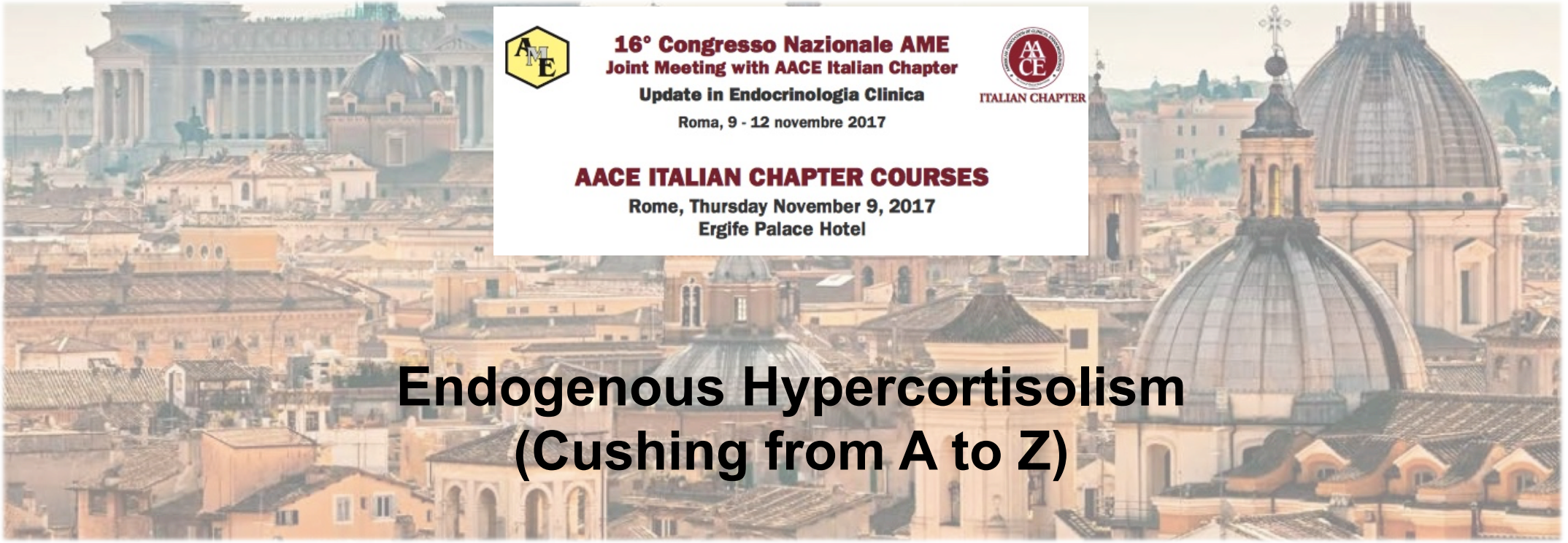


16° Congresso Nazionale AME
Joint Meeting with AACE Italian Chapter
Update in Endocrinologia Clinica
Roma, 9 - 12 novembre 2017

AACE ITALIAN CHAPTER COURSES
Rome, Thursday November 9, 2017
Ergife Palace Hotel

Endogenous Hypercortisolism (Cushing from A to Z)

Localization Studies

Dimitra A. Vassiliadi M.D., Ph.D.

Department of Endocrinology, Diabetes and Metabolism

Evangelismos Hospital

Athens, Greece

Causes of Cushing's syndrome

ACTH-dependent

85-90%

ACTH-independent

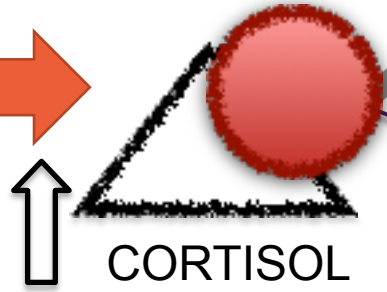
10-15%

CUSHING'S DISEASE

ECTOPIC ACTH

ACTH

Complete endocrine testing



ADENOMA
Cancer

CORTISOL

Localising the source of Cushing’s syndrome

- The diagnosis of Cushing's syndrome and its cause lie entirely in the domain of the endocrine laboratory.

- Imaging procedures provide no information about function and are useful only for tumor localization

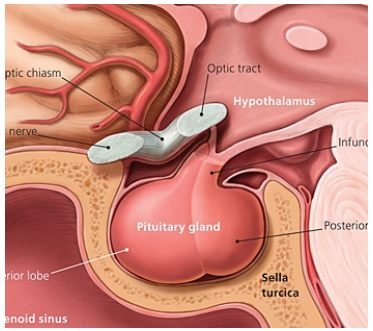
ACTH-dependent Cushing's syndrome

It is essential to

- Distinguish Cushing's disease from the uncommon EAS
- In EAS to make every effort to localize the source of ectopic ACTH

Successful Treatment

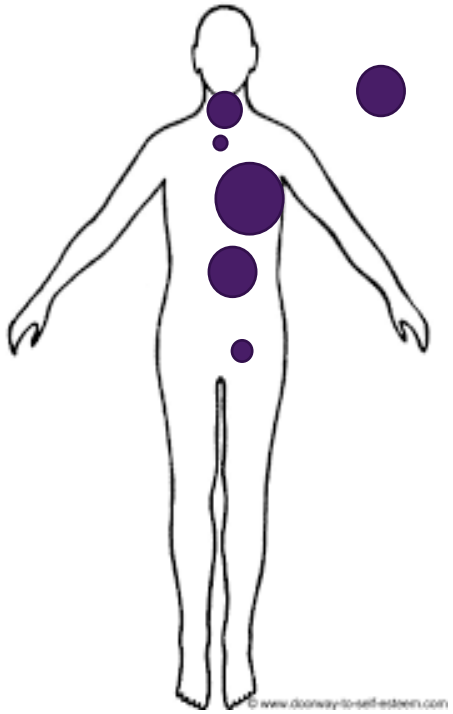
Cushing's disease



- Pituitary adenoma
  - Micro-
  - Macro-
- Ectopic corticotroph adenomas
- Adenomas in the neurohypophysis
- Double adenomas

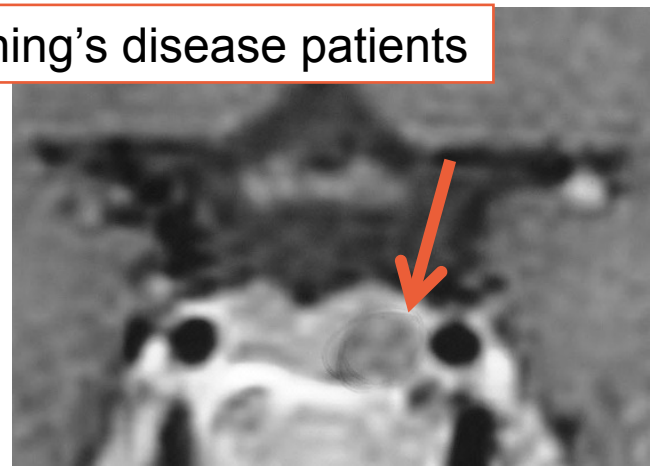
CRH test
HDST
IPSS
MRI?

Ectopic ACTH syndrome (EAS)



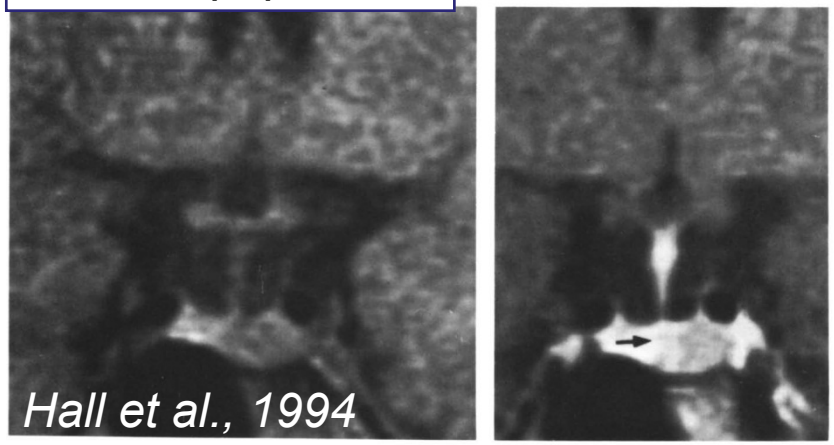
Usefulness of Pituitary MRI in the diagnosis of Cushing's disease

Cushing's disease patients



- Unenhanced & gadolinium-enhanced high resolution MRI
- Dynamic MRI or spoiled gradient improves sensitivity but lowers specificity
- Still, it detects about 50% of corticotroph tumors
- **PPV 86% -**false positive rate **c.12-18%**

General population



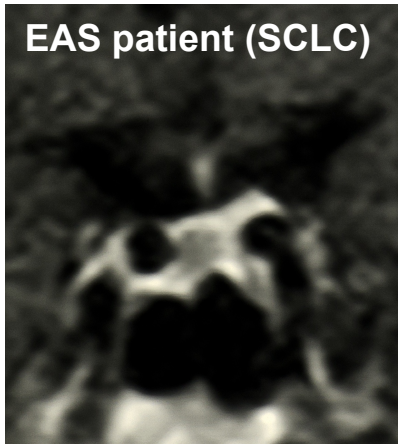
MRI scans from volunteers
randomly mixed with scans of 57 patients with Cushing's disease and interpreted independently by three blinded reviewers.

- **10%** had focal areas 3 to 6 mm of decreased signal intensity in the after administration of Gd-DTPA.

