Altogether
to Beat
Cushing's
Syndrome

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

11.00-13.00 **SESSIONE 2: IL CUSHING ECTOPICO**
moderatori **Ettore Degli Uberti, Diego Ferone**

11.00-11.30 L'INQUADRAMENTO CLINICO-DIAGNOSTICO
Giovanni Vitale

11.30-12.00 L'APPROCCIO TERAPEUTICO
Manuela Albertelli

12.00-12.30 IL RUOLO DEGLI ANALOGHI
DELLA SOMATOSTATINA E DEL PASIREOTIDE
Giorgio Arnaldi

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

TABLE 1. Causes of Cushing's syndrome (data based on the authors' patient population; n = 423)

Diagnosis	Patient (%)
ACTH-dependent	
Pituitary-dependent Cushing's syndrome (Cushing disease)	65
Ectopic ACTH syndrome (*i.e.* bronchial, thymic, pancreatic carcinoids, medullary thyroid carcinoma, *etc.*)	7
Ectopic CRH syndrome	<1
ACTH-independent	
Adrenal adenoma	18
Adrenal carcinoma	6
PPNAD (including the Carney complex)	1
AIMAH (aberrant expression of ectopic and eutopic membrane receptors: gastric inhibitory polypeptide, catecholamines, or LH/human chorionic gonadotropin, vasopressin, and serotonin)	3

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

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, John Newell-Price, Martin O. Savage, Paul M. Stewart, and Victor M. Montori

J Clin Endocrinol Metab. May 2008, 93(5):1526–1540

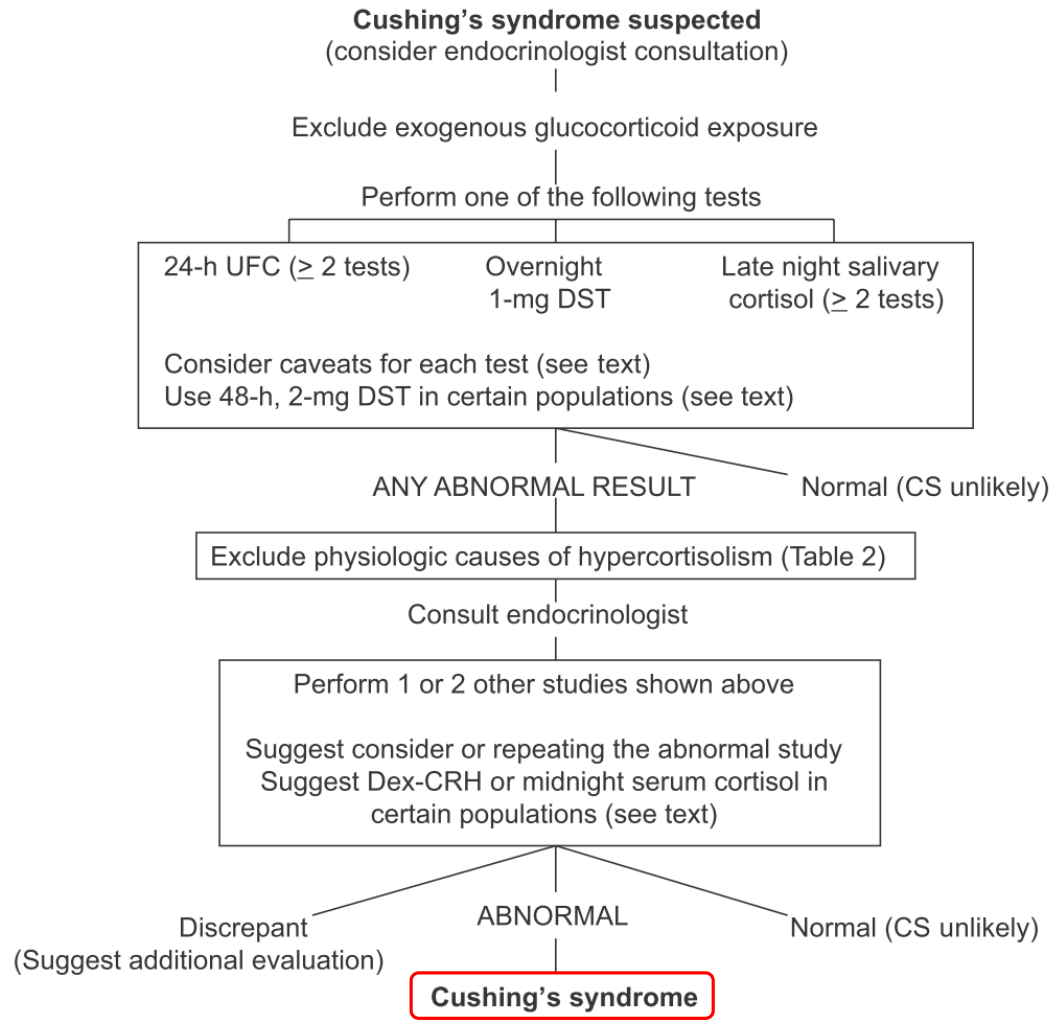

FIG. 1. Algorithm for testing patients suspected of having Cushing's syndrome (CS). All statements are recommendations except for those prefaced by suggest. Diagnostic criteria that suggest Cushing's syndrome are UFC greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 145 ng/dl (4 nmol/liter).

Normal ranges vary substantially, depending on the method used, so it is essential to interpret test results in the context of the appropriate normal range.

TABLE 2. Conditions associated with hypercortisolism in the absence of Cushing's syndrome[a]

Conditions
Some clinical features of Cushing's syndrome may be present
Pregnancy
Depression and other psychiatric conditions
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of Cushing's syndrome
Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not urine cortisol)

[a] Whereas Cushing's syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

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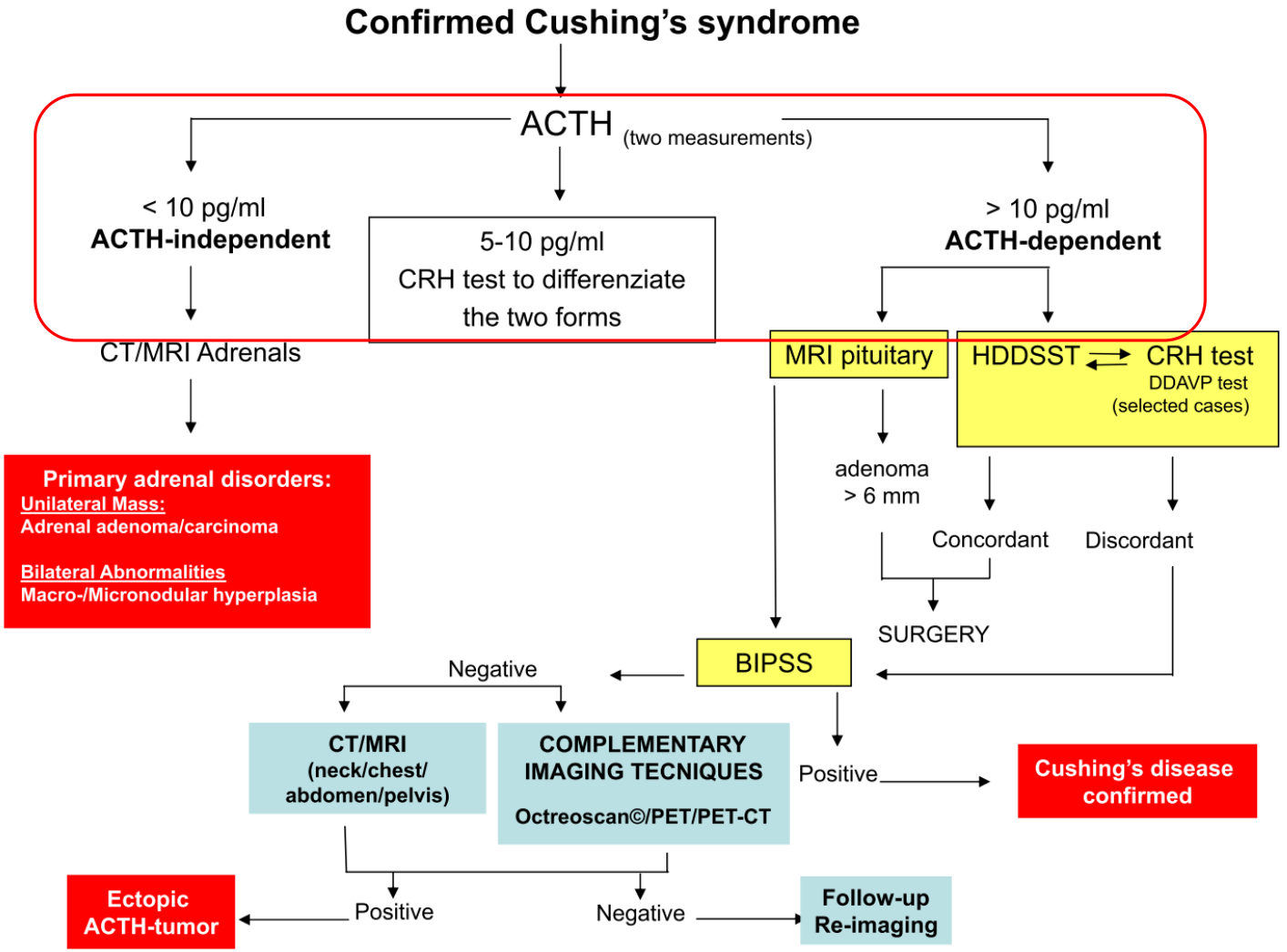

FIG. 1. Clinical decision-making flow chart.

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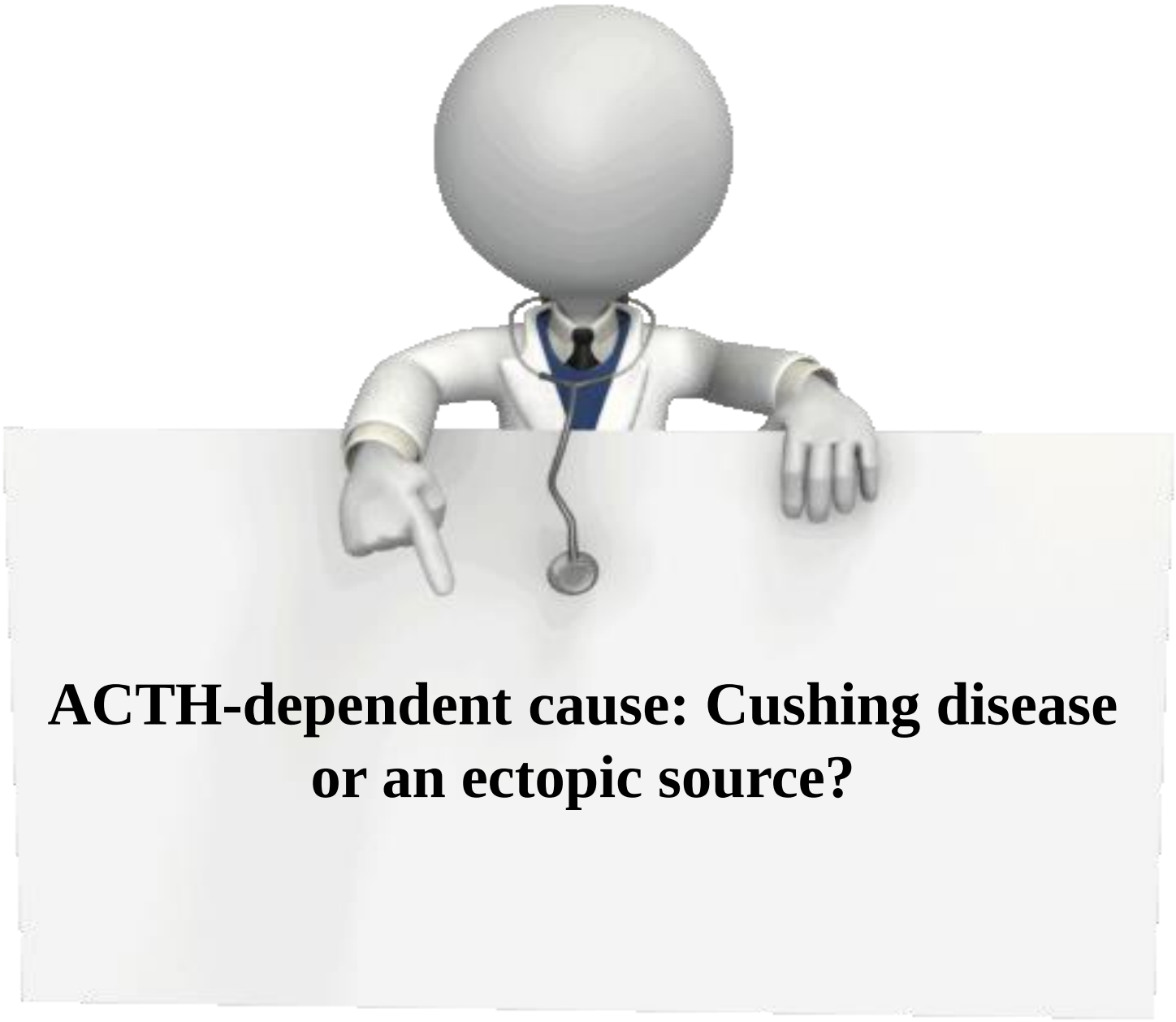
ACTH

normal ACTH concentrations (37, 38). In adrenal-dependent forms, circulating plasma ACTH is suppressed (<10 pg/ml), whereas it is normal or increased in ACTH-dependent forms. It should be noted that there is significant overlap in circulating ACTH levels in patients with either a pituitary or an ectopic tumor despite the fact that ACTH levels are generally higher in the latter. Moreover, some patients with pituitary disease can show ACTH levels in the low-normal range, and conversely, some patients with adrenal forms can present ACTH levels that are not fully suppressed. To improve the sensitivity of this test, we suggest measuring plasma ACTH levels at least two times before further evaluation. Because some patients with adrenal Cushing may show unsuppressed ACTH, for ACTH levels between 10 and 20 pg/ml, a CRH stimulation test is suggested; a blunted ACTH response is observed in adrenal Cushing, whereas a brisk rise in ACTH is observed in pituitary forms (2, 9, 11). Because ACTH is rapidly degraded by plasma protease, blood should be collect in prechilled EDTA tubes, and plasma should be rapidly centrifuged and stored to avoid falsely low values (37).



ACTH-dependent cause: Cushing disease or an ectopic source?

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

Cushing's disease

Xavier Bertagna, MD, PhD *, Laurence Guignat, MD, Lionel Groussin, Jérôme Bertherat, MD, PhD

Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 607–623

Severe Cushing's disease mimicking the classical ectopic ACTH syndrome

The clinical presentation may be severe enough to mimic the classical form of the ectopic ACTH syndrome, with rapid-onset, profound myopathy, severe hypokalaemia and definite hyperpigmentation. In some cases the correct diagnosis may be further obscured by unexpected responses to dynamic tests, such as lack of suppressibility on the high-dose dexamethasone suppression test and/or a lack of ACTH response to the CRH test. In most cases, however, the pituitary imaging will point to the source of ACTH often showing a large macroadenoma. If necessary, and if possible, bilateral inferior petrosal sinus sampling should ultimately provide the unequivocal solution.

Mild ectopic ACTH syndrome mimicking the classic Cushing's disease

It has become increasingly recognised that some non-pituitary tumours provoke a Cushing's syndrome with both clinical and biochemical features similar to those of the classic Cushing's disease. Mild and slowly progressive symptoms are found together with dynamic tests compatible with a non-autonomous, glucocorticoid responsive, ACTH-dependent cortisol overproduction. Although it is quite exceptional, some of these tumours even respond to CRH with an ACTH rise. Because most of these patients have small and indolent bronchial tumours (carcinoids) that may escape the most sensitive imaging approaches, this 'occult' ectopic ACTH secretion syndrome can be easily misdiagnosed as Cushing's disease and even undergo unwarranted, and unsuccessful, pituitary surgery. This is again a situation where the bilateral inferior petrosal sinus sampling is most useful to help the right diagnosis, except in rare cases of concomitant ectopic ACTH–CRH secretion.[49]

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)

TABLE 1. Patient distribution and demographic data

	Cushing's disease	Adrenal adenoma	Adrenal carcinoma	Ectopic ACTH/CRH secretion	Nodular adrenal hyperplasia
Number of patients	288	80	24	25	9
Mean age at diagnosis (yr)	36 ± 0.8	37 ± 1.3	41 ± 3.1	44 ± 3.6	35 ± 6.1
Range	11–72	15–67	1.2–65	14–71	0.5–62
Sex (F/M)	239/49	75/5	14/10	10/15	7/2
Time between first symptoms and diagnosis (months)	29 ± 1.7	27 ± 2.8	13 ± 4.8	18 ± 4.7	22 ± 4.8

The mean age of patients with ectopic ACTH syndrome (EC) is almost one decade older than in Cushing's disease (CD).

