NAPOLI 5-7 MAGGIO 2015

A peculiar aspect of treatment in Cushing's disease:

Pasireotide between present and future

THE ROLE OF PASIREOTIDE ON TUMOR MASS

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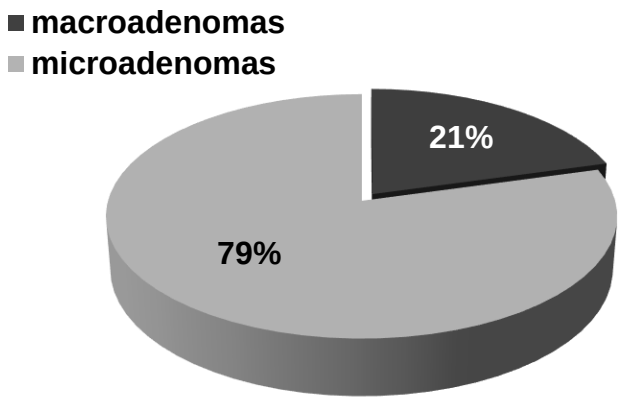
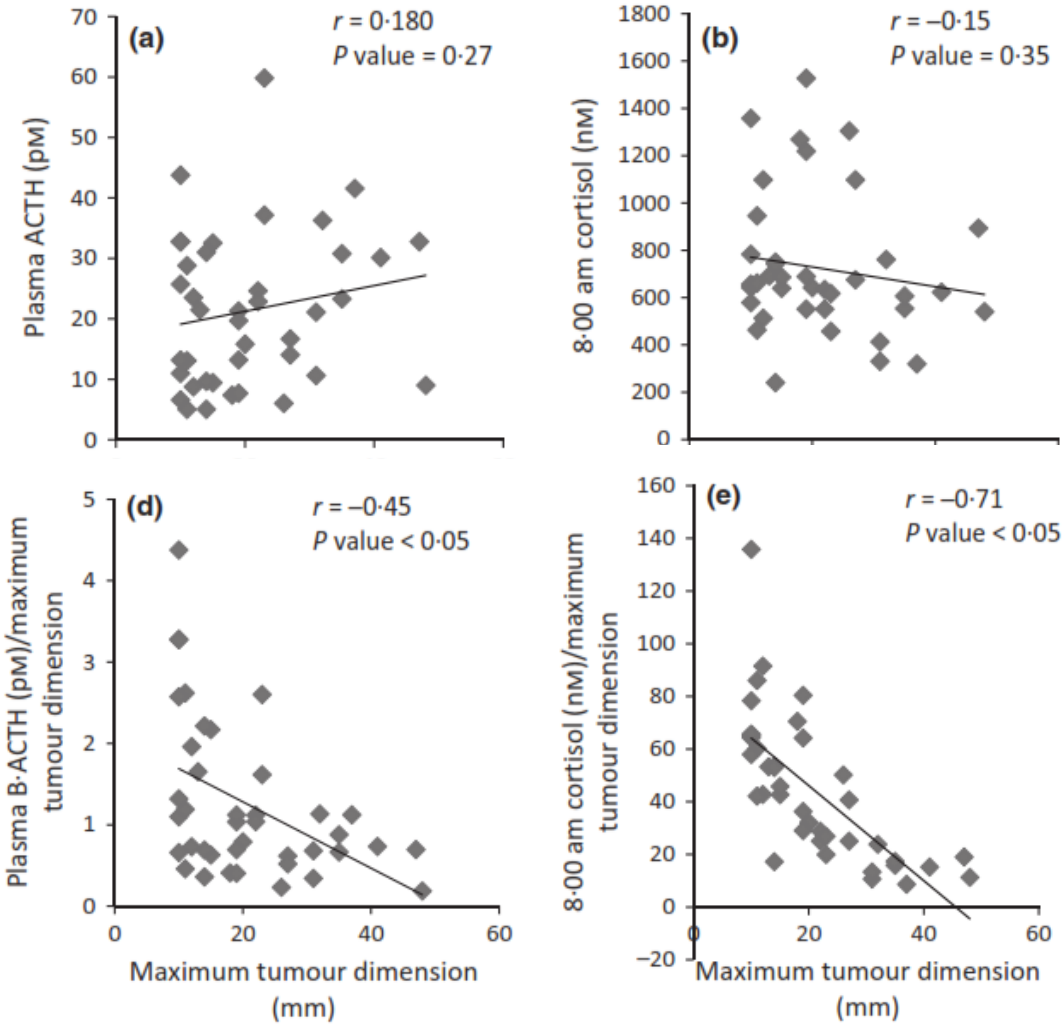
Clinical Endocrinology (2014) **81**, 336–342

Clinical, biochemical and imaging characteristics of Cushing's macroadenomas and their long-term treatment outcome

Harshal Ramesh Kakade*, Rajeev Kasaliwal*, Kranti S. Khadilkar*, Swati Jadhav*, Amol Bukan*, Shruti Khare*, Sweta R. Budyal*, Atul Goel†, Anurag R. Lila*, Tushar Bandgar* and Nalini S. Shah*

