Società Medico Chirurgica di Ferrara dal 1846

Ferrara, 9 febbraio 2013

SEDUTA MULTIDISCIPLINARE

INQUADRAMENTO CLINICO DELL'INCIDENTALOMA SURRENALICO

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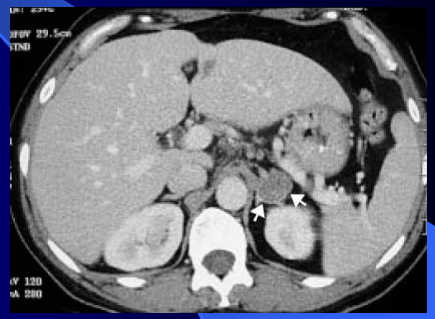
Inquadramento Clinico dell'Incidentaloma Surrenalico

ADRENAL INCIDENTALOMA (AI)

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



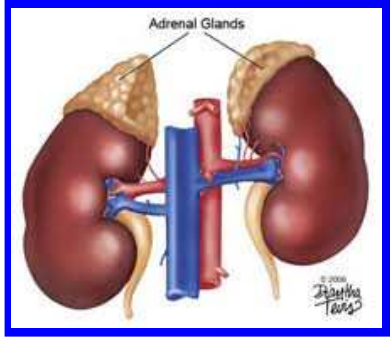
Prevalence

Radiological studies ⇨ 3-4%

0.2 %	young age (< 30 yr)
2- 4 %	middle age
7-10 %	elderly

Autopsy studies ⇨ 2% (ranging from 1 to 8.7%)

< 1 %	young age (< 30 yr)
7 %	elderly (> 70 yr)



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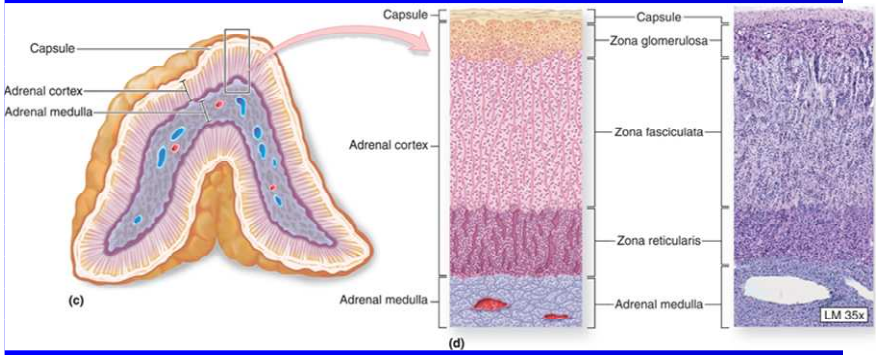
CAUSES OF ADRENAL INCIDENTALOMA (AI)



medullary

PHAEOCROMOCYTOMA
GANGLIONEUROMA
GANGLIO-NEUROBLASTOMA
NEUROBLASTOMA
CARCINOMA

MYELOLIPOMA
LIPOMA
LYMPHOMA
HAEMANGIOMA
ANGIOMYOLIPOMA

cortical

ADENOMA
NODULAR HYPERPLASIA
CARCINOMA

CYSTS
PSEUDOCYSTS

INFECTIONS
GRANULOMA

HAEMATOMA
HAEMORRHAGE

metastases

breast, kidney, lung, ovarian cancer, melanoma, lymphoma, leukaemia

pseudoadrenal masses

stomach, pancreas, kidney, liver, lymphnodal, vascular lesions, technical artefacts

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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
Aldosterone secreting	2.5	1.6–3.3
Pheochromocytoma	7.0	1.5–14
Carcinoma	8.0	1.2–11
Metastasis#	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
Metastasis #	7.0	0–21

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

Bilateral masses in 10-15% of cases

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

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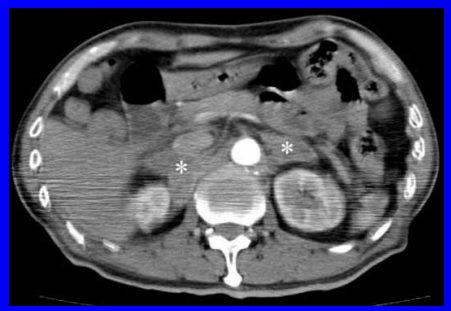
Bilateral adrenal masses (up to 15% of AI)

The most likely diagnoses are

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

In oncological patients

50–75% of adrenal incidentalomas are metastases



bilateral adrenal enlargement consistent with lung cancer metastases

Unknown primary cancer may present as

- Bilateral adrenal masses in 5.8% of cases
- Monolateral adrenal mass in 0.2%

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Discovery of an adrenal mass raises two questions that determine the degree of evaluation and the need for therapy:

1. **Is it malignant ?**

2. **Is it functioning ?**

Over time, in case of conservative approach:

1. Can the adrenal mass become malignant ?

2. Can the adrenal mass become hyperfunctioning ?

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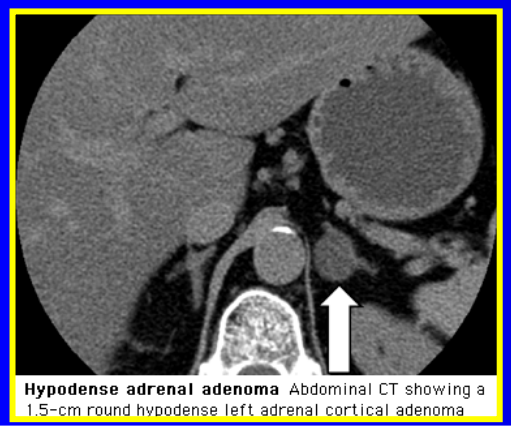
Evaluation for malignancy

