Altogether to Beat Cushing's Syndrome

ABC

VIAGGIO ALLA (RI)SCOPERTA DELLA SINDROME DI CUSHING

seconda edizione

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

giovedì 16 maggio 2013 | Certosa

INTRODUZIONE AL LAVORO DEI GRUPPI DI STUDIO

SESSIONE 2: IL CUSHING ECTOPICO

L'approccio Terapeutico

Manuela Albertelli

Endocrinologia- Dipartimento di Medicina Interna
Università di Genova

EAS manifestazioni cliniche aggressive

Necessita di terapia aggressiva

1° scelta : CHIRURGIA

Su primitivo (intento curativo)
Su metastasi (debulking)

MA….

Cushing Syndrome Due to Ectopic Adrenocorticotropic Hormone Secretion

Jaroslaw P. Aniszewski, M.D.,[1] William F. Young Jr., M.D.,[1] Geoffrey B. Thompson, M.D.,[2] Clive S. Grant, M.D.,[2] Jon A. van Heerden, M.D.[2]

World J. Surg. 25, 934–940, 2001

[1]Division of Endocrinology, Metabolism, Nutrition, and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA
[2]Division of Gastroenterologic and General Surgery, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA

106 EAS (tra 1956-1998 Mayo Clinic)

Curative resection in 13 → 12%

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

The Journal of Clinical Endocrinology & Metabolism 90(8):4955–4962

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

90 EAS (tra 1983-2004 NIH) Surgery in 59 su 90 (65%)

Curative resection in 42 su

Curative resection, primi 6 mesi, 26 su 90 → 29%

Curative resection in 26 → 29%

The Ectopic Adrenocort… Features, Diagnosis, Ma… Follow-Up

The Journal of Clinical Endocrinology & Metabolism 91(2):371–377

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

40 EAS (tra 1969-2001 St. Barth UK) Surgery in 12 su 40 (30%)

Curative resection i…

Curative resection in 10 su 40 → 25%

Miglior outcome nei NET bronchiali

EAS manifestazioni cliniche aggressive

Necessita di terapia aggressiva

1° scelta : CHIRURGIA

Su primitivo (intento curativo)
Su metastasi (debulking)

Sempre quando possibile, ma…
Metastasi diffuse
Malattia occulta
Inoperabilità per altre cause
% cura e % recidiva
Fase preoperatoria

TERAPIA MEDICA

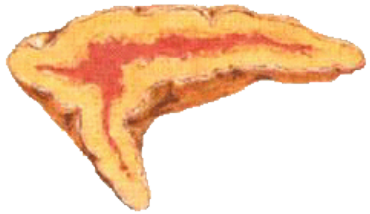
Ketoconazolo

Aminoglutethimide

Metyrapone

Mitotane

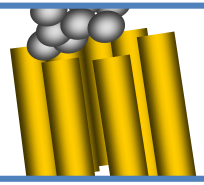
Etom



EAS manifestazioni cliniche aggressive

SSA

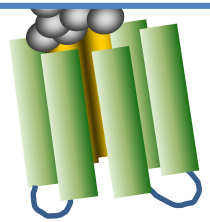
Pasireotide



sstr

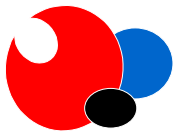
Necessità di abbassare aggressivamente cortisolemia

Cabergolina



DR

Mifepristone



GR

Review Article

Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics

Journal of Oncology
Volume 2012, Article ID 685213,

Carlotta Pozza, Chiara Graziadio, Elisa Giannetta, Andrea Lenzi, and Andrea M. Isidori

Table 2: Medical treatments for Cushing's syndrome (in clinical use or investigational).

Drug	Mechanism of action	Dose (range)	Side effects	Safety monitoring
Ketoconazole	Inhibits steroidogenesis via inhibition of cytochrome P450 function	200–1800 mg per os (in divided doses, b.i.d.-t.i.d.)	Reversible liver dysfunction, severe liver toxicity, GI disorders, skin rash, loss of libido, impotence	Transaminase, testosterone, and SHBG in men
Metyrapone	Inhibits 11-β hydroxylase in the adrenal gland	750–6000 mg per os (in divided doses, t.i.d.-q.i.d.)	Hirsutism, acne, GI disorders, dizziness, hypertension, edema, hypokalemia	Androgens, mineralocorticoid, electrolytes
Mitotane	Inhibits steroidogenesis via inhibition of cytochrome P450; adrenolytic (high doses)	500 mg–12 g per os (daily)	Severe nausea, vomiting, diarrhea, rash, somnolence, ataxia, vertigo, dyslipidemia	Plasma mitotane, blood count, electrolytes, liver function, cholesterol
Etomidate	Inhibits 11-β hydroxylase and 17–20 lyase	<0.1 mg/kg/hr i.v.	Sedative effects, anesthesia	Monitoring by anesthesiologists
Mifepristone (RU-486)	Glucocorticoid, androgen, and progesterone receptor antagonist	300–1200 mg per os, daily dose	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia	Blood count, electrolytes, pelvic US
Cabergoline	D2 receptor agonist	1–7 mg per os, weekly dose	Nausea, vomiting, dizziness, valvulopathy	Echocardiogram
Temozolomide	Alkylating agent	150–200 mg/m^2 per os for 5 days once every 28 days, or 75 mg/m^2 daily for 21 days with 7 day break	Bone marrow suppression, nausea, vomiting, dizziness diarrhea, rash	Blood count, liver and renal function, electrolytes

Management of Cushing's Syndrome due to Ectopic Adrenocorticotropin Secretion with 1,Ortho-1, Para′-Dichloro-Diphenyl-Dichloro-Ethane: Findings in 23 Patients from a Single Center

J Clin Endocrinol Metab, February 2010, 95(2):537–544

Bruno Donadille, Lionel Groussin, Charlotte Waintrop, Halim Abbas, Florence Tenenbaum, Marie-Annick Dugué, Joël Coste, Xavier Bertagna, and Jérôme Bertherat

23 EAS Parigi 1990-2006 Mitotane 2-4.5 g/die, dosaggio mitotanemia
21 su 23 normalizzato UFC, *side effects* gastro e neurologici