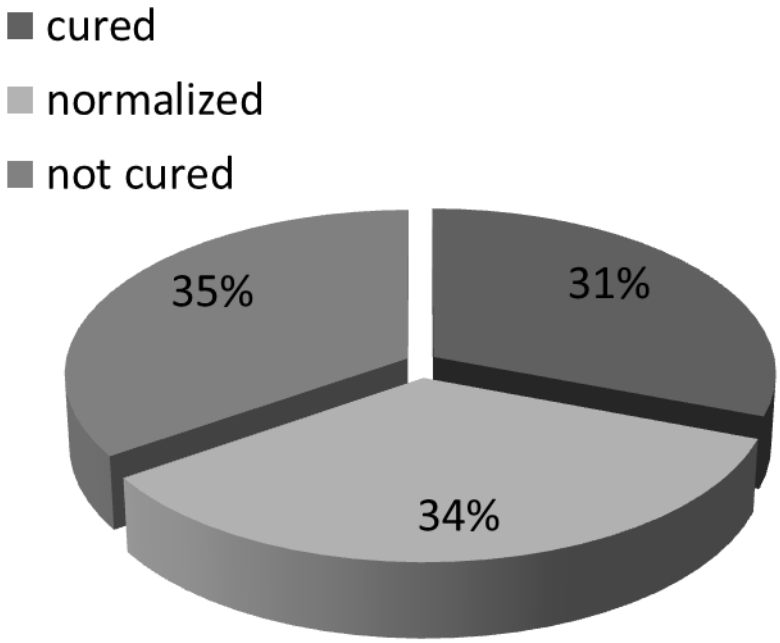


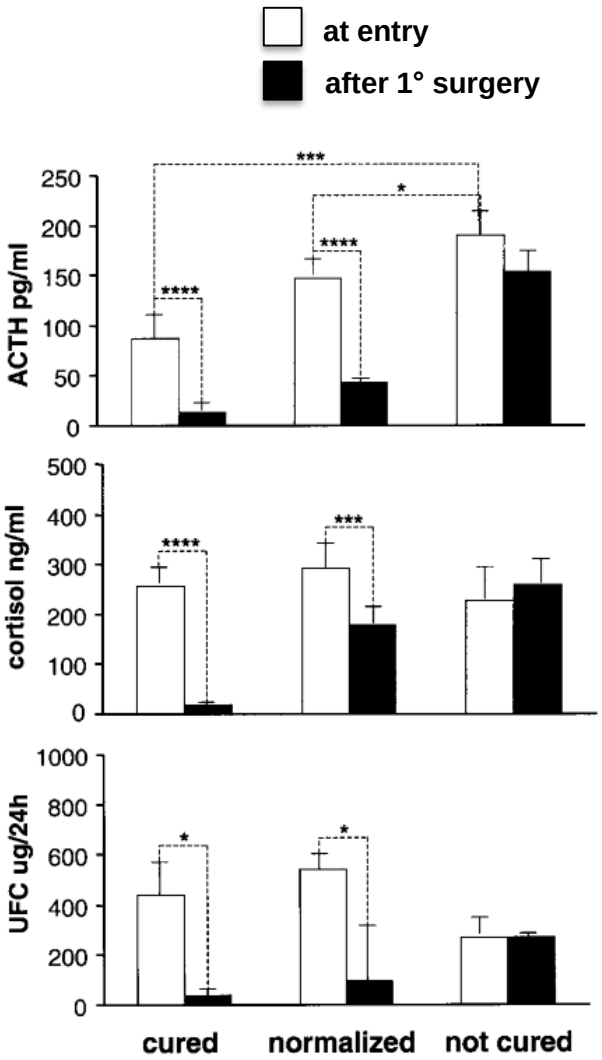


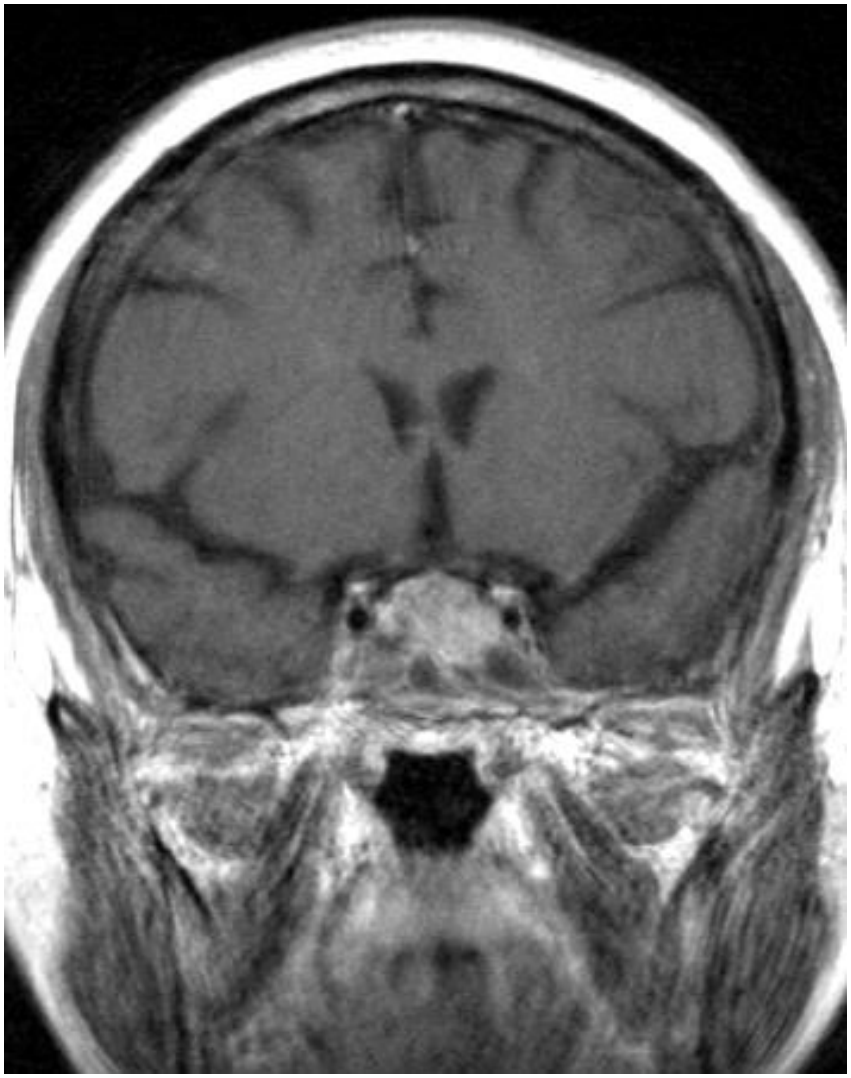
European Journal of Endocrinology (2003) **149** 195–200

Long-term results of treatment in patients with ACTH-secreting pituitary macroadenomas

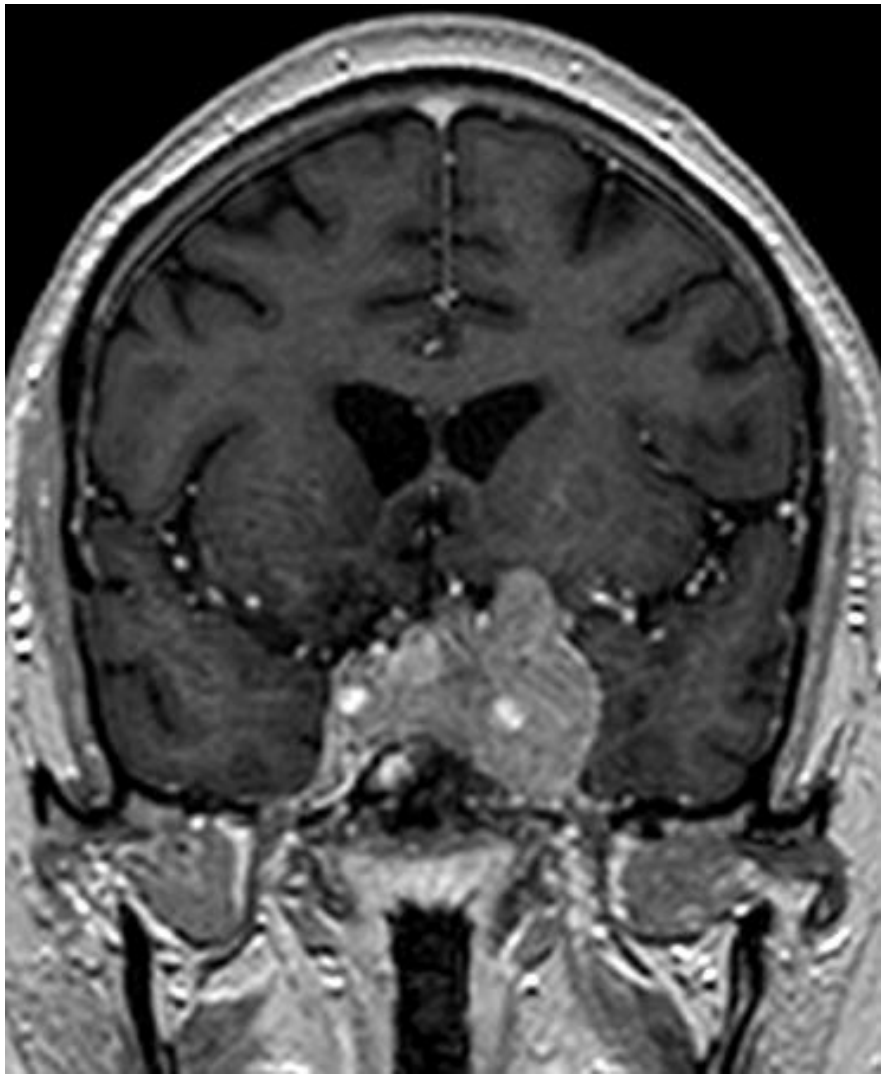
S Cannavò, B Almoto, C Dall'Asta[1], S Corsello[2], R M Lovicu[2], E De Menis[3], F Trimarchi and B Ambrosi[1]