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

NIH Conference 2003

4 cm cut-off

93% sensitivity, 76% sensibility



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

Change in size over time

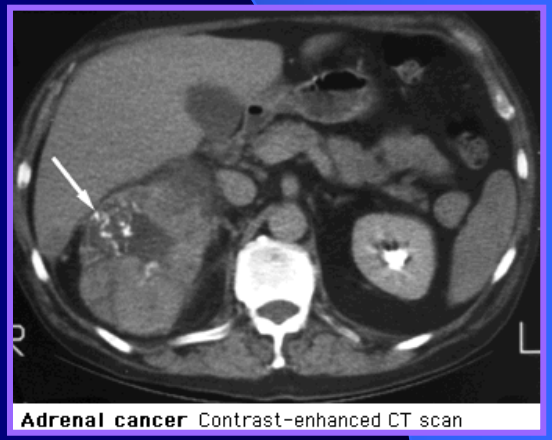
⇩

growth > 1 cm/year

(ACC rapid growth >2 cm/yr)

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)



Adrenal cancer Contrast-enhanced CT scan

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Evaluation for malignancy

Imaging phenotype

CT scan

noncont: excluded non adenomatous lesions
HU ≤20 and tumor size ≤4 cm
homogeneous lesion with a smooth border
[...sitivity; 50-100% specificity]

contrast-enhanced CT: rapid washout (absolute >60%, relative on delayed images >40%)
[82-100% sensitivity; 83-100% specificity]

MRI

...sequences
can distinguish adenomas from malignancy and pheochromocytoma
[...ensitivity; 92-100% specificity]

High signal intensity on T2 weighted MRI (pheocromocytoma)

FDG PET/CT

high sensitivity for detecting malignancy
[93-100% sensitivity; 80-100% specificity]

FNAB
(Fine-needle aspiration biopsy)

in selected cases suspicious of metastases
(after biochemical exclusion of pheochromocytoma)
[81-96% sensitivity; 99-100% specificity]
Inconclusive biopsies in 6-50% of cases

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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

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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

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Evaluation for hormonal hypersecretion

Screening for pheochromocytoma 4-7% (1-20%)

About 30% of all pheochromocytomas are discovered incidentally
this prevalence increases with time

Th ...able

All patients with adrenal incidentaloma
should undergo
biochemical testing
for pheochromocytoma

In patients with incidentally detected pheochromocytoma

- Normal blood pressure in more than 50% of cases
- Mild to moderate hypertension in the other
- No paroxysmal symptoms of adrenergic excess

Even when clinically silent this tumor can be lethal

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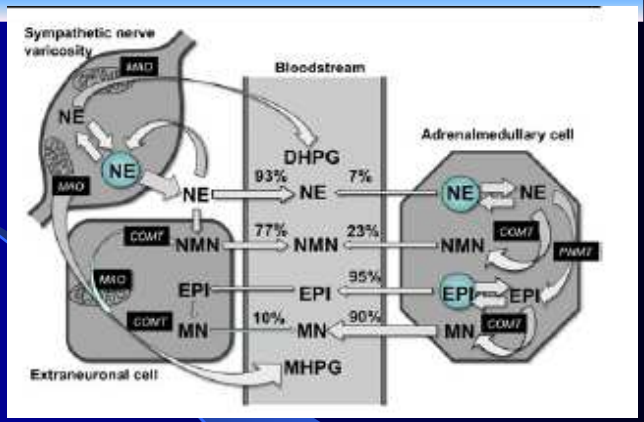
Screening for pheochromocytoma

The optimal type of screening test is debated
and it is institution/laboratory-dependent

	Sensitivity	Specificity
Plasma-free metanephrines	99%	89%
Plasma catecholamines	84%	81%
Urinary catecholamines	86%	88%
Urinary-fractionated metanephrines	97%	69%
Urinary total metanephrines	77%	93%
VMA	64%	95%



Because of the continuous high rate of intratumoral catecholamine O-methylation, and because some tumors secrete catecholamines episodically or in low amounts, patients with pheochromocytoma usually have relatively larger and more consistent increases of plasma normetanephrine or metanephrine than of catecholamines

Measurements of fractionated metanephrines in plasma and urine provide superior diagnostic sensitivity to measurements of catecholamines

Measurement of plasma metanephrines is difficult (and not widely available) because their concentration is 2000-fold lower than those of urinary metanephrines

Lenders JWM et al. Lancet 2005, 366:665
Pacak K et al. Nat Clin Prac Endocrinol & Metab 2007,3:92
Eisenhofr G Curr Hypertens Rep 2012, 14:130

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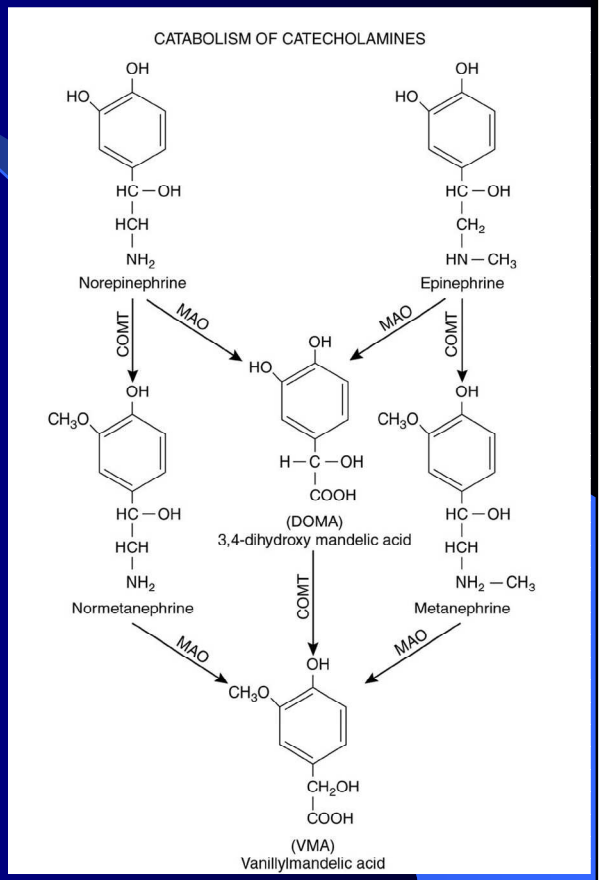
Screening for pheochromocytoma

