INQUADRAMENTO DIAGNOSTICO DELL'INCIDENTALOMA SURRENALICO

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BIBLIOGRAFIA PRINCIPALE

European Journal of Endocrinology (2011) **164** 851–870 ISSN 0804-4643

REVIEW

AME Position Statement on adrenal incidentaloma

M Terzolo, A Stigliano[1], I Chiodini[2], P Loli[3], L Furlani[4], G Arnaldi[5], G Reimondo, A Pia, V Toscano[1], M Zini[6], G Borretta[7], E Papini[8], P Garofalo[9], B Allolio[10], B Dupas[11], F Mantero[12] and A Tabarin[13]

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a.net)

AACE/AAES Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS MEDICAL GUIDELINES FOR THE MANAGEMENT OF ADRENAL INCIDENTALOMAS

Martha A. Zeiger, MD, FACS, FACE; Geoffrey B. Thompson, MD, FACS, FACE; Quan-Yang Duh, MD, FACS; Amir H. Hamrahian, MD, FACE; Peter Angelos, MD, PhD, FACS, FACE; Dina Elaraj, MD; Elliot Fishman, MD; Julia Kharlip, MD

ENDOCRINE PRACTICE Vol 15 (Suppl 1) July/August 2009 1

ilable evidence on adrenal incidentaloma and provide recommen-

inted by the Italian Association of Clinical Endocrinologists (AME)) ality of the relevant studies, summarized their results, and discussed ensus.

ced computed tomography (CT) is recommended as the initial test lue of ≤ 10 Hounsfield units (HU) to differentiate between adenomas with a higher baseline attenuation value, we suggest considering tudies. Positron emission tomography (PET) or PET/CT should be ve, whereas fine needle aspiration biopsy may be used only in selected fter biochemical exclusion of pheochromocytoma).

nocytoma and excessive overt cortisol should be ruled out in all eronism has to be considered in hypertensive and/or hypokalemic amethasone suppression test is the test recommended for screening of SCS) with a threshold at 138 nmol/l for considering this condition. A udes SCS with an area of uncertainty between 50 and 138 nmol/l.

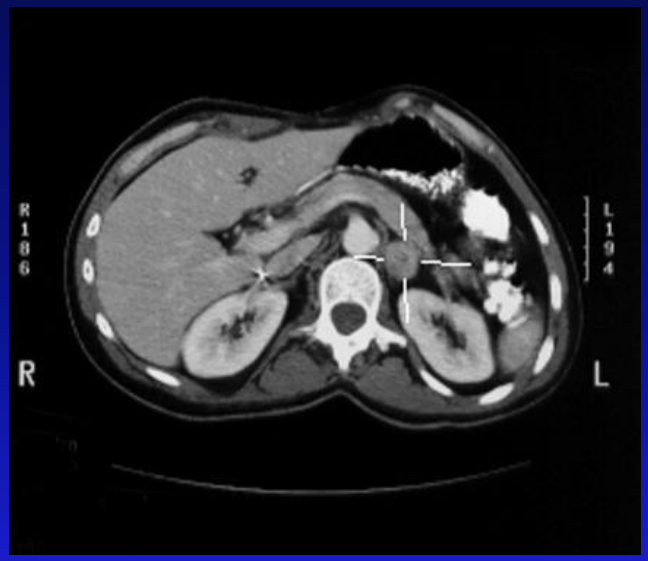
Management: Surgery is recommended for masses with suspicious radiological aspects and masses causing overt catecholamine or steroid excess. Data are insufficient to make firm recommendations for or against surgery in patients with SCS. However, adrenalectomy may be considered when an adequate medical therapy does not reach the treatment goals of associated diseases potentially linked to hypercortisolism.

Adrenal Incidentaloma

DEFINITION: A previously unsupected adrenal mass discovered on an imaging study performed for an unrelated reason

PREVALENCE:

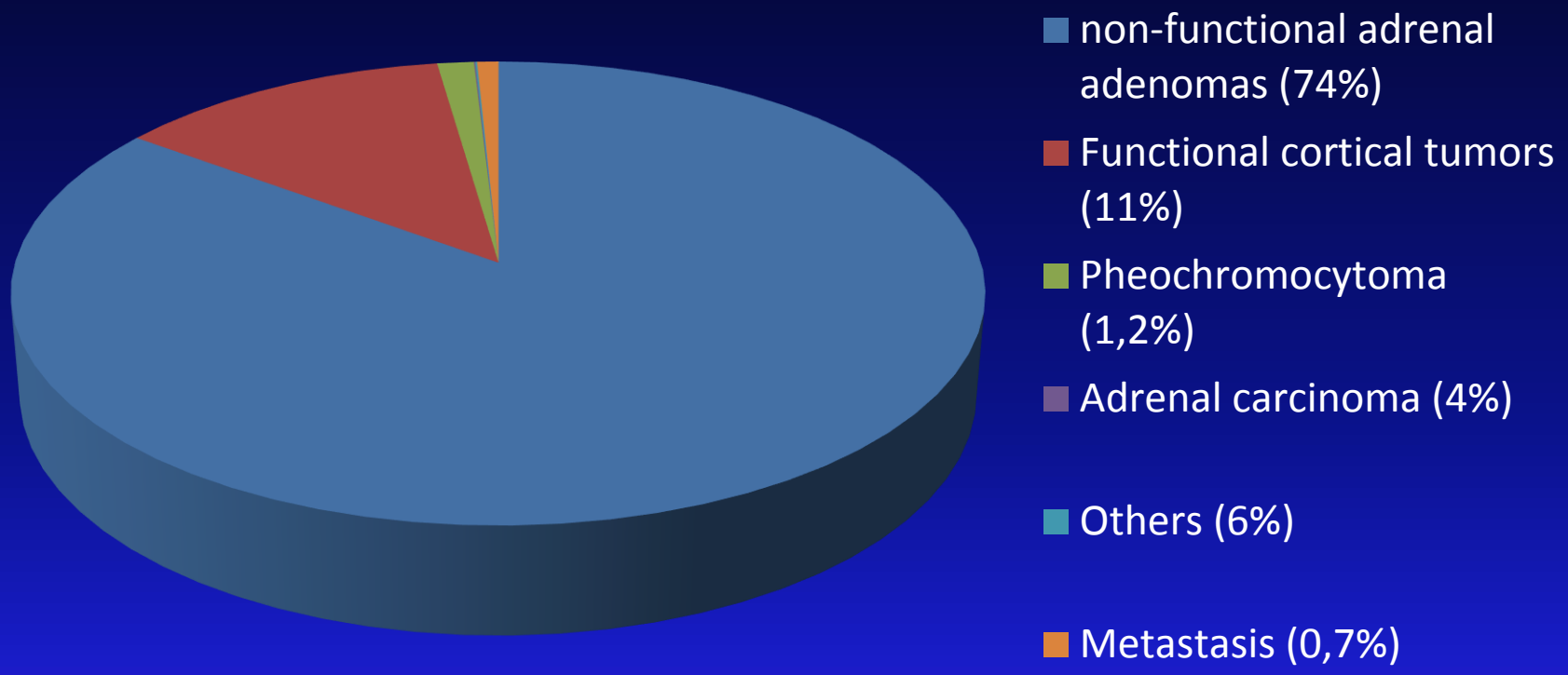
Author		Sample size	Prevalence
Russi (1941)	Autopsy (> 1 cm)	131/9000	1.5
Kokko (1967)	Autopsy (> 5 mm)	21/1495	1.5
Hedeland (1967)	Autopsy (> 2 mm)	64/739	8.7
Glazer (1982)	CT scan	16/2200	0.7
Abecassis (1985)	CT scan	19/1459	1.3
Belldegrun (1986)	Ct scan	88/12000	0.7
Herrera (1991)	CT scan	259/61054	0.4



Radiological studies → **3-4%**
0,2% young age (<30 yrs)
2-4 % middle age
7-10 % elderly

Autopsy studies → **2% (ranging from 1 to 8,7%)**
< 1% young age (< 30 yrs)
7 % elderly (> 70 yrs)

Prevalence of Incidentaloma in 1004 Patients



Cicala MV, Best Practice 2006; 20: 451-466

Differential Diagnosis

- ***Adenoma*** (functional vs nonfunctional)
  - Cushing's (hypercortisolemia can be subclinical
  - Conn's (hyperaldosteronemia)
  - Testosterone secreting
- ***Pheochromocytoma***
- ***Adrenal cortical carcinoma***
- ***Metastasis from extra-adrenal malignancy***
- ***Myelolipoma/angiomyelipoma***
- ***Cyst***
- ***Hematoma***
- ***Ganglioneuroma***

