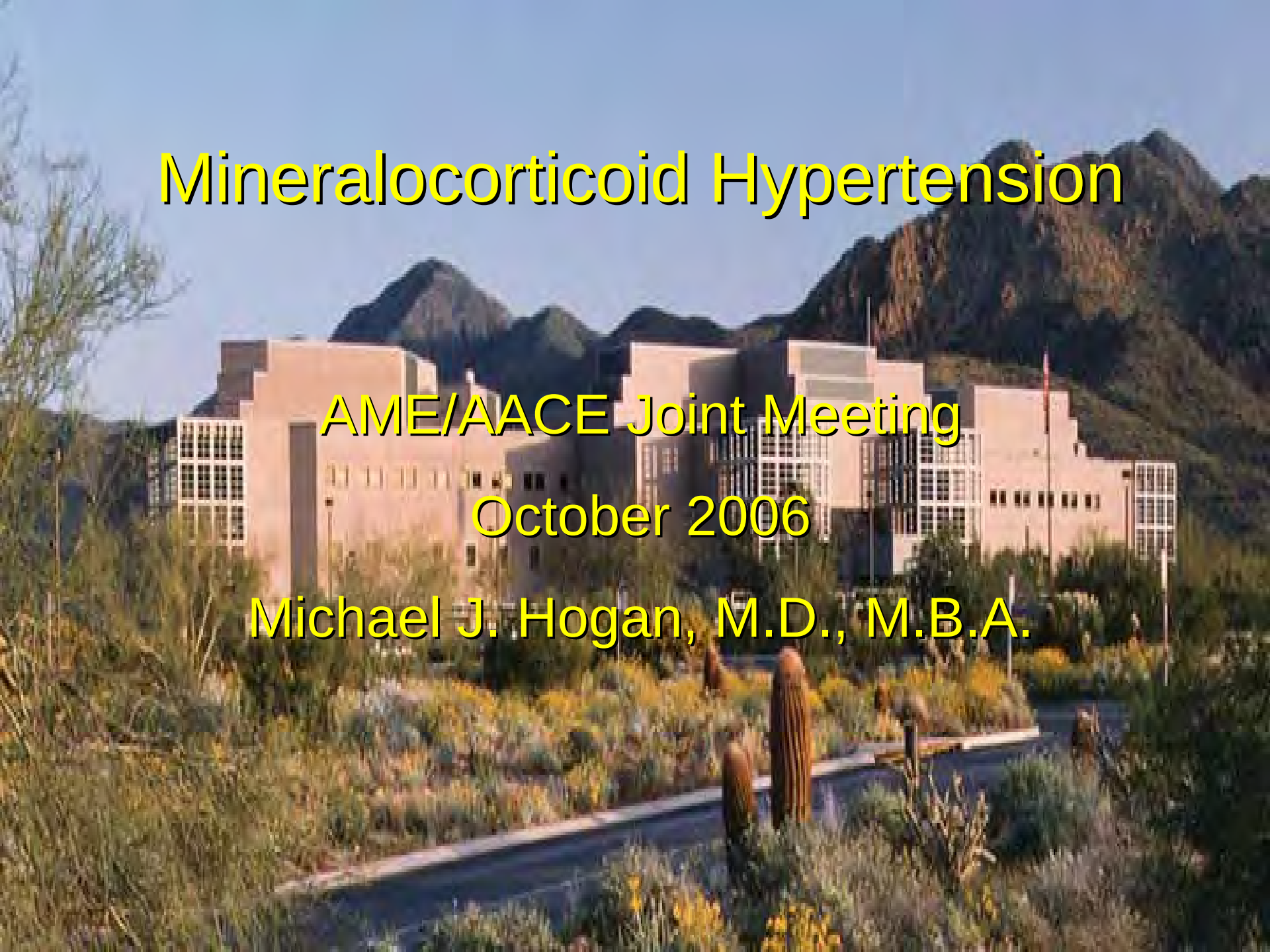

KAHLER
HOTEL



Mineralocorticoid Hypertension

AME/AACE Joint Meeting

October 2006

Michael J. Hogan, M.D., M.B.A.

The speaker, unfortunately, has no financial relationship with any pharmaceutical corporation or medical-device manufacturer.

BLOOD PRESSURE CONTROL

ANGIOTENSINOGEN

↓ ***RENIN***

ANGIOTENSIN - I

(*Inactive*)

ACE

ANGIOTENSIN - II

(Vasoconstrictor)

↓

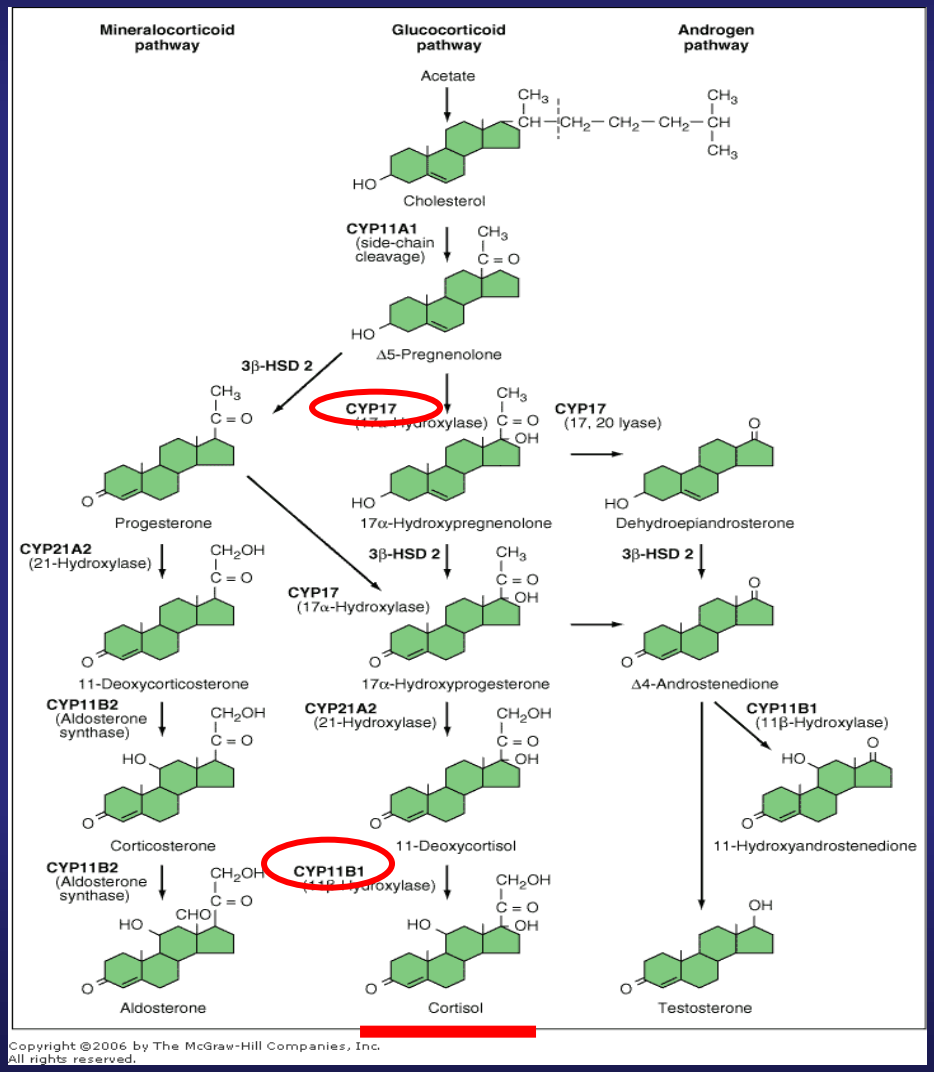
ALDOSTERONE RELEASE

↓

Na^+ REABSORPTION

MINERALOCORTICOID HYPERTENSION

MCH - ↓ Sex Steroids



MCH - ↓ GC activity

MINERALOCORTICOID HYPERTENSION

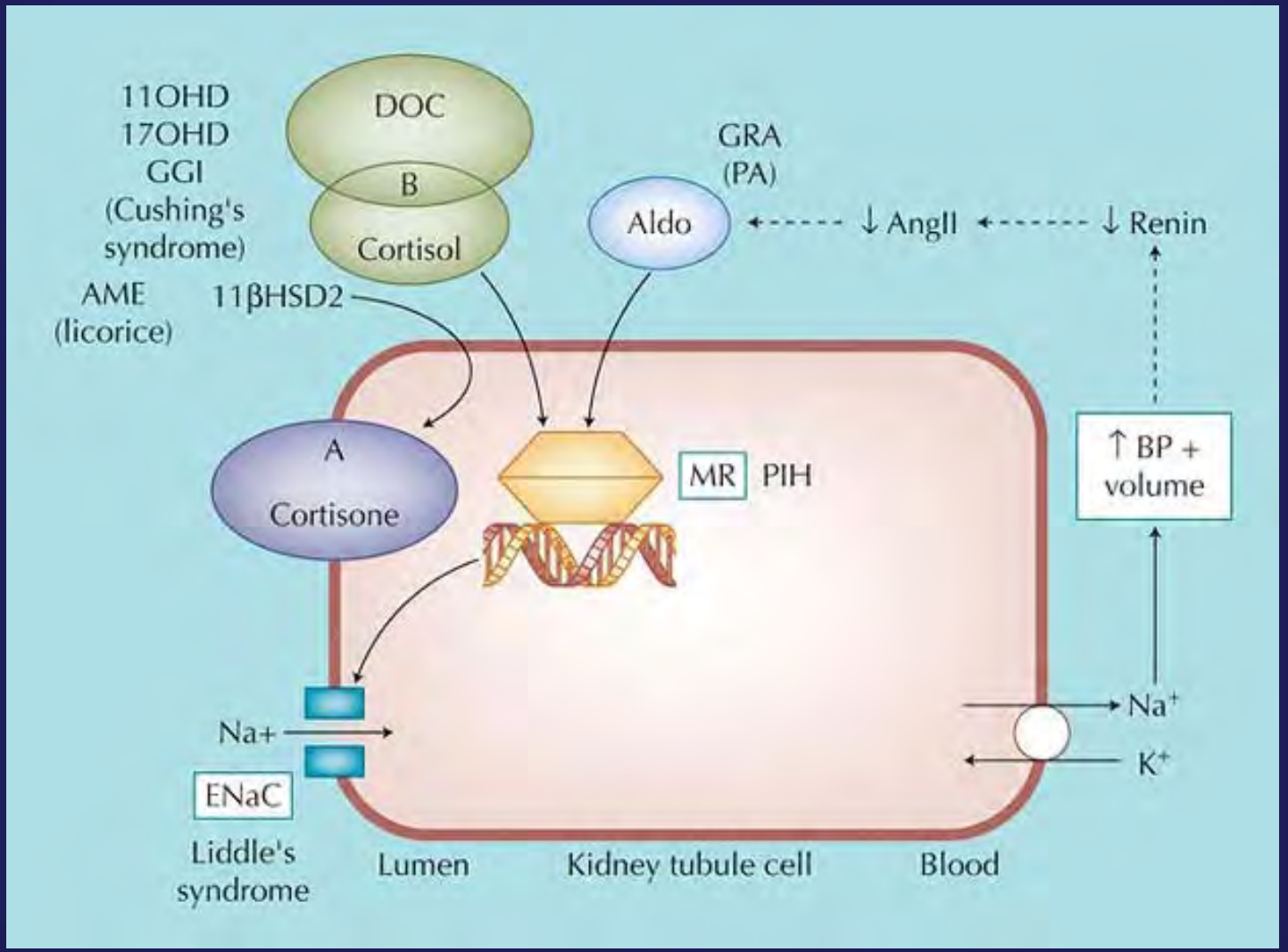
PRIMARY ALDOSTERONISM

Screen: Serum Aldosterone/PRA

Diagnosis:

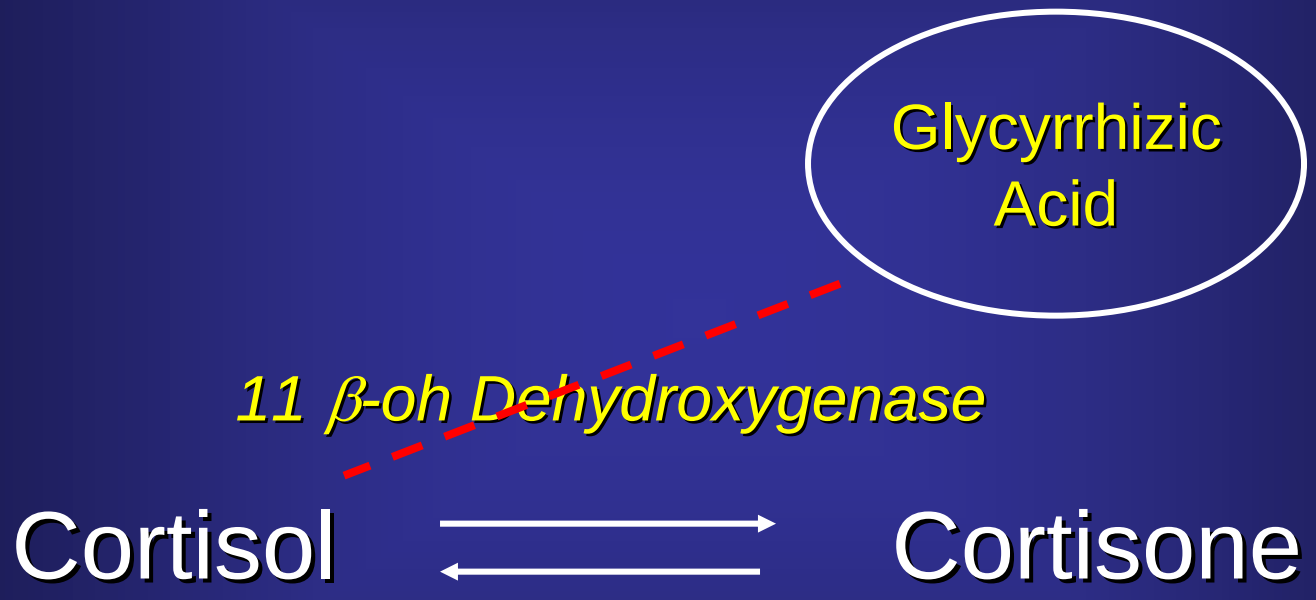
1) Hypertension
2) Hypokalemia (salt replete)
3) Suppressed PRA
4) Elevated Aldosterone excretion rate

MINERALOCORTICOID HYPERTENSION



Auchus R.J. Curr. Card. Reports, 2005

LICORICE-INDUCED HYPERTENSION



MINERALOCORTICOID HYPERTENSION

PRIMARY ALDOSTERONISM

- Unprovoked hypokalemia
- Diuretic sensitivity

  (hypernatremia = volume expansion)
- Inappropriately "normal" K^+ (e.g. ACE Rx + K^+-sparing diruetic)

MINERALOCORTICOID HYPERTENSION

PRIMARY ALDOSTERONISM

Screen: Serum Aldosterone/PRA

Diagnosis:

1) Hypertension
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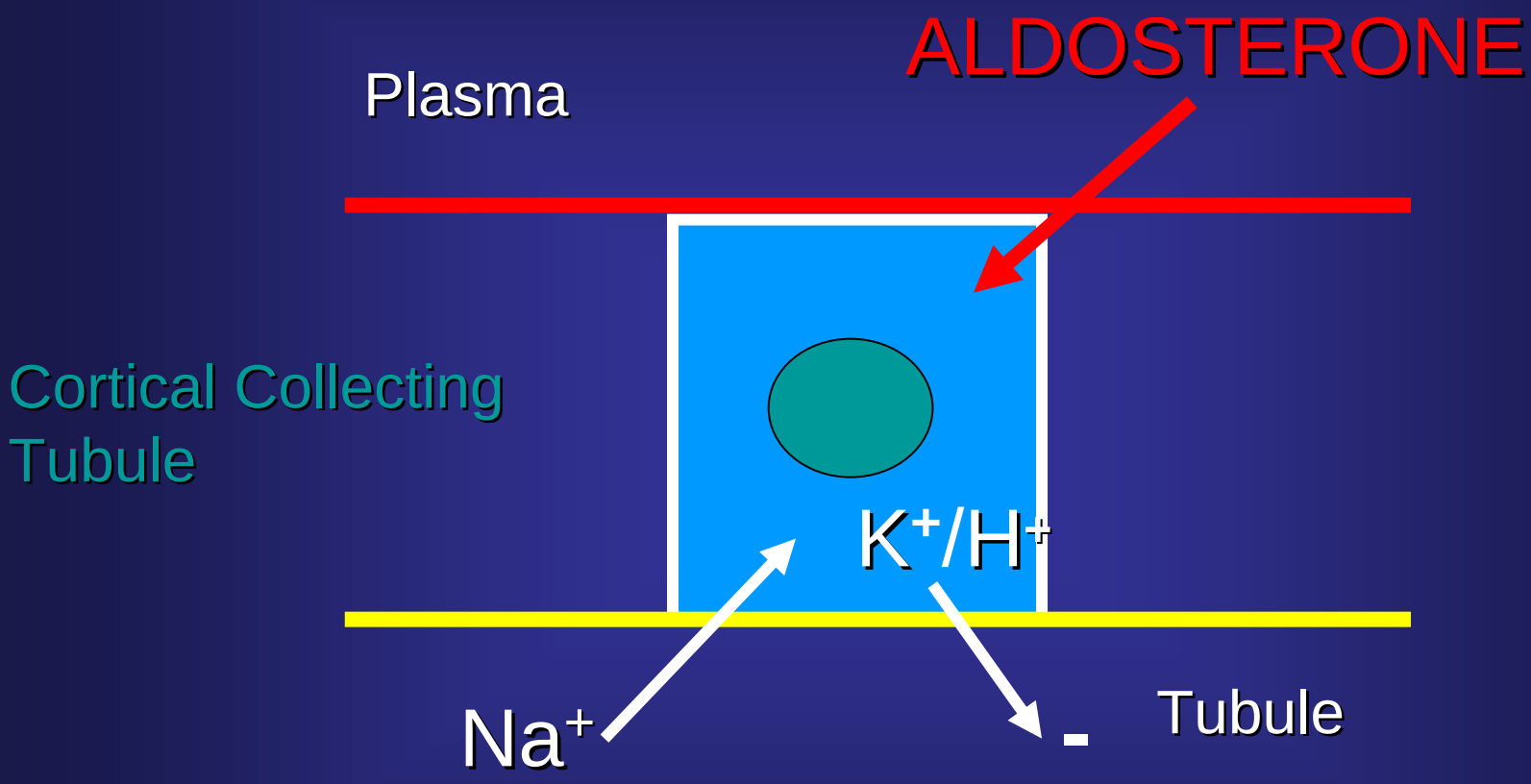
BLOOD PRESSURE CONTROL