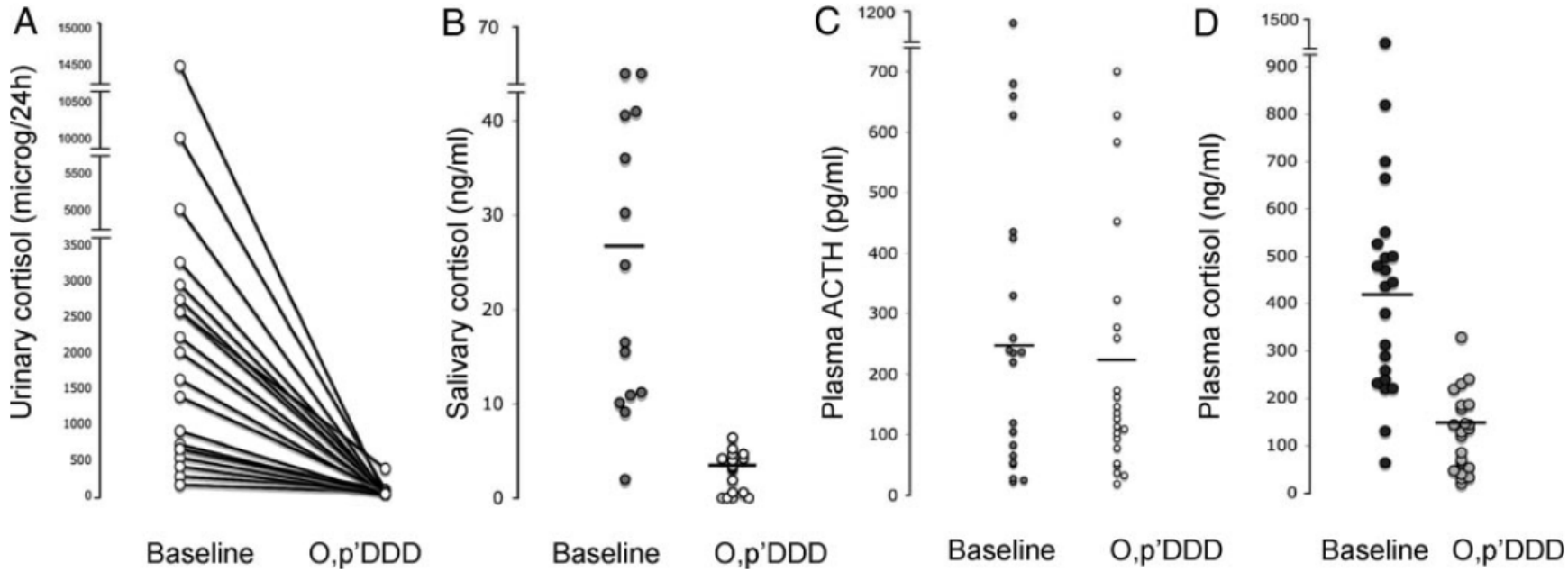


FIG. 1. Hormonal response in patients receiving O,p′DDD. Twenty-four-hour urinary cortisol (A), early morning salivary cortisol (B), early morning plasma ACTH (C), and early morning plasma cortisol (D) at baseline (*left panels*) and during O,p′DDD treatment (*right panels*).

Review Article

Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics

Journal of Oncology
Volume 2012, Article ID 685213,

Carlotta Pozza, Chiara Graziadio, Elisa Giannetta, Andrea Lenzi, and Andrea M. Isidori

Table 2: Medical treatments for Cushing's syndrome (in clinical use or investigational).

Drug	Mechanism of action	Dose (range)	Side effects	Safety monitoring
Ketoconazole	Inhibits steroidogenesis via inhibition of cytochrome P450 function	200–1800 mg per os (in divided doses, b.i.d.-t.i.d.)	Reversible liver dysfunction, severe liver toxicity, GI disorders, skin rash, loss of libido, impotence	Transaminase, testosterone, and SHBG in men
Metyrapone	Inhibits 11-β hydroxylase in the adrenal gland	750–6000 mg per os (in divided doses, t.i.d.-q.i.d.)	Hirsutism, acne, GI disorders, dizziness, hypertension, edema, hypokalemia	Androgens, mineralocorticoid, electrolytes
Mitotane	Inhibits steroidogenesis via inhibition of cytochrome P450; adrenolytic (high doses)	500 mg–12 g per os (daily)	Severe nausea, vomiting, diarrhea, rash, somnolence, ataxia, vertigo, dyslipidemia	Plasma mitotane, blood count, electrolytes, liver function, cholesterol
Etomidate	Inhibits 11-β hydroxylase and 17–20 lyase	<0.1 mg/kg/hr i.v.	Sedative effects, anesthesia	Monitoring by anesthesiologists
Mifepristone (RU-486)	Glucocorticoid, androgen, and progesterone receptor antagonist	300–1200 mg per os, daily dose	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia	Blood count, electrolytes, pelvic US
Cabergoline	D2 receptor agonist	1–7 mg per os, weekly dose	Nausea, vomiting, dizziness, valvulopathy	Echocardiogram
Temozolomide	Alkylating agent	150–200 mg/m^2 per os for 5 days once every 28 days, or 75 mg/m^2 daily for 21 days with 7 day break	Bone marrow suppression, nausea, vomiting, dizziness diarrhea, rash	Blood count, liver and renal function, electrolytes

