

Altogether
to Beat
Cushing's
Syndrome

SESSIONE 2: IL CUSHING ECTOPICO

moderatori **Ettore Degli Uberti, Diego Ferone**

L'INQUADRAMENTO CLINICO-DIAGNOSTICO
Giovanni Vitale

L'APPROCCIO TERAPEUTICO
Manuela Albertelli

IL RUOLO DEGLI ANALOGHI
DELLA SOMATOSTATINA E DEL PASIREOTIDE
Giorgio Arnaldi



**VIAGGIO ALLA
(R)SCOPERTA
DELLA SINDROME
DI CUSHING**

seconda edizione

Capri \ 15-18 maggio 2013
Certosa di San Giacomo
Hotel della Piccola Marina

Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement

Part V: Management of Ectopic ACTH Syndrome, Nelson's Syndrome, Special Patient Populations, and the Patient after Successful Surgical Treatment

Tumor-directed therapy involves a multidisciplinary, individualized approach and can include **somatostatin analogs**, systemic chemotherapy, interferon- , chemoembolization, radiofrequency ablation, and radiation therapy.

EXTENSIVE CLINICAL EXPERIENCE

Cushing's Syndrome Due to Ectopic Corticotropin Secretion: Twenty Years' Experience at the National Institutes of Health

J Clin Endocrinol Metab 90: 4955–4962, 2005)

Ioannis Ilias, David J. Torpy, Karel Pacak, Nancy Mullen, Robert A. Wesley, and Lynnette K. Nieman

Studiati

90 pazienti

Trattati con SSA

0

The Ectopic Adrenocorticotropin Syndrome: Clinical Features, Diagnosis, Management, and Long-Term Follow-Up

J Clin Endocrinol Metab 91: 371–377, 2006)

Andrea M. Isidori, Gregory A. Kaltsas, Carlotta Pozza, Vanni Frajese, John Newell-Price, Rodney H. Reznek, Paul J. Jenkins, John P. Monson, Ashley B. Grossman, and G. Michael Besser

Studiati

40 pazienti

Trattati con SSA

0

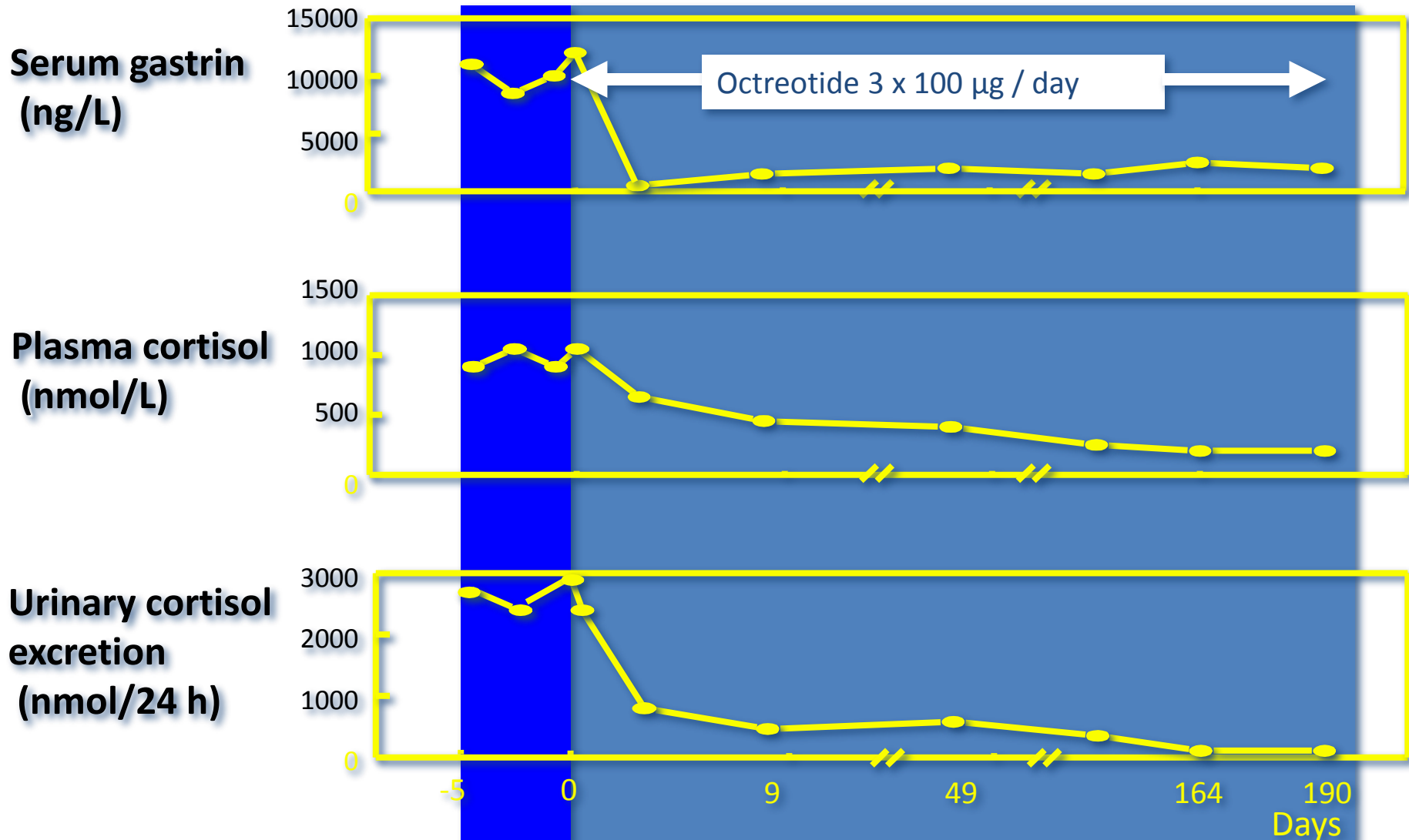
Ectopic ACTH-secreting Tumors Treated with Octreotide

Primary tumor	n°	Initial Response	Prolonged Response
Small Cell Lung Ca.	3	2/3	
Bronchial Carcinoid	11	8/11	3/4
Thymus Ca. / Carcinoid	3	1/3	
Functional Pancreas NET	9	8/9	4/5
Medullary Thyroid Carcinoma	2	2/2	
Gastro-intestinal Carcinoid	3	0/3	1/1
Occult Tumor	6	4/6	3/5
TOTAL	37	25/37	11/15

da De Herder, *et al.*, Metabolism 1996

Octreotide Treatment of ACTH-secreting Metastatic Gastrinoma

Lamberts, *et al.*, J. Clin. Endocrinol. Metab. 1988; 67: 1080-83.



Ruolo degli analoghi della somatostatina nella secrezione ectopica di ACTH

- Riduzione o normalizzazione della ipersecrezione di ACTH e quindi di cortisolo
- Concomitante riduzione di altre secrezioni ormonali associate
- Effetto antiproliferativo
- Ruolo nell'imaging
- Veicolo per terapia radiorecettoriale

Comparison between hormonal response to acute octreotide administration and results of pentreotide scintigraphy in ACTH-secreting Bronchial Carcinoids

Case	Octreotide test (100 mcg sc) *	¹¹¹ In-pentetreotide scintigraphy
1	No response	Positive
2	Response	Positive
3	Response	Negative
4	Response	Positive
5	No response	Negative
6	No response	Positive

* Response = decreases in
plasma ACTH and cortisol greater than 30%

Loli et al, JCEM 2003

Is there a therapeutic role for octreotide in patients with ectopic Cushing's syndrome?

G.I. Uwaifo¹, C.A. Koch², B. Hirshberg³, C.C. Chen⁴, P. Hartzband⁵, L.K. Nieman² and K. Pacak²

	Parameter	Case 1	Case 2	Case 3				
1	Age (yr)	40	36	43				
2	Ethnicity	Caucasian	Caucasian	Caucasian				
3	Gender	Male	Male	Male				
4	Diagnosis	Medullary thyroid Carcinoma	Unknown	Small Cell Carcinoma				
5	Metastases	Present	Absent	Present				
6	Serum cortisol nmol/l (normal: <207 nmol/l)	1380-1518	1076.4	1628	Cortisol response to octreotide	Increase	Decrease	No effect
7	Plasma ACTH (pmol/l) (normal: 2-13 pmol/l)	39.6-46.2	18.7	46	Octreotide scan	Positive	Negative	Positive
8	24-h urine free cortisol (nmol/day) (normal: 66-298 nmol/day)	4416-12,420	2343	2967				
9	24-h urine 17-hydroxysteroid (mg/day) (normal: 8-26 mg/day)	221	34.8	81.6				
	Duration of symptoms before referral (yr)	1	3	0.4				

J. Endocrinol. Invest. 26: 710-717, 2003

Table 3
Biochemical Response to Octreotide in Ectopic Corticotropin-Secreting Tumors

Reference	No. patients	Eucortisolism, No. of patients	Normal corticotropin, No. of patients	Treatment duration
Ruszniewski et al (14)	1	1	1	9 months
Woodhouse et al (15)	6	3	1 of 2	1 day to 1 year
De Rosa et al (16)	1	1	1	6 months
Van den Bruel et al (17)	1	1	1	8 years
Uwaifo et al (18)	3	1	1	1 day to 2 years
Cheung et al (19)	2	0	1	5 to 7 days

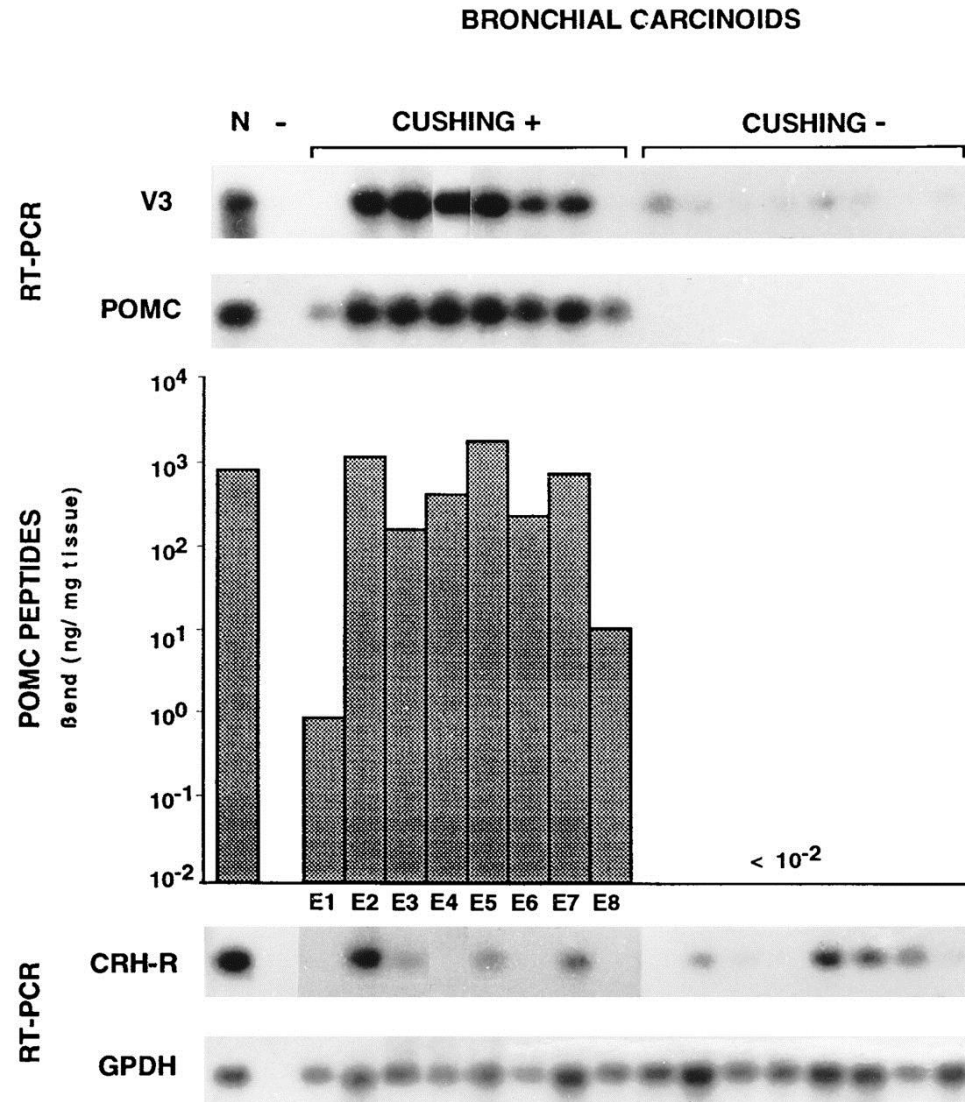
Bruno et al. Endocr Pract. 2010;16:829-834)