In women with ACTH dependent Cushing's syndrome, CD is 20-fold more prevalent than ectopic CS, while in men the ratio is 3:1.

Cushing's Syndrome

Rosario Pivonello, MD, PhD*,
Maria Cristina De Martino, MD, Monica De Leo,
Gaetano Lombardi, MD, Annamaria Colao, MD,

Endocrinol Metab Clin N Am
37 (2008) 135–149

ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA

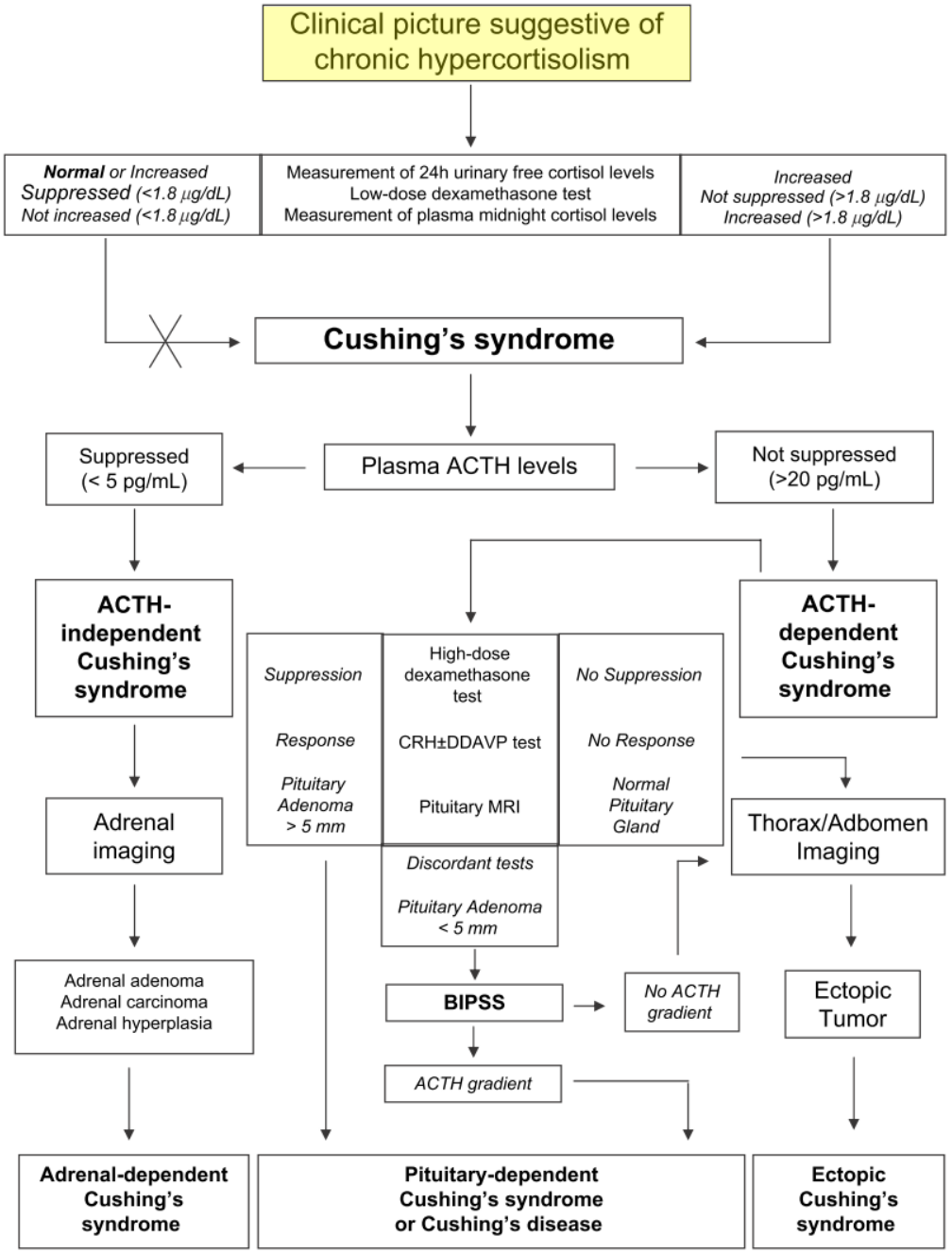


Fig. 1. Schematic procedure for the diagnosis and differential diagnosis of Cushing's syndrome.

The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics

European Journal of Endocrinology (2011) **165** 383–392

Elena Valassi, Alicia Santos, Maria Yaneva[1], Miklós Tóth[2], Christian J Strasburger[3], Philippe Chanson[4,5,6], John A H Wass[7], Olivier Chabre[8], Marija Pfeifer[9], Richard A Feelders[10], Stylianos Tsagarakis[11], Peter J Trainer[12], Holger Franz[13], Kathrin Zopf[3], Sabina Zacharieva[1], Steven W J Lamberts[10], Antoine Tabarin[14], Susan M Webb and on behalf of The ERCUSYN Study Group

Table 2 Baseline clinical presentation in the overall population of patients with Cushing's syndrome and of each aetiologic group. Data for each aetiologic group and the overall series are expressed as number of patients with a sign or symptom/total number of patients with records available for that sign or symptom. Percentages are shown in parenthesis.

	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Overall
Weight gain	240/294 (82)	93/113 (82)	16/23 (70)	8/10 (80)	357/440 (81)
Hypertension	233/306 (76)	103/126 (82)	21/24 (88)	6/10 (60)	363/466 (78)
Skin alterations	227/292 (78)*	78/122 (64)	18/24 (75)	6/10 (60)	329/448 (73)
Myopathy	181/272 (67)	69/107 (64)	20/24 (83)	6/8 (75)	276/411 (67)
Hirsutism[a]	145/232 (63)*,‡	37/100 (37)†	12/13 (92)	4/8 (50)‡	198/353 (56)
Menstrual irregularities[a]	123/195 (63)*	35/82 (43)	4/9 (44)	3/8 (38)	165/294 (56)
Reduced libido	61/123 (50)	15/43 (35)	5/10 (50)	3/4 (75)	84/180 (47)
Depression	93/243 (38)	31/106 (29)	9/22 (41)	4/10 (40)	137/381 (36)
Diabetes mellitus	96/294 (33)†	43/127 (34)†	17/23 (74)	2/10 (20)†	158/454 (35)
Hair loss	76/224 (34)	29/98 (30)	4/19 (21)	1/10 (10)	110/351 (31)
Fractures	55/263 (21)	21/114 (18)	7/22 (32)	2/9 (22)	85/408 (21)

PIT-CS, pituitary-dependent CS; ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other aetiologies. *$P<0.01$ versus adrenal; †$P<0.01$ versus ectopic; ‡$P<0.05$ versus ectopic.
[a]Data refer to female patients.

There are no clear features to differentiate the two ACTH-dependent forms, but …

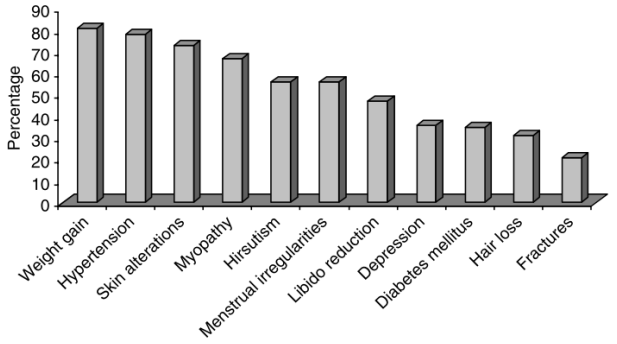


Figure 1 Distribution of symptoms in the overall population of patients with Cushing's syndrome.

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

J Clin Endocrinol Metab, August 2005, 90(8):4955–4962

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

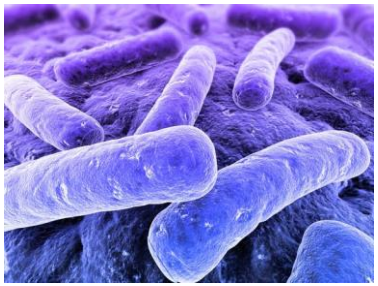
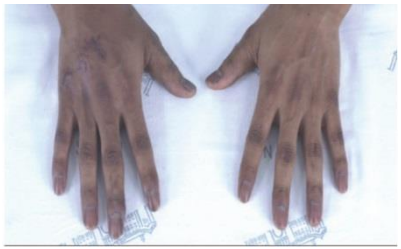


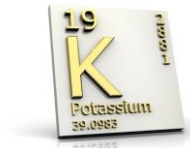
TABLE 1. Clinical signs and symptoms of patients with CS caused by known or presumed ectopic ACTH secretion (n = 90)

	n (%)
Muscle weakness	74/90 (82)
Body weight	
Increase	64/90 (70)
Decrease	9/90 (10)
Hypertension	70/90 (78)
Menstrual irregularities or amenorrhea	28/36 (78)
Hirsutism	36/48 (75)
Osteopenia or osteoporosis[a]	27/36 (75)
Hypokalemia	64/90 (71)
Psychiatric disorders	48/90 (53)
Bruising	47/90 (52)
Infections	46/90 (51)
Diabetes	45/90 (50)
Violaceous striae	40/90 (44)
Truncal obesity	35/90 (39)
Edema	34/90 (38)
Body mass index > 28 kg/m^2	32/90 (36)
Fractures[b]	27/90 (30)
Insomnia	26/90 (29)
Libido	
Decrease	21/88 (24)
Increase	1/88 (1)
Impaired cognition or memory	20/90 (22)
Hyperpigmentation	17/90 (19)

[a] Assessed with dual-photon absorptiometry or dual-energy x-ray absorptiometry.

[b] Assessed with x-rays; in some patients fractures were noted in more than one location; 14 had vertebral fractures/compression, six had fractures in the lower and three in the upper limbs, and 10 had rib fractures.

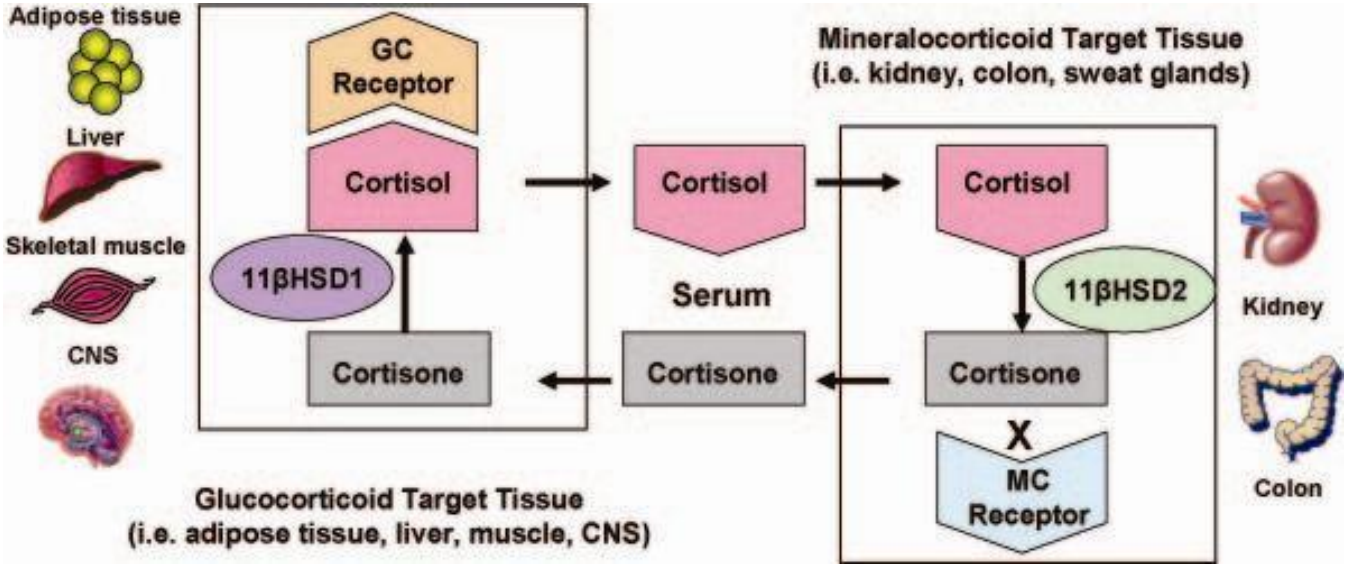




40-70%

Howlett TA et al. Clin Endocrinol (Oxf). 1986 Jun;24(6):699-713.

Almost 100% of patients with ectopic ACTH-dependent CS, present with **hypokalemia**, which is found only in about 10% of patients with CD. This is related to higher levels of cortisol, resulting in a syndrome of apparent mineralcorticoid excess (hypokalemia, **hypertension, edema and metabolic alkalosis**). Indeed hypercortisolism saturates **11-β-hydroxysteroid dehydrogenase type 2**. This enzyme is responsible for converting cortisol to cortisone and preventing its mineralocorticoid effect in the kidney.



Bone Demineralization and Vertebral Fractures in Endogenous Cortisol Excess: Role of Disease Etiology and Gonadal Status

J Clin Endocrinol Metab, May 2006, 91(5):1779–1784

Libuse Tauchmanovà, Rosario Pivonello, Carolina Di Somma, Riccardo Rossi, Maria Cristina De Martino, Luigi Camera, Michele Klain, Marco Salvatore, Gaetano Lombardi, and Annamaria Colao

TABLE 2. Parameters of bone turnover, bone density, and fractures in patients and controls

Variable	ACTH-secreting pituitary adenoma	Adrenal adenoma	Adrenal carcinoma	Ectopic ACTH excess	Controls
No. of subjects	37	18	15	10	80
Serum calcium (mmol/liter)	2.36 ± 0.13	2.38 ± 0.15	2.34 ± 0.14	2.39 ± 0.16	2.33 ± 0.11
Albumin (g/dl)	3.99 ± 0.44	4.06 ± 0.36	3.86 ± 0.5	4.28 ± 0.3	4.1 ± 0.3
Urinary calcium excretion (mg/24 h)	182 ± 95	215 ± 88	171 ± 44	192 ± 62	166 ± 73
iPTH (ng/liter)	43.4 ± 12	40.2 ± 14	38 ± 15	44.5 ± 13	41.2 ± 16
Osteocalcin (ng/ml)	1.5 ± 0.5[a]	2.3 ± 0.7	2.4 ± 0.9	1.2 ± 0.4[a]	8.9 ± 2.4[b]
ALP (U/liter)	153 ± 52	174.5 ± 58	185 ± 61	187 ± 49	168 ± 58
Creatinine (μmol/liter)	86 ± 8.6	88 ± 8.9	90 ± 9	87 ± 8.7	82 ± 9.8
Hydroxyprolinuria (μmol/m^2)	135 ± 41.5	129 ± 36	127.5 ± 32	137 ± 40	102 ± 16[b]
Lumbar Z score (SD)	−1.97 (−5.15 to −0.06)	−1.8 (−4 to −0.36)	−1.8 (−2.9 to 0.9)	−3.53 (−4.9 to −3.0)[c]	−0.03 ± 1.1[d]
Femoral Z score (SD)	−1.04 (−2.6 to 0.3)	−1.5 (−2.6 to 1.2)	−0.8 (−2.3 to 0.7)	−0.6 (−2.45 to −0.2)	0.05 ± 0.8[b]
Prevalence (%) of any vertebral fracture	29 (78%)	12 (67%)	10 (67%)	10 (100%)	1 (1.3%)[d]
Clinical fractures[e]	15 (52%)	6 (60%)	4 (40%)	7 (70%)	0 (0%)[b]
Multiple fractures[e]	25 (86%)	9 (75%)[f]	8 (80%)[f]	10 (100%)	0 (0%)[d]

Data are expressed as mean ± SD or median and range, as appropriate.

[a] $P < 0.05$ *vs.* all other groups of patients.

[b] $P < 0.05$ *vs.* all groups of patients.

[c] $P < 0.01$ *vs.* all other groups of patients.

[d] $P < 0.01$ *vs.* all groups of patients.

[e] The percentage of clinical and multiple fractures was calculated as a subset of patients with any fracture. Reference ranges: calcium, 2.2–2.6 mmol/liter; ALP, 98–275 U/liter; creatinine, less than 133 μmol/liter; albumin, 3.6–5.2 g/dl; osteocalcin, 2–22 ng/ml; PTH, 10–75 ng/liter; hydroxyproline excretion, 60–190 μmol/m^2.

[f] $P < 0.05$ *vs.* ectopic ACTH hypersecretion.