Pituitary MRI in ACTH-dependent Cushing's Syndrome

	CD (n = 47)	oEAS (n = 7)
Age (yr)	42.4 ± 12.6	44.0 ± 20.4
Sex (F/M)	36/11	1/6
HDST (S/NS)	35/10[a]	2/5
CRH (R/NR)	39/8	0/7
No. of CRH responders and HDST suppress	29/45[a]	0/7
No. of patients with basal ratio > 2	29/47	0/7
No. of patients with stimulated ratio > 2	46/47	0/7
Mean basal IPS/P ratio	4.6 ± 3.9	1.07 ± 0.1
Mean stimulated IPS/P ratio	19.6 ± 23.7	1.3 ± 0.1
MRI of pituitary gland		
Negative[b]	15	3
Equivocal[c]	9	
Micro[d]	21	3
Macro[e]	2	

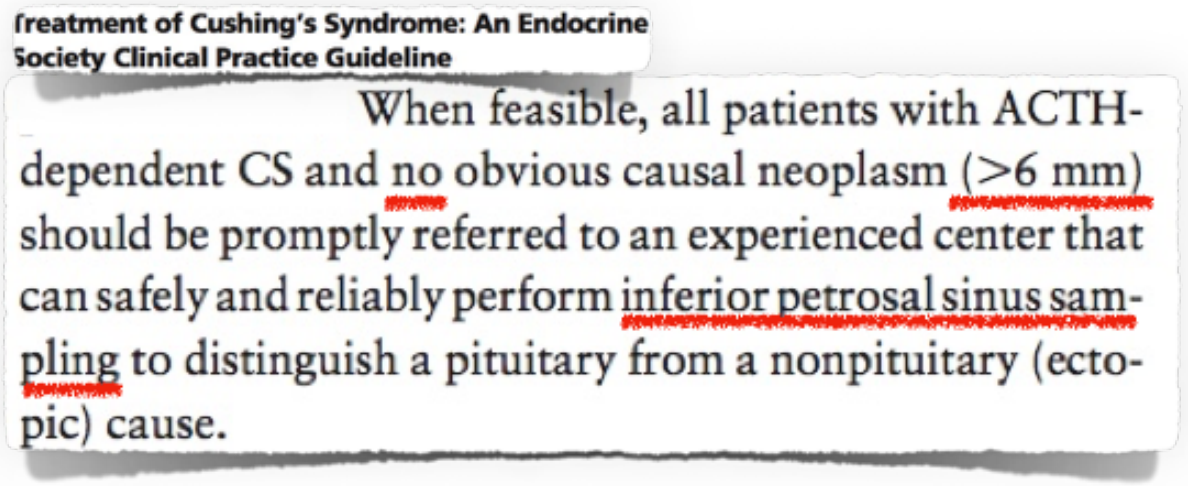
Tsagarakis et al, JCEM, 2007



- ✓ The absence of a pituitary adenoma on MRI does not exclude Cushing's disease
- ✓ The presence of a pituitary microadenoma on MRI does not confirm Cushing's disease

When to perform pituitary MRI

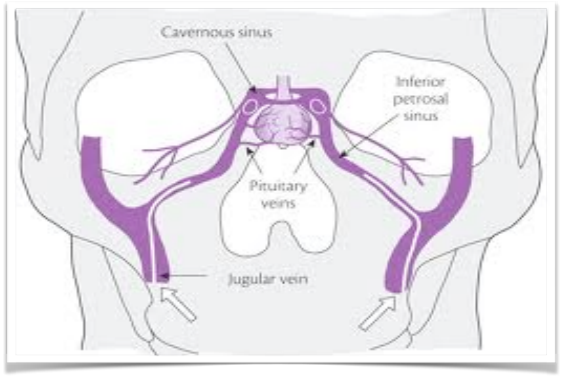
- When hormonal workup is compatible with Cushing's disease
  - Pituitary imaging is not necessary in patients in whom endocrine testing suggests ectopic ACTH secretion.
- Before trans-sphenoidal exploration to document the anatomy of the sella turcica.

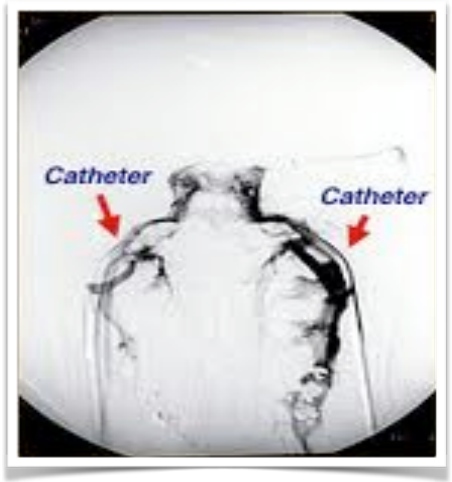


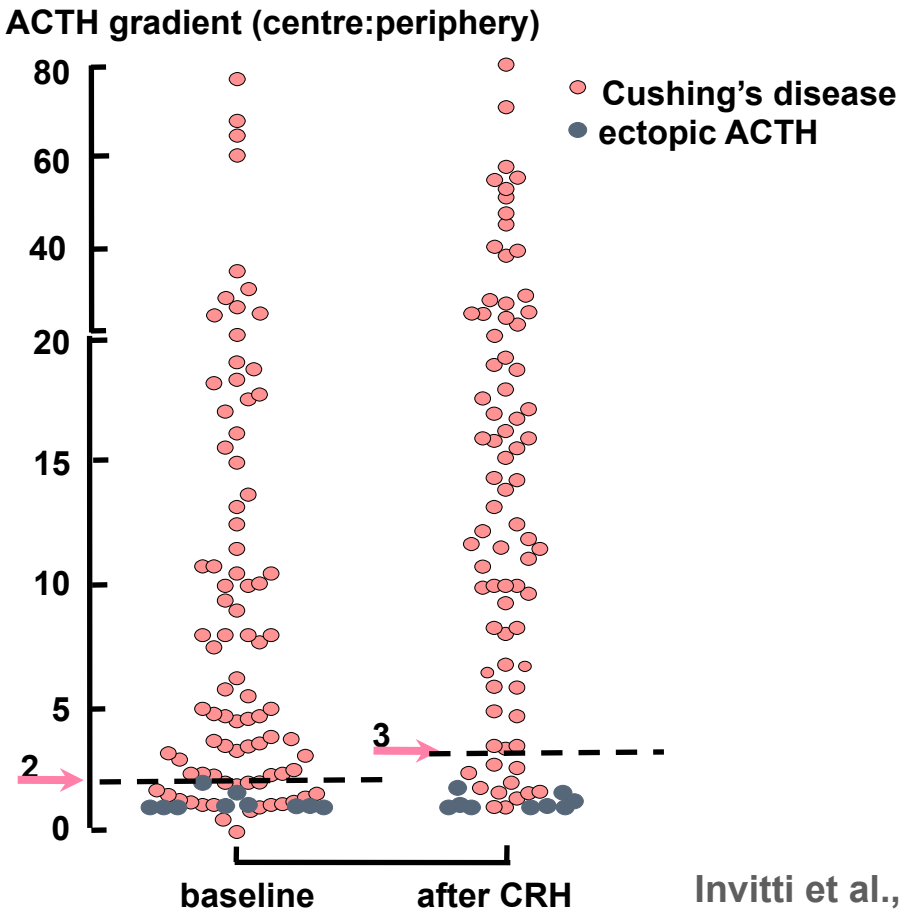
Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

When feasible, all patients with ACTH-dependent CS and no obvious causal neoplasm (>6 mm) should be promptly referred to an experienced center that can safely and reliably perform inferior petrosal sinus sampling to distinguish a pituitary from a nonpituitary (ectopic) cause.

Bilateral Inferior Petrosal Sinus Sampling







- High diagnostic accuracy (Sensitivity & Specificity: 95-99%)
- Invasive and technically demanding

False negative:

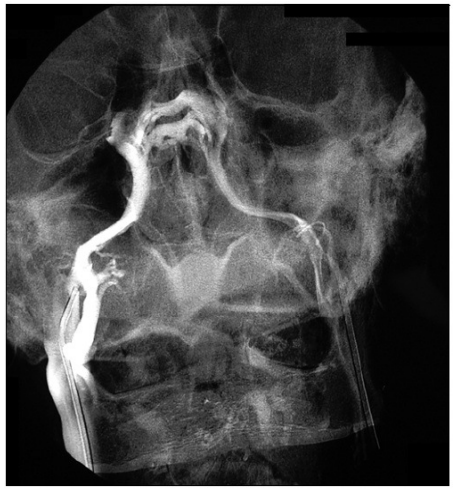
- **Incorrect catheter placement**
- **Hypoplastic petrosal sinus**
- **Unresponsiveness to CRH**

Invitti et al., 1999

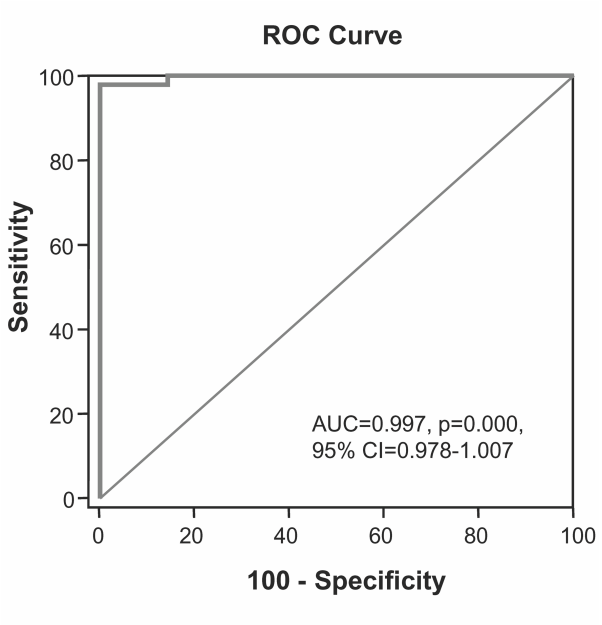
The Application of the Combined Corticotropin-Releasing Hormone plus Desmopressin Stimulation during Petrosal Sinus Sampling Is Both Sensitive and Specific in Differentiating Patients with Cushing's Disease from Patients with the Occult Ectopic Adrenocorticotropin Syndrome

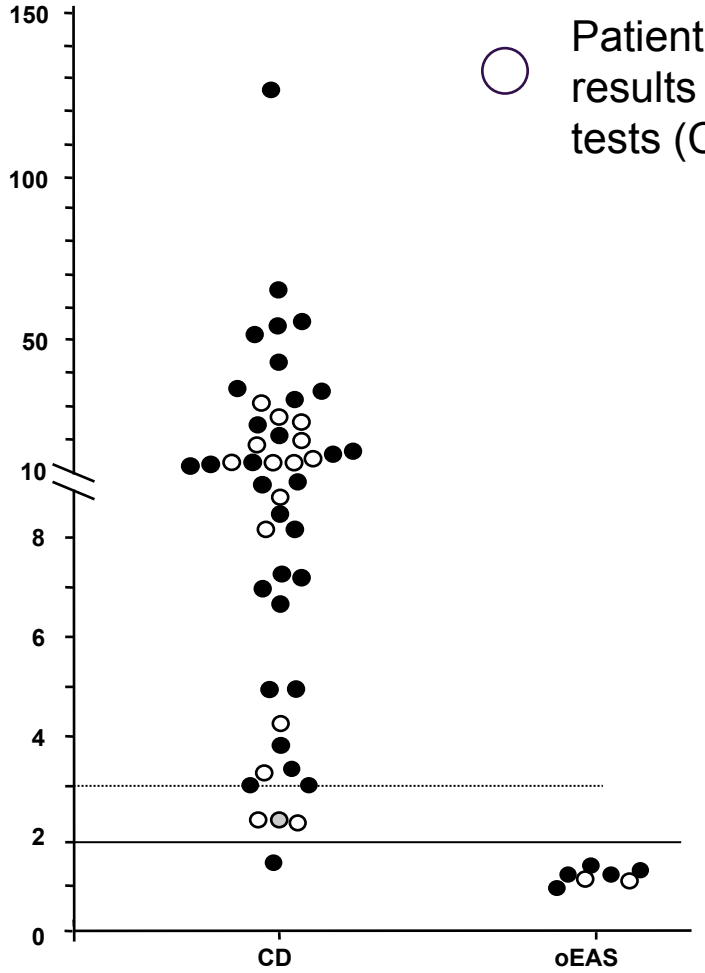
S. Tsagarakis, D. Vassiliadi, I. S. Kaskarelis, J. Komninos, E. Souvatzoglou, and N. Thalassinos