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%



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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

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Screening for pheochromocytoma in patients with adenal incidentaloma

Normal results rule out pheochromocytoma

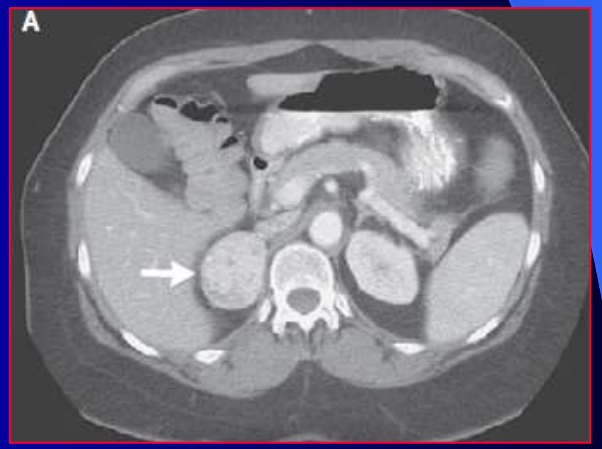
An **elevation of more than fourfold** above the reference interval establishes the diagnosis, requiring
➥**further diagnostic and therapeutic management**

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



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Evaluation for hormonal hypersecretion

Screening of primary aldosteronism

Aldosterone-secreting incidentaloma
➡ 2% (1.5-7%)

In all hypertensive or hypokaliemic patients

Normokaliemic primary aldosteronism ➡up to 40% of cases

Reported cases of normotensive patients with primary aldosteronism

The best screening test

Sensitivity and specificity 90-100%

The ratio (ARR) between morning
➥ plasma aldosterone (PA, ng/dl) and plasma renin activity (PRA, ng/ml/h)
using a diagnostic threshold of 30–50

➥plasma aldosterone (PA, ng/dl) and direct renin concentration (DRC, mIU/l)
using a diagnostic threshold of 3.7 – 4.9

Tezolo 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

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Raccommandation for ARR measurement

Endocrine Society Guidelines for the diagnosis and treatment of patients with primary aldosteronism. J Clin Endocrinol Metab, 2009

- **Correct hypokalemia and liberalize sodium intake**

- **Withdraw agents that markedly affect the ARR for at least 4 wk:**

- Spironolactone, eplerenone, amiloride, and triamterene
- Potassium-wasting diuretics
- Products derived from licorice root

- If the results of ARR off the above agents are not diagnostic, withdraw other interfering medications for at least 2 wk:

- Beta- blockers, central α-2 agonists, nonsteroidal antiinflammatory drugs
- Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, dihydropyridine calcium channel antagonists

- **Hypertension can be controlled with non-interfering medication** (verapamil slow-release/doxazosin)

- Establish OC and HRT status, because estrogen-containing medications may lower DRC and cause false-positive ARR when DRC (rather than PRA) is measured

- Collect blood morning, after the patient has been up (sitting, standing, or walking) for at least 2 h and seated for 5–15 min

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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

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Screening of hypercortisolism

Subclinical Cushing Syndrome

Prevalence: 5% -48%
[depending on work-up protocol, diagnostic criteria and screening methods used on different studies]

Autonomous cortisol secretion in patients
who do not have
the typical signs and symptoms of hypercortisolism

some patients may have

previously
undiagnosed
mild hypercortisolism

comorbidities
[hypertension, obesity,
diabetes mellitus, osteoporosis]
potentially associated
with
cortisol hypersecretion

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Subclinical Cushing's Syndrome (SCS)

Definition
Presence of at least two abnormal tests of HPA axis
in patients with adrenal incidentalomas
without classic clinical stigmata of cortisol excess

Tests abnormalities observed in patients with SCS:

- Lack of cortisol suppression after low-dose dexamethasone suppression test
- Elevated 24 h urinary-free cortisol (UFC)*
- Low morning ACTH levels
- Elevated midnight serum cortisol
- Elevated midnight salivary cortisol (MSC)
- Low DHEAS concentration
- ACTH/cortisol abnormal response to CRH test

*UFC may be normal in mild Cushing syndrome

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

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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

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)

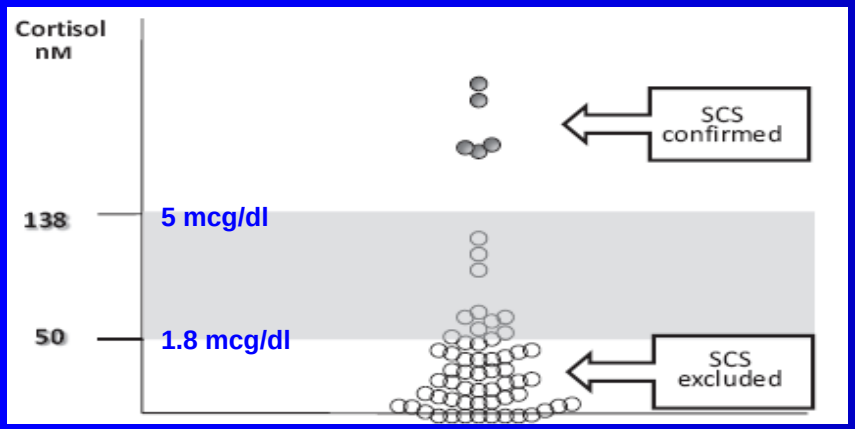
Retesting after 3-6 months

> 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

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Clinical features in patients with SCS

Metabolic syndrome

- Central obesity
- Hyperinsulinemia/insulin resistance
- Diabetes mellitus type 2 or IGT
- Systolic and diastolic hypertension
- Dyslipidemia (hypertrigliceridemia, low HDL cholesterol)
- Accelerated atherosclerosis

→ Increased cardiovascular risk

Skeletal disease

- Osteopenia/osteoporosis

→ Increased risk of fractures

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Subclinical Cushing's Syndrome