MINERALOCORTICOID HYPERTENSION

PRIMARY ALDOSTERONISM

Screen: Serum Aldosterone/PRA

Diagnosis:

1) Hypertension
2) Hypokalemia (salt replete)
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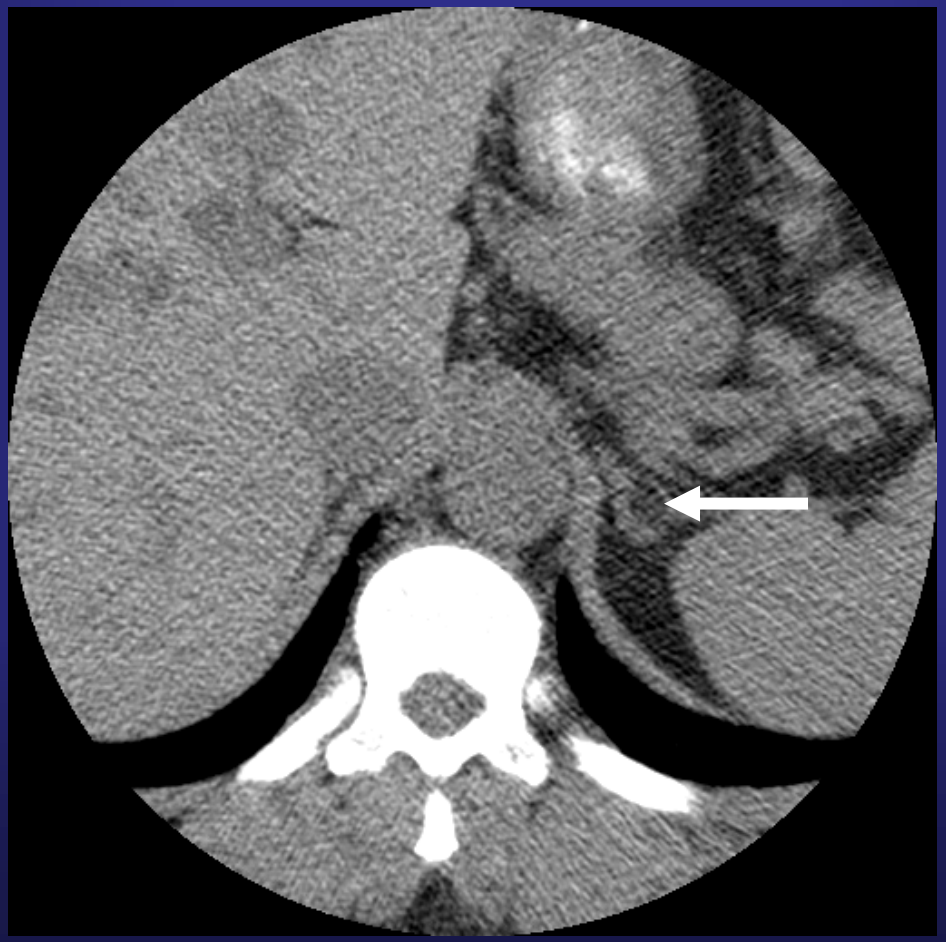
4) Elevated Aldosterone excretion rate

MINERALOCORTICOID HYPERTENSION

APA Localization:



MINERALOCORTICOID HYPERTENSION

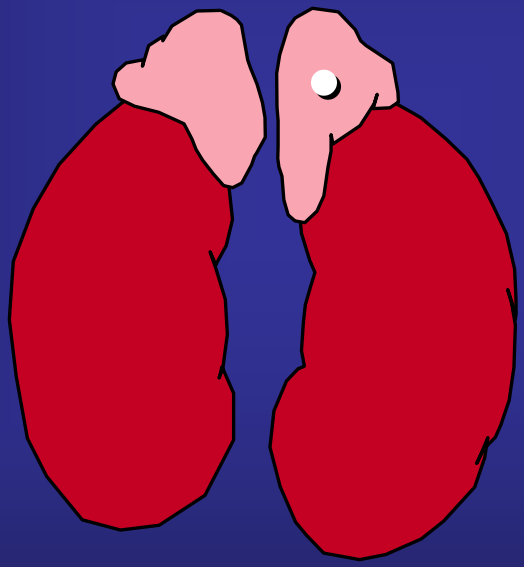
Adrenal Vein Catheterization

A-585/C-360

(1.6)

A-2672/C-334

(8)

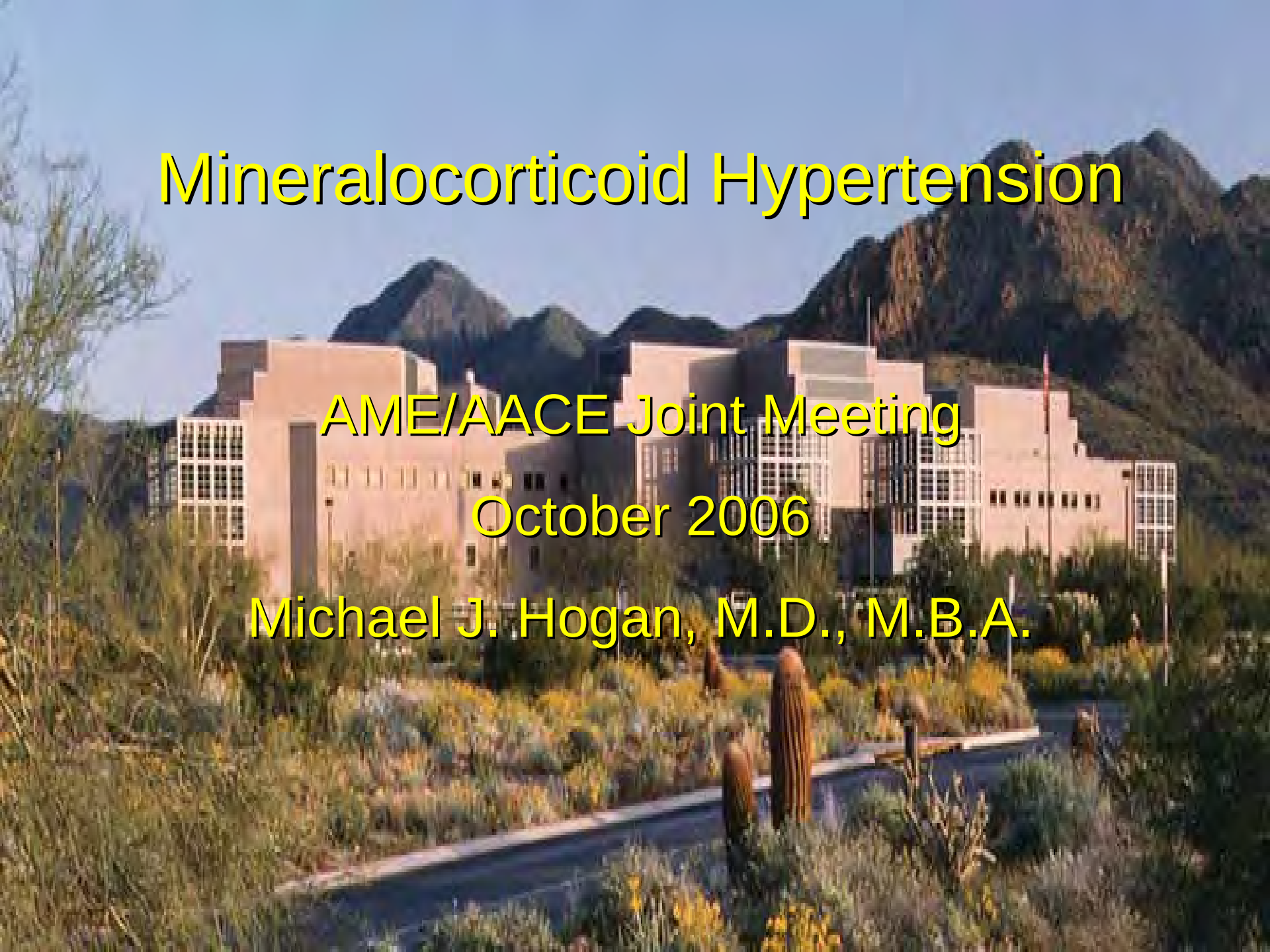


IVC: A-45/C-24

(1.9)

Thank you

Grazie



Mineralocorticoid Hypertension

AME/AACE Joint Meeting

October 2006

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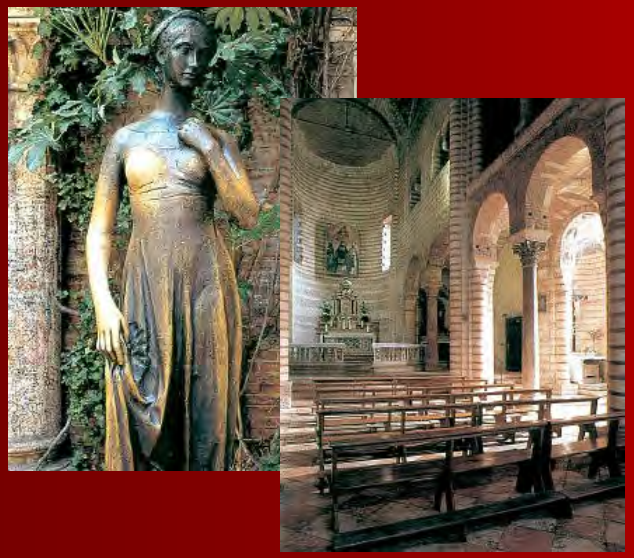
Adrenal Hypertension

Pheochromocytoma:

Screening tests
Confirmatory tests
Imaging assessment



Paola Loli
S.C. Endocrinologia
Ospedale Niguarda Cà Granda

Pheochromocytoma- Epidemiology

Incidence

- 1-2 / 100.000 adults per year (Beard CM, 1983)
- <1 / 100.000 adults per year (Stenstrom, 1986)

Prevalence

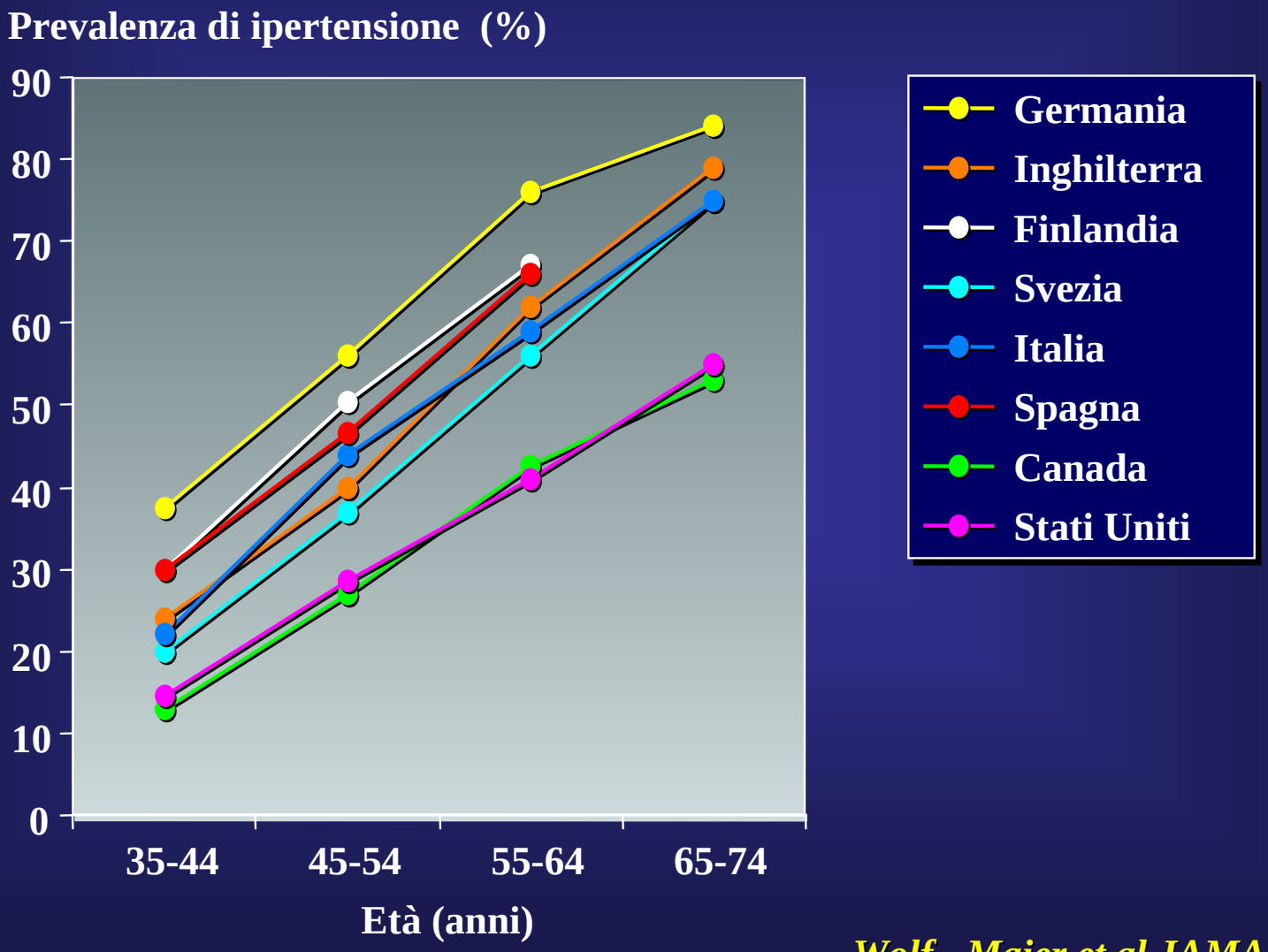
- 0,05% per 2031 autopsies (McNeil, 2000)

Pheochromocytoma - Epidemiology

Prevalence of pheochromocytoma in hypertensive patients

- **0,1 – 0,6%** **(Mannelli, 1999; Omura, 2004)**

Prevalenza di ipertensione per fasce d'età e sesso



Wolf - Maier et al JAMA 2003

Pheochromocytoma - Epidemiology

Prevalence of secondary hypertension

- **5 – 9,1%** **(Greminger, 2003; Omura 2004)**

Prevalence of pheochromocytoma in secondary hypertension

- **6%** **(Omura, 2004)**

Pheochromocytoma - Epidemiology

- **Patients with refractory hypertension**
- **Patients with paroxysmal hypertension**
- **Hypertension in young age**

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Resistant or Difficult-to-Control Hypertension

Table 2. Secondary Causes of Resistant Hypertension.*

Pheochromocytoma	Palpitations; headache; diaphoresis; paroxysms of hypertension	<0.5	Abnormal urinary catecholamine excretion (including norepinephrine, >80 μg/24 hr, and VMA, >5 mg/24 hr); plasma metanephrines; imaging studies (CT or MRI)	
			metanephrines; imaging studies (CT or MRI)	
Cushing's syndrome	Obesity; striae; muscle weakness; increased serum glucose level; fluid retention	<0.5	Increased levels of urinary cortisol (>55 μg/24 hr); positive results on a dexamethasone suppression test; imaging studies (CT or MRI)†	Surgical intervention
Hyperthyroidism or hypothyroidism	Tachycardia; weight loss; anxiety (in hyperthyroidism); weight gain; fatigue (in hypothyroidism)	1.0–3.0	Increased systolic blood pressure (hyperthyroidism); increased diastolic blood pressure (hypothyroidism)	Treatment of underlying disorders
Sleep apnea	Interrupted sleep; snoring; daytime somnolence; obesity	NA	Sleep studies	Weight loss; continuous positive airway pressure; possibly, aldosterone antagonists
Coarctation of the aorta	Brachial or femoral pulse differential; systolic bruits (back and chest)	<1.0	Echocardiography; imaging studies (CT or MRI)	Surgery; balloon angioplasty

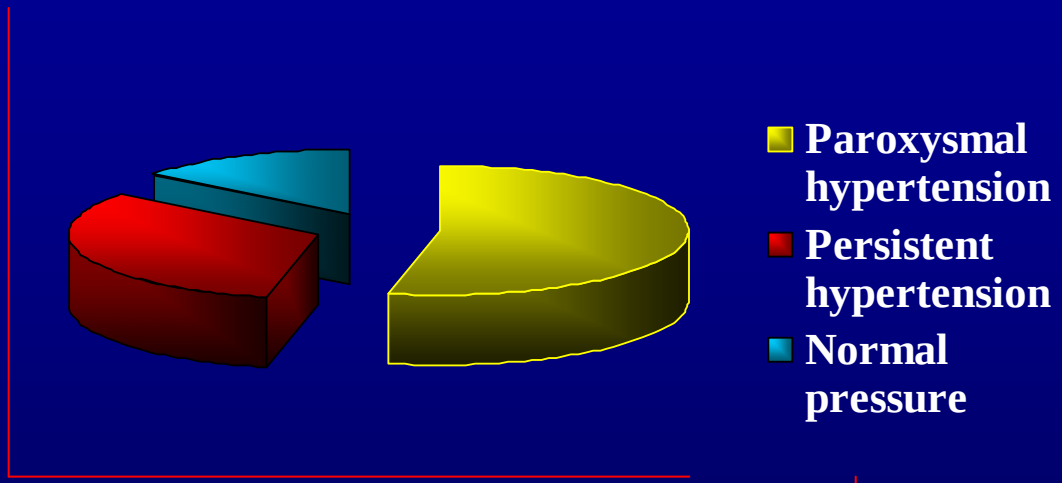
* ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, MRA magnetic resonance angiography, VMA vanillylmandelic acid, CT computed tomography, MRI magnetic resonance imaging, and NA not available.
† Positive results on a dexamethasone suppression test denote an absence of the lowering of plasma cortisol levels below 3 μg per deciliter after the administration of 1 mg of dexamethasone.

