmann, M.D.,[1] Michal Hlavac, M.D.,[1] Ramon Martinez, M.D.,[1] Michael Buchfelder, M.D., Ph.D.,[1] Otto Albrecht Müller, M.D., Ph.D.,[2] and Rudolf Fahlbusch, M.D., Ph.D.[1]

Overall complications	5.9% (25/426)
Mortality	3 (0.7%) including: 1: overweight, ARDS, 1: meningitis 1: stress-induced GI bleeding
Mesenteric infarction	2 (0.4%)
Rhinorrhea requiring operation	2 (0.5%)
Meningitis	3 (0.7%)
Transient oculomotor nerve palsy	1 (0.2%)
Additional insufficiencies of >1 anterior pituitary lobe hormones	4 (0.9%)
Diabetes insipidus	4 (0.9%)
Deep venous thrombosis	8 (1.8%)

Complications differ in MRI+ and MRI- ACTH-sec. tumors (N=230)

Postoperative complications	Total n = (%) 230	Positive MRI n = (%) 160	Negative MRI n = (%) 70
CSF leakage			
CSF leakage intraoperatively	29 (12.6)	22 (13.7)	7 (10)
CSF leakage postoperatively	0 (0)	0 (0)	0 (0)
Endocrinology disorders			
Transient diabetes insipidus	51 (22)	27 (16.8)	24 (34.2)
Long-term diabetes insipidus	15 (6.4)	8 (5)	7 (10)
Partial anterior pituitary insufficiency	4 (1.8)	1 (0.6)	3 (4.3)
Complete anterior pituitary insufficiency	3 (1.4)	3 (1.9)	0 (0)
SIADH	8 (3.4)	4 (2.5)	4 (5.7)
Visual complications	2 (0.8)	0 (0)	2 (2.8)
Other			
Vascular injury	0 (0)	0 (0)	0 (0)
Epistaxis	6 (2.6)	5 (3.1)	1 (1.4)
Deep venous thrombosis	3 (1.3)	2 (1.25)	1 (1.42)
Pulmonary emboli	1 (0.4)	0 (0)	1 (1.42)
Meningitis	0 (0)	0 (0)	0 (0)

Cebula H et al, Acta Neurochir 2017

Risk of complications from repeat TSS

In case of tumor remnant, the first step is a thorough re-exploration of the original resection site.

The higher incidence of postop complications after repeat TTS is the more aggressive approach, i.e. hemihypophysectomy and total hypophysectomy.

Postoperative panhypopituitarism are as high as 45% after hypophysectomy and 0–5% after repeat selective adenomectomy.

*Selective adenomectomy vs. subtotal hypophysectomy**

Procedure & Outcome	No. of Cases
selective adenomectomy	20
in remission	19
hypopituitarism	1
subtotal or total hypophysectomy	12
in remission	5
hypopituitarism	6
no tissue in sella at repeat surgery	1
in remission	0
hypopituitarism	1

Friedman RB et al, J Neurosurg 1989
Benveniste RJ et al, J Neurosur 2005
Geer EB, Pituitary 2014

Conclusions

Trans-sphenoidal surgery is an effective, definitive treatment for Cushing's disease.

There are differences between MRI+ or MRI- micro and macroadenomas in terms of outcome and relapse.

Molecular factors could play a role in invasiveness and relapse.

Not all patients achieve remission, some experience relapse after variable time from *apparent* remission.

Remission criteria require disambiguity (*loose link* between tumor surgery, rate of remission and risk of relapse).