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)

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Time between first symptoms and diagnosis (months)	29 ± 1.7	27 ± 2.8	13 ± 4.8	18 ± 4.7	22 ± 4.8

The time between the first clinical symptom of hypercortisolism and diagnosis of ectopic Cushing's syndrome was shortest in patients with small cell lung cancer (**SCLC**) (3–4 months) and **pancreatic islet cell tumours** (6–8 months), in contrast with **bronchial carcinoids** (6–24 months).

In comparison with other NETs, which present a classic Cushingoid appearance in nearly all cases, only 2/3 of patients with SCLC showed the clinical signs (moon face and central obesity) of overt hypercortisolism. These differences are probably due to the rapidity of onset and the severity of the hypercortisolaemia.

Approach to the Patient with Possible Cushing's Syndrome

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J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

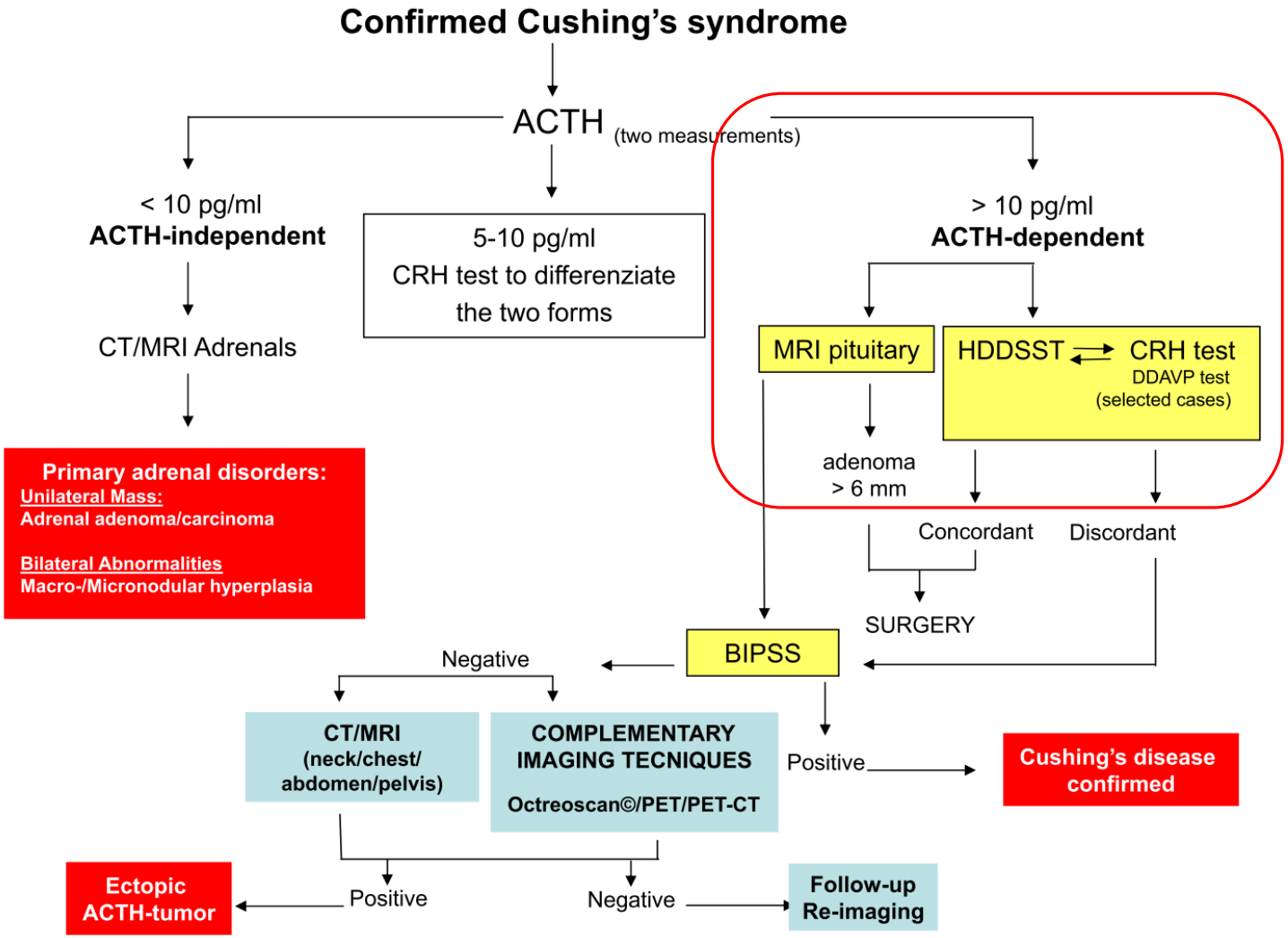
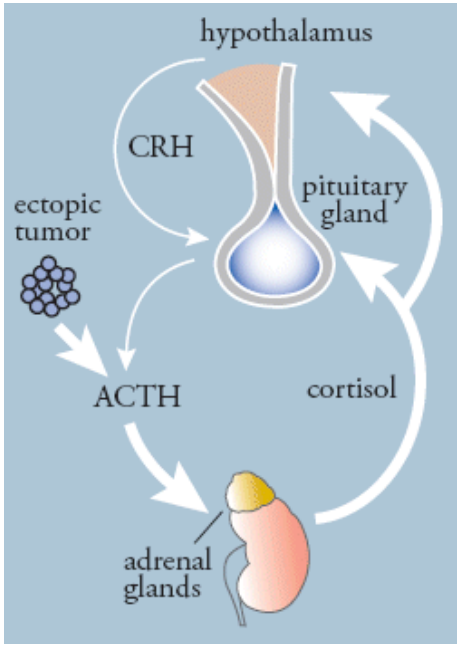


FIG. 1. Clinical decision-making flow chart.

Ectopic ACTH Syndrome

ANDREA M. ISIDORI
ANDREA LENZI

Arq Bras Endocrinol Metab 2007;51/8



Tumours causing **EAS** are usually characterized by their ***unresponsiveness* to CRH, glucocorticoid feedback or desmopressin responsiveness**.

Approach to the Patient with Possible Cushing's Syndrome

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Although the CRH test is considered the most reliable dynamic noninvasive test for the differential diagnosis of ACTH-dependent Cushing's syndrome, this test cannot make a 100% differentiation between pituitary and ectopic causes. From literature data, the sensitivity and specificity using ACTH criteria is approximately 90% (9, 11, 42). Unfortunately, there is yet no consensus on the criteria for interpreting the test as positive. Variability in interpretation depends on the type of CRH used (usually ovine in the United States and human in Europe), the weight-based (1 μg/kg) or the 100-μg fixed dose, and the wide range of response parameters (increase above baseline in peak ACTH, 30–50%, *vs.* peak cortisol, 14–20%) (9, 11, 42).

Optimal Response Criteria for the Human CRH Test in the Differential Diagnosis of ACTH-Dependent Cushing's Syndrome

J. NEWELL-PRICE, D. G. MORRIS, W. M. DRAKE, M. KORBONITS, J. P. MONSON, G. M. BESSER, AND A. B. GROSSMAN

J Clin Endocrinol Metab, April 2002, 87(4):1640–1645

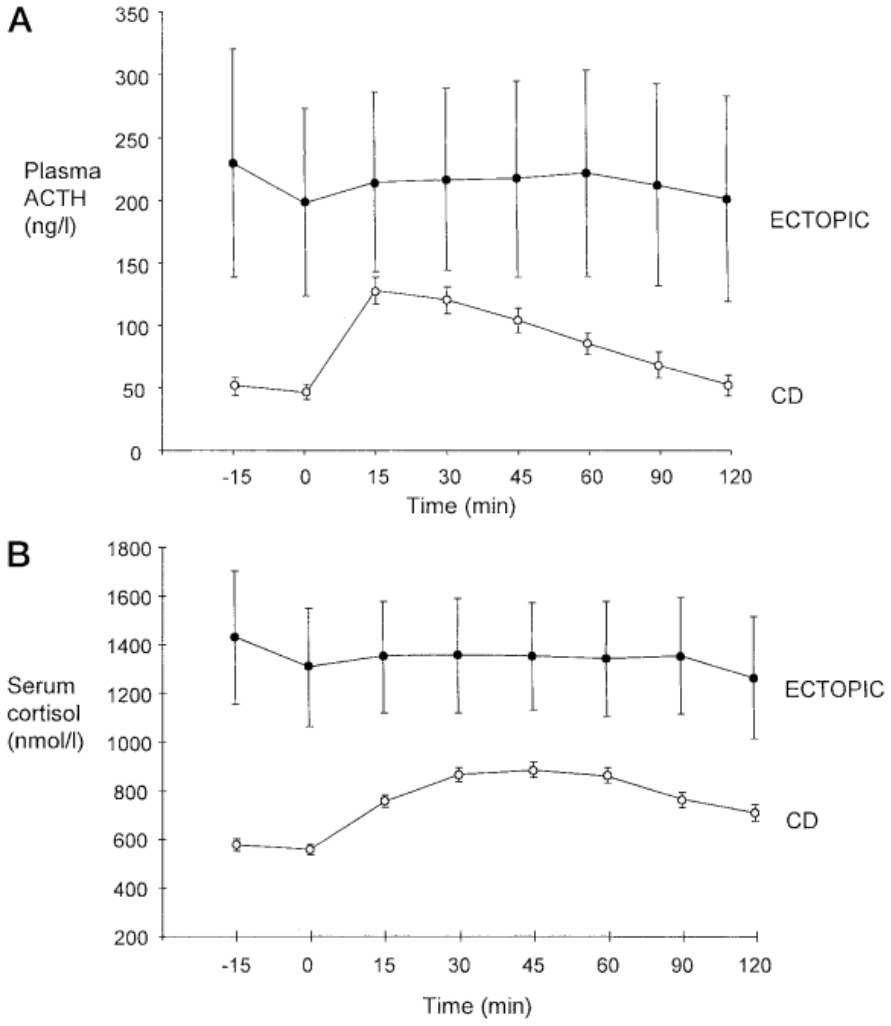

FIG. 1. Mean (±SEM) plasma ACTH (A) and serum cortisol (B) responses to hCRH (100 μg iv) in the patients with CD and the EC.

With the classic CRH stimulation test, an ACTH increase >35% and cortisol >20% above baseline levels is considered to be a specific response for CD when ovine CRH is used, and an increase >105% and >14% respectively when human CRH is used.

The CRH test had a sensitivity of 94% for cortisol and ACTH responses.
CRH test to show a higher diagnostic accuracy than the HDDST.

However, **approximately 10–15% of patients with EAS have been shown to respond to CRH administration.**

Desmopressin stimulation, alone or in combination with CRH, did not substantially improve the test's sensitivity or specificity.

Arq Bras Endocrinol Metab 2007;51/8

Lucio Vilar
Maria da Conceição Freitas
Manuel Faria
Renan Montenegro
Luiz Augusto Casulari
Luciana Naves
Oscar D. Bruno

An alternative to CRH stimulation test is the *desmopressin stimulation test* that involves the intravenous administration of 10 μg of desmopressin (47,48). Desmopressin stimulates ACTH and cortisol release in Cushing's disease by selective stimulation of the V2- and V3-vasopressin receptors (49). Combining the data of all published series reveals that for the desmopressin test the cortisol responses have a sensitivity of 84% and specificity of 83%, while ACTH responses provide poorer discrimination with a sensitivity of 77% and specificity of 73% (1,4). Therefore, testing with desmopressin would be inferior to testing with CRH in terms of sensitivity and specificity, although this peptide is cheaper and more easily available worldwide. A possible explanation for the relatively poorer specificity of the desmopressin test is the more common expression of the V_{1b} (or V_3) receptor in ACTH-secreting nonpituitary tumors (4,50). However, it should be noted that some patients with Cushing's disease respond only to one peptide or the other (1,4,49). In our series, the diagnostic accuracy of both tests was similar (1). On the other hand, a combined test with CRH and desmopressin has been used (4), but larger series have suggested that overlap remains between responses in patients with Cushing's disease and ectopic ACTH secretion (3,51).

Rosario Pivonello, MD, PhD*,
Maria Cristina De Martino, MD, Monica De Leo,
Gaetano Lombardi, MD, Annamaria Colao, MD,

Endocrinol Metab Clin N Am
37 (2008) 135–149

ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA

High dose DST (HDDST)

High doses of glucocorticoids partially suppress ACTH secretion from most corticotroph pituitary tumors, whereas ectopic tumors are generally resistant to feedback inhibition. There are several versions of the HDDST, including the standard 2 days' oral high dose (2 mg every 6 h for eight doses), the 8-mg overnight oral, and the intravenous (IV) 4- to 7-mg tests. Plasma and/or urinary cortisol levels are evaluated before, during, and/or after dexamethasone administration.

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Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

Although the HDDST showed a relatively high sensitivity in identifying patients with Cushing's disease, its specificity is low and in clinical practice has little diagnostic utility whatever the protocol and the cutoff of cortisol suppression used. In accord with other authors, we do not recommend the routine use of HDDST alone in the differential diagnosis of Cushing's syndrome (42, 44, 45).

Ectopic ACTH Syndrome

ANDREA M. ISIDORI
ANDREA LENZI

Arq Bras Endocrinol Metab 2007;51/8

Indeed **22–40%** of **EAS** patients demonstrate either serum or urinary 17-OHCS **suppression** on **HDDST**. Patients with bronchial carcinoids seem to show a significant degree of cortisol suppression (approximately 60%) following the HDDST.

The ectopic ACTH syndrome

Rev Endocr Metab Disord (2010) 11:117–126

Krystallenia I. Alexandraki · Ashley B. Grossman

Because of the limitations of each test individually, a **combination of tests, such as HDDST and CRH tests**, is of clinical value, since the lack of response to both tests had a sensitivity of 100% and a diagnostic accuracy of 98%; hence, this combination resulted in a **100% correct diagnosis for Cushing's disease or 79% for EAS**, while a 1% false positive response was shown in patients with EAS.

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

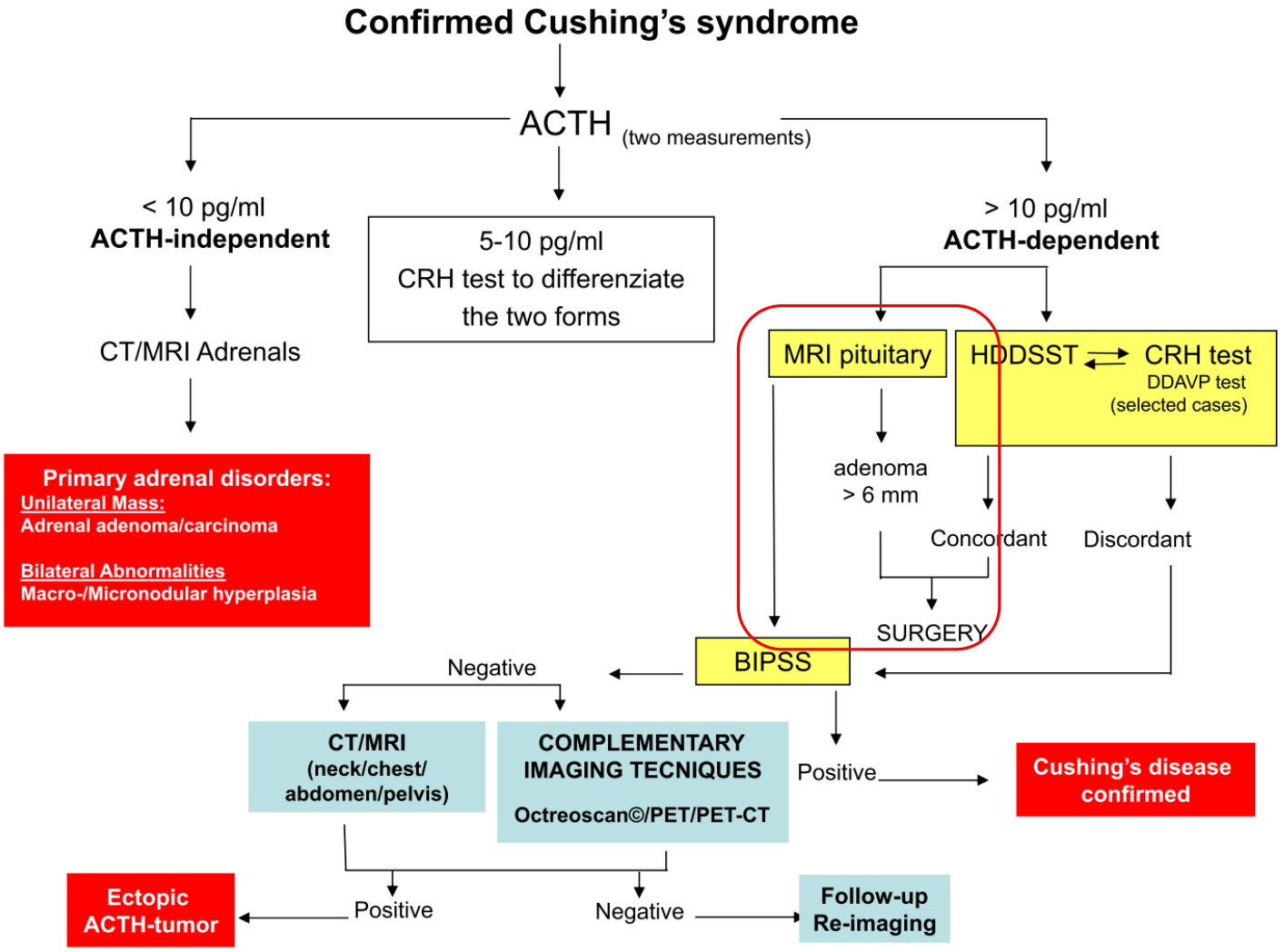

FIG. 1. Clinical decision-making flow chart.