Impact of surgical intervention on cardiometabolic outcome

Removal of adrenal mass in patients with SCS

is associated with

SIGNIFICANT **IMPROVEMENT**
in
ALL (or some=BP)
Features of Metabolic Syndrome

Erbil et al. 2006 (n 11, follow-up 1 yr)
Toniato et al. 2009 (n 23, mean follow-up 7.7 yr)
Mauclère-Denost et al. 2009 (n 8, mean follow-up 12 mo)
Guerrieri et al. 2010 (n 19, mean follow-up 4 yr)
Chiodini et al. 2010 (n 25, follow-up 18-48 mo)
Iacobone et al. 2012 (n 20, mean follow-up 54±34 mo)

No effect on cardiometabolic outcome

➧ *only a minority of operated patients had SCS*

Sereg et al. 2009 [n 47 (5 SCS) mean follow-up: 9.1 yr (5-16)]

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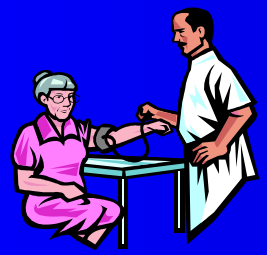
Subclinical Cushing's Syndrome

Impact of surgical intervention on cardiometabolic outcome

Conservative approach

Not operated patients with SCS

experienced



worsening
of
- blood pressure
- body weight
- glucose and cholesterol levels

Guerrieri et al. 2010
Chiodini et al. 2010
Iacobone et al. 2012

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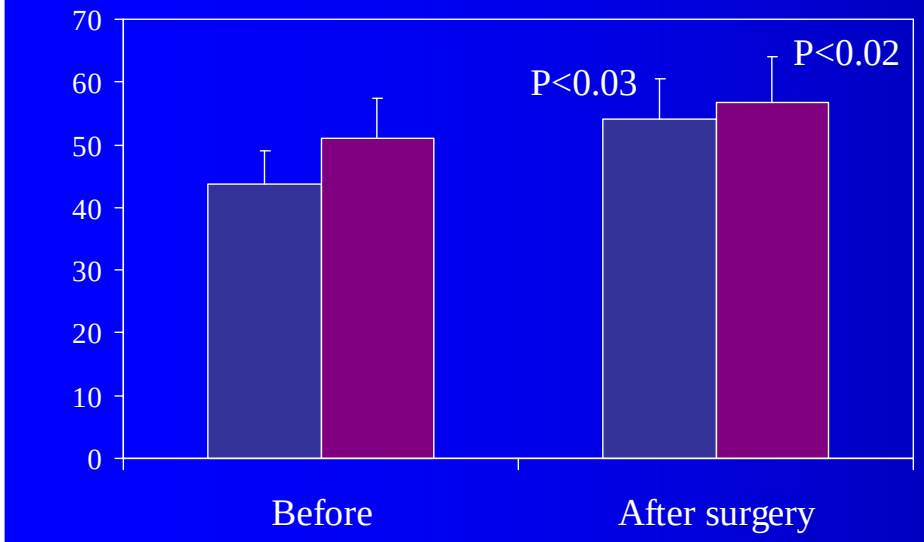
Subclinical Cushing's Syndrome

Impact of surgical intervention on quality of life

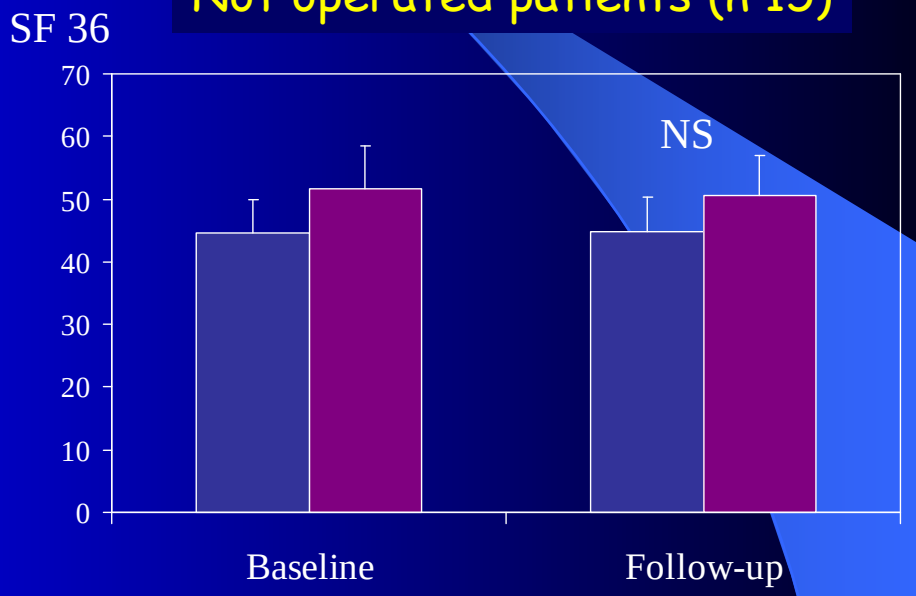
-SF-36 Health Survey questionnaire in 35 patients with AI and SCS -

(mean follow-up 54±34 mo)

Operated patients (n 20)



Not operated patients (n 15)



SF-36 MCS, Mental Component Summary

SF-36 PCS, Physical Component Summary

After adrenalectomy
➥significant IMPROVEMENT
in quality of life

Iacobone M et al. Surgery 2012

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Proposed management of Subclinical Cushing's Syndrome

The NIH state-of-the-science statement (2002)

↘ either adrenalectomy or careful observation is a treatment option for patients with SCS

Adrenalectomy has been demonstrated to correct the biochemical abnormalities, but its effect on long term outcome and quality of life is unknown

The AACE/AAES Medical Guidelines (2009)

↘ [until further evidence is available regarding the long-term benefits of adrenalectomy]

surgical resection should be reserved for SCS patients with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis

(recommendation with a low level of evidence)

The AME position statement (2011)

↘ it seems reasonable to elect for surgery younger patients with SCS who display diseases potentially attributable to excessive cortisol (hypertension, diabetes, abdominal obesity, and osteoporosis) that are of recent onset, or are resistant to optimal medical treatment or are rapidly worsening