ACTH ectopico e
tumore ipofisario corticotropo

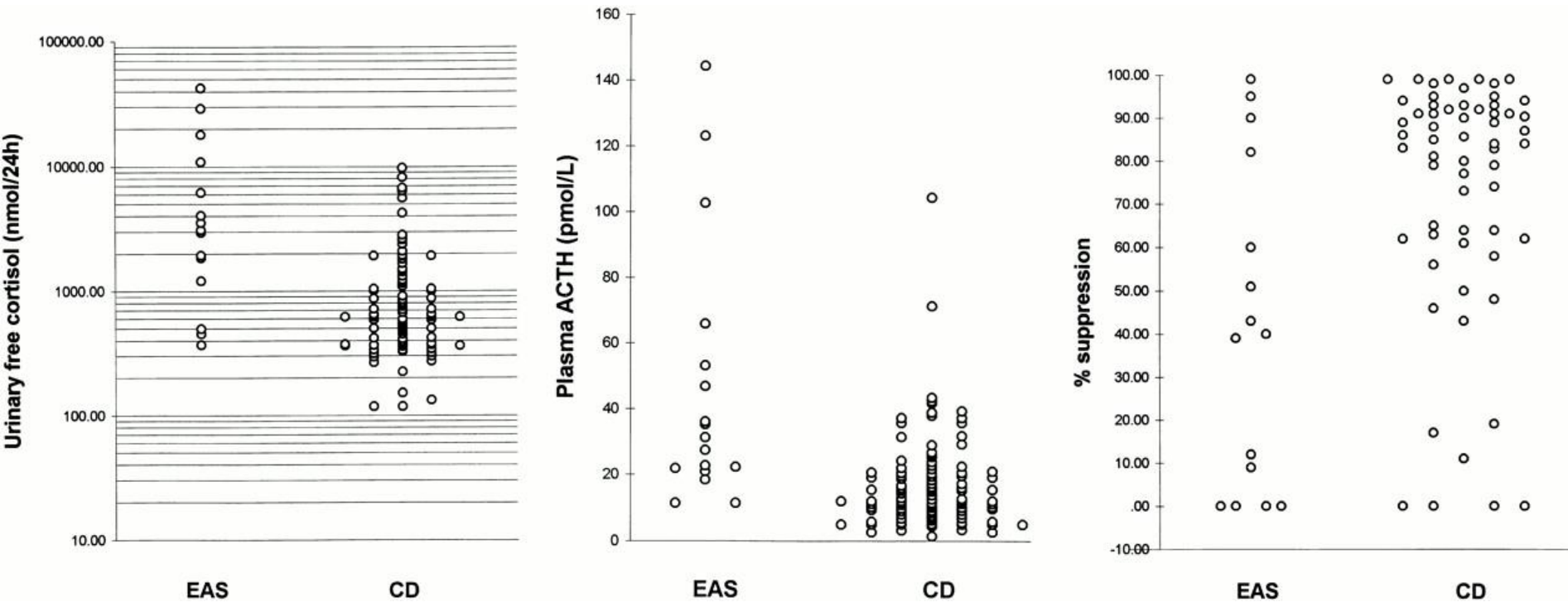
Simile ma non uguale

Eterogeneità

The pituitary V3 vasopressin receptor and the corticotroph phenotype in ectopic ACTH syndrome

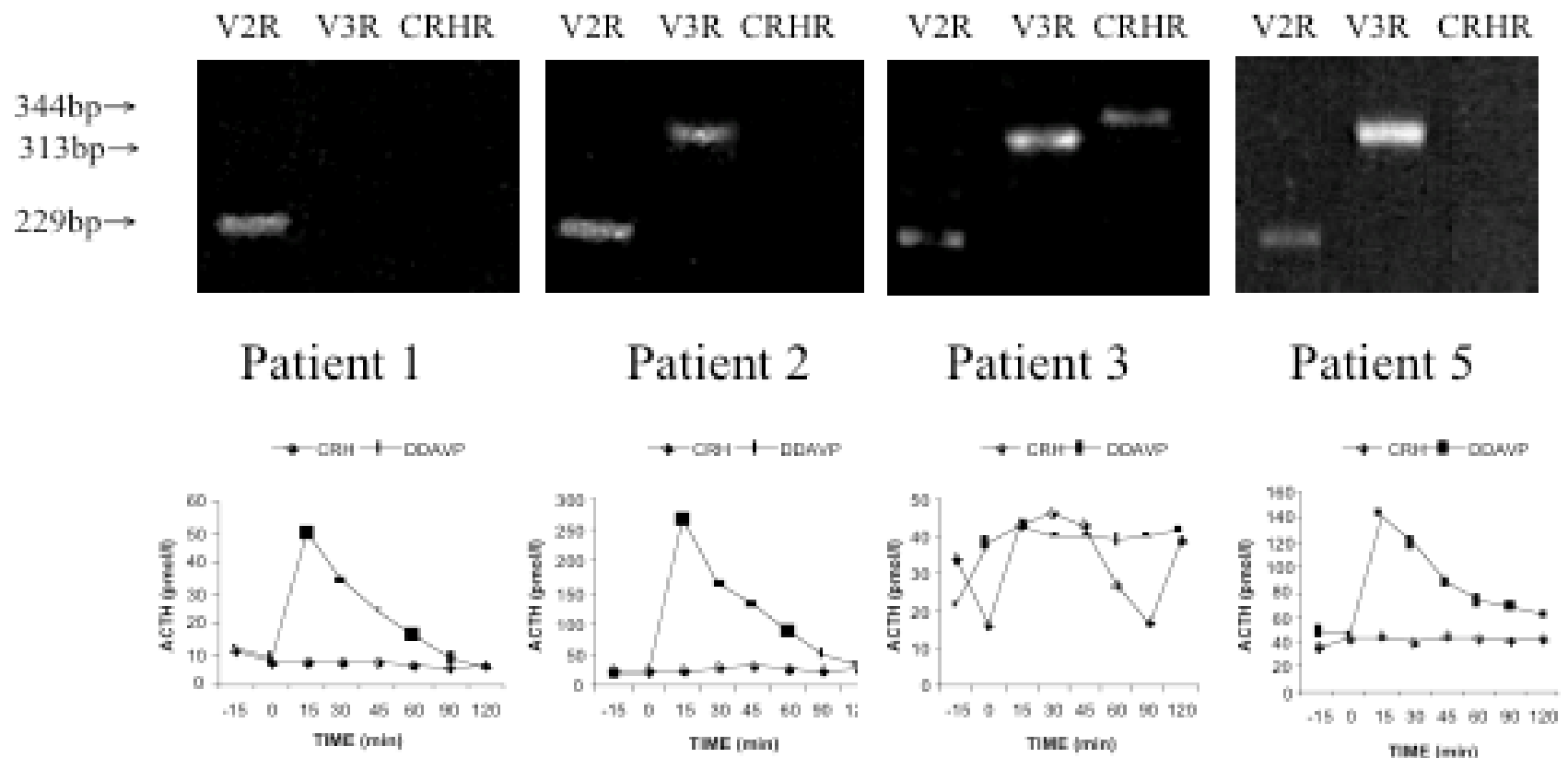


Effectiveness *Versus* Efficacy: The Limited Value in Clinical Practice of High Dose Dexamethasone Suppression Testing in the Differential Diagnosis of Adrenocorticotropin-Dependent Cushing's Syndrome



Aron, D. C. et al. J Clin Endocrinol Metab 1997;82:1780-1785

VASOPRESSIN RECEPTOR mRNA EXPRESSION AND ACTH RESPONSES TO DESMOPRESSIN IN TUMOURS WITH ECTOPIC ACTH SECRETION



Tsagarakis et al, JCEM, 2002

Approach to the Patient with Possible Cushing's Syndrome

Causes of ectopic ACTH syndrome

Localization	Frequency % (No.)			
	<i>Aniszewski et al., 2001</i>	<i>Ilias et al., 2005</i>	<i>Isidori et al., 2005</i>	<i>Salgado et al., 2006</i>
Bronchial carcinoid	25% (26/106)	40% (35/90)	34% (12/35)	40% (10/25)
Pancreatic carcinoid	16% (17/106)	1% (1/90)	8% (3/35)	12% (3/25)
Small-cell lung cancer	11% (12/106)	3% (3/90)	6% (2/35)	nd
Thymic carcinoid	5% (5/106)	5% (5/90)	6% (2/35)	16% (4/25)
Unknown/occult	7% (7/106)	19% (17/90)	14% (5/35)	8% (2/25)
Other	36% (39/106)	32% (27/90)	32% (11/35)	24% (6/25)

Boscaro & Arnaldi. J Clin Endocrinol Metab 94: 3121–3131, 2009

Recettori della somatostatina e NET

TUMOR	sst1	sst2	sst3	sst4	sst5
Gastrinoma	79%	93%	36%	61%	93%
Insulinoma	76%	81%	38%	58%	57%
Non-functioning pancreatic tumor	58%	88%	42%	48%	50%
Carcinoid tumor of the gut	76%	80%	43%	68%	77%

U. Plockinger MD, 2007

Expression of Somatostatin and Dopamine 2 Receptors in Neuroendocrine Tumours and the Potential Role for New Biotherapies