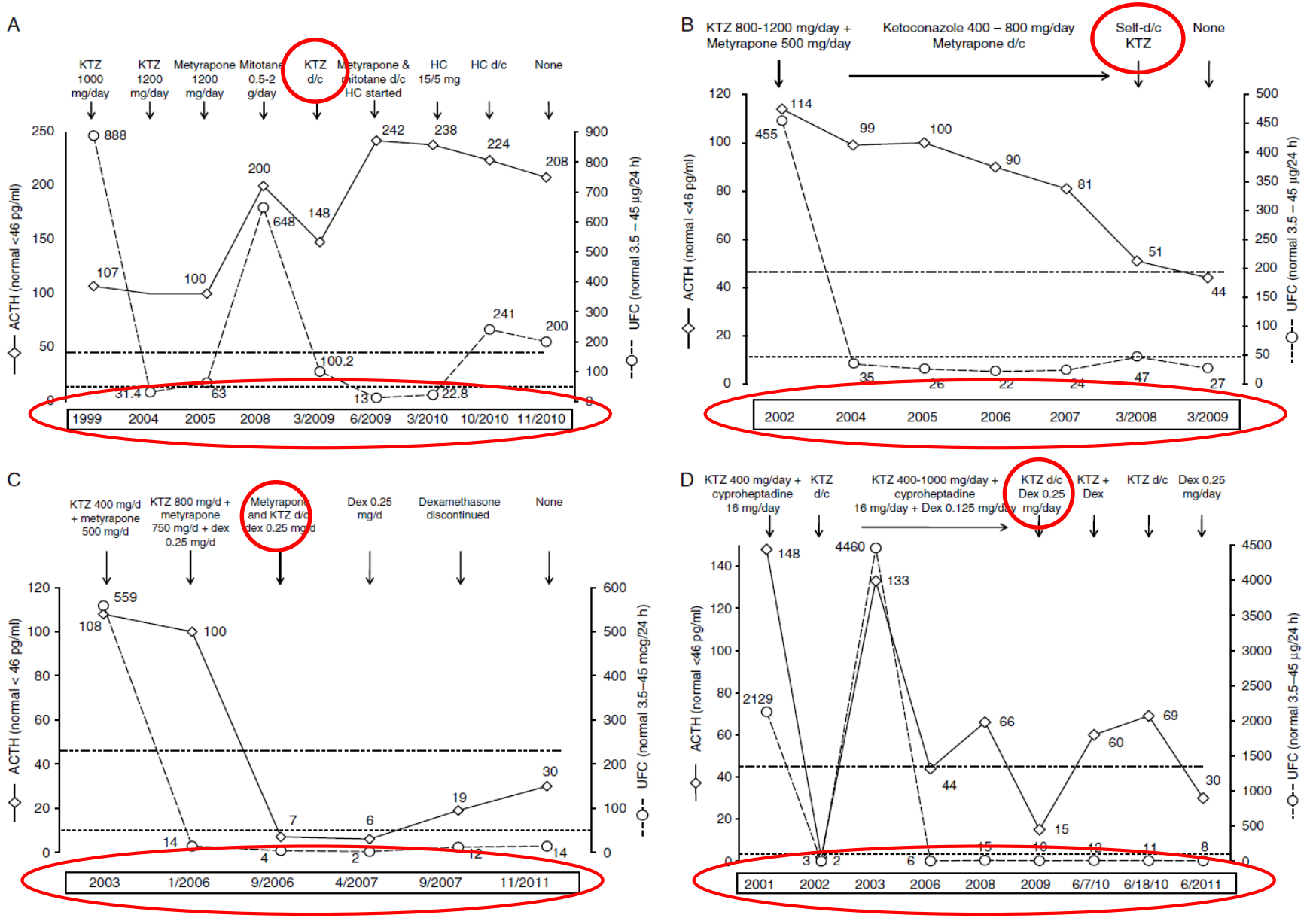


Figure 1 (A–D) Twenty-four hour urinary free cortisol (UFC) and ACTH levels over time in (A) case 1, (B) case 2, (C) case 3, and (D) case 4. The *X*-axis represents time. The primary *Y*-axis shows ACTH levels (pg/ml) and the secondary *Y*-axis shows UFC levels (µg/24 h). To convert ACTH level to picomoles per liter, multiply by 0.2202. To convert UFC level to nanomoles per day, multiply by 2.759. The dashed line represents the upper limit of normal for the ACTH assay (46 pg/ml). The dotted line represents the upper limit of normal for UFC (45 µg/24 h). Values where the reference ranges were different have been adjusted for the purpose of combined graphical representation. KTZ, ketoconazole; HC, hydrocortisone; d/c, discontinued; dex, dexamethasone.

Review Article

Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics

Journal of Oncology
Volume 2012, Article ID 685213,

Carlotta Pozza, Chiara Graziadio, Elisa Giannetta, Andrea Lenzi, and Andrea M. Isidori

Table 2: Medical treatments for Cushing's syndrome (in clinical use or investigational).

Drug	Mechanism of action	Dose (range)	Side effects	Safety monitoring
Ketoconazole	Inhibits steroidogenesis via inhibition of cytochrome P450 function	200–1800 mg per os (in divided doses, b.i.d.-t.i.d.)	Reversible liver dysfunction, severe liver toxicity, GI disorders, skin rash, loss of libido, impotence	Transaminase, testosterone, and SHBG in men
Metyrapone	Inhibits 11-β hydroxylase in the adrenal gland	750–6000 mg per os (in divided doses, t.i.d.-q.i.d.)	Hirsutism, acne, GI disorders, dizziness, hypertension, edema, hypokalemia	Androgens, mineralocorticoid, electrolytes
Mitotane	Inhibits steroidogenesis via inhibition of cytochrome P450; adrenolytic (high doses)	500 mg–12 g per os (daily)	Severe nausea, vomiting, diarrhea, rash, somnolence, ataxia, vertigo, dyslipidemia	Plasma mitotane, blood count, electrolytes, liver function, cholesterol
Etomidate	Inhibits 11-β hydroxylase and 17–20 lyase	<0.1 mg/kg/hr i.v.	Sedative effects, anesthesia	Monitoring by anesthesiologists
Mifepristone (RU-486)	Glucocorticoid, androgen, and progesterone receptor antagonist	300–1200 mg per os, daily dose	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia	Blood count, electrolytes, pelvic US
Cabergoline	D2 receptor agonist	1–7 mg per os, weekly dose	Nausea, vomiting, dizziness, valvulopathy	Echocardiogram
Temozolomide	Alkylating agent	150–200 mg/m^2 per os for 5 days once every 28 days, or 75 mg/m^2 daily for 21 days with 7 day break	Bone marrow suppression, nausea, vomiting, dizziness diarrhea, rash	Blood count, liver and renal function, electrolytes

Mitotane, Metyrapone, and Ketoconazole Combination Therapy as an Alternative to Rescue Adrenalectomy for Severe ACTH-Dependent Cushing's Syndrome

Peter Kamenický, Céline Droumaguet, Sylvie Salenave, Anne Blanchard, Christel Jublanc, Jean-François Gautier, Sylvie Brailly-Tabard, Sophie Leboulleux, Martin Schlumberger, Eric Baudin, Philippe Chanson, and Jacques Young

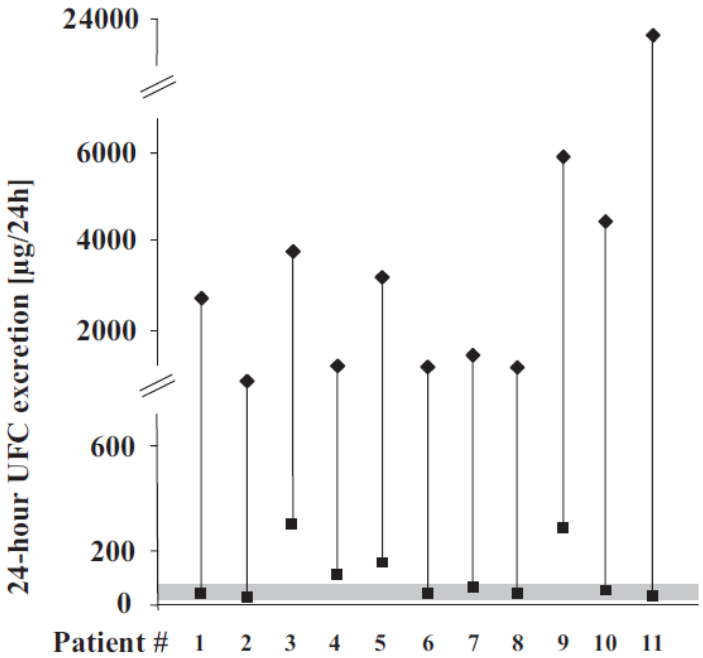


FIG. 2. UFC levels in each of our 11 patients before and 1–3 d after the initiation of triple therapy (see text for details). The *gray area* indicates the normal range of UFC excretion (10–65 μg/24 h) determined in 24-h urine specimens from 120 healthy volunteers. ♦, Baseline UFC excretion (each value is the average of individual determinations in three consecutive daily urine samples); ■, UFC excretion on triple therapy.