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Clinical features in patients with NFAI

A growing body evidence supports the notion that also nonfunctioning adrenal incidentalomas (NFAI) are associated with **features of metabolic syndrome**

Authors (year of publication)	Number of patients examined	Type of AI based on endocrine activity	Cardiometabolic abnormalities associated with AIs
Ivović *et al.* (2006)	*n* = 22	NFAIs	Impaired insulin sensitivity
Zhang *et al.* (2006)	*n* = 24	NFAIs	Abdominal obesity, hypertension, dyslipidaemia, hyperglycaemia
Comlekci *et al.* (2009)	*n* = 376	NFAIs (predominantly)	Type 2 diabetes, hypertension, hyperlipidaemia
Yilmaz *et al.* (2009)	*n* = 32	NFAIs	Obesity, hypertension, impaired glucose tolerance
Wagnerova *et al.* (2009)	*n* = 92	NFAIs (predominantly)	Obesity, hypertension, diabetes
Yener *et al.* (2009)	*n* = 49	NFAIs	Increased carotid intima–media thickness
Yener *et al.* (2009)	*n* = 45	NFAIs	Increased D-dimer levels
Peppa *et al.* (2010)	*n* = 29	NFAIs	Impaired fasting and postabsorptive glucose, obesity, hypertension, dyslipidaemia, fatty liver disease, abnormal fat distribution

Peppa M et al. J Int Med 2010

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Non Functioning Adrenal Incidentalomas

Impact of surgical intervention on cardiometabolic outcome

Removal of adrenal mass in patients with NFAI

is associated with

IMPROVEMENT of Metabolic Syndrome Features

Rossi et al. 2000 (n 13, median follow-up 30 mo)
Midorikawa et al. 2001 (n 8, follow-up 48 mo)
Bernini et al. 2003 (n 9, follow-up 12 mo)

or

NO EFFECT on
- Metabolic Syndrome Features
- Cardiovascular Morbidity and Mortality

Sereg et al 2009 (n 7, mean follow up 9 yr)
Giordano et al 2010 (n 102, median follow-up 3 yr, range 1- 10)

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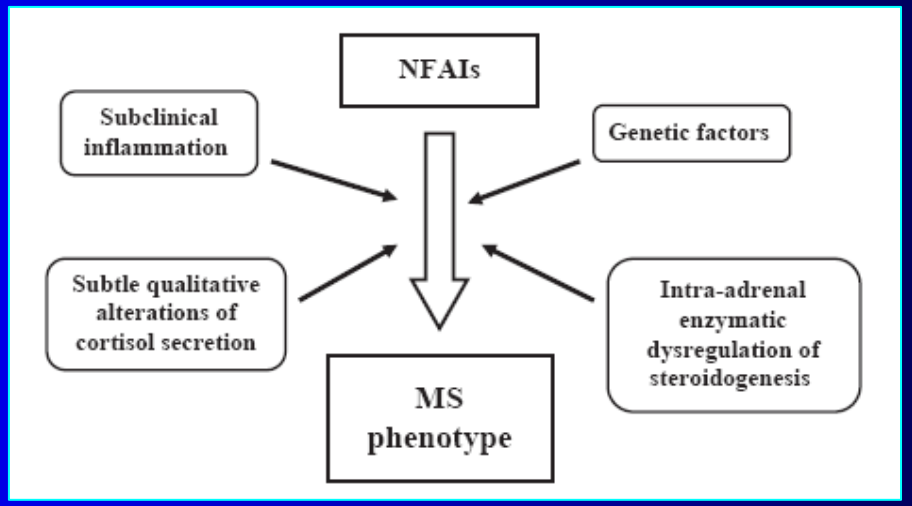
Non Functioning Adrenal Incidentalomas

About 15% of lesions classified as non-functioning demonstrate a single abnormal test of the HPA axis

Test	Non-hypersecreting (%)	Subclinical Cushing's syndrome (%)
Low morning ACTH levels	15	79
Above normal UFC	11	75
Abnormal circadian rhythm of plasma cortisol	17	43
Blunted ACTH response to CRH	17	55
Cortisol not adequately suppressed by 1 mg dexamethasone	10	73

Mantero et al 2000

Subtle adrenal hormone excess and increased proinflammatory state might explain
the development of metabolic syndrome disturbances



Peppa M et al. J Int Med 2010

EFE 2013

ADRENAL INCIDENTALOMA: CLINICAL AND METABOLIC ASPECTS DURING LONG-TERM FOLLOW-UP

Patients and Methods

78 patients (48 F; aged 35-79 yr) with adrenal incidentaloma

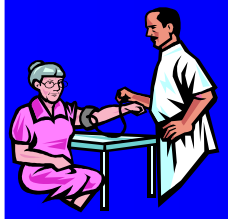
- ✓ unilateral mass (37 right, 28 left) in 65 cases
- ✓ mass diameter: 27±9.1 mm (range 9-52)

52 assigned to follow-up

- 13 with subclinical Cushing's syndrome (SCS)
- 39 with normal adrenal function, all with mass diameter < 4 cm and radiological characteristic of benign mass

26 assigned to surgery

- 13 with subclinical Cushing's syndrome (SCS)
- 13 with normal adrenal function, but mass diameter >4 cm and/or radiological characteristic suspected for malignancy



Exclusion criteria:

- Clinical Cushing's Syndrome
- Pheochromocytoma
- Primary hyperaldosteronism
- Extra-adrenal malignancy

24 adrenal adenomas
1 adrenal pseudocystis
1 adrenal mielolypoma

All patients were followed-up for 48-168 months (mean 84±35; median 74) after baseline evaluation and laparoscopic adrenalectomy in 26 cases

Bondanelli et al. JEI 2010 (abstract)

Clinical and hormonal data at baseline in SCS patients compared with normal adrenal function