F.M.G., 55 aa, ♀

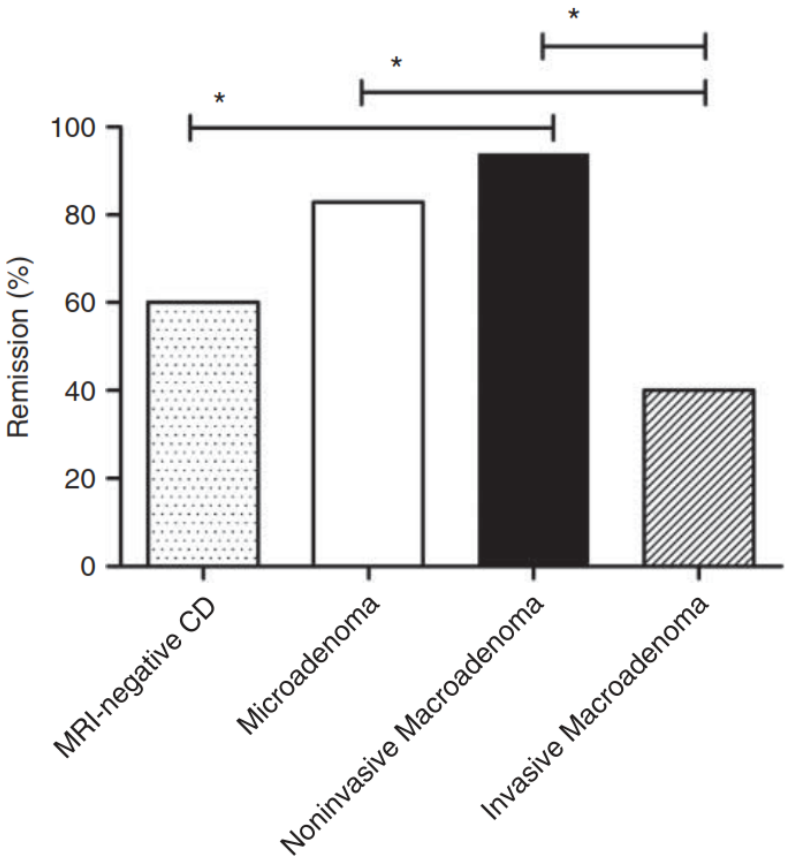


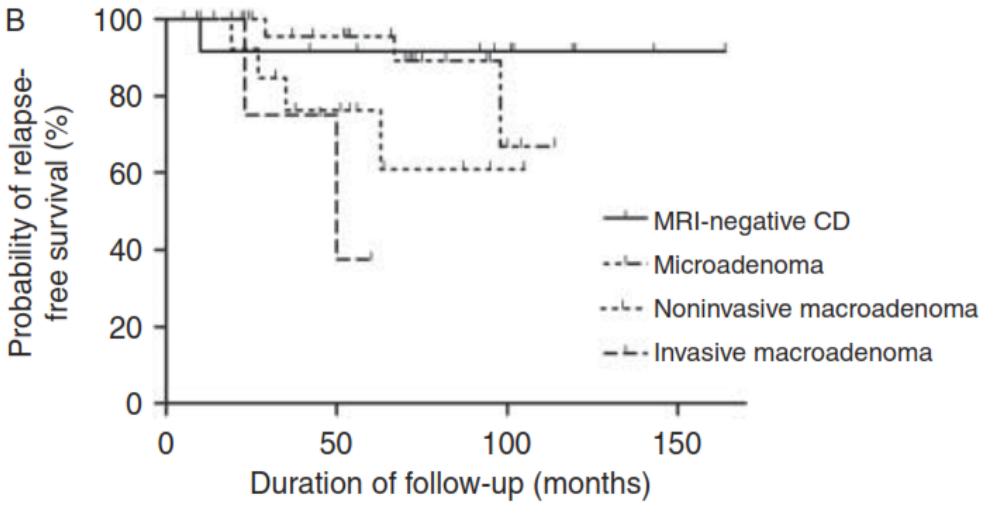
F.M.G., 35 aa, ♂

European Journal of Endocrinology (2013) **169** 329–337

Endoscopic transsphenoidal pituitary surgery: a good and safe primary treatment option for Cushing's disease, even in case of macroadenomas or invasive adenomas

M A E M Wagenmakers[1], H D Boogaarts[2], S H P P Roerink[1], H J L M Timmers[1], N M M L Stikkelbroeck[1], J W A Smit[1], E J van Lindert[2], R T Netea-Maier[1], J A Grotenhuis[2] and A R M M Hermus[1]





J. Endocrinol. Invest. *25:* 172-175, 2002

Macroprolactinoma associated with Cushing's disease, successfully treated with cabergoline

G. T'Sjoen*, I. Defeyter**, J. Van De Saffele*, R. Rubens*, and M. Vandeweghe*

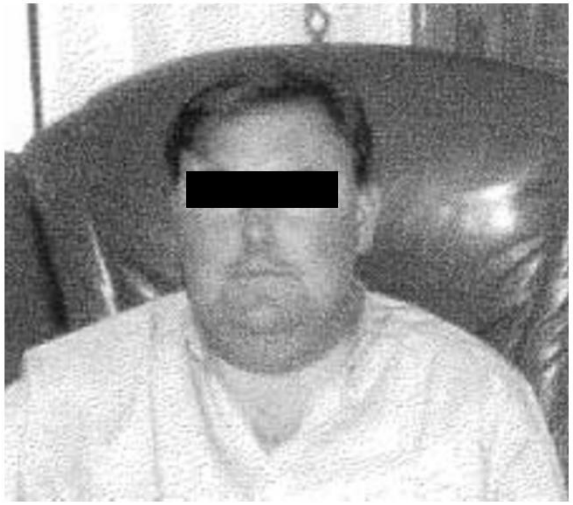


Table 1 - *Laboratory investigations at presentation.*

		Normal value
Cortisol µg/dl	47.6	4-24
F (after 1 mg dexa) µg/dl	35.6	<3
ACTH pg/ml	113.2	9-52
TSH µU/ml	0.22	1.3-4.3
Free T_4 ng/dl	1.0	0.9-1.7
PRL ng/ml	842	4-17

Table 2 - *Effect of treatment on hormonal parameters.*

	7-week treatment with cabergoline	37-month treatment with cabergoline	Normal values
Cortisol	3.3	15.9	4-24
ACTH	21.4	23.9	9-52
PRL	5.8	1.8	4-17

J Clin Endocrinol Metab, January 2009, 94(1):223–230

The Medical Treatment of Cushing's Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery

Rosario Pivonello, Maria Cristina De Martino, Paolo Cappabianca, Monica De Leo, Antongiulio Faggiano, Gaetano Lombardi, Leo J. Hofland, Steven W. J. Lamberts, and Annamaria Colao

	Responsive patients (n = 15)			Resistant patients (n = 5)		
Parameter	Baseline	3-month treatment	*P* value	Baseline	3-month treatment	*P* value
Body mass index (kg/m^2)	27.5 ± 0.8	28.0 ± 0.8	0.115	27.7 ± 1.3	28.4 ± 1.3	0.066
Waist to hip ratio	1.10 ± 0.04	1.08 ± 0.04	0.001	1.05 ± 0.06	1.07 ± 0.06	0.221
Systolic blood pressure (mm Hg)	146.0 ± 3.6	135.7 ± 2.9	0.001	149.0 ± 5.8	138.0 ± 3.7	0.041
Diastolic blood pressure (mm Hg)	94.0 ± 2.4	87.3 ± 2.2	0.002	95.0 ± 4.2	88.0 ± 3.7	0.038
Heart rate (beats/min)	69.5 ± 1.8	74.1 ± 2.3	0.014	63.2 ± 1.3	65.0 ± 0.5	0.109
Fasting serum glucose (mg/dl)	129.3 ± 5.6	121.8 ± 4.0	0.004	124.2 ± 7.7	116.2 ± 3.1	0.136
Fasting serum insulin (μU/ml)	11.0 ± 1.2	10.1 ± 1.2	0.001	14.4 ± 1.2	13.7 ± 1.1	0.104
HOMA-IR	3.6 ± 0.5	3.1 ± 0.4	0.002	4.4 ± 0.5	4.0 ± 0.3	0.138
HOMA-B (%)	65.0 ± 7.2	65.4 ± 7.4	0.865	92.0 ± 17.1	94.0 ± 9.4	0.500
Plasma ACTH (pg/ml)	64.9 ± 3.3	56.3 ± 3.1	0.002	78.0 ± 10.3	78.6 ± 9.6	0.893
Serum cortisol (μg/liter)	239.3 ± 13.9	177.1 ± 13.4	0.001	288.8 ± 21.1	276.8 ± 14.5	0.686
Urinary cortisol (μg/d)	561.9 ± 52.5	192.0 ± 29.1	0.001	674.4 ± 100.5	642.2 ± 70.6	0.345
Tumor volume (mm^3)	246.5 ± 40.9	230.7 ± 41.5	0.047	565.3 ± 391.2	573.1 ± 394.3	0.109

Parameter	Baseline (10 patients)	12-month treatment (10 patients)	24-month treatment (8 patients)	*P* value
Tumor volume (mm^3)	224.3 ± 31.9	158.1 ± 46.2[a]	133.7 ± 56.7[a]	0.084

radiological features of patients with CD long-term responsive to cabergoline treatment

[a] $P < 0.05$ compared with baseline.

