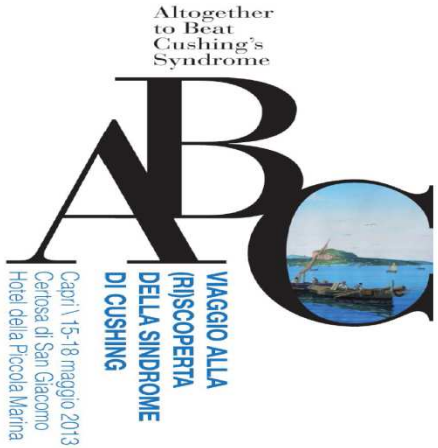


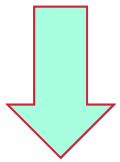
Il Cushing ipofisario:
il tumore non visibile e il tumore aggressivo

Emanuela Arvat

Divisione di Endocrinologia Oncologica
Dipartmento di Scienze Mediche
Universita' di Torino

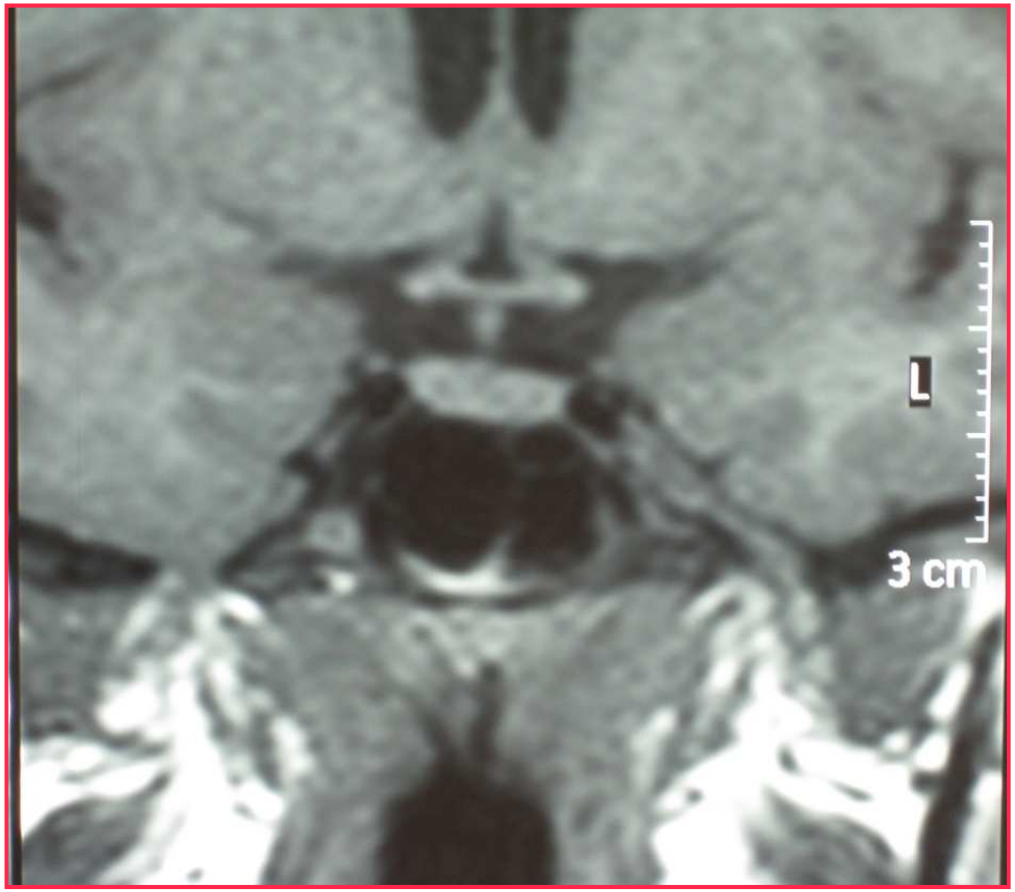
Grazia, 37 aa

- ✓ UFC: 178 e 195 µg/24h (1650-1700 cc) (v.n. 20-90)
- ✓ Test DEXA 1 mg: cortisolo 10.8 µg/dl (v.n. <1.8)
- ✓ Cortisolo sierico ore 8: 21.5 µg/dl (v.n. 5-20)
- ✓ Cortisolo sierico ore 24: 11.9 µg/dl (v.n. <7.5)
- ✓ ACTH: 57 pg/ml (v.n. 8-53)



Sindrome di Cushing ACTH-dipendente

Grazia, 37 aa



Sensibilità RMN 50-60%

Esami ormonali

a. <u>Test al CRH</u>

ACTH basale: 51.6 pg/ml, picco: 89.0 pg/ml (+71%)

Cortisolo basale: 22.5 µg/dl, picco: 41.1 µg/dl (+79.5%)

b. <u>Test al desametasone 8 mg overnight</u>

cortisolo: 20.4 µg/dl; nadir 1.8 µg/dl (-91%)

Sindrome di Cushing ACTH-dipendente verosimilmente sostenuta da adenoma ipofisario

JOHN NEWELL-PRICE
ASHLEY B. GROSSMAN

Differential Diagnosis of Cushing's Syndrome

Arq Bras Endocrinol Metab 2007;51/8

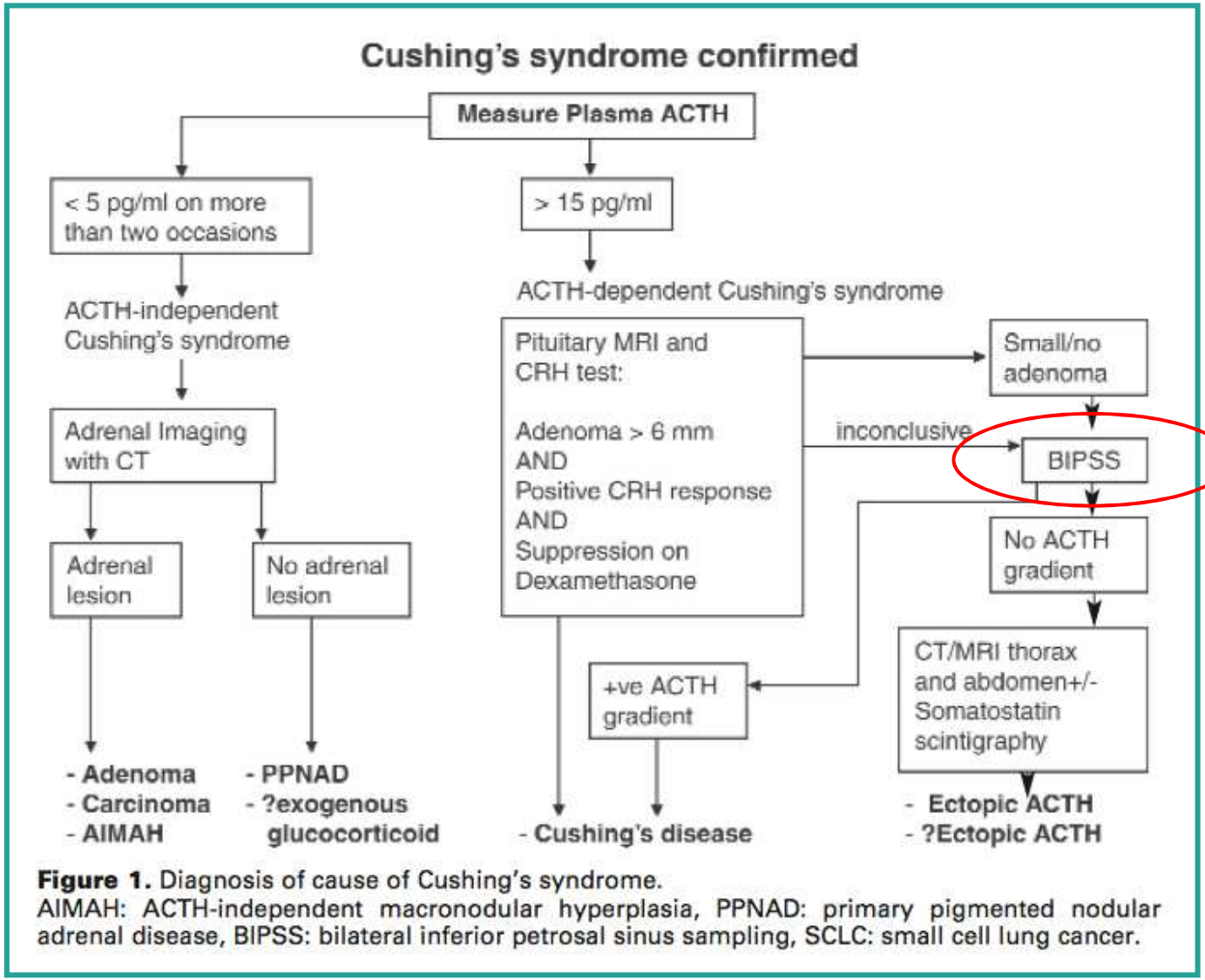


Figure 1. Diagnosis of cause of Cushing's syndrome.
AIMAH: ACTH-independent macronodular hyperplasia, PPNAD: primary pigmented nodular adrenal disease, BIPSS: bilateral inferior petrosal sinus sampling, SCLC: small cell lung cancer.

Bilateral inferior petrosal sinus sampling

…the most reliable test for discriminating between pituitary and non-pituitary sources of ACTH…

Pifalls for BIPSS

False positive results:
Cyclical ACTH secretion
Treatments lowering cortisol levels
Ectopic CRH secretion

False
Techn
Petros
Anom
→ Sim

Prolactin as a Marker of Successful Catheterization during IPSS in Patients with ACTH-Dependent Cushing's Syndrome

S. T. Sharma, H. Raff, and L. K. Nieman (*J Clin Endocrinol Metab* 96: 3687–3694, 2011)

ılts…

The usefulness of combined biochemical tests in the diagnosis of Cushing's disease with negative pituitary magnetic resonance imaging

R M Testa, N Albiger, G Occhi, F Sanguin, M Scanarini[1], S Berlucchi[1], M P Gardiman[2], C Carollo[3], F Mantero and C Scaroni