NEJM, 355, 4, 2006

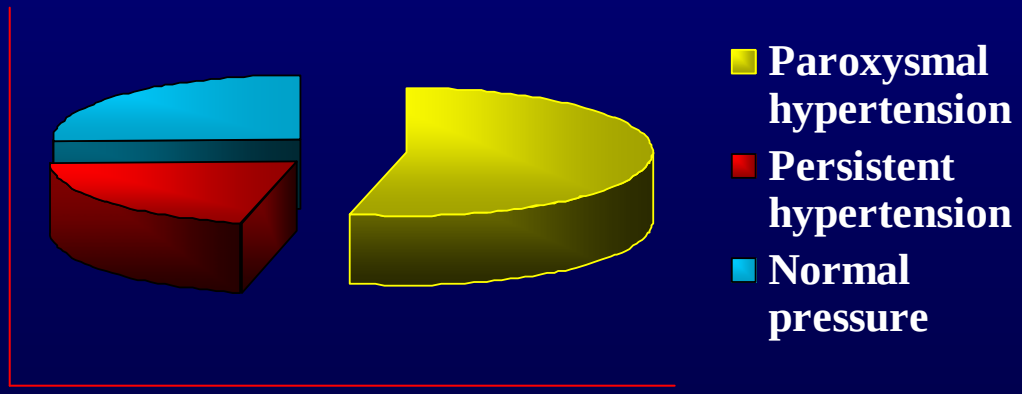
Pheochromocytoma - Epidemiology

- Patients with refractory hypertension
- **Patients with paroxysmal hypertension**
- **Hypertension in young age**

Pheochromocytoma – Blood pressure



Bravo, 2003

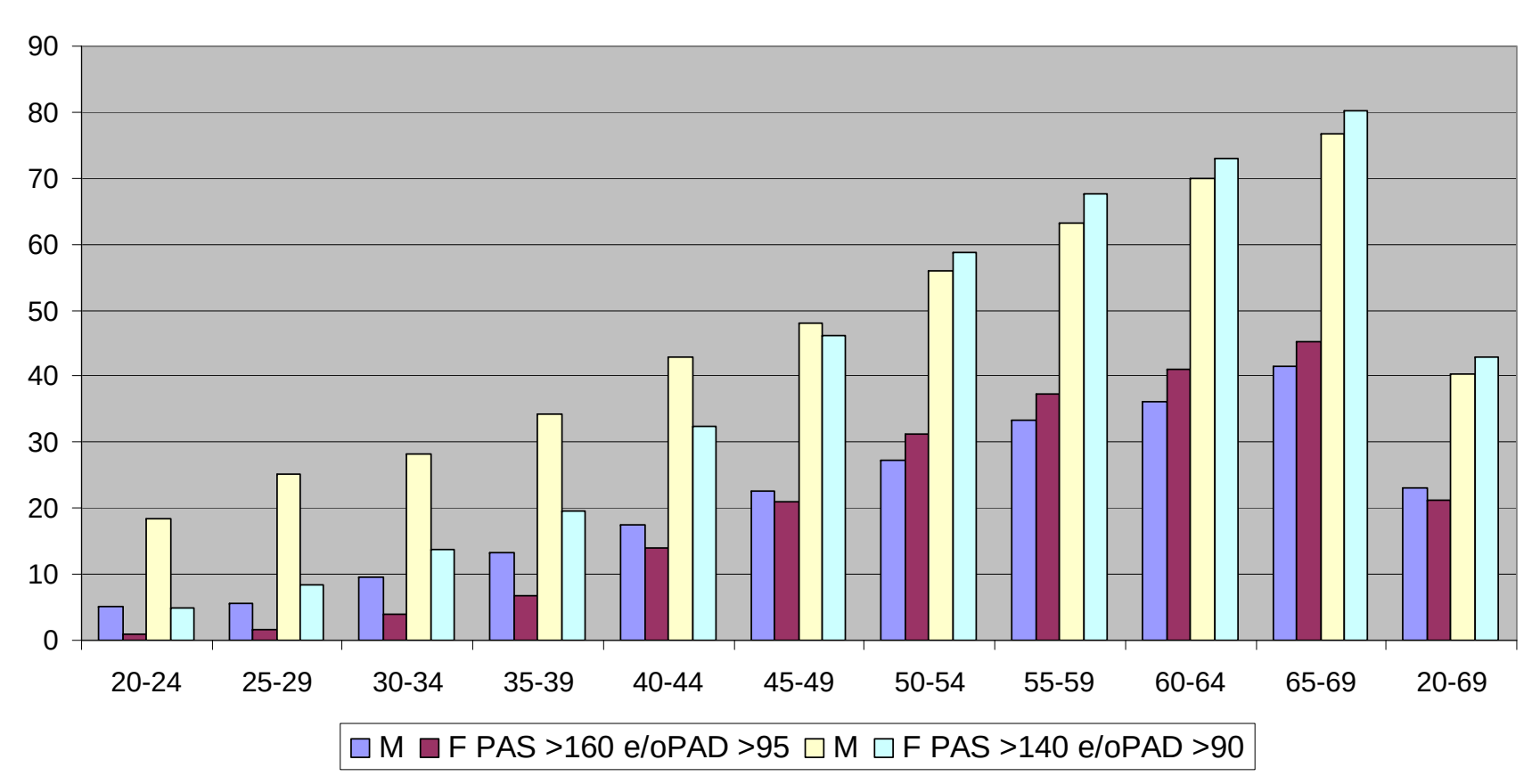


Mannelli, 1999

Pheochromocytoma - Epidemiology

- Patients with refractory hypertension
- Patients with paroxysmal hypertension
- Hypertension in young age

Prevalenza ipertensione in Italia: Studio Rifle (1978-1984)

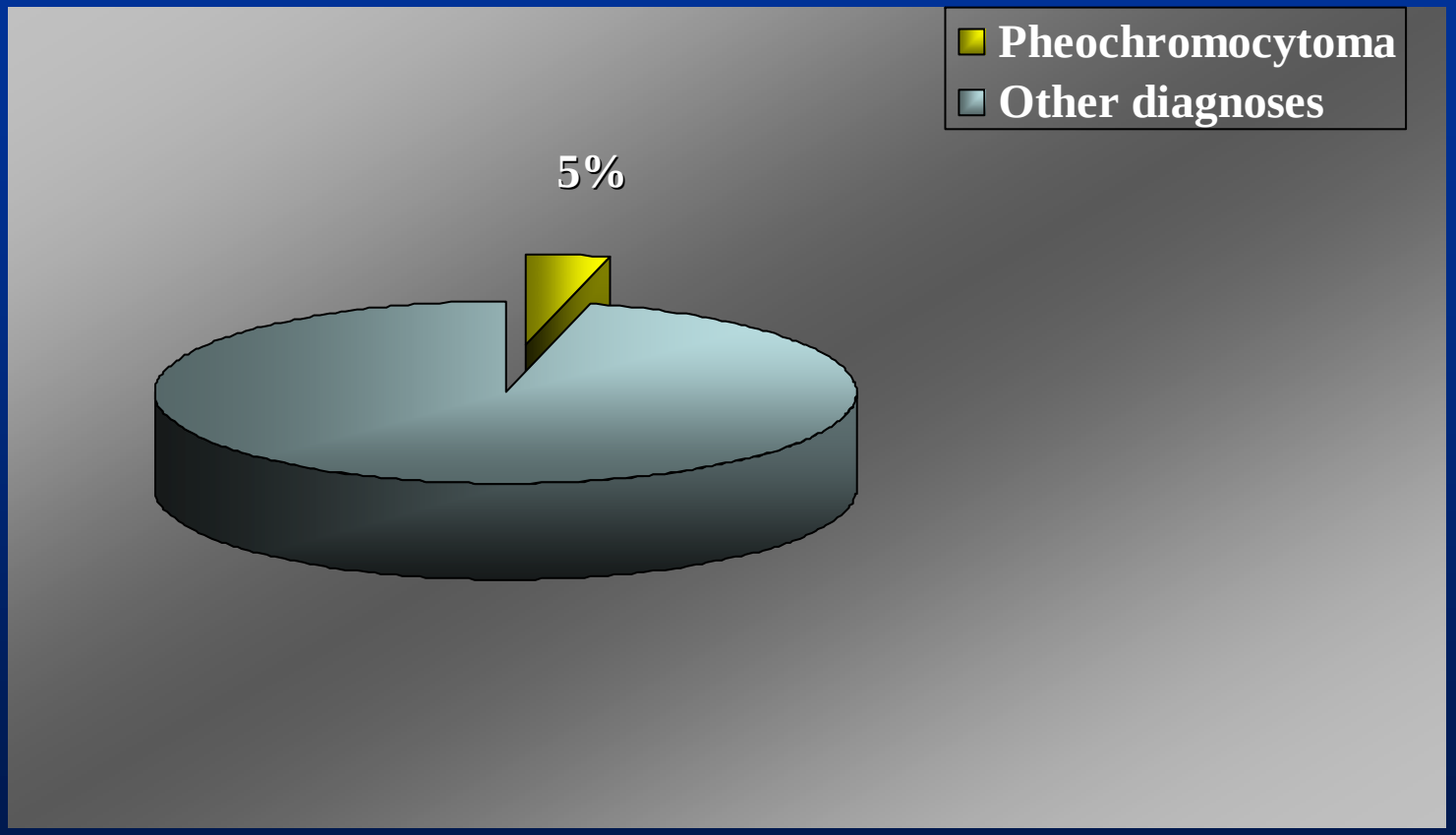


G. Ital. Cardiol 1995; 1539-72

Manifstations and occurrences suggestive of a pheochromocytoma

- episodic symptoms of headaches, tachycardia, and diaphoresis
- family history of pheochromocytoma (MEN, VHL, NF1, PGL 1-4 syndromes)
- Incidentally discovered adrenal mass
- unexplained paroxysms of tachy-bradyarrhythmias and/or hypertension during intubation, induction of anesthesia, parturition,
- Prolonged and unexplained hypotension after an operation;
- Adverse cardiovascular responses to ingestion, inhalation or injection of certain drugs including anesthetic agents, histamine, glucagon, tyramine, TRH, ACTH, antidopaminergic agents, naloxone, phenothiazine, beta blockers, guanethidine, trycyclic antidepressants
- attacks occurring during exertion, straining, coitus, or micturition.

Prevalence of pheochromocytoma in 339 incidentally discovered adrenal masses



S.C. Endocrinologia, 1987 - 2005

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- attacks occurring during exertion, straining, coitus, or micturition.

Pheochromocytoma – diagnostic tests

- Plasma catecholamines
- Urinary catecholamines
- Total urinary metanephrines
- Urinary fractionated metanephrines
- Plasma metanephrines
- Chromogranin A

PLASMA CATECHOLAMINES

- **Sensitivity 67% - 94%** *Lenders, 1995*

- **False positives**

  Emotional stress

  Congestive heart failure

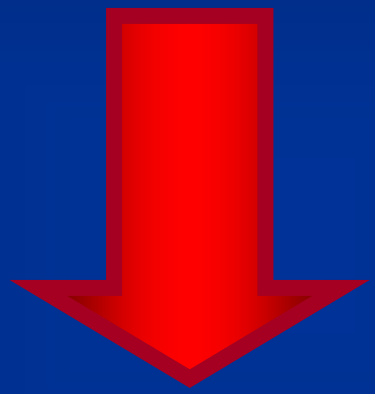
Thomas JA, Am J Cardiol. 1978;
Cryer PE. N Engl J Med. 1980

Sensitivities and specificities of biochemical tests for diagnosis of pheochromocytoma

	sensitivity	specificity
Plasma free metanephrines	99% (211/214)	89% (575/644)
Plasma catecholamines	84% (178/212)	81% (523/643)
Urine fractionated metanephrines	97% (102/105)	69% (310/452)
Urine catecholamines	86% (151/175)	88% (471/535)
Urine total metanephrines	77% (88/114)	93% (170/183)
Urine vanillylmandelic acid	64% (96/151)	95% (442/465)

modificata da Lenders, Ann. N.Y. Acad. Sci, 2002

Improuvement in radiological technology and genetic assessment



Limits of current diagnostic testing

Plasma fractionated metanephrines

- Produced almost exclusively by the intratumoral metabolism of catecholamines
- Produced continuously, and independently of variation in exocytotic catecholamine release
- Independent from relevant increases in catecholamine release from autonomous nervous system

Biochemical Diagnosis of Pheochromocytoma

Which Test Is Best?

Jacques W. M. Lenders, MD, PhD
Karel Pacak, MD, PhD
McClellan M. Walther, MD
W. Marston Linehan, MD
Massimo Mannelli, MD
Peter Friberg, MD, PhD
Harry R. Keiser, MD
David S. Goldstein, MD, PhD
Graeme Eisenhofer, PhD

Context Diagnosis of pheochromocytoma depends on biochemical evidence of catecholamine production by the tumor. However, the best test to establish the diagnosis has not been determined.

Objective To determine the biochemical test or combination of tests that provides the best method for diagnosis of pheochromocytoma.

Design, Setting, and Participants Multicenter cohort study of patients tested for pheochromocytoma at 4 referral centers between 1994 and 2001. The analysis included 214 patients in whom the diagnosis of pheochromocytoma was confirmed and 644 patients who were determined to not have the tumor.

PHEOCHROMOCYTOMAS AR
chromaffin cell tumors typ
cally arising in the adren
glands and characterized by e
cessive production of catecholamines,
ten leading to increased blood pressu
and symptoms of catecholamine e
cess. If not diagnosed or if left u
treated, the excessive secretion of ca
echolamines by these tumors can ha
devastating consequences. Thus, a
though pheochromocytomas are rare t
mors, they must be considered in ma
patients with hypertension, the latt
representing up to a quarter of the adu
population in Western countries.

Table 3. Sensitivities and Specificities of Biochemical Tests for Diagnosis of Hereditary and Sporadic Pheochromocytoma*

	Sensitivity, %†		Specificity, %‡	
	Hereditary	Sporadic	Hereditary	Sporadic
Plasma				
Free metanephrines	97 (74/76)	99 (137/138)	96 (326/339)	82 (249/305)
Catecholamines	69 (52/75)	92 (126/137)	89 (303/339)	72 (220/304)
Urine				
Fractionated metanephrines	96 (26/27)	97 (76/78)	82 (237/288)	45 (73/164)
Catecholamines	79 (54/68)	91 (97/107)	96 (312/324)	75 (159/211)
Total metanephrines	60 (27/45)	88 (61/69)	97 (91/94)	89 (79/89)
Vanillylmandelic acid	46 (30/65)	77 (66/86)	99 (310/312)	86 (132/153)

*The reference limits used to calculate sensitivity and specificity are presented in Table 2.
†For free plasma metanephrines or urinary fractionated metanephrines, sensitivity was calculated from patients with pheochromocytoma and false-negative test results for both normetanephrine and metanephrine. For plasma and urine catecholamines, sensitivity was calculated from patients with both false-negative test results for nonrepinephrine and epinephrine. Numbers in parentheses indicate true positive over true positive plus false-negative.
‡For free plasma metanephrines or urinary fractionated metanephrines, specificity was calculated from patients without pheochromocytoma and with false-positive test results for either normetanephrine or metanephrine. For plasma and urine catecholamines, specificity was calculated from patients without pheochromocytoma and with false-positive test results for either nonrepinephrine or epinephrine. Numbers in parentheses indicate true negative over true negative plus false-positive.

JAMA, 2002

A Comparison of Biochemical Tests for Pheochromocytoma: Measurement of Fractionated Plasma Metanephrines Compared with the Combination of 24-Hour Urinary Metanephrines and Catecholamines

ANNA M. SAWKA, ROMAN JAESCHKE, RAVINDER J. SINGH, AND WILLIAM F. YOUNG, JR.