Pituitary incidentaloma

Israel B. Orija, Attending Physician and Director of Endocrine Section [a],
Robert J. Weil, Director of the Neurological Institute Surgical Operation

Best Practice & Research Clinical Endocrinology & Metabolism 26 (2012) 47–68
Contents lists available at ScienceDirect
Best Practice & Research Clinical Endocrinology & Metabolism
journal homepage: www.elsevier.com/locate/beem

Table 1
Summary of Autopsy data on Pituitary incidentalomas.

Year	Author(s)	Number of pituitary glands studied	Number of pituitaries with adenomas	Prevalence (%)
1933	Susman	260	22	8.5
1934	Close	130	39	22.3
1936	Costello	1000	225	22.5
1969	Hardy	1000	27	2.7
1971	McCormick & Halmi	1600	140	8.8
1980	Kovacs et al.	150	20	13
1981	Burrow et al.	120	32	26.7
1981	Muhr et al.	205	3	1.5
1981	Parent et al.	500	42	8.5
1984	De Stephano et al.	100	14	14
1984	Sequeira et al.	450	36	8
1986	Char et al.	350	35	10
1991	Kontogeorgos et al.	470	49	10.4
1994	Uei et al.	1117	36	3.2
1994	Teramoto et al.	1000	31	3.1
1995	Camaris et al.	434	14	3.2
1999	Tomita & Gates	100	24	24
2001	Kurosaki et al.	692	79	11.4
2006	Buurman & Saeger	3038	306	10.4
2007	Kim et al.	120	8	6.7

A meta-analysis involving 3577 patients from 10 studies revealed an overall pituitary adenoma prevalence of 16.7%; 22.5% at autopsy; and 14.4% at imaging studies (CT and MRI). Imaging studies yielded a pituitary macroadenoma prevalence of 0.16–0.2%.[37]

Diagnosis and Complications of Cushing's Syndrome: A Consensus Statement

J Clin Endocrinol Metab, December 2003, 88(12):5593–5602

G. ARNALDI, A. ANGELI, A. B. ATKINSON, X. BERTAGNA, F. CAVAGNINI, G. P. CHROUSOS, G. A. FAVA, J. W. FINDLING, R. C. GAILLARD, A. B. GROSSMAN, B. KOLA, A. LACROIX, T. MANCINI, F. MANTERO, J. NEWELL-PRICE, L. K. NIEMAN, N. SONINO, M. L. VANCE, A. GIUSTINA, AND M. BOSCARO

Pituitary MRI. A pituitary MRI with gadolinium enhancement should be performed in all patients with ACTH-dependent CS. This procedure will reveal a discrete pituitary adenoma in up to 60% of patients (2, 20). In the patient with a classic clinical presentation and dynamic biochemical studies compatible with pituitary CS, the presence of a focal lesion (>6 mm) on pituitary MRI may provide a definitive diagnosis, and no further evaluation may be required. However, it is important to realize that 10% of the general population harbor incidental pituitary tumors disclosed on MRI, although the majority of these lesions are less than 5 mm in diameter.

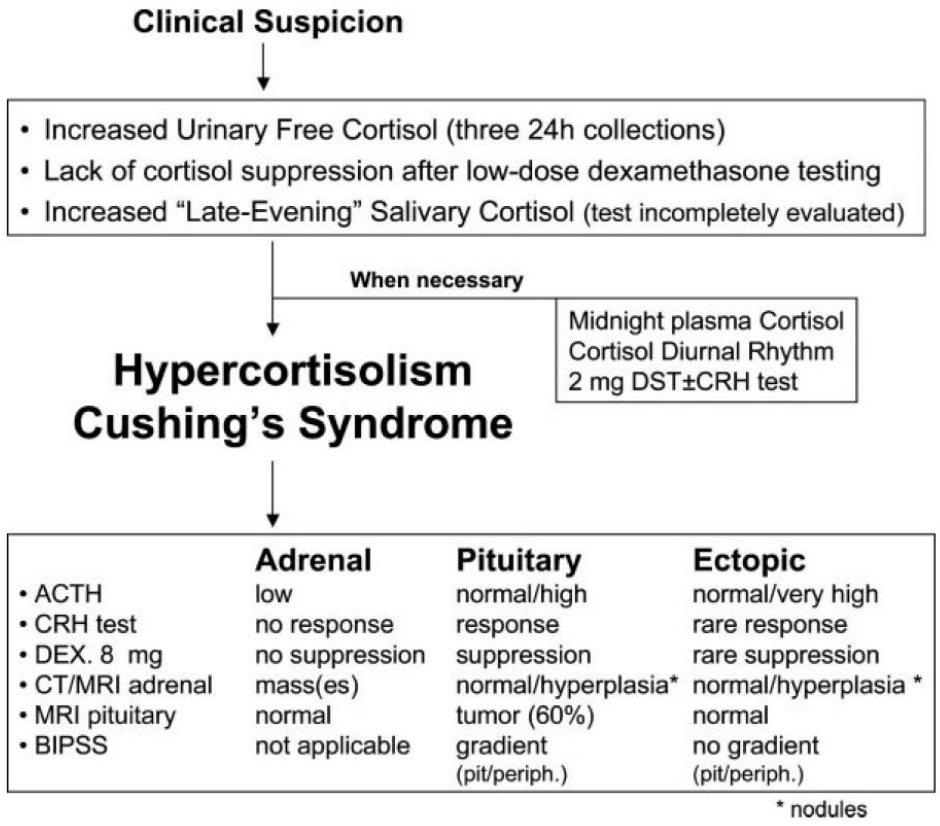

FIG. 1. Pathways to the diagnosis of CS.

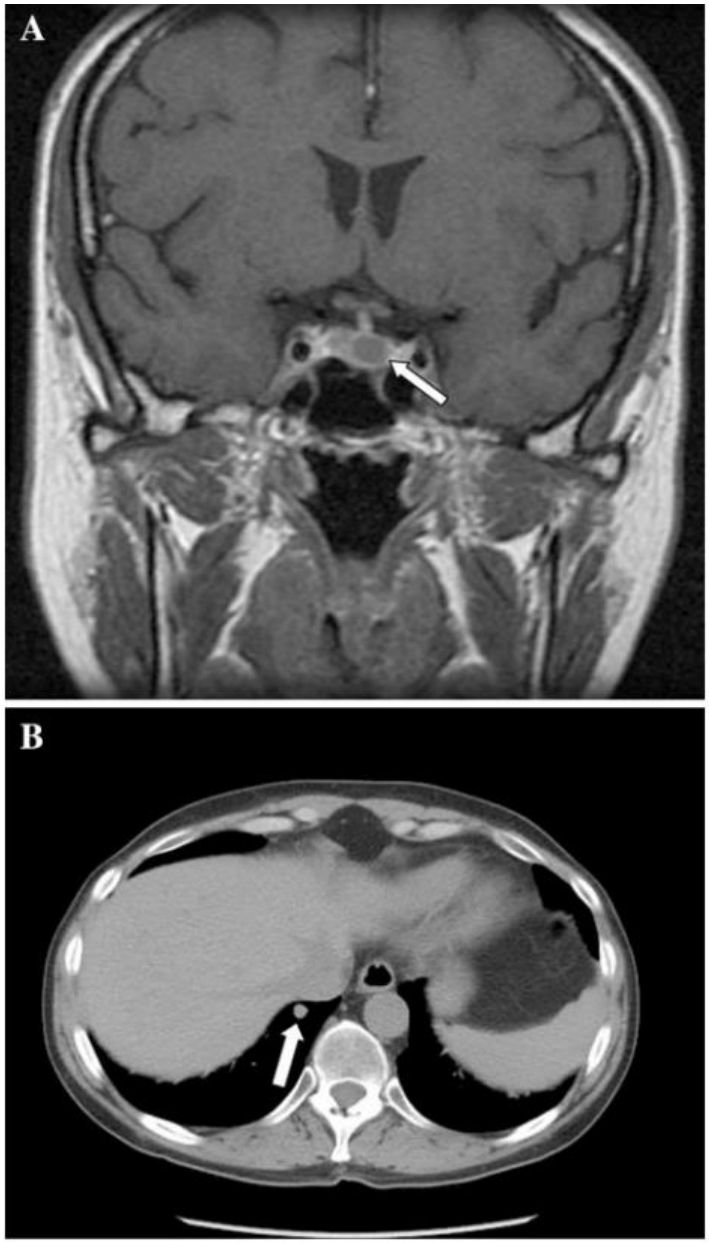

Fig. 1 Pituitary MRI showing a 7-mm left paramedian adenoma and slight ipsilateral stalk deviation (**a**). Chest CT. *Arrow* indicates a small (8 × 11 mm), contrast-enhanced, apparently non-specific nodule in the right posterior costophrenic excavation (**b**)

Differential diagnosis of ACTH-dependent hypercortisolism: imaging versus laboratory

Massimiliano Andrioli · Francesca Pecori Giraldi · Martina De Martin · Agnese Cattaneo · Chiara Carzaniga · Francesco Cavagnini

Pituitary (2009) 12:294–296

Abstract Differential diagnosis of ACTH-dependent Cushing's syndrome often presents major difficulties. Diagnostic troubles are increased by suboptimal specificity of endocrine tests, the rarity of ectopic ACTH secretion and the frequent incidental discovery of pituitary adenomas. A 43-year-old female reported with mild signs and symptoms of hypercortisolism, and initial hormonal tests and results of pituitary imaging (7-mm adenoma) were suggestive for Cushing's disease. However, inadequate response to corticotrophin-releasing hormone and failure to suppress after 8 mg dexamethasone pointed towards an ectopic source. Total body CT scan visualized only a small, non-specific nodule in the right posterior costophrenic excavation. Inferior petrosal sinus sampling revealed an absent center:periphery ACTH gradient but octreoscan and ^{18}F-FDG-PET-CT failed to detect abnormal tracer accumulation. We weighed results of the laboratory with those of imaging and decided to remove the lung nodule. Pathology identified a typical, ACTH-staining carcinoid and the diagnosis was confirmed by postsurgical hypoadrenalism. In conclusion, imaging may prove unsatisfactory or even misleading for the etiologial diagnosis of ACTH-dependent Cushing's syndrome and should therefore be interpreted only in context with results of hormonal dynamic testing.

Clinical and Biochemical Characteristics of Adrenocorticotropin-Secreting Macroadenomas

Y. Sammy Woo, Andrea M. Isidori, Winnie Z. Wat, Gregory A. Kaltsas, Fari Afshar, Ian Sabin, Paul J. Jenkins, John P. Monson, G. Michael Besser, and Ashley B. Grossman

J Clin Endocrinol Metab, August 2005, 90(8):4963–4969

TABLE 3. Responsivity to HDDST

	Macroadenomas	Microadenomas	*P* value
No. of patients with HDDST performed	17	174	
% suppression	57.6 ± 8.7 (95% CI, 39.2–76.0)	74.4 ± 2.1 (95% CI, 70.3–78.5)	0.02
% of patients having >50% suppression	64.7% (11/17)	87.4% (152/174)	0.023

CI, Confidence interval.

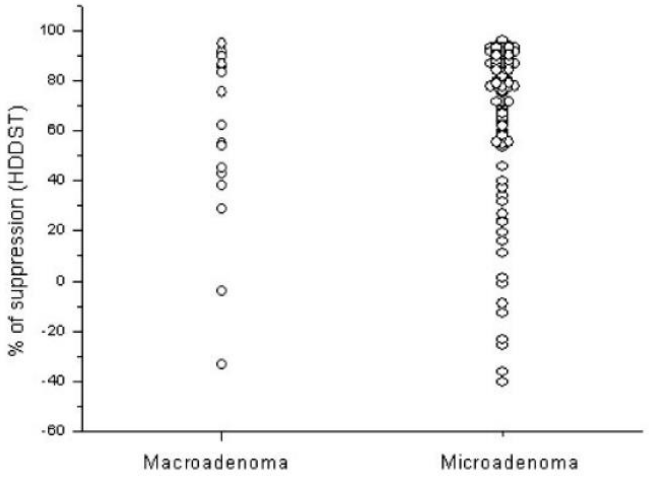

FIG. 3. Percent suppression of serum cortisol after a standard HDDST in Cushing's disease patients with macroadenomas and microadenomas.

The presence of an ACTH-secreting pituitary macroadenoma could lead to a paradoxical diagnostic gap.

In these patients, responses to both CRH stimulus and HDSST test are more frequently negative.

TABLE 4. Cortisol responsivity to CRH stimulation test

	Macroadenomas	Microadenomas	*P* value
No. of patients	17	73	
% of cortisol rise from baseline	30.6 ± 9.7% (95% CI, 10.2–51.1%)	54.9 ± 6.0% (95% CI, 43.0–66.8%)	0.071
Positive CRH test response	64.7% (11/17)	83.6% (61/73)	0.097

CI, Confidence interval.

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

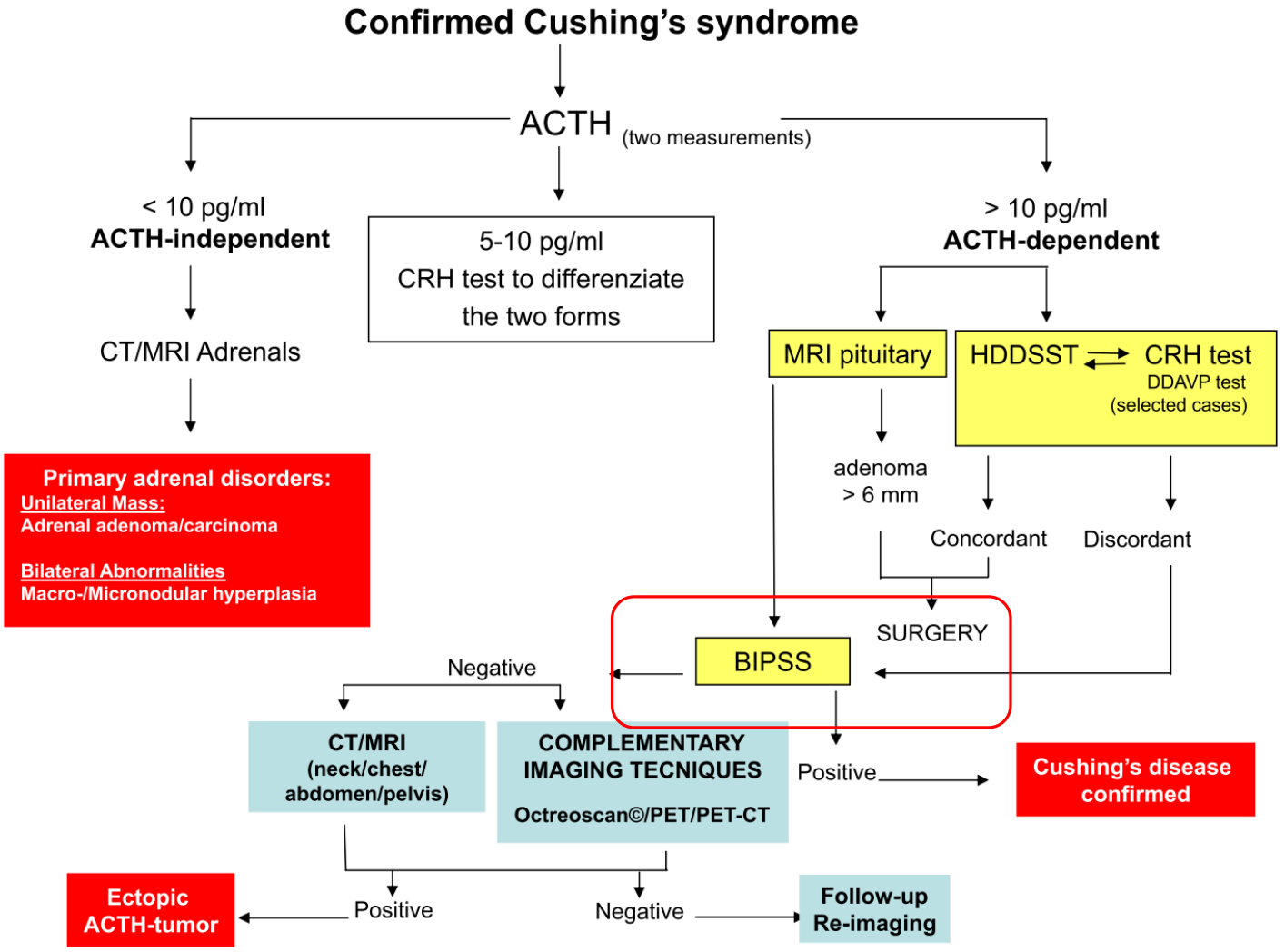

FIG. 1. Clinical decision-making flow chart.