European Journal of Endocrinology (2007) **156** 241–248

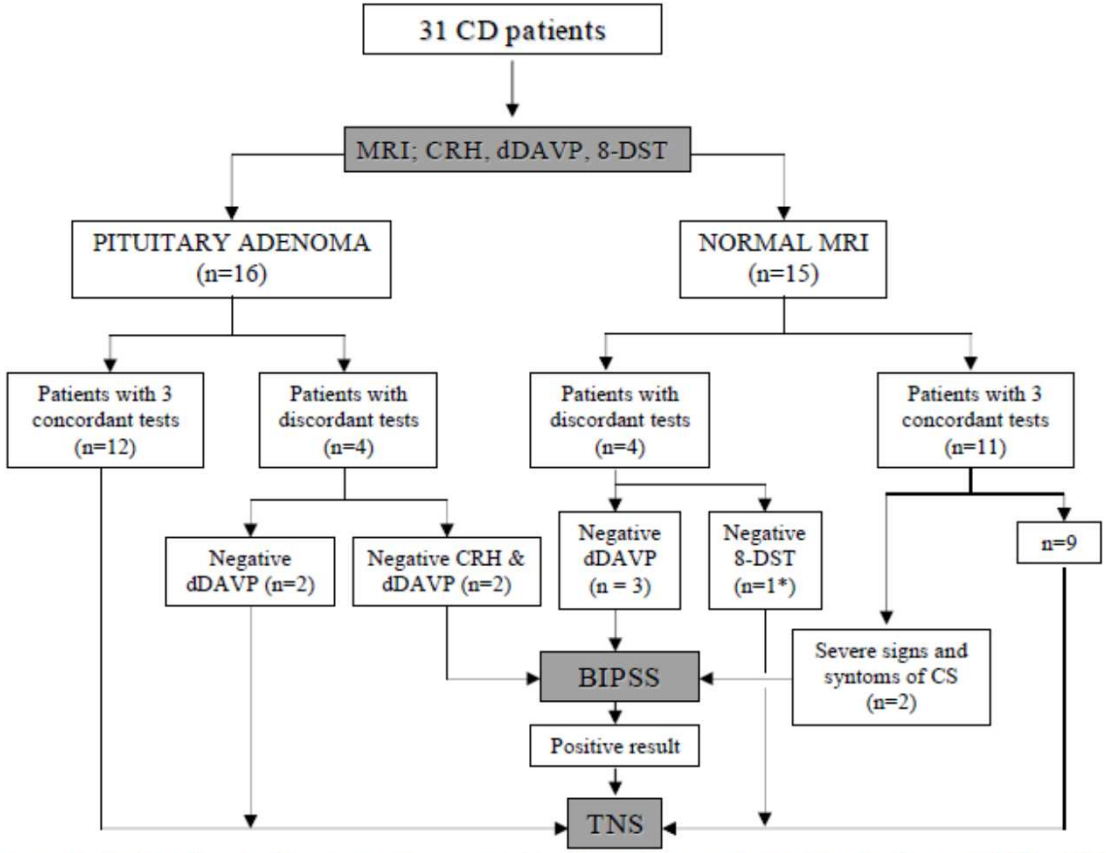


Figure 1 Flow diagram displaying diagnostic approach we used in 31 patients with Cushing's disease (CD). BIPSS, bilateral inferior petrosal sinus sampling; TNS, transsphenoidal surgery; *this patient refused other examinations.

The usefulness of combined biochemical tests in the diagnosis of Cushing's disease with negative pituitary magnetic resonance imaging

Diagnosis and Management of Cushing's Syndrome: Results of an Italian Multicentre Study*

CECILIA INVITTI, FRANCESCA PECORI GIRALDI, MARTINA DE MARTIN, FRANCESCO CAVAGNINI, AND THE STUDY GROUP OF THE ITALIAN SOCIETY OF ENDOCRINOLOGY ON THE PATHOPHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS†

J Clin Endocrinol Metab 84: 440–448, 1999)

Pituitary Magnetic Resonance Imaging Findings Do Not Influence Surgical Outcome in Adrenocorticotropin-Secreting Microadenomas

J Clin Endocrinol Metab, July 2004, 89(7):3371–3376

SYLVIE SALENAVE, BLANDINE GATTA, SYLVIE PECHEUR, FRANÇOIS SAN-GALLI, ANDRÉ VISOT, PIERRE LASJAUNIAS, PATRICK ROGER, JÉRÔME BERGE, JACQUES YOUNG, ANTOINE TABARIN, AND PHILIPPE CHANSON

Corticotropinomi non visibili
Terapia chirurgica

Minore % di remissione
Maggiore incidenza di recidiva
Maggiore incidenza di ipopituitarismo

vs adenomi visibili

Tritos A et al, Nat. Endocrinol 2011
Erickson E et al, Clin Endocrinol 2009
Biller B et al, J Clin Endocrinol Metab 2008

Corticotropinomi non visibili
Terapia chirurgica

	adenoma visibile (% remissione)	adenoma NON visibile (%remissione)
Bochiccio *et al*. 1995	87	74
Barrou *et al*. 1997	93	58
Rees *et al*. 200		69
Rollin *et al*. 200		71
Salenave *et al*.		78
Testa *et al*. 200		73
Jehle *et al*. 2008	82	79
Alwani *et al*. 2010	62	50

Adenoma visibile 62-100%
Adenoma NON visibile 50-78%

Corticotropinomi non visibili

nuove imaging ??

Preliminary Experience with 3-Tesla MRI and Cushing's Disease

SKULL BASE/VOLUME 17, NUMBER 4 2007

Louis J. Kim, M.D.,[1] Gregory P. Lekovic, M.D., Ph.D., J.D.,[1] William L. White, M.D.,[1] and John Karis, M.D.[2]

Table 1 Patient Characteristics, Tumor Imaging Results, and Inferior Petrosal Sinus Sampling Lateralization

Patient	Age/Sex	1.5T MRI	3T MRI	IPSS	Surgical Location of Tumor	Retrospective Reanalysis
1	37/F	Stalk deviation	Hypodensity Rt anterior	Lt side	Rt anterior	Better delineated on 3T
2	14/F	Enlarged, symmetric gland	Enlarged, symmetric gland	Rt side	Anterior midline	Indeterminate on 1.5T or 3T
3	35/F	Slight Lt hypodensity	Clear Lt hypodensity	Lt side	Lt side	Better delineated on 3T
4	50/F	Indeterminate	Indeterminate	Lt side	Lt side	Indeterminate on 1.5T or 3T
5	34/M	Rt-sided tumor	Lt-sided tumor	Equivocal	Lt side	Better delineated on 3T

T, Tesla; IPSS, inferior petrosal sinus sampling; F, female; M, male; Lt, left; Rt, right.

Initial experience of 3 Tesla versus conventional field strength magnetic resonance imaging of small functioning pituitary tumours

David B. Stobo*, Robert S. Lindsayt, John M. Connell‡, Laurence Dunn§ and Kirsten P. Forbes*

Clinical Endocrinology (2011) **75**, 673–677

Table 2. Histological findings following transsphenoidal surgery correlated with imaging and clinical outcomes

10 confirmed ACTH-secreting adenomas	
Concordant 3T and 1·5T findings 6 positive at both field strengths	Discrepant 3T and 1·5T findings 1 positive at 3T, negative at 1·5T (midline lesion confirmed surgically) 2 positive at 3T, suspicious at 1·5T (left-sided lesions confirmed surgically) 1 suspicious at 3T, negative at 1·5T (right-sided lesion confirmed surgically)

Initial experience of 3 Tesla versus conventional field strength magnetic resonance imaging of small functioning pituitary tumours

David B. Stobo*, Robert S. Lindsay†, John M. Connell‡, Laurence Dunn§ and Kirsten P. Forbes*

Clinical Endocrinology (2011) 75, 673–677

8 with biochemical evidence of Cushing's disease but no proven adenoma

Concordant 3T and 1·5T findings	No discrepant 3T and 1·5T findings
3 negative at both field strengths (no surgically identifiable lesion and incomplete postoperative disease control)	
1 negative at both field strengths (left-sided gland swelling at surgery and sustained control of cortisol levels postleft hemihypophysectomy – potential imaging false negative)	
1 negative at both field strengths (incomplete clinical follow-up available)	
1 positive at both field strengths (poor postoperative disease control requiring adrenalectomy – potential imaging false positive)	
1 positive at both field strengths (good postoperative disease control – potential histological false negative)	
1 suspicious left-sided lesion at both field strengths (good postoperative disease control after left hemihypophysectomy – potential histological false negative)	

3 Tesla magnetic resonance imaging with and without corticotropin releasing hormone stimulation for the detection of microadenomas in Cushing's syndrome

Dana Erickson*, Bradley Erickson†, Robert Watson†, Alice Patton†, John Atkinson‡, Fredric Meyer‡, Todd Nippoldt*, Paul Carpenter*, Neena Natt*, Adrian Vella* and Prabin Thapa§

Clinical Endocrinology (2010) **72**, 793–799

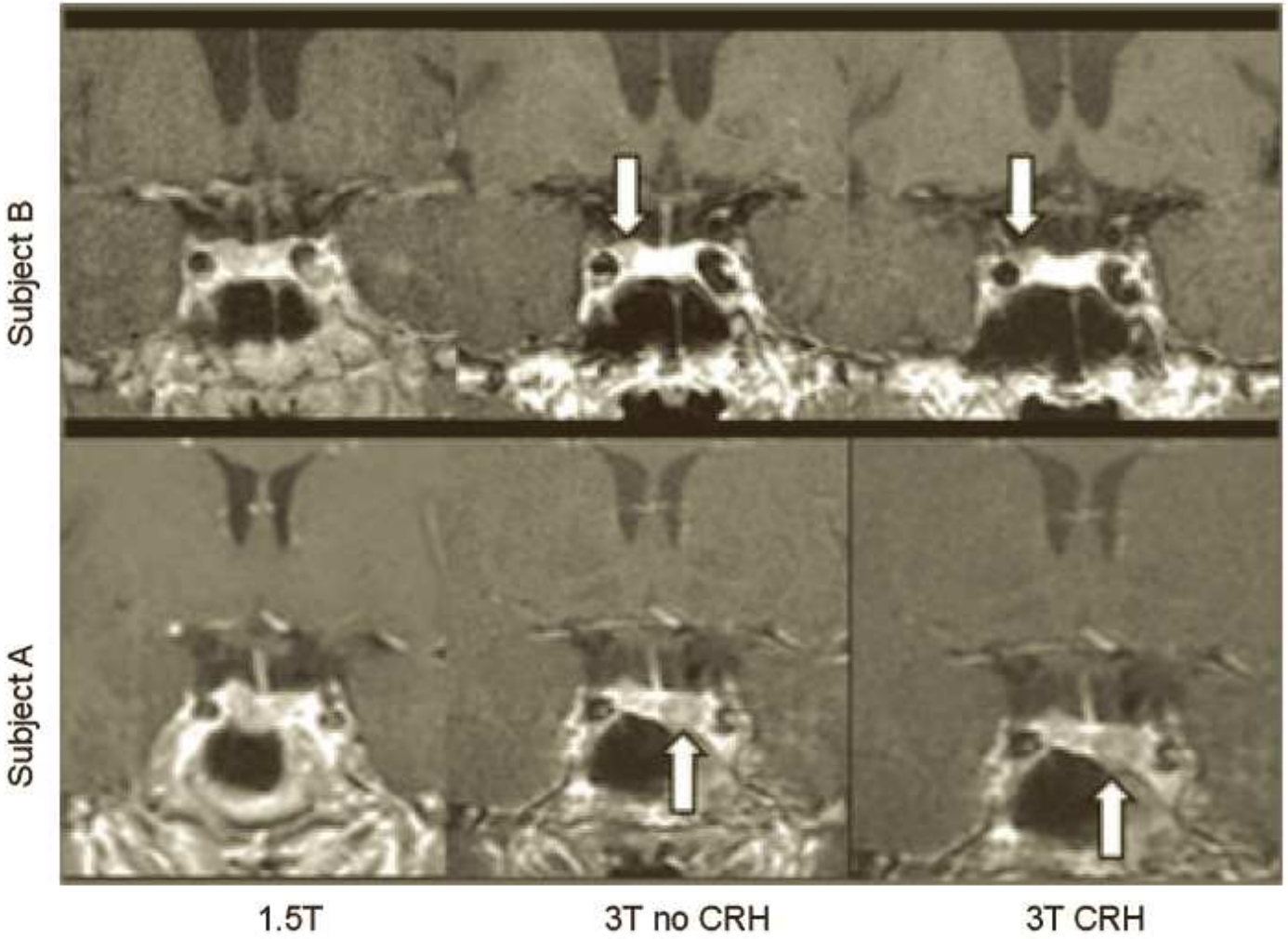


Fig. 2 Two example cases showing the dynamic scans from a 1·5T MRI, and 3T without and with o-CRH stimulation. Both of these cases show the lesion more clearly on the 3T images (arrows), although there is not a clear difference between the o-CRH stimulated and nonstimulated images. Subject B paradoxically had angulation of the pituitary stalk *towards* the adenoma, likely as a result of the uneven sellar floor.