Division of Endocrinology, Metabolism, Nutrition, and Internal Medicine (W.F.Y.), and Division of Clinical Biochemistry and Immunology (R.J.S.), Mayo Clinic, Rochester, Minnesota 55905; and Department of Medicine (A.M.S., R.J.), St. Joseph's Healthcare of McMaster University, Hamilton, Ontario, Canada L8N 4A6

TABLE 1. Comparison of diagnostic efficacy of biochemical assays for detection of pheochromocytoma

Biochemical test	Sensitivity[a]	Specificity[a]	Likelihood ratio of a positive test (95% CI)	Likelihood ratio of a negative test (95% CI)
Fractionated plasma metanephrines	30/31 (97)	221/261 (85)	6.3 (4.7–8.5)	0.04 (0.006–0.26)
24-h urinary total metanephrines and catecholamines (either test positive)	28/31 (90)	257/261 (98)	58.9 (22.1–156.9)	0.10 (0.03–0.29)

[a] Data represent number of patients (percentage).

JCE&M, 2003

Optimizing the measurement of plasma and urine fractionated metanephrines (to reduce false positives)

Establishing appropriate cut off values for the different groups of patients at risk

Perform additional biochemical testing

Choice of biochemical testing directed by the degree of clinical suspicion

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Establishing appropriate cut off values for the different groups of patients at risk

Perform addditional biochemical testing

Choice of biochemical testing directed by the degree of clinical suspicion

Research article

Measurement of fractionated plasma metanephrines for exclusion of pheochromocytoma: Can specificity be improved by adjustment for age?

Anna M Sawka*[1,2], Lehana Thabane[3,4], Amiram Gafni[4], Mitchell Levine[1,3,4] and William F Young Jr[5]

Abstract

Background: Biochemical testing for pheochromocytoma by measurement of fractionated plasma metanephrines is limited by false positive rates of up to 18% in people without known genetic predisposition to the disease. The plasma normetanephrine fraction is responsible for most false positives

McNemar's test).

Conclusion: An adjustment for age in the interpretation of results may significantly decrease false positives when using this test to e Such improvements in false positive rate may result in savings of imaging.

However, the false positive rate with traditional interpretation of fractionated plasma metanephrine measurements was 16.3% (22/135, 95% CI, 11.0%, 23.4%) and that of the age-adjusted score was significantly lower at 3.0% (4/135, 95% CI, 1.2%, 7.4%) ($p < 0.001$ using McNemar's test).

Conclusion: An adjustment for age in the interpretation of results of fractionated plasma metaNephrines may significa when using this test to exclude sporadic pheochr Such improvements in false positive rate may res related to Confirmatory imaging.

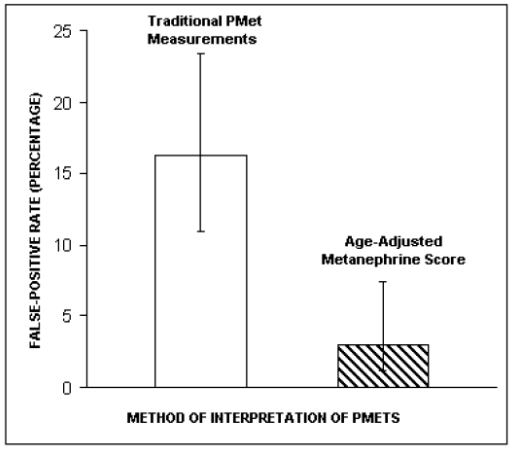

Figure 1
Percentage of false positive test results (and 95% confidence interval) at 100% sensitivity in using a traditional interpretation of fractionated plasma metanephrine measurements or an age-adjusted metanephrine score.

BMC Endocrine disorders, 2005

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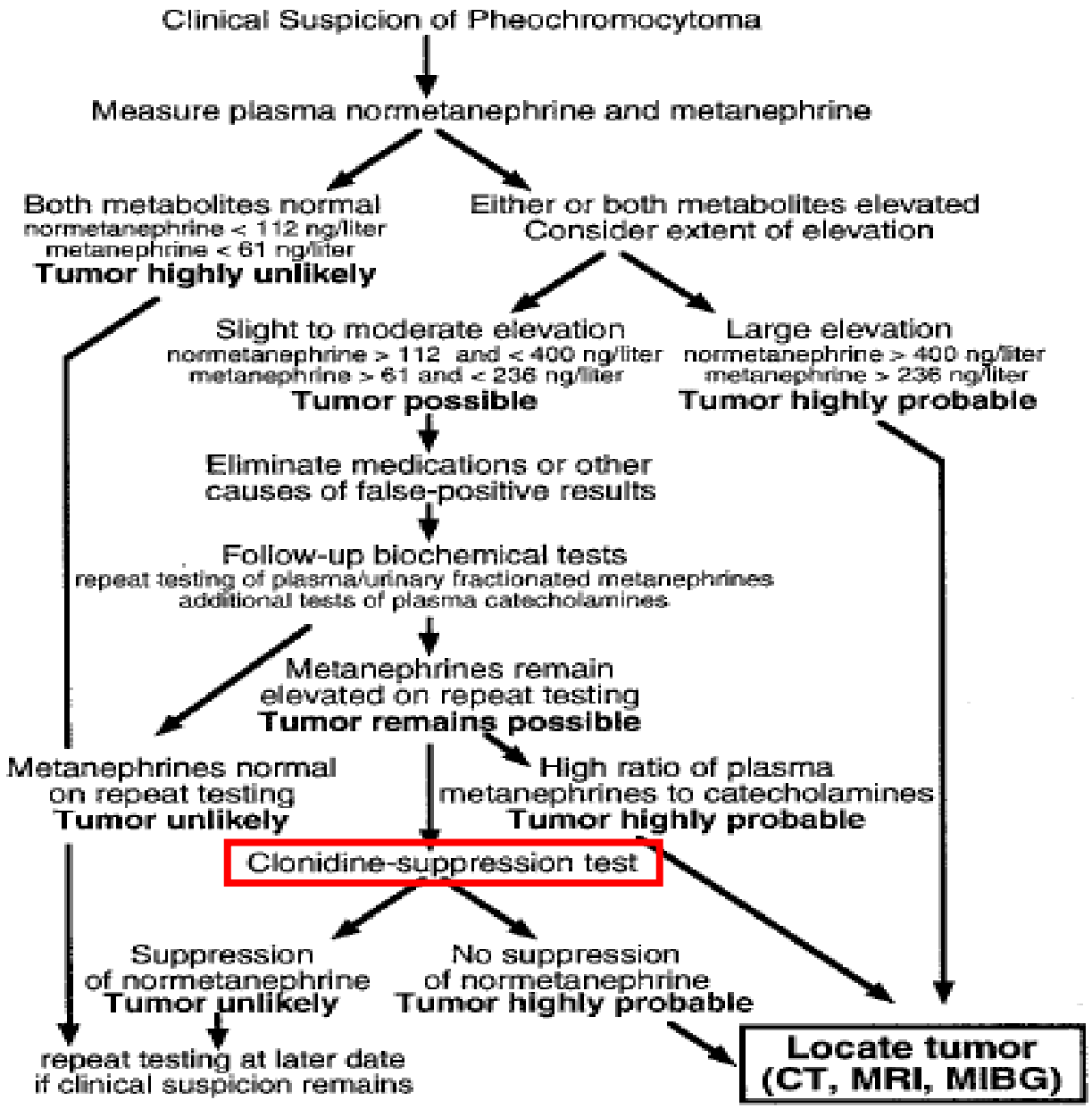

FIG. 6. Algorithm for biochemical diagnosis of pheochromocytoma. To convert values to nanomoles per liter, divide by 183 for normetanephrine, and 197 for metanephrine.

J CE&M, 2003,

Clonidine suppression test

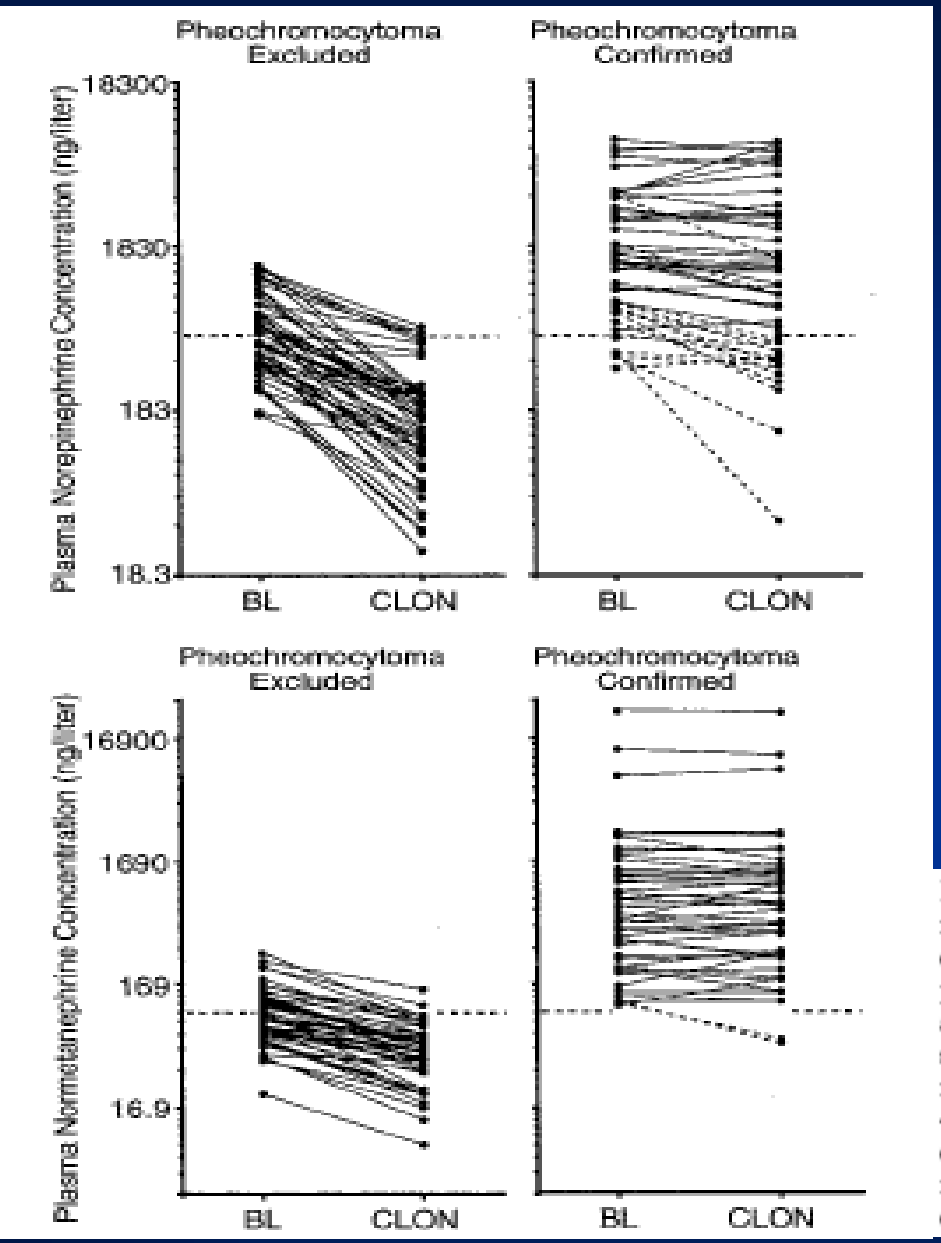

FIG. 4. Plasma concentrations of norepinephrine and normetanephrine before and after clonidine in patients with and without pheochromocytoma. Results in patients with (n = 48) and without (n = 49) pheochromocytoma are shown at baseline (BL) compared with after administration of clonidine (CLON). The *dashed horizontal lines* show the upper reference limits for each test. False-positive test results, either reflecting larger than 50% falls in norepinephrine or 40% falls in normetanephrine, or normal levels of both amines after clonidine are indicated by the *dotted lines*. To convert values to nanomoles per liter, divide by 183 for normetanephrine and 169 for norepinephrine.

Eisenhofer, JCE&M, 2003

Chromogranin A

Table 4. Percentage sensitivity, specificity, positive and negative likelihood ratios (95% confidence interval)* of chromogranin A, catecholamines and metabolites

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Chromogranin A	91 (69–98)	95 (73–99)	95 (74–99)	90 (68–98)
Epinephrine	82 (59–94)	100 (80–100)	100 (78–100)	83 (62–94)
Norepinephrine	77 (54–91)	100 (80–100)	100 (77–100)	80 (59–92)
Metanephrine	84 (59–96)	100 (78–100)	100 (76–100)	86 (63–96)
Normetanephrine	89 (65–98)	94 (71–99)	94 (71–99)	89 (65–98)

*Ninety-five per cent confidence intervals were calculated according to the efficient-score method.

Grossrubatscher, 2006

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Pheochromocytoma - Localization -

- CT
- MRI
- MIBG Scintigraphy
- Octreoscan
- PET 18F-fluorodeoxyglucose
  11C-hydroxyephedrine
  [18F]DOPA
  6-[18F]fluorodopamine

Pheochromocytoma - Localization -

- **CT**
- **MRI**
- **MIBG scintigraphy**
- **Octreoscan**
- **PET** **[18F]FDG PET**
  [^{11}C]-hydroxyephedrine
  [^{18}F]DOPA
  [^{18}F]DA

Pheochromocytoma localization - Conventional imaging

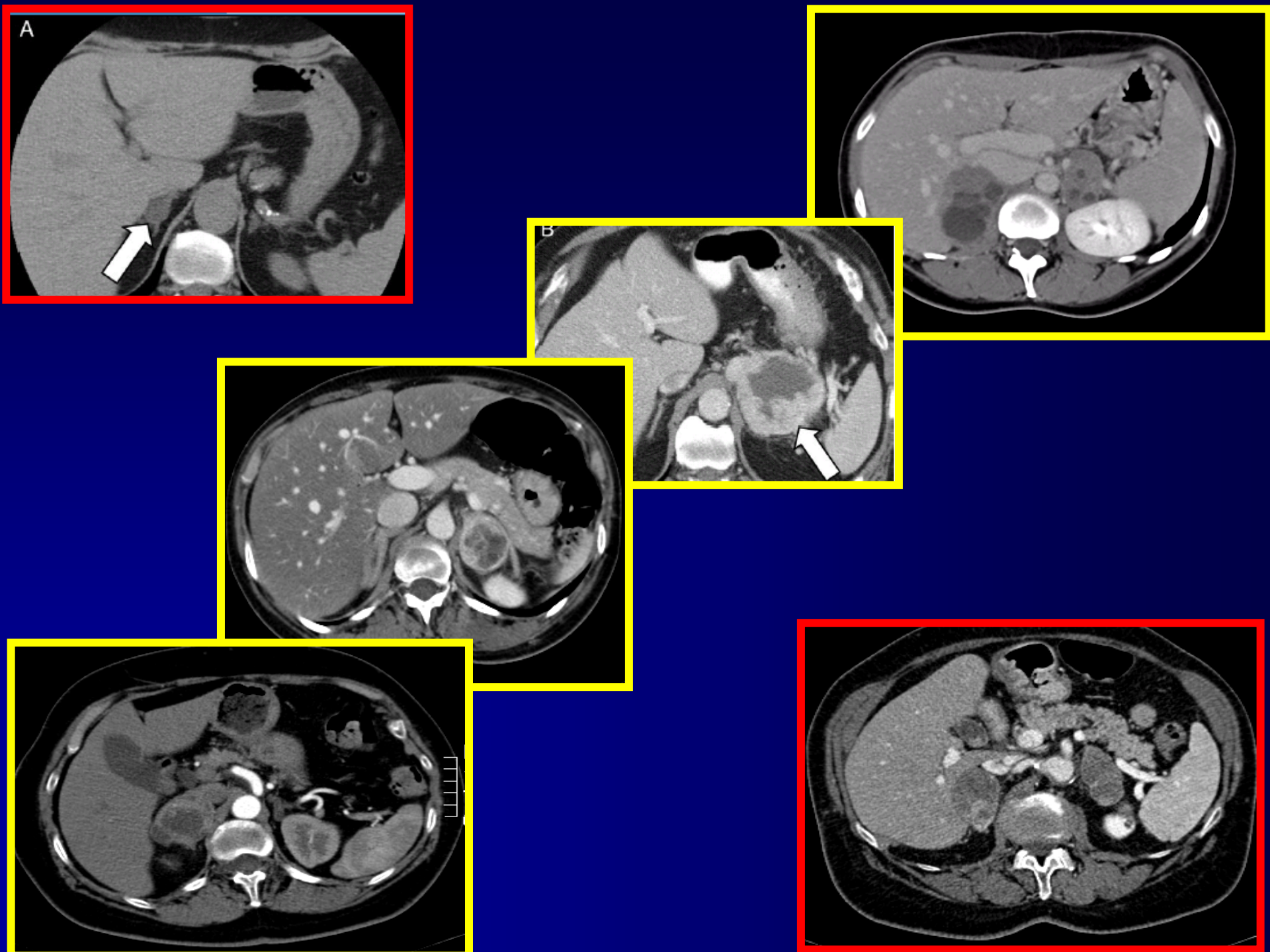
Intraadrenal pheochromocytoma

CT	Sensitivity	93-100%
RM	Specificity	70%

Extraadrenal pheochromocytoma

CT sensitivity 90% (Mannelli, 1999)

RM > sensitivity in extraadrenal pheochomocytoma (Francis, 1996)


A
B

AJR 2003; 181:1663-1668

Low-Density Pheochromocytoma on CT: A Mimicker of Adrenal Adenoma

Michael A. Blake[1], Saravanan K. Krishnamoorthy[1], Giles W. Boland[1], Ann T. Sweeney[2], Martha B. Pitman[3], Mukesh Harisinghani[1], Peter R. Mueller[1] and Peter F. Hahn[1]

[1] Department of Radiology, Division of Abdominal Imaging and Intervention, Massachusetts General Hospital, 55 Fruit St., White 270, Boston, MA 02114.
[2] Department of Medicine, Division of Endocrinology, St. Elizabeth's Medical Center, 736 Cambridge St., Boston, MA 02135.
[3] Department of Pathology, Massachusetts General Hospital, Boston, MA 02114.