TABLE 2 ... nt, and treatment outcomes

Patient	...ation of mitotane ...otherapy (months)	Follow-up (months)	Outcome
1	27	42	Surgery, remission
2	3	14	Surgery, mitotane
3	3	14	Surgery, remission
4	3	25	Surgery, remission
5	13	19	Mitotane
6		1	Death (respiratory distress)
7	2	35	Surgery, remission
8	10	14	Death (tumor progression)
9		1	Death (myocardial infarction)
10		4	Death (tumor progression)
11		6	Surgery, remission

CD, Cushin ... . For details, see text.

UFC normalizzato in tutti i pazienti nei primi 3 gg di trattamento

M ... g/24 h, Ketokonazole 400-1200 mg/24 h

Review Article

Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics

Journal of Oncology
Volume 2012, Article ID 685213,

Carlotta Pozza, Chiara Graziadio, Elisa Giannetta, Andrea Lenzi, and Andrea M. Isidori

Table 2: Medical treatments for Cushing's syndrome (in clinical use or investigational).

Drug	Mechanism of action	Dose (range)	Side effects	Safety monitoring
Ketoconazole	Inhibits steroidogenesis via inhibition of cytochrome P450 function	200–1800 mg per os (in divided doses, b.i.d.-t.i.d.)	Reversible liver dysfunction, severe liver toxicity, GI disorders, skin rash, loss of libido, impotence	Transaminase, testosterone, and SHBG in men
Metyrapone	Inhibits 11-β hydroxylase in the adrenal gland	750–6000 mg per os (in divided doses, t.i.d.-q.i.d.)	Hirsutism, acne, GI disorders, dizziness, hypertension, edema, hypokalemia	Androgens, mineralocorticoid, electrolytes
Mitotane	Inhibits steroidogenesis via inhibition of cytochrome P450; adrenolytic (high doses)	500 mg–12 g per os (daily)	Severe nausea, vomiting, diarrhea, rash, somnolence, ataxia, vertigo, dyslipidemia	Plasma mitotane, blood count, electrolytes, liver function, cholesterol
Etomidate	Inhibits 11-β hydroxylase and 17–20 lyase	<0.1 mg/kg/hr i.v.	Sedative effects, anesthesia	Monitoring by anesthesiologists
Mifepristone (RU-486)	Glucocorticoid, androgen, and progesterone receptor antagonist	300–1200 mg per os, daily dose	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia	Blood count, electrolytes, pelvic US
Cabergoline	D2 receptor agonist	1–7 mg per os, weekly dose	Nausea, vomiting, dizziness, valvulopathy	Echocardiogram
Temozolomide	Alkylating agent	150–200 mg/m^2 per os for 5 days once every 28 days, or 75 mg/m^2 daily for 21 days with 7 day break	Bone marrow suppression, nausea, vomiting, dizziness diarrhea, rash	Blood count, liver and renal function, electrolytes

Endocrine Journal 2010, **57** (12), 1061-1069

ORIGINAL

Clinical features and management of ectopic ACTH syndrome at a single institute in Japan

Masaru Doi, Toru Sugiyama, Hajime Izumiyama, Takanobu Yoshimoto and Yukio Hirata

16 EAS Tokyo Medical University Hospital 1992-2009
Metyrapone 0.75-3 g/day

Table 3. Multidisciplinary treatment and clinical outcome in 16 EAS patients at TMDU Hospital

Occult/unknown EAS (n=6)

Case #	Medical therapy	Cortisol (μg/dL)	Follow-up (month)	Outcome
11	Met (0.75g/day)	0.2	92	alive
12	Met (2.25g/day)	0.44	42	alive
13	Met (0.75g/day)	11.1	127	alive
14	Met (0.75g/day)	5.4	36	alive
15	Met (1.5g/day), Mit (2g/day)	5.9	65	alive
16	Met (1.25g/day)	0.51	43	alive
		3.9±4.4	67.5±28	

ChT:chemotherapy, Met:metyrapone, Mit:mitotane, Oct:octreotide, Tx:tumor resection, Rad:radiation, TAE: transcatheter arterial embolization, TAI: transcatheter arterial infusion LTx; liver transplantation, Hypox: hypophysectomy, Adx: adrenalectomy, Thymex: thymectomy

16 Thymic hyperplasia - Hypox, Met, Adx, Thymex 256 alive

Review Article

Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics

Journal of Oncology
Volume 2012, Article ID 685213,

Carlotta Pozza, Chiara Graziadio, Elisa Giannetta, Andrea Lenzi, and Andrea M. Isidori

Table 2: Medical treatments for Cushing's syndrome (in clinical use or investigational).

Drug	Mechanism of action	Dose (range)	Side effects	Safety monitoring
Ketoconazole	Inhibits steroidogenesis via inhibition of cytochrome P450 function	200–1800 mg per os (in divided doses, b.i.d.-t.i.d.)	Reversible liver dysfunction, severe liver toxicity, GI disorders, skin rash, loss of libido, impotence	Transaminase, testosterone, and SHBG in men
Metyrapone	Inhibits 11-β hydroxylase in the adrenal gland	750–6000 mg per os (in divided doses, t.i.d.-q.i.d.)	Hirsutism, acne, GI disorders, dizziness, hypertension, edema, hypokalemia	Androgens, mineralocorticoid, electrolytes
Mitotane	Inhibits steroidogenesis via inhibition of cytochrome P450; adrenolytic (high doses)	500 mg–12 g per os (daily)	Severe nausea, vomiting, diarrhea, rash, somnolence, ataxia, vertigo, dyslipidemia	Plasma mitotane, blood count, electrolytes, liver function, cholesterol
Etomidate	Inhibits 11-β hydroxylase and 17–20 lyase	<0.1 mg/kg/hr i.v.	Sedative effects, anesthesia	Monitoring by anesthesiologists
Mifepristone (RU-486)	Glucocorticoid, androgen, and progesterone receptor antagonist	300–1200 mg per os, daily dose	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia	Blood count, electrolytes, pelvic US
Cabergoline	D2 receptor agonist	1–7 mg per os, weekly dose	Nausea, vomiting, dizziness, valvulopathy	Echocardiogram
Temozolomide	Alkylating agent	150–200 mg/m^2 per os for 5 days once every 28 days, or 75 mg/m^2 daily for 21 days with 7 day break	Bone marrow suppression, nausea, vomiting, dizziness diarrhea, rash	Blood count, liver and renal function, electrolytes

European Journal of Endocrinology (2009) **160** 1003–1010 ISSN 0804-4643

CLINICAL STUDY

Merits and pitfalls of mifepristone in Cushing's syndrome

F Castinetti, M Fassnacht[1], S Johanssen[1], M Terzolo[2], P Bouchard[3], P Chanson[4], C Do Cao[5], I Morange, A Picó[6], S Ouzounian[3], J Young[4], S Hahner[1], T Brue, B Allolio[1] and B Conte-Devolx

Table 3 Efficacy and adverse effects of mifepristone in the 21 patients of the literature.