A modified protocol using half-dose gadolinium in dynamic 3-Tesla magnetic resonance imaging for detection of ACTH-secreting pituitary tumors

Lesly Portocarrero-Ortiz · Dulce Bonifacio-Delgadillo · Arturo Sotomayor-González · Arturo Garcia-Marquez · Raul Lopez-Serna

Pituitary (2010) 13:230–235

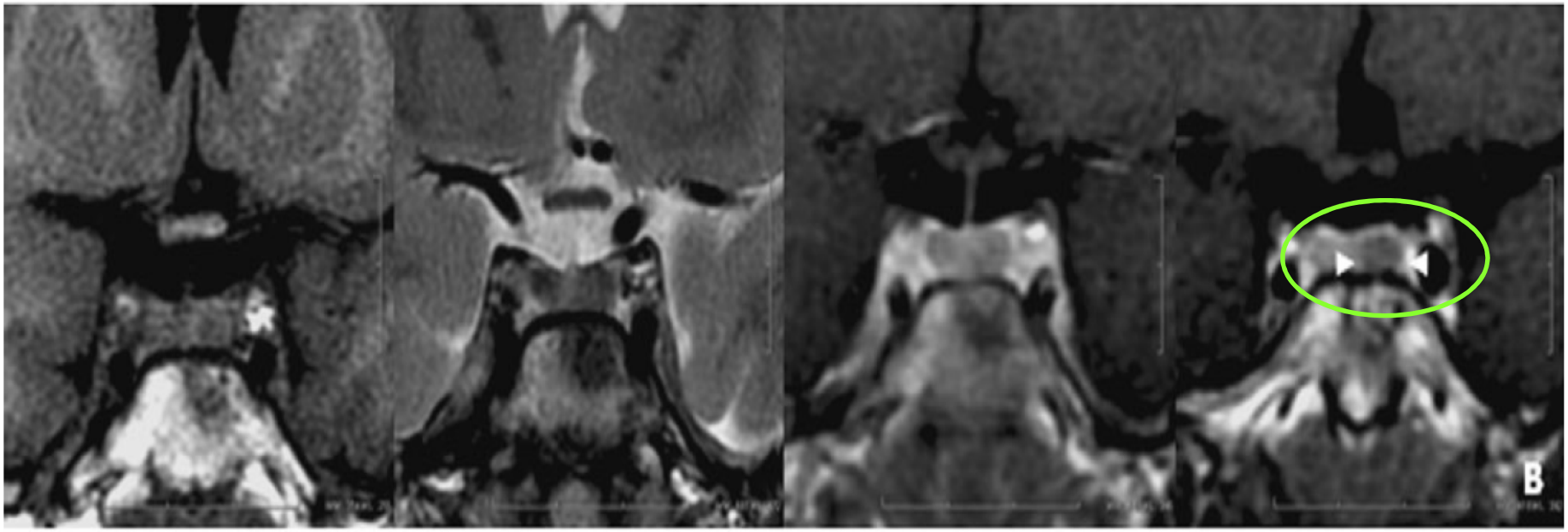


Fig. 1 Comparative coronal 3-Tesla MRI images of pituitary glands of five patients with Cushing disease. (**a**,**b**,**c**,**d**,**e**). *First and second column* show simple T1- and T2-weighted images. *Third column* shows the same slices after administration of full contrast material and the *fourth column* show patients after administration of half-dose gadolinium: a focal area of low signal intensity is clearly seen in the pituitary with a different pattern of enhancement with respect to the normal gland (*white arrowheads*)

Usefulness of composite methionine–positron emission tomography/3.0-tesla magnetic resonance imaging to detect the localization and extent of early-stage Cushing adenoma

Clinical article

HIDETOSHI IKEDA, M.D., PH.D.,[1] TAKEHIKO ABE, M.D., PH.D.,[2] AND KAZUO WATANABE, M.D., PH.D.[3]

Results. The diagnostic accuracy of superconductive MR imaging for detecting the localization of Cushing microadenoma was only 40%. The causes of unsatisfactory results for superconductive MR imaging were false-negative results (10 cases), false-positive results (6 cases), and instances of double pituitary adenomas (3 cases). In contrast, the accuracy of microadenoma localization using MET-PET/3.0-T MR imaging was 100% and that of FDG-PET/3.0-T MR imaging was 73%. Moreover, the adenoma location was better delineated on MET-PET/MR images than on FDG-PET/MR images. There was no significant difference in maximum standard uptake value of adenomas evaluated by MET-PET between preclinical Cushing disease and overt Cushing disease.

Conclusions. Composite MET-PET/3.0-T MR imaging is useful for the improvement of the delineation of Cushing microadenoma and offers high-quality detectability for early-stage Cushing adenoma.

Corticotropinomi non visibili

Problematiche aperte

Quale workup diagnostico??

Quali test?

Quale imaging?

IPSS sempre?

Terapia chirurgica

Ruolo del neurochirurgo?

Altre opzioni?

Corticotropinomi aggressivi/carcinomi

CLINICAL REVIEW: Diagnosis and Management of Pituitary Carcinomas

J Clin Endocrinol Metab, May 2005, 90(5):3089–3099

Gregory A. Kaltsas, Panagiotis Nomikos, George Kontogeorgos, Michael Buchfelder, and Ashley B. Grossman

Pituitary tumors are relatively common tumors; approximately 10–20% of normal subjects may harbor such tumors

A number of them, between 45 and 55% depending on the criteria used, can become invasive, infiltrating dura, bone, and/or surrounding tissue (2–6).

Corticotropinomi aggressivi/carcinomi

Criteri agressività?

Clinici?

Istologici?

Radiologici?

Distinzione adenoma aggressivo e carcinoma?

CLINICAL REVIEW: Diagnosis and Management of Pituitary Carcinomas

J Clin Endocrinol Metab, May 2005, 90(5):3089–3099

Gregory A. Kaltsas, Panagiotis Nomikos, George Kontogeorgos, Michael Buchfelder, and Ashley B. Grossman

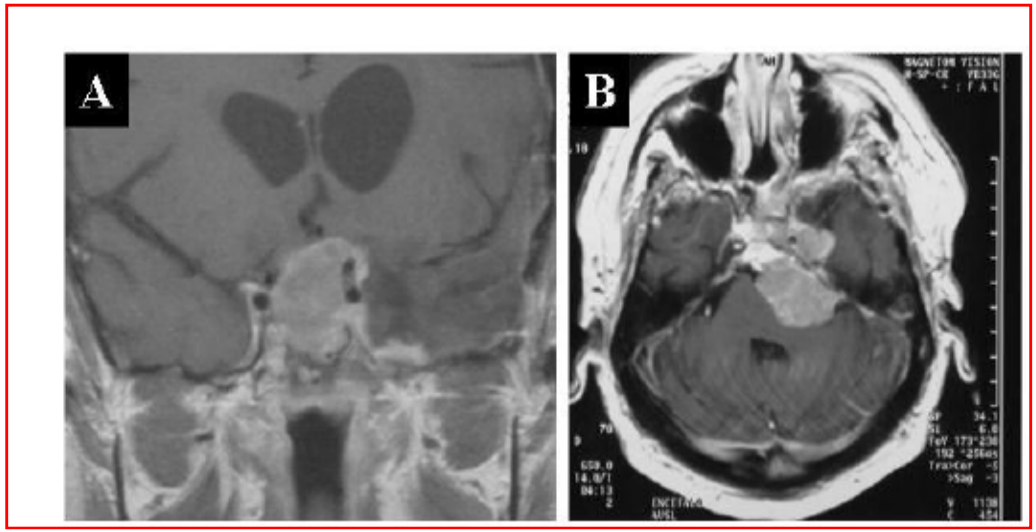
TABLE 1. Criteria needed to be fulfilled for the classification of pituitary carcinomas

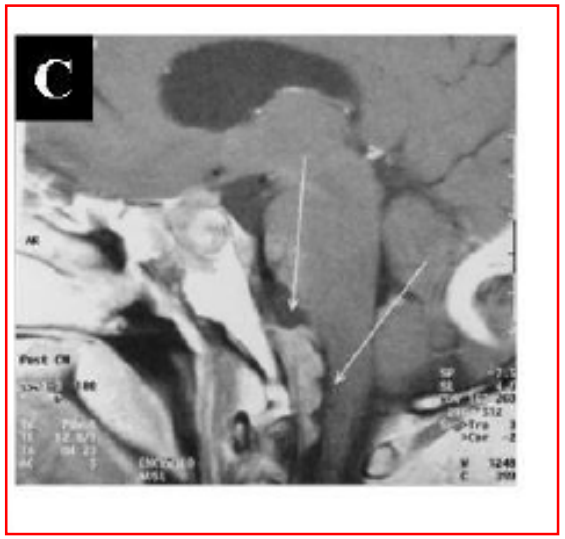
The primary tumor must be identified as a pituitary tumor by histology
organs
The structural features or marker expressions of the metastases should correspond or be similar to those of the pituitary tumor

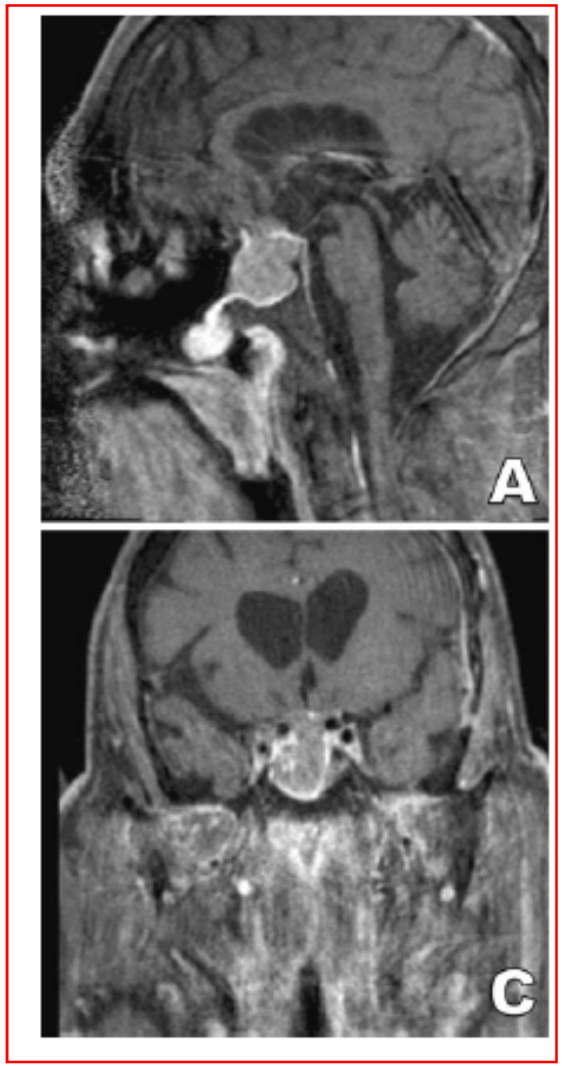
Adopted from Refs. 18, 115, and 116.

true carcinomas are defined only by the presence of craniospinal and/or systemic metastases (Table 1) (1, 2, 4).