	Subclinical Cushing's Syndrome	Normal adrenal function
Sex	7M 19F	23M 29F
Age yr	59.7±9.23	62.8±7.76
Hypertension	21/26 (81%)	30/52 (55.7%)
SBP mmHg	144.29±18.3 *	135.24±16.15
DBP mmHg	86.2±9.86	82.02±8.84
Well-controlled Hypertension	6/21 (28.6%) **	20/30 (66.6%)
Diabetes	6/26 (23%)	6/52 (11.5%)
IGT/IFG	11/26 (42.3%)	17/52 (32.7%)
Dyslipidemia	20/26 (76.9%)	29/52 (55.7%)
Cardio- or cerebrovascular events	4/26 (15.4%)	7/52 (11.5%)
BMI (kg/m2)	30.92±6.65	28.8±4.93
ACTH (pg/ml)	6.96±8.83 **	17.03±10.32
Morning cortisol (mcg/dl)	18.39±6.07	17.24±6.19
Midnight cortisol (mcg/dl)	7.03±2.14	5.36±2.92
Cortisol after DXT 1 mg	5.85±4.55 ***	1.64±0.86
UFC (mc/24 h)	154.32±103.6 *	106.72±41.2
DHEAS (mc/dl)	51.73±33.24	68.86±36.62
Total Cholesterol (mg/dl)	235.05±40.07**	208.95±33.77
Triglycerides (mg/dl)	142.57±81.04	132.1±79.43
Glycemia (mg/dl)	142.57±81.04**	100.67±46.85
Mass size (mm)	28.3±7.8	26.7±6.9

No significant differences for prevalence of metabolic complicances between the two groups

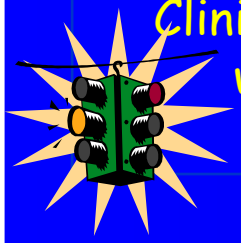
Patients with SCS had higher total cholesterol, glucose, blood pressure, and body weight

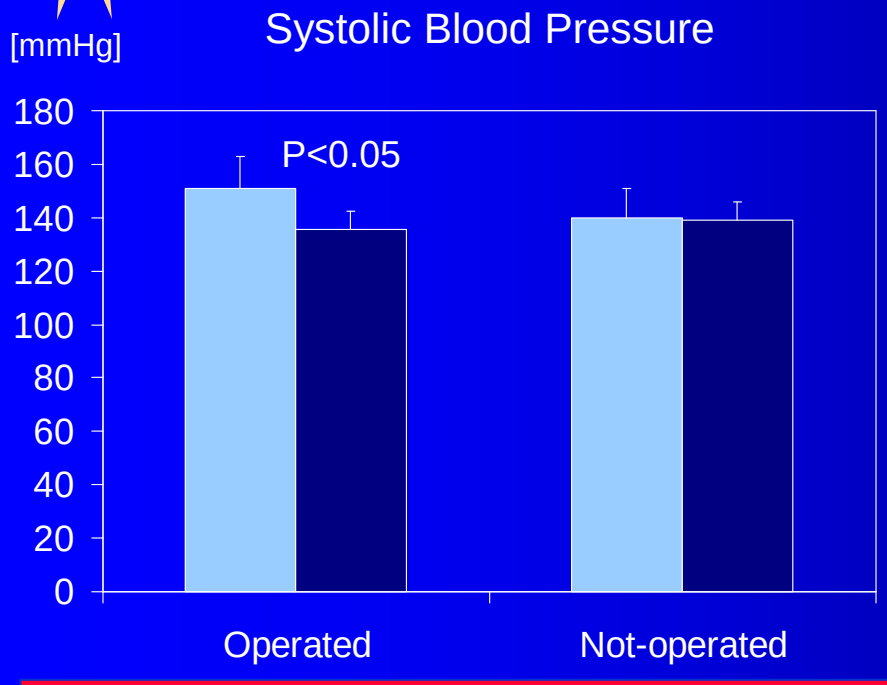
*p<0.05, **p<0.01, ***p<0.001 vs. normal adrenal function

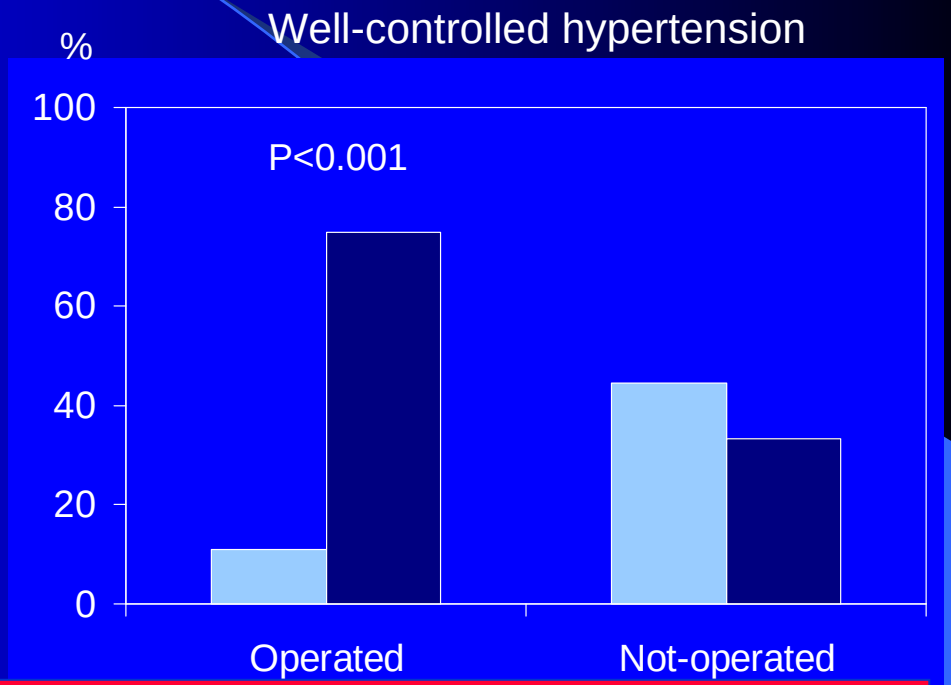
Bondanelli et al. JEI 2010 (abstract)