TheScientificWorldJOURNAL (2010) 10, 2132–2138

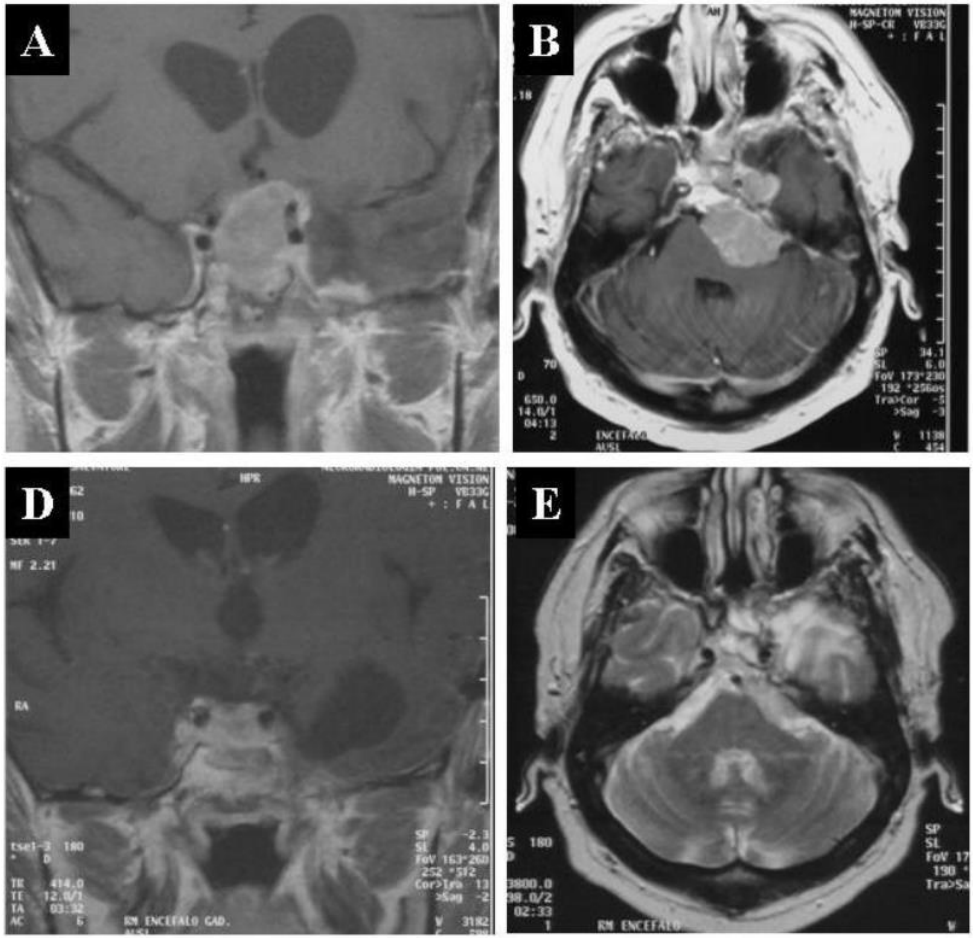
Temozolomide-Induced Shrinkage of a Pituitary Carcinoma Causing Cushing's Disease — Report of a Case and Literature Review

Lorenzo Curtò[1,*], Maria L. Torre[1], Francesco Ferraù[1], Vincenzo Pitini[2], Giuseppe Altavilla[2], Francesca Granata[3], Marcello Longo[3], Leo J. Hofland[4], Francesco Trimarchi[1], and Salvatore Cannavò[1]

Basal and Dynamic Evaluation of the Hypothalamic-Pituitary-Adrenal Axis	At Presentation
Morning ACTH (pg/ml)	93.0 (normal range 5.0–50.0)
Morning cortisol (μg/dl)	44.3 (normal range 5.0–25.0)
Urinary free cortisol (μg/24 h)	367.6 (normal range 5.0–72.0)
ACTH after high-dose dexamethasone[§]	69.0
Cortisol after high-dose dexamethasone[§]	27.8
CRH (i.v. 1 μg/kg) stimulated ACTH (pg/ml)	118 (peak = 143)
CRH (i.v. 1 μg/kg) stimulated cortisol (μg/ml)	41 (peak = 45.2)
DDAVP* (i.v. 10 μg) stimulated ACTH (pg/ml)	82 (peak = 378)
DDAVP* stimulated cortisol (μg/ml)	35.7 (peak = 63.4)

§ Oral dexamethasone suppression test (8 mg daily for 2 days, consecutively).

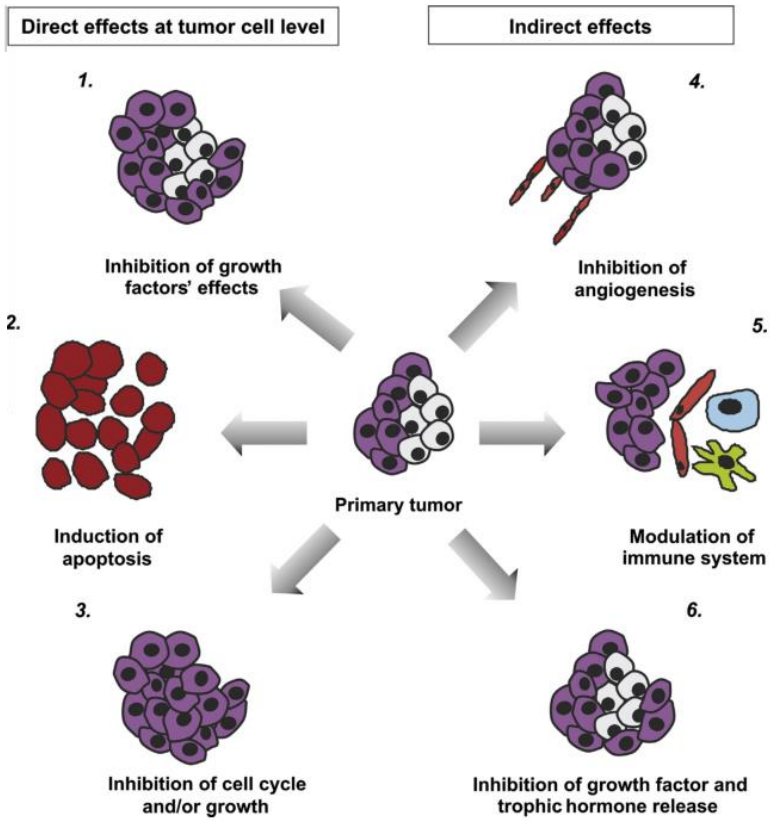
* Desmopressin acetate.