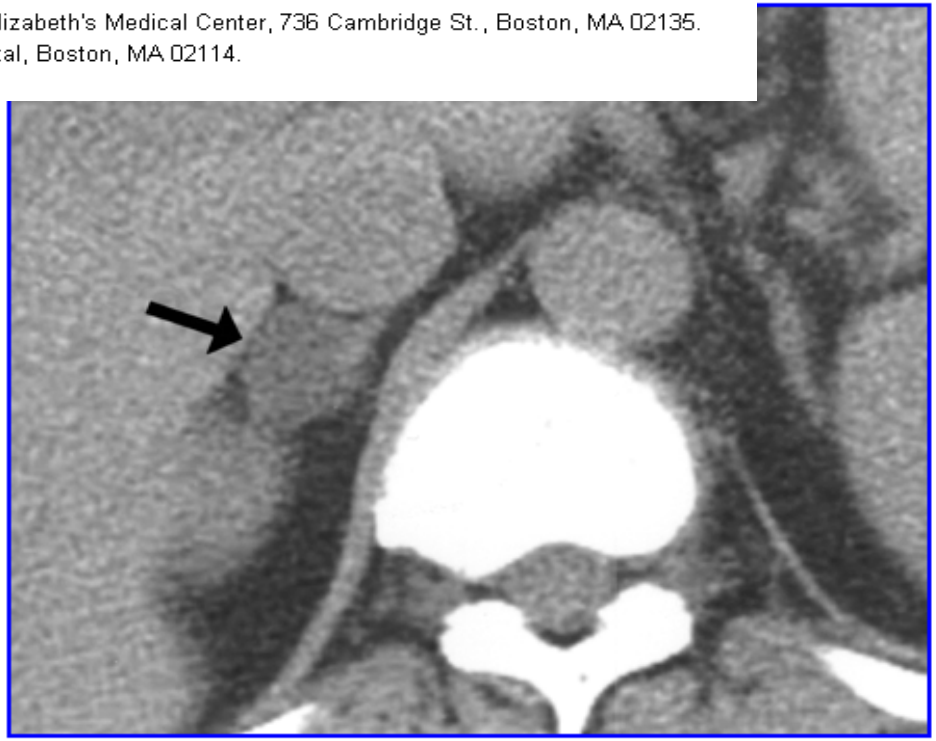
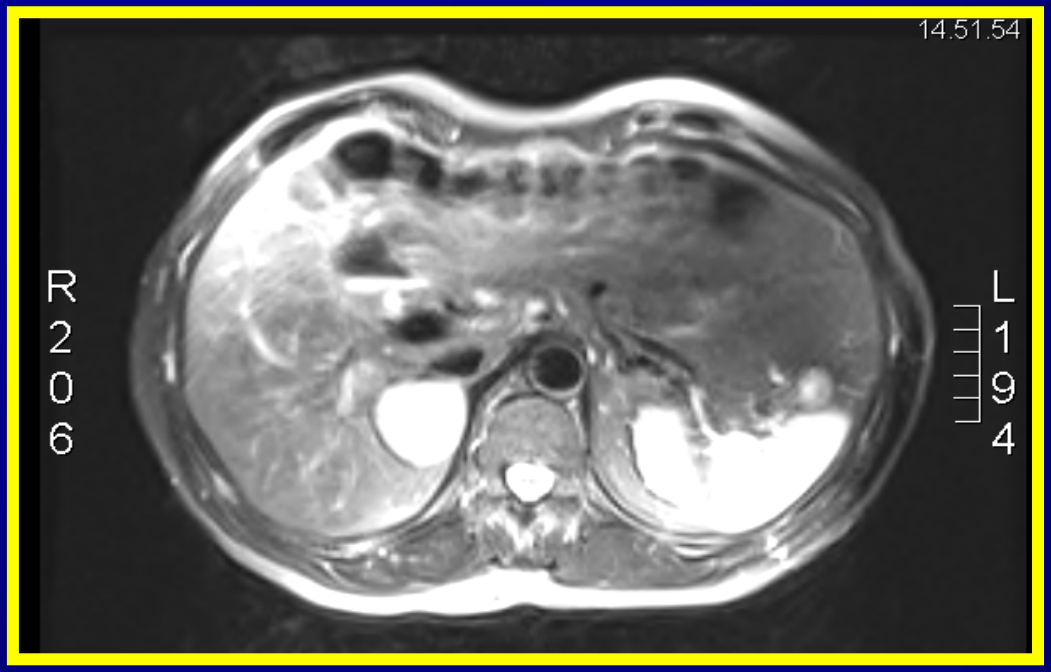


Fig. 2A. —49-year-old woman with low-density pheochromocytoma who has neurofibromatosis 1. CT scan shows rounded low-density right adrenal mass (*arrow*) with attenuation value of 9 H.


14.51.54
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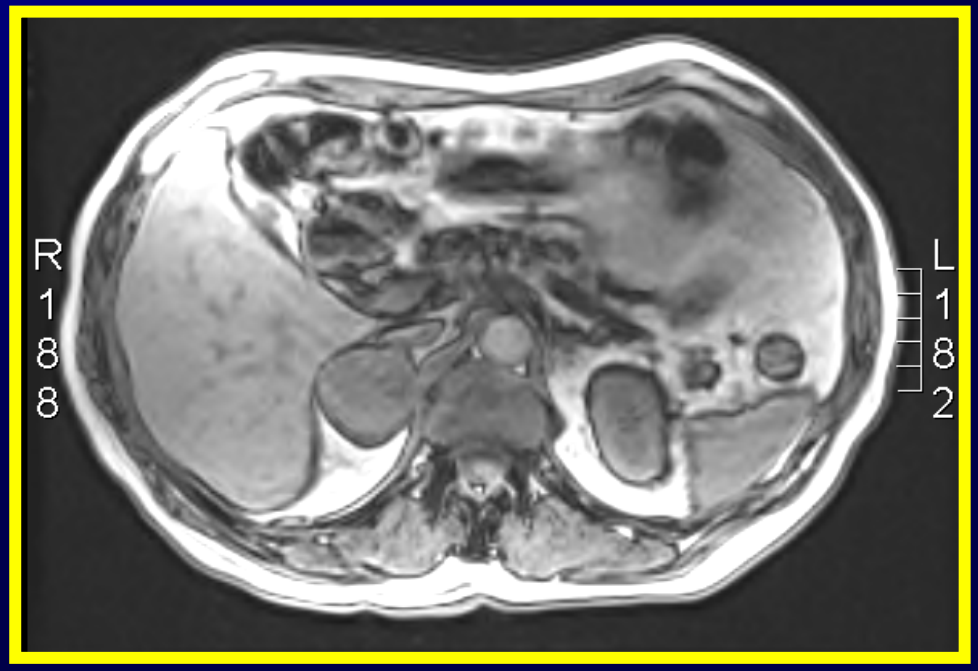
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Pheochromocytoma - Localization -

- CT
- MRI
- **MIBG scintigraphy**
- **Octreoscan**
- **PET** **[18F]FDG PET**
  [^{11}C]-hydroxyephedrine
  [^{18}F]DOPA
  [^{18}F]DA

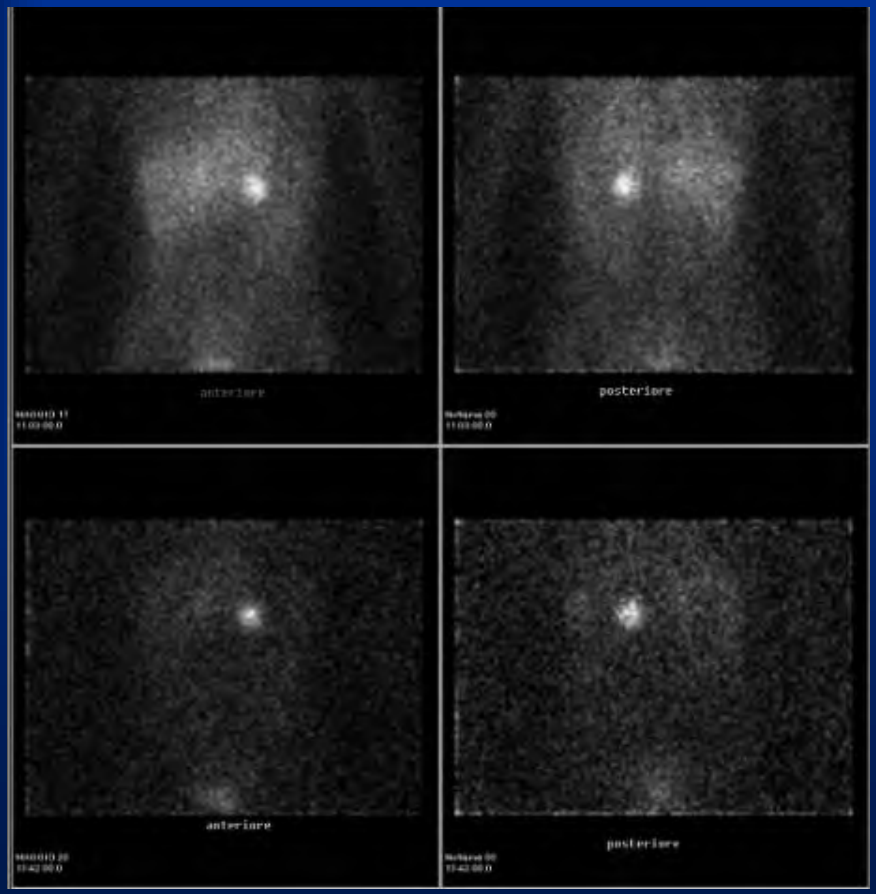
Functional imaging

Extra adrenal lesions

Multiple lesions

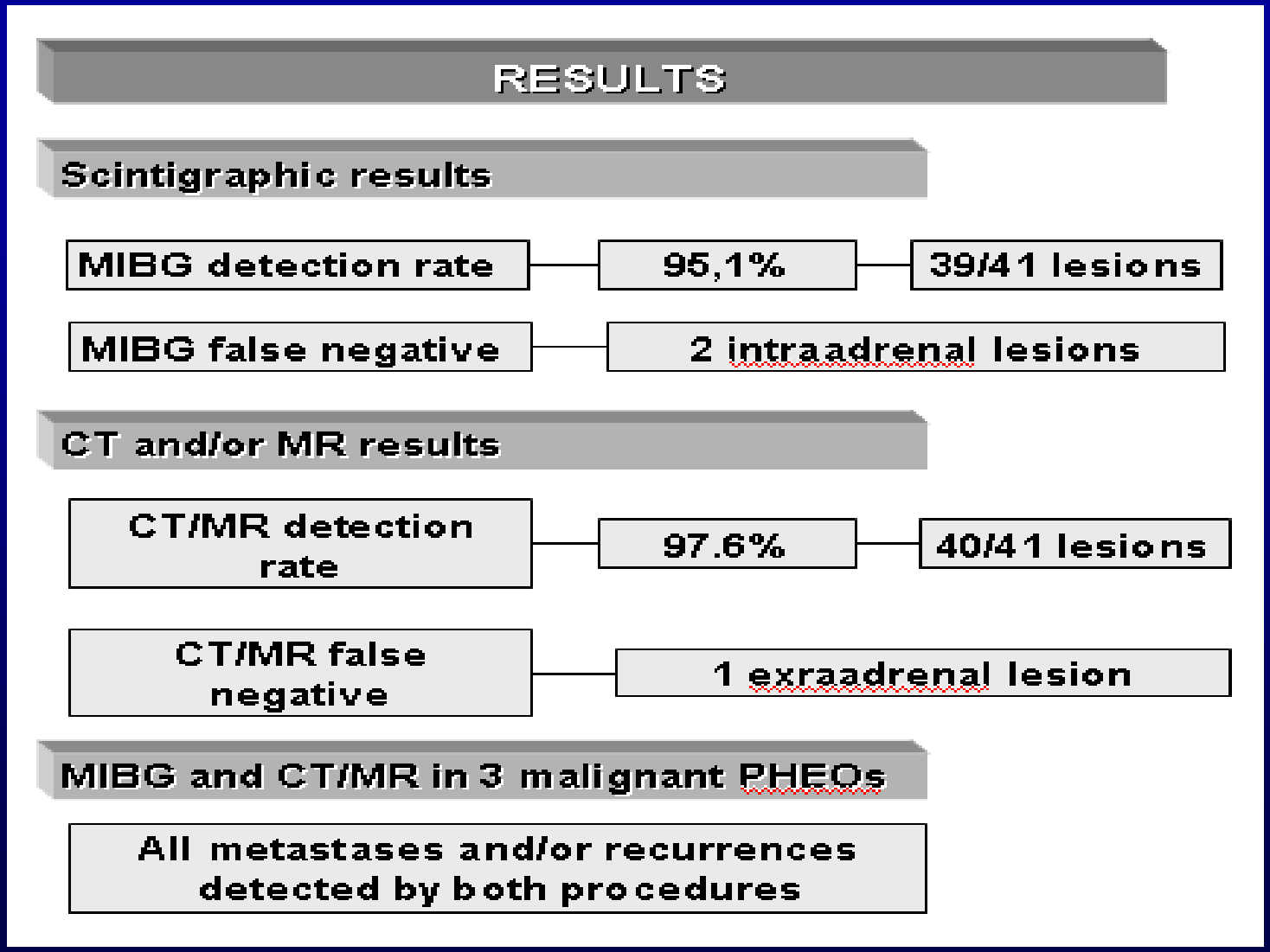
Metastases

MIBG Scintigraphy



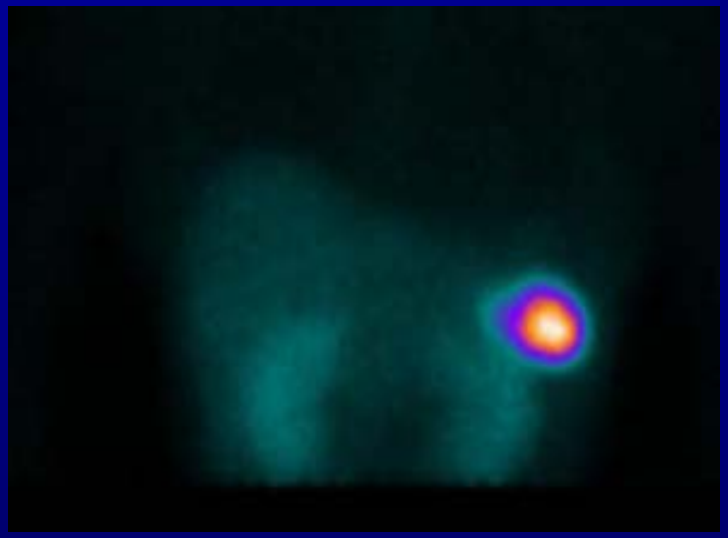
- Catecholamine analog
- uses the amine precursor uptake and storage mechanism
- ^{123}I or ^{131}I
- Sensitivity 83 – 100%
- Specificity 95 – 100%
- False negatives and false positives

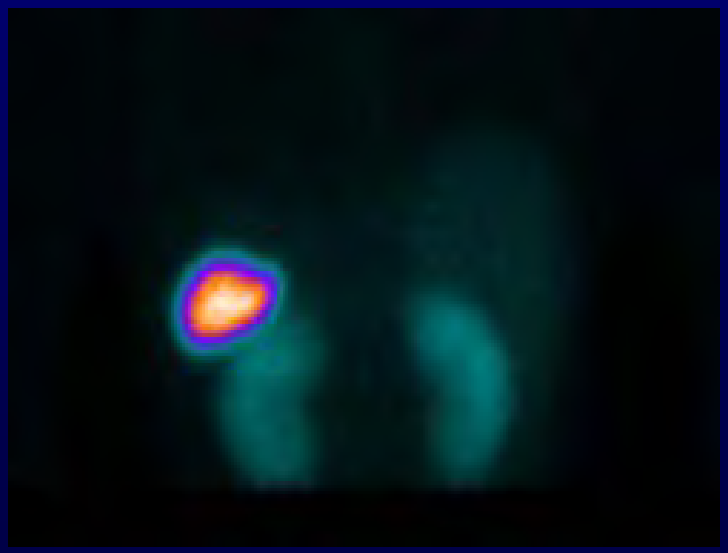
Metaiodobenzylguanidine scintigraphy in patients with pheochromocytoma



Grossrubatscher E., 2002

Octreoscan





- Low sensitivity
- More effective in detecting malignant, metastatic pheo than benign, intraadrenal lesions
- Complementary role

Pheochromocytoma - Localization – FDG - PET

TABLE 2
Findings at FDG PET and MIBG Scintigraphy in Benign Pheochromocytomas

	MIBG	
FDG	Positive	Negative
Positive	5	2
Negative	5	0

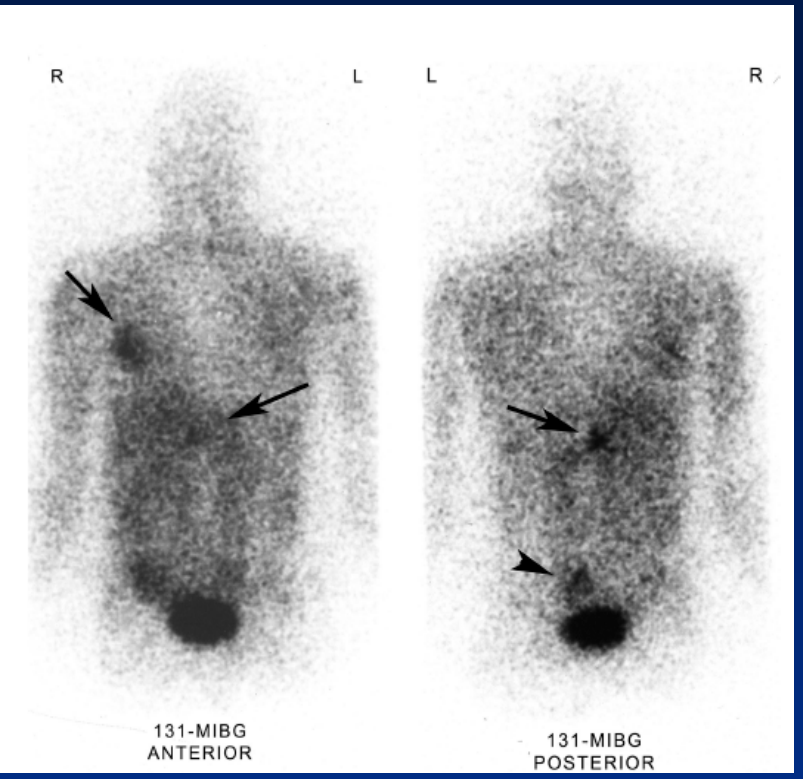
Note.—Data are the number of patients.