Inquadramento clinico dell'Incidentaloma Surrenalico

Frequency of different type of adrenal incidentaloma

Type	Average (%)	Range
Clinical studies*		
Adenoma	80	33-96
Non-functioning	75	71-84
Cortisol secreting	12	1.0-29
Pheochromocytoma	7.0	1.5-14
Carcinoma	8.0	1.2-11
Metastases§	5.0	0-18
Surgical studies**		
Adenoma	55	49-69
Non-functioning	69	52-75
Cortisol secreting	10	1.0-15
Aldosterone secreting	6.0	2.0-7.0
Pheochromocytoma	10	11-23
Carcinoma	11	1.2-12
Myelolipoma	8.0	7.0-15
Cyst	5.0	4.0-22
Ganglioneuroma	4.0	0-8.0
Metastases#	7.0	0-21

Bilateral masses in 10-15% of cases

 # lung, breast, ovarian, kidney, melanoma and lymphoma

M. Terzolo et al. Eur J Endocrinol 2011: 164, 851

Inquadramento clinico dell'Incidentaloma Surrenalico

Bilateral adrenal mass (up to 15% of AI)

The most likely are

- Metastatic diseases
- Infiltrative diseases
- Congenital adrenal hyperplasia
- Bilateral cortical adenomas
- ACTH-indipendent macronodular adrenal hyperplasia (AIMAH)
- Infection (tubercolosis, fungal), hemorrhage
- Pheochromocitoma

- **In oncological patients**

50-75% of adrenal incidentalomas are metastases

Unknown primary cancer may present as

- Bilateral adrenal masses in 5.8% of cases
- Monolateral adrenal masses in 0,2%

Clinical recommendations based on epidemiology of the adrenal incidentalomas

1. We recommend considering the possibility of primary adrenal malignancies and metastases from extra-adrenal tumors in all patients with adrenal incidentalomas. 1⊕⊕⊕O

2. We recommend excluding adrenal metastases in oncologic patients with adrenal incidentalomas. 1⊕OOO

3. We recommend excluding primary adrenal malignancies in all pediatric patients with

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The Panel used the GRADE system to classify evidence in 4 quality levels that are showed by cross-filled circles, such that ⊕OOO denotes very low quality evidence; ⊕⊕OO, low quality; ⊕⊕⊕O, moderate quality; and ⊕⊕⊕⊕, high quality. Although usually high or moderate quality evidence generate strong recommendations (term used: "we recommend" and the number 1) and low or very low quality evidences generate weak recommendations (term used: "we suggest" and the number 2), this link is not mandatory.

Three main questions

1. *Does it have radiologic characteristics suggestive of a malignant lesion?*
2. *Does the patient have a history of a previous malignant lesion?*
3. *Is the tumor hormonally active?*

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Inquadramento clinico dell'Incidentaloma Surrenalico

Evaluation for malignancy

SIZE	Risk of ACC
≤4 cm	<2 %
>4 <6 cm	6%
≥6 cm	25%

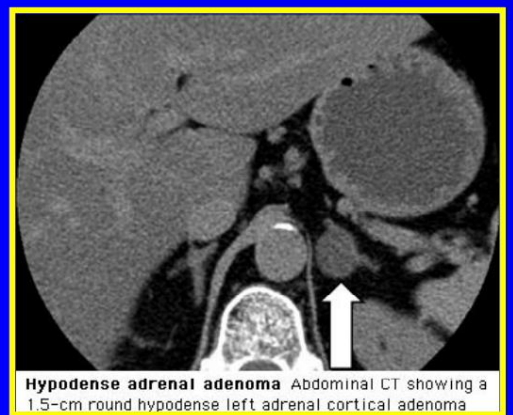
NIH Conference 2003

4 cm cut-off

93% sensitivity, 76% specificity

Imaging phenotype

- Unenhanced CT scan
- Contrast enhanced CT
- MRI
- FDG PET/CT (selected cases, when CT is inconclusive)
- FNAB (selected cases suspicious of metastases)
- NP 59 scintigraphy (unilateral vs. bilateral uptake)
- MIBG, F-DOPA PET, FDA PET (pheochromocytoma)



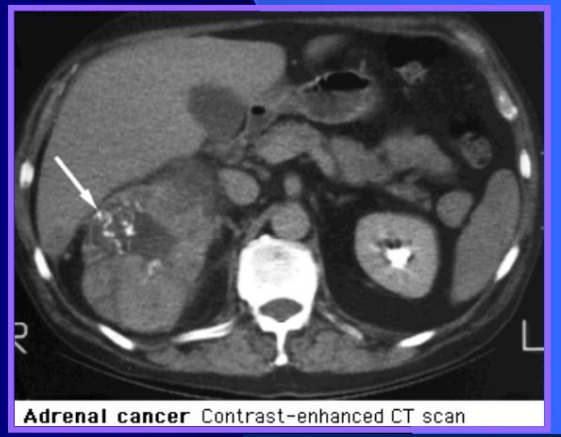
Hypodense adrenal adenoma Abdominal CT showing a 1.5-cm round hypodense left adrenal cortical adenoma

Change in size over time

⇩

growth > 1 cm/year

(ACC rapid growth >2 cm/yr)



Adrenal cancer Contrast-enhanced CT scan

Clinical reccomandations the radiological assessment of the adrenal incidentalomas

1. We recommend unenhanced CT as the initial imaging procedure. We recommend to repeat unenhanced CT whenever the baseline scan leading to the discovery of an adrenal mass was of suboptimal technique. 1⊕⊕OO
2. We recommend against diagnostic US as a routine imaging technique to characterize an adrenal incidentaloma. 1⊕⊕OO
3. We recommend against adrenal scintigraphy as a routine imaging technique to characterize an adrenal incidentaloma. 1⊕⊕OO
4. We recommend the use of an attenuation value of ≤10 HU on unenhanced CT to diagnose an adrenal adenoma. 1⊕⊕⊕O
5. For tumors with a higher baseline attenuation value, we suggest considering delayed contrast-enhanced CT studies. 2⊕⊕OO
6. We recommend against FDG-PET as a routine imaging technique to characterize adrenal incidentalomas. 1⊕⊕OO
7. We suggest considering PET or PET/CT when CT densitometry or washout analysis is inconclusive or suspicious for malignancy. 2⊕⊕OO
8. We recommend against FNAB as a routine diagnostic technique. It may be used only in selected patients with adrenal masses suspicious for metastases of extra-adrenal cancer and inconclusive results of imaging tests (after biochemical exclusion of pheochromocytoma). 2⊕⊕OO

Inquadramento Clinico dell'Incidentaloma Surrenalico

Adrenocortical Carcinoma (ACC)

- a rare tumor with very poor prognosis -

Prevalence
- general population ➡ 12 in 1.000.000
- adrenal incidentaloma ➡ 2% (varing widely 0-12%)

The reason for the higher frequency in adrenal incidentaloma compared to population is unclear

Survival
- mean ➡ 18 months
- 5-year ➡ < 20%

Functional
- Cushing syndrome
- Virilizing syndrome
- Mixed Cushing-Virilizing syndrome
- Estrogen-secreting (rare)
- Aldosterone-secreting (rare)

or

Non-functional

Early diagnosis and definitive treatment is critical

Evaluation for hormonal hypersecretion

Non-functiong adenoma	80% (50-95)
Functioning adenoma	10-15%
Cortisol-secreting	10-15% (1-48)
Aldosterone-secreting	2% (1.5-7)
Androgen or estrogen-secreting	0-11%
Pheochromocytoma	4-7% (1-20)