	Sex/age	Etiology	Dose	Duration	Clinical improvement	Adverse effects
1	F/45	ACC	5–22 mg/kg	2	Yes	
2	F/32	ACC	400	2	Yes	
3	F/NA	ACC	30–20 mg/kg	4	Yes	Vaginal bleeding, hypoglycemia, water retention
4	M/62	ACC	400	9	Yes	
5	M/43	ACC	800–400	0.5	Yes	Hypoglycemic episodes, increase in eosinophils
6	M/36	EAS	5–22 mg/kg	10	Yes	Hashimoto thyroiditis, gynecomastia, impotence, inhibition of cortisol synthesis
7	M/42	EAS	5–22 mg/kg	12	Yes	Nausea, gynecomastia
8	F/63	EAS	5–22 mg/kg	4	Yes	Adrenal insufficiency
9	F/55	EAS	5–22 mg/kg	2.25	Yes	
10	F/46	EAS	800–1600	0.3	Yes	
11	M/25	EAS	5–20 mg/kg	2.25	Yes	
12	F/2	EAS	25–100 thrice/day	2	Yes	
13	F/43	EAS	600	2	Yes	Hypokalemia, myelemia
14	F/38	EAS	800	10	Yes	
15	F/38	AA	5–22 mg/kg	1.5	Yes	Nausea
16	M/51	CD	400–2000	18	Yes	Severe hypokaliemia, adrenal crisis
17						
18						
19						
20						
21						synthesis

Metanalisi dalla letteratura con 9 casi di EAS trattati con mifepristone, con beneficio

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

C. de Bruin, L. J. Hofland, L. K. Nieman, P. M. van Koetsveld, A. M. Waaijers, D. M. Sprij-Mooij, M. van Essen, S. W. J. Lamberts, W. W. de Herder, and R. A. Feelders

J Clin Endocrinol Metab, February 2012, 97(2):455–462

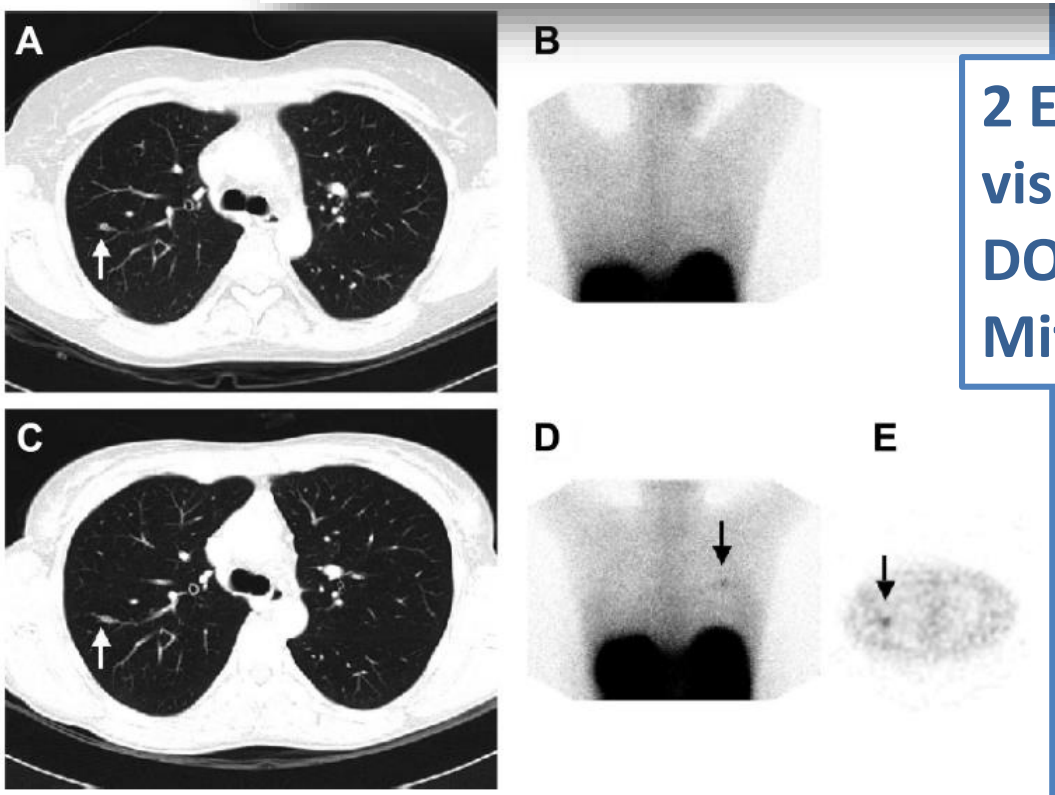
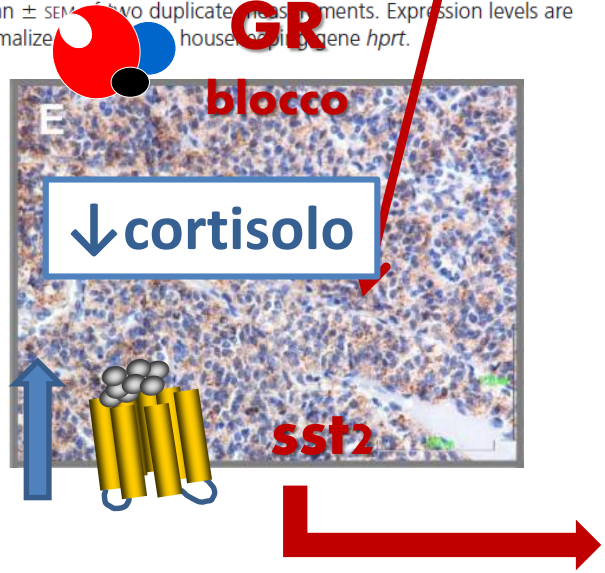


FIG. 1. [^{111}In-DTPA^{0}]octreotide and CT imaging results in patient 1 before (A and B) and after 6 months of therapy with mifepristone (C–E). Before therapy was initiated, a CT scan (A) shows a small round nodule in the right upper lung (*white arrow*), which is not visible at the [^{111}In-DTPA^{0}]octreotide scan (B). After 6 months of therapy, the CT scan shows the same lesion (*white arrow*) within the upper lobe of the right lung (C). At that time a repeat [^{111}In-DTPA^{0}]octreotide scan shows pathological uptake at the site of the lesions (D and E; *black arrows*).