Departments of Endocrinology, Diabetes and Metabolism (S.T., D.V., J.K., E.S., N.T.) and Radiology (I.S.K.), Evangelismos Hospital, 105 052 Athens, Greece



98% sensitivity
100% specificity





○ Patients with equivocal results to biochemical tests (CRH/HDST)

BIPSS- Lateralization

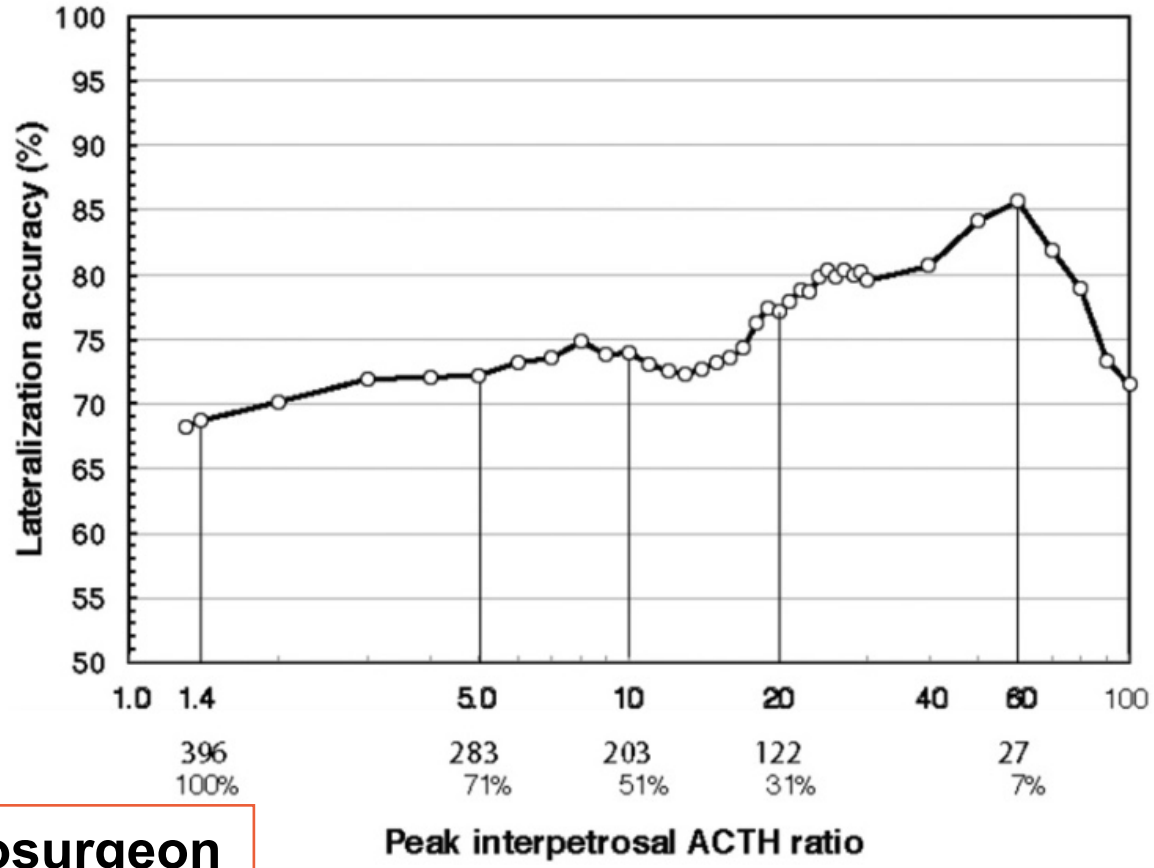
IPS:P ACTH gradient of at least 1.4 between the inferior petrosal sinuses

491 patients

Interpetrosal ratios >=1.4 PPV 69%

- Left-sided IPSS lateralization
- Consistent lateralization before and after CRH

Preop MRI (when positive) PPV 86%



Pituitary exploration by an experienced neurosurgeon

Wind et al., JCEM 2013

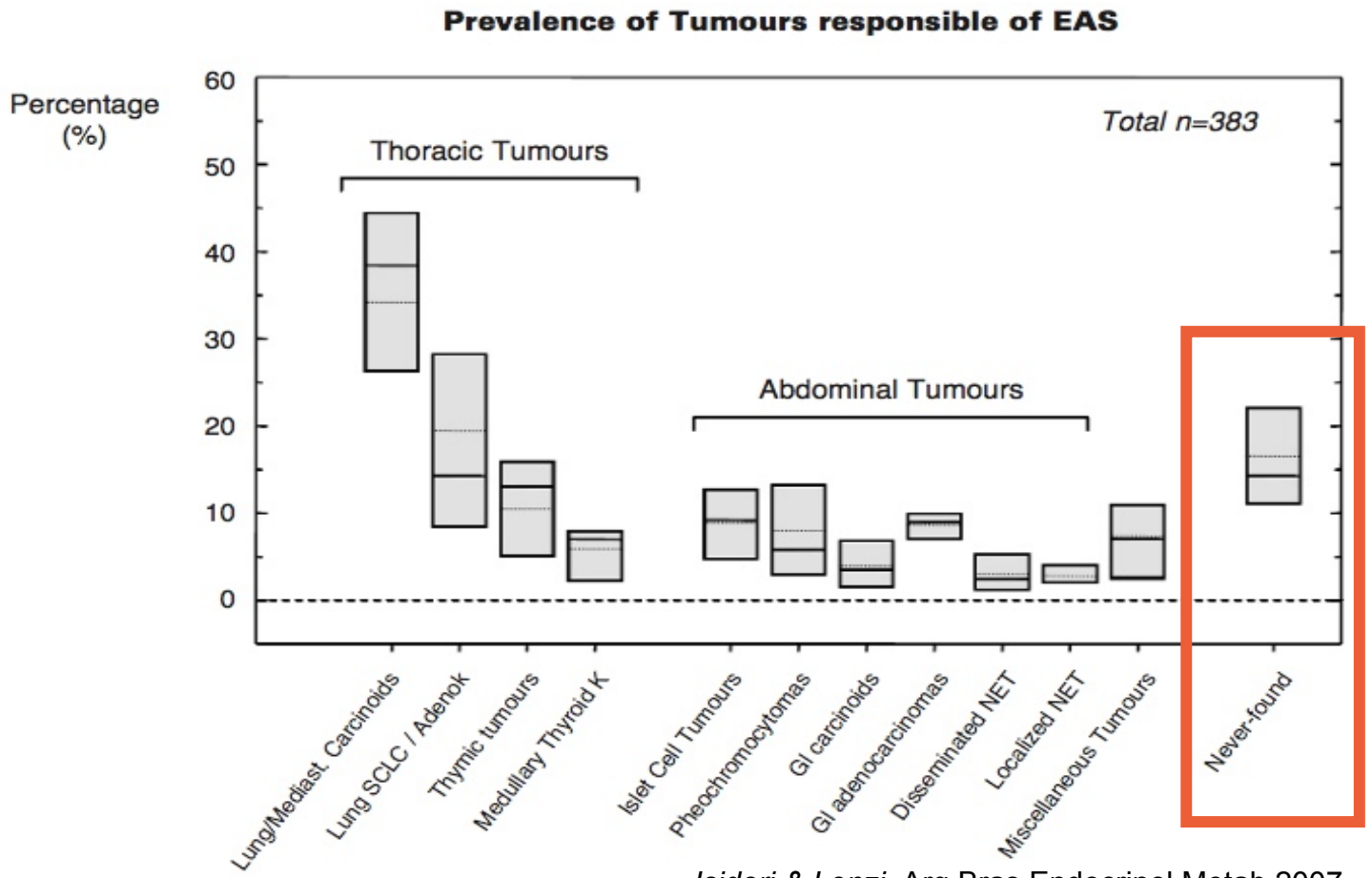
Ectopic ACTH SYNDROME (EAS)

- It is the underlying cause in 10–20% of patients presenting with ACTH-dependent Cushing's syndrome
- ACTH can be produced inappropriately (ectopically) by a variety of extrapituitary tumors.
- Optimal treatment depends on localization and removal of the ACTH- secreting tumour

Tumor Types Associated with EAS

Tumor origin	
Lung	48-66
Bronchial carcinoids	21-46
Small cell carcinoma	20-27
Pancreatic islet cells	16
Thymus	10
Medullary thyroid carcinoma	5
Adrenal	6
Pheochromocytoma	5
Neuroblastoma	0.8
Ovarian uterine cervix carcinomas	2
Prostate cancer	1
Other sporadic cases	7

Ectopic Cushing's Syndrome
D. Vassiliadi, S. Tsagarakis, N. Thalassinos

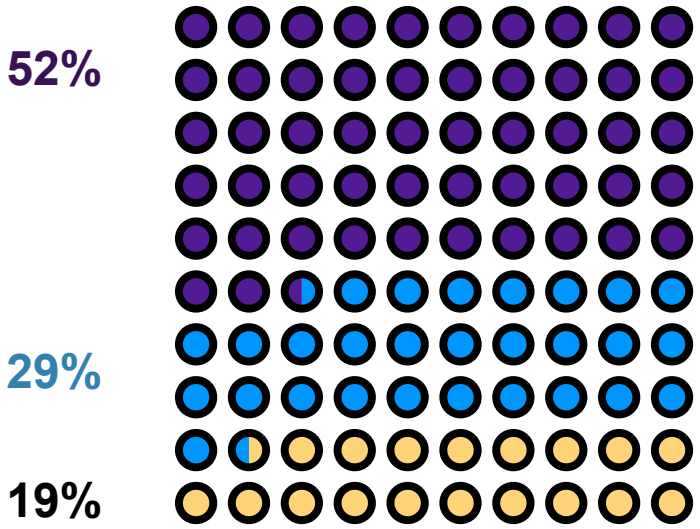


Isidori & Lenzi Arq Bras Endocrinol Metab 2007

Overt And Occult Ectopic ACTH Syndrome

The term **'occult' EAS** was introduced for cases with unequivocal non-pituitary CS in which the source of ectopic ACTH secretion was not obvious