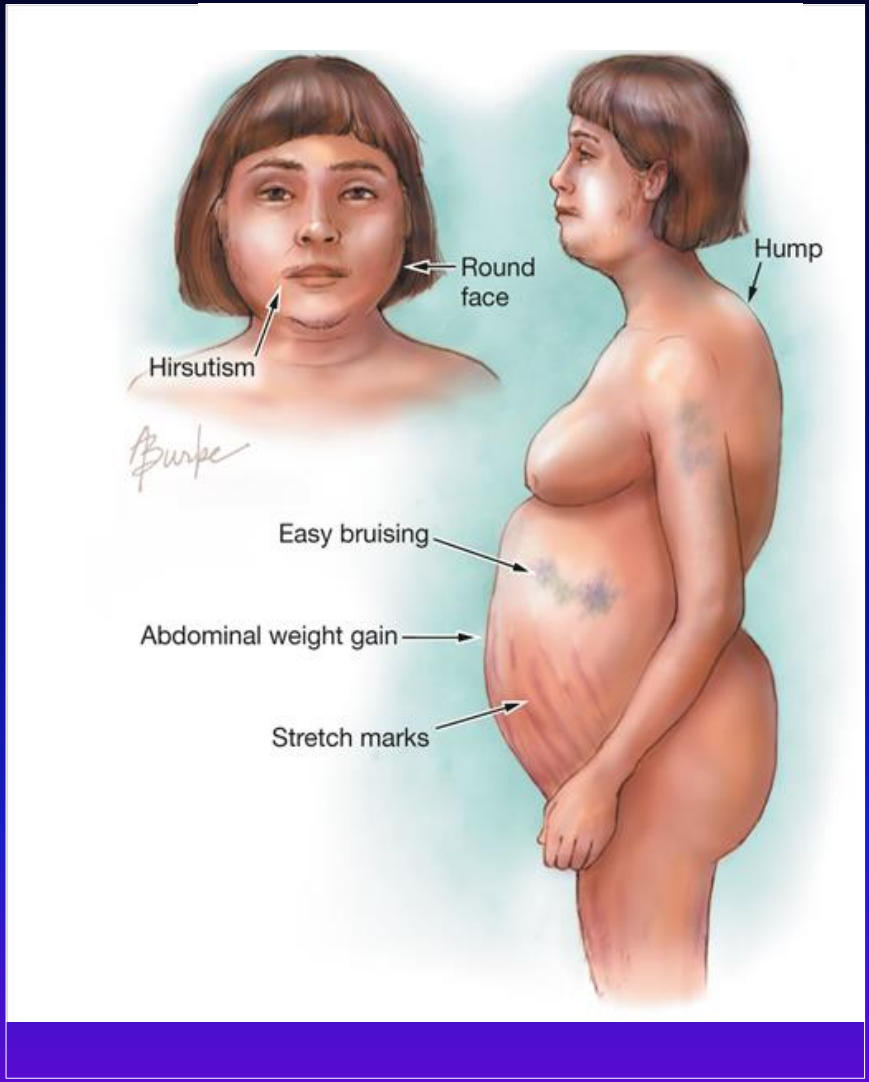
Cawood J et al. EJE 2009; Terzolo M et al 2012; Arnaldi et al. 2012

Biochemical Evalutation

- ***1-mg dexamethasone suppression test***
  - diagnosis of SCS is suspected if the serum cortisol level exceeds 5.0 µg/dL after a 1-mg.
  - A low or suppressed level of ACTH or a low dehydroepiandrosterone sulfate concentration further supports the diagnosis. A second abnormal test result of HPA axis function, such as a 2-day low-dose dexamethasone suppression test, may be needed to establish the diagnosis of SCS
- ***Ratio of plasma aldosterone concentration (PAC) (ng/dL) to plasma renin activity (PRA) (ng/ml per hour)***
  - In hypertensive patients ratio >20 while not taking spironolactone and mineralocorticoid receptor blockers should undergo further assessment for the presence of primary aldosteronism
- **Plasma free metanephrine and normetanephrine levels and 24-hour total urinary metanephrines and fractionated catecholamines** suggest the presence of a pheochromocytoma
- *In general, testing the patient for the production of excess sex hormones is not indicated unless the patient has obvious clinical stigmas.*

Signs and Symptoms of Cushing Disease

- Weight gain, typically with a round face and a hump on the upper back, but often normal arms and legs
- Stretch marks on thighs and abdomen
- Easy bruising
- **Hirsutism** in women (excessive hair on face, abdomen, and legs)
- Irregular menstrual periods in women; sexual difficulties in men
- Severe fatigue, weak muscles, and easy fractures of bones
- High blood pressure
- Diabetes
- Infections
- Anxiety, irritability, and depression
- Decreased ability to concentrate and reduced memory



Subclinical Cushing's Syndrome (SCS)

Low-dose (1 mg) dexamethasone (DXT) suppression test

Cortisol levels after 1 mg DXT

< 1.8 mcg/dl

exclude autonomous cortisol secretion

> 1.8 < 5 mcg/dl

indeterminate non-diagnostic values

Further testing in patients with comorbidities
(features of Cushing's Syndrome)

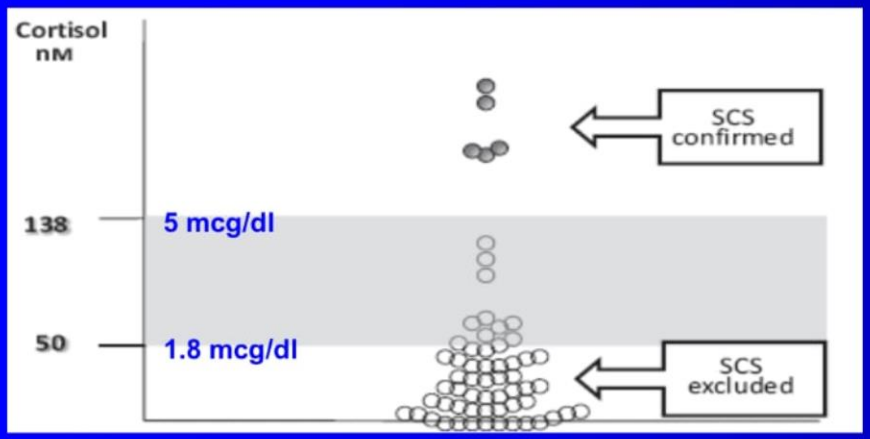
Retesting after 3-6 months

> 5 mcg/dl

likely indicate subclinical hypercortisolism
(if no interferring condition is present)

Potential SCS
especially in presence of obesity, hypertension, diabetes and osteoporosis.

Further testing
- Midnight salivary cortisol (MSC)
- ACTH and DHEAS as supportive criteria



Terzolo M et al. AME Position Statement EJE 2012
Arnaldi G et al. Best Pract Clin Endocrinol Metab 2012

Subclinical Cushing's Syndrome (SCS)

The low-dose (1 mg) dexamethasone (DXT) suppression test

is

the recommended initial test to diagnose Subclinical Cushing's Syndrome

- *NIH Conference 2002*
- *Endocrine Society Guidelines 2008*
- AACE/AAES Giudelines 2009
- Cawood J et al. EJE 2009
- *AME Position Statement 2012*
- *Arnaldi G et al. Best Pract Clin Endocrinol Metab 2012*

73-100% sensitivity, 90% specificity

1 mg DXT cut-off

1.8 mcg/dl
Endocrine Society Guidelines, 2008
French Society of Endocrinology, 2008

3 mcg/dl
Bondanelli Met al. 1997
Morelli V et al. 2010
Chiodini et al. 2011

5 mcg/dl
NIH Conference, 2002
AACE/AAES Guidelines, 2009

La Sindrome di Cushing Subclinica

Condizione caratterizzata dalla presenza di almeno 2 alterazioni dei test di valutazione dell'asse HPA, senza segni e sintomi riconducibili ad uno stato di ipercortisolismo cronico

- *Alterato ritmo circadiano del cortisolo plasmatico/salivare*
- *Valore lievemente incrementati di CLU*
- *Anormale soppressione al test con Decadron 1 mg overnight*
- *Valori ridotti/soppressi di ACTH*
- *Valori ridotti di DHEAS*