2 EAS da Carcinoidi Bronchiali visibili all'Octreoscan solo DOPO trattamento con Mifepristone 400-800 mg/die

FIG. 3. Somatostatin and dopamine receptor mRNA subtype expression in carcinoid tissue of patient 1. Values represent the mean ± SEM of two duplicate measurements. Expression levels are normalized to the housekeeping gene *hprt*.



Review Article

Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics

Journal of Oncology
Volume 2012, Article ID 685213,

Carlotta Pozza, Chiara Graziadio, Elisa Giannetta, Andrea Lenzi, and Andrea M. Isidori

Table 2: Medical treatments for Cushing's syndrome (in clinical use or investigational).

Drug	Mechanism of action	Dose (range)	Side effects	Safety monitoring
Ketoconazole	Inhibits steroidogenesis via inhibition of cytochrome P450 function	200–1800 mg per os (in divided doses, b.i.d.-t.i.d.)	Reversible liver dysfunction, severe liver toxicity, GI disorders, skin rash, loss of libido, impotence	Transaminase, testosterone, and SHBG in men
Metyrapone	Inhibits 11-β hydroxylase in the adrenal gland	750–6000 mg per os (in divided doses, t.i.d.-q.i.d.)	Hirsutism, acne, GI disorders, dizziness, hypertension, edema, hypokalemia	Androgens, mineralocorticoid, electrolytes
Mitotane	Inhibits steroidogenesis via inhibition of cytochrome P450; adrenolytic (high doses)	500 mg–12 g per os (daily)	Severe nausea, vomiting, diarrhea, rash, somnolence, ataxia, vertigo, dyslipidemia	Plasma mitotane, blood count, electrolytes, liver function, cholesterol
Etomidate	Inhibits 11-β hydroxylase and 17–20 lyase	<0.1 mg/kg/hr i.v.	Sedative effects, anesthesia	Monitoring by anesthesiologists
Mifepristone (RU-486)	Glucocorticoid, androgen, and progesterone receptor antagonist	300–1200 mg per os, daily dose	Hypoadrenalism, hypokalemia, hypertension, irregular menses, endometrial hyperplasia	Blood count, electrolytes, pelvic US
Cabergoline	D2 receptor agonist	1–7 mg per os, weekly dose	Nausea, vomiting, dizziness, valvulopathy	Echocardiogram
Temozolomide	Alkylating agent	150–200 mg/m^2 per os for 5 days once every 28 days, or 75 mg/m^2 daily for 21 days with 7 day break	Bone marrow suppression, nausea, vomiting, dizziness diarrhea, rash	Blood count, liver and renal function, electrolytes

Dopamine Receptor Expression and Function in Corticotroph Ectopic Tumors

The Journal of Clinical Endocrinology & Metabolism 92(1):65–69

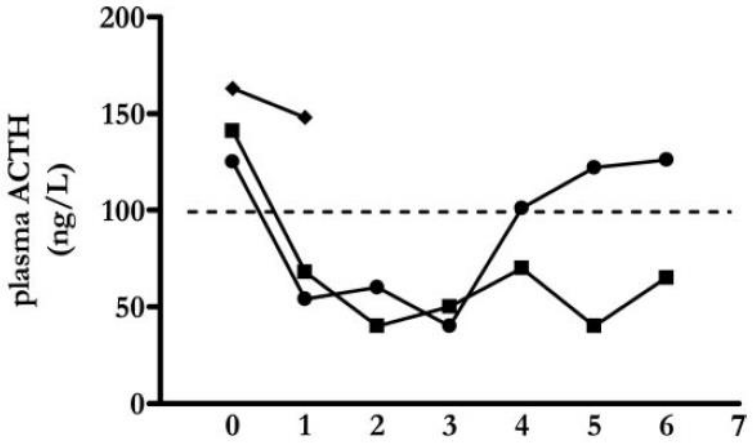
Rosario Pivonello, Diego Ferone, Wouter W. de Herder, Antongiulio Faggiano, Lisa Bodei, Ronald R. de Krijger, Gaetano Lombardi, Annamaria Colao, Steven W. J. Lamberts, and Leo J. Hofland

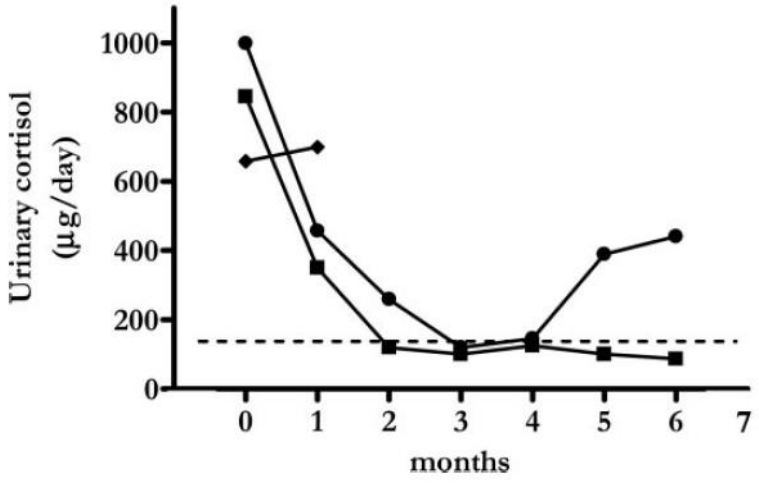
TABLE 1. Histological diagnosis, IHC, and RT-PCR results in the ACTH-secreting tumors deriving from patients with EAS

Cases	Histology	IHC			RT-PCR						
		Chromogranin	ACTH	D_2	D_1	D_2	D_2 isoforms	D_2 number[a]	D_3	D_4	D_5
1	Lung carcinoid	+++	+++	+++	−	+	S/L	0.16	−	+	−
2	Lung carcinoid	++	+	++	−	+	L	0.08	−	+	−
3	Lung carcinoid	++	++	+	−	+	L	0.07	−	−	−
4	Lung carcinoid	++	+	+++	nd	nd	nd	nd	nd	nd	nd
5	Thymic carcinoid	++	++	+	nd	nd	nd	nd	nd	nd	nd
6	Pancreatic carcinoid	++	+	−	nd	nd	nd	nd	nd	nd	nd

IHC: +, weakly positive; ++, moderately positive; +++, strongly positive; −, negative; RT-PCR: +, positive; −, negative; S, short isoform; L, long isoform; nd, not determined.

[a] The D_2 receptor has been explained as the ratio between the number of copy of messenger RNA of D_2 and the number of copy of mRNA of HPRT. The D_2 number in five cases of ACTH-secreting pituitary tumors, used as controls, was 1.57 ± 1.10 (range, 0.09–6.0).





Cabergoline plus Lanreotide for Ectopic Cushing's Syndrome

Rosario Pivonello, M.D., Ph.D.