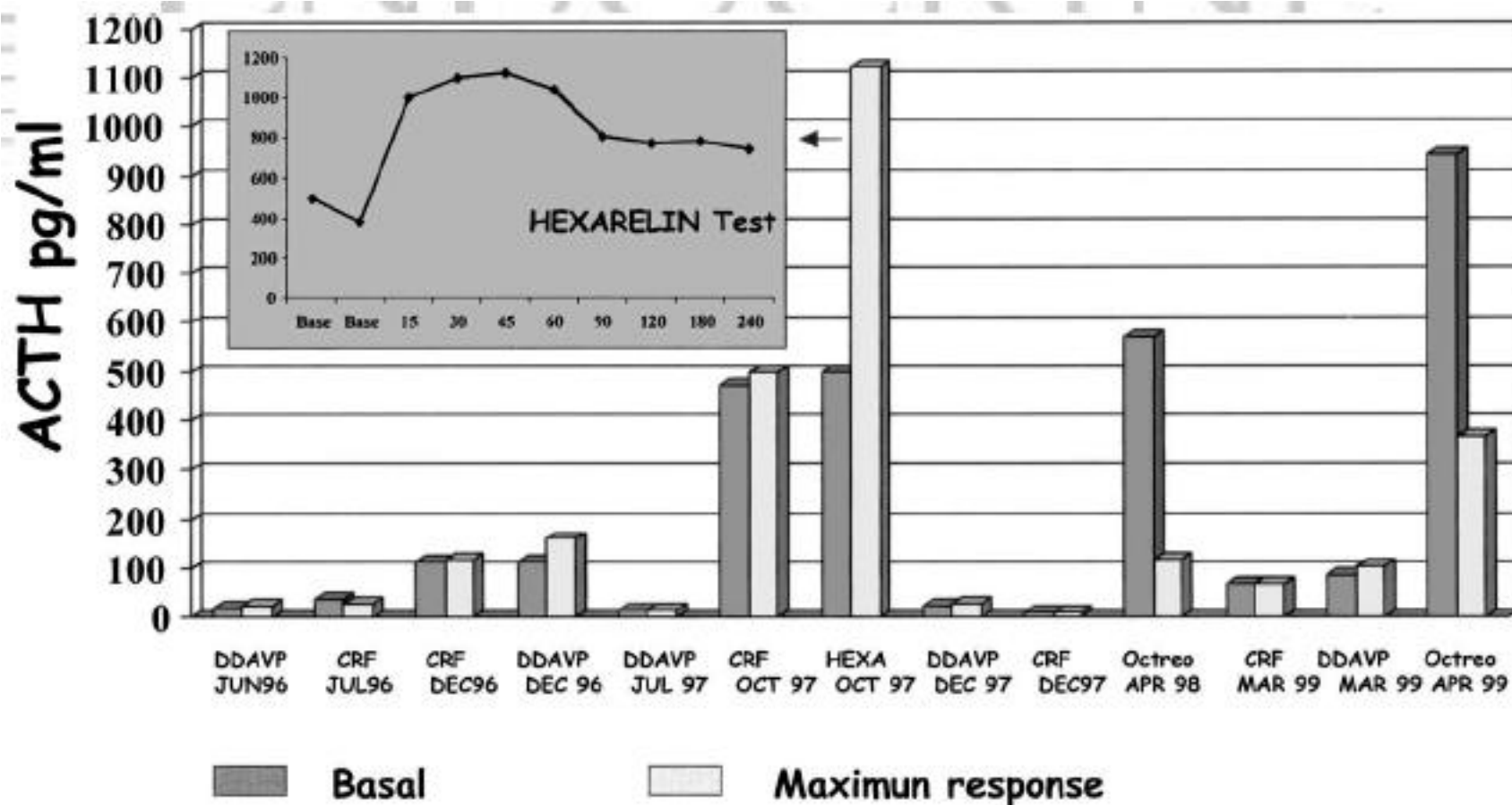
Srirajaskanthan R. · Watkins J. · Marelli L. · Khan K. · Caplin M.E.

Neuroendocrinology 2009;89:308–314 (DOI: 10.1159/000179899)

Location	Grade and/ or type	Total cases n	SSTR-2		SSTR-5		D2R		Octreo- tide scan, n	Positive octreotide scan, n
			positive n	score	positive n	score	positive n	score		
Bronchial	AC/intermediate	1	1	4	1	6	1	3	1	1
	LCNEC/high	2	0		1	4	0		1	0
Gastric	low	1	1	9	1	9	1	6	0	n/a
	intermediate	1	1	2	1	6	1	2	0	n/a
	high	1	1	6	1	6	0	0	1	0
MTC	low	2	2	4–9	2	4–9	2	4	1	1
Pancreatic	low	6	6	4–9	6	6–9	5	4–9	4	4
	intermediate	2	2	4	2	6–9	2	4–6	2	2
	high	3	2	2–6	2	4	1	2	2	2
Duodenal	low	1	1	3	1	6	1	9	0	n/a
Ileal	low	14	14	1–9	14	4–9	14	1–9	11	11
	intermediate	7	7	3–9	7	4–9	7	4–6	3	3
	high	1	1	6	0		0		0	n/a
Colon	low	3	3	6–9	3	4–9	3	3–9	1	1
	intermediate	2	2	2	2	4	1	9	1	1
	high	1	0		0		0		0	n/a
Ovarian	intermediate	1	1	9	1	9	1	6	1	1
Unknown	low	2	2	4–6	2	6	1	2	0	n/a
	intermediate	3	3	6–9	3	4–6	1	4	0	n/a
	high	2	2	1–3	2	2–6	2	3–6	0	n/a

Cyclical Cushing's Syndrome in a Patient With a Bronchial Neuroendocrine Tumor (Typical Carcinoid) Expressing Ghrelin and Growth Hormone Secretagogue Receptors

Arnaldi et al, JCEM 2003



SST2 vs SST5

ACTH ectopico e
tumore ipofisario corticotropo

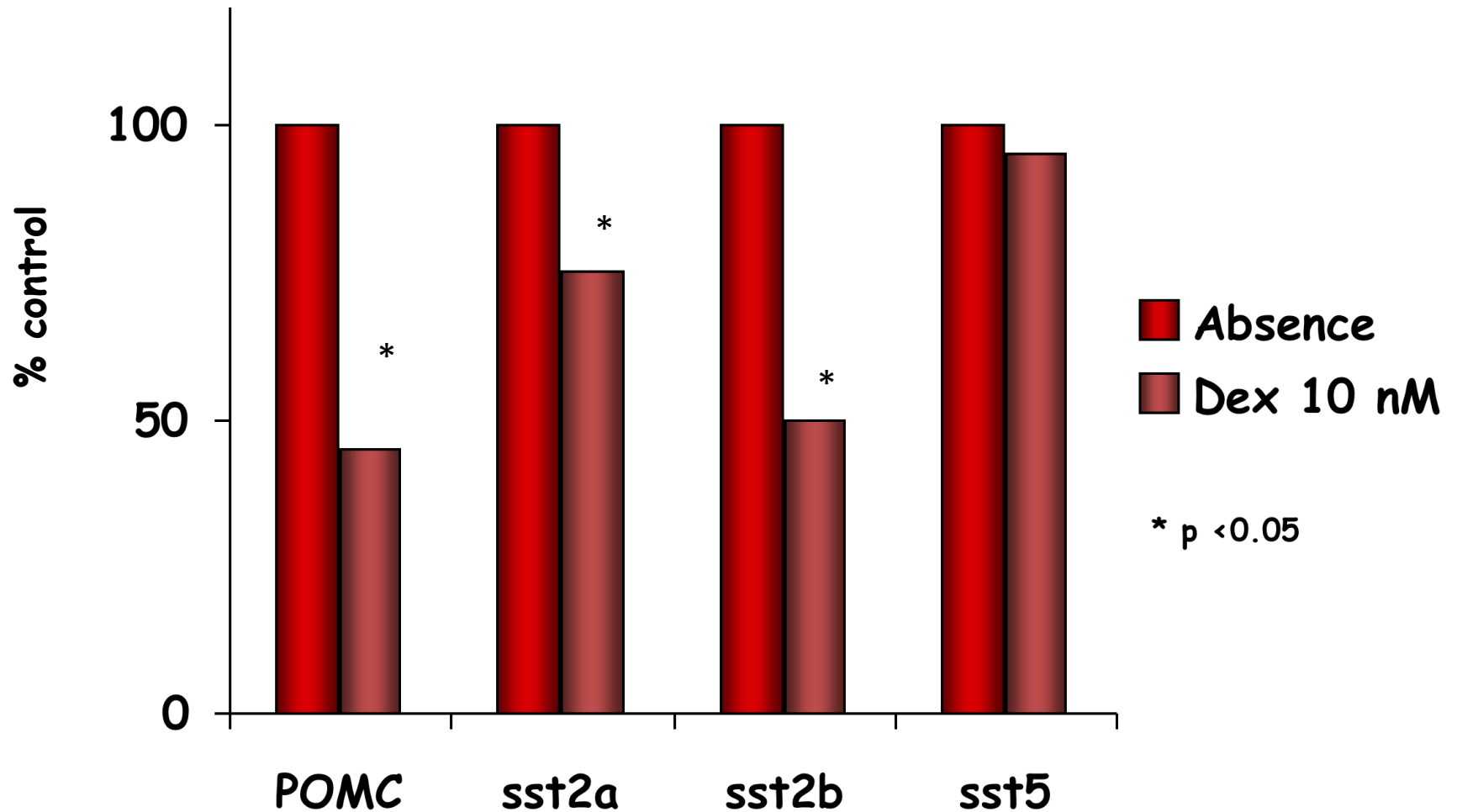
Simile ma non uguale

Eterogeneità

Differente espressione recettoriale

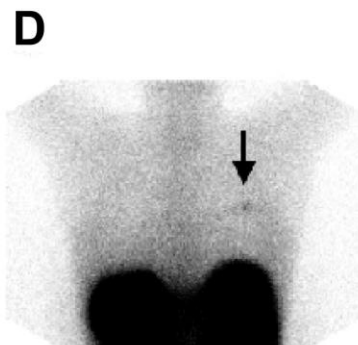
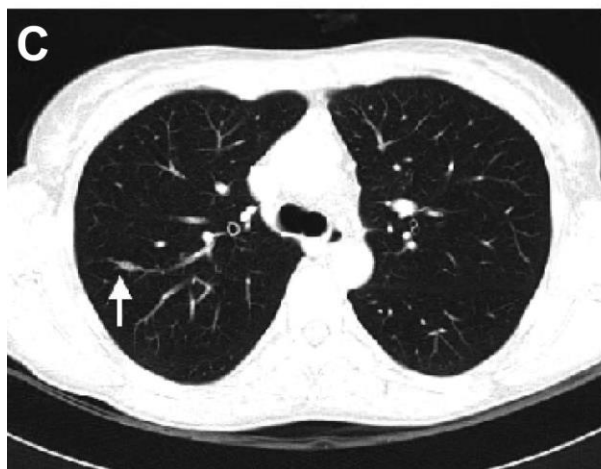
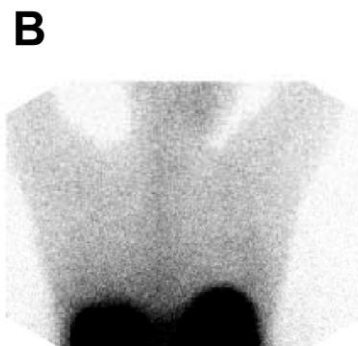
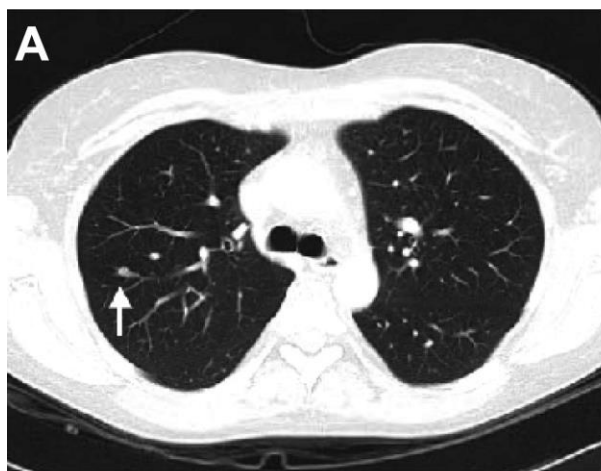
Altro ?