Advances in endocrine testing, anatomical and functional imaging changed the clinical spectrum of patients investigated for EAS.



overt — easily detected by the initial investigations

covert — discovered on subsequent follow-up

occult — not identified even after prolonged and repeated follow-up

Isidori et al., JCEM 2015

Localization studies for EAS

*cost-effective to obtain images of the chest first

Thin-cut multi-slice CT (**chest***- abdomen-pelvis)
+/- MRI (chest-abdomen)- (35% of cases with neg CT)

False positive rate c.4-35%

50-55%

Overt EAS

Repeat
- CT/MRI

Additional
- Radionuclide investigation
- PET-CT
- Invasive diagnostic procedures (catheterization, surgical exploration)

- *To what extent ?*
- *When to shift from adrenolytic drugs to adrenalectomy ?*

25-30%

Covert EAS

12-18%

Occult EAS

Every effort should be made to localize the source of oEAS, even if this requires several years

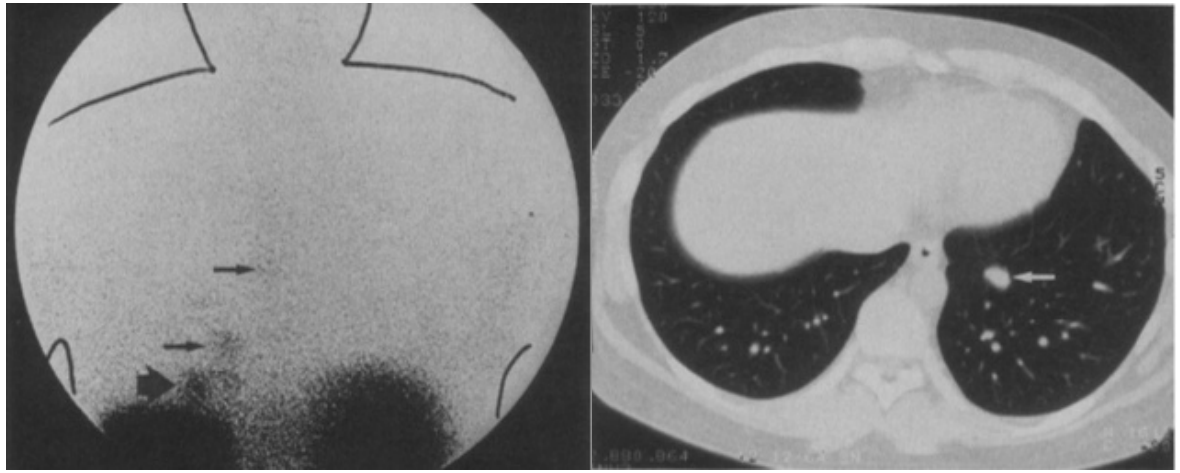
Radiolabeled somatostatin analog (^{111}In-pentetreotide) scintigraphy (OCT)

- The majority of EAS tumors are of neuroendocrine origin and therefore may express somatostatin receptor subtypes.
- Scintigraphy
  - provides whole body information
  - reveals both anatomy and function

Somatostatin Receptor Scintigraphy: Its Value in Tumor Localization in Patients with Cushing's Syndrome Caused by Ectopic Corticotropin or Corticotropin-Releasing Hormone Secretion

WOUTER W. DE HERDER, M.D., ERIC P. KRENNING, M.D., CARL D. MALCHOFF, M.D., LEO J. HOFLAND, Ph.D., JEAN-CLAUDE REUBI, M.D., DIK J. KWEKKEBOOM, M.D., H. YOE OEI, M.D., HUIBERT A.P. POLS, M.D., HAJO A. BRUINING, M.D., FRANK R.E. NOBELS, M.D., STEVEN W.J. LAMBERTS, M.D., *Rotterdam, the Netherlands*

The American Journal of Medicine, 1994



EAS- usefulness of octreoscan

Lack of Utility of ^{111}In-Pentetreotide Scintigraphy in Localizing Ectopic ACTH Producing Tumors: Follow-Up of 18 Patients

D. J. TORPY, C. C. CHEN, N. MULLEN, J. L. DOPPMAN, J. A. CARRASQUILLO, G. P. CHROUSOS, AND L. K. NIEMAN

Developmental Endocrinology Branch, National Institute of Child Health and Human Development (D.J.T., G.P.C., L.K.N.); Departments of Radiology (C.C., J.L.D., J.C.) and Nursing (N.M.), Clinical Center, National Institutes of Health, Bethesda, Maryland 20892

Usefulness of Somatostatin Receptor Scintigraphy in Patients with Occult Ectopic Adrenocorticotropin Syndrome

A. TABARIN, N. VALLI, P. CHANSON, Y. BACHELOT, V. ROHMER, V. BEX-BACHELLERIE, B. CATARGI, P. ROGER, AND F. LAURENT

Department of Endocrinology (A.T., V.B.-B., B.C., P.R.), Department of Nuclear Medicine (N.V.), and Department of Radiology (F.L.), CHU de Bordeaux, Hopital Haut-Levêque, 33604 Pessac, France; Department of Endocrinology (P.C.), CHU de Bicêtre, 94275 Le Kremlin-Bicêtre, France; Department of Endocrinology (Y.B.), CHU de Grenoble, Hopital Nord, 38043 Grenoble Cedex 09, France; and Department of Internal Medicine and Endocrinology (V.R.), CHU d'Angers, 49033 Angers Cedex 01, France

JCEM, 1999

The diagnostic yield of SRS was inferior to conventional imaging and no patient with an initial negative scan became positive during follow-up.

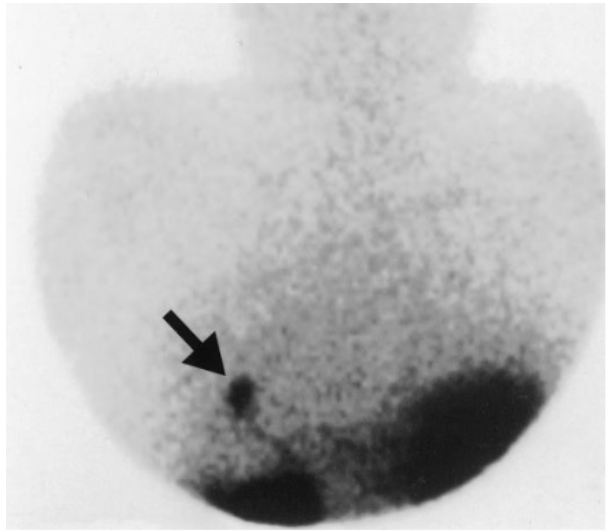
A Reappraisal of the Utility of Somatostatin Receptor Scintigraphy in Patients with Ectopic Adrenocorticotropin Cushing's Syndrome

JCEM, 2003

S. TSAGARAKIS, M. CHRISTOFORAKI, H. GIANNOPOULOU, F. RONDOGIANNI, I. HOUSIANAKOU, C. MALAGARI, D. RONTOGIANNI, I. BELLENIS, AND N. THALASSINOS

Departments of Endocrinology, Diabetes, and Metabolism (S.T., M.C., N.T.), Nuclear Medicine (H.G., F.R., I.H.), Radiology (C.M.), Pathology (D.R.), and Thoracic and Vascular Surgery (I.B.), Evangelismos Hospital, 10676 Athens, Greece

OCT identified the tumor in all six patients with bronchial carcinoids
either initially or during follow-up evaluation (8-27mo)
In 2 pts it preceded conventional imaging



Conventional Imaging:
false positive in the tail of the pancreas

EAS- usefulness of octreoscan

The sensitivity ranges from 30-60%

Low false positive rate (radiation fibrosis, inflammation, follicular thyroid adenoma, accessory spleen)

The ability of OCT to identify the tumors depends on

- The dose of the radiopharmaceutical
  - High-dose OCT (HOCT- 18mCi) may be superior
- The type/degree of somatostatin receptor expression
- The degree of hypercortisolism (higher- lower uptake)
- Tumor size

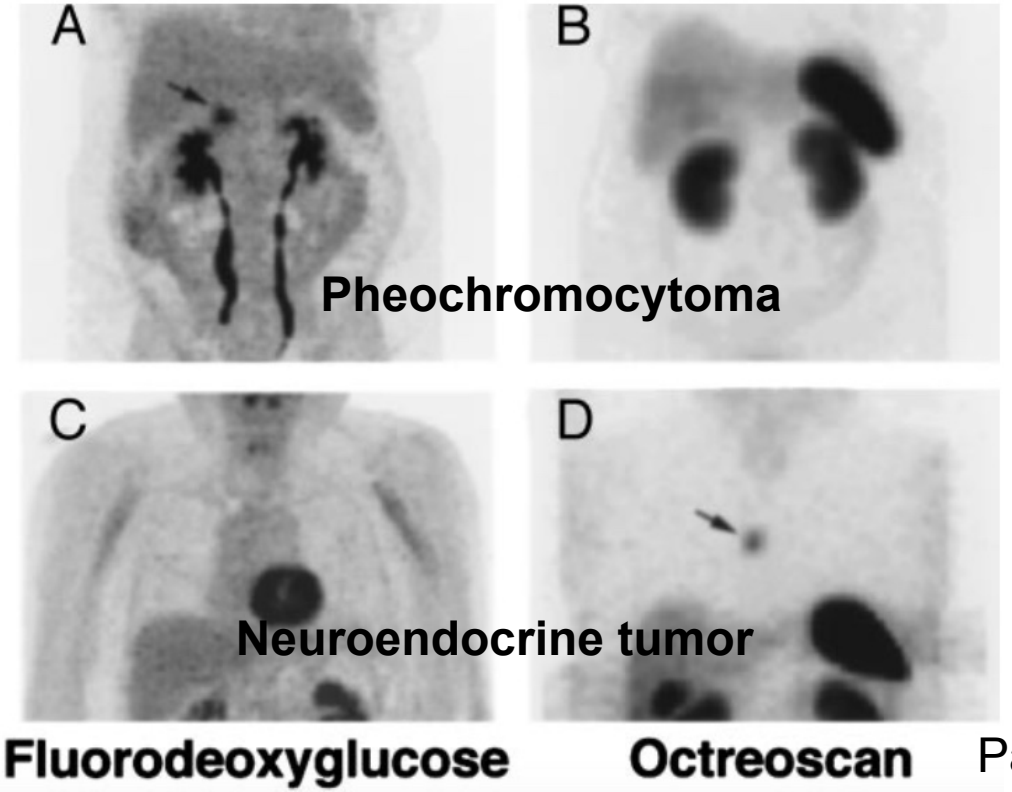
Positive HOCT in
3/9 negative LOCT

Zemskova et al., JCEM 2010

Useful method in localizing small bronchial carcinoids
It may become positive even years after initial presentation