Iperaldosteronismo Primario: ARR

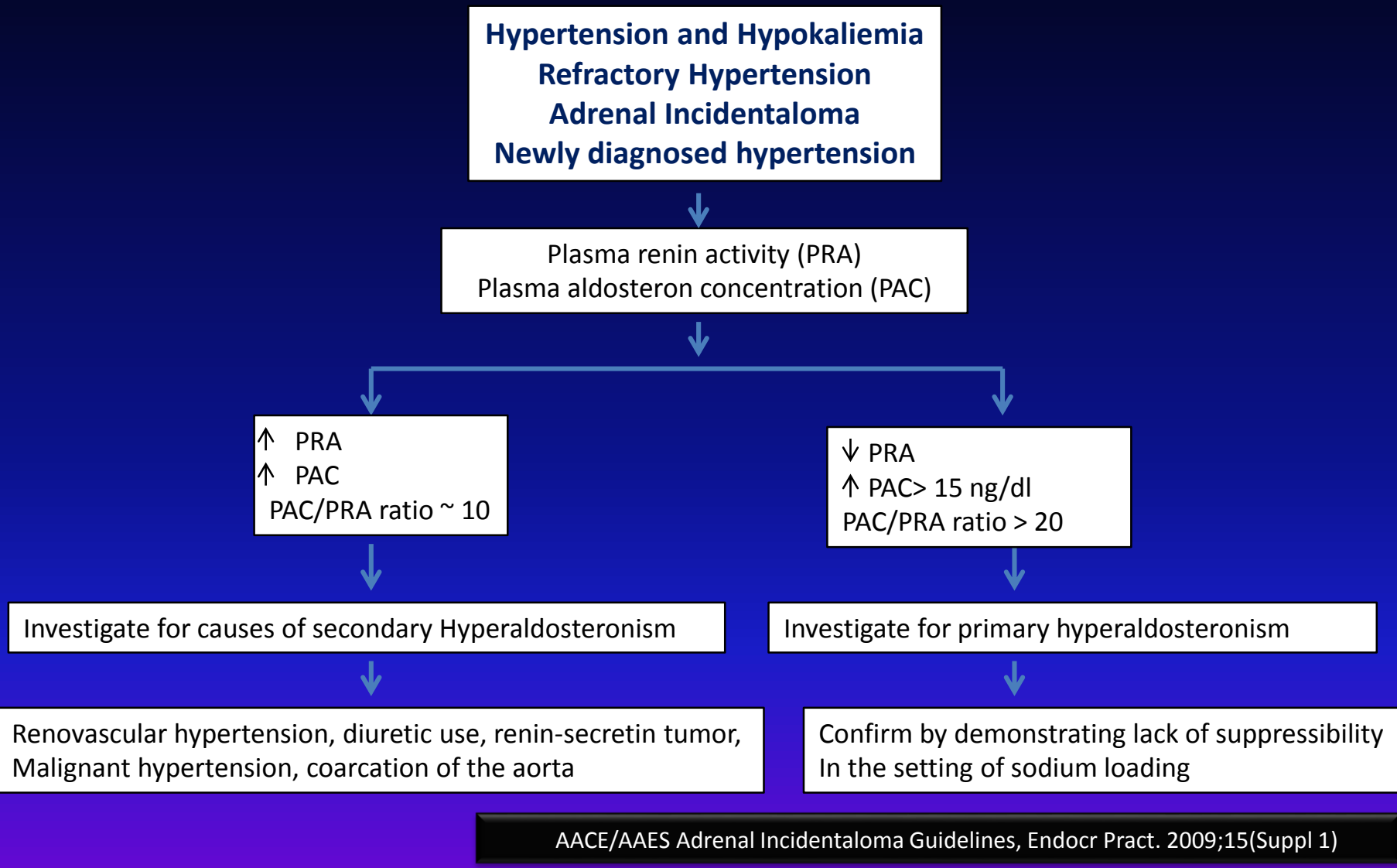
JAMA Diagnostic Test Interpretation
Aldosterone-Renin Ratio in the Assessment of Primary Aldosteronism
Bharat Kumar, MD; Melissa Swee, MD

JAMA July 9 2014 Volume 312, Number 2, pp. 184-185

✓ blood samples for testing renin and aldosterone levels sholud be obtained during mid-morning after the patient has been awake for more than 2 hours and sitting for at least 15 minuts

- although there is no established threshold for an abnormal result, an ARR > 30 when PAC exceeds 15 ng/dl is most commonly used.
- low renin levels increase the likelihood of a falsely positive elevated ARR
- potassium should be supplemented if needed
- liberalize sodium intake
- medication than interfere with the renin-angiotensin-aldosterone system must be stopped for at least 2 weeks

Algorithm showing use of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) and their ratio (PAC/PRA) for diagnosing aldosteronism in patients with resistant hypertension, hypokalemia, or both



AACE/AAES Adrenal Incidentaloma Guidelines, Endocr Pract. 2009;15(Suppl 1)

Iperaldosteronismo Primario: confondenti l'ARR

JAMA Diagnostic Test Interpretation
Aldosterone-Renin Ratio in the Assessment of Primary Aldosteronism
Bharat Kumar, MD; Melissa Swee, MD

JAMA July 9 2014 Volume 312, Number 2, pp. 184-185

Il controllo degli elettroliti è fondamentale!

Conditions that may affect the Aldosterone-Renin Ratio (ARR)			
Condition	Effect on PAC	Effect on PRA	Overall Effect on the AAR
Hypokaliemia	Decreased	May be increased	Decreased
Potassium loading	Increased	May be decreased	Increased
Sodium restriction	Increased	Increased	Increased
Sodium loading	Decreased	Decreased	Decreased
Advanced age	Decreased	Decreased	Decreased
Renal impairment	Unchanged	Decreased	Increased
Pregnancy	Increased	Increased	Decreased
Luteal phase of menstrual cycle	Increased	Unchanged	increased

Iperaldosteronismo Primario: farmaci interferenti su ARR

Medication	ARR
1. Significant effect	
- K+ sparing diuretic	
▪ spironolattone o eplerenone	↓
▪ amiloride o triamterene	↓
- K+ wasting diuretic	↓
- Other (licorice root)	↓ or ← →
2. Lesser effect	
- ACE inhibitor	↓
- Angiotensin receptor blocker	↓
- ß-blocker	↑
- α-agonist (central) clonidine, α methyldopa	↑
- NSAID	↑
- Dihydropyridine CCB	↓
3. Minimal effect	
- Verapamil ± hydralazine	← →
- prazosin, doxazosin, terazosin	← →

Wash out 4 weeks

Wash out 2 weeks

Can be used to control hypertension

Inquadramento Clinico dell'Incidentaloma Surrenalico

Evaluation for hormonal hypersecretion

Screening of primary aldosteronism

In patients with HIGH ARR

- PA (ng/dl) / PRA (ng/ml/h) > 30-50

or

- PA (ng/dl) / DRC (mIU/l) > 3.7

CONFIMATORY EVALUATION
(according to the Endocrine Society Guidelines, 2009)

- saline infusion, oral sodium loading, fludrocortisone suppression, or captopril test

Adrenal venous sampling may also be required to localize aldosterone production

Terzolo M et al. AME Position Statement on Adrenal Incidentaloma EJE 2012
Arnaldi G et al. Best Pact Clin Endocrinol 2012
AACE/AAES Adrenal Incidentaloma Giudelines 2009
Cawood J et al. EJE 2009

Biochemical Testing for Diagnosis of Pheochromocytoma

1. The initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractioned metanephrines
2. For measurement of plasma metanephrines is indicated drawing blood with the patient in the supine position
3. We suggest using liquid chromatography with mass spectrometric or electrochemical detection methods

Guidelines on Pheochromocytoma and Paraganglioma
J Clin Endocrinol Metab, June 2014

Inquadramento Clinico dell'Incidentaloma Surrenalico

Screening for pheochromocytoma in patients with adenal incidentaloma

- Plasma free metanephrines (sensitivity 97-100%; specificity 85- 89%)
  ➥ the best initial test

  NIH conference 2003
  AACE/AAES Adrenal Incidentaloma Guidelines, Endocr Pract. 2009

- 24h Urinary fractionated metanephrines (sensitivity 95-97%)
  or
  Plasma free metanephrines (sensitivity 98-99%)

  Cawood TJ et al. Eur J Endocrinol 2009
  Terzolo M et al. AME Position Statement on Adrenal Incidentaloma EJE 2012

- Plasma free metanephrines
  in patients with high probability of pheochromocytoma
  (eg, vascular, dense adrenal mass, with slow contrast washout)

  or

  24h Urinary fractionated metanephrines and catecholamines
  in patients with low probability of pheochromocytoma
  (eg, hypodense adrenal mass with rapid contrast washout)

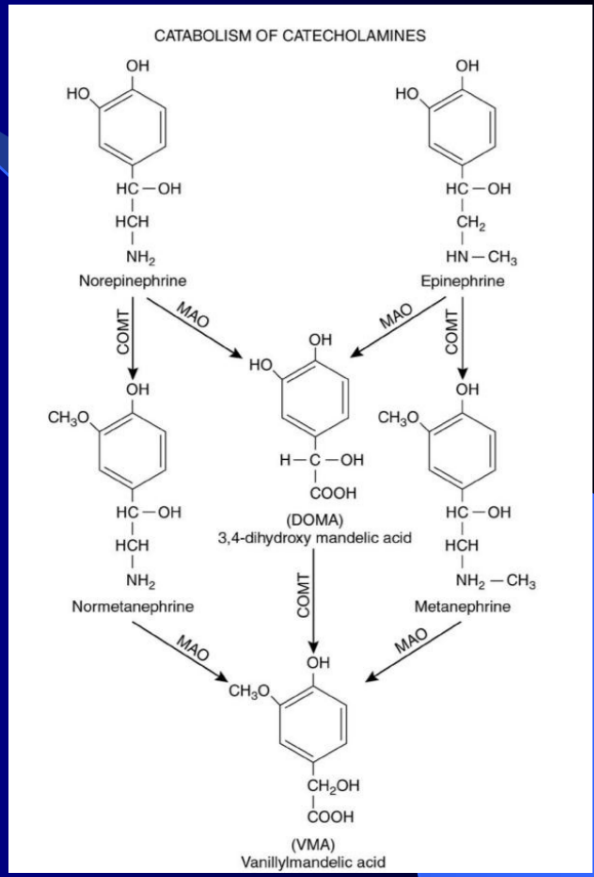
  F Young F et al. 2012 www.uptodate.com