Effect of glucocorticoids on POMC and sst mRNA expression levels in AtT20 cells (24 h)



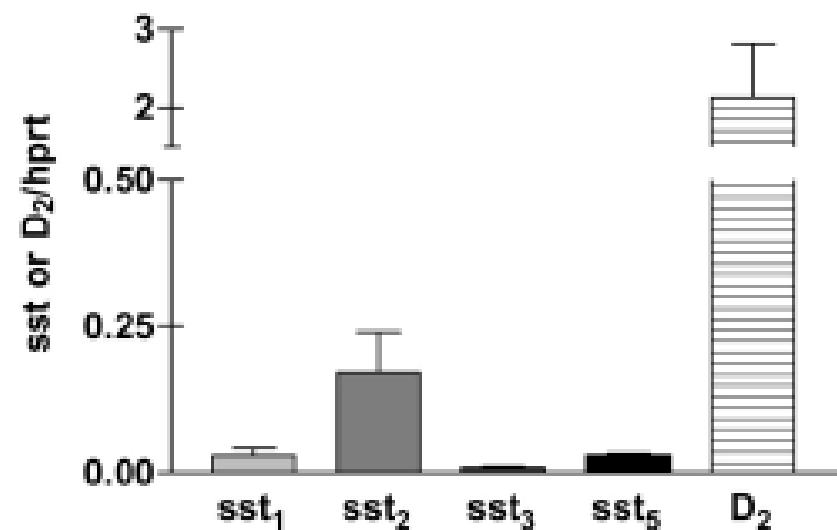
Van der Hoek et al, 2005

Mifepristone Effects on Tumor Somatostatin Receptor Expression in Two Patients with Cushing's Syndrome due to Ectopic Adrenocorticotropin Secretion

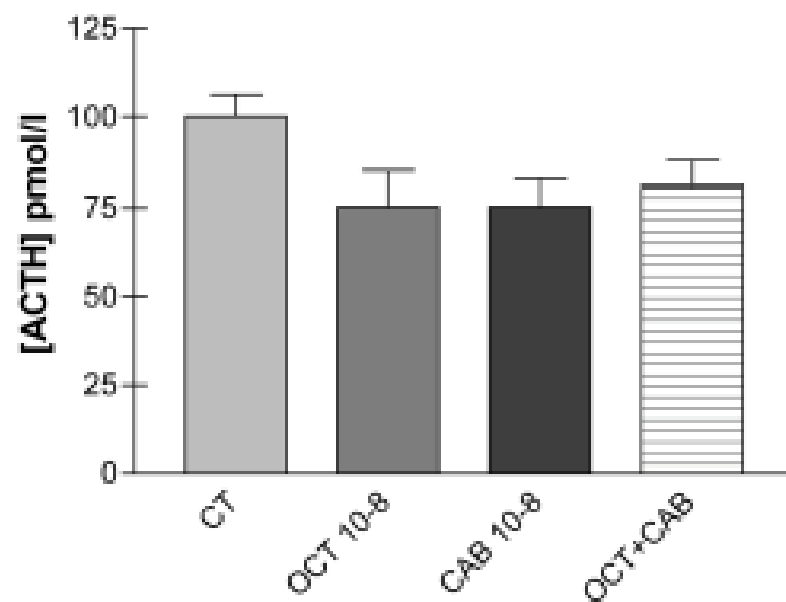


Mifepristone Effects on Tumor Somatostatin Receptor Expression in Two Patients with Cushing's Syndrome due to Ectopic Adrenocorticotropin Secretion

mRNA expression in patient 1



Inhibition of ACTH release in cultured tumoral cell of patients 1



Octreotide/lanreotide in monoterapia
o in combinazione ?

Cabergoline plus Lanreotide for Ectopic Cushing's Syndrome

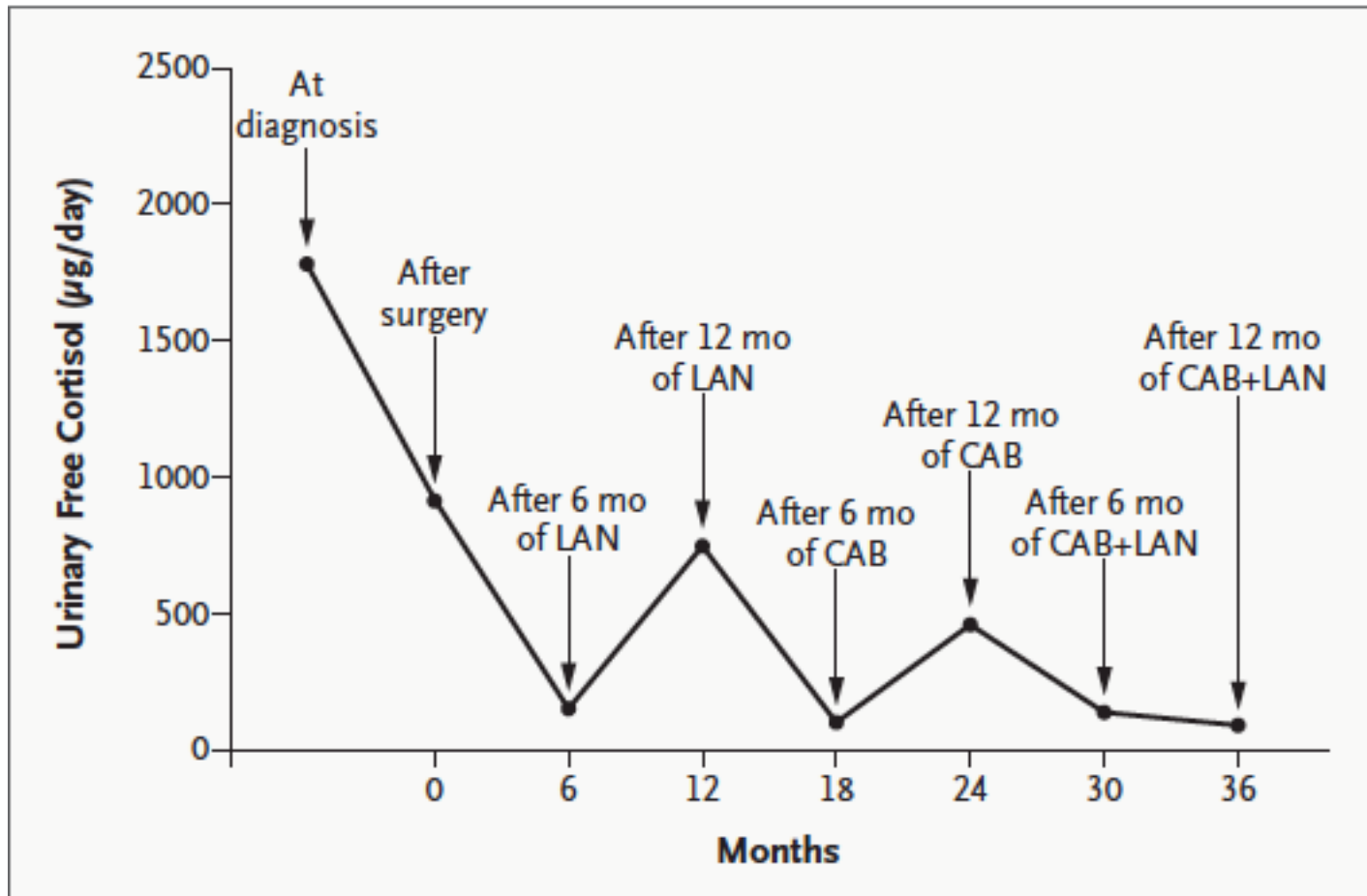
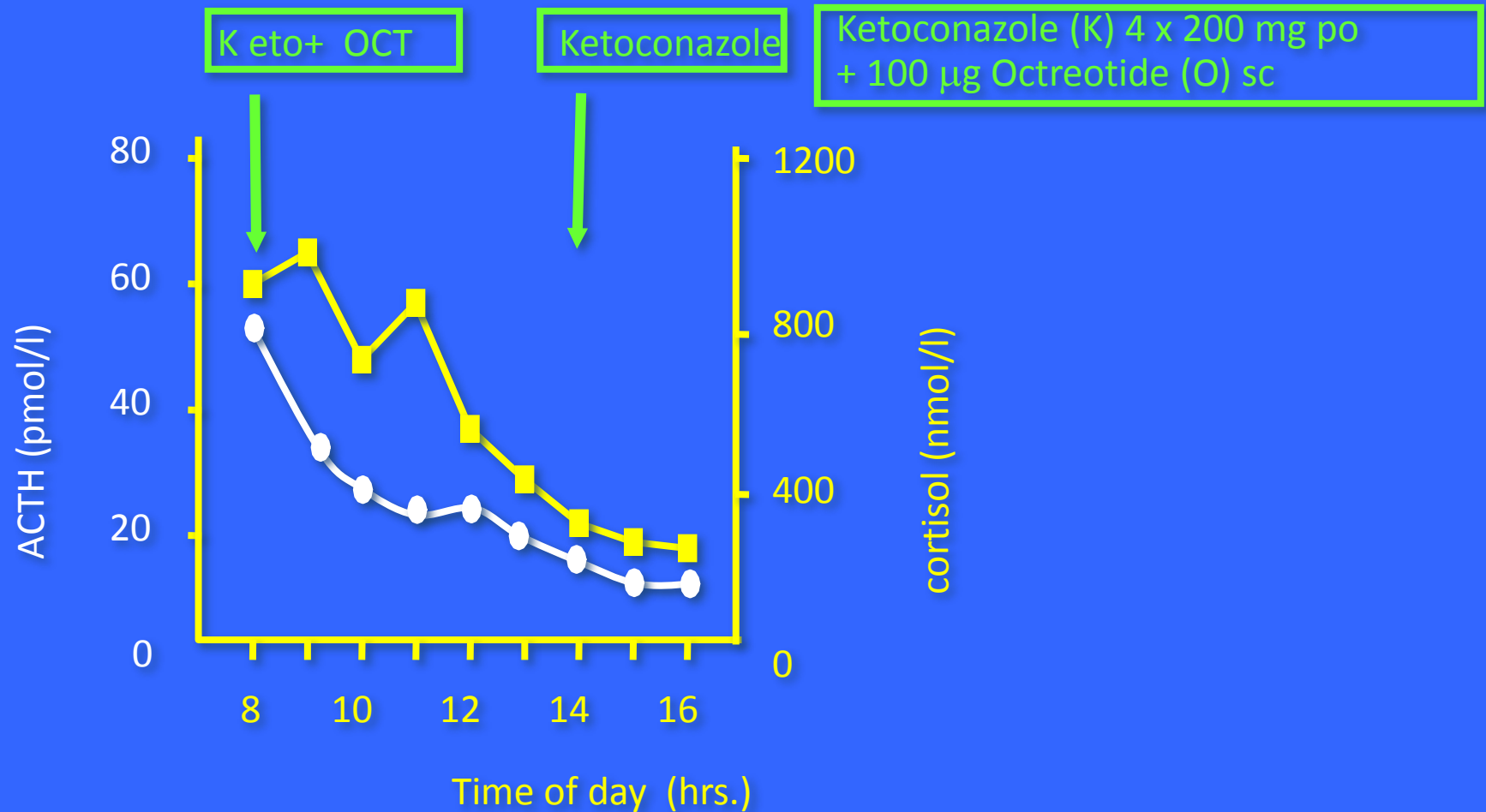


Figure 1. Urinary Cortisol Levels after Various Treatments in a Patient with the Ectopic Corticotropin Syndrome Associated with a Corticotropin-Secreting Lung Carcinoid.

LAN denotes lanreotide, and CAB cabergoline.