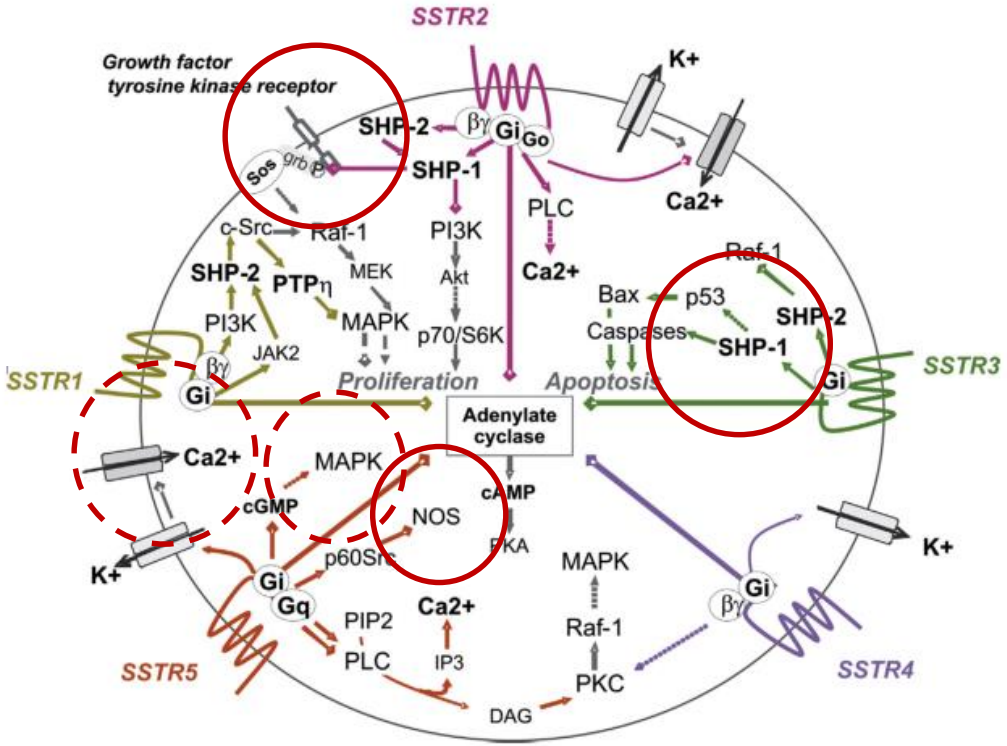


Frontiers in Neuroendocrinology 34 (2013) 228–252

Somatostatin receptors: From signaling to clinical practice

Marily Theodoropoulou *, Günter K. Stalla

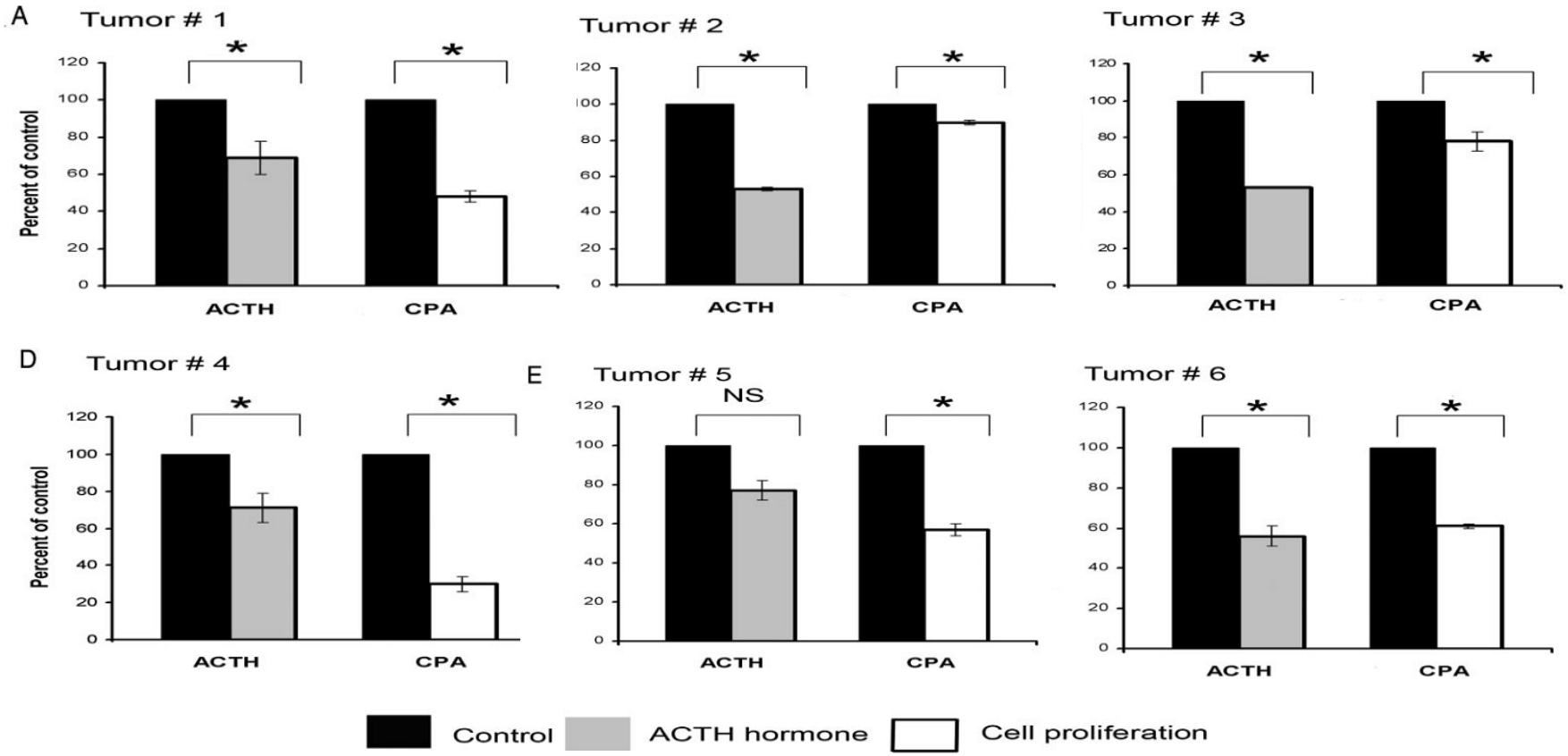




The Journal of Clinical Endocrinology & Metabolism 91(11):4482–4488

The Effects of SOM230 on Cell Proliferation and Adrenocorticotropin Secretion in Human Corticotroph Pituitary Adenomas

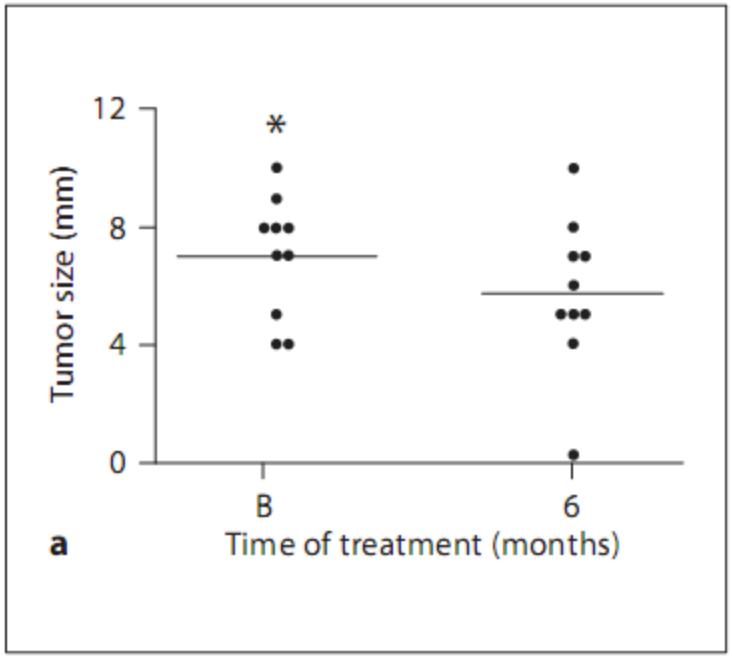
Dalia L. Batista, Xun Zhang, Roger Gejman, Peter J. Ansell, Yunli Zhou, Sarah A. Johnson, Brooke Swearingen, E. Tessa Hedley-Whyte, Constantine A. Stratakis, and Anne Klibanski



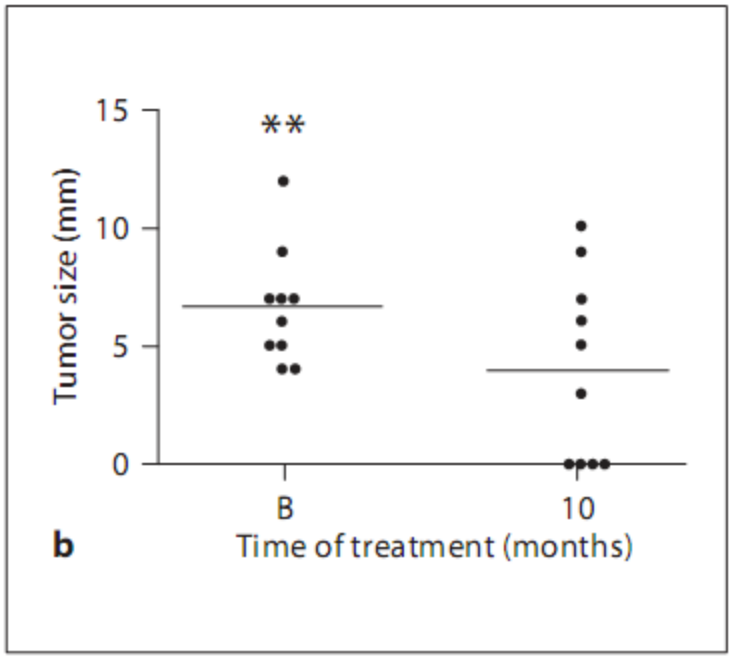
Neuroendocrinology
DOI: 10.1159/000327429

Effect of SOM230 (Pasireotide) on Corticotropic Cells: Action in Dogs with Cushing's Disease

Victor Castillo[a] Marily Theodoropoulou[b] Johanna Stalla[b]
Maria Florencia Gallelli[a] Maria Fernanda Cabrera-Blatter[a] Mariana R. Haedo[c, d]
Marta Labeur[b] Herbert A. Schmid[e] Günter K. Stalla[b] Eduardo Arzt[c, d]



Group 1: p 0.04

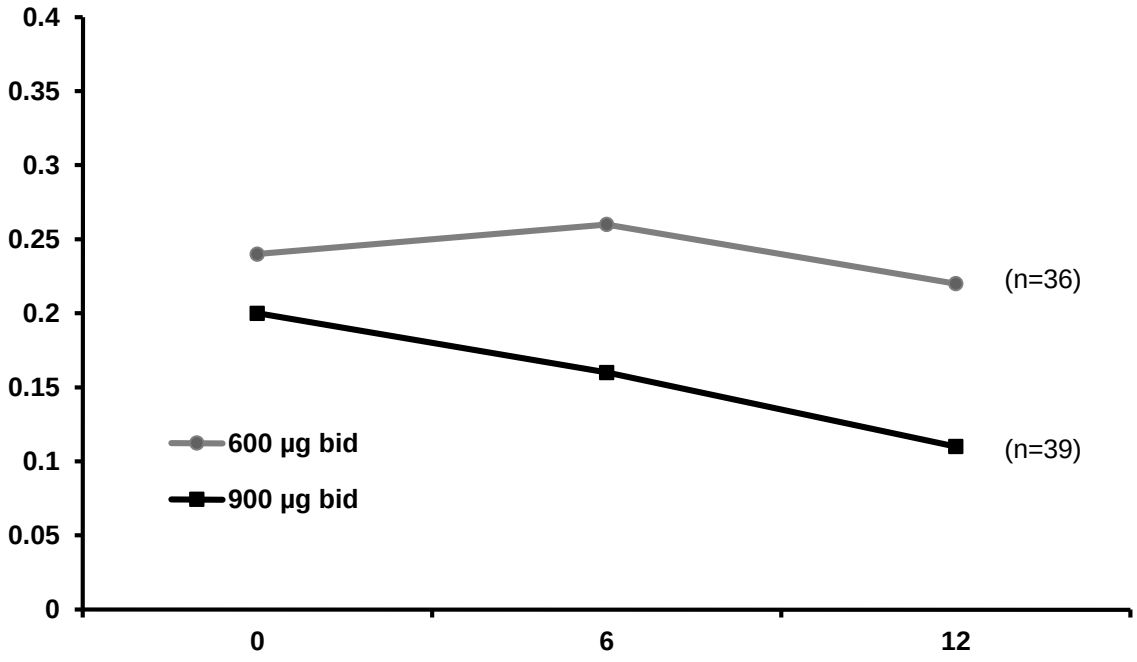


Group 2: p 0.002

N Engl J Med 2012;366:914-24.