Federico II University
80131 Naples, Italy
rpivone@tin.it

Diego Ferone, M.D., Ph.D.

University of Genoa
16132 Genoa, Italy

Steven W.J. Lamberts, M.D., Ph.D

Erasmus Medical Center
3015 GD Rotterdam, the Netherlands

Annamaria Colao, M.D., Ph.D.

Federico II University
80131 Naples, Italy

N ENGL J MED 352;23
JUNE 9, 2005

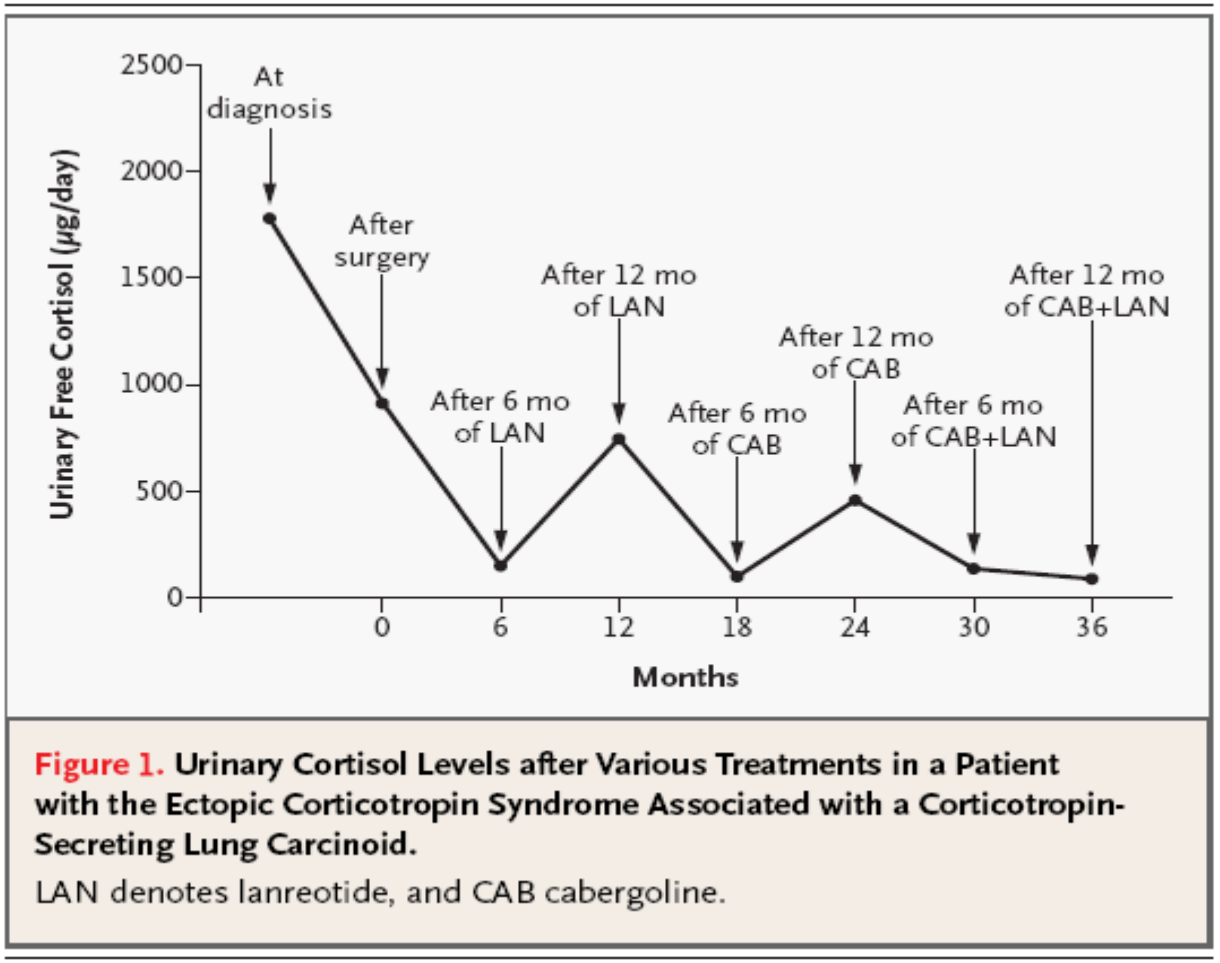
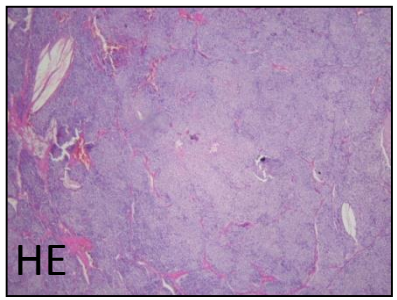
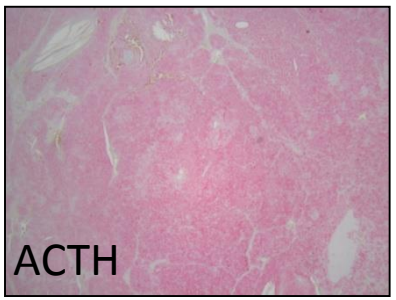
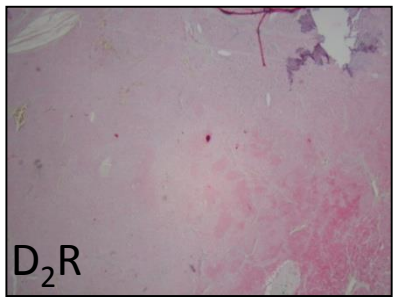


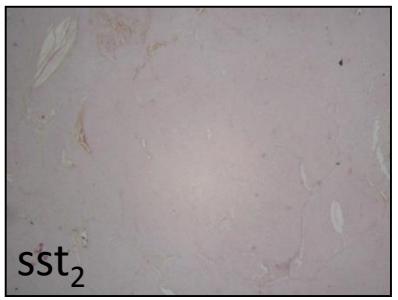
Figure 1. Urinary Cortisol Levels after Various Treatments in a Patient with the Ectopic Corticotropin Syndrome Associated with a Corticotropin-Secreting Lung Carcinoid.