The Role of Bilateral Inferior Petrosal Sinus Sampling in the Diagnosis of Cushing's Syndrome

ANDREA UTZ
BEVERLY M.K. BILLER

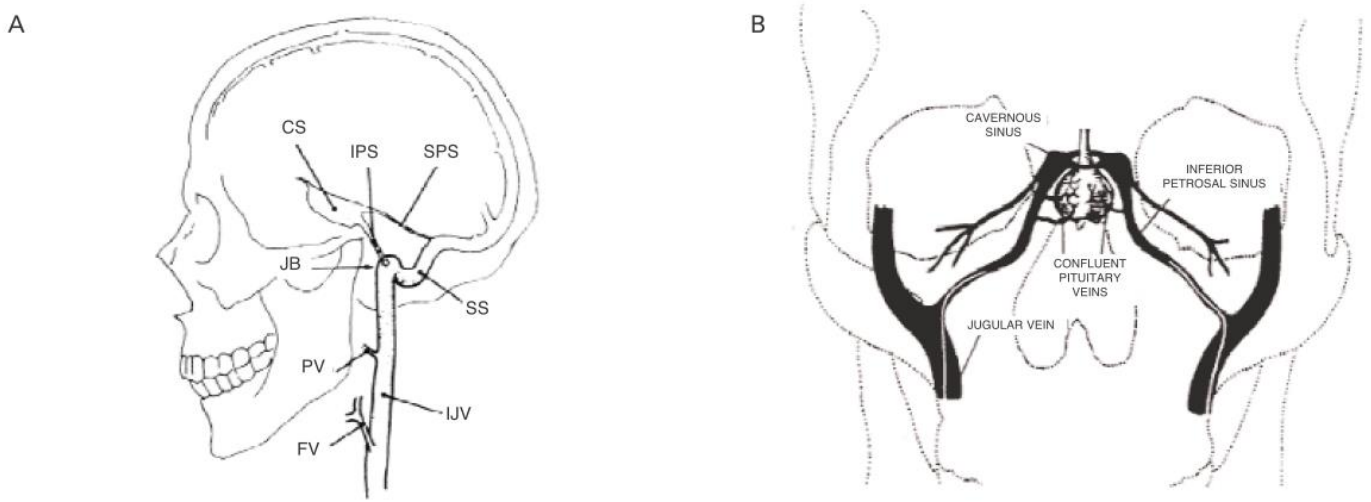

Figure 2. Schematic views of the pituitary venous drainage. **(A)** Sagittal, **(B)** Coronal CS: cavernous sinus, IPS: inferior petrosal sinus, SPS: superior petrosal sinus, JB: jugular bulb, SS: sigmoid sinus, IJV: internal jugular vein, FV: facial vein, PV: pharyngeal vein. [Reproduced from (14,37) with permission]

Table 2. Basic BIPSS procedure.

Conscious sedation
Sterile preparation of bilateral femoral veins at the groin with insertion of venous sheaths
Heparin infusion
Fluroscopically-guided placement of catheters into bilateral inferior petrosal sinuses
Contrast-enhanced fluoroscopy to confirm reflux into ipsilateral cavernous sinus
Obtain baseline blood samples
CRH injection
Obtain post-CRH injection blood samples
Catheter removal and groin pressure until venous hemostasis

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

On the contrary, bilateral inferior petrosal sinus sampling (BIPSS), considered the gold standard for establishing the origin of ACTH secretion, is recommended in patients with ACTH-dependent Cushing's syndrome whose clinical, biochemical, or radiological studies are discordant or equivocal (9, 11, 42). Moreover, in our opinion, BIPSS should also be performed in all patients with negative MRI. A ratio of central to peripheral ACTH of more than 2 in the basal state or more than 3 after CRH stimulation is consistent with Cushing's disease. However, this invasive and costly technique has technical difficulties and related risks, and it should be performed only in an experienced center. Technical problems and anomalous venous drainage may result in false-negative results (46).

Finally, the use of BIPPS appears of limited usefulness in identifying the localization of adenoma within the pituitary (17, 42, 51).

Desmopressin test during petrosal sinus sampling: a valuable tool to discriminate pituitary or ectopic ACTH-dependent Cushing's syndrome

European Journal of Endocrinology (2007) **157** 271–277

F Castinetti, I Morange, H Dufour[1], P Jaquet, B Conte-Devolx, N Girard[2] and T Brue

Abstract

Corticotropin-releasing hormone (CRH)-stimulated petrosal sinus sampling is currently the gold standard method for the differential diagnosis between pituitary and ectopic ACTH-dependent Cushing's syndrome. Our objective was to determine sensitivity and specificity of desmopressin test during petrosal sinus sampling.

Patients and methods: Forty-three patients had petrosal sinus sampling because of the lack of visible adenoma on magnetic resonance imaging (MRI) and/or because of discordant cortisol response to high-dose dexamethasone suppression test. ACTH sampling was performed in an antecubital vein, right and left petrosal sinuses, then at each location 5 and 10 min after injection of desmopressin. Diagnosis was based on the ACTH ratio between petrosal sinus and humeral vein ACTH after desmopressin test. Diagnosis was confirmed after surgery. A receiver operating characteristics curve was used to determine optimal sensitivity and specificity.

Results: Thirty-six patients had Cushing's disease (CD) and seven had ectopic ACTH secretion. A ratio >2 after desmopressin was found in 35 of the 36 cases of CD (sensitivity: 95%). A ratio ≤ 2 was found in the seven patients with ectopic ACTH secretion (specificity: 100%). Sinus sampling was ineffective in determining the left or right localization of the adenoma (sensitivity $= 50\%$). No major adverse effects were observed during or after the procedure.

Conclusion: Desmopressin test during petrosal sinus sampling is a safe and effective diagnostic procedure in ACTH-dependent Cushing's syndrome. It thus represents a valuable alternative to CRH.

Table 3 Performance (specificity and sensitivity) of the desmopressin test during inferior petrosal sinus sampling (IPSS) alone or coupled with corticotropin-releasing hormone (CRH), in the present study and published reports.

Author	Procedure	Patients with CD	Patients with EAS	Sensitivity	Specificity
Our study	Desmopressin	36	7	0.97	1
Machado *et al.* (26)	Desmopressin	50	5	0.92	1
Tsagarakis *et al.* (33)	CRH and desmopressin	47	7	0.97	1

Number of patients (*n*) described with Cushing's disease (CD) or ectopic ACTH secretion (EAS).

The Role of Bilateral Inferior Petrosal Sinus Sampling in the Diagnosis of Cushing's Syndrome

Arq Bras Endocrinol Metab 2007;51/8

Andrea Utz
Beverly M.K. Biller

Table 4. Pitfalls in BIPSS.

False positives (BIPSS predicts pituitary Cushing's in the absence of a corticotroph adenoma):	**<1%**
Lack of suppression of normal corticotrophs:	
Cyclic Cushing's syndrome	
Cortisol blocking drugs (ketoconazole, metyrapone, mitotane, aminoglutethamide)	
Bilateral adrenalectomy	
Normal individuals with factitious hypercortisolemia	
Pseudo-Cushing's syndrome	
Adrenal Cushing's syndrome (with mild hypercortisolemia)	
Ectopic CRH-secreting tumor	
False negative (BIPSS predicts non-pituitary Cushing's in the presence of a corticotroph adenoma):	**2-4%**
Aberrant pituitary venous drainage	
Incorrect BIPSS technique (inability to cannulate each inferior petrosal sinus or dislodgement during the procedure)	

Identification of Patients with Cushing's Disease with Negative Pituitary Adrenocorticotropin Gradients during Inferior Petrosal Sinus Sampling: Prolactin as an Index of Pituitary Venous Effluent

JAMES W. FINDLING, MICHAEL E. KEHOE, AND HERSHEL RAFF

J Clin Endocrinol Metab, December 2004, 89(12):6005–6009

Inferior petrosal sinus sampling for ACTH differentiates pituitary ACTH-dependent Cushing's (CD) from the ectopic ACTH syndrome (EAS). Petrosal sinus to peripheral (IPS:P) ACTH ratios greater than 2.0 in the basal state or a peak greater than 3.0 after CRH are diagnostic of CD. However, false-negative rates of 1–10% have been reported. We report three patients with features of CD with peak IPS:P ACTH ratios less than 3.0 after CRH suggesting EAS. We compared IPS:P prolactin (PRL) as an index of pituitary venous effluent in these three index cases with 44 patients with CD and five with EAS. The dominant basal IPS:P PRL ratio was greater than 1.8 in all 49 patients but was less than 1.2 in the three index cases. The IPS:P ACTH ratio normalized to IPS:P PRL was greater than 0.8 in all CD patients but was less than 0.6 in EAS patients. The IPS:P ACTH ratios normalized to IPS:P PRL were greater than 1.2 in the index cases, which was similar to those with CD. The three index cases had clinical and biochemical remissions after pituitary surgery.

PRL is an index of pituitary venous effluent during inferior petrosal sinus sampling in patients with CD who fail to have a peak IPS:P ACTH ratio greater than 3.0 after CRH. IPS:P PRL should be measured when results indicate EAS. (*J Clin Endocrinol Metab* 89: 6005–6009, 2004)

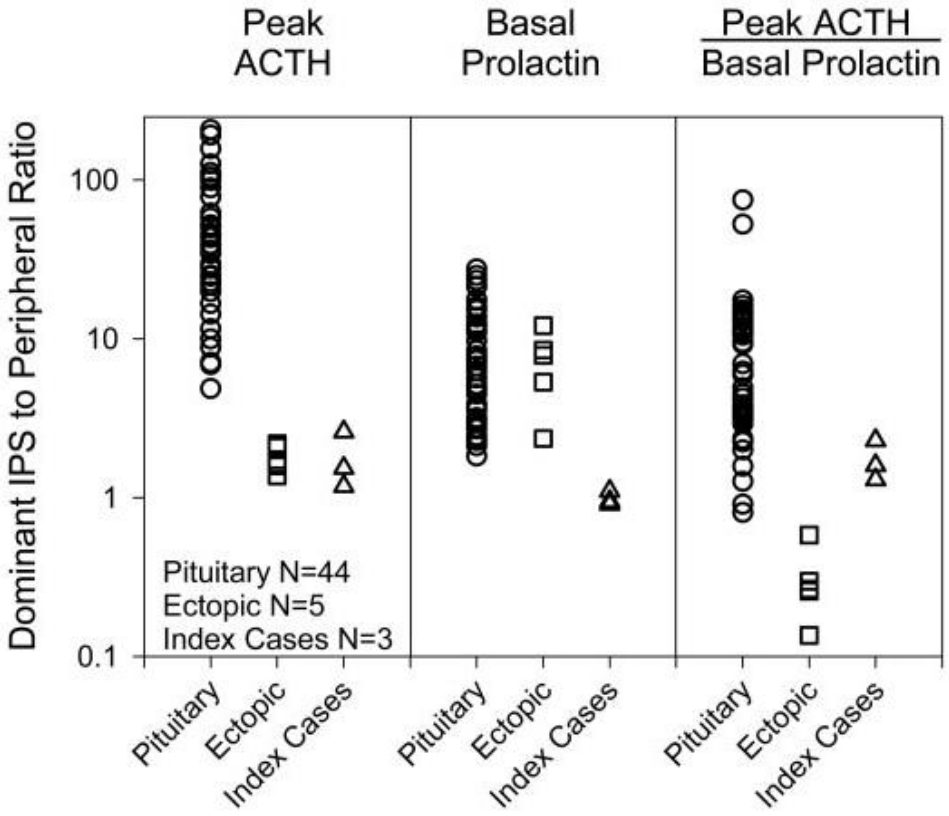

FIG. 2. IPS:P ratios for patients with proven Cushing's disease (pituitary; *circles*), ectopic ACTH syndrome (ectopic; *squares*), and the three index cases (*triangles*). The *left panel* is the post-CRH IPS to peripheral ACTH ratio. The *middle panel* is the basal (pre-CRH) IPS to peripheral PRL ratio from the same sites as the ACTH ratios. The *right panel* is the *left panel* divided by the *middle panel* giving IPS:P ratios normalized to the ipsilateral PRL ratio. Notice the overlap of the IPS-peripheral ACTH ratio for the ectopic ACTH and index cases, that the index cases had IPS-peripheral PRL ratios that were lower than in pituitary and ectopic ACTH, and that normalizing the peak ACTH IPS:P ratio to the ipsilateral PRL ratio led to results in index cases (with subsequently proven Cushing's disease) similar to prospectively proven pituitary Cushing's disease.

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, December 2011, 96(12):3687–3694

Findling *et al.* (8) reported on the utility of prolactin in three index cases, 44 patients with proven Cushing's disease and five patients with proven EAS. They concluded that an inferior petrosal sinus to peripheral (IPS/P) prolactin ratio of greater than 1.8 before CRH administration indicated successful catheterization when calculated on the same side as the peak ACTH IPS/P ratio. In another recent series, Mulligan *et al.* (9) evaluated 35 patients with Cushing's disease and one with EAS who underwent IPSS and found that false-negative IPSS ACTH results had a prolactin IPS/P ratio of less than 1.3. Furthermore, in the Findling series, after normalizing the peak ACTH IPS/P ratio by dividing it by this prolactin IPS/P ratio, values greater than 0.8 suggested Cushing's disease, whereas a ratio less than 0.6 indicated EAS.

8. **Findling JW, Kehoe ME, Raff H** 2004 Identification of patients with Cushing's disease with negative pituitary adrenocorticotropin gradients during inferior petrosal sinus sampling: Prolactin as an index of pituitary venous effluent. J Clin Endocrinol Metab 89:6005–6009

9. **Mulligan GB, Eray E, Faiman C, Gupta M, Pineyro MM, Makdissi A, Suh JH, Masaryk TJ, Prayson R, Weil RJ, Hamrahian AH** 2011 Reduction of false-negative results in inferior petrosal sinus sampling with simultaneous prolactin and corticotrophin measurement. Endocr Pract 17:33–40

The ectopic ACTH syndrome

Rev Endocr Metab Disord (2010) 11:117–126

Krystallenia I. Alexandraki · Ashley B. Grossman

Biochemical tumoural markers may be associated with NETs. Calcitonin and gastrin have been both found to be the most commonly elevated tumour markers, regardless of tumour type, in all recent series [2, 14]; calcitonin has been

(GHRH) [10, 44]. In general, one or other of such tumour markers is increased in 72% of patients with EAS [15]. Calcitonin and urinary catecholamines need to be measured to exclude MTC and phaeochromocytoma as a source respectively [19].