Corticotropinomi aggressivi/carcinomi







CLINICAL REVIEW: Diagnosis and Management of Pituitary Carcinomas

J Clin Endocrinol Metab, May 2005, 90(5):3089–3099

Gregory A. Kaltsas, Panagiotis Nomikos, George Kontogeorgos, Michael Buchfelder, and Ashley B. Grossman

TABLE 2. Histological and immunohistochemical parameters commonly employed to predict the biological behavior of pituitary tumors

Parameter	Pituitary adenoma	Atypical adenoma	Pituitary carcinoma
Size	Micro/macroadenoma	Micro/macroadenoma	Macroadenoma[a]
Cellular atypia	Variable	Variable	Variable[b]
Pleomorphism	Variable	Variable	Variable[b]
Mitotic activity	Usually low	Variable (2/10 hpf)[c]	Usually high (6/10 hpf)[d]
Proliferative index Ki-67 (%) LI	<3	>3 (usually >4.7)	>3 (usually >10)[e]
p53 positivity	Negative	Mostly negative	Mostly positive[f]
Microvascular density	Low	Variable	Mostly increased[g]

[a] A case of a microadenoma with metastases to the liver has been described (15).
[b] Ref. 51.
[c] Mitotic figures per high powered field.
[d] Ref. 3.
[e] Ref. 3, 30, and 53.
[f] Ref. 29.
[g] Ref. 70.

In keeping with the recent World Health Organization classification of endocrine neoplasms, primary endocrine tumors that exhibit a high mitotic activity, an increased (>3%) Ki-67% LI, and/or p53 immunoreactivity should be termed atypical adenomas to denote their aggressive potential and the possibility of future malignant transformation (18). Our

Malignant pituitary corticotroph adenomas: report of two cases and a comprehensive review of the literature

Agatha A. van der Klaauw · Tina Kienitz · Christian J. Strasburger · Johannes W. A. Smit · Johannes A. Romijn

Pituitary (2009) 12:57–69

Table 2 Summary of clinical features of the reported cases of malignant Cushing's disease

Characteristics ($n = 58$)		
Gender, male (n (%))		19 (33)
Age (years)		39 (13–71)
Presentation (n (%))	Cushing's syndrome	37 (64)
	Visual complaints, silent adenoma	15 (26)
	Not documented	6 (10)
Initial therapy (n (%))	Transsphenoidal or transcranial surgery	43 (74)
	Radiotherapy	29 (50)
	Uni-/bilateral adrenalectomy	2 (3)/16 (28)
	Medicamentous therapy[a]	9 (16)
Metastatic sites (n (%))	Intracranial central nervous system	25 (43)
	Extracranial central nervous system	14 (24)
	Extramedullary	36 (62)
Mean time interval diagnosis-metastases (years)		8.8 (0.25–34)
Mean interval metastases-death (years)		1.7 (0–21)
Alive at publication (n (%))		18 (31)

[a] Steroid synthesis inhibitors, octreotide, OP'DDD, chemotherapy (in 1 case)

Carcinomi ipofisari ACTH-secernenti

- si manifestano **alla diagnosi** come **macroadenomi invasivi**;

-rappresentano **il 30% dei carcinomi ipofisari;**

-70% nel sesso femminile, età media presentazione 39aa, latenza di 8.8 aa per la manifestazione delle metastasi;

- **possibile presentazione clinica come sindrome di Nelson;**

- **possibile presentazione clinica come silenti;**

- frequenti recidive e segni di progressione dopo NCH e RT;

- **sopravvivenza media dalla diagnosi delle metastasi**: **4aa;**

- **Markers specifici: galectina 3, CGA protooncogene HER-2/neu** espressi ad elevate concentrazioni, **elevato numero di mitosi;**

- raramente descritti casi di **co-secrezione ACTH, CRH e precursore della proopiomelanocortina;**

-

Kaltsas GA et al. JCEM 2005;90(5):3089-3099
Van der Klauw AA et al. Pituitary 2009;12:57-69
Raverot G et al. Clinical Endocrinology 2012;76:769-775

Corticotropinomi aggressivi

Fattori predittivi di aggressività?:

macroadenoma invasivo
marker istochimici
(K67, atipie cellulari, indice mitotico, invasività vascolare)
variante ACTH silente
variante a cellule di Crooke

Tritos N et al, Nat Rev Endocrinol 2011;7:279–289
Karavitaki N et al. Arq Bras Endocrinol Metab 2007;51(8):1314-1318
George DH et al Am J Surg Pathol 2003;27:1330-1336

Corticotropinomi aggressivi
corticotropinomi silenti

- 1-6% degli adenomi ipofisari operati, **17-22% dei tumori ACTH positivi;**

- **controversi i dati sulla sesso dipendenza;**

- **generalmente macroadenomi (87-100%) con tendenza all' invasività (30-52%);**

-**diagnosi in seguito all'effetto massa** (generalmente cefalea 8.3-70.4% ed alterazioni visive 41.7-86.7%) **ed alterazioni endocrine secondarie all' effetto massa** (amenorrea-DE 11%, ipopituitarismo 26-33.3%);

- **tendenza alla recidiva 32.1-37% dei casi;**

- **descritti rari casi di trasformazione in carcinoma ipofisario.**

Karavitaki N et al. Arq Bras Endocrinol Metab 2007;51(8):1314-1318
Moshkin O et al. Hormones 2011;10(2):162-167

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Gena M. Mastrogianakis, MD‡
Matthew J. Schniederjan, MD§
Daniel Brat, MD, PhD§
Anthony V. Pileggi, BS¶
Nelson M. Oyesiku, MD, PhD, FACS*‡

Silent Corticotroph Adenomas: Emory University Cohort and Comparison With ACTH-Negative Nonfunctioning Pituitary Adenomas

Neurosurgery 71:296–304, 2012

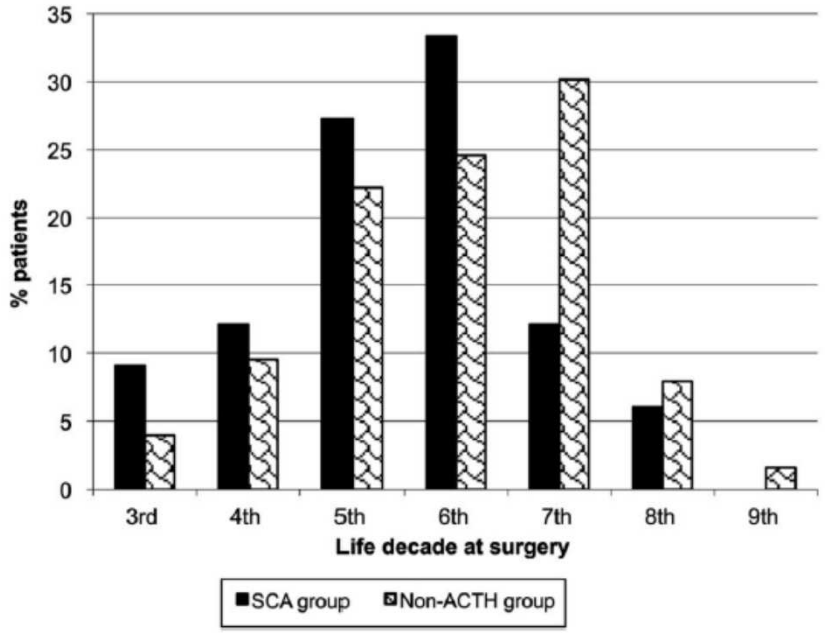

FIGURE 2. *Distribution of the age at time of the surgery in the silent corticotroph adenoma (SCA) and corticotroph (ACTH)-negative nonfunctioning pituitary adenoma groups of patients. Composite endpoint: tumor progression, tumor recurrence, and death.*

TABLE 1. Baseline Characteristics of Patients in the Silent Corticotroph Adenoma and Corticotropin-Negative Groups[a]

	SCAs, n = 33	ACTH-Negative Adenomas, n = 126	*P* Value
Age at surgery, y	49.6 ± 14.1	55.6 ± 12.8	.02
Sex, % men	57.6	57.1	.96
Presenting symptoms, %			
Headaches	30.3	18.3	.13
Vision loss	39.4	46.8	.44
Hypogonadism[b]	39.4	11.1	.001
Incidentaloma	0	23	.002
Acute apoplexy	9.1	4.0	.36
Maximum diameter, cm	2.83 ± 0.97	2.84 ± 0.99	.98
Cavernous sinus invasion, %	45.5	30.2	.09
Prolactin, ng/mL	24.7 ± 20.7	20.1 ± 16.56	.23
Hypopituitarism, %	75.8	50	.008

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Silent Corticotroph Adenomas: Emory University Cohort and Comparison With ACTH-Negative Nonfunctioning Pituitary Adenomas

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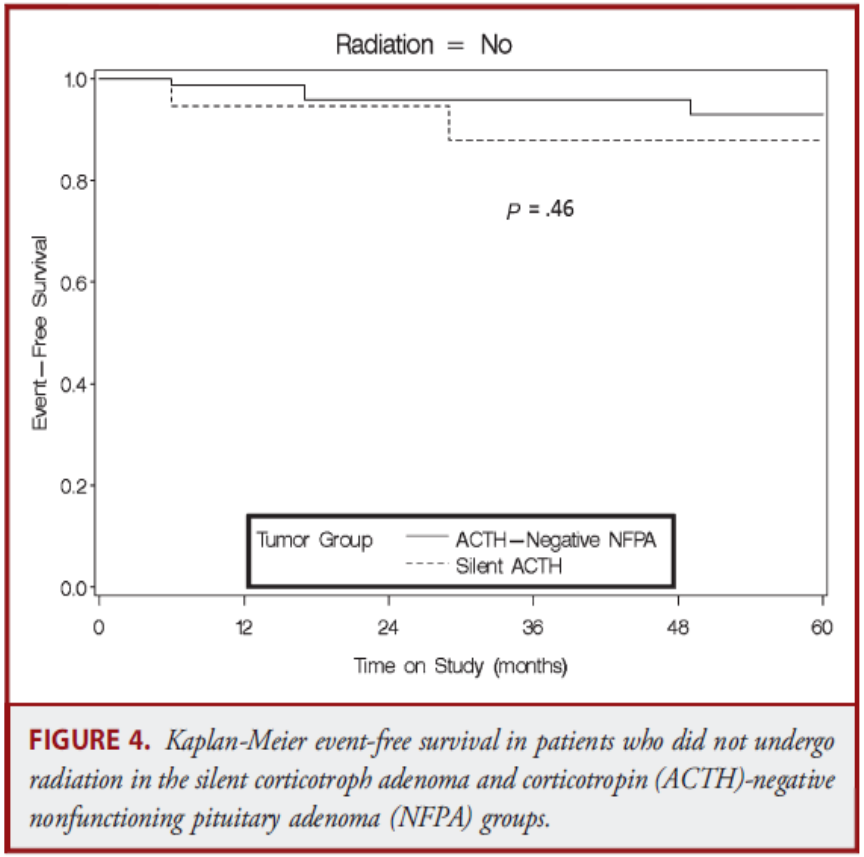


FIGURE 4. *Kaplan-Meier event-free survival in patients who did not undergo radiation in the silent corticotroph adenoma and corticotropin (ACTH)-negative nonfunctioning pituitary adenoma (NFPA) groups.*