Inquadramento Clinico dell'Incidentaloma Surrenalico

Screening for pheochromocytoma

Considering the relatively large number of false-positive results with metanephrine determination, experts suggest to combine measurements of 24-h urinary metanephrines and catecholamines

Sawka AM, JCEM 2003	Sensibility	Specificity
Plasma fractionated metanephrines *	97 %	85%
24-h urinary metanephrines and catecholamines (both elevated)	90 %	98%



Screening for pheochromocytoma in patients with adenal incidentaloma

- **Normal results rule out pheochromocytoma**

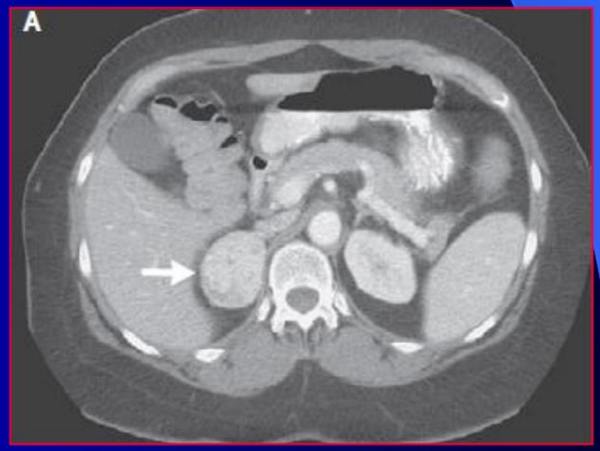
- An **elevation of more than fourfold** above the reference interval establishes the diagnosis, requiring
  - ➥further diagnostic and therapeutic management

- False-positive results should be considered in patients with equivocal elevation of plasma or urinary normetanephrine
  (drugs, dietary interferences, illness requiring hospitalization, inappropriate sampling, other)

	Nature of interference
Analytical methods	
Coffee (including decaffeinated coffee)	HPLC assays: plasma catecholamines
Labetalol	Spectrophotometric and fluorometric assays: urinary catecholamines and metanephrines;
Sotalol	HPLC assays: plasma catecholamines
Buspirone	HPLC assays: urinary metanephrines
Paracetamol	HPLC assays: plasma-free metanephrines
Levodopa	HPLC assays: catecholamines and metabolites
α-methyldopa	HPLC assays: catecholamines
Sympathomimetics (eg, amfetamines, ephedrine)	Spectrophotometric and fluorometric assays: plasma and urinary catecholamines
Pharmacodynamic or pharmacokinetic interference	
Tricyclic antidepressants	Blocks norepinephrine reuptake, causing rises in plasma and urinary norepinephrine, normetanephrine, and VMA
Phenoxybenzamine	Blocks presynaptic α2 adrenoceptors, causing increases in plasma and urinary norepinephrine, normetanephrine, and VMA
Monoamine oxidase inhibitors	Blocks deamination, causing up to five-fold increases in plasma and urinary metanephrines
Levodopa	Metabolised by enzymes that also convert catecholamines
α-methyldopa	Metabolised by enzymes that also convert catecholamines
Stimulants (eg, caffeine, nicotine)	Increased plasma and urinary catecholamines
Sympathomimetics (eg, amfetamines, ephedrine)	Increased plasma and urinary catecholamines
Calcium-channel blockers (dihydropyridines)	Increased plasma catecholamines due to sympathetic activation

Lenders JWM et al. Lancet 2005, 366:665

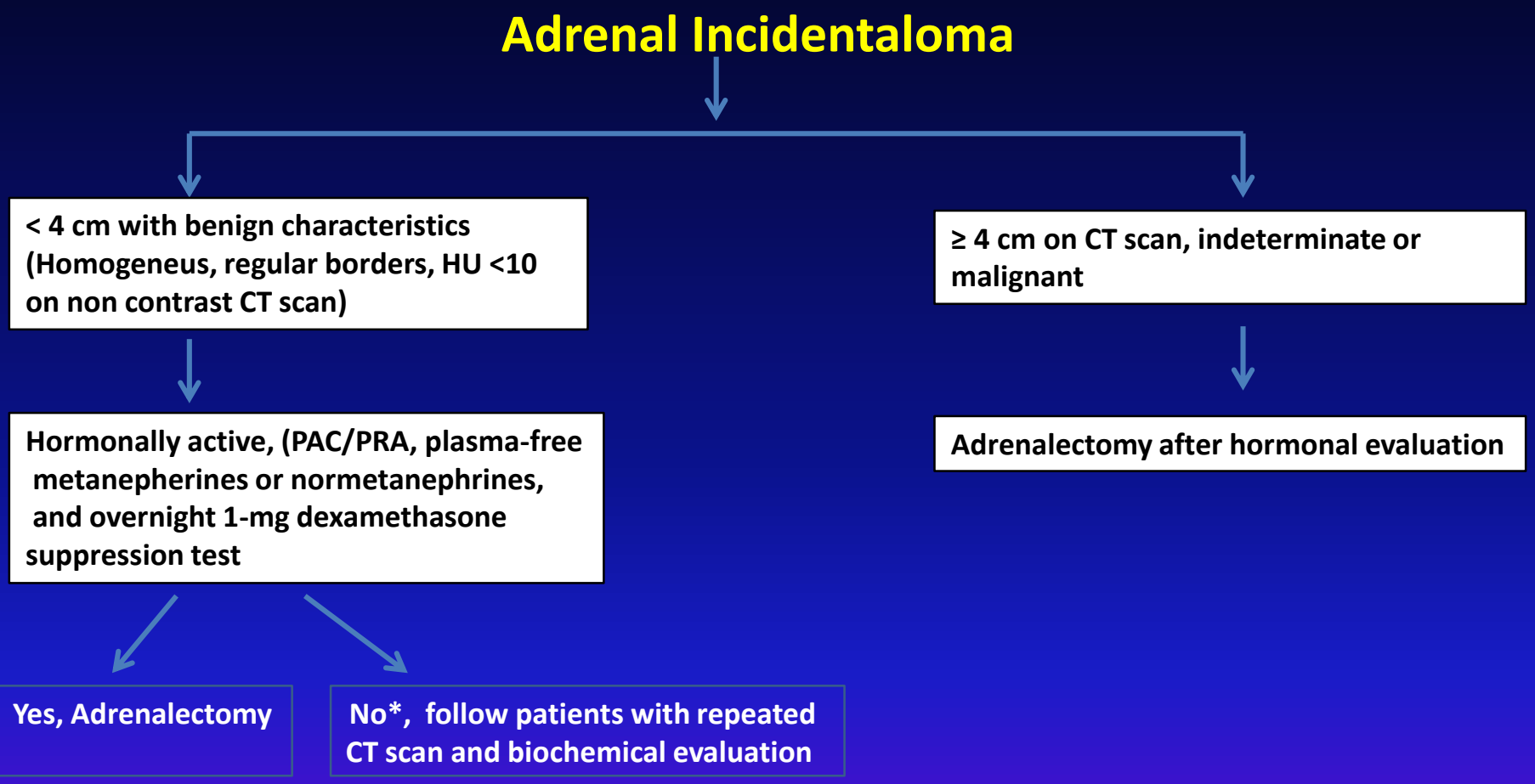
Terzolo M et al.
AME Position Statement on
Adrenal Incidentaloma
EJE 2012



Clinical recommendations on the hormomal assessment of the adrenal incidentalomas

1. We recommend ruling out pheochromocytoma in all patients with adrenal incidentalomas. 1⊕⊕⊕O
2. We recommend ruling out primary aldosteronism in all hypertensive and/or hypokalemic patients with adrenal incidentalomas. 1⊕⊕OO
3. We recommend ruling out overt Cushing's syndrome in all patients with adrenal incidentalomas. 1⊕⊕OO
4. We recommend the 1-mg overnight DST for screening of subclinical Cushing's syndrome. 1⊕OOO
5. We suggest to not proceed with further testing in patients suppressing cortisol below 1.8 μg/dl (50 nmol/l) after DST. 2⊕OOO
6. We suggest considering subclinical Cushing's syndrome in patients not suppressing cortisol below 5.0 μg/dl (138 nmol/l). We suggest further testing in these patients. 2⊕OOO
7. Present evidence is insufficient to recommend for or against considering subclinical Cushing's syndrome in patients with post-dexamethasone cortisol between 1.8 μg/dl (50 nmol/l) and 5.0 μg/dl (138 nmol/l). In selected cases with clinical features suggestive of Cushing's syndrome further testing may be indicated.