Localization of the ectopic ACTH secreting tumor

ANDREA M. ISIDORI
ANDREA LENZI

Arq Bras Endocrinol Metab 2007;51/8

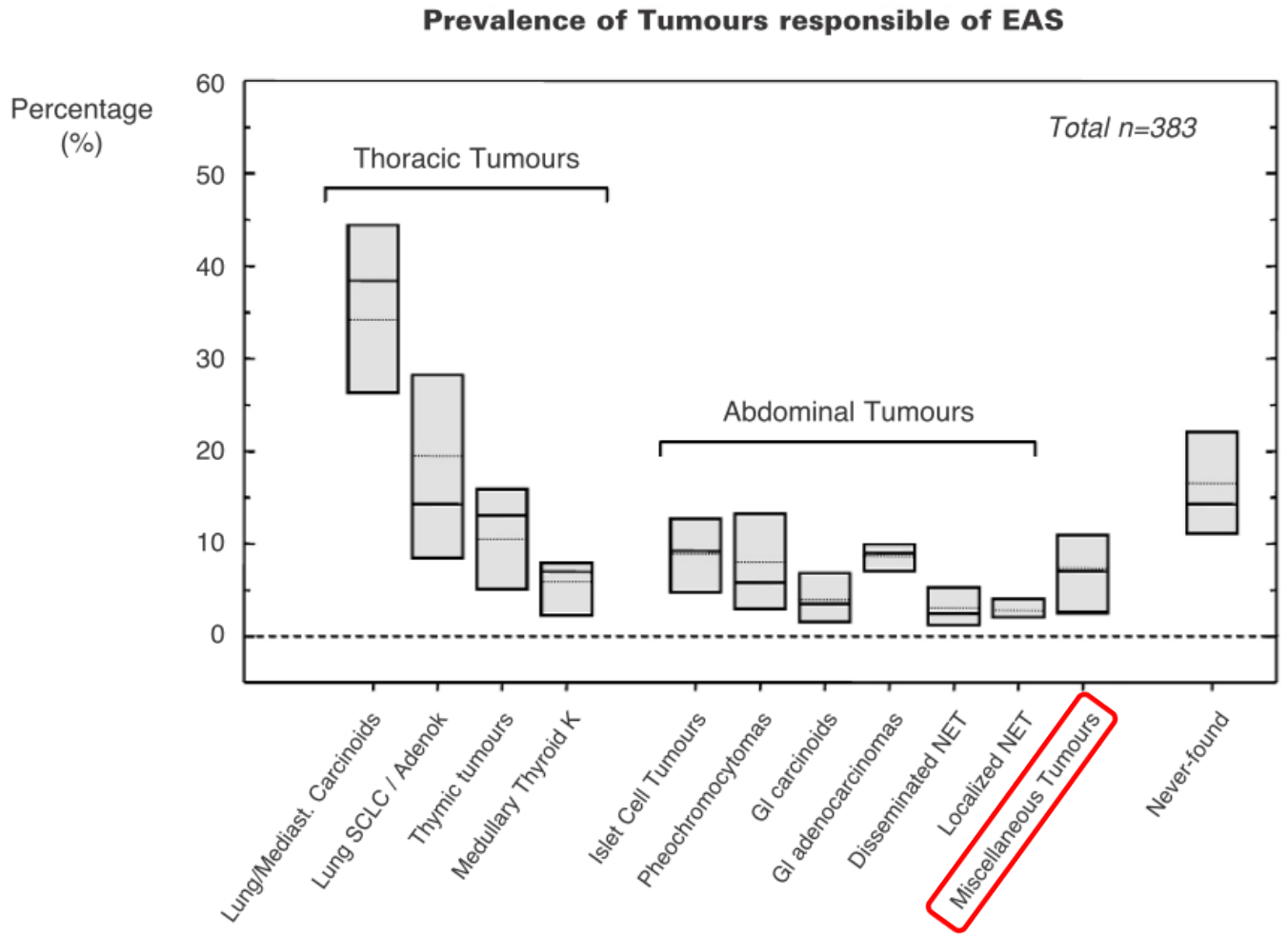

Figure 1. Distribution of the most frequent source (> 2%) of ectopic ACTH secretion in a group of 383 patients with EAS syndrome based on the following published series: Aniszewski et al. (16), Findling et al. (13), Imura et al. (15), Doppman et al. (12), Howlett et al. (14), Ilias et al. (11), Isidori et al. (9), Salgado et al. (17).

Table 1. Tumours rarely associated with EAS. The frequency is calculated among all reported cases in literature.

	FREQUENCY 1–3%	FREQUENCY ≤ 1%
Tumours associated with EAS	Ovarian carcinoma	Esophageal carcinoma
	Colonic/anal carcinoma	Kidney tumor
	Prostate	Hepatocarcinoma
	Uterine cervix carcinoma	Breast carcinoma
	Neuroblastoma	Salivary gland tumor
		Mesothelioma
		Lymphoma
	[Ectopic pituitary adenoma]	Melanoma
		Leydig cell tumor
		Larynx carcinoma
		Gallbladder tumours

Imaging of the **thorax, abdomen and pelvis with CT** will yield the highest detection rate in searching for an occult ACTH-secreting neoplasm.

Most SCLCs are detected using **plain chest X ray**, **CT** and/or **MRI**.

Bronchial carcinoids can be relatively small and thus be missed with conventional imaging; however, early application of 2–3 mm **high-resolution CT chest scans**, particularly with the new generation of multidetector CT, identifies the vast majority of such cases.

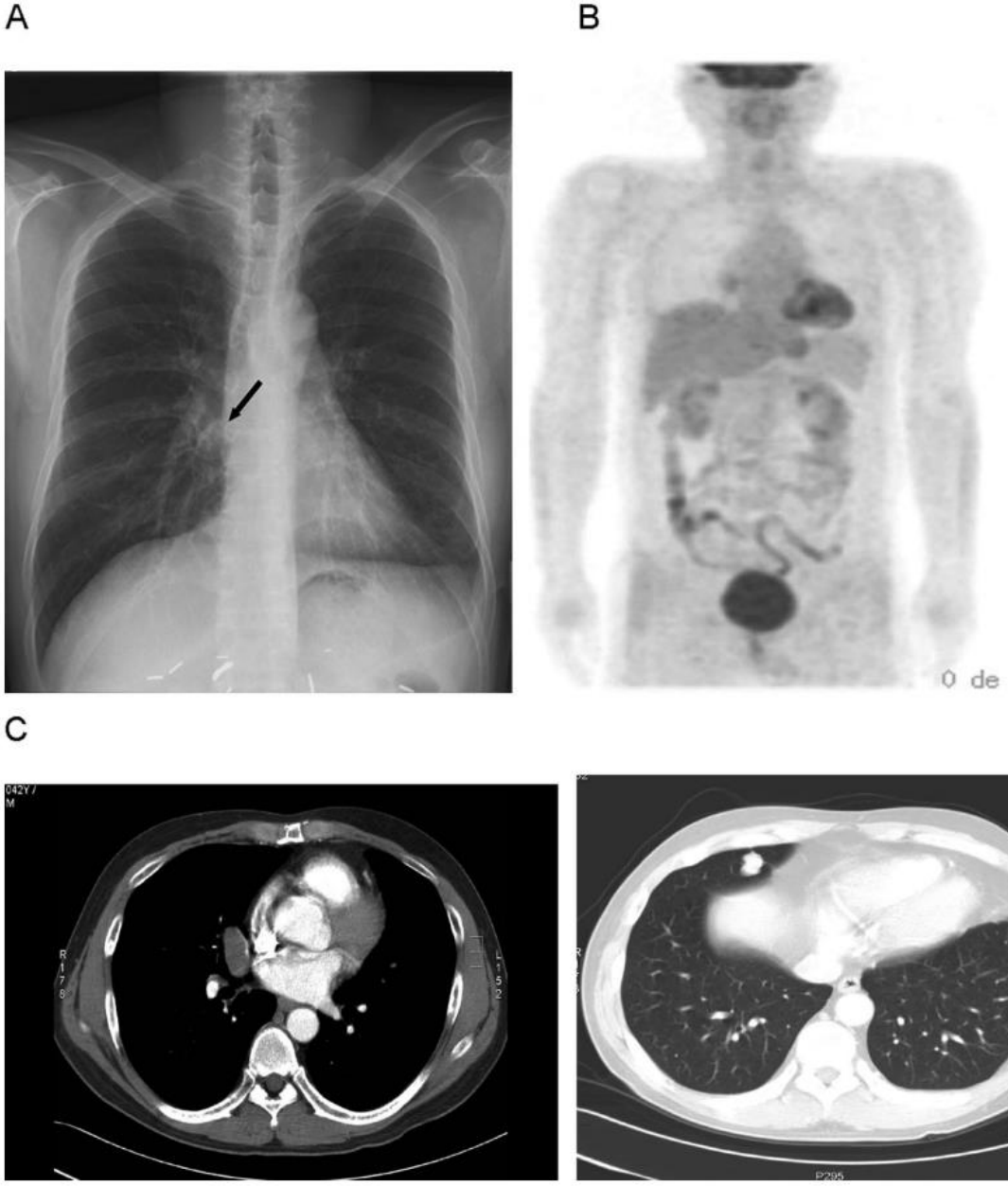

FIGURE 1. *A*, chest radiograph showing a 3-cm sized round opacity in the right lung; *B*, positron emission tomography with ^{18}fluorodeoxyglucose demonstrating hypermetabolism (mSUV = 2.6) on right middle lobe; *C*, chest CT imaging of the chest showing nodules with regular margin in the right middle lobe (left: the biggest nodule, right: second nodule, third nodule was not shown).

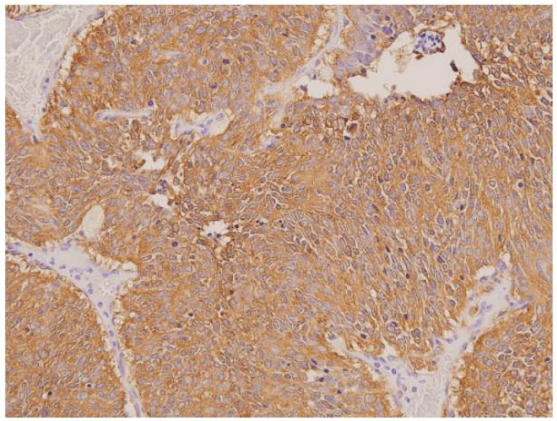

FIGURE 2. The specimen was immunohistochemical stained by ACTH (×400).

Ectopic Cushing's syndrome due to a mesenteric neuroendocrine tumour

Ann R Coll Surg Engl 2012; **94**: e251–e253

N Mashoori, AH Rabani, AR Kazemeini

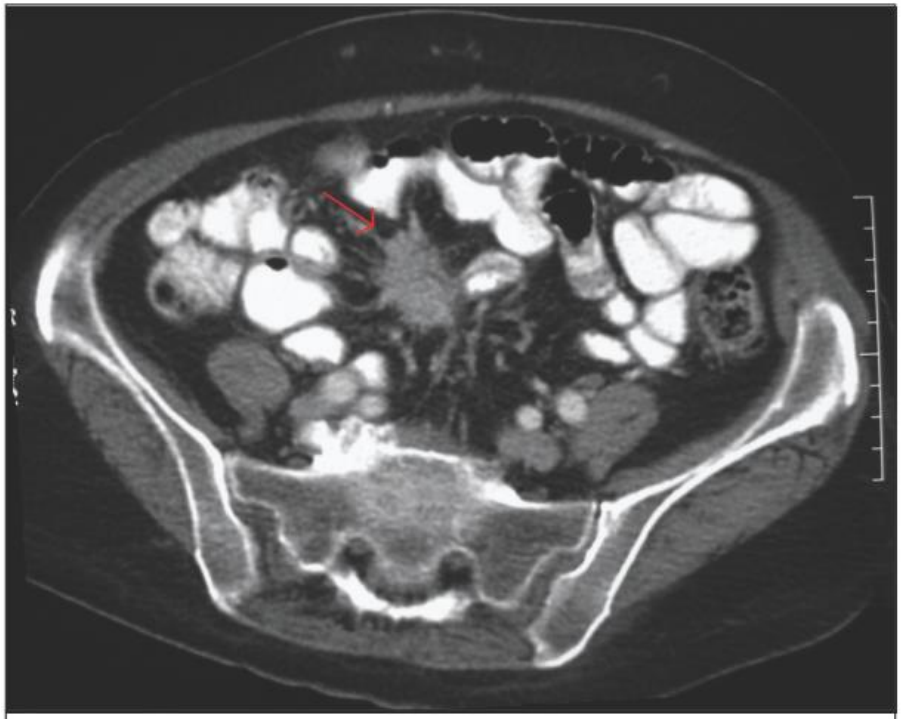

Figure 1 Mesenteric mass

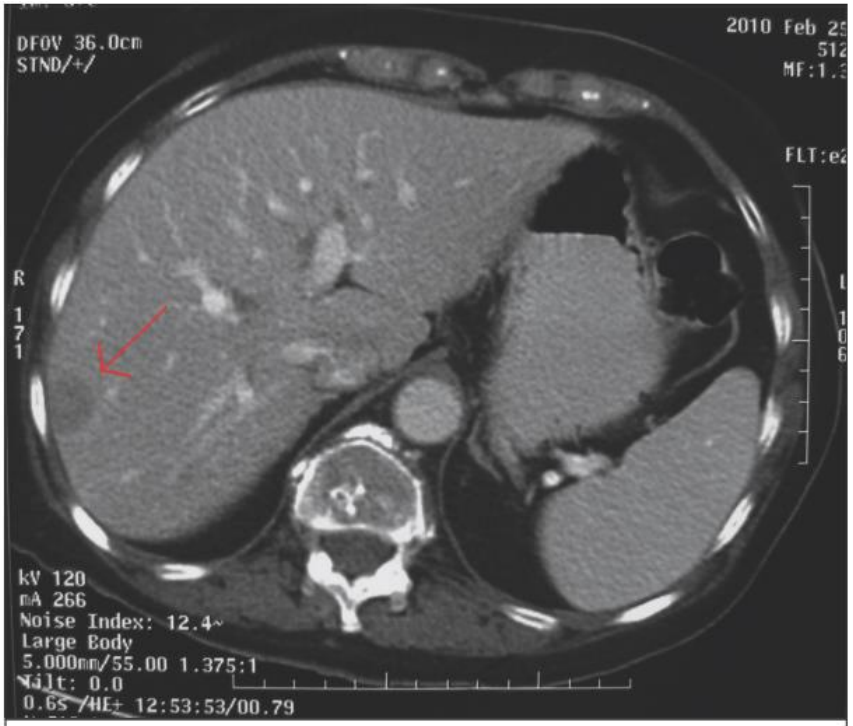

Figure 2 Liver metastases

MRI is useful in resolving equivocal CT findings or where CT is negative and a high index of suspicion persists, particularly for tumours within the abdomen.

In the chest, MRI is of limited value in identifying bronchial carcinoids but may be of value in imaging the **mediastinum for thymic lesions**.

MRI of the chest may also provide some additional benefit because some **bronchial carcinoids** have a **central location** and may be mistaken on CT scanning for a blood vessel.

Detection of ACTH-Producing Bronchial Carcinoid Tumors:
MR Imaging vs CT

John L. Doppman[1,2]
Harvey I. Pass[3]
Lynnette K. Nieman[4]
James W. Findling[5]
Andrew J. Dwyer[1]
Irwin M. Feuerstein[1,2]
Alexander Ling[1,2]
William D. Travis[6]
Gordon B. Cutler, Jr.[4]
George P. Chrousos[4]
D. Lynn Loriaux[4]

AJR 156:39–43, January 1991

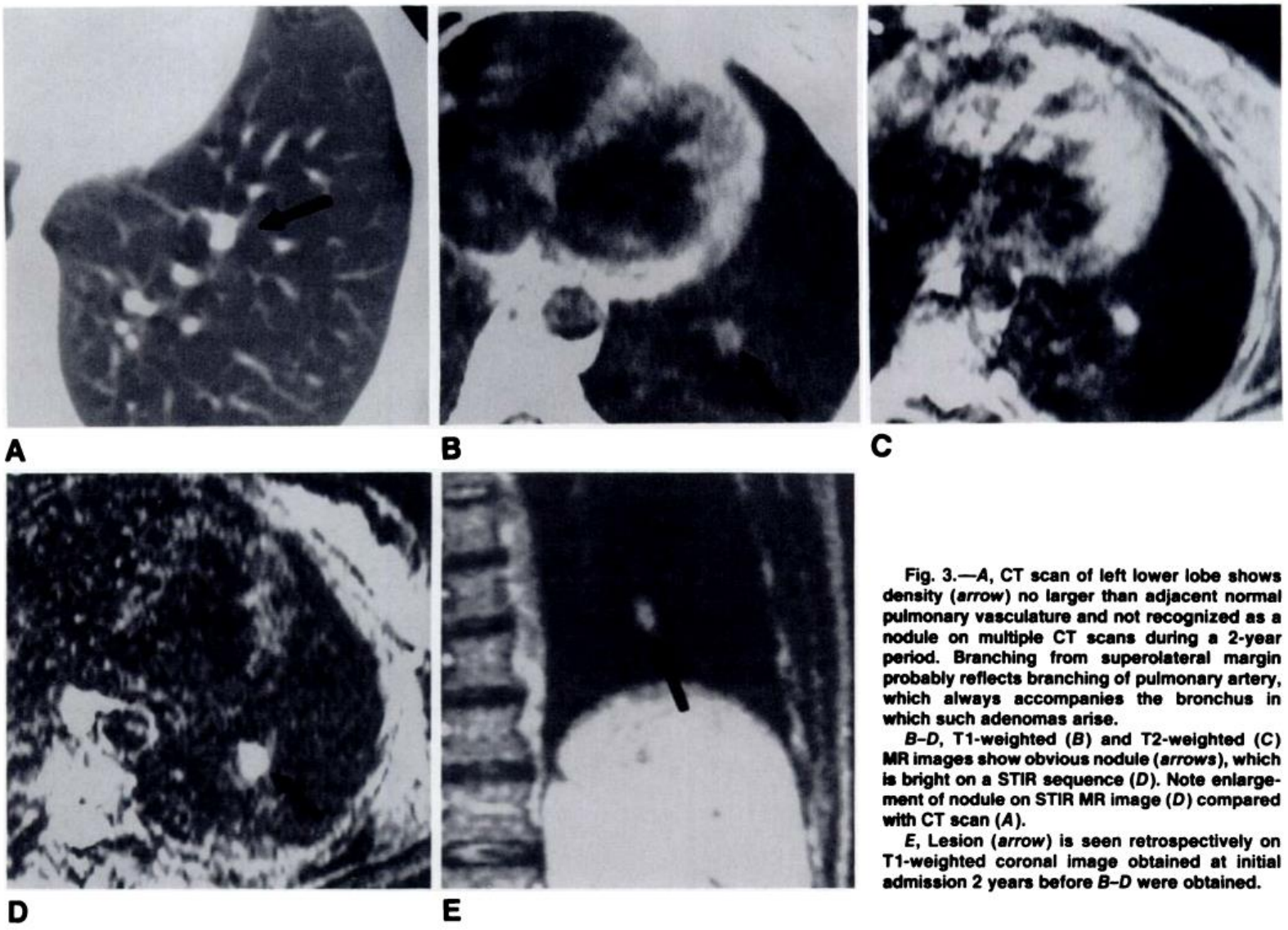

Fig. 3.—*A*, CT scan of left lower lobe shows density (*arrow*) no larger than adjacent normal pulmonary vasculature and not recognized as a nodule on multiple CT scans during a 2-year period. Branching from superolateral margin probably reflects branching of pulmonary artery, which always accompanies the bronchus in which such adenomas arise.