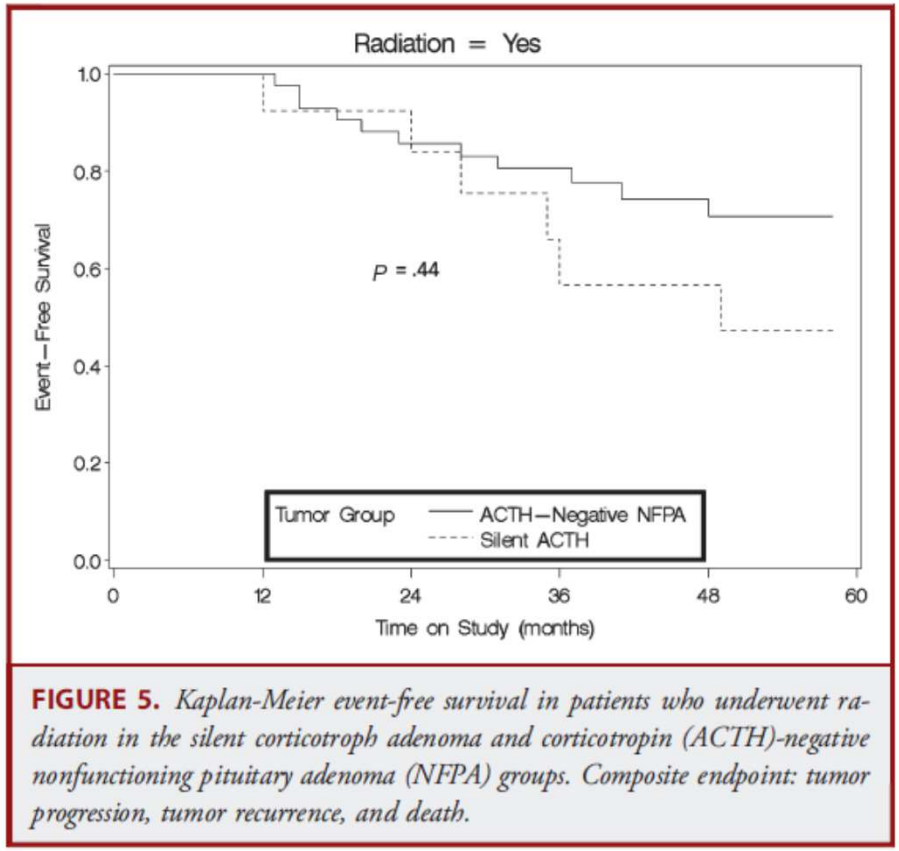


FIGURE 5. *Kaplan-Meier event-free survival in patients who underwent radiation in the silent corticotroph adenoma and corticotropin (ACTH)-negative nonfunctioning pituitary adenoma (NFPA) groups. Composite endpoint: tumor progression, tumor recurrence, and death.*

Silent corticotroph adenomas have unique recurrence characteristics compared with other nonfunctioning pituitary adenomas

Hwa Young Cho*, Sun Wook Cho*, Sang Wan Kim*,†, Chan Soo Shin*, Kyong Soo Park* and Seong Yeon Kim*

Clinical Endocrinology (2010) 72, 648–653

Table 4. Comparison of recurrence rate and characteristics according to

Conclusion The overall recurrence rate was similar between SCAs and non-SCAs. However, young patients with SCAs had a higher frequency of multiple and late recurrences, which showed more aggressive tumour behaviour. Therefore, we suggest that patients with SCAs, especially patients diagnosed at a young age, require careful long-term monitoring.

*No. of patients (%).
CR, conventional radiotherapy; GKS, gamma knife surgery.

Clinical, hormonal and molecular characterization of pituitary ACTH adenomas without (silent corticotroph adenomas) and with Cushing's disease

Gérald Raverot[1,2,3], Anne Wierinckx[1,2,4], Emmanuel Jouanneau[1,2,5], Carole Auger[1,2], Françoise Borson-Chazot[2,3], Joël Lachuer[1,2,4], Michel Pugeat[2,3] and Jacqueline Trouillas[1,2,6]

European Journal of Endocrinology (2010) **163** 35–43

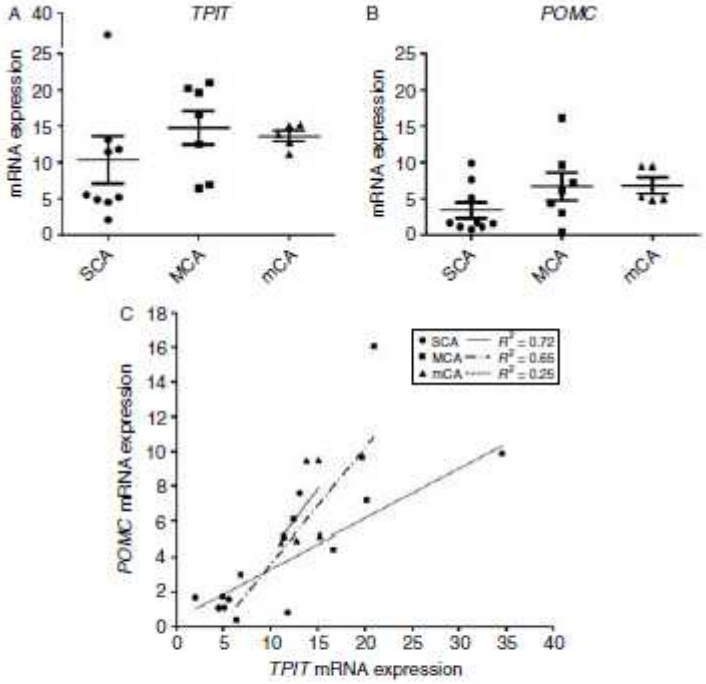


Figure 1 Relative mRNA expression of *TPIT* (A) and *POMC* (B) in the three groups of ACTH tumours and correlation between *TPIT* and *POMC* (C) mRNA expression levels in each group. Gene expression in normal pituitary tissue was used as a standard and set to 1. RPL4 was used as an internal standard. Bars represent the median.

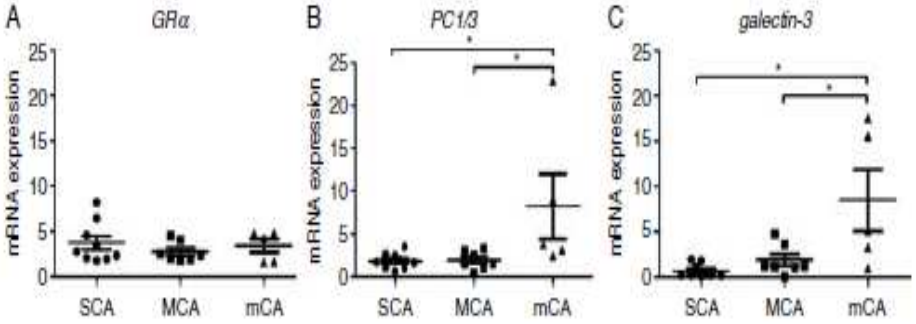


Figure 2 Relative mRNA expression of genes associated with SCA phenotype: *GRα* (A), *PC1/3* (B) and *galectin-3* (C) in the three groups of ACTH tumours. Gene expression in normal pituitary tissue was used as a standard and set to 1. RPL4 was used as an internal standard. Bars represent the median. $^*P<0.05$.

Crooke's Cell Adenoma of the Pituitary

(*Am J Surg Pathol* 2003;27:1330–1336)

An Aggressive Variant of Corticotroph Adenoma

David H. George, MD, Bernd W. Scheithauer, MD, Kalman Kovacs, MD, PhD, Eva Horvath, PhD, William F. Young, Jr., MD, Ricardo V. Lloyd, MD, PhD, and Frederic B. Meyer, MD

corticotrophs. In general, corticotroph adenoma cells do not undergo significant Crooke's change, presumably because they lack normal feedback inhibitory responses to the elevated cortisol levels that they produce, possibly due to loss of functional glucocorticoid receptors.[16] CCAs represent the exception to this rule.

dant, hyalinized cytoplasm (hematoxylin and eosin, original magnification ×132). B, Crooke's hyalinization results from the accumulation of a ring of cytokeratin filaments around the nucleus (CAM 5.2 immunostain ×132). C, ACTH-positive granules are displaced to the periphery of the cell (immunostain ×132).

Crooke's Cell Adenoma of the Pituitary

An Aggressive Variant of Corticotroph Adenoma

(*Am J Surg Pathol* 2003;27:1330–1336)

David H. George, MD, Bernd W. Scheithauer, MD, Kalman Kovacs, MD, PhD, Eva Horvath, PhD, William F. Young, Jr., MD, Ricardo V. Lloyd, MD, PhD, and Frederic B. Meyer, MD

Casistica maggiore in letteratura: 36 pz

- **4.9% dei pz con malattia di Cushing, 3.9% degli adenomi silenti** (casistica Mayo Clinic);

-**tendenzialmente macroadenomi (81%) e generalmente invasivi;**

- **nella maggior parte dei casi pazienti cushingoidi (65%) con predominanza al femminile (75%), età media 46 anni;**

- **39% dei pazienti trattati hanno richiesto entro 1 anno ulteriore terapia;**

- **il 60% dei pz ha recidivato quando seguito oltre 1 anno;**

- **il 24% dei pz ha avuto più recidive;**

- **descritti alcuni rari casi di carcinoma a cellule di Crooke** (***Krovacs GL et al, Eur J Clin Invest 2013;43(1):20-26***).

Corticotropinomi aggressivi/carcinomi
Terapia

Neurochirurgia → **elevata % persistenza malattia recidive**

RT → **elevata % progressione**

Terapia medica??

Corticotropinomi aggressivi
Terapia medica

Sustained Improvements in Plasma ACTH and Clinical Status in a Patient With Nelson's Syndrome Treated With Pasireotide LAR, a Multireceptor Somatostatin Analog.

Katznelson L.

J Clin Endocrinol Metab. 2013 May;98(5), 2013-1497

Abstract

Here, the first case report of a patient with **Nelson's syndrome treated with pasireotide** is presented...

...she began **pasireotide long-acting release 60 mg/28 days im**. At baseline, fasting plasma ACTH was 42 710 pg/mL (normal, 5-27 pg/mL), and fasting plasma glucose was 98 mg/dL. **After 1 month, ACTH declined** to 4272 pg/mL, and **it has remained stable over 19 months** of follow-up. Hyperpigmentation progressively improved. **Magnetic resonance imaging scans show reduction in the suprasellar component**. **Fasting plasma glucose increased** to 124 mg/dL, and the patient underwent diabetes management....

...**Pasireotide may represent a useful tool in the medical management of Nelson's syndrome**. Further study of the potential benefits and risks of pasireotide in this population is necessary.

Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment

Gérald Raverot*,†, Frédéric Castinetti‡, Emmanuel Jouanneau†, Isabelle Morange‡, Dominique Figarella-Branger§, Henry Dufour¶, Jacqueline Trouillas† and Thierry Brue‡

Clinical Endocrinology (2012) 76, 769–775

Table 1. Patients treated by temozolomide for pituitary carcinomas or aggressive pituitary tumours, reported in the literature

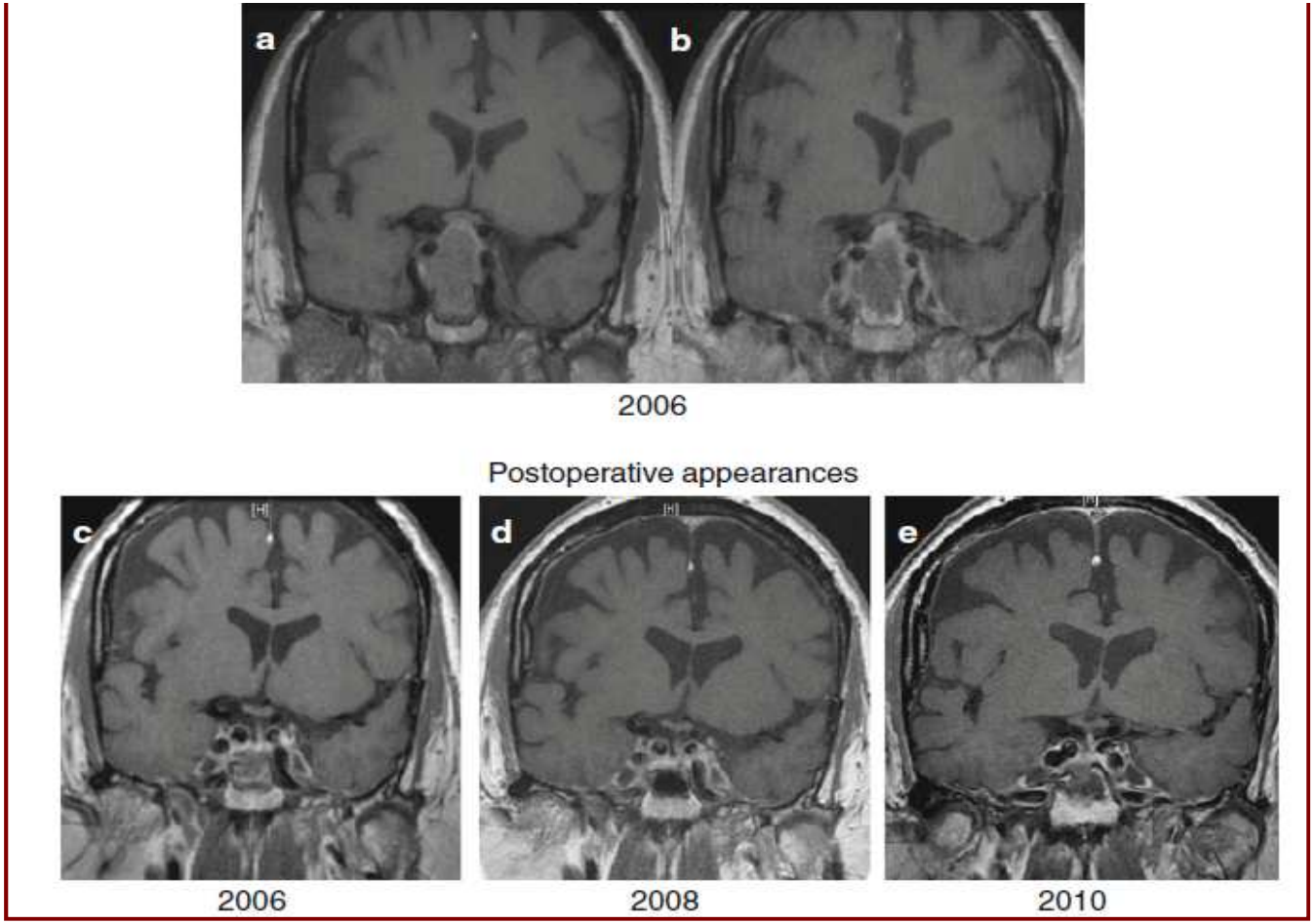
Tumour type	ACTH	PRL	NFPA	GH	Total
Total	18	15	8	3	44
Carcinomas	8	7	3	1	19
Aggressive adenomas	10	8	5	2	25
F/M	7/10 (1NA)	4/10 (1NA)	1/2 (5NA)	1/2	13/24 (7NA)
Age (years)	46·7 ± 9·6	49 ± 12·3	28·6 ± 9·0	36 ± 16·9	44·6 ± 12·9
Number of cycles	3–16	3–26	2–15	3	3–26
Hormonal response (%)	67	73	NA	33	60
Tumoural response (%)	56	66	38	33	61

NFPA, nonfunctioning pituitary adenoma; F/M, females/males; NA, not available; PRL, prolactinoma.
Number of cycles: 5-day administration of 200 mg/m^2 given daily on a monthly basis.

Temozolomide responsiveness in aggressive corticotroph tumours: a case report and review of the literature

A. K. Annamalai · A. F. Dean · N. Kandasamy · K. Kovacs · H. Burton · D. J. Halsall · A. S. Shaw · N. M. Antoun · H. K. Cheow · R. W. Kirollos · J. D. Pickard · H. L. Simpson · S. J. Jefferies · N. G. Burnet · M. Gurnell

Pituitary (2012) 15:276–287



Salvage therapy with temozolomide in patients with aggressive or metastatic pituitary adenomas: experience in six cases

Marco Losa[1], Elena Mazza[2], Maria Rosa Terreni[3], Ann McCormack[4], Anthony J Gill[5,6], Micaela Motta[2], Maria Giulia Cangi[3], Anna Talarico[3], Pietro Mortini[1] and Michele Reni[2]

European Journal of Endocrinology (2010) **163** 843–851

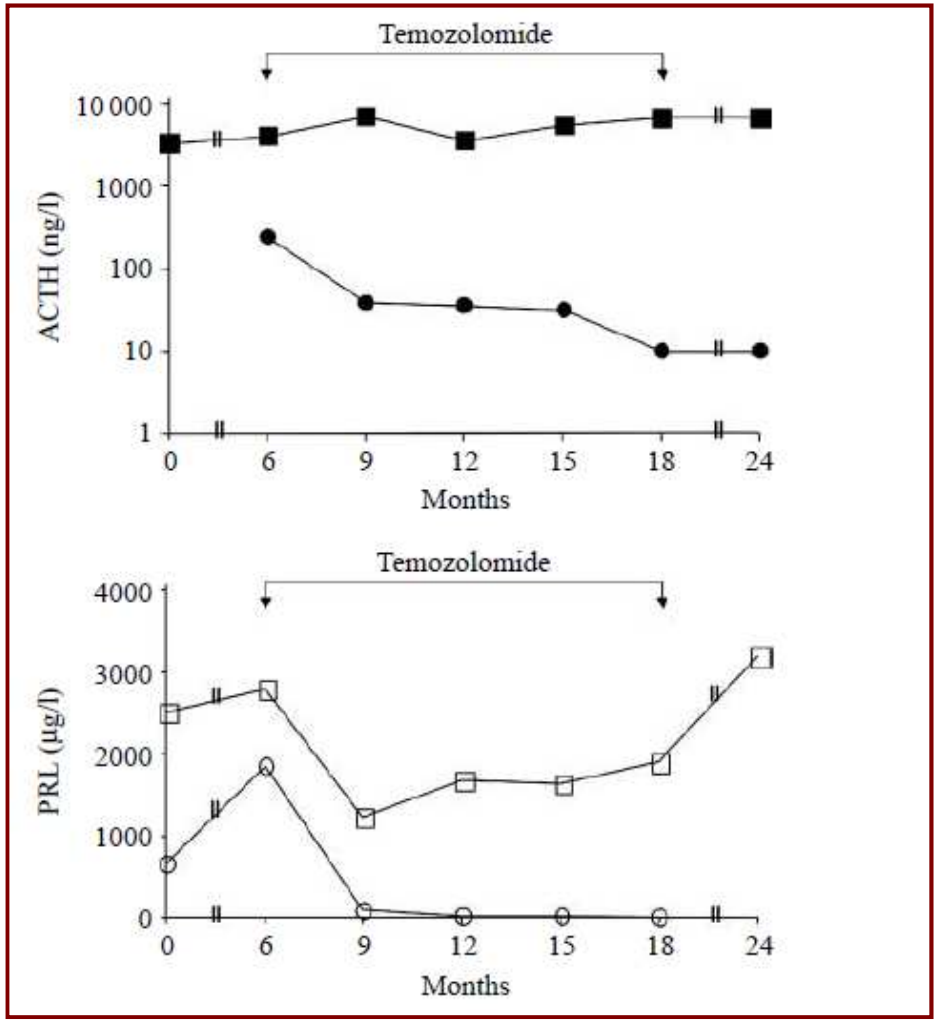


Figure 2 Hormone levels before, during, and after temozolomide treatment in four patients with pituitary carcinoma or atypical adenoma not responding to standard treatments. The upper panel shows the ACTH levels in Patient #2 (solid circles) who had Cushing's disease and in Patient #3 (solid squares) who had Nelson's syndrome. Note the logarithmic scale. The lower panel shows the PRL levels in Patients #5 (open squares) and #6 (open circles) who had a prolactinoma.

Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment

Gérald Raverot*,†, Frédéric Castinetti‡, Emmanuel Jouanneau†, Isabelle Morange‡, Dominique Figarella-Branger§, Henry Dufour¶, Jacqueline Trouillas† and Thierry Brue‡

Clinical Endocrinology (2012) 76, 769–775

Table 2. MGMT immunohistochemistry as a predictive marker of temozolomide efficacy

			Temozolomide efficacy		
Tumour type	MGMT immunohistochemistry	Patients	Yes	No	Positive predictive value
ACTH		$n = 14$	$n = 9$	$n = 5$	
	Negative/low	8	7	1	
	Intermediate	2	1	1	
	High/positive	4	1	3	79%
PRL		$n = 9$	$n = 5$	$n = 4$	
	Negative/low	7	5	2	
	Intermediate	1	0	1	
	High/positive	1	0	1	67%
NFPA		$n = 8$	$n = 5$	$n = 3$	
	Negative/low	1	0	1	
	Intermediate	1	1	1	
	High/positive	6	4	1	25%
GH		$n = 2$	$n = 1$	$n = 1$	
	Negative	1	1	0	
	Positive	1	0	1	100%
Total		33	20	13	
	Negative/low	17	13	4	
	Intermediate/high	16	7	9	67%

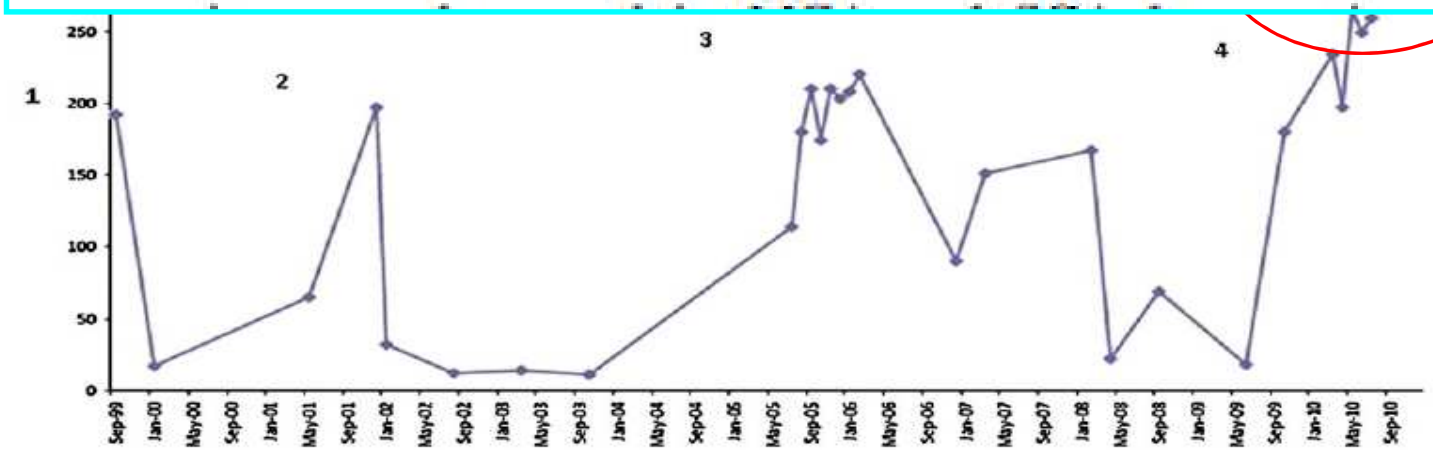
New targeted therapies in pituitary carcinoma resistant to temozolomide