Algorithm for the evaluation and management of an adrenal incidentaloma

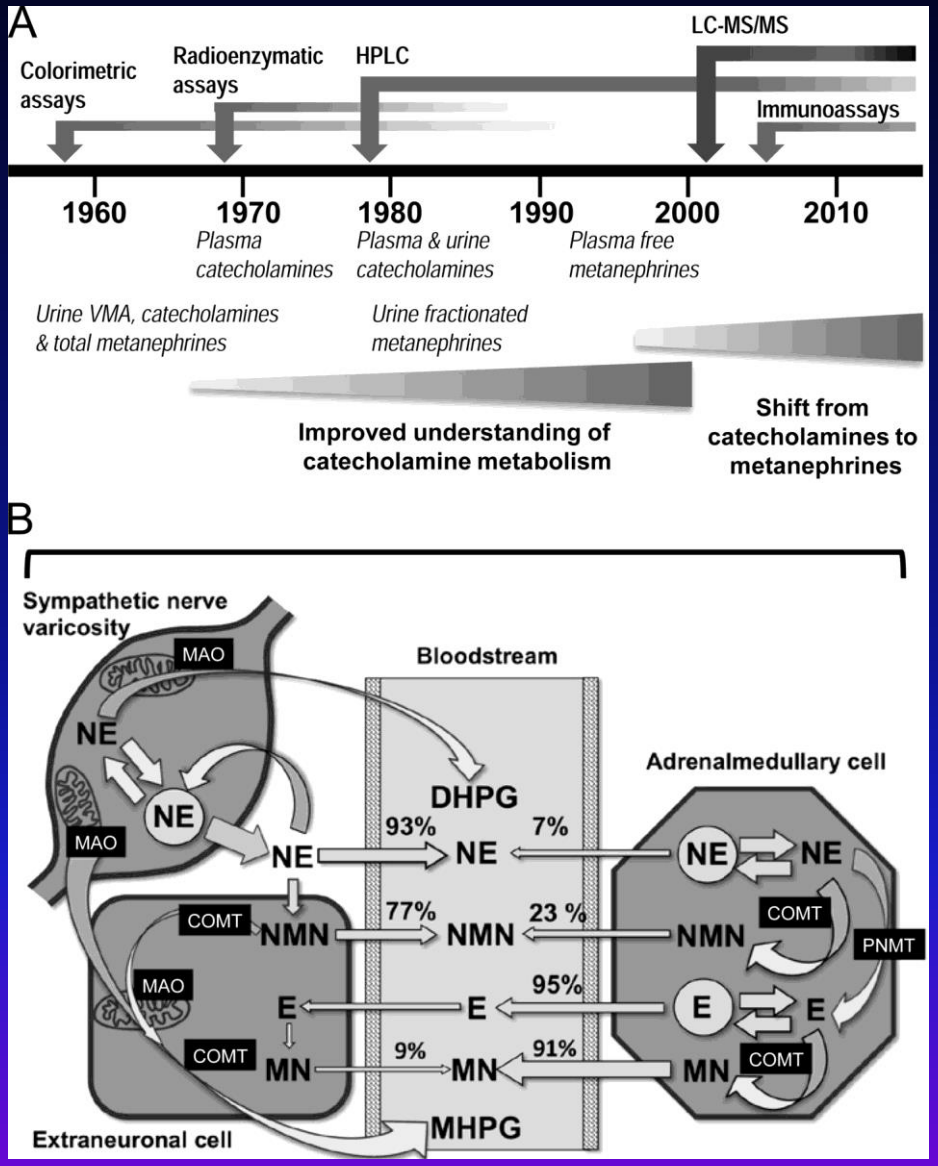


*Reimage in 3 to 6 months and annually for 1 to 2 years; repeat functional studies annually for 5 years. If mass grows more than 1 cm or becomes hormonally active, then adrenalectomy is recommended.

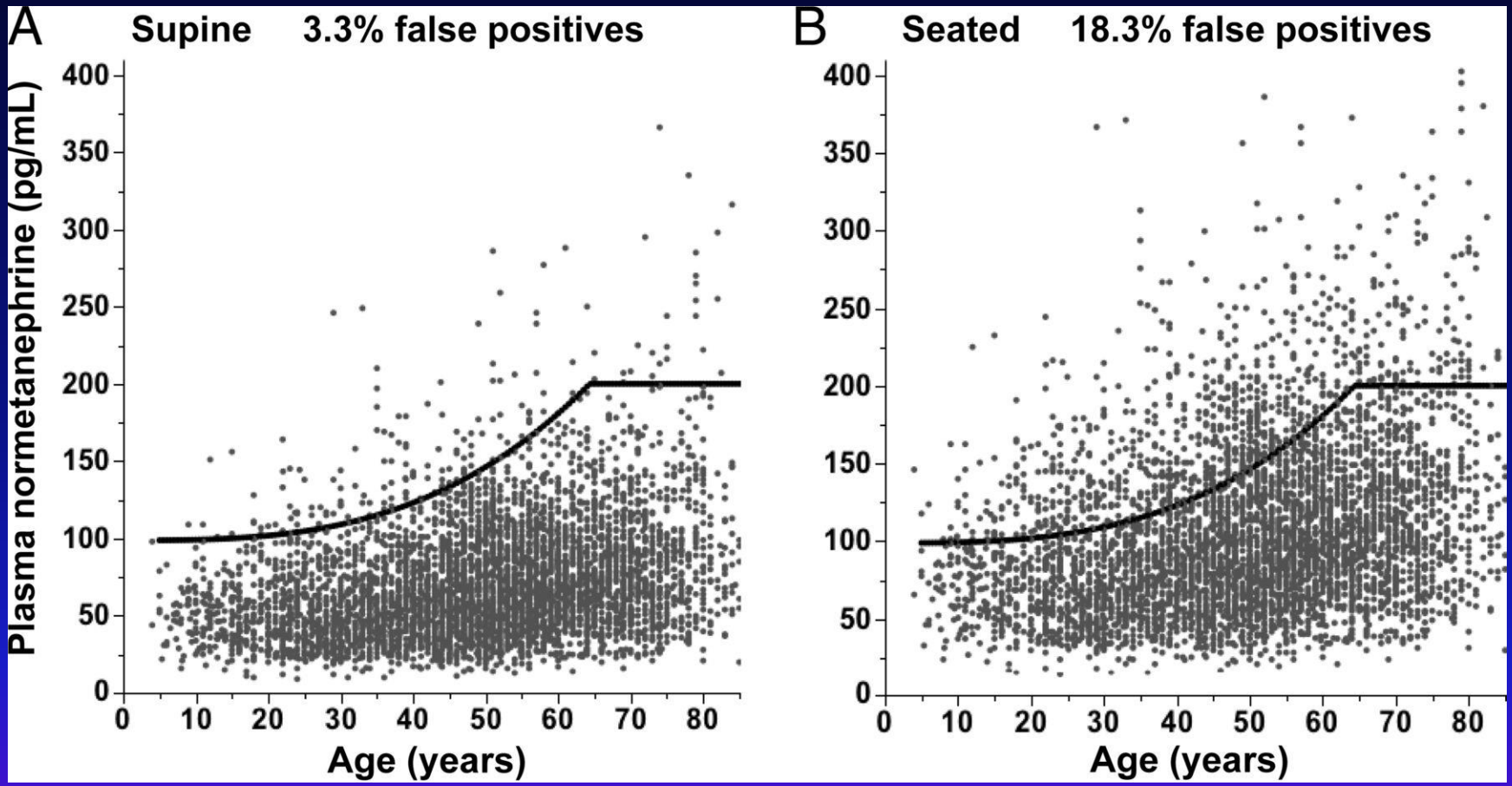
Laboratory Evaluation of Pheochromocytoma and Paraganglioma

Fig. A. Timeline illustrating developments in assay technology shifting emphasis from catecholamines to metanephrines for diagnosis of PPGLs

Fig. B. improved understanding of catecholamine metabolism



Clinical Chemistry December 2014 vol. 60 no. 12 1486-1499


A
Supine
3.3% false positives
Plasma normetanephrine (pg/mL)
400
350
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Age (years)
B
Seated
18.3% false positives
400
350
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Age (years)