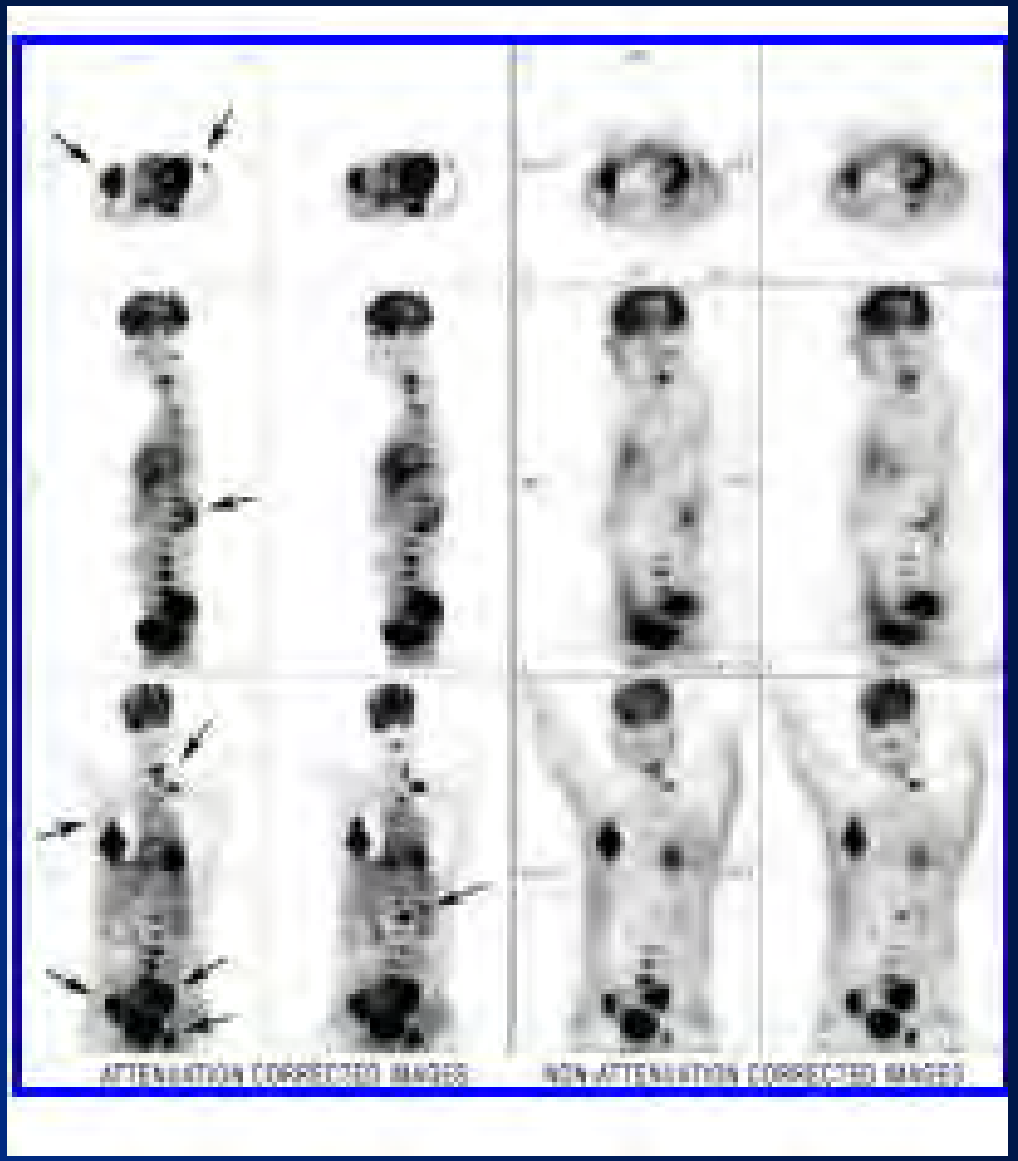
TABLE 4
Findings at FDG PET and MIBG Scintigraphy in Malignant Pheochromocytomas

	MIBG	
FDG	Positive	Negative
Positive	15 (12)	2 (2)
Negative	5 (4)	0 (0)

Note.—Data are the number of scans. Data in parentheses are the number of patients.

Shulkin, Radiology 1999





Ezuddin, Clin Nucl Med, 2005

Feocromocitoma - Localizzazione – FDG - PET

- FDG PET è indagine soggetta a falsi negativi in pazienti con feocromocitoma
- La visualizzazione di un feocromocitoma con FDG PET non indica che la lesione sia maligna
- FDG PET non è indagine specifica per feocromocitoma
- FDG PET non ha un ruolo primario nella localizzazione del feocromocitoma
- FDG PET può essere indagine aggiuntiva rispetto ad altre metodiche di imaging quando queste siano negative

Feocromocitoma - Localizzazione – (^{11}C) idrossiefedrina

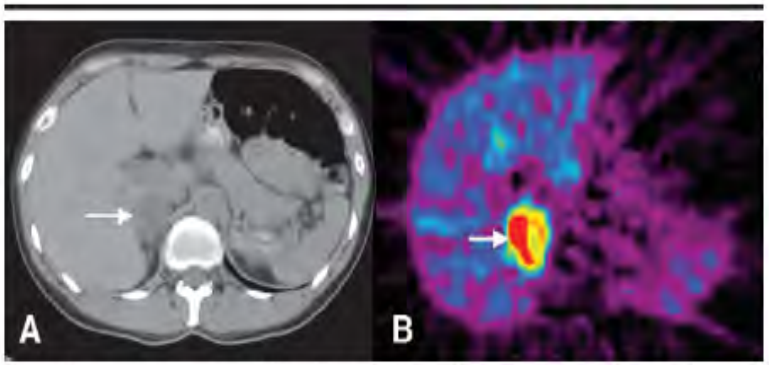


Figure 1. Transverse images obtained in a patient with hypertension and increased urinary catecholamine levels. *A*, CT image shows a 3-cm-diameter tumor in the right adrenal gland (arrow). *B*, HED PET image shows intense uptake within the right adrenal mass (arrow). Pheochromocytoma was confirmed at surgery.

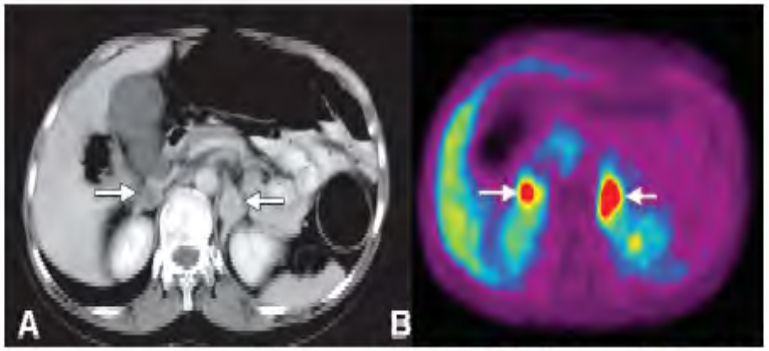


Figure 2. Transverse images obtained in a patient with multiple endocrine neoplasia type 2 and an increase in urinary catecholamine levels. *A*, CT image shows bilateral adrenal tumors (arrows), a 2-cm-diameter tumor on the right side, and a 4-cm-diameter tumor on the left side. *B*, HED PET image shows intense uptake in both adrenal lesions (arrows). Surgery revealed bilateral pheochromocytomas.

Trampal, radiology 2004

Feocromocitoma - Localizzazione (^{18}F) DOPA

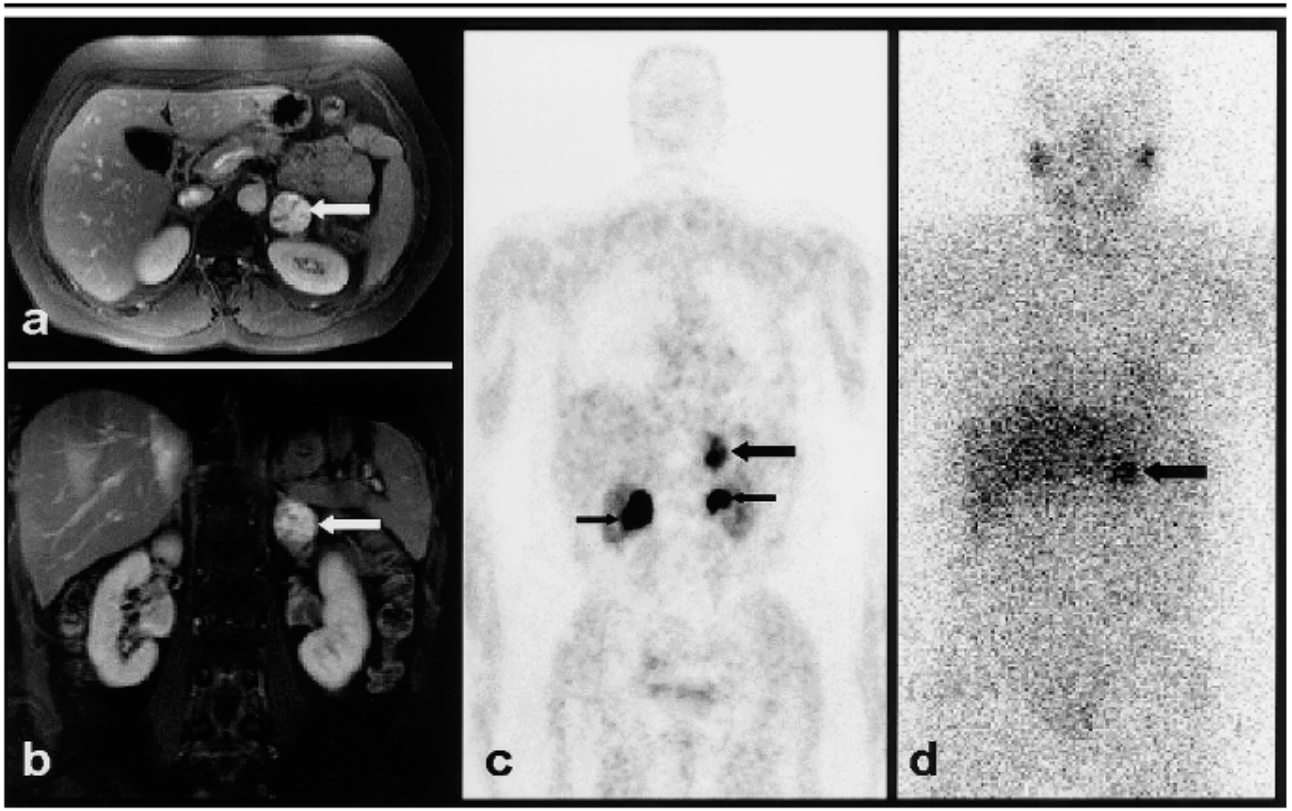
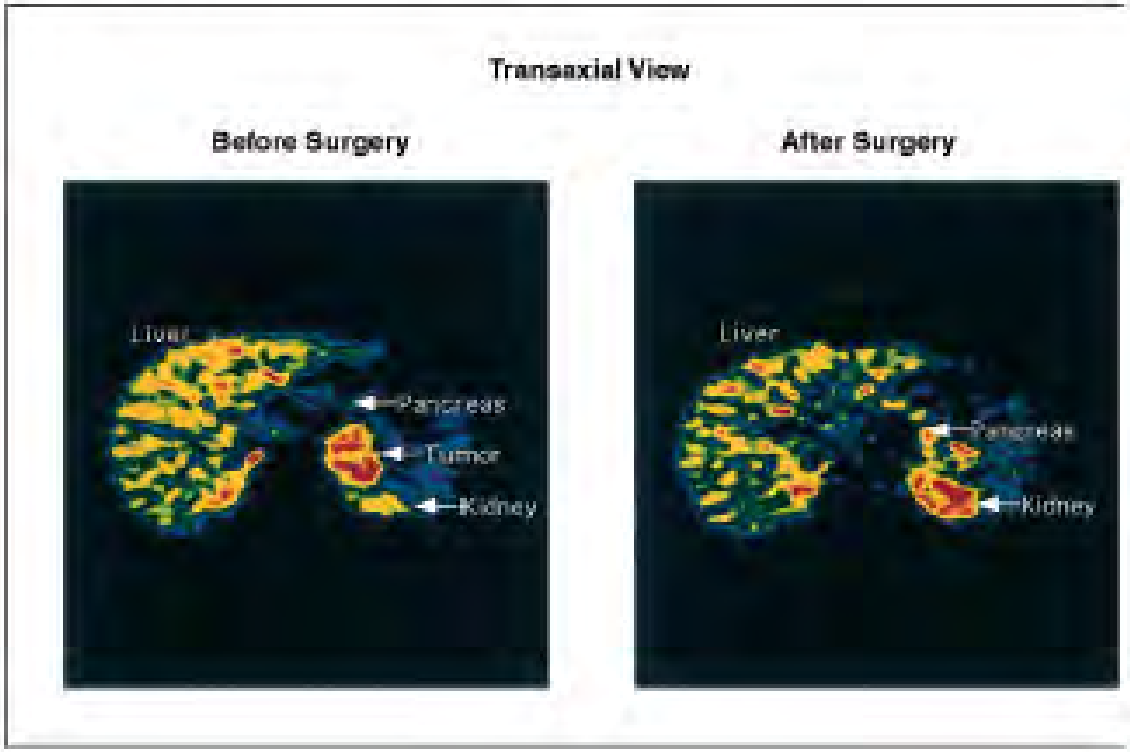


Figure 1. Pheochromocytoma of the left adrenal gland (large arrow) in a 44-year-old woman (patient 12). Transverse *(a)* and coronal *(b)* contrast-enhanced MR (144/4), coronal ^{18}F DOPA PET *(c)*, and planar MIBG scintigraphic *(d)* images show concordant findings. The small arrows in *c* point to the normal accumulation of ^{18}F DOPA in the renal collecting system.

Hoegerle, radiology 2002

Feocromocitoma - Localizzazione (^{18}F) DA

Figure 3. 6-[^{18}F]Fluorodopamine positron emission tomography before and after left adrenelectomy for a large pheochromocytoma.



NIH Conference, Ann Intern Med, 2001

Update in Clinical Endocrinology
Verona, ITALY October 27-29, 2006

ADRENAL HYPERTENSION

Indications for and outcome of surgical treatment

Massimo Terzolo

UNIVERSITÀ DEGLI STUDI DI TORINO

Review

Laparoscopic adrenalectomy

A. Assalia and M. Gagner

Division of Laparoscopy and Department of Surgery, Weill-Cornell College of Medicine, New York-Presbyterian Hospital, New York, New York 10021, USA

Laparoscopic adrenalectomy has become the procedure of choice for small benign lesions. Compared with open adrenalectomy, it appears to achieve superior results in terms of recovery, cosmesis and morbidity.

British Journal of Surgery 2004; 91: 1259–1274

ADRENAL DISORDERS THAT MAY BE TREATED LAPAROSCOPICALLY

- Unilateral adrenalectomy
  - Aldosterone-producing adenoma
  - Cortisol-producing adenoma
  - Androgen- or estrogen-producing adenoma
  - Benign sporadic pheochromocytoma
  - Adrenal incidentaloma
- Bilateral adrenalectomy
  - ACTH-dependent Cushing's syndrome that failed attempts at removal of ACTH-secreting tumor (pituitary or ectopic)
  - ACTH-independent Cushing's syndrome caused by primary pigmented nodular adrenal disease or bilateral adrenal macronodular hyperplasia
  - Congenital adrenal hyperplasia
  - Familial pheochromocytoma (*e.g.*, multiple endocrine neoplasia type IIA)

ACTH, adrenocorticotropic hormone.

Young WF, Current opinion in Endocrinology and Diabetes 1999

Table 1 Outcome in selected large series of laparoscopic adrenalectomy

Reference	No. of procedures	Approach	Operating time* (min.)	Blood loss* (ml)	Conversions (%)	Complications (%)	Mortality (%)	Hospital stay (days)*
3	100 (10)	LTA	123	70	3	12	0	2·4

Reported contraindications to LA included unacceptable cardiopulmonary risk and uncorrectable or untreated coagulopathy.

Obesity and previous abdominal surgery were not considered as contraindications.