FDG- PET

FDG-PET may highlight tumors with high metabolic activity,
but shows a low sensitivity (35%) to identify NETs causing EAS that may be metabolically less active



Pacak et al., JCEM 2004

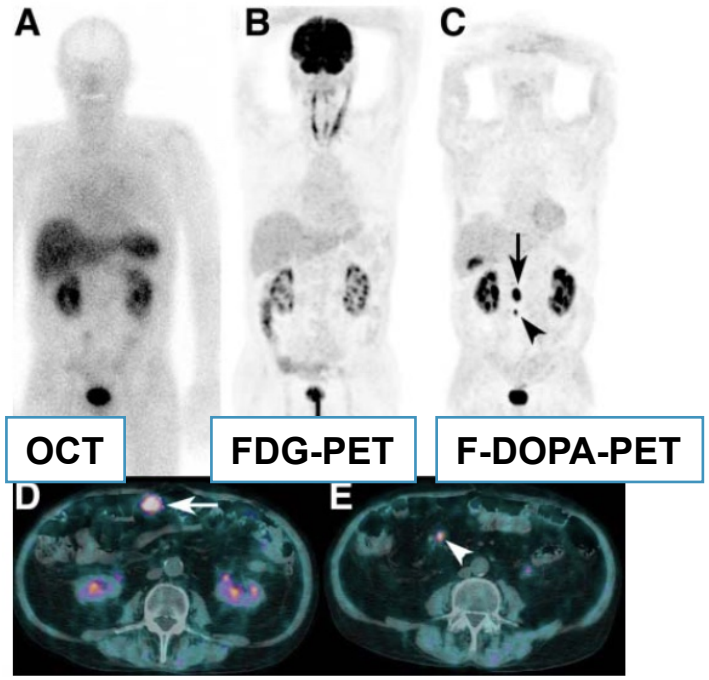
FDG-PET remains a complementary imaging tool, for use only when other imaging techniques fail to characterize the ACTH-secreting tumour.

Newer functioning imaging modalities

F-DOPA-PET

APUD-derived NETs take up, accumulate, and decarboxylate amine precursors

Jejunal NET

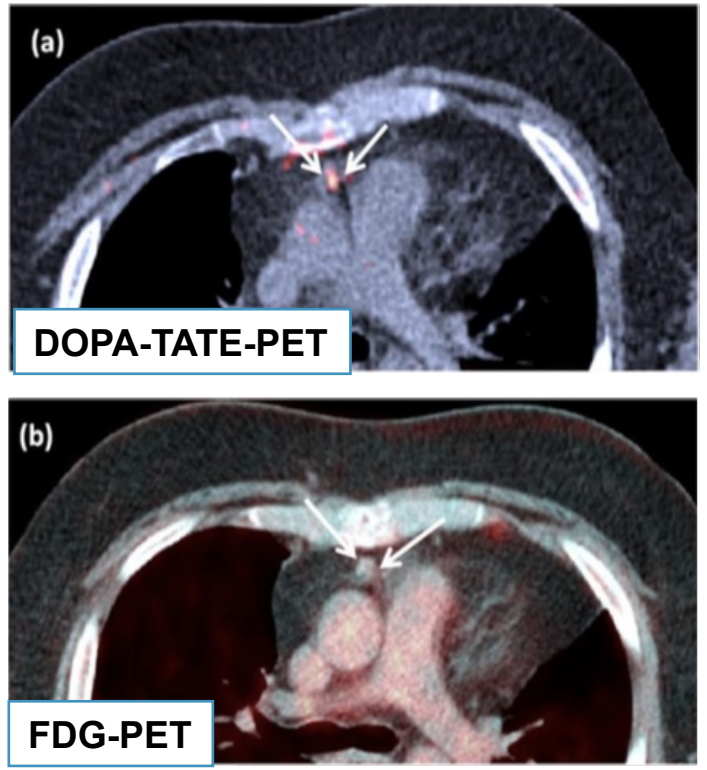


Ducry et al., 2015

^{68}Gallium-DOTA-TATE-PET

SSTR scintigraphy but with higher spatial resolution

Thymic carcinoid



Utility of Various Functional and Anatomic Imaging Modalities for Detection of Ectopic Adrenocorticotropin-Secreting Tumors *JCEM, 2015*

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

Reproductive Biology and Medicine Branch (M.S.Z., B.G., I.C., L.K.N.), National Institute of Child Health and Human Development; Biostatistics and Clinical Epidemiology Service (N.S.); Nuclear Medicine Division (C.C.C., J.A.C., M.W.), Radiology and Imaging Sciences Department; and Diagnostic Radiology Department (A.M.G.), National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

Comparison of the various modalities- prospective evaluation at one clinical research center

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.	28/41	26/40	16/39	6/20	7/14	6/13

	LOCT		LOCT and/or HOCT		FDG-PET		DOPA-PET	
	Combined with CT	Combined with MRI	Combined with CT	Combined with MRI	Combined with CT	Combined with MRI	Combined with CT	Combined with MRI
Tumor identified patients (n = 30)								
A. Sensitivity, % (95% CI) (B below × 100)	57 (39–73)	52 (34–69)	68 (49–82)	63 (44–78)	64 (35–85)	60 (31–83)	55 (28–79)	55 (28–79)
B. No. of patients with concordant TP lesions/no. with imaging study	16/28	14/27	19/28	17/27	7/11	6/10	6/11	6/11
C. PPV, % (D below × 100)	91	100	93	100	67	60	100	100
D. No. of concordant TP lesions/no. of total lesions on imaging	21/23	26/26	26/28	27/27	8/12	6/10	8/8	8/8

Initial imaging of patients with presumed EAS include thoracic CT and MRI followed by LOCT.

Comparison of the various modalities- systematic review

Conventional and Nuclear Medicine Imaging in Ectopic Cushing's Syndrome: A Systematic Review

JCEM, 2015

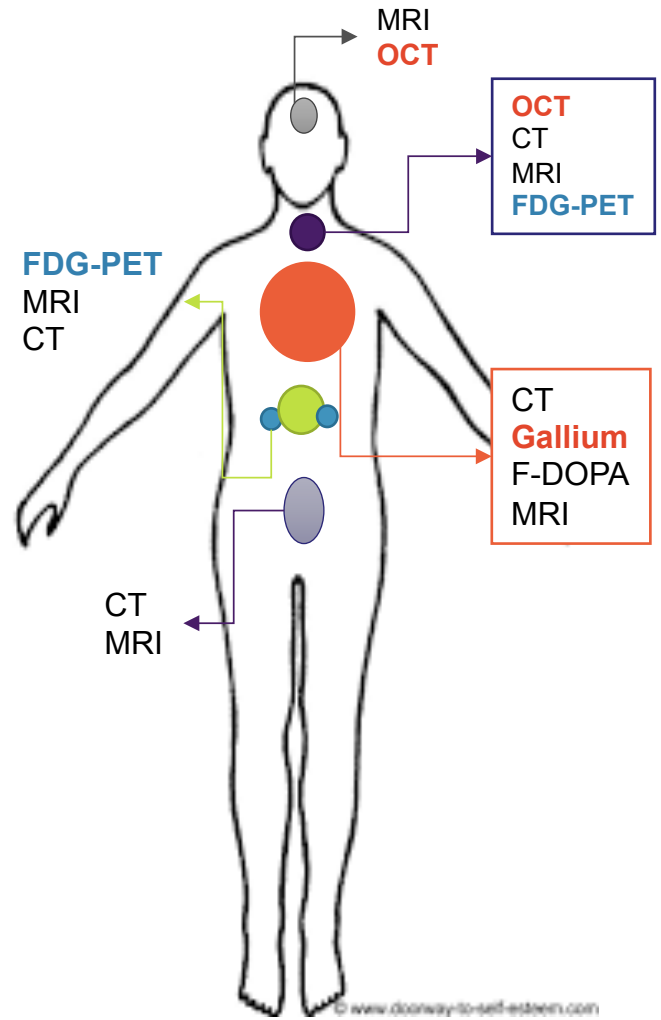
Andrea M. Isidori, Emilia Sbardella, Maria Chiara Zatelli, Mara Boschetti, Giovanni Vitale, Annamaria Colao, and Rosario Pivonello, on behalf of the ABC Study Group*

231 pts, at least one conventional and one nuclear medicine investigation

SENSITIVITY	CT	MRI	LOCT	FDG-PET	F-DOPA-PET	MIBG	^{68}Gallium-SSTR-PET/CT
	66%	52%	49%	52%	57%	31%	82%
OVERT (detected on first imaging)							
	98%	93%	64%	71%	54%	38%	70%
COVERT (detected on follow up)							
	44%	45%	64%	59%	86%	50%	100% 9 cases

False (+)	CT	MRI	LOCT	FDG-PET	F-DOPA-PET	MIBG	^{68}Gallium-SSTR-PET/CT
	4%	2%	1%	1%	5%	13%	4%
OVERT (detected on first imaging) 1/23							
	1%		2%		7%	20%	
COVERT (detected on follow up)							
	10%	7%		3%			10%

False (-)	CT	MRI	LOCT	FDG-PET	F-DOPA-PET	MIBG	^{68}Gallium-SSTR-PET/CT
	34%	48%	51%	48%	41%	60%	17%
OVERT (detected on first imaging)							
	2%	7%	36%	29%	43%	50%	31%
COVERT (detected on follow up)							
	51%	52%	36%	39%	14%	50%	



Whole body catheterization studies

Genitourinary Radiology

John L. Doppman, MD • Lynnette Nieman, MD • Donald L. Miller, MD • Harvey I. Pass, MD • Richard Chang, MD • Gordon B. Cutler, Jr, MD • Marcus Schaaf, MD • George P. Chrousos, MD • Jeffrey A. Norton, MD • Harvey A. Ziessman, MD • Edward H. Oldfield, MD • D. Lynn Loriaux, MD, PhD