Pituitary (2012) 15:37–43

Emmanuel Jouanneau · Anne Wierinckx · François Ducray · Véronique Favrel · Françoise Borson-Chazot · Jérôme Honnorat · Jacqueline Trouillas · Gérald Raverot

everolimus (5 mg/day) and octreotide (30 mg/month)

The transcriptomic analysis of the 18 ACTH adenomas demonstrated important variations between the three tumor groups (mCA, MCA and SCA groups). Only slight activation of the PI3/AKT/mTOR signaling was noted without any statistically significant difference between the groups (Table 1). AKT1 was activated in all three groups, PI3K



Anti-VEGF therapy in pituitary carcinoma

Leon D. Ortiz · Luis V. Syro · Bernd W. Scheithauer · Ayca Ersen · Humberto Uribe · Camilo E. Fadul · Fabio Rotondo · Eva Horvath · Kalman Kovacs

Pituitary (2012) 15:445–449

Intravenous bevacizumab therapy

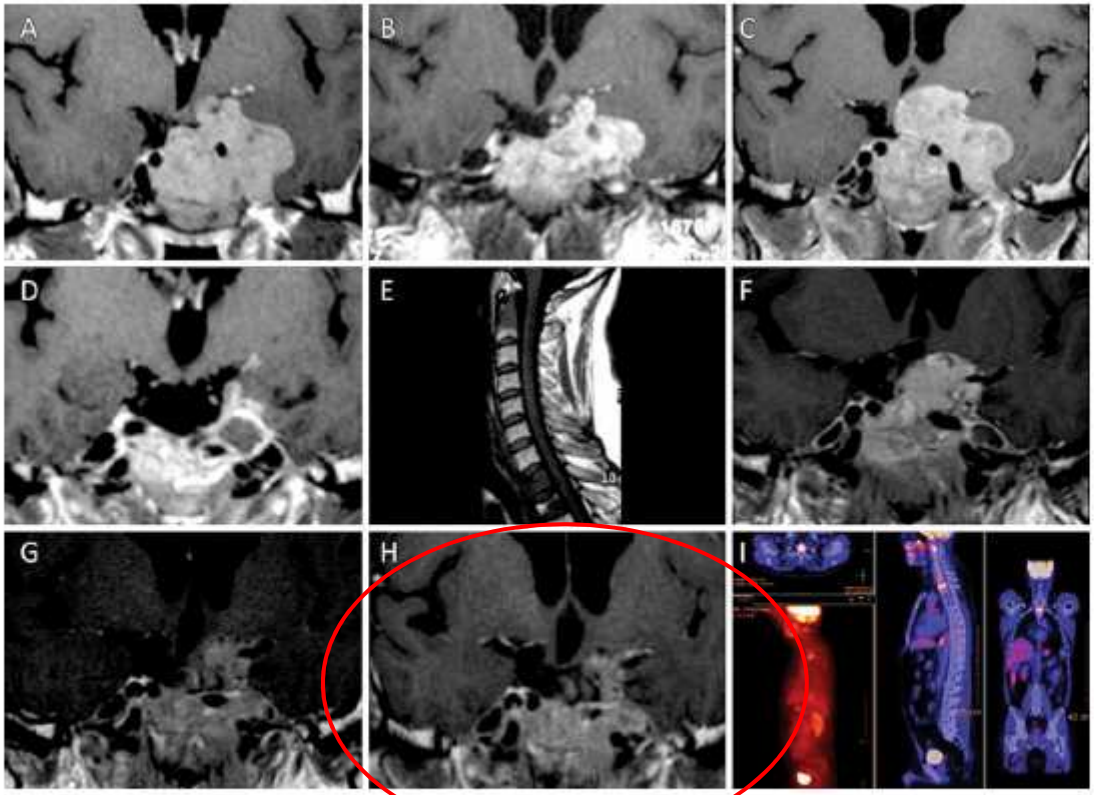


Fig. 1 Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans documenting the evolution of the patient. **a** Preoperative MRI scan. **b** Postoperative MRI scan demonstrating subtotal resection. **c** Tumor regrowth after 8 months of standard-regimen temozolomide treatment. **d** Postoperative MRI after subtotal re-excision. **e** Spinal metastases at C2 and T1 after 16 months of standard-regimen temozolomide treatment. **f** Sellar tumor recurrence after 8 months of temozolomide treatment at metronomic dose. **g** Postoperative MRI. **h** MRI after 24 months of bevacizumab therapy showing stabilization of the sellar lesion. **i** PET scan with no new metastatic lesions

Corticotropinomi aggressivi/carcinomi

Problematiche aperte…

Distinzione/evoluzione adenoma aggressivo-carcinoma

Quali marker predittivi di aggressività?

Clinici?

Istologici?

Radiologici?

Terapia?

Quando RT?

Quando terapia medica e con quali farmaci?

Problematiche aperte…

Corticotropinomi non visibili

Quale workup diagnostico??

Quali test?

Quale imaging?

IPSS sempre?

Terapia chirurgica

Ruolo del neurochirurgo?

Altre opzioni?

Corticotropinomi aggressivi/carcinomi

Distinzione/evoluzione adenoma aggressivo-carcinoma

Quali marker predittivi di aggressività?

Clinici?

Istologici?

Radiologici?

Terapia?

Quando RT?

Quando terapia medica e con quali farmaci?

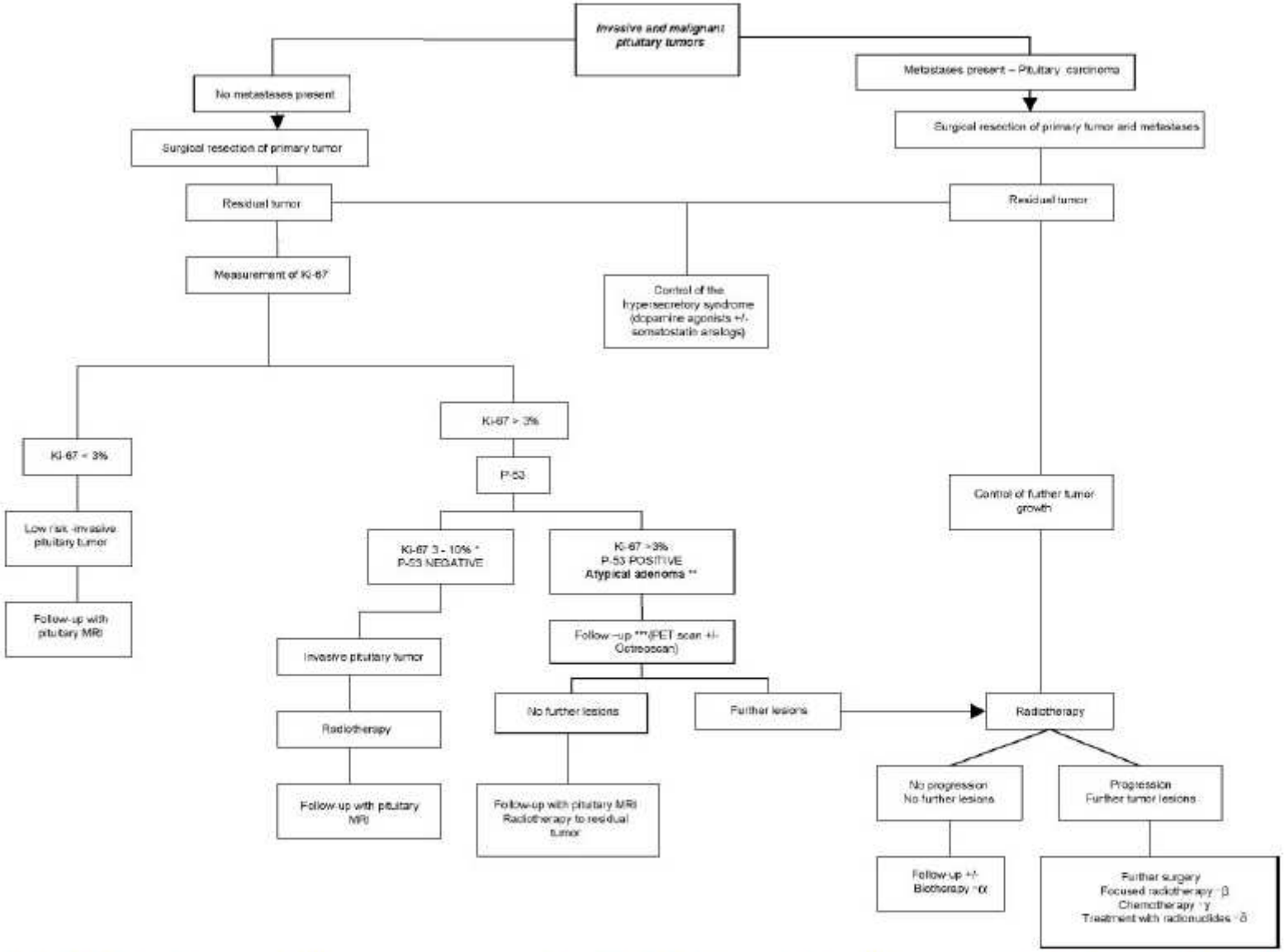
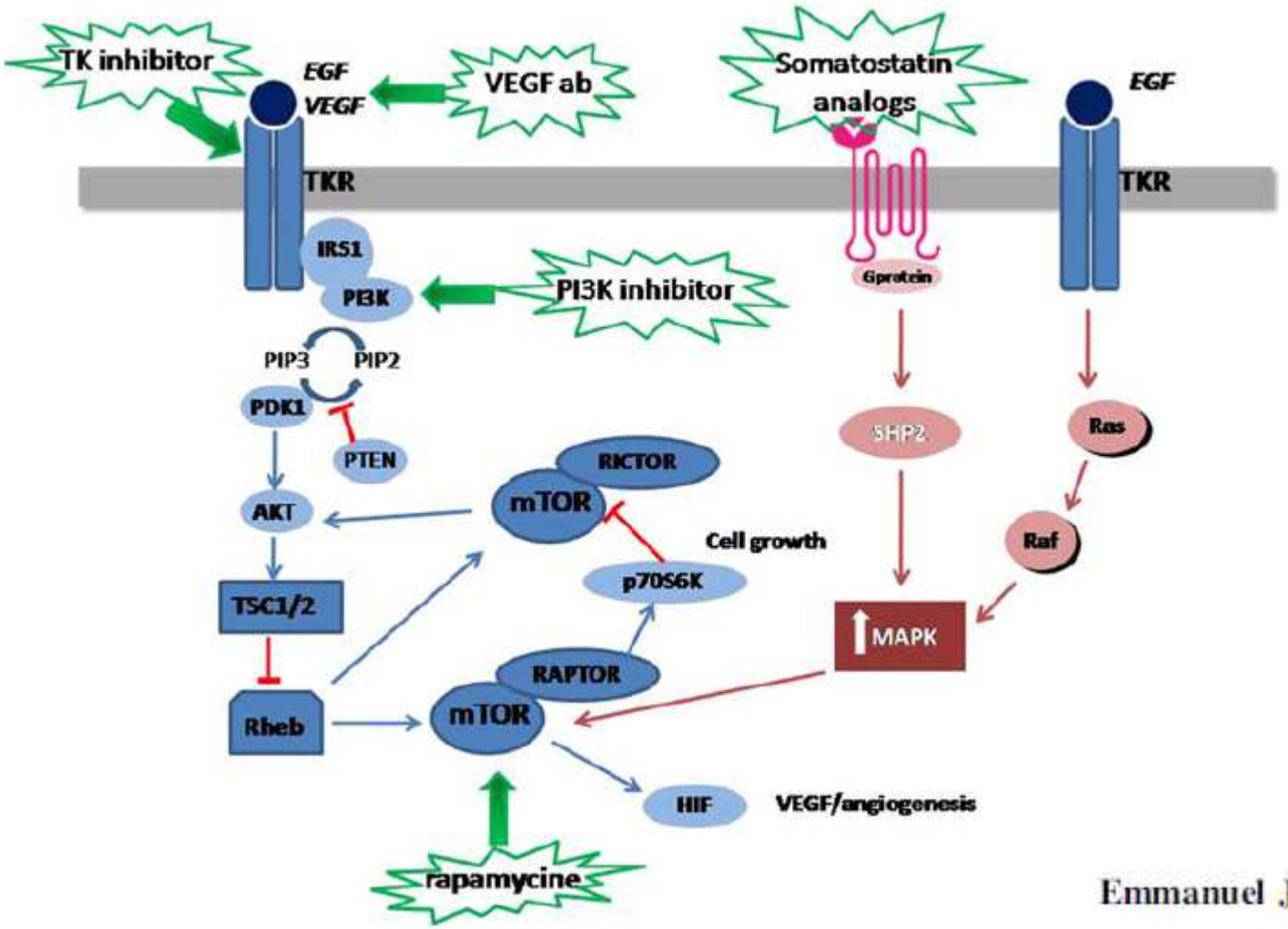