A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D.,
John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D.,
Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc.,
Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D.,
for the Pasireotide B2305 Study Group*

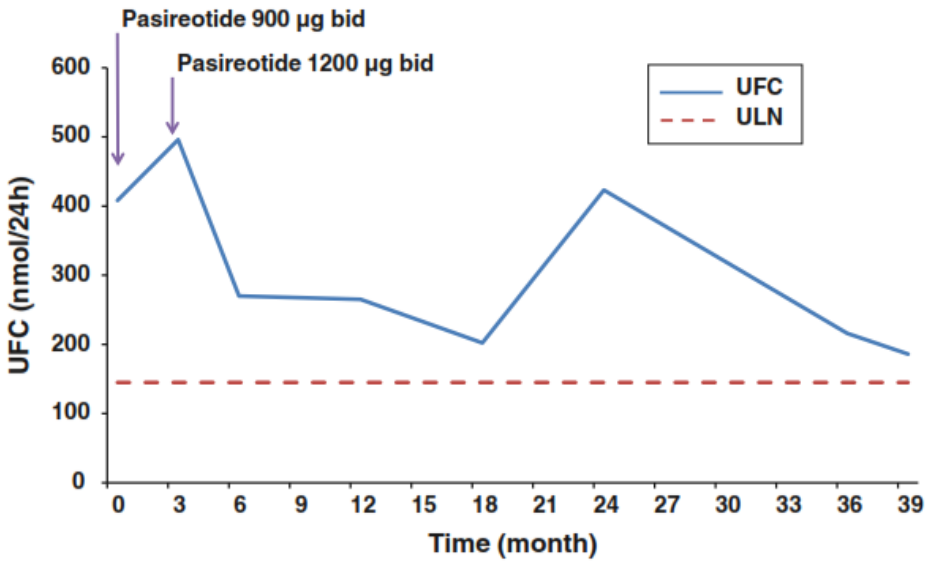


Pituitary (2012) 15:608–613

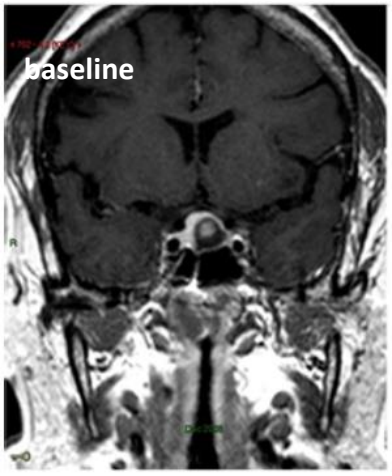
Pituitary-directed medical therapy with pasireotide for a corticotroph macroadenoma: pituitary volume reduction and literature review

Ilan Shimon · Liat Rot · Edna Inbar

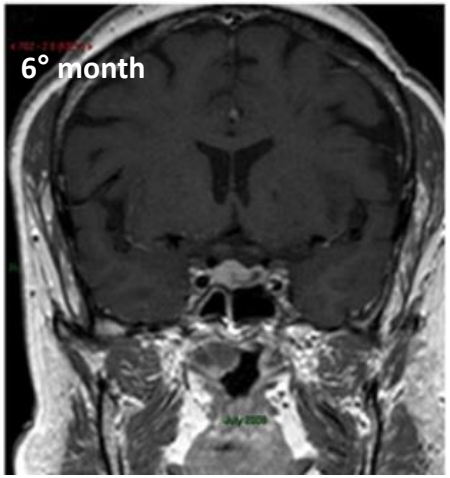
	patient	n.v.	units
UFC	694-705	<208	nmol/24 h
Cortisol h 8.00	743	<690	nmol/L
ACTH	11.7	1.1-10.1	pmol/L
Cortisol 1mg-Dex	558	<50	nmol/L

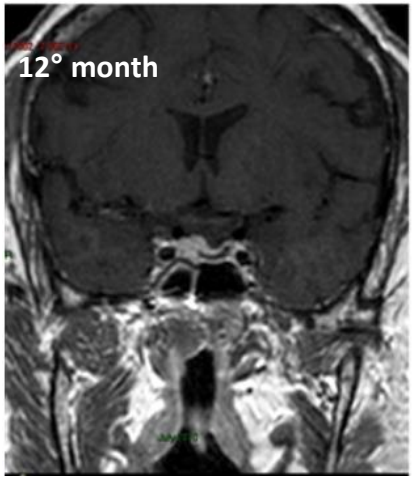


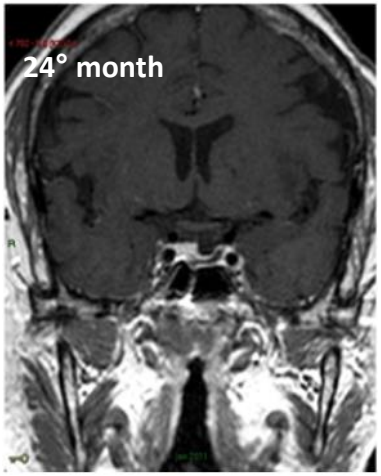
Cortisol h 8.00: 738 nmol/L



Cortisol h 8.00: 523 nmol/L







Endocr. Pract. 2013;19:e92-e96

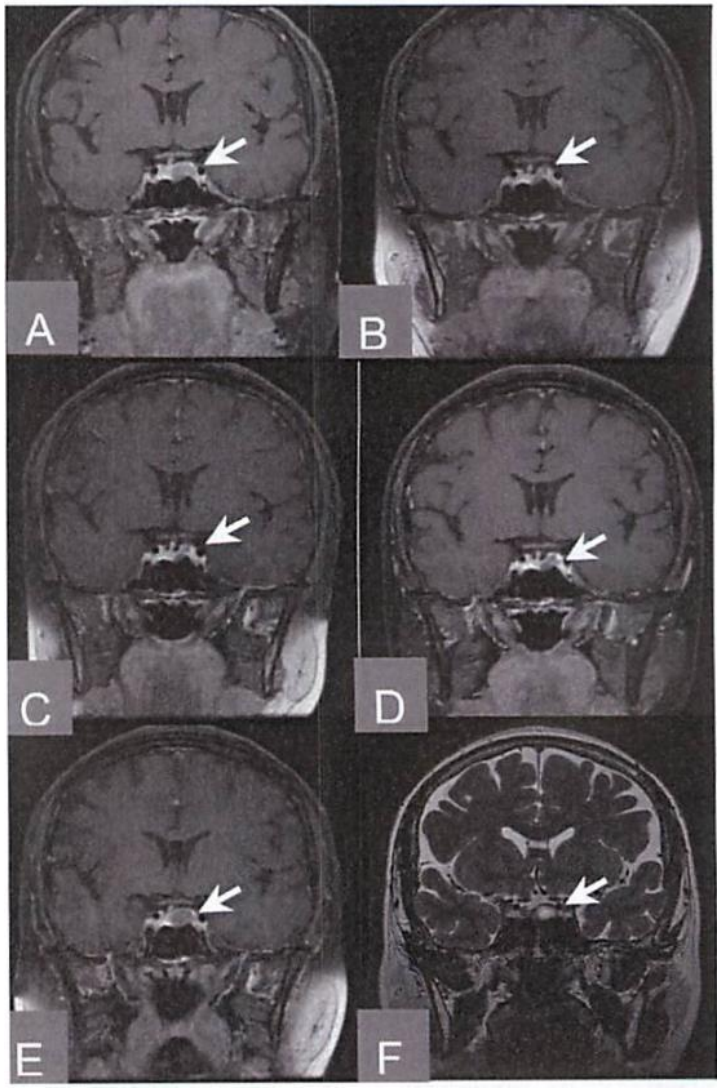
EFFECTIVE LONG-TERM TREATMENT OF CUSHING'S DISEASE WITH PASIREOTIDE: A CASE REPORT