ADRENAL INCIDENTALOMA: CLINICAL AND METABOLIC ASPECTS DURING LONG-TERM FOLLOW-UP

Clinical characteristics of **Subclinical Cushing's Syndrome (SCS)** patients who underwent surgery compared with not-operated SCS patients, at baseline and follow-up



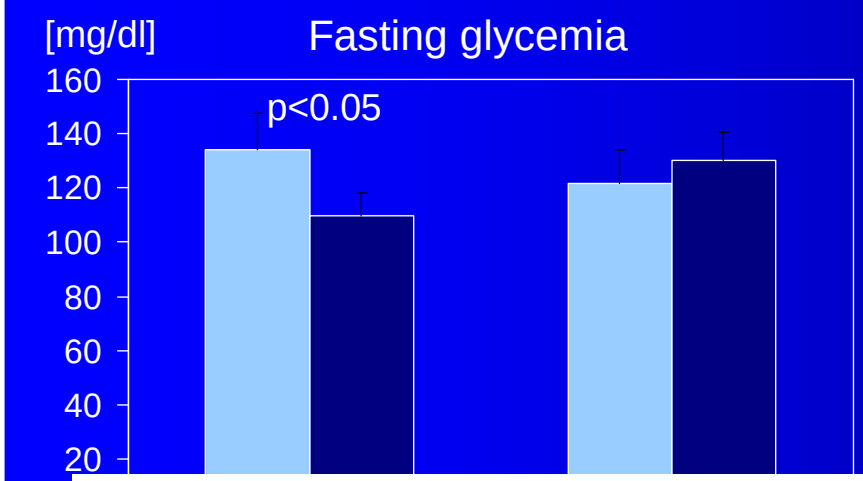


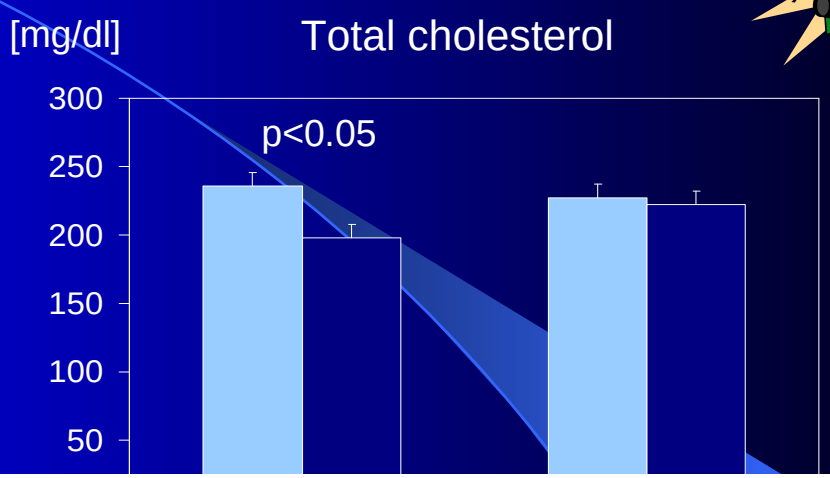


Normalization of cortisol secretion in operated patients was associated with significant improvement in blood pressure levels

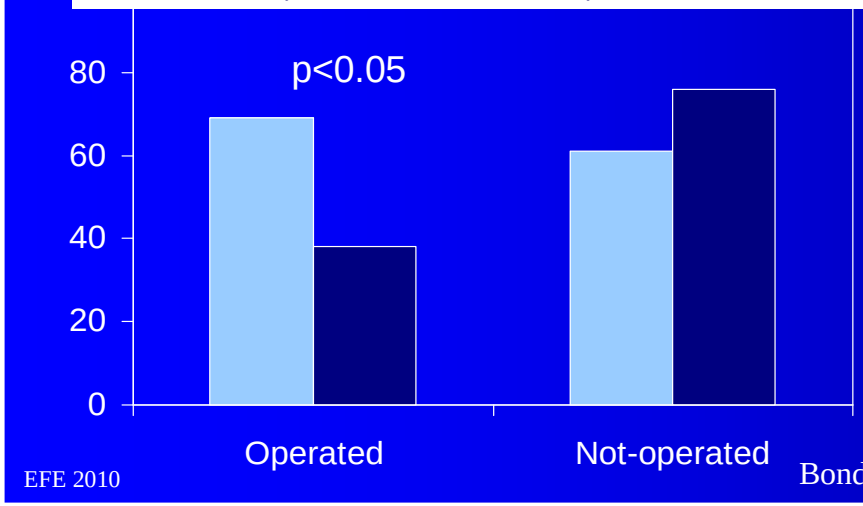
ACTH (pg/ml)	5.9±7.2	26.15±9.9 +	9.12±10.5	12.67±10.3
Morning Cortisol (µg/dl)	17.68±3.9	15.77±3.6	18.99±7.5	19.02±9.3
Cortisol after DXT (µg/dl)	7.84±5.4	1.02±0.3 +	3.63±1.4	3.22±1.1
UFC (µg/24h)	220.17±110.1	119.01±45.1 +	106.8±87.9	150.51±69.2 +

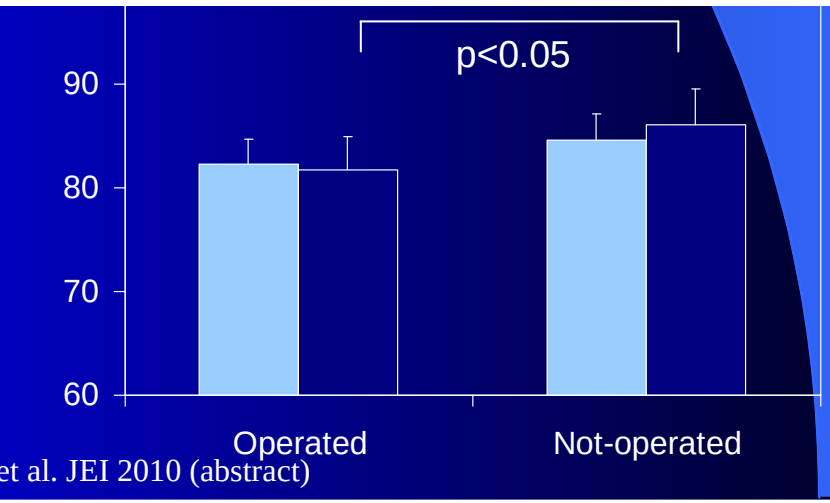
Clinical characteristics of **Subclinical Cushing Syndrome (SCS)** patients who underwent surgery compared with not-operated SCS patients,
at baseline and at follow-up