LAN denotes lanreotide, and CAB cabergoline.









clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii120–vii123, 2012
doi:10.1093/annonc/mds267

Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Öberg[1], P. Hellman[2], P. Ferolla[3] & M. Papotti[4], on behalf of the ESMO Guidelines Working Group*

Streptozotocina + 5FU
+ DOX

Cisplatino- Etoposide

Cyclofosfamide-DOX-Vincristina

RGIA

Sempre quando possibile, ma…
Metastasi diffuse

… "In general, chemotherapy results are discouraging and survival data have to be interpreted with caution. No randomized trials have been performed that could guide the treatment. „

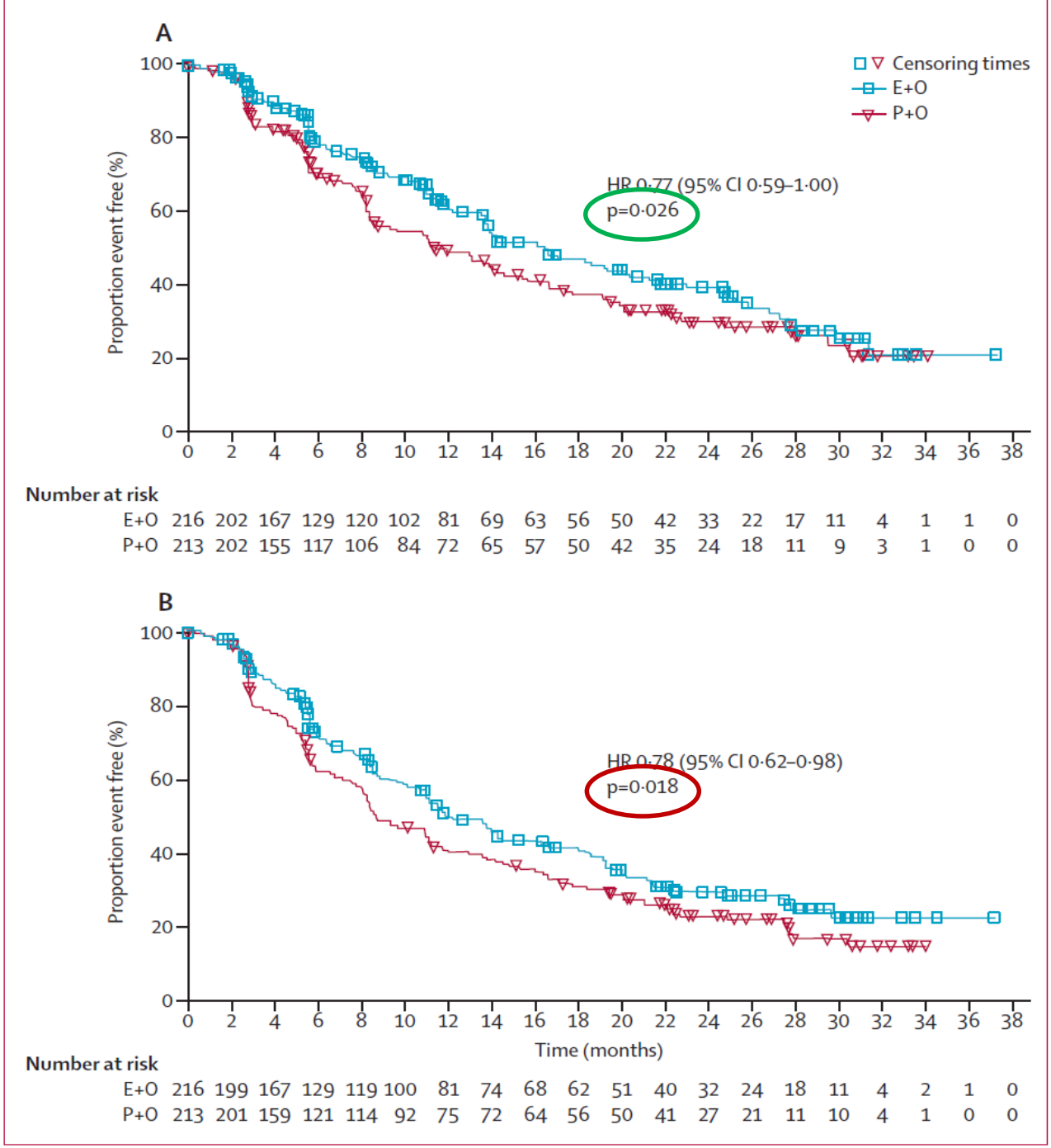


Figure 2: Kaplan-Meier plots of progression-free events

Clin Cancer Res 2007;13(10) May 15, 2007

Temozolomide as Monotherapy Is Effective in Treatment of Advanced Malignant Neuroendocrine Tumors

Sara Ekeblad,[1] Anders Sundin,[2] Eva Tiensuu Janson,[1] Staffan Welin,[1] Dan Granberg,[1] Henrik Kindmark,[1] Kristina Dunder,[1] Gordana Kozlovacki,[1] Håkan Örlefors,[1] Mattias Sigurd,[1] Kjell Öberg,[1] Barbro Eriksson,[1] and Britt Skogseid[1]

PR o SD
Bronchial Carcinoids 62%
Thymic Carcinoids 71%

Table 4. Radiologic response

	All patients (*N* = 36)	EPT (*n* = 12)	Bronchial carcinoids (*n* = 13)	Thymic carcinoids (*n* = 7)	Other (*n* = 4)
Complete response	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Partial response	5 (14%)	1 (8%)	4 (31%)	0 (0%)	0 (0%)
Stable disease	19 (53%)	8 (67%)	4 (31%)	5 (71%)	2 (50%)
Progressive disease	12 (33%)	3 (25%)	5 (38%)	2 (29%)	2 (50%)

EAS manifestazioni cliniche aggressive

Necessita di terapia aggressiva

SSA

CT **-Streptozotocina+5 FU**

-Temozolomide

-Capecitabina

-Cisplatino+Etoposide **(high proliferating tumors)**

Inibitori mTOR (everolimus RADIANT-2)

Radiofrequenza

E

P

Surrenectomia Bilaterale

pre quando possibile, ma…

astasi diffuse

ttia occulta

erabilità per altre cause

ra e % recidiva

preoperatoria

CONCLUSIONI

Malattia aggressiva che necessita di approccio terapeutico altrettanto aggressivo.
La chirurgia da eseguire sempre quando possibile: curativa o palliativa.
Importante ruolo ancora per la surrenectomia bilaterale in EAS.

Terapia medica ruolo fondamentale nel controllo ipercortisolemia e miglioramento della sindrome, che deve avvenire al più presto.
Spesso associazioni di diverse molecole, inibitori della steroidogenesi, agonisti, antagonisti recettoriali, anche se necessari ulteriori studi per efficacia e dosaggi.

La terapia medica, che controlla sindrome, consente di ristadiare il paziente nel tempo, portando in alcuni casi all'identificazione della fonte occulta dell'EAS

L'approccio terapeutico all'EAS deve essere quello della "Tailored Therapy", valutando le caratteristiche di ogni singolo paziente , la potenziale efficacia clinica dei farmaci e i loro effetti collaterali.

Grazie per l'attenzione!

Francesco Minuto
Diego Ferone
Mara Boschetti
Massimo Giusti
Federico Gatto
Francesca Annunziata
Davide Malpassi
Lara Vera
Mara Dolcino
Claudia Teti
Miryam Talco
Lorenzo Mortara
Elena Nazzari