Ketoconazole + Octreotide in a 25-year-old Man with Cushing's Disease

Vignati & Loli, J. Clin. Endocrinol. Metab. 1996; 81: 2885-90. (PT 2)



CASO CLINICO

donna di 53 anni

HISTORY

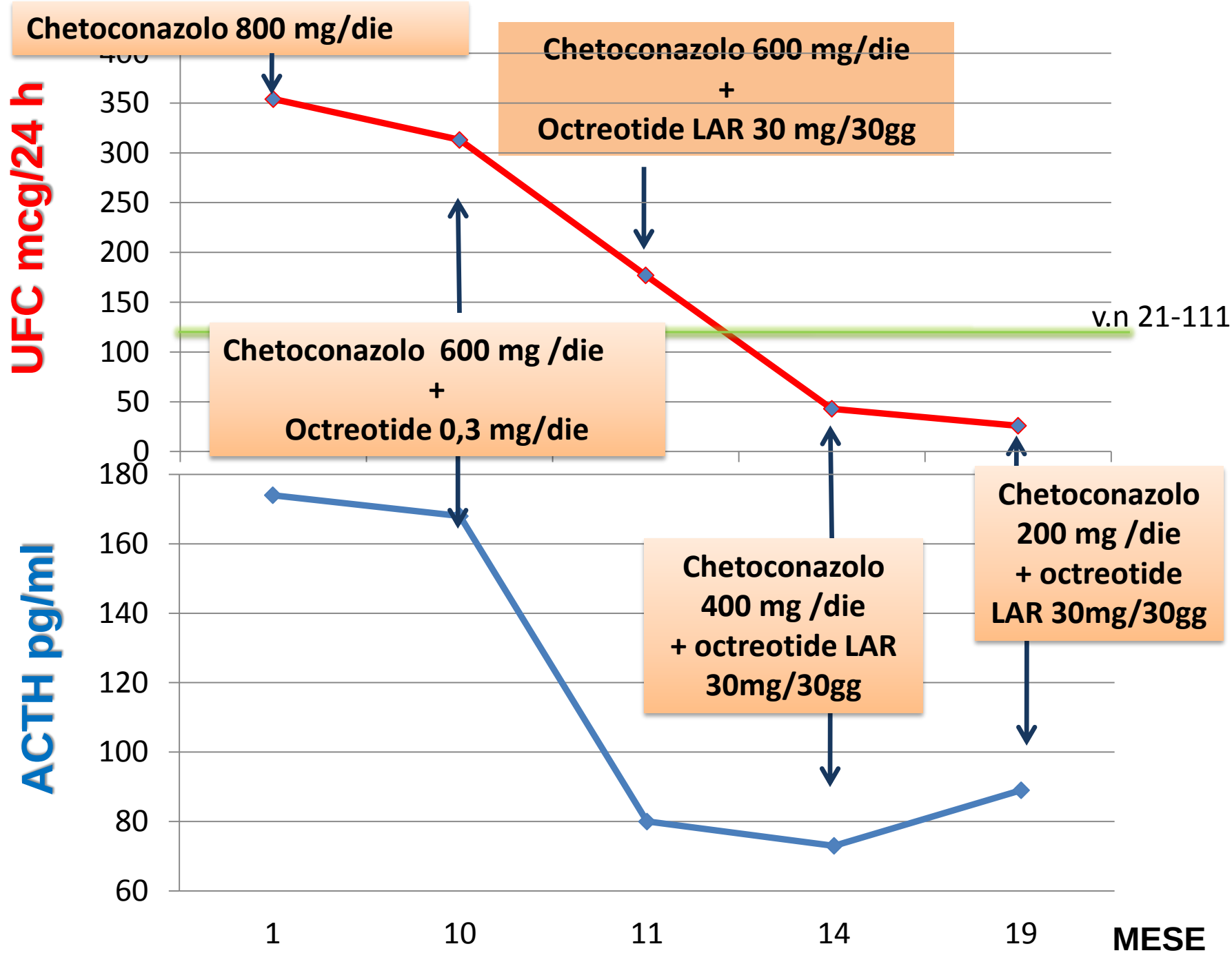
- 2008: ulcera gastrica perforata
frattura di L2 → osteoporosi
- 2009: ascessi epatici multipli
ipertensione arteriosa
diabete mellito
ipokaliemia

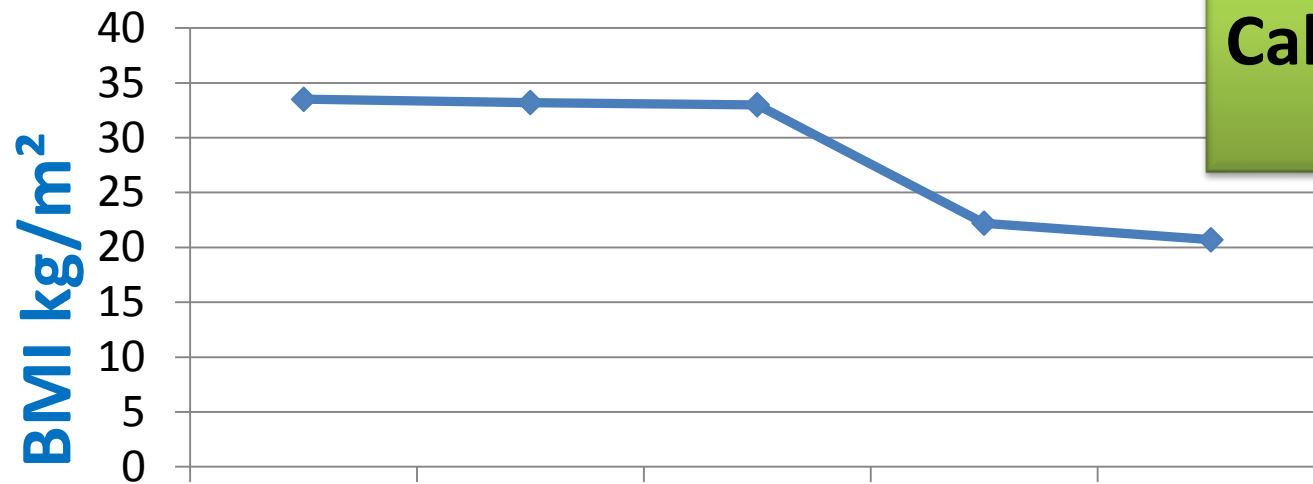


- ACTH 178 pg/ml
- CLU aumentato
- DEXA 1 mg → cortisolo 24 mcg/dl
- DEXA 8 mg → cortisolo soppresso del 90%
- Assente risposta di ACTH e cortisolo al CRH e al DDAVP
- RMN ipofisi negativa
- CATETERISMO negativo
- TAC total body negativa
- PET con FDG negativa
- Scintigrafia con Gallio-DOTANOC negativa



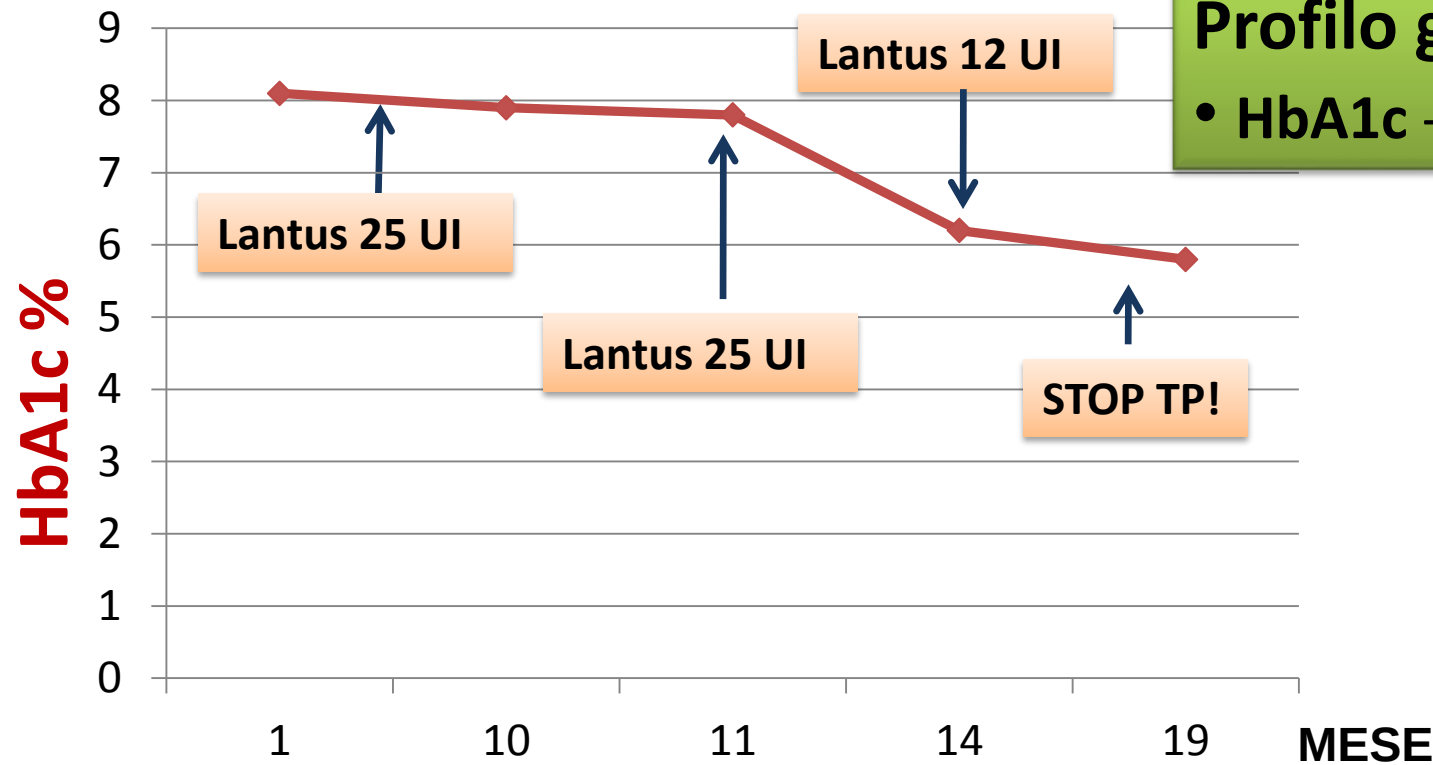
**CUSHING DA SECREZIONE ECTOPICA DI ACTH
OCCULTO**





Calo ponderale:

- BMI -38,2%



Profilo glucidico:

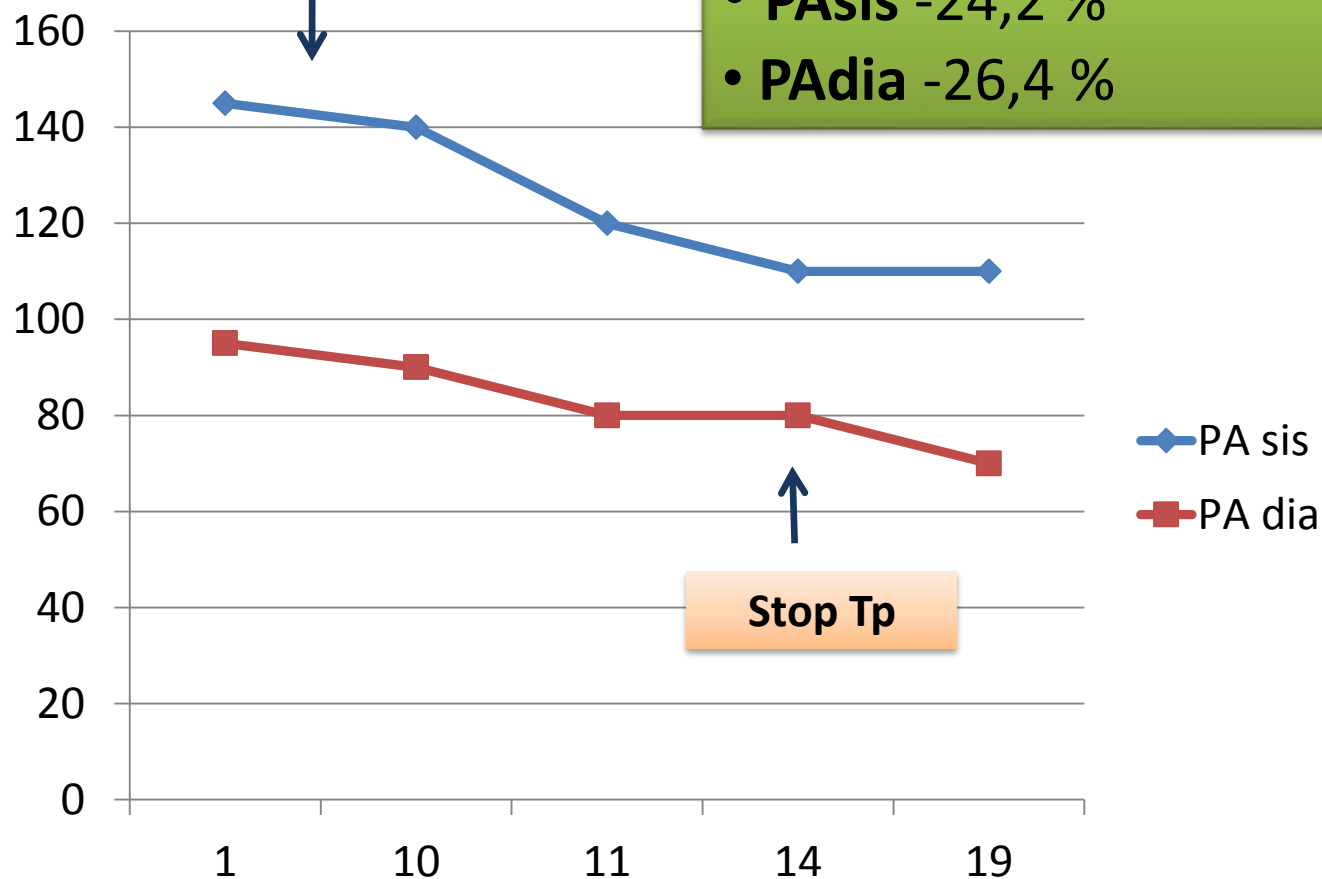
- HbA1c -28,4%

Idroclorotiazide 25 mg/die

Pressione arteriosa:

- PA_{sis} -24,2 %
- PA_{dia} -26,4 %

PA (mmHg)

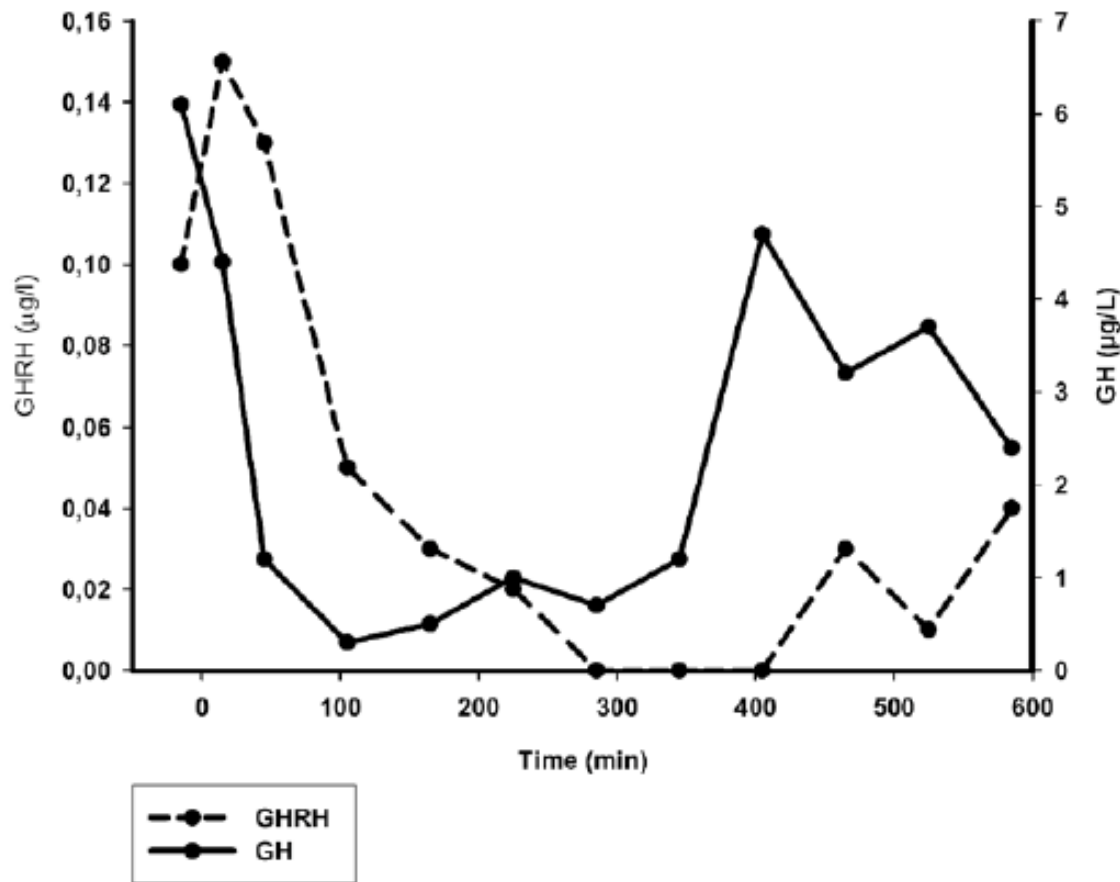


Pasireotide vs Octreotide nell'ACTH ectopico

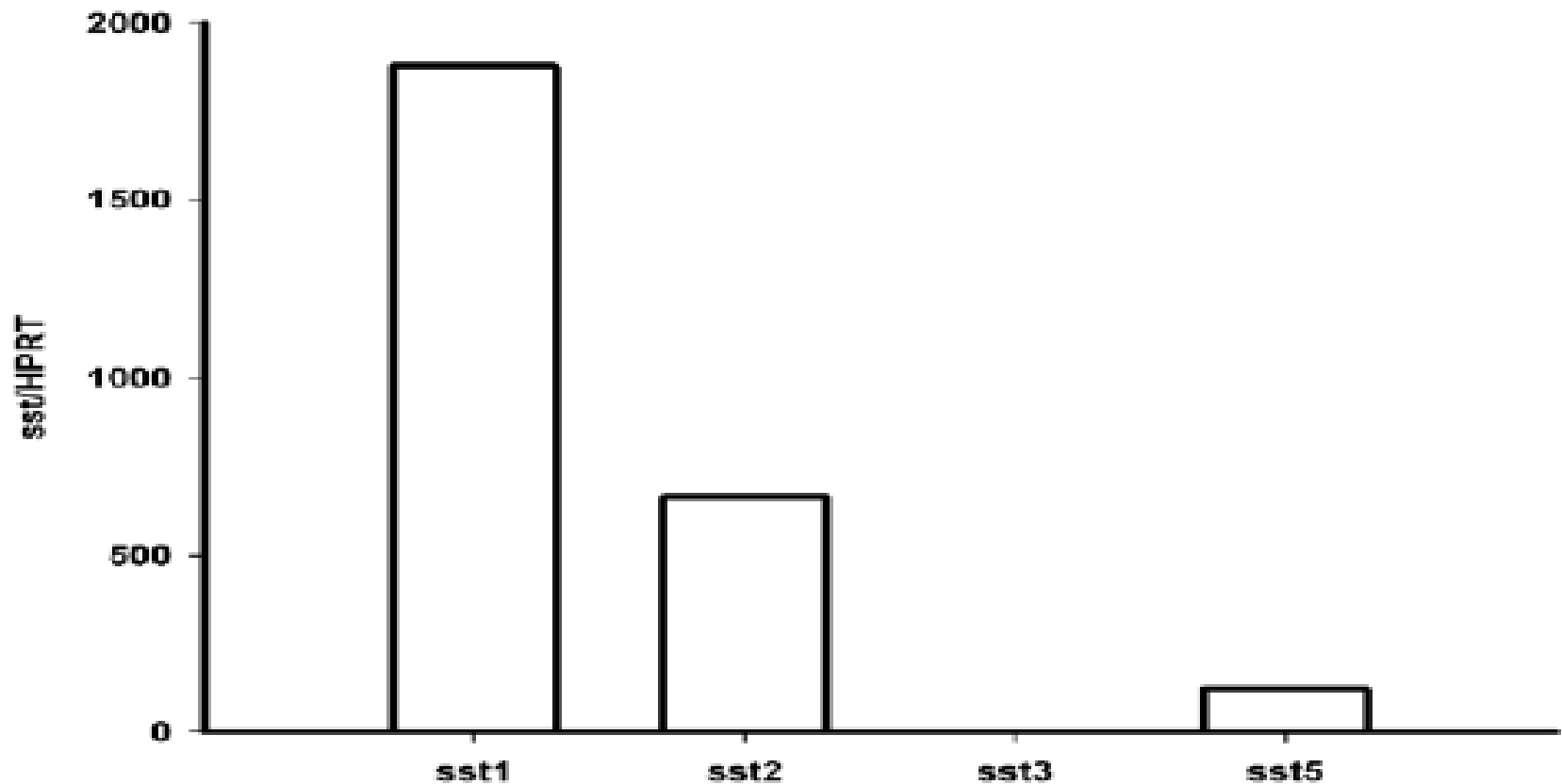
Trial in corso



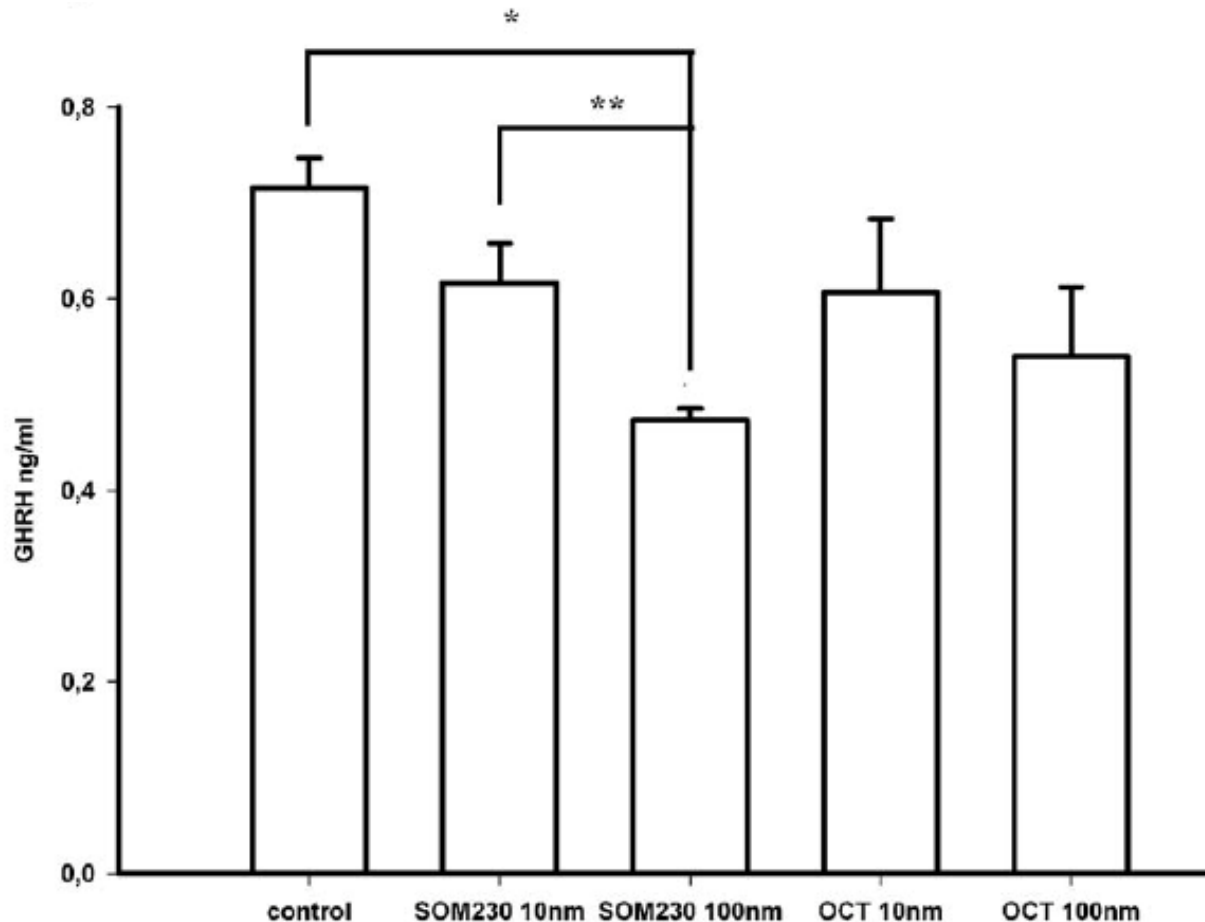
Effects of somatostatin analogs on a growth hormone-releasing hormone secreting bronchial carcinoid, in vivo and in vitro studies



Effects of somatostatin analogs on a growth hormone-releasing hormone secreting bronchial carcinoid, in vivo and in vitro studies



Effects of somatostatin analogs on a growth hormone-releasing hormone secreting bronchial carcinoid, in vivo and in vitro studies



Zatelli MC, Maffei P, Piccin D, Martini C, Rea F, Rubello D, Margutti A, Culler MD, Sicolo N, gli Uberti EC.