Lin Lu, MD; Lian Duan, MD; Zimeng Jin, MD; Zhaolin Lu, MD; Feng Gu, MD

Table 1
Treatment Responses After Pasireotide Injection

Months after treatment	Pasireotide injection dosage	UFC, μg/24h	Morning serum cortisol, μg/dL	Morning plasma ACTH, ng/L	Tumor volume, cm^3
Baseline	ND	151.1	18.1	130	0.797
1 month	900 μg bid	7.4	7.3	71	ND
2 months	600 μg bid	9.2	7.1	65	ND
3 months	600 μg bid	15.2	8.7	49	ND
5 months	600 μg bid	32.2	9.7	61	ND
6 months	600 μg bid	31.2	12.3	63	0.375
9 months	600 μg bid	33.9	13.8	54	ND
12 months	600 μg bid	86.2	12.0	46	0.277
15 months	900 μg bid	19.7	16.5	63	ND
18 months	900 μg bid	103.6	10.4	51	0.359
21 months	900 μg bid	58.3	9.4	46	ND
24 months	900 μg bid	12.7	11.9	74	0.365
30 months	900 μg bid	97.1	12.6	58	

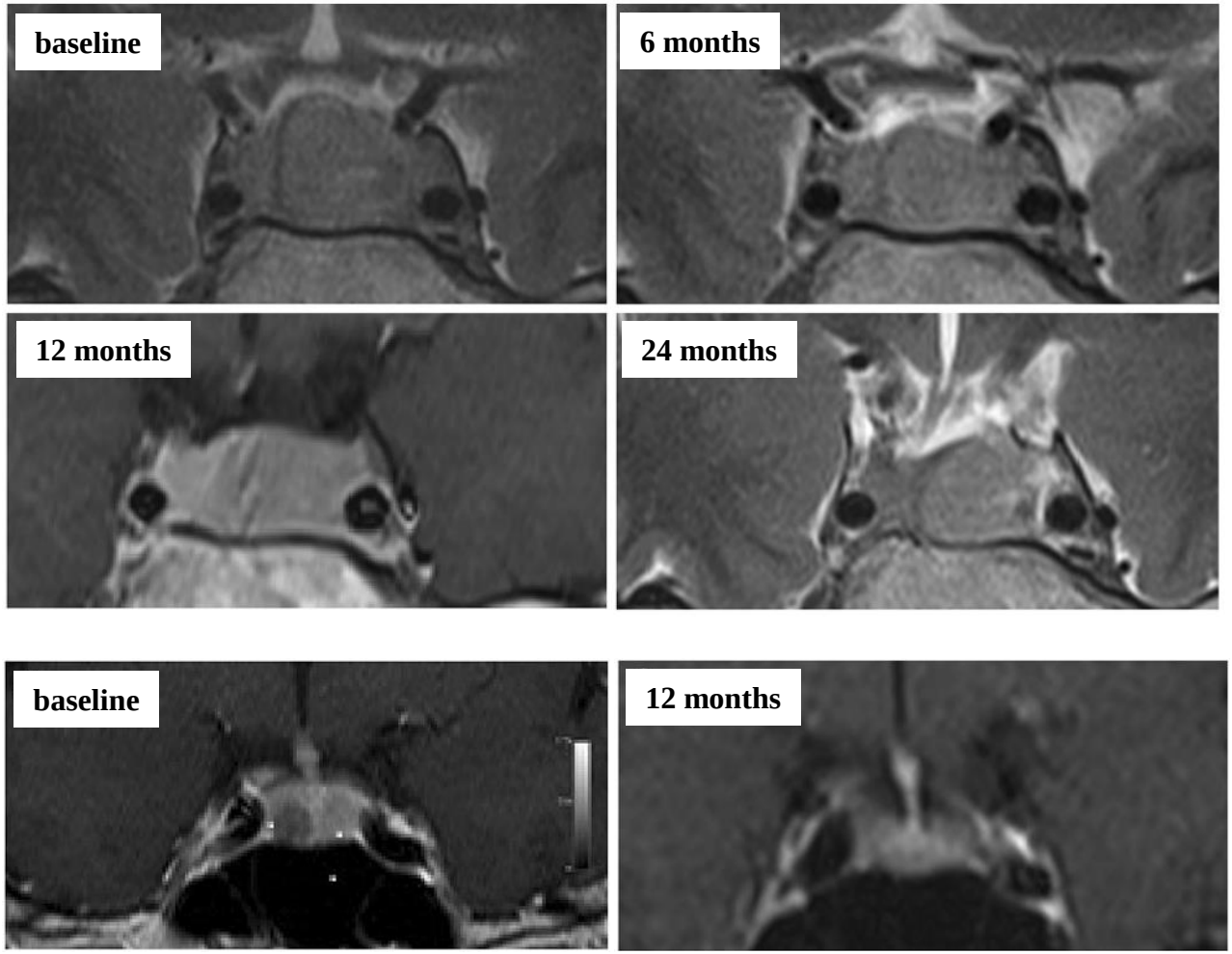
Abbreviations: ACTH = adrenocorticotropic hormone; ND = not done; UFC = urinary free cortisol.
UFC normal range: 10.9–52.5 μg/24h; plasma ACTH normal range: 0–46 ng/L; morning serum cortisol normal range: 4.3–22.4 μg/dL.

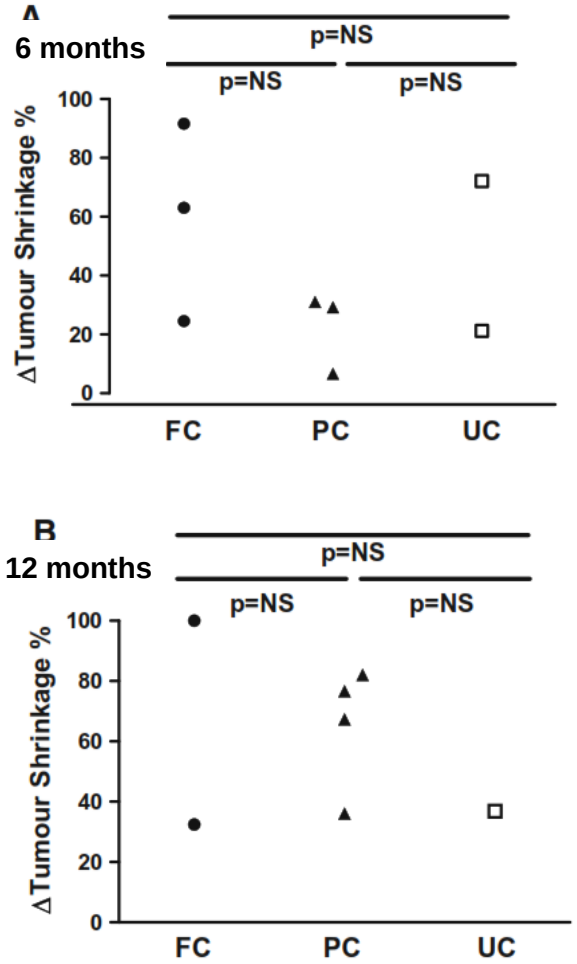


Endocrine
DOI 10.1007/s12020-015-0557-2

The treatment with pasireotide in Cushing's disease: effects of long-term treatment on tumor mass in the experience of a single center

Chiara Simeoli · Renata Simona Auriemma · Fabio Tortora · Monica De Leo · Davide Iacuaniello · Alessia Cozzolino · Maria Cristina De Martino · Claudia Pivonello · Ciro Gabriele Mainolfi · Riccardo Rossi · Sossio Cirillo · Annamaria Colao · Rosario Pivonello