***B–D*, T1-weighted (*B*) and T2-weighted (*C*) MR images show obvious nodule (*arrows*), which is bright on a STIR sequence (*D*). Note enlargement of nodule on STIR MR image (*D*) compared with CT scan (*A*).**

***E*, Lesion (*arrow*) is seen retrospectively on T1-weighted coronal image obtained at initial admission 2 years before *B–D* were obtained.**

The Role of [^{18}F]Fluorodeoxyglucose Positron Emission Tomography and [^{111}In]-Diethylenetriaminepentaacetate-D-Phe-Pentetreotide Scintigraphy in the Localization of Ectopic Adrenocorticotropin-Secreting Tumors Causing Cushing's Syndrome

J Clin Endocrinol Metab, May 2004, 89(5):2214–2221

KAREL PACAK, IOANNIS ILIAS, CLARA C. CHEN, JORGE A. CARRASQUILLO, MILLIE WHATLEY, AND LYNNETTE K. NIEMAN

Conventional imaging modalities cannot localize the source of ACTH in 30–50% of patients with Cushing's syndrome (CS) caused by ectopic ACTH secretion (EAS). We prospectively evaluated whether [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) or [^{111}In]-diethylenetriamine-pentaacetate-D-Phe-pentetreotide (OCT) at higher than standard doses of radionuclide (18 mCi; H-OCT), can detect these tumors. Seventeen patients with presumed EAS based on inferior petrosal sinus sampling results underwent routine anatomical imaging studies [computed tomography (CT) and magnetic resonance imaging (MRI)] and OCT scintigraphy with 6 mCi (L-OCT). Research studies included FDG-PET in all patients and H-OCT if L-OCT was negative. ACTH-secreting tumors were localized in 13 patients and were occult in four. Nine of 17 CT, six of 16 MRI, six of 17 FDG-PET, eight of 17 L-OCT, and one of nine H-OCT studies were true positives. The sensitivity of CT and combined H- and L-OCT scintigraphy was higher (both 53%; 95% confidence interval, 29–76%) than that of MRI (37%; 95% confidence interval, 16–64%) or FDG-PET (35%; 95% confidence interval, 15–61%). FDG-PET did not detect tumors that were occult on CT/MRI. L-OCT was a useful complementary modality to CT and MRI. As H-OCT identified a tumor in one patient with otherwise negative imaging, it should be considered only when other imaging modalities fail to localize the ACTH-secreting tumor in patients with EAS. (*J Clin Endocrinol Metab* 89: 2214–2221, 2004)

^{18}Flurodeoxyglucose positron emission tomography in the localization of ectopic ACTH-secreting neuroendocrine tumours

Clinical Endocrinology (2006) **64**, 371–374

J. Kumar*, M. Spring†, P. V. Carroll*, S. F. Barrington‡ and J. K. Powrie*

Patients Three patients with ectopic ACTH-dependent Cushing's syndrome with varying difficulty in NET localization are included in the report.

Table 1. Biochemical investigation of the three patients with ectopic ACTH secretion

		Time 0900	Post-LDDST	Post-HDDST	Left petrosal (post-CRH)	Right petrosal (post-CRH)	Peripheral blood (post-CRH)
					(BSIPSS)	(BSIPSS)	(BSIPSS)
Patient 1	Cortisol						
	(120–500 nmol/l)	3046	2676				
	ACTH	292	224		224	229	173
	(10–36 ng/l)						
Patient 2	Cortisol	845	898	728			
	ACTH	197			683	677	676
Patient 3	Cortisol	< 30					
	ACTH	1704	1394	1277			

LDDST, low-dose dexamethasone suppression test, 0·5 mg dexamethasone 6-hourly for 48 h.
HDDST, high-dose dexamethasone suppression test, 2 mg dexamethasone 6-hourly for 48 h.
BSIPSS, bilateral simultaneous inferior petrosal sinus sampling.
CRH, corticotrophin-releasing hormone.
Note: patient 3 had previously undergone bilateral adrenalectomy, the morning endogenous cortisol before hydrocortisone therapy was therefore < 30 nmol/l, and ACTH was measured rather than cortisol during the dexamethasone suppression tests.

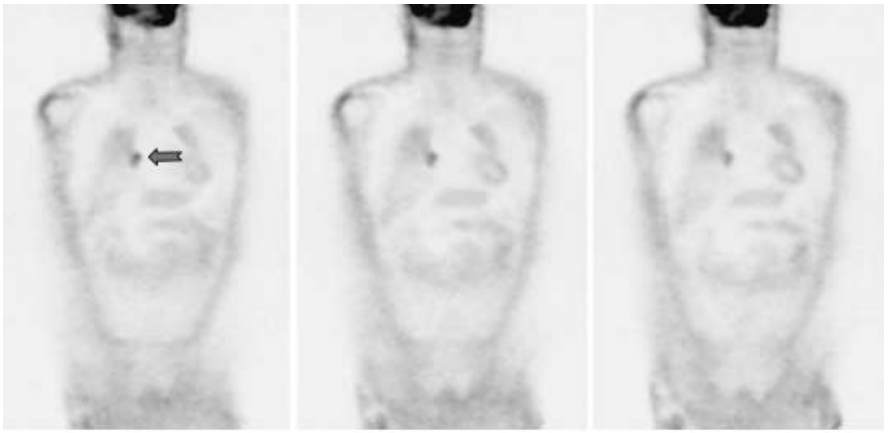

Fig. 1 ^{18}FDG-PET study of patient 1. The study demonstrates an area of increased FDG uptake adjacent to the right atrium (arrow). Cardiac-gated MRI confirmed the presence of a lesion, which was surgically removed and was shown to have carcinoid histopathological characteristics.

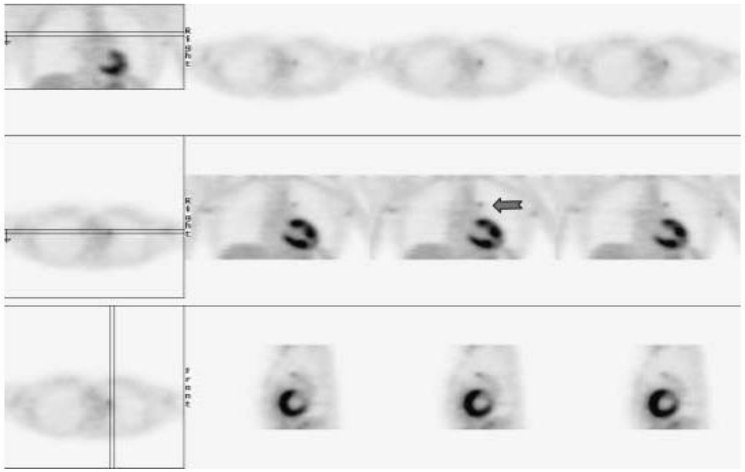

Fig. 2 ^{18}FDG-PET study of patient 2. The study demonstrates an area of increased FDG uptake near the hilum of the left lung (arrow). The lesion was subsequently resected and shown to be a neuroendocrine tumour with ACTH immunostaining.

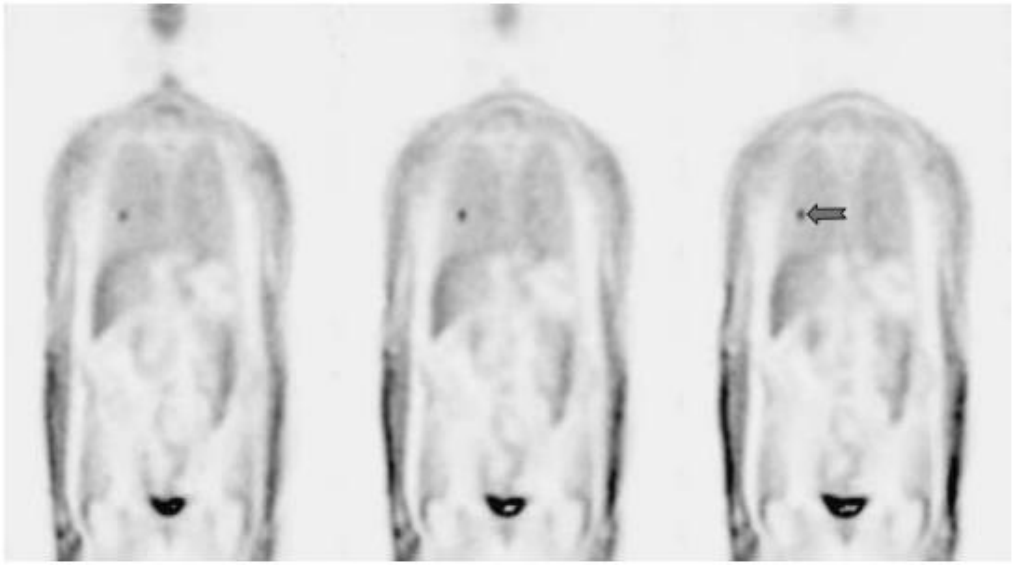

Fig. 3 ^{18}FDG-PET study of patient 3. The study demonstrates an area of increased FDG uptake (arrow) in the mid-zone of the right lung. This was subsequently removed and shown to be an ACTH-staining NET.

Utility of Various Functional and Anatomic Imaging Modalities for Detection of Ectopic Adrenocorticotropin-Secreting Tumors

J Clin Endocrinol Metab, March 2010, 95(3):1207–1219

Marina S. Zemskova,* Bhaskar Gundabolu,* Ninet Sinaii, Clara C. Chen, Jorge A. Carrasquillo, Millie Whatley, Iffat Chowdhury, Ahmed M. Gharib, and Lynnette K. Nieman

Context: Because ectopic ACTH-secreting (EAS) tumors are often occult, improved imaging is needed.

Objective: Our objective was to evaluate the utility of [^{111}In-DTPA-D-Phe]pentetreotide scintigraphy [octreotide (OCT)] imaging at 6 mCi [low OCT (LOCT)] and 18 mCi [high OCT (HOCT)], [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) and [^{18}F]L-3,4-dihydroxyphenylalanine (F-DOPA)-PET scans, computed tomography (CT), and magnetic resonance imaging (MRI).

Design and Setting: The study was a prospective evaluation at a clinical research center.

Patients: Forty-one subjects participated, 30 (17 female) with resected EAS tumors and 11 (three female) with occult EAS, based on inferior petrosal sinus sampling results and imaging studies.

Intervention: Intervention included CT and MRI of neck, chest, abdomen, LOCT (with or without HOCT) and FDG- or F-DOPA-PET without CT every 6–12 months.

Main Outcome Measure: Tumor identification was the main outcome measure.

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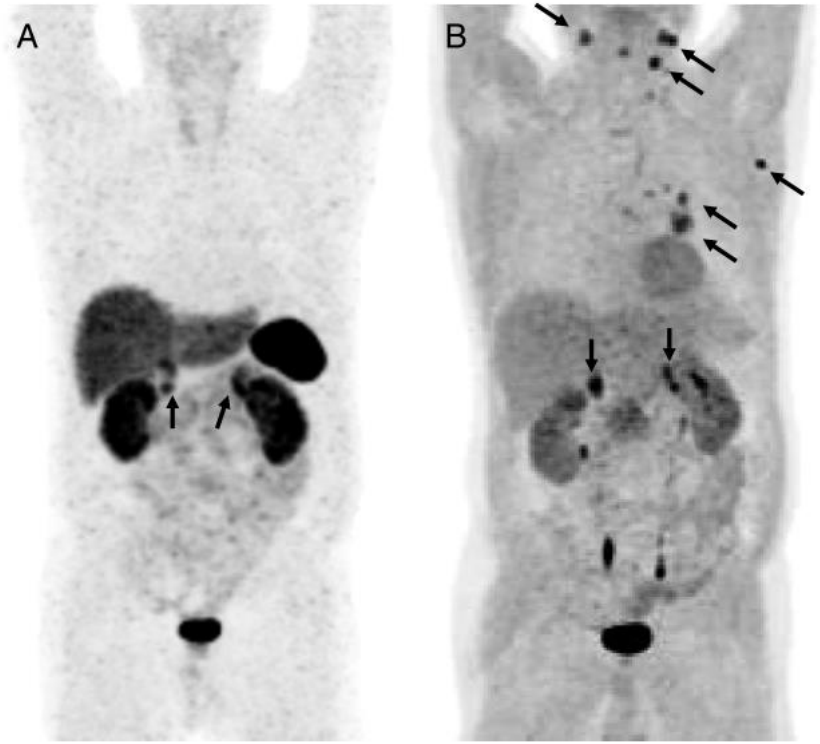
TABLE 3. Sensitivity, PPV, and proportion of falsely positive lesions for each modality in subjects whose tumor was identified and in all subjects with EAS

	CT	MRI	LOCT	HOCT	FDG- PET	DOPA-PET
Tumor-identified patients (n = 30)						
A. Sensitivity, % (95% CI) (B below × 100)	93 (79–98)	90 (74–96)	57 (39–73)	50 (25–75)	64 (35–85)	55 (28–79)
B. No. of patients with TP lesions/no. with imaging study	28/30	26/29	16/28	6/12	7/11	6/11
C. PPV, % (D below × 100)	66	74	79	89	53	100
D. No. of TP lesions/no. of total lesions on imaging	48/73	37/50	22/28	8/9	8/15	8/8
E. Proportion of FP lesions, %	34	26	21	11	47	0
All patients with EAS (n = 41)						
A. Sensitivity, % (95% CI) (B below × 100)	68 (53–80)	65 (50–78)	41 (27–57)	30 (14–52)	50 (27–73)	46 (23–71)
B. No. of patients with TP lesions/no. with imaging study	28/41	26/40	16/39	6/20	7/14	6/13
C. PPV, % (D below × 100)	57	67	76	73	50	89
D. No. of TP lesions/no. of total lesions on imaging	48/84[a]	37/55[a]	22/29	8/11	8/16	8/9
E. Proportion of FP lesions, %	43	33	27	27	50	11

F, False positive; TP, true positive.

[a] Patient 33 had lesion detected by CT and MRI with inconclusive characteristics but in the same location; this was not considered to be true positive lesion. Patient 41 had elongated inhomogeneous lesion detected by CT and MRI in the same location; this was not considered to be true positive lesion.