Many series reported that the maximal size of laparoscopically resected tumors ranged 10–12 cm.

Conversions (%)	Complications (%)	Mortality (%)	Hospital stay (days)*
3·6	9·5	0·2	3·3

Assalia & Gagner, 2004

Table 2 Complications of laparoscopic adrenalectomy

	Rate (%)
Intraoperative	29·2
Bleeding due to vascular injury	18·5
18 adrenal vein	6·5
19 renal vein	0·6
20 inferior vena cava	1·8
21 other	10·1
Postoperative	70·8
Bleeding	21·5
Wound	13
Long term	3·6
Short term	9·4
Infectious	3
Cardiovascular	4·2
Pulmonary	3·5
Gastrointestinal	4·2
Urinary	6
Thromboembolic	4·7
Endocrine	1·2
Other	9·5

Bleeding was the most prevalent complication both during and after operation. However, need for blood transfusion was only 2.1%.

Assalia A et al, 2004

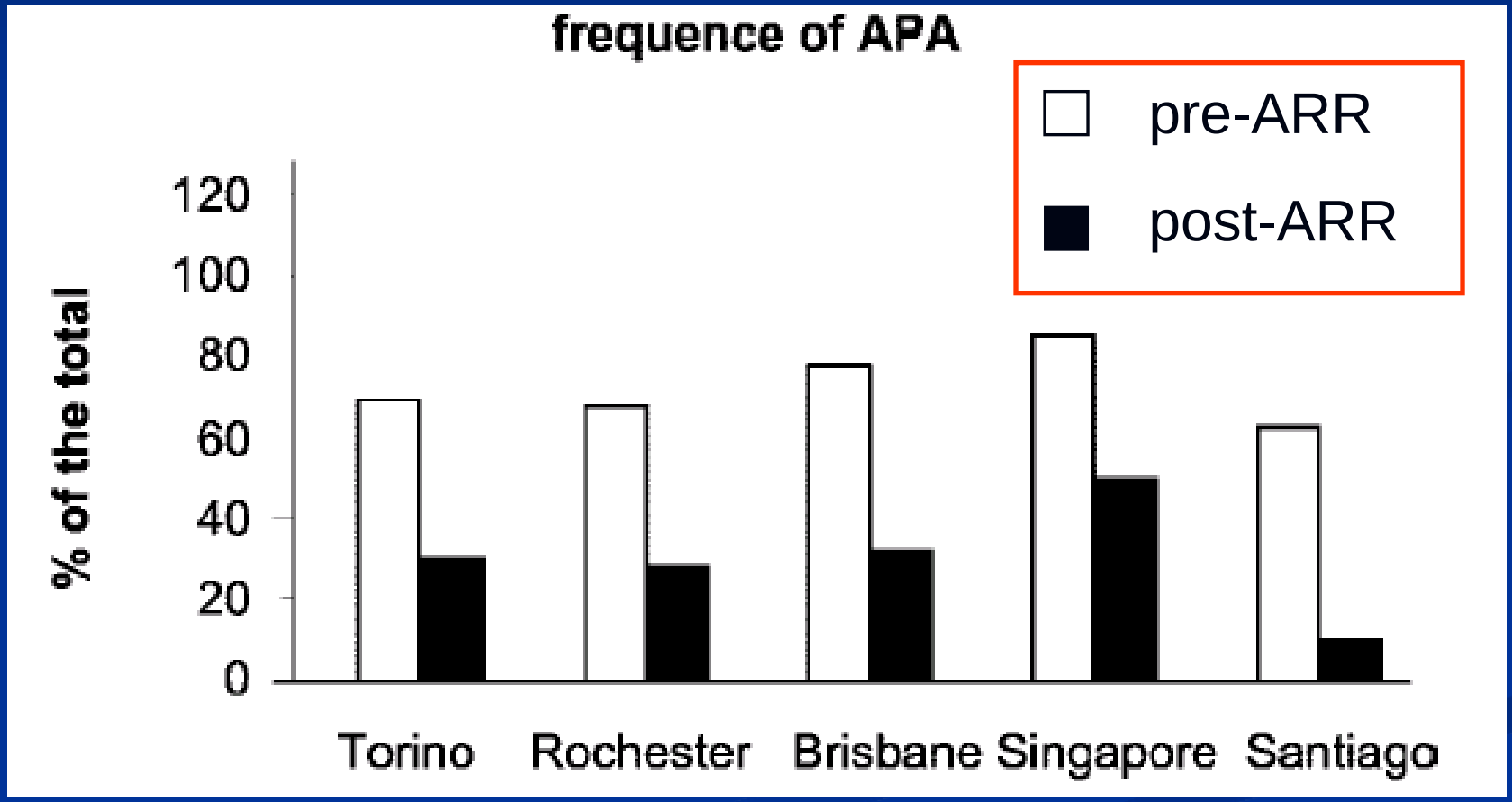
Table 4 Laparoscopic compared with open adrenalectomy

	No. of patients		Tumour size (cm)*		Operating time (min)*		Blood loss (ml)*		Complications (%)		Mortality (%)		Hospital stay (days)*	
Reference	LA	OA	LA	OA	LA	OA	LA	OA	LA	OA	LA	OA	LA	OA
60	38	36	2·3	2·6	225	122	138	188	11	8	0	0	8·5	12·9
61	42	38	n.a.		n.a.		n.a.		0	11	0	0	n.a.	
62	19	48	3·3	5·2	198	228	n.a.		3	60	0	0	1·5	6·3
63	22	17	n.a.		288	270	n.a.		n.a.		n.a.		1·7	6·7
64	20	20	13·9†	11·5†	193	178	245	283	10	25	0	0	3·1	7·2
65	21	20	3·2	9·2	206	177	n.a.		n.a.		n.a.		2·2	6·1
66	18	147	4	7	116	132	n.a.		0	12	0	0	2·2	6·3
67	12	7	2	6·4	116	166	132	278	8	0	0	0	2·1	5·4
68	12	56	1·8	1·6	160	120	50	150	0	9	0	0	3	5
69	21	17	1·8	2·5	219	140	183	266	29	76	0	0	2·7	6·2
14	110	100	29‡	28·6‡	189	219	125	563	15	32	n.a.		1·9	7·6
70	24	28	3·6	2·9	188	139	n.a.		16	39	0	0	4	7·5
71	10	10	n.a.		110	123	n.a.		10	30	0	0	3·7	5·8
72	19	19	2·5	3·3	164	151	109	263	5	38	0	0	2·3	5·1
73	17	12	n.a.		289	201	198	500	21	56	0	0	3	7·9
7	36	23	n.a.		158	85	n.a.		6	52	3§	0	3·5	8·5
5														7·5
6														5·7
8														18
74														18·2
Total														
Mean														7·2¶

Blood loss (ml)*		Complications (%)		Mortality (%)		Hospital stay (days)*	
LA	OA	LA	OA	LA	OA	LA	OA
154	309	10·9	35·8	0	0	2·9¶	7·2¶

Assalia & Gagner, 2004

Primary Aldosteronism



Mulatero et al., 2004

World Journal of Surgery 2005; 29, 155–159

Long-term Follow-up after Adrenalectomy for Primary Aldosteronism.

Meyer A, Brabant G, Behrend M

- **24 patients (15 female and 9 male) with a mean age of 48.3 ± 10.8 yr underwent surgery for PA between 1988 and 2001. All subjects were reexamined with a complete clinical work-up after a mean follow-up period of 86 ± 48 months.**
- **Preoperatively, the mean number of antihypertensive drugs taken by each patient was 2.3. Potassium supplementation was needed in 12 patients. The preoperative mean blood pressure on treatment was 143/89 mmHg.**

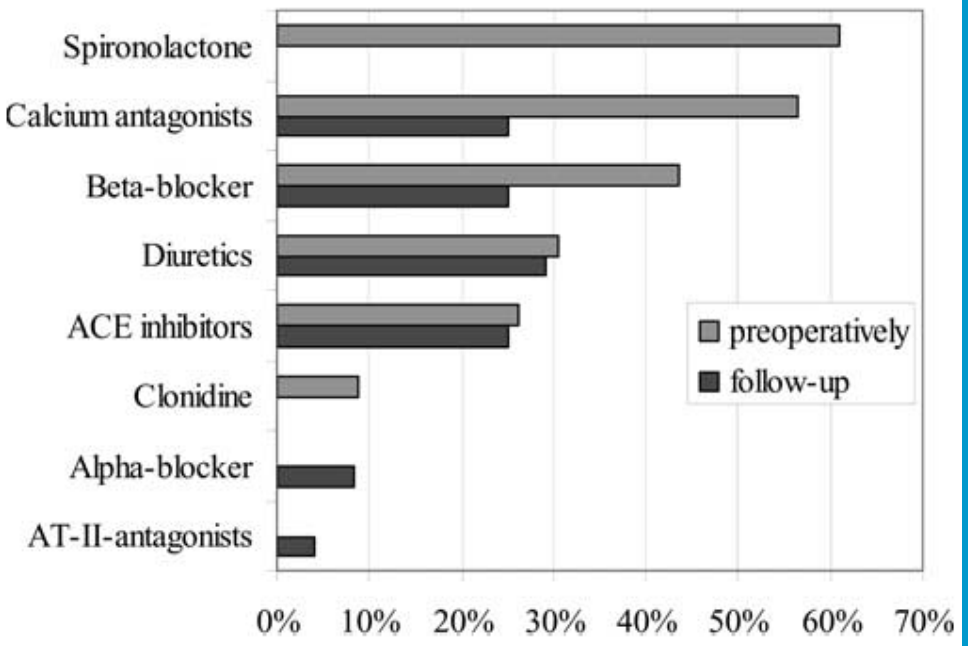


Fig. 1. Type of antihypertensive drugs used preoperatively and at the time of follow-up.

At the last follow-up,

- ✓ **8 patients required no antihypertensive drugs;**
- ✓ **16 were still hypertensive (1.2 antihypertensive agents were being taken on average).**

Annals of Internal Medicine 135:258-261 2001

Primary aldosteronism: factors associated with normalization of blood pressure after surgery.

Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA

- **Follow-up in 93 patients.**
- **Hypertension resolved (<140/90 mmHg without antihypertensive drugs) in 31/93 patients (33%).**
- **Of the patients with unresolved hypertension, 61 of 62 (98%) had improved control of hypertension.**
- **Factors associated with resolution of hypertension were: family history of hypertension in one or no first-degree relative, preoperative use of two or fewer antihypertensive agents, younger age, shorter duration of hypertension, higher preoperative ratio of plasma aldosterone to plasma renin activity, and a higher 24-hour urinary aldosterone level.**

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DOI: 10.1097/01.ju.0000041281.22237.97

LAPAROSCOPIC MANAGEMENT OF PRIMARY HYPERALDOSTERONISM: CLINICAL EXPERIENCE WITH 212 CASES

PAUL MERIA, BÉATRICE FIQUET KEMPF, JEAN FRANÇOIS HERMIEU, PIERRE FRANÇOIS PLOUIN AND JEAN MARC DUCLOS

From the Department of Urology, St-Joseph Hospital and Department of Arterial Hypertension, Georges Pompidou's European Hospital of Paris, Paris, France

- **From 1994-2001, 212 consecutive patients (119 women and 93 men) with a mean age of 48 years (26-72 yr) and a confirmed diagnosis of primary hyperaldosteronism underwent a total of 213 transperitoneal operations, consisting of laparoscopic adrenalectomy in 193 and laparoscopic tumor enucleation in 20.**

- **Conversion to open surgery was necessary in 30 cases (14%) due to bleeding in 8, and adhesions in 22, 16 of which were related to procedure length greater than 3 hours.**

TABLE 1. *Clinical and biological results*

- **Postoperatively, 58% of patients had normal BP without any treatment.**
- **In the other patients medical treatment was decreased.**
- **Mean systolic and diastolic BP decreased 20 to 30 mm.**
- **Hypokalemia normalized in all patients.**

FACTORS ASSOCIATED WITH POST-OPERATIVE OUTCOME

- Patient's age
- Duration of hypertension
- Blood pressure response to spironolactone
- Significant lateralization of adrenal vein sampling
- Histology

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Evidence for an Increased Rate of Cardiovascular Events in Patients With Primary Aldosteronism

Paul Milliez, MD,* Xavier Girerd, MD, PHD,† Pierre-François Plouin, MD,‡ Jacques Blacher, MD, PHD,§ Michel E. Safar, MD,§ Jean-Jacques Mourad, MD, PHD‖

Paris and Bobigny, France

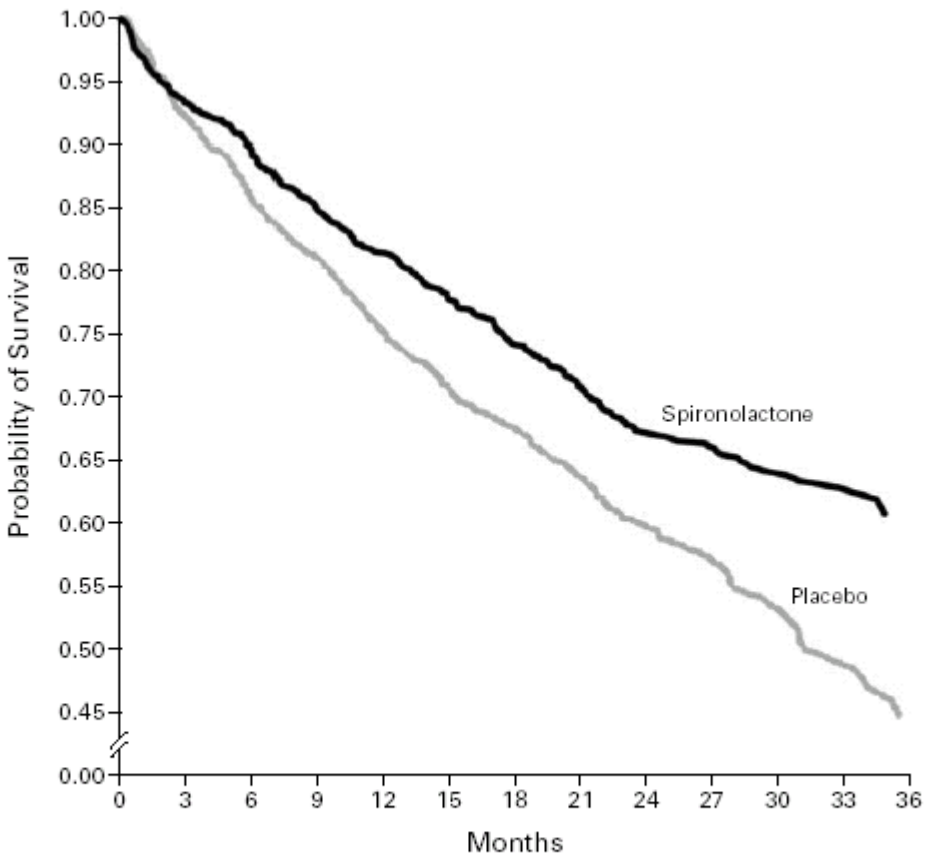
Table 3. Rate of Cardiovascular Events and Cardiac Structure in Primary Aldosteronism Patients and Controls

	Primary Aldosteronism (n = 124)	Essential Hypertension (n = 465)	Odds Ratio (95% CI)	p Value
Stroke (%)	12.9	3.4	4.2 (2.0–8.6)	<0.001
Myocardial infarction (%)	4.0	0.6	6.5 (1.5–27.4)	<0.005*
Atrial fibrillation (%)	7.3	0.6	12.1 (3.2–45.2)	<0.0001*
Echocardiographic LVH (%)	34	24	1.6 (1.1–2.5)	<0.01
Electrocardiographic LVH (%)	32	14	2.9 (1.8–4.6)	<0.001

*Fisher exact test.
CI = confidence interval; LVH = left ventricular hypertrophy.

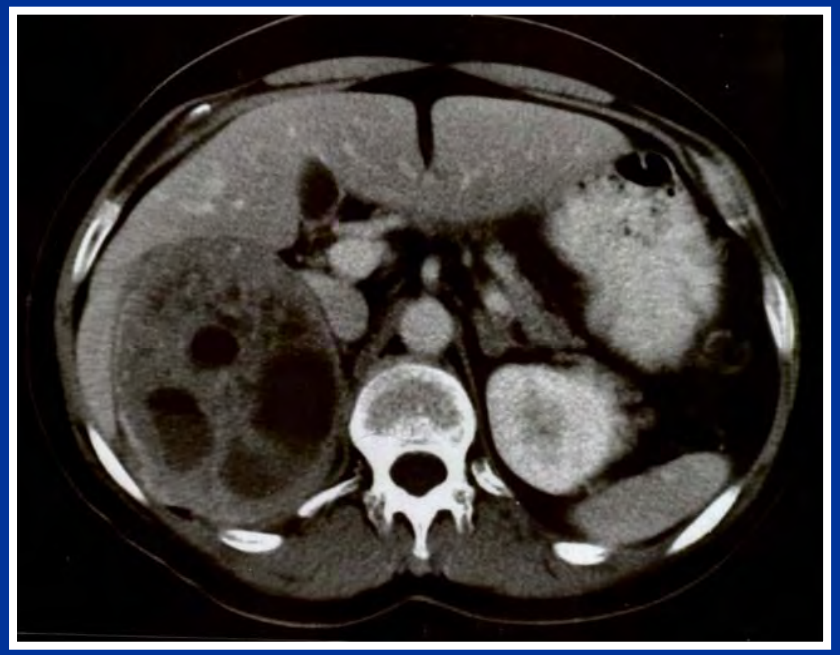
THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Pheochromocytoma



About 50% of patients with incidentally detected pheo are normotensive or have low-grade hypertension.