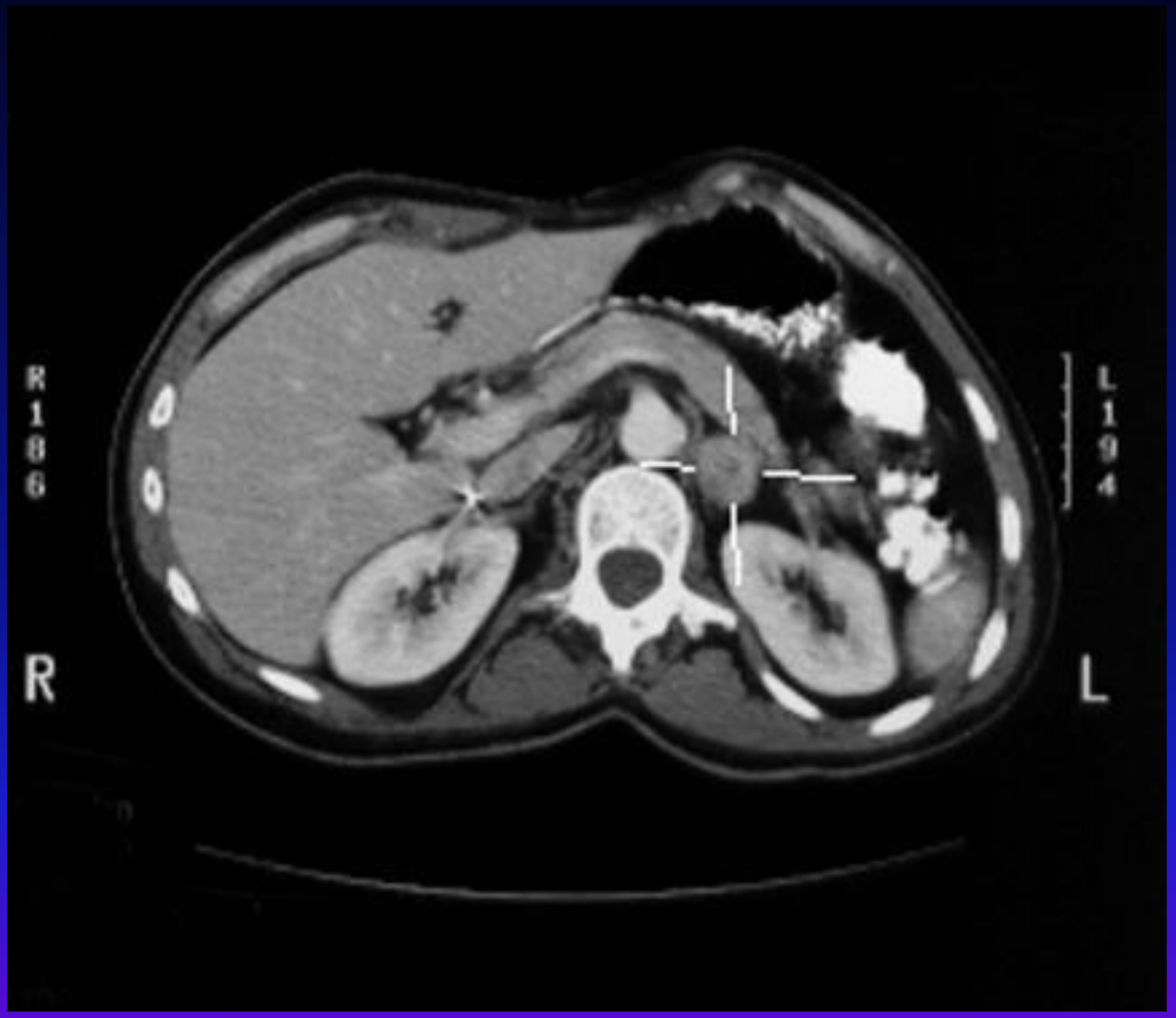
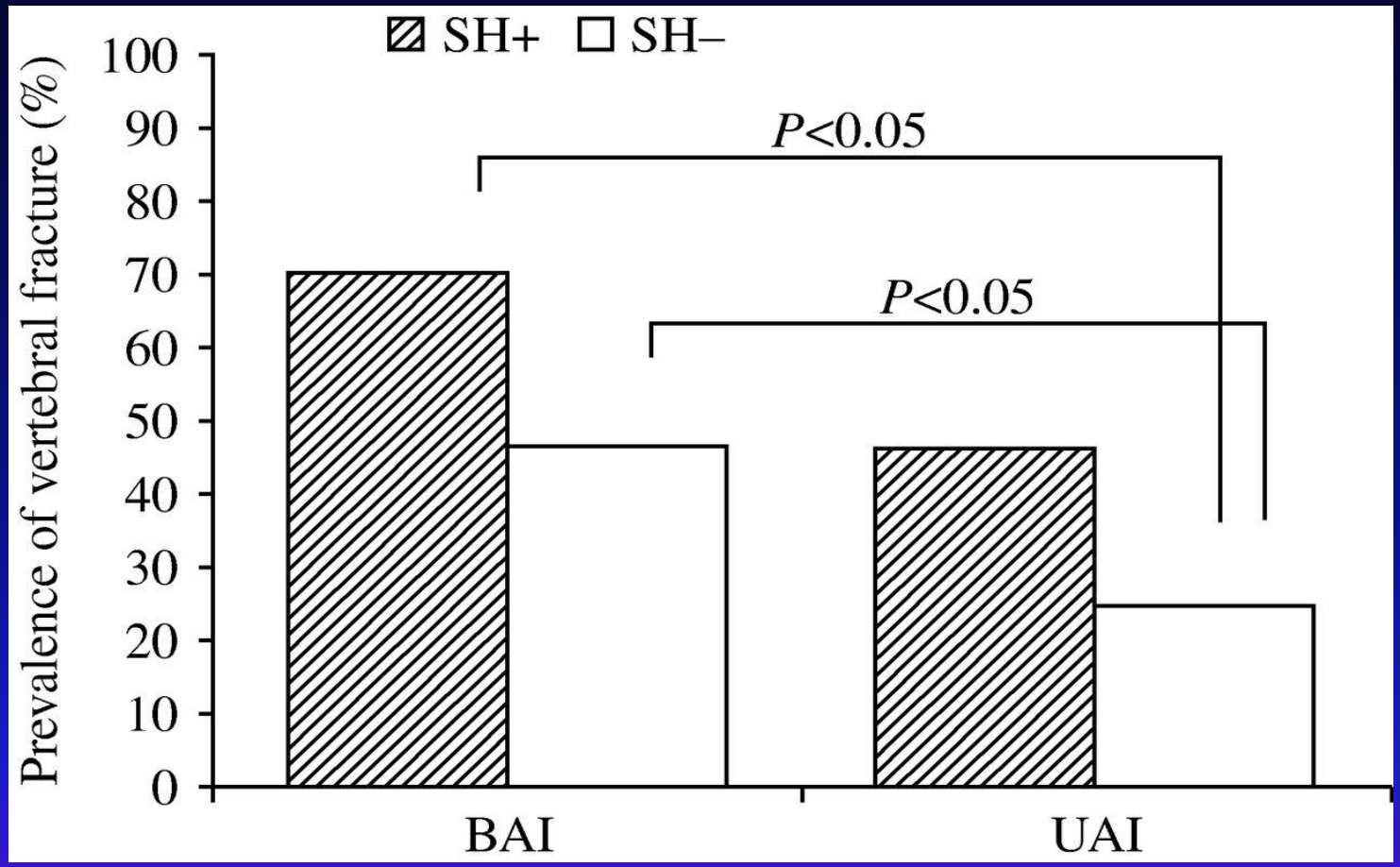

R186
L194
R
L

Figure 1 Prevalence of vertebral fractures in BAI and UAI, with and without SH. UAI, unilateral adrenal incidentaloma; BAI, bilateral adrenal incidentaloma; SH+, presence of SH; SH−, absence of SH. SH, subclinical hypercortisolism was diagnosed in the presence of at least two out of UFC >70 µg/24 h (>193 nmol/24 h), 1 mg DST >3.0 µg/dl (>83 nmol/l) or ACTH levels <10 pg/ml (<2.2 pmol/l).



V Morelli et al. Eur J Endocrinol 2013;168:235-241

Linee guida per la diagnosi delle masse surrenaliche sulla base dei dati epidemiologici	Grado di raccomandazione
1. In tutti i pazienti con riscontro di massa surrenalica è necessario considerare la possibilità che si tratti di una lesione maligna. La probabilità aumenta in modo significativo se il diametro è > 6 cm e si riduce se < 4 cm	Raccomandato
2. In tutti i pazienti con storia di malattia neoplastica e riscontro di massa surrenalica è necessario escludere che si tratti di una lesione metastatica	Raccomandato