**Somatostatin analogs in vitro effects in a growth
hormonereleasing hormone-secreting bronchial carcinoid.**

J Clin Endocrinol Metab 2005 April;90(4):2104-9.

- **sst5 specific analog BIM- 23206 the most inhibition (-75 %),**
- **sst2 specific analog BIM- 23120 (-55 %)**
- **lanreotide (-30 %)**
- **sst1 specific analog BIM-23926 was less effective (-20 %).**

CASO CLINICO uomo di 55 anni

HISTORY

- 2003: obesità tronculare
ipertensione arteriosa
diabete mellito
osteoporosi severa
- 2006: diagnosi di Sindrome di Cushing (il pz non inizia alcun trattamento)
- 2013: Giunge alla nostra osservazione

GENNAIO 2013

- **ACTH** 136 pg/ml **cortisolo** 26,9 µg/dl
- **Ritmo del cortisolo** assente
- **UFC** aumentato (392 µg/dl)
- **Cortisolo salivare** 1,08 µg/dl
- **DEXA 1 mg** → cortisolo (14,1 µg/dl)
- **DEXA 8 mg** → cortisolo soppresso (5,6 µ/dl)
- **Test al CRH** assente risposta di ACTH e cortisolo
- **Test al DDAVP**
ACTH 92 → 603 → 499 → 402 pg/ml
cortisolo 27,4 → 39,8 → 51,5 → 53,8 µ/dl
- **RMN** ipofisi negativa

CUSHING DA SECREZIONE ECTOPICA DI ACTH

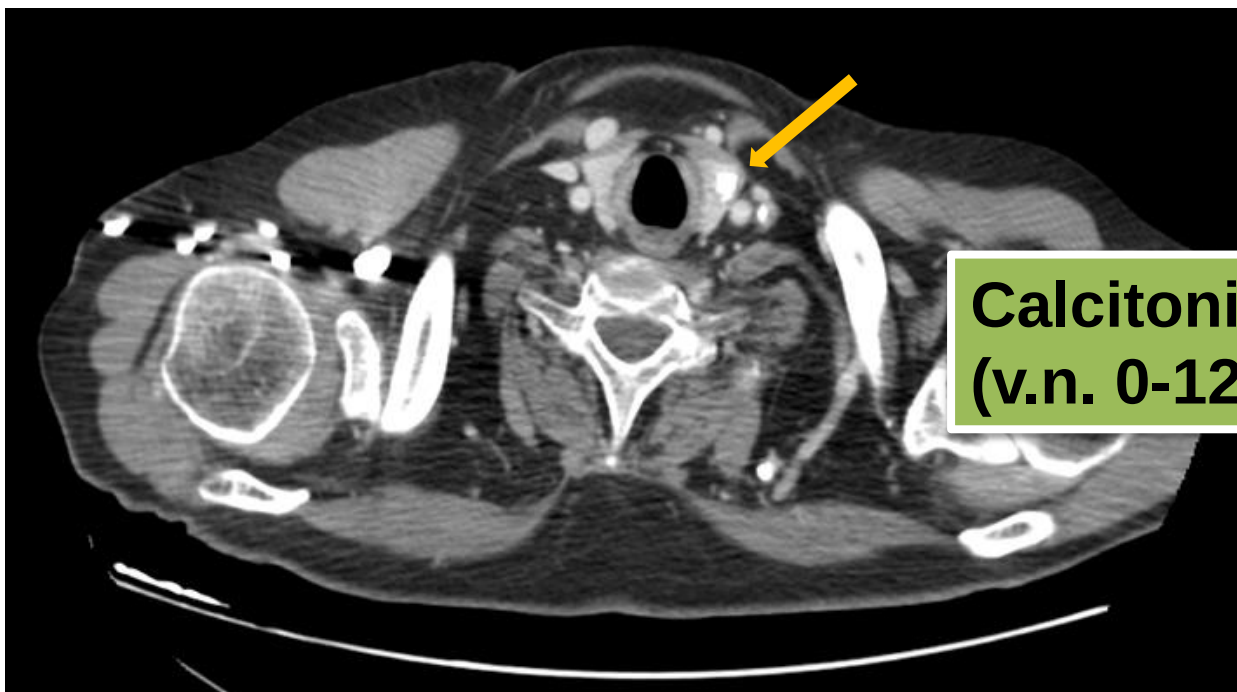


GENNAIO 2013

ECOGRAFIA DEL COLLO: nodulo calcifico sx di 1,1 x 1,4 cm e nodulo ipoecogeno laterocervicale sx di 0,8 cm (linfadenopatia ?) (primo riscontro).



AGO ASPIRATO E ESAME CITOLOGICO su linfadenopatia sx: linfociti e cellule epiteliali atipiche talora multinucleate, con citoplasma vacuolizzato, sospette per neoplasia di cui non si esclude l'origine tiroidea/paratiroidea



**Calcitonina 1557 pg/ml
(v.n. 0-12 pg/ml)**

MARZO 2013

**TIROIDECTOMIA TOTALE PIU LINFOADENECTOMIA LATERO-CERVICALE E DEL
COMPARTIMENTO CENTRALE**



ISTOLOGICO: carcinoma della tiroide misto , midollare e papillifero con estesa
metaplasia ossea. Metastasi linfonodali sostenute dalla componente midollare
Immunoistochimica positiva per ACTH

Immediato postoperatorio

CORTISOLO: 22 µg/dl

Cortisolo SALIVARE h8 – h23: 1,4 → 1,3 µg/dl

ACTH 75pg/ml **UFC** 210 µg/24h

CALCITONINA 789 pg/ml

MARZO 2013

**TIROIDECTOMIA TOTALE PIU LINFOADENECTOMIA LATERO-CERVICALE E DEL
COMPARTIMENTO CENTRALE**



ISTOLOGICO: carcinoma della tiroide misto , midollare e papillifero con estesa metaplasia ossea. Metastasi linfonodali sostenute dalla componente midollare
Immunohistochimica positiva per ACTH

MAGGIO 2013

RITMO DEL CORTISOLO: 22,7 → 23,7 → 21,8 µg/dl

SALIVARE: 1,5 → 1,4 → 1,3 µg/dl

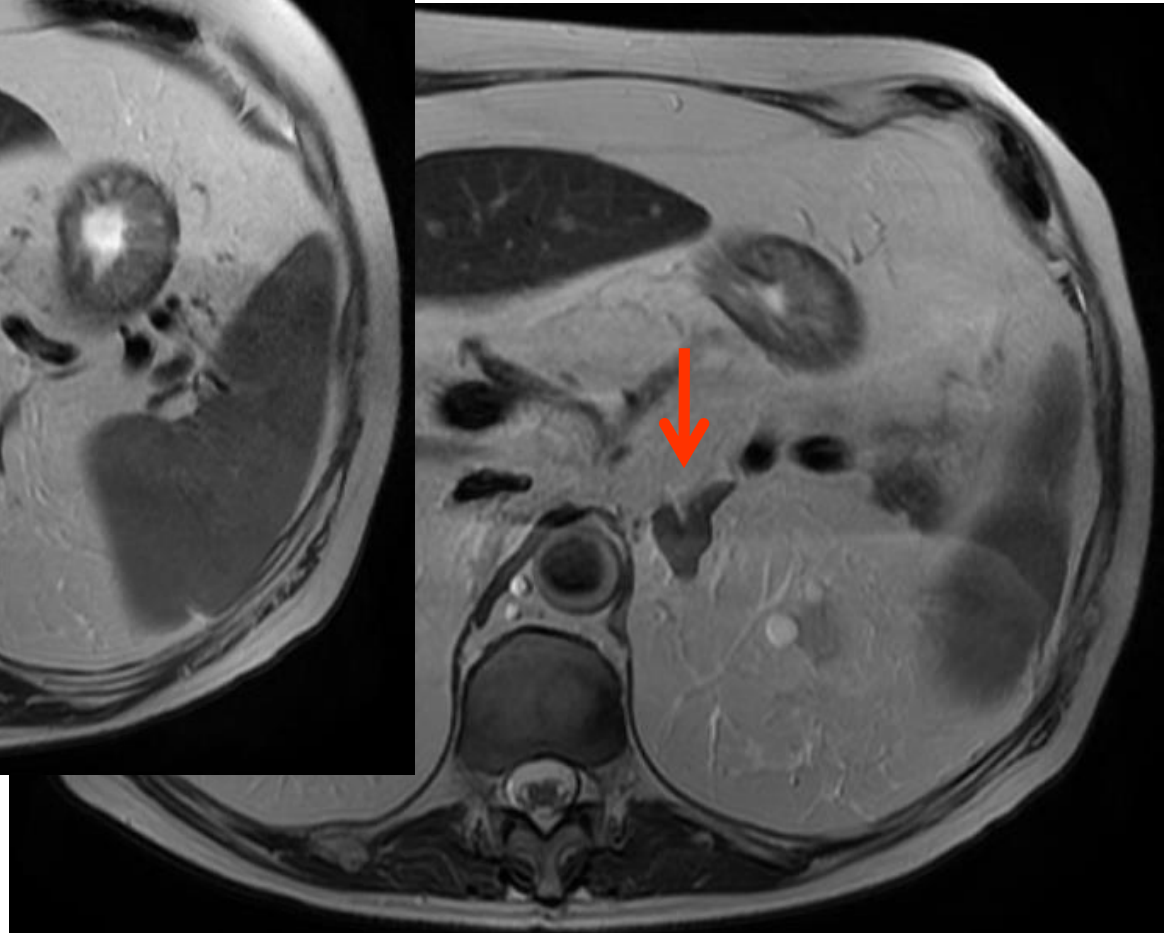
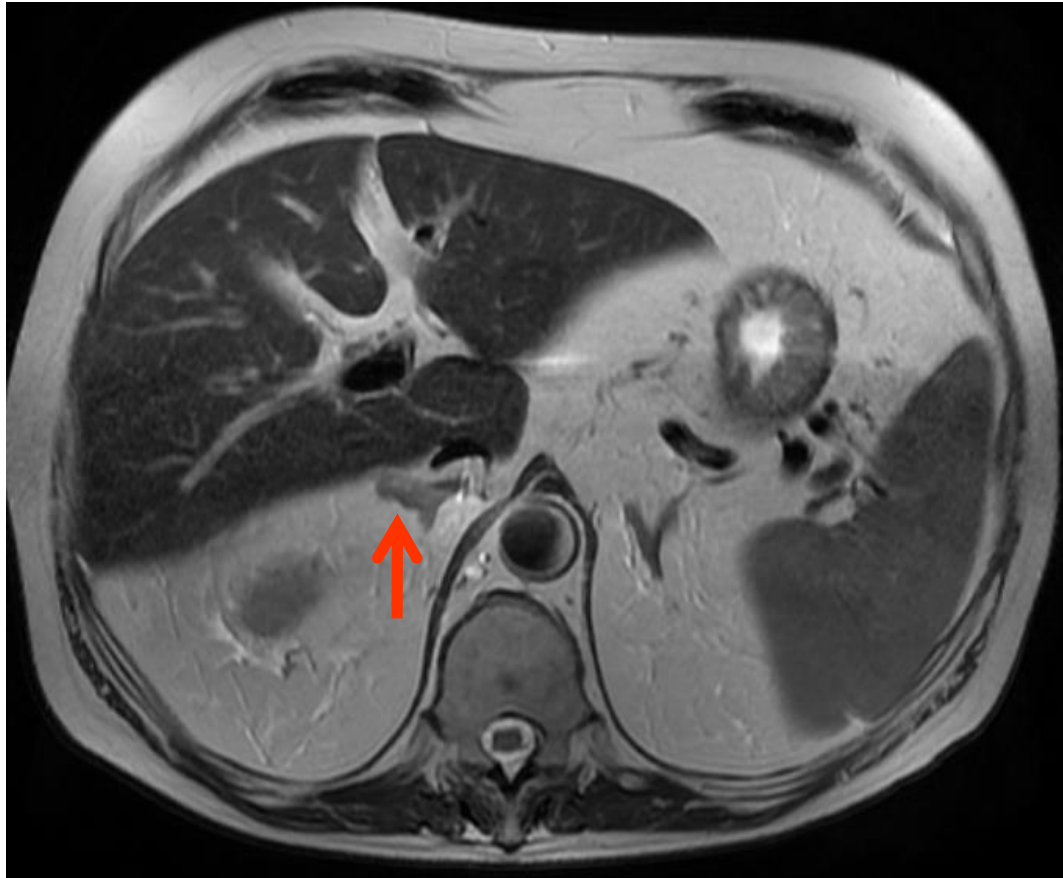
ACTH 84 pg/ml UFC 193 µg/24h