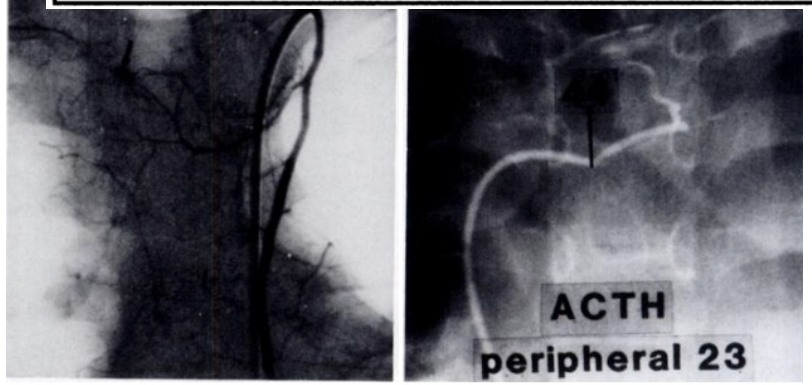
1989

Ectopic Adrenocorticotropic Hormone Syndrome: Localization Studies in 28 Patients[1]

John L. Doppman, MD • Harvey I. Pass, MD • Lynnette K. Nieman, MD • Donald L. Miller, MD Richard Chang, MD • Gordon B. Cutler, Jr, MD • George P. Chrousos, MD Gitie S. Jaffe, MD • Jeffrey A. Norton, MD

1992

Corticotropin-secreting Carcinoid Tumors of the Thymus: Diagnostic Unreliability of Thymic Venous Sampling[1]



a. b.

Figure 7. **(a)** Selective left internal mammary arteriogram demonstrates a 4-mm hypervascular stain (arrow) opacified from the thymic branch. Although an ectopic inferior parathyroid gland was considered in the diagnosis, the twofold elevation in ACTH level in a selective thymic vein sample **(b)** directed toward the right upper thymic lobe suggested the presence of an ACTH-producing thymic carcinoid. Thymectomy was performed and a normal parathyroid gland was found. The source of ectopic ACTH production in this 10-year-old girl remains undetected, and bilateral adrenalectomy has been performed.

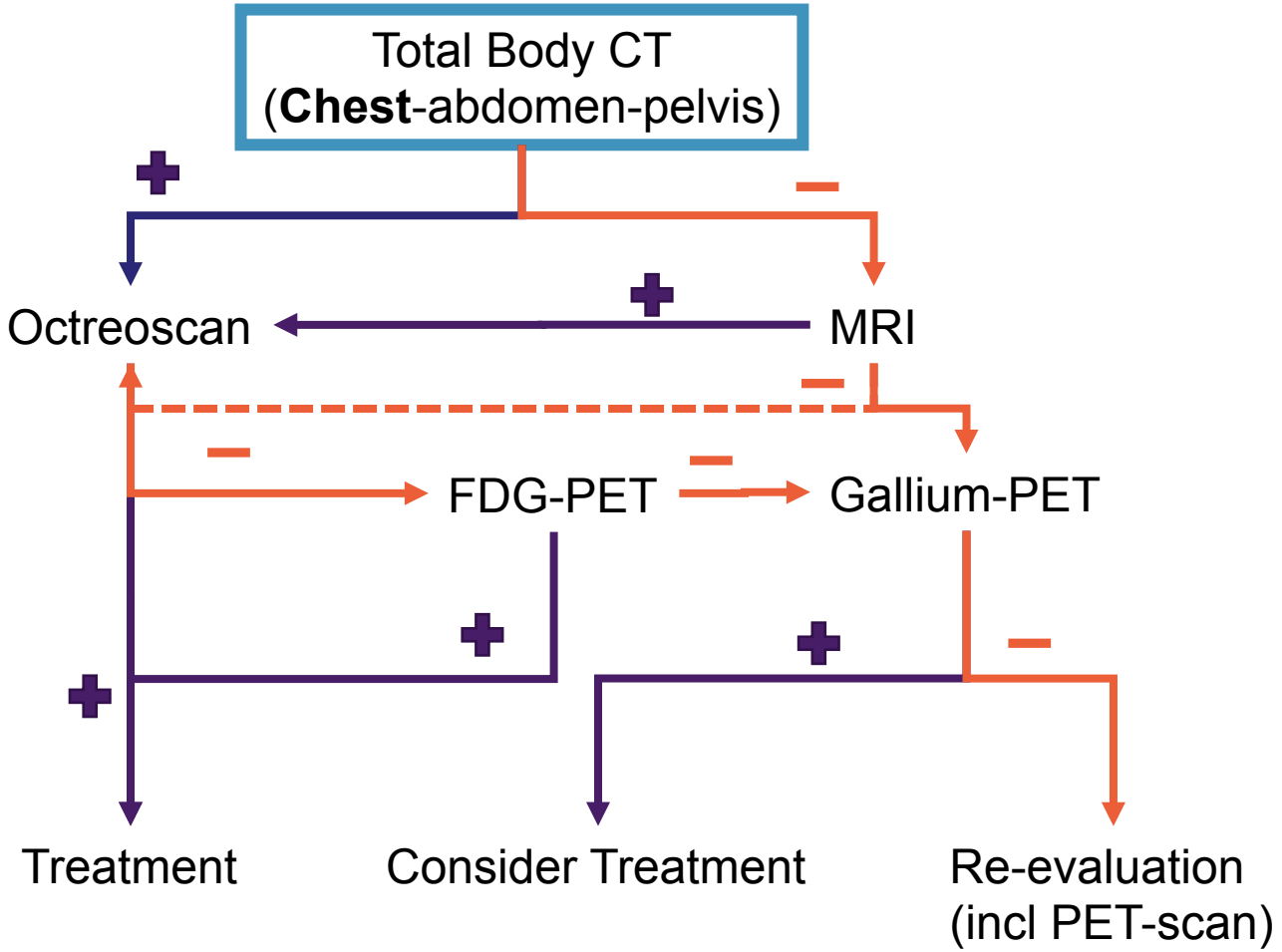
Selective venous sampling from suspected sources of ectopic ACTH secretion is

- technically difficult
- of limited overall value

Venous sampling is not necessary for the evaluation of EAS except for IPSS.

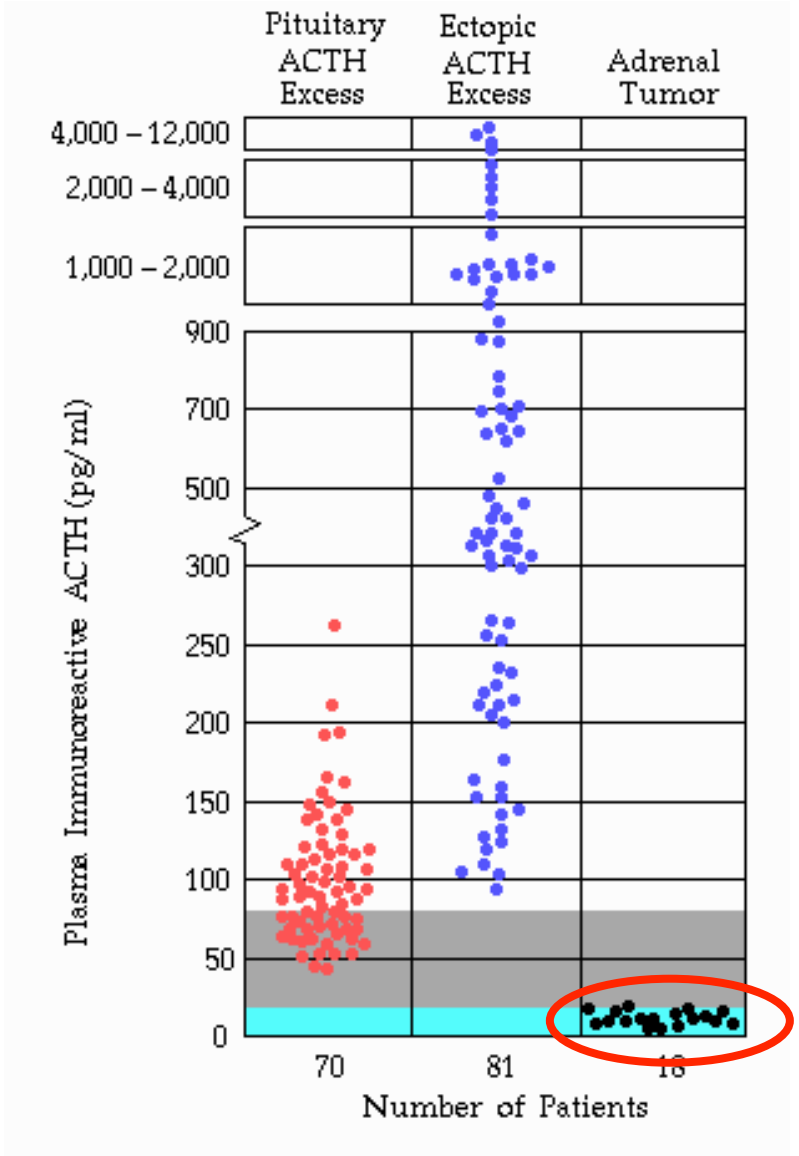
EAS- integrated approach

- No single imaging technique has optimal accuracy
- Increased sensitivity bears the risk of false-positive findings
- Obtain two different types of imaging on the premise that false- positive lesions would not be concordant in both.
- Perhaps more useful is the combination of anatomic and functional imaging.