Mantero et al., 2000
Bulow & Ahren, 2002

Up to 80% of patients with unsuspected pheo who underwent surgery or anesthesia have died.

Kloos et al., 1995

Phaeochromocytoma

Lancet 2005; 366: 665–675

Jacques W M Lenders, Graeme Eisenhofer, Massimo Mannelli, Karel Pacak

- **Laparoscopic removal of intra- and extra-adrenal PHEOs is now the preferred surgical procedure.**
- **With adequate pretreatment, perioperative mortality has fallen to less than 3%.**
- **There are no randomised prospective studies that are large enough to establish the most effective drug regimen before surgery.**
- **The major aim of medical pretreatment is to prevent catecholamine-induced, serious, and potentially life-threatening complications during surgery, including hypertensive crises, cardiac arrhythmias, pulmonary oedema, and cardiac ischaemia.**

Seminar

Phaeochromocytoma

Lancet 2005; 366: 665–675

Jacques W M Lenders, Graeme Eisenhofer, Massimo Mannelli, Karel Pacak

- **Even if a diagnosis is considered in rare life-threatening conditions stabilisation and elective surgery is preferred, since emergency tumour resection without proper preparation results in poor survival.**
- **After surgery, patients need to be under close surveillance for the first 24 h in an intensive or intermediate care unit.**
- **The two major postoperative complications are hypotension and hypoglycaemia.**
- **Hypertension might persist after surgery in nearly 50% of patients.**

Journal of Internal Medicine 2005; 258: 55–66

Long-term outcome of a large series of patients surgically treated for pheochromocytoma

A. KHORRAM-MANESH, H. AHLMAN, O. NILSSON, P. FRIBERG, A. ODÉN, G. STENSTRÖM, G. HANSSON, O. STENQUIST, B. WÄNGBERG, L.-E. TISELL & S. JANSSON
From the Lundberg Laboratory for Cancer Research, Sahlgrenska University Hospital, Göteborg, Sweden

121 consecutive patients (68 females and 53 males) with pheochromocytoma/paraganglioma (mean age at surgery of 47.4 ± 19.0 yr for females and 47.0 ± 13.4 yr for males), surgically treated between 1950 and 1997.

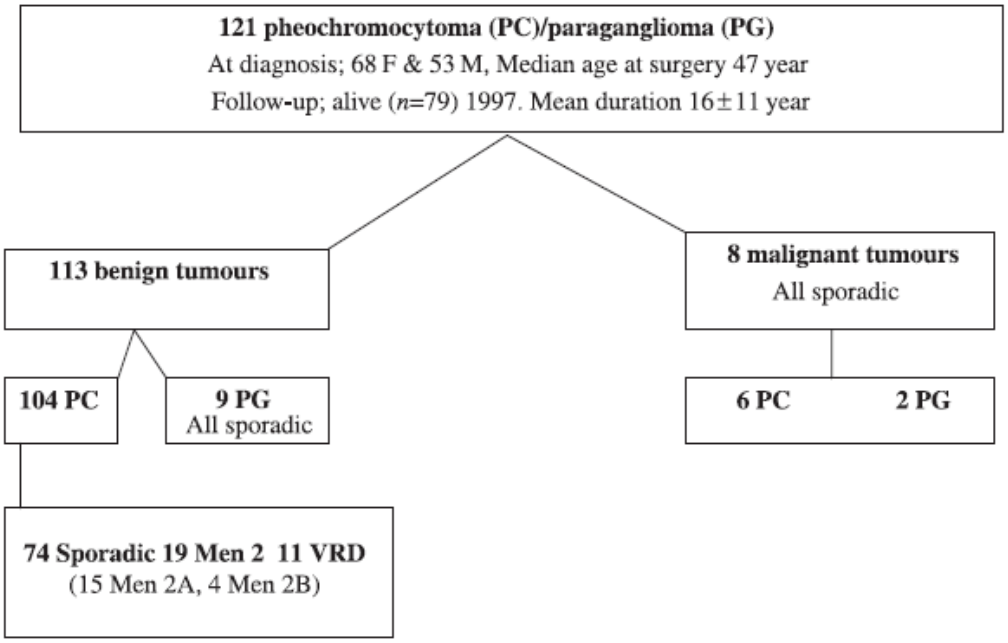


Fig. 1 Eight of 121 patients with pheochromocytoma (PC) or paraganglioma (PG) had verified malignant tumours, all sporadic. Of 113 benign tumours 83 were sporadic and 30 hereditary [multiple endocrine neoplasia type 2 (MEN 2) and von Recklinghausen's disease (VRD)].

Table 1 Characteristics of eight sporadic cases with malignant pheochromocytoma (PC) or paraganglioma (PG)

							Obs survival after		At last follow-up	
Patient no.	Sex & age (years)	Tumour type & site	Year of adx	Latency to recurrence (years)	Type of recurrence	Treatment of recurrence	Recurrence (years)	First surgery (years)	Age and outcome	
17	F 29	PC/left[a]	1967	7	Distant	Surgery + PBZ	23	30	59	DOD
25	M 48	PC/left	1968	17	Distant	PBZ	6	23	71	DOD
35	F 22	PG/left	1972	15	Local	Surgery	11	27	49	NED
54	F 41	PC/left	1979	13	Distant	PBZ	6	20	61	AWD
58	F 71	PC/left[a]	1980	6	Distant	Radiotherapy	2	8	84	DOD
61	M 61	PG/left[a]	1982	4	Loc + Dist	Surgery + PBZ	5	9	70	DOD
54	M 54	PC/left[a]	1986	1	Local	Surgery + PBZ	11	12	66	AWD
59	M 59	PC/right	1989	5	Distant	PBZ	1	6	65	OCD
	49 ± 18			8.5 ± 6			8 ± 7	17 ± 9	65 ± 10	

Adx, unilateral adrenalectomy; PBZ, phenoxybenzamine; distant, distant metastasis; local, local recurrence; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; OCD, other cause of death. [a]Primary tumour with histology suggesting malignancy.

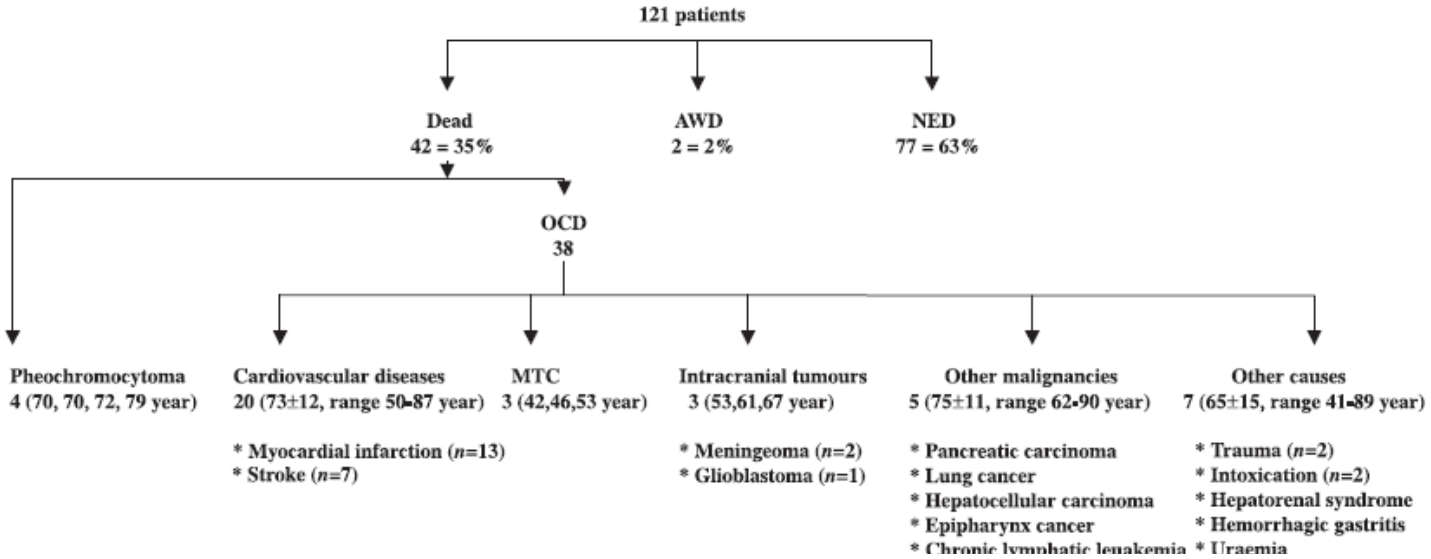
Pre- and post-operative blood pressures.

121 PC/PG patients

Blood pressure available ($n = 116$)						Blood pressure not available ($n = 5$)		
Sporadic $n = 87$		VRD $n = 11$		Men 2 $n = 18$		Sporadic $n = 4$	VRD $n = 0$	Men 2 $n = 1$
At diagnosis								
HP $n = 79$	NP $n = 8$	HP $n = 8$	NP $n = 3$	HP $n = 11$	NP $n = 7$			
One year postoperatively; 100 patients evaluable								
HP, $n = 46$ 16 mt		HP, $n = 3$ 2 mt		HP, $n = 8$ 1 mt		Dead $n = 1$ No results available, $n = 10$		
At follow up 1997; 66 patients evaluable								
HP, $n = 15$		HP, $n = 4$		HP, $n = 7$		Dead $n = 42$ No results available, $n = 13$		

HP=Hypertension NP=Normotension

- At diagnosis 85% were hypertensive; less than half had antihypertensive treatment.
- One year after surgery more than half of patients had hypertension, but only one third received medical treatment.
- At latest follow- up, 66 of 98 patients with initial hypertension were alive (59 ± 14 yr); 25 of these 66 patients were hypertensive. Thirty-two patients had died at old age (80 ± 13 yr).
- The survival analysis showed that pre- or post-operative hypertension did not influence the risk of death in this cohort versus controls ($P > 0.30$).



- **Pheochromocytoma can be safely treated by surgery.**
- **After successful surgery, patients still have an increased risk of death compared with the general Swedish population.**
- **A life-long follow-up of patients with screening for recurrent tumor in sporadic cases and also for associated tumors in hereditary cases is mandatory. This strategy would also be helpful in diagnosing cardiovascular disease at an early stage.**

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The Journal of Clinical Endocrinology & Metabolism 90(4):2110–2116

doi: 10.1210/jc.2004-1398

Year of Diagnosis, Features at Presentation, and Risk of Recurrence in Patients with Pheochromocytoma or Secreting Paraganglioma

Laurence Amar, Aude Servais, Anne-Paule Gimenez-Roqueplo, Franck Zinzindohoue, Gilles Chatellier, and Pierre-François Plouin

The rate of recurrence was 17%

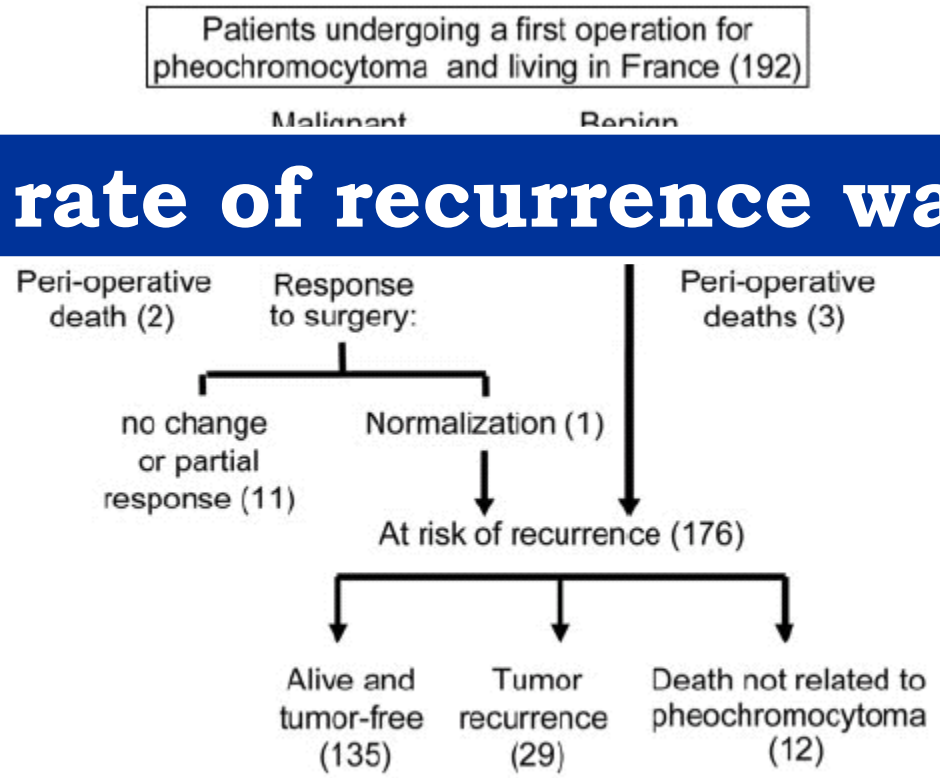


FIG. 1. One hundred seventy-six patients were at risk of recurrence and were followed postoperatively for 9.1 (interquartile range, 5.5, 15.3) yr, a total of 1792 patient-years.

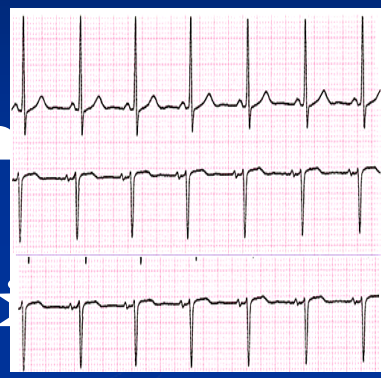
Hazard ratios for the risk of recurrence stratified by quartile of date of operation.

	P·VALUE	HAZARD· RATIO	95%· CONFIDENCES· INTERVAL
Age,·per·yr.	0.602	0.992	0.963-1.022
Familial·*vs.*·sporadic	0.018	3.437	1.234-9.584
Bilateral·*vs.*·left·adrenal	0.760	1.421	0.149-13.58
Right·*vs.*·left·adrenal	0.138	3.085	0.696-13.69
Extraadrenal·*vs.*·left·adrenal	0.003	11.24	2.219-56.99
Tumor·diameter,·per·cm	0.015	1.150	1.027-1.289

Amar et al., 2005

Manifestazioni cardiache del feocromocitoma

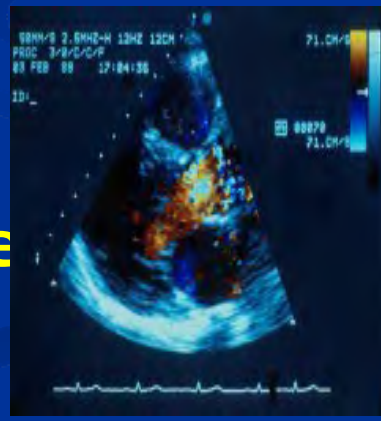
- **Alterazioni elettrocardiografiche:**
  - - sovra e sottoslivellam
ST
  - (qu ecroti
nelle d
    - - gative
    - - sova



Potenzialmente reversibili

se la diagnosi è precoce

e il trattamento adeguato



- **Alterazioni del ritmo e de conduzione**
  - - tachicardia sinusale
  - - aritmie sopraventricolari o

Improvement of Insulin Sensitivity after Adrenalectomy in Patients with Pheochromocytoma

T. D. WIESNER, M. BLÜHER, M. WINDGASSEN, AND R. PASCHKE

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Our data provide evidence that endogenous catecholamine excess in patients with pheochromocytoma can induce or aggravate insulin resistance both in patients with type 2 diabetes and patients with normal glucose tolerance. (*J Clin Endocrinol Metab* 88: 3632–3636, 2003)

Archives of Surgery 2004;139:526-531

Outcome of Laparoscopic Adrenalectomy for Pheochromocytomas vs Aldosteronomas

Kim AW, Quiros RM, Maxhimer JB, El-Ganzouri AR, Prinz RA

- **Retrospective analysis of 149 patients who underwent laparoscopic adrenalectomy (LA) between 1993-2002.**
- **75 patients (38 women and 37 men) were identified as having undergone LA for either a PHEO (n=30) or an APA (n=45).**
- **Before data analysis, the initial 35 of 149 LAs performed were excluded to account for the learning curve, which eliminated 4 PHEO patients and 11 APA patients.**

Demographic, Intraoperative, and Postoperative Variables

Variable	Pheochromocytoma Group (n = 26)	Aldosteronoma Group (n = 34)	*P* Value
Location, No.			<.001
Right	19	6	
Left	7	28	
Tumor size, mean ± SD, cm	4.9 ± 1.8	2.7 ± 1.7	<.001
ORT, mean ± SD, min	191 ± 49	162 ± 48	.02
EBL, mean ± SD, mL	276 ± 298	196 ± 324	.33
Transfusions, No.	6	2	.05
Conversions, No.	1	1	.84
PO LOS, mean ± SD, d	4 ± 4	2 ± 3	.08

Abbreviations: EBL, estimated blood loss; ORT, operative time; PO LOS, postoperative length of hospital stay.

- ✓ **For PHEO, LA was associated with the removal of more right-sided lesions, larger tumors, longer operative times, and more complications.**
- ✓ **Trends toward greater estimated blood losses and longer hospital stays were observed for PHEO vs APA.**
- ✓ **LA for PHEO is associated with a more complex course than APA.**
- ✓ **Surgeons should begin doing LA for APA early in their experience to avoid the potential pitfalls associated with PHEO.**