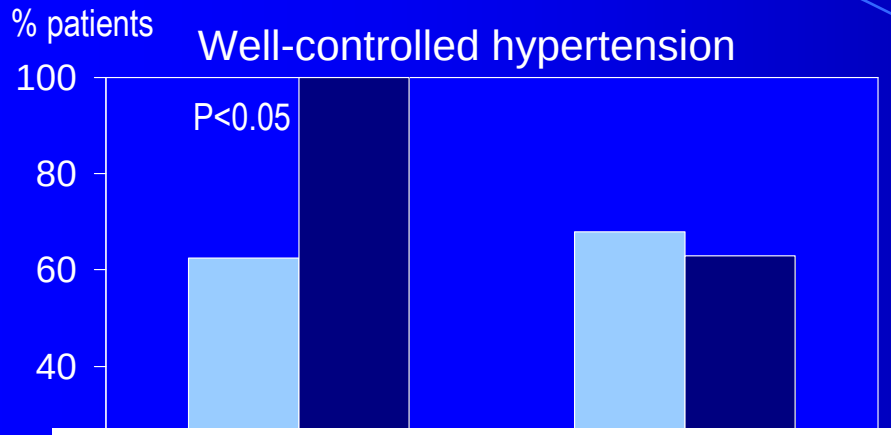
- Normalization of cortisol secretion in operated patients was associated with significant reduction in cholesterol and glucose levels
- Not-operated SCS patients showed an increase in body weight

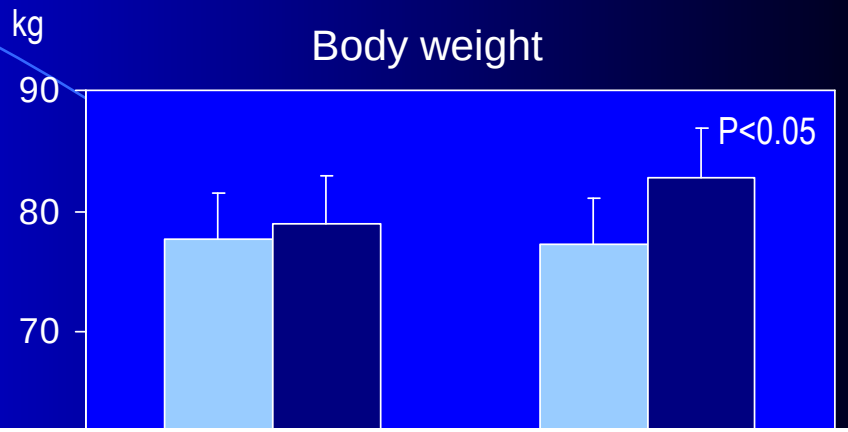




Bondanelli et al. JEI 2010 (abstract)

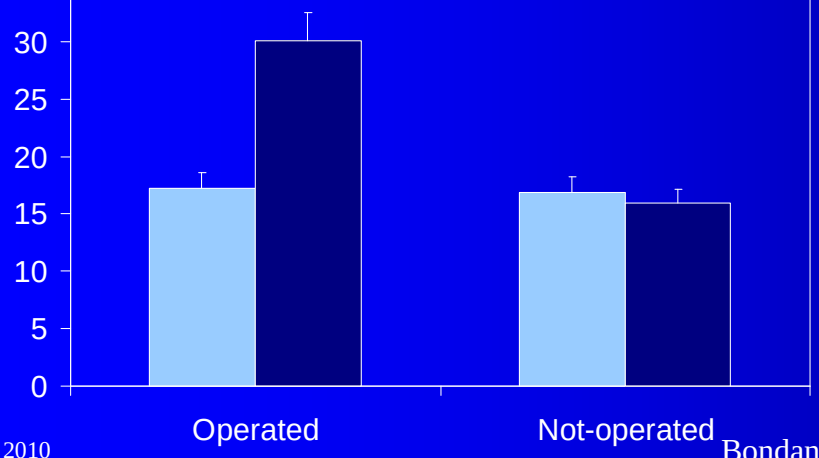
Clinical and hormonal characteristics of patients with **normal adrenal function** at baseline and at follow-up

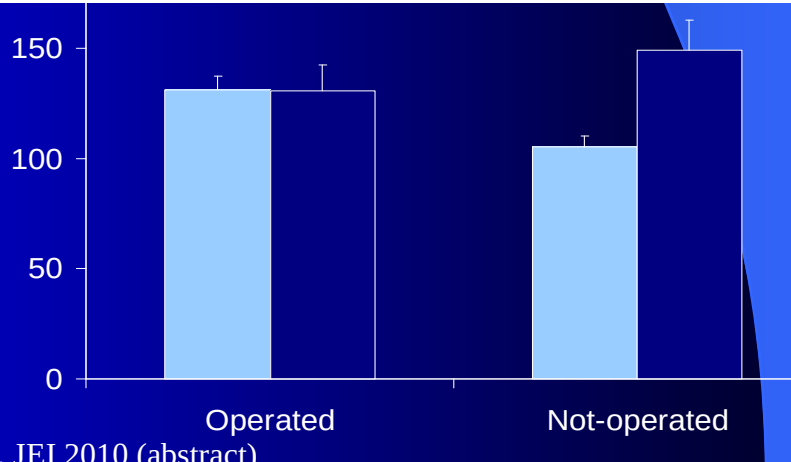




During follow-up

- Operated patients showed an improvement in blood pressure levels associated with an increase in ACTH levels
- Not-operated patients showed an increase in body weight, associated with an increase in UFC and persistently low ACTH levels