CALCITONINA 869 pg/ml

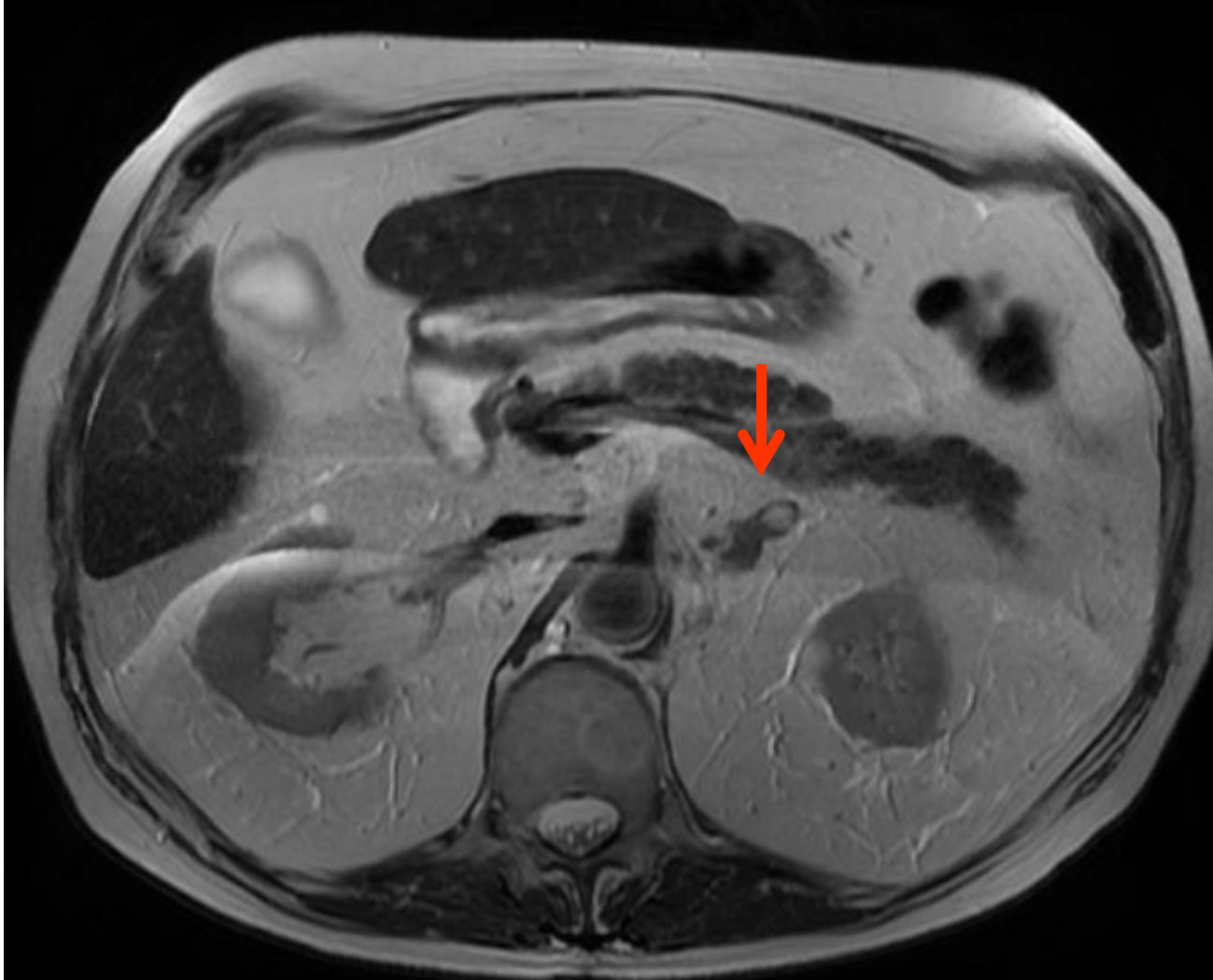
TIREOGLOBULINA 0,14 ng/ml

AC. ANTI- TIREOGLOBULINA negativi

MAGGIO 2013

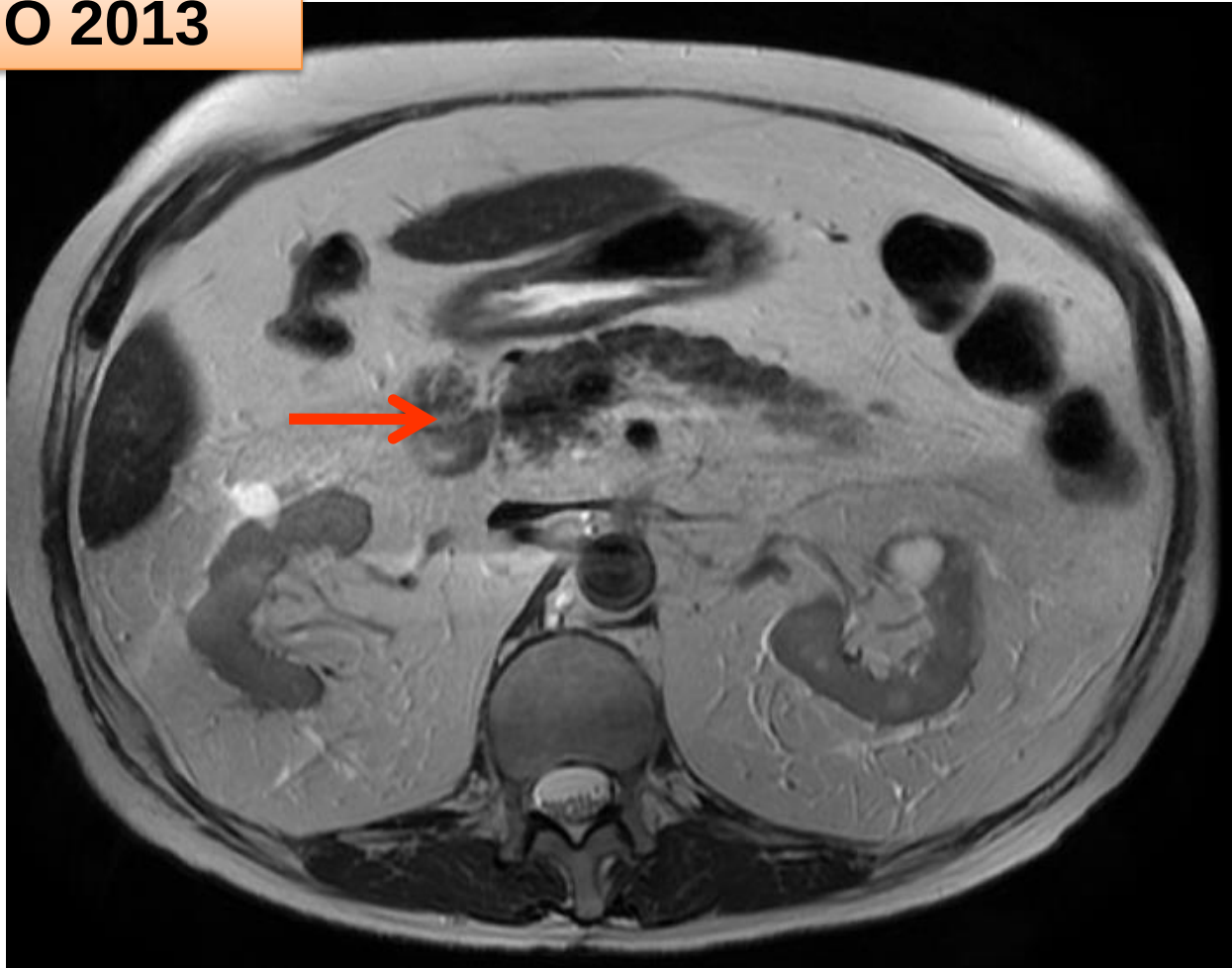


MAGGIO 2013



....piccola lesione
pseudonodulare (1cm)
a carlco dell'aletta
laterale del surrene di
sinistra compatibile con
lipoma...

MAGGIO 2013



...tessuto solido (2 cm) localizzato caudalmente al bulbo duodenale e lateralmente alla testa del pancreas, apparentemente distinto da quest'ultima, pur presentando caratteristiche di segnale simili a parenchima pancreatico, verosimilmente in relazione a parenchima pancreatico ectopico..

TEST ALL'OCTREOTIDE (100 µg s.c)

	Basale (h 8)	h 10	h 12	h 14	h16	h 23
Cortisolo µg/dl	30,9	34,1	32	38,2	30,8	27
ACTH pg/ml	81	86	82	33	51	56
C. Salivare µg/dl	2,5	3,3	-	-	-	2,0
Calcitonina pg/ml	1024	926	1038	969	1017	981

TEST ALL'OCTREOTIDE (100 µg s.c)

	Basale (h 8)	h 10	h 12	h 14	h16	h 23
Cortisolo µg/dl	30,9	34,1	32	38,2	30,8	27
ACTH pg/ml	81	86	82	33	51	56
C. Salivare µg/dl	2,5	3,3	-	-	-	2,0
Calcitonina pg/ml	1024	926	1038	969	1017	981

TEST AL PASIREOTIDE (600 µg s.c)

	Basale (h 8)	h 10	h 12	h 14	h16	h 23
Cortisolo µg/dl	30,2	31,2	26,1	27,7	34,2	33,7
ACTH pg/ml	57	80	53	42	79	86
C. Salivare µg/dl	2,7	2,6	-	-	-	3,79
Calcitonina pg/ml	658	692	658	794	890	675

Pasireotide vs Octreotide nell'ACTH ectopico

.....ne riparlamo ad ABC 2014

Grazie per l'attenzione