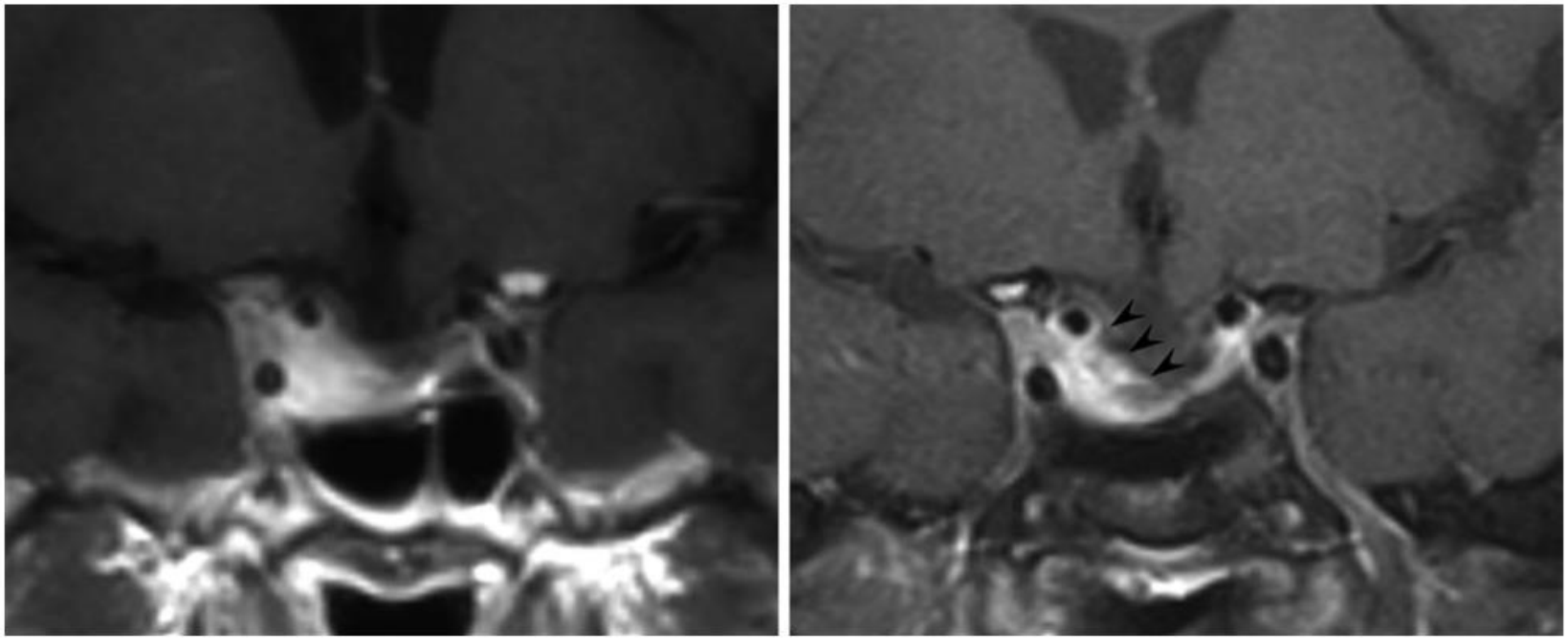


FC: full controlled
PC: partial controlled
UC: uncontrolled

J Neurooncol (2015) 122:189–196

Temozolomide and pasireotide treatment for aggressive pituitary adenoma: expertise at a tertiary care center

Filippo Ceccato · Giuseppe Lombardi · Renzo Manara · Enzo Emanuelli · Luca Denaro · Laura Milanese · Marina Paola Gardiman · Roberta Bertorelle · Massimo Scanarini · Domenico D'Avella · Gianluca Occhi · Marco Boscaro · Vittorina Zagonel · Carla Scaroni



Case	Sex, age (years)	PA	MIB-1 (%)	p53	Prior surgery (n)	RT (months)	Age at start of TMZ (years)	TLS to T0 (months)	No. of TMZ cycles	HR	Response to TMZ	Tumor volume change with TMZ (%)
1	F, 67	NFPA	<3	Neg	1	No	69	26	6	n.a.	PD	+42
2	F, 39	GH	<3	Pos	2	No	48	28	3	no	PD	+45
3	M, 40	NFPA[a]	<3	Pos	4	Yes (1)	43	29	12	n.a.	PR	−49
4	M, 32	ACTH	>3	Pos	4	Yes (126)	47	26	24	yes	PR	−63
5	M, 47	NFPA[a] → ACTH	>3	Pos	2	Yes (86)	60	93	12	n.a.	SD	−6, −21[b]

Legend: *PA* Pituitary adenoma, *NFPA* non-functioning PA, *TMZ* temozolomide, *TLS to T0* time from latest surgery to starting TMZ in months, *HR* hormonal response, *n.a.* not applicable, *RT* radiotherapy (in brackets time from radiotherapy to TMZ treatment start), *PD* progression of disease, *PR* partial response, *SD* stable disease

[a] NFPA with positive ACTH immunohistochemistry

[b] Adenoma reduction after 6 months of combination treatment Pasireotide + TMZ

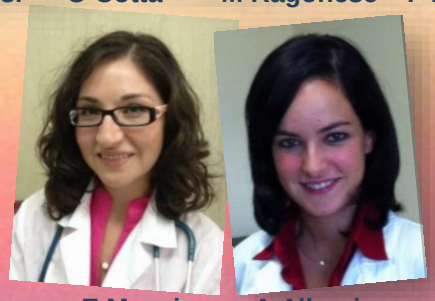
TAKE HOME MESSAGES

- Lo *shrinkage* del tumore ipofisario è stato l'*end point* primario solo di pochissimi, recenti studi, ma è un obbiettivo di primaria importanza nel *management* dei pazienti con macroadenoma, soprattutto se gigante e/o invasivo, o in presenza di voluminoso residuo tumorale dopo chirurgia.
- I dati preliminari dimostrano che la terapia con pasireotide è capace di indurre un significativo *shrinkage* dei tumori ipofisari ACTH-secernenti, anche in pazienti *partial* o *non responders*.
- Alcune esperienze aneddotiche inducono a ritenere che un rapido controllo biochimico sia predittivo di un marcato *shrinkage* in tempi medio-lunghi.
- Il significato prognostico dello *shrinkage* nei microadenomi sarà certamente oggetto di future valutazioni e interpretazioni in relazione all'*outcome* terapeutico.

Grazie a voi…

e a loro

ML Torre S Puglisi O Cotta M Ragonese F Ferraù PD Romeo



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Malattie Ipotalamo Ipofisarie

Coordinatori Silvia Grottoli e Salvo Cannavò

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Presentazione

Nell'ambito delle attività della SIE, la costituzione di un Club delle Malattie Ipotalamo-Ipofisarie (MIC) è finalizzata alla promozione della ricerca scientifica, della formazione specialistica e dell'assistenza clinica dedicate alla fisiologia e alla fisiopatologia dell'asse ipotalamo-ipofisario. Il Club promuove la collaborazione fra studiosi dediti alla ricerca, sia clinica che di base, nell'ambito della fisiopatologia ipotalamo-ipofisaria e il confronto interdisciplinare fra medici specialisti coinvolti a vario titolo nell'assistenza al paziente, sia adulto che bambino, con malattie dell'asse ipotalamo-ipofisario.

In particolare, il MIC si propone:

- *di favorire la collaborazione e gli scambi tra i vari centri italiani di riferimento per il trattamento dei pazienti con patologie ipotalamo-ipofisarie*
- *di favorire un approccio multidisciplinare ai pazienti con patologie della regione ipotalamo-ipofisaria, che veda la partecipazione di figure professionali differenti quali i neuroradiologi, i neurochirurghi, i pediatri, gli oculisti, ecc.*
- *di sostenere studi multicentrici osservazionali e di intervento, favorendo l'integrazione tra la ricerca di base e quella clinica*
- *di favorire gli scambi culturali fra i componenti del club, anche nella forma di stage e esperienze professionali fuorisede*
- *di organizzare eventi informativo-divulgativi che coinvolgano anche le associazioni dei pazienti*
- *di sostenere esigenze uniformi di assistenza nell'ambito delle malattie ipotalamo-ipofisarie su tutto il territorio italiano*

Tutti coloro che fossero interessati ad aderire al club devono richiederlo inviando una mail all'indirizzo

mic@societaitalianadiendocrinologia.it

Club Malattie Ipotalamo Ipofisarie

TORINO 2016
4I live here

4I Incontri Italiani Ipotalamo Ipofisari

IX EDIZIONE

Torino, 11-13 febbraio 2016

Sede: ***Cavallerizza Reale***
Via G. Verdi, 9

Comitato Coordinatore Locale

E. Arvat
E. Ghigo
S. Grottoli - *Coordinatore*

G. Aimaretti, F. Broglio, L. Ghizzoni, L. Granata, R. Granata, F. Lanfranco, M. Maccario, F. Orlandi, M. Terzolo, F. Zenga

Segreteria Locale

V. Gasco, F. Guaraldi, N. Prencipe, P. Razzore

Club SIE Ipotalamo-Ipofisi

Coordinatori

S. Cannavò, S. Grottoli

Consiglio Direttivo SIE

F. Trimarchi - *Presidente*
A. Lenzi - *Presidente Eletto*
E.A. Jannini - *Segretario*
M. Gasperi - *Tesoriere*

Consiglieri

G. Aimaretti, M. Arosio, A. Avogaro
M.G. Castagna, A. Colao, F. Pecori Giraldi
C.G. Krausz, R.C. Melcangi, G. Napolitano
R. Pasquali, M. Tonacchera

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