FIG. 3. A histopathologically based diagnostic and therapeutic approach for invasive pituitary tumors. *, Tumors with Ki-67 greater than 10% should be regarded as atypical adenoma. **, Atypical adenoma. ***, Suggested imaging modalities for follow-up. α, Ref. 112; β, Refs. 4, 12, 83, 100, and 101; γ, Ref. 54; δ, Ref. 104.

Corticotropinomi aggressivi/carcinomi
Terapia



Emmanuel Jouanneau

Pituitary (2012) 15:37–43

Corticotropinomi aggressivi
ruolo della MGMT

O-6-Methylguanine-DNA Methyltransferase (MGMT) Immunohistochemical Expression in Pituitary Corticotroph Adenomas

Salehi F et al.
Neurosurgery 70:491–496, 2012

TABLE 1. Clinical Data and MGMT Immunostaining of Patients With Cushing Disease (n = 40)[a]

MGMT, %	n	Sex, F:M	Mean Age (Range), y	Recurrence, n	Macroadenoma, n	Invasive, n
<10	18	10:8	39.4 (15-57)	4	6	4
10-25	7	3:4	38.7 (18-24)	5	3	5
25-50	3	3:0	44.3 (46-60)	0	2	2
50-75	9	9:0	46.3 (36-62)	2	3	3
>75	3	3:0	43.8 (39-40)	0	2	2
Total	40	28:12	40.6 (15-62)	11	16	16

60%

[a]MGMT, O-6-methylguanine-DNA methyltransferase.

O-6-Methylguanine-DNA Methyltransferase (MGMT) Immunohistochemical Expression in Pituitary Corticotroph Adenomas

Salehi F et al.

Neurosurgery 70:491–496, 2012

European Journal of Endocrinology (2009) **161** 553–559 ISSN 0804-4643

TABLE 2. MGMT Immunoreactivity in Adrenocorticotropin-Producing Pituitary Adenomas[a]

Adenoma Type	n	<10%, n (%)	10%-25%, n (%)	25%-50%, n (%)	50%-75%, n (%)	>75%, n (%)
Crooke cell	12	6	1	2	2	1
Cushing disease	40	17	7	6	7	3
Silent subtype I	7	7	0	0	0	0
Total	59	30 (50)	8 (14)	8 (14)	9 (15)	4 (7)

[a]MGMT, O-6-methylguanine-DNA methyltransferase.

TABLE 1: Diagnostic accuracy of 1.5- and 3.0-T MR imaging*

Stage of Disease	No. of Patients (%)	
	1.5 T	3.0 T
preclinical CD	2/5 (40)	1/7 (14)
overt CD	6/9 (67)	3/9 (33)
total accuracy	8/14 (57)	4/16 (25)

* CD = Cushing disease.

Results. The diagnostic accuracy of superconductive MR imaging for detecting the localization of Cushing microadenoma was only 40%. The causes of unsatisfactory results for superconductive MR imaging were false-negative results (10 cases), false-positive results (6 cases), and instances of double pituitary adenomas (3 cases). In contrast,

Ikeda K et al, J Neurosurg 2010;112:750–755

Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment

Gérald Raverot*,†, Frédéric Castinetti‡, Emmanuel Jouanneau†, Isabelle Morange‡, Dominique Figarella-Branger§, Henry Dufour¶, Jacqueline Trouillas† and Thierry Brue‡

Clinical Endocrinology (2012) 76, 769–775

Table 2. MGMT immunohistochemistry as a predictive marker of temozolomide efficacy

Tumour typ					dictive value
ACTH					
PRL					
NFPA					
GH					
	Positive	1	0	1	100%
Total		33	20	13	
	Negative/low	17	13	4	
	Intermediate/high	16	7	9	67%

- Temozolomide should be used with caution in the treatment of pituitary tumours because of the lack of formal controlled trial data. The preferred dosing regimen should be 200 mg/m^2 daily for 5 days every 28 days.[38] The optimal duration of temozolomide treatment remains unclear.
- Rapid tumour shrinkage or hormonal response to temozolomide treatment is usually observed within weeks after treatment initiation in responding patients. As a consequence, the lack of response after three cycles predicts further resistance to this treatment.[56] In contrast, an initial response to temozolomide is not always associated with short- or long-term control.[6,52,54,67]

Corticotropinomi non visibili
Terapia medica ??

Table 3 | Medical therapies currently used or studied in patients with Cushing disease

Medication	Mechanism of action	Dose range	Effectiveness (%)*	Adverse effects	Comments
Ketoconazole[63,64]	Inhibits several steps of steroidogenesis	200–1,200 mg/daily orally (divided bid)	70–80	Gastrointestinal symptoms, transaminitis, severe hepatotoxicity, rash, gynecomastia	Might be preferred over metyrapone in women
Metyrapone[66,73]	Inhibits 11β hydroxylase	750–6,000 mg/daily orally (divided bid or qid)	75	Gastrointestinal symptoms, dizziness, rash, hirsutism (women), hypertension, edema	The most commonly used medication in pregnancy; might be preferred over ketoconazole in men
Mitotane[69]	Inhibits several steroidogenic steps; adrenolytic	1–12 g/daily orally	83	Nausea, diarrhea, dizziness, neurologic symptoms, dyslipidemia	Should be avoided in women desiring pregnancy in the next 5 years
Etomidate[71]	Inhibits 11β hydroxylase	<0.1 mg/kg/hr iv	100 (short-term)	Excessive sedation, anesthesia	Useful when rapid control of hypercortisolism is needed, but its use requires anesthesiologist evaluation and monitoring
Cabergoline[77,78]	D2 dopamine receptor agonist	1–7 mg/week orally (divided biw or daily)	50–75 (short-term); 30–40 (2–3 years)	Nausea, vomiting, dizziness; possible risk of valvulopathy	May be more useful in combination therapy with ketoconazole and/or pasireotide[84,85]
Pasireotide[83]	Somatostatin receptor agonist (types 1, 2, 3 and 5)	600 μg sc bid	76 (short-term)	Gastrointestinal side-effects, hyperglycemia	Currently investigational
Mifepristone[87]	Type II glucocorticoid receptor antagonist	300–1,200 mg/daily orally	70–80‡	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia, rash	Currently investigational

*The definition of response varies between studies. Data shown include both complete and partial responses in aggregate. ‡Data include patients with Cushing syndrome of various etiologies.
Abbreviations: bid, twice daily; biw, twice weekly; iv, intravenously; qid, four times daily; sc, subcutaneously.

Tritos NA, Nat Rev Endocrinol 2011

Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease

F Castinetti, I Morange, P Jaquet, B Conte-Devolx and T Brue

European Journal of Endocrinology (2008) **158** 91–99

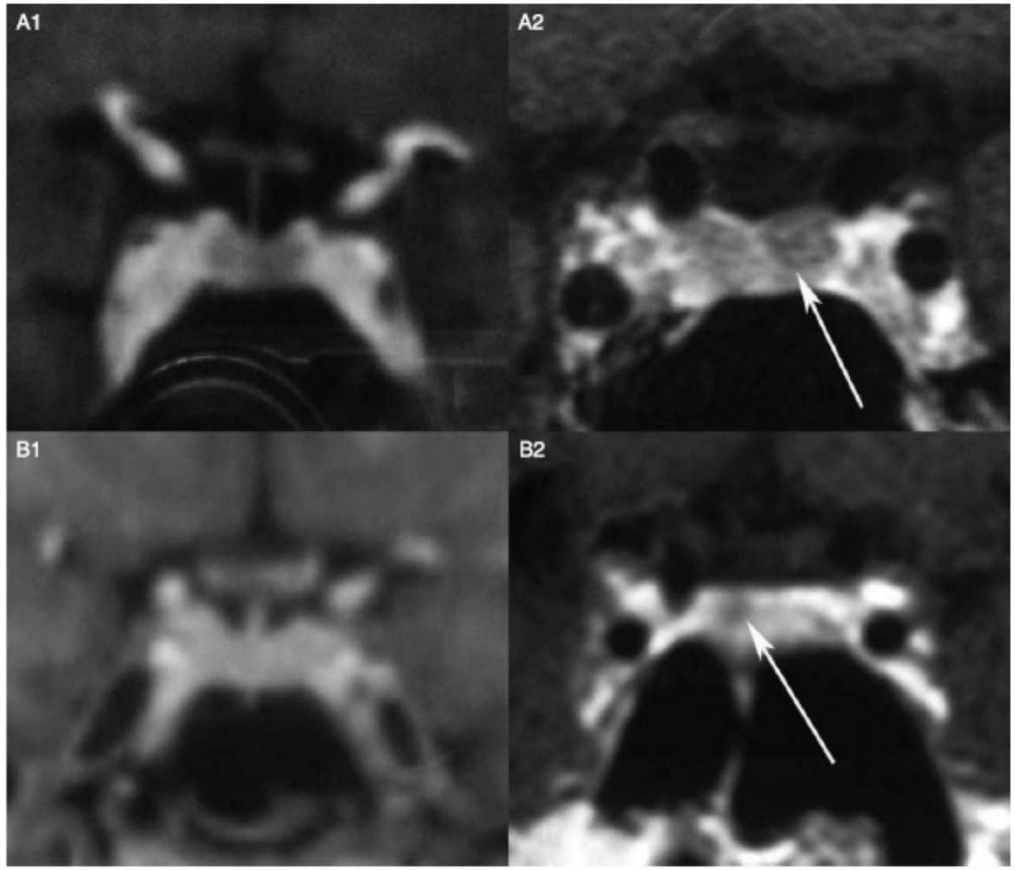


Figure 2 Pituitary MRI (sagittal, T1-weighted sequence after gadolinium injection) before and after ketoconazole treatment, disclosing the delayed visualization of an adenoma. (A1) Before ketoconazole treatment, heterogeneous pituitary without evident image of an adenoma. (A2) After 30 months of ketoconazole treatment, visualization of a left latero-sellar microadenoma. (B1) Before ketoconazole treatment, lack of pituitary adenoma image. (B2) After 12 months of treatment, a right latero-sellar microadenoma is visualized. In both cases, surgery was performed and allowed histological confirmation of the diagnosis and remission.