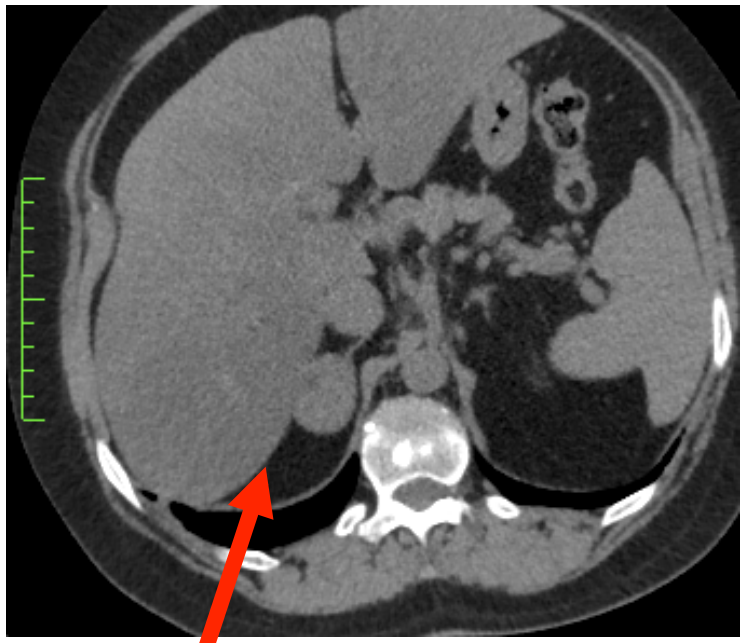


Isidori et al., JCEM 2015

Adrenal Cushing's syndrome

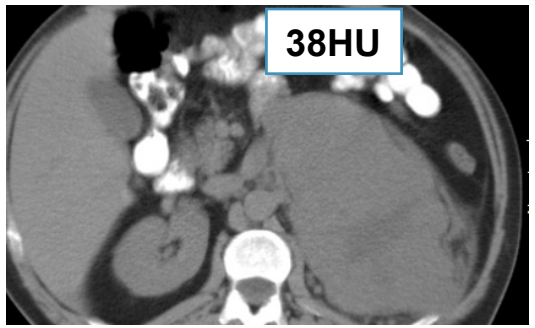


ACTH<10 pg/ml



Adrenal CT scan

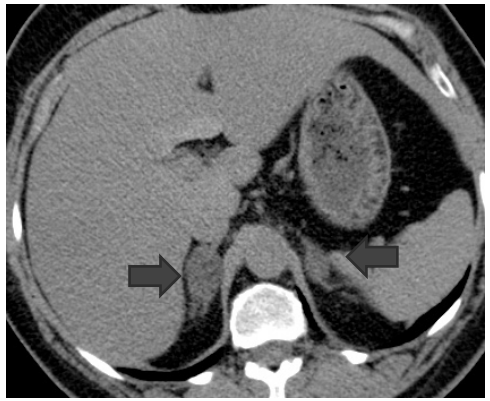
Adrenocortical cancer



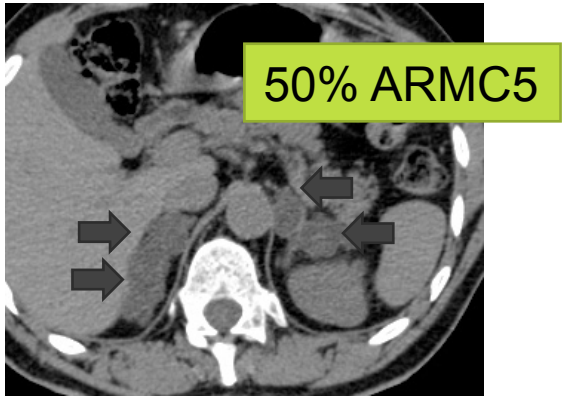
Bilateral adrenal masses

Uncommon finding <2% in overt adrenal Cushing's syndrome
Much more common in the context of adrenal incidentalomas with Autonomous Cortisol Secretion

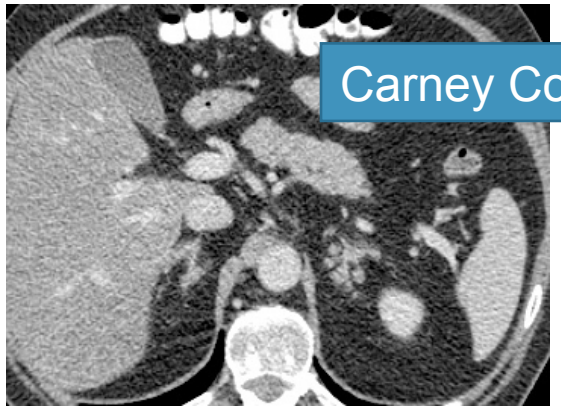
Bilateral adenomas



Macronodular hyperplasia



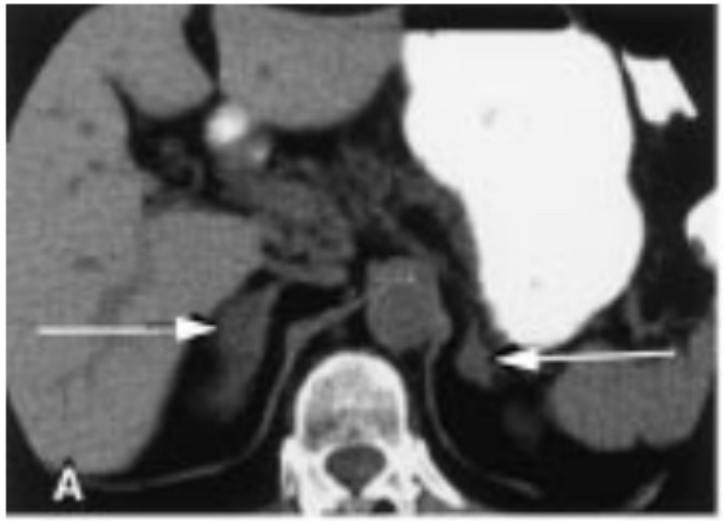
Micronodular hyperplasia

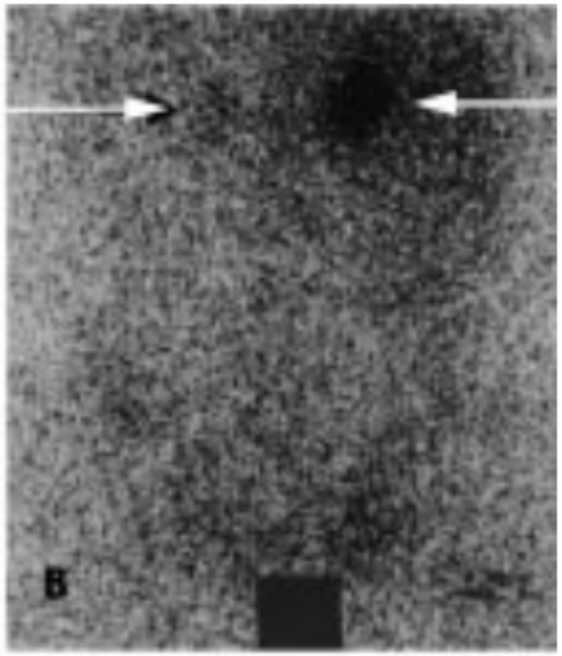


Deciphering whether cortisol hypersecretion is bilateral or unilateral is crucial for proper management
Bilateral adrenalectomy poses the patient at life-long risk of adrenal insufficiency

Adrenal Scintigraphy

Uptake correlates with size





CT adrenal scan (mm)		Scinti scan uptake		
left	right	left	right	side
70	22	2+	2+	L
25	17	2 + +	+	L
22	20	NA		L
60	32	NA		L
52	30	NA		L
34	29	NA		L
20	30	+	2 + +	R
50	55	NA		R
58	45	2 + +	+	L
80	100	+	2 + +	R
65	70	NA		R
70	23	2 + +	+	L
21	27	+	2 + +	R
NA	38	NA		R
30	50	+	2 + +	R

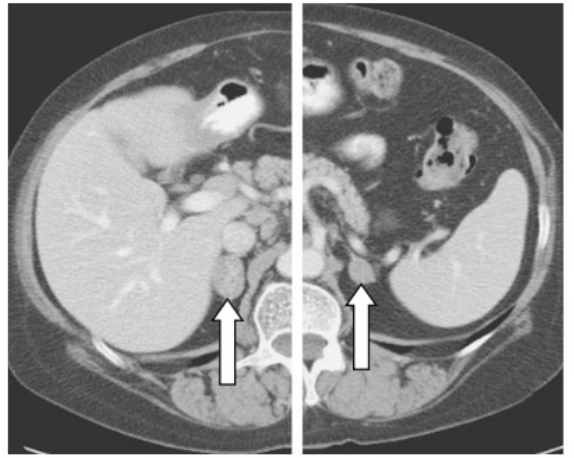
The adrenal with the maximum uptake of 131-norcholesterol was always the larger on CT scan

Debillon et al., JCEM 2015

Adrenal venus sampling

Patient no., age (years), sex	Clinical presentation	BMI, kg/m^2	Adrenal mass maximum diameter (cm), right, left	Cortisol hypersecretion on AVS (lateralization ratio)[a]	Surgery[b]	Adrenal tissue weight, g[c]	Pathology	Follow-up, months
1, 69, F	CS	23.1	3.1, 2.1	Bilateral (1.1)	Bilateral total; posterior open approach	19.7	Bilateral adenomas, atrophic cortex	123
2, 42, F	SCS	34.7	2.2, 2.9	Bilateral (1.3)	Bilateral subtotal; laparoscopic	18.5	Bilateral adenomas, atrophic cortex	51
3, 39, F	SCS	37.0	2.8, 1.2	Right (11.1)	Right; laparoscopic	14.3	Adenoma, atrophic cortex	51
4, 63, F	SCS	26.9	3.5, 3.5	Left (2.3)	Left; laparoscopic	16.5	Adenoma, atrophic cortex	24
5, 60, F	SCS	46.0	4.6, 2.4	Right (3.5)	Right; laparoscopic converted to open	85.0	Adenoma, mixed cortical atrophy and hyperplasia	30
6, 67, F	SCS	24.4	6.0, 3.5	Bilateral (1.1)	Right; laparoscopic	52.6	AIMAH	42
7, 57, F	CS	46.4	2.0, 5.0	Bilateral (1.3)	Left; laparoscopic converted to open	52.0	Adenoma, atrophic cortex	37
8, 54, F	SCS	28.9	2.8, 1.8	Right (6.3)	Right; laparoscopic	9.8	Adenoma, atrophic cortex	1
9, 56, M	CS	39.1	4.0, 2.2	Right (5.1)	Bilateral subtotal; laparoscopic	52.7	Nodular hyperplasia	2
10, 56, F	SCS	34.8	5.4, 4.4	Bilateral (2.0)	Bilateral total; laparoscopic	91.5	AIMAH	1

A



B **Bilateral Adrenal Venous Sampling**

Vein	Cortisol, µg/dL	AV/PV ratio	Cortisol ratio*
R adrenal vein	190	20.7	6.3
L adrenal vein	30	3.3	
Peripheral vein	9.2		

*Lateralization ratio: Right adrenal vein cortisol divided by left adrenal vein cortisol.