Conclusions: High sensitivity and PPV suggest thoracic CT/MRI plus LOCT scans for initial imaging, with lesion confirmation by two modalities. (***J Clin Endocrinol Metab*** **95: 1207–1219, 2010)**



^{18}F-DOPA PET/CT But Not ^{68}Ga-DOTA-TOC PET/CT Revealed the Underlying Cause of Ectopic Cushing Syndrome

Camilla Schalin-Jäntti, PhD, MD,† Aapo Ahonen, PhD, MD,‡§ and Marko Seppänen, PhD, MD||*

(*Clin Nucl Med* 2012;37: 904–905)

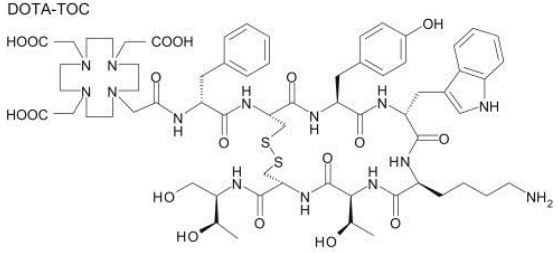
FIGURE 1. ^{18}F-DOPA PET/CT but not ^{68}Ga-DOTA-TOC PET/CT revealed the underlying cause of ectopic Cushing syndrome in a 61-year-old man. The patient presented with rapid weight gain, swollen legs, and sleep disturbances. His plasma potassium level was 2.7 mM (reference range, 3.3–4.9 mM), 24-hour urinary cortisol level was 13,124 nmol (reference range, 30–144 nmol), and plasma adrenocorticotropin (ACTH) level was 61 ng/L (reference range, <48 g/L). To identify the underlying cause, CT was performed. It demonstrated prominent lymph nodes in the left lung hilus and hyperplastic adrenals but no primary tumor. Next, ^{68}Ga-DOTA-TOC PET/CT, which is recommended as the first-line PET imaging, was performed, but it was not diagnostic. Imaging with ^{18}F-DOPA PET/CT revealed the underlying cause. Bronchial neuroendocrine tumors (NETs), small cell lung carcinomas, and pancreatic and thymic NETs often underlie ectopic Cushing syndrome.[1–3] The underlying tumor is often difficult to localize or may remain undiagnosed.[2] As in the present case, conventional imaging is often unsuccessful. ^{18}F-FDG PET is of limited value for the assessment of NETs.[2,3] Recently, PET/CT imaging with ^{68}Ga-DOTA peptides was recommended as the first-line PET imaging and considered more accurate than imaging with ^{18}F-DOPA.[4] However, in the present case of severe ectopic Cushing syndrome, ^{68}Ga-DOTA-TOC PET/CT (**A**) did not reveal the underlying cause and demonstrated heavy uptake in the adrenals only (arrows). This was interpreted as adrenal hyperplasia because of the massive stimulation of adrenal cortisol secretion by ACTH.[5] Next, ^{18}F-DOPA PET/CT (**B**) was performed, and this investigation revealed several pathological lesions in the left lung (arrow), mediastinum (arrow), neck (arrows), left armpit (arrow), and adrenals (arrows). The patient experienced severe hypercortisolism, which was not controlled by metyrapone treatment. Bilateral adrenalectomy was performed, and the metastatic lesion in the armpit revealed by ^{18}F-DOPA PET/CT was removed during the same operation. Histopathology of the metastatic lesion from the left armpit and both adrenals revealed a rather uncommon cause of ectopic Cushing syndrome. In addition to the hyperplastic changes, both adrenals also demonstrated metastatic lesions. The patient did not have a thymic NET or small cell lung carcinoma, although he was a heavy smoker. The morphological characteristics and immunohistochemistry of the specimens were compatible with poorly differentiated pulmonary large cell neuroendocrine carcinoma (LCNEC).[6] The Ki-67 proliferation index was high (70%), and TTF-1 (a marker of lung carcinoma) was strongly positive. As previously reported, careful examination can diagnose LCNEC of the lung at the metastatic site.[6] After adrenalectomy, hydrocortisone and fludrocortisone replacement therapy was initiated. The patient was referred for carboplatin and etoposide treatment of the underlying neuroendocrine carcinoma. This case underlines the need for multiple imaging in ectopic Cushing syndrome. Conventional imaging often fails, and ^{68}Ga-DOTA-TOC PET/CT should not be regarded as the only approach, although it was recommended as the first-line PET imaging.[7–9] In the present case, ^{18}F-DOPA PET/CT enabled correct diagnosis and treatment.

Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE

Eur J Nucl Med Mol Imaging (2010) 37:2004–2010

Irene Virgolini · Valentina Ambrosini · Jamshed B. Bomanji · Richard P. Baum · Stefano Fanti · Michael Gabriel · Nikolaos D. Papathanasiou · Giovanna Pepe · Wim Oyen · Clemens De Cristoforo · Arturo Chiti

DOTA-TOC



DOTA-TATE

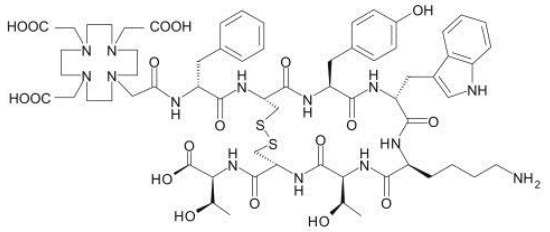


Table 1. Advantages of SSTR PET/CT Over Conventional Scintigraphy.
↑↑ sensitivity: <5mm lesion characterization
↑ specificity
Fully tomographic (3D)
Multi-slice CT near universal
↓ uptake time: 45-60 min vs. 24-48 hrs
↓ imaging time: 12-15 min vs. 45-60 min
Quantitative
↓↓ radiation dose to patient
In-house on demand production

More recently, PET with the ^{68}Ga-DOTA-conjugated peptides [^{68}Ga-DOTA^{0}-Tyr^{3}]octreotide (^{68}Ga-DOTA-TOC, ^{68}Ga-edotreotide), [^{68}Ga-DOTA^{0}-1NaI^{3}]octreotide (^{68}Ga-DOTA-NOC) and [^{68}Ga-DOTA^{0}-Tyr^{3}]octreotate (^{68}Ga-DOTA-TATE) has brought about dramatic improvements in spatial resolution and is increasingly being used in specialized centres [18–20]. Although ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE can all bind to SST receptor 2, they have different affinity profiles for other SST receptor subtypes [4]. In particular, ^{68}Ga-DOTA-NOC also shows a good affinity for SST receptors 3 and 5, ^{68}Ga-DOTA-TOC also binds to SST receptor 5 (although with lower affinity than DOTA-NOC). ^{68}Ga-DOTA-TATE has a predominant affinity for SST receptor 2.

Initial patient studies have demonstrated the potential of PET technology using ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE. In particular PET clearly offers higher resolution and improved pharmacokinetics as compared to SST receptor scintigraphy, with promising results for the detection of SST receptor-expressing tumours [16, 17], and provides prognostic information [21].

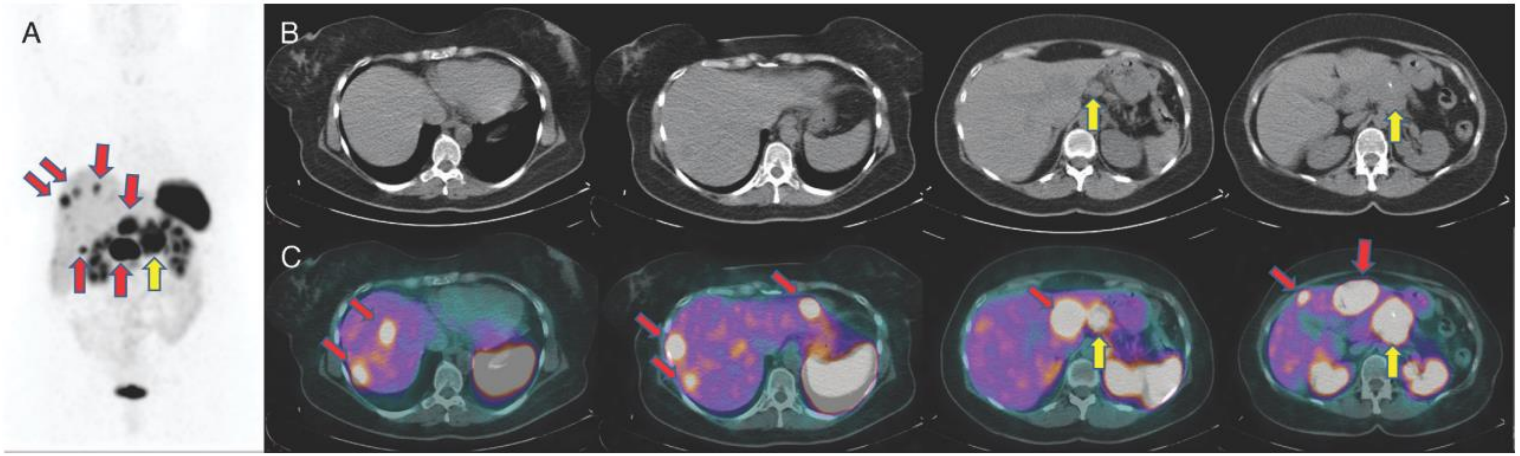


FIGURE 1. A 43-year-old female patients with clinical (hirsutism, amenorrhea, muscle weakness, and edema of lower extremities and face) and hormonal (increased serum cortisol and ACTH; increased urinary free cortisol) evidence of Cushing syndrome (CS) by suspected ectopic adrenocorticotropin hormone (ACTH) secretion based on hormonal (absent hormonal inhibition to overnight dexamethasone suppression test) and conventional imaging data (a normal pituitary at MRI; a pancreatic mass and multiple liver lesions at CT and ultrasonography of the abdomen) underwent a ^{68}Ga-DOTANOC PET/CT to confirm the source of ectopic ACTH secretion. Maximum intensity projection (MIP) PET image (**A**), axial CT (**B**), and PET/CT (**C**) images revealed increased radiopharmaceutical uptake in a 6-cm pancreatic mass (yellow arrow) and in multiple liver lesions (red arrows) suggesting a pancreatic NET with liver metastases.

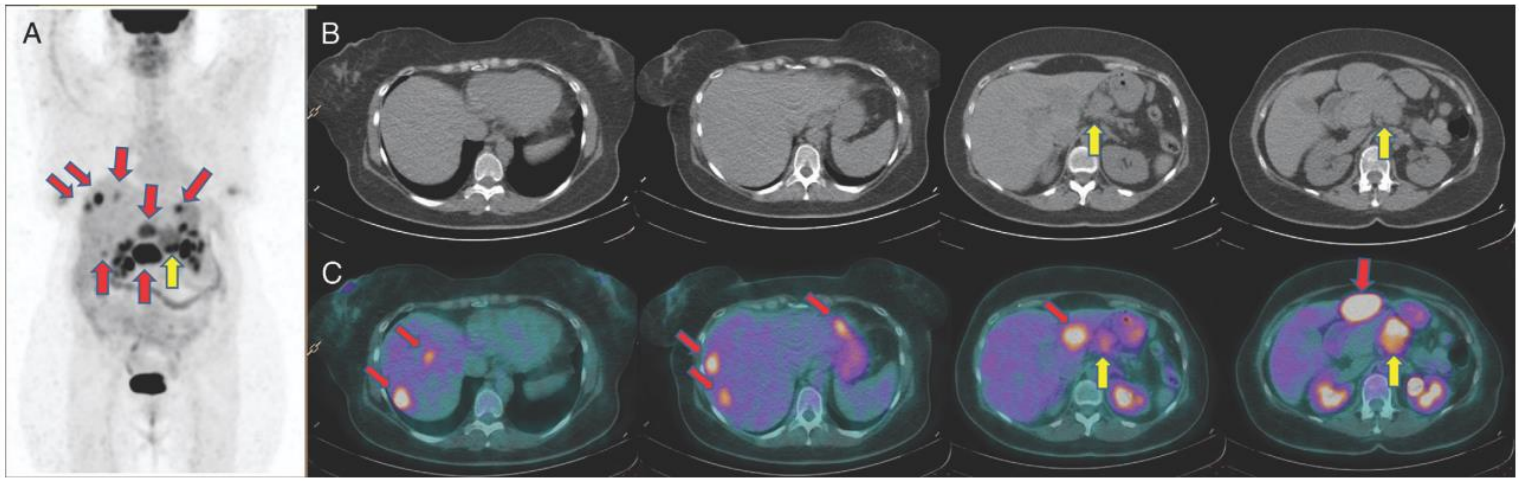


FIGURE 2. To assess glucose metabolism of tumor lesions, which in turn reflects the proliferative activity of tumor cells, the patient underwent a ^{18}F-FDG PET/CT. MIP PET image (**A**), axial CT (**B**), and PET/CT (**C**) images revealed increased radiopharmaceutical uptake in the pancreatic mass (yellow arrow) and in multiple liver lesions (red arrows).

Comparison of ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE PET/CT Within Patients with Gastroenteropancreatic Neuroendocrine Tumors

J Nucl Med 2013; 54:364–372

Damian Wild[1,2], Jamshed B. Bomanji[1], Pascal Benkert[3], Helmut Maecke[2], Peter J. Ell[1], Jean Claude Reubi[4], and Martyn E. Caplin[5]

TABLE 2
Lesion-Based Comparison of ^{68}Ga-DOTATATE PET, ^{68}Ga-DOTANOC PET, and Conventional Imaging (CT, MR Imaging, or ^{18}F-FDG PET/CT)

Tumor location/tumor type	Patients*	^{68}Ga-DOTATATE lesions	^{68}Ga-DOTANOC lesions	P†	CT, MR imaging, ^{18}F-FDG PET/CT
Liver	13	68	88	<0.001	93
Lymph nodes	7	39	42	0.36	43
Bone	10	89	82	0.02	89
Other organs	14	16	20	0.28	23
Total	18	212	232	0.005	248
G1 GEP-NET	4	43	51	0.02	52
G2 GEP-NET	7	78	81	0.53	85
G3 GEP-NET	7	91	100	0.12	111
Total	18	212	232	0.005	248

*Number of patients in whom lesion analysis was available.
†^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC were compared in lesion-by-lesion analysis using multivariate mixed-effects model.

Conclusion: The sst2,3,5-specific radiotracer ^{68}Ga-DOTANOC detected significantly more lesions than the sst2-specific radiotracer ^{68}Ga-DOTATATE in our patients with GEP-NETs.

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

TABLE 3. Causes of ectopic ACTH secretion from literature data (Refs. 54–58)

	Frequency, % (No.)			
Localization	**Aniszewski *et al.*, 2001 (54)**	**Ilias *et al.*, 2005 (55)**	**Isidori *et al.*, 2005 (56)**	**Salgado *et al.*, 2006 (57)**
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[a]	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)

ND, Not done.

[a] Generally, this aggressive cancer is evident and is often recognized in patients with overt hypercortisolism. These patients are probably not referred to an endocrine expert center.

Unusual Causes of Cushing's Syndrome

Dimitra Vassiliadi
Stylianos Tsagarakis

Arq Bras Endocrinol Metab 2007;51/8

Table 1. Unusual causes of ACTH-dependent Cushing's syndrome.

Cushing's disease
Ectopic corticotroph adenomas
Adenomas in the neurohypophysis
Double adenomas
Non-adenohypophyseal pituitary tumors
Gangliocytomas
Ectopic CRH Syndrome
"Isolated" ectopic CRH syndrome
Ectopic ACTH/CRH syndrome
Other peptides with CRH-like activity
Urocortins (?)
Bombesin

Ectopic corticotropin-releasing hormone (CRH) syndrome from metastatic small cell carcinoma: a case report and review of the literature

Sadeka Shahani[1], Rodolfo J Nudelman[2], Ramaswami Nalini[1,3], Han-Seob Kim[2,3], Susan L Samson[1,3*]

Diagnostic Pathology 2010, **5**:56

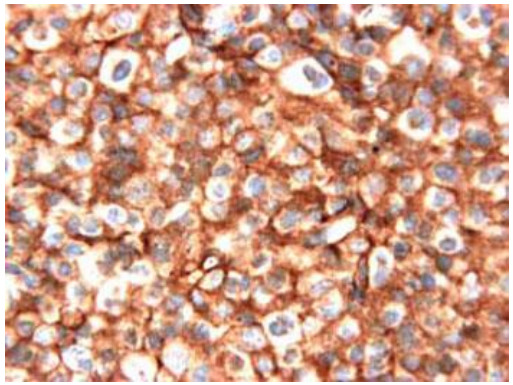
Table 2 CRH Positive and ACTH negative Tur Cushing's Syndrome

NEOPLASM	% of CASES (n = 21)
Medullary Thyroid Cancer	33
Pheochromocytoma	19
Prostate Cancer	14
Small Cell Lung Carcinoma	9.5
Small Cell Carcinoma (occult primary)[1]	9.5
Carcinoid	5
Other	< 10

[1] Including the case presented here.

ACTH-dependent disease: Cushing disease or an ectopic source?

For **definitive proof** one should require reversal of the clinical picture after resection of the tumour and/or demonstration of **ACTH immunohistochemical staining in the tumour tissue** or in metastatic deposits, and/ or **complete/partial resolution of the hypercortisolaemia** after tumour removal/ debulking.



Thank you for your attention