Summary of management strategy for patients with adrenal incidentaloma

Experts opinion	Endocrine tests	Tests and frequency	Duration	Imaging	Frequency
NIH Consensus statement 2002[4]	1 mg DST, plasma free metanephrines, K and PRA/aldo in hypertensive patients	Annual	4 years	Monitor mass <4 cm. In addition to size use additional criteria in 4–6 cm mass	Two CTs, at least 6 months apart, no data to support continued imaging if size remain stable
Young, 2007[13]	1 mg DST, urinary metanephrines and catecholamines, K and PRA/aldo in hypertensive patients	Annual	4 years	Monitor mass <4 cm	CT at 6, 12 and 24 months
French Society of Endocrinology Consensus, 2008[62]	1 mg DST, glycemia, plasma and urinary metanephrines, K and PRA/aldo in hypertensive patients	1 mg DST, plasma and urinary metanephrine at 6 months then 1 mg DST at 2 and 5 years	5 years	Monitor mass <4 cm	CT at 6 months and then at 2 and 5 years
AACE/AAES Medical Guidelines, 2009[23]	1 mg DST, plasma and urinary metanephrines/catecholamines and PRA/aldo in hypertensive patients	Annual	5 years	Monitor mass <4 cm	Imaging reevaluation at 3–6 months and then annually for 1–2 years.
Nieman, 2010[27]	1 mg DST or late-night cortisol test, plasma and urinary metanephrines/catecholamines and PRA/aldo in hypertensive patients	Annual No repeat screening for aldosteronism if previously excluded	4 years if mass <3 cm, nonfunctional and benign at imaging 1–2 years (or more)	Monitor mass <4 cm, in addition to size use additional criteria	Imaging reevaluation at 1–2 years (or more) and for intermediate mass at 3–12 months.
AME Position[3]	1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldo in hypertensive and/or hypokalemic patients	To be judged on individual basis after clinical monitoring	To be judged on individual basis after clinical monitoring	Monitor 2–4 cm mass; in addition to size use additional criteria	CT or MRI at 3–6 months. No further imaging if mass is <2 cm with clear benign features. If mass >2 cm judge on individual basis
Arnaldi, 2012	1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldo in hypertensive patients	Annual No repeat screening for aldosteronism if previously excluded	5 years	Monitor mass <4 cm; in addition to size use additional criteria	CT or MRI at 6 months (before if suspect mass) then after 3 and 5 years

Arnaldi G & Boscaro M . Best Pract Clin Endocrinol Metab 2012

Natural history of AI

Follow-up of adrenal incidentaloma thought to be benignant and non-functioning after the initial diagnostic work-up

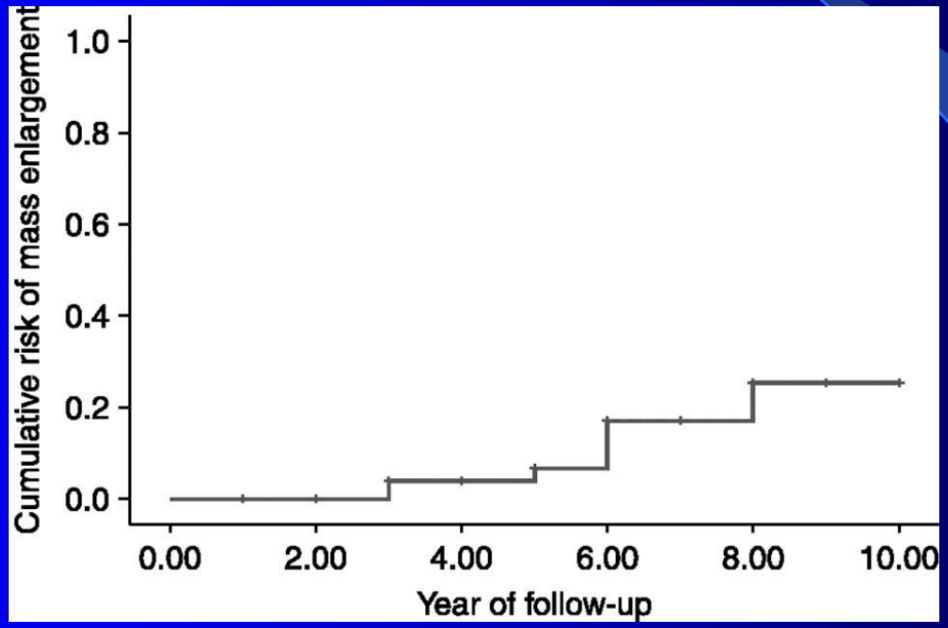
11 studies (>20 pts/study) including 1410 patients, with mean follow-up of 3.2 yr (range 1-7, median 2.1)

	mean	range	median
Increased in size (%)	**14.7**	**0-41.5**	**14.1**
Decreased in size (%)	**7.0**	**0-44**	**0**
Became malignant (%)	**0.2**	**0-1.6**	**0**
Developed ACC (%)	**0**	**0**	**0**
Developed metastases (%)	**0.1**	**0**	**0**
Became functional (%)	**0.9**	**0-8**	**0**
Developed overt CS (%)	**0.3**	**0-2.7**	**0**
Developed SCS (%)	**0.3**	**0-4**	**0**
Developed pheochromocytoma (%)	**0.2**	**0-1.3**	**0**
Developed aldosteronoma (%)	**0**	**0**	**0**

Adapted from Cawood TJ et al Eur J Endocrinol 2009

Natural history of AI

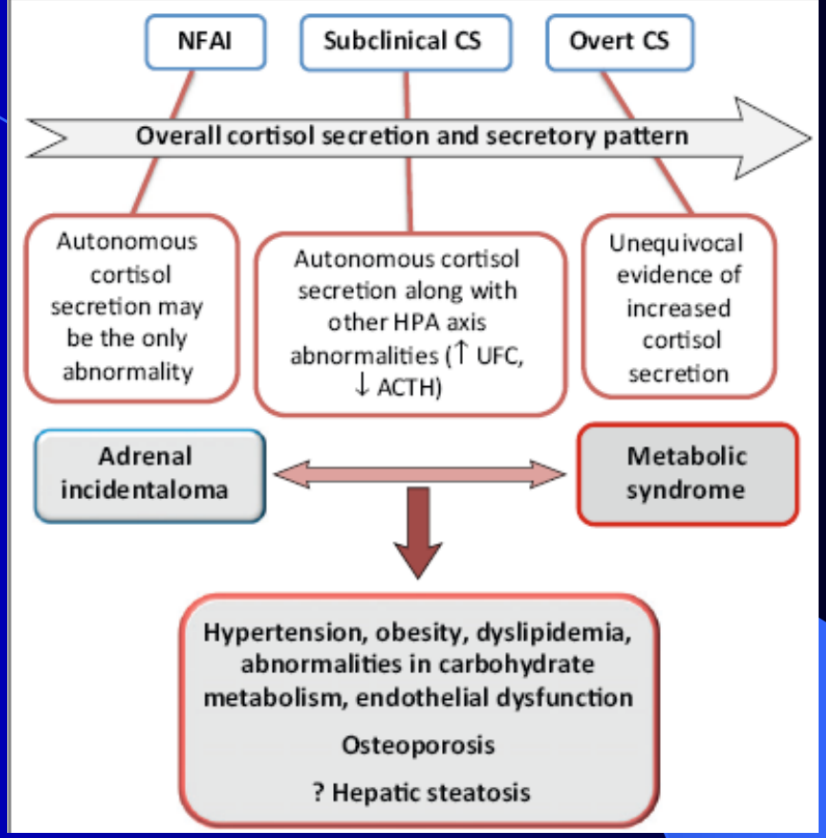
Estimated cumulative **risk of adrenal mass enlargement** over time in patients with adrenal incidentalomas (n=118)



The cumulative risk of mass enlargement was globally low (25%) but progressive up to 8 years independently of mass size and side at entry

Giordano R et al. Eur J Endocrinol 2010;162:779

Natural history of AI



Kaltsas G et al Trends Endocrinol Metab 2012

The risk of progression

from subclinical (SCS) to overt Cushing's syndrome

from non functioning adenoma (NFA) to SCS

is MINIMAL (< 1%)

Terzolo M et al. Clin Endocrinl 2012
De Leo M et al Best Pract Clin Endocrinol 2012
Cawood TJ et al. Eur J Endocrinol 2009

Clinical recommendation on the management of adrenal incidentalomas (1)

1. Surgery for adrenal mass with radiological aspects compatible with malignancy; the threshold for mass size clearly indicative of malignancy is unknown
2. Surgery in patients with functional tumors
3. Surgery in all patients with pheochromocitoma
4. No recommendations for or against surgery in patients with SCS
5. Post-operative glucocorticoid replacement in all patients who undergo surgery for a presumed cortical adenoma. Replacement is mandatory in patients with SCS and in patients without pre-operative testing
6. Data are insufficient to make firm recommendations on endocrine and radiologic follow-up

Clinical recommendation on the management of adrenal incidentalomas (2)

7. Repeat imaging CT or MRI 3-6 months after discovery to recognize early a rapidly growing mass, except when the adrenal mass is small (≤ 2 cm) with clear benign feature (density ≤ 10 HU). If myelolipoma or cyst no additional follow up.

8. We suggest careful clinical monitoring of patients at high cardiovascular risk and to treat.

9. Consider adrenalectomy if the mass enlarges by 1 cm or more and/or change its appearance during observation

10. Consider adrenalectomy in SCS when an adeguate medical therapy does not reach the treatment goals of associated diseases potentially linked to hypercortisolism

11. We recommend laparoscopic adrenalectomy in all patients with presumably benign tumors