Young et al., 2008

In all cases with lateralization the adrenal with the cortisol hypersecretion was the larger on CT scan

Size matters

The Role of Unilateral Adrenalectomy in Corticotropin-Independent Bilateral Adrenocortical Hyperplasias

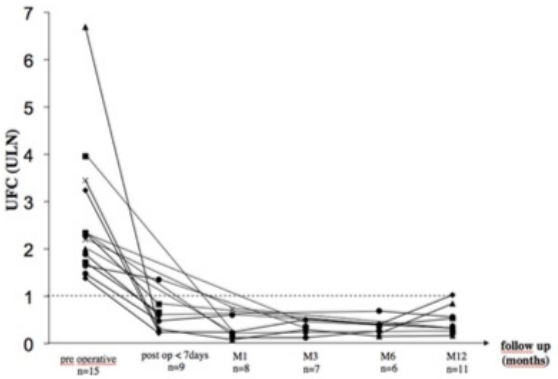
Yunze Xu · Wenbin Rui · Yicheng Qi · Chongyu Zhang · Juping Zhao · Xiaojing Wang · Yuxuan Wu · Qi Zhu · Zhoujun Shen · Guang Ning · Yu Zhu

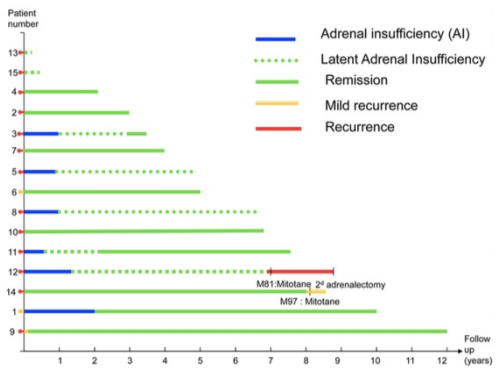
27 patients (14 patients with BMAH and 13 patients with PPNAD)
Unilateral adrenalectomy
(largest gland or in case of normal-sized or minimally enlarged or symmetrically hyperplastic adrenals 131-norcholesterol/ right adrenal)
achieved long-term remission of CS and improved glycemic control and BP values

ORIGINAL ARTICLE

Unilateral Adrenalectomy as a first-line treatment of Cushing's syndrome in patients with Primary Bilateral Macronodular Adrenal Hyperplasia

Emmanuelle Debillon[1], Fritz-line Velayoudom-Cephise [2], Sylvie Salenave[3], Philippe Caron[4], Philippe Chaffanjon[5], Tristan Wagner[6], Maximilien Massoutier[7], Benoit Lambert[8], Marine Benoit[1], Jacques Young[3], Antoine Tabarin[2], Olivier Chabre[1]





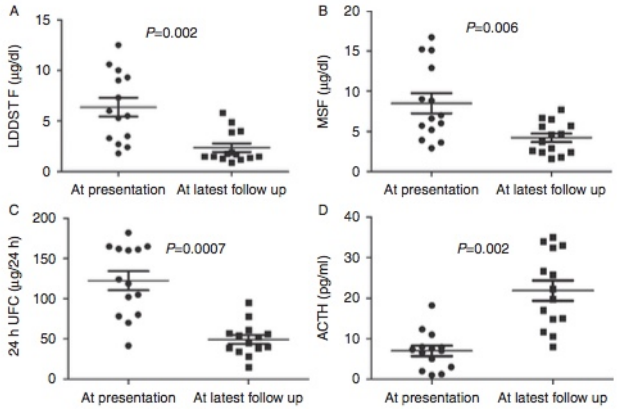
Clinical Study | I Perogamvros and others | Surgery in bilateral adrenal incidentalomas | 173:6 | 719–725

Biochemical and clinical benefits of unilateral adrenalectomy in patients with subclinical hypercortisolism and bilateral adrenal incidentalomas

I Perogamvros, D A Vassiliadi[1], O Karapanou, E Botoula, M Tzanela and **S Tsagarakis**

Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, 106 76 Athens, Greece and [1]Endocrine Unit, Second Department of Internal Medicine-Propaedeutic, Research Institute and Diabetes Center, Attiko University Hospital, 12462 Athens, Greece

Correspondence should be addressed to S Tsagarakis **Email** stsagara@otenet.gr

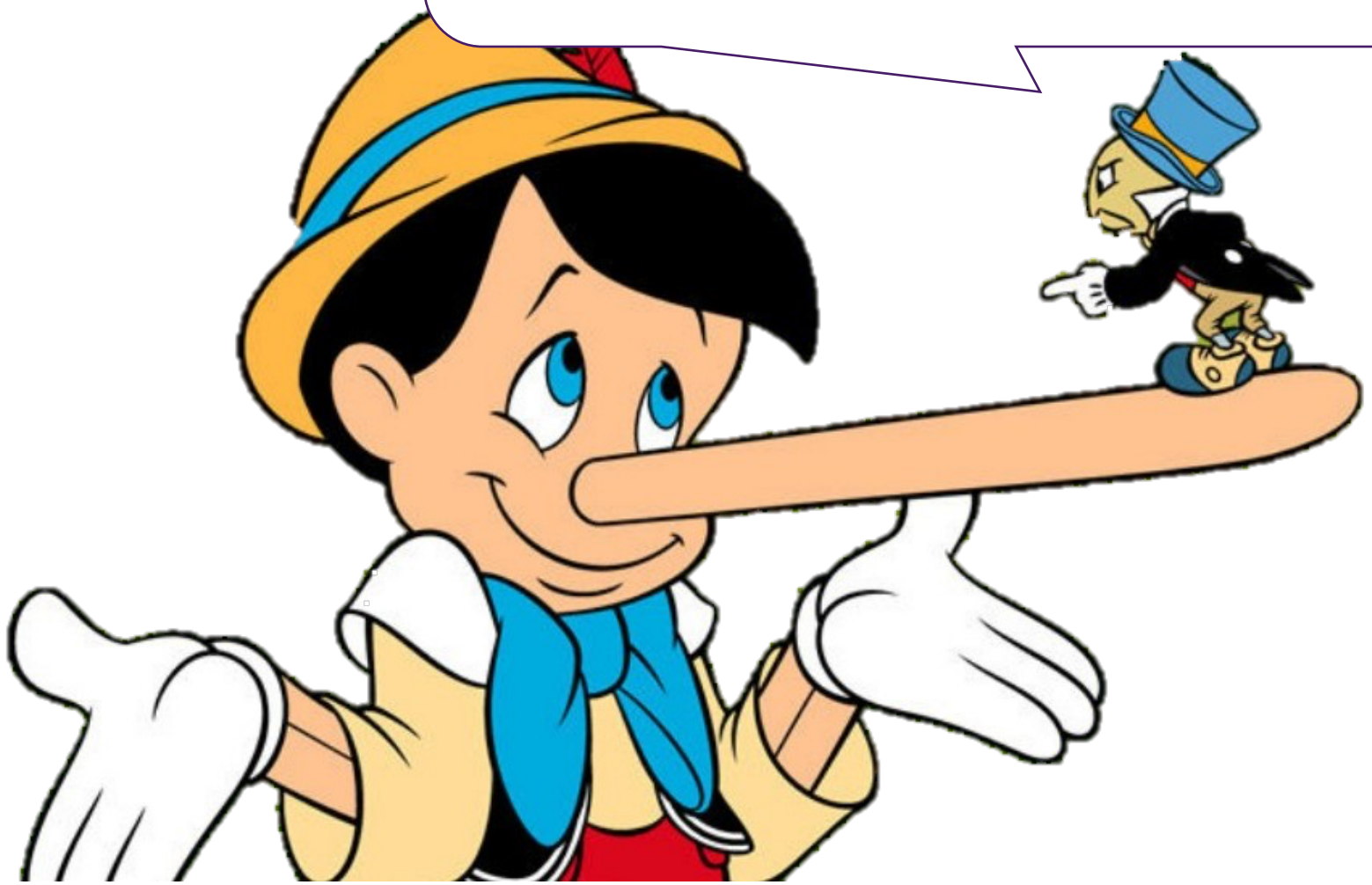


Characteristics	Group A (SH) ($n=12$)	Group B (SH) ($n=11$)	*P*
Cortisol post-LDDST (μg/dl)	5.7±3.0	3.7±1.4	NS
24 h UFC (μg/24 h)	125.13±43.7	103.8±63.5	NS
MSF (μg/dl)	8.8±5.0	6.9±2.5	NS
ACTH (pg/ml)	7.1±5.2	8.9±5.1	NS
Improvement of hypertension	4/6	0/6	0.01
Improvement of DM2 or IGT	4/4	0/2	0.01
Improvement of dyslipidemia	2/7	0/3	NS
Improvement of osteoporosis	2/3	0/4	0.05

Summary

- Diagnosing and localizing the cause of Cushing's syndrome is a continuous challenge
- Modern techniques increased our ability to confidently localize the source of ACTH secretion in many cases but there are still ongoing challenges
  - on how to localize the small "invisible" pituitary adenomas
  - on the optimal strategy for detecting occult ACTH producing tumors.

I had warned you
to never say that Cushing’s syndrome is simple



Utility of Various Functional and Anatomic Imaging Modalities for Detection of Ectopic Adrenocorticotropin-Secreting Tumors *JCEM, 2015*

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

Reproductive Biology and Medicine Branch (M.S.Z., B.G., I.C., L.K.N.), National Institute of Child Health and Human Development; Biostatistics and Clinical Epidemiology Service (N.S.); Nuclear Medicine Division (C.C.C., J.A.C., M.W.), Radiology and Imaging Sciences Department; and Diagnostic Radiology Department (A.M.G.), National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

Comparison of the various modalities- prospective evaluation at one clinical research center

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

- LOCT and PET detected only lesions seen by CT/MRI
- Abnormal LOCT or F-DOPA-PET improved PPV of CT/MRI.

	LOCT		LOCT and/or HOCT		FDG-PET		DOPA-PET	
	Combined with CT	Combined with MRI	Combined with CT	Combined with MRI	Combined with CT	Combined with MRI	Combined with CT	Combined with MRI
Tumor identified patients (n = 30)								
A. Sensitivity, % (95% CI) (B below × 100)	57 (39–73)	52 (34–69)	68 (49–82)	63 (44–78)	64 (35–85)	60 (31–83)	55 (28–79)	55 (28–79)
B. No. of patients with concordant TP lesions/no. with imaging study	16/28	14/27	19/28	17/27	7/11	6/10	6/11	6/11
C. PPV, % (D below × 100)	91	100	93	100	67	60	100	100
D. No. of concordant TP lesions/no. of total lesions on imaging	21/23	26/26	26/28	27/27	8/12	6/10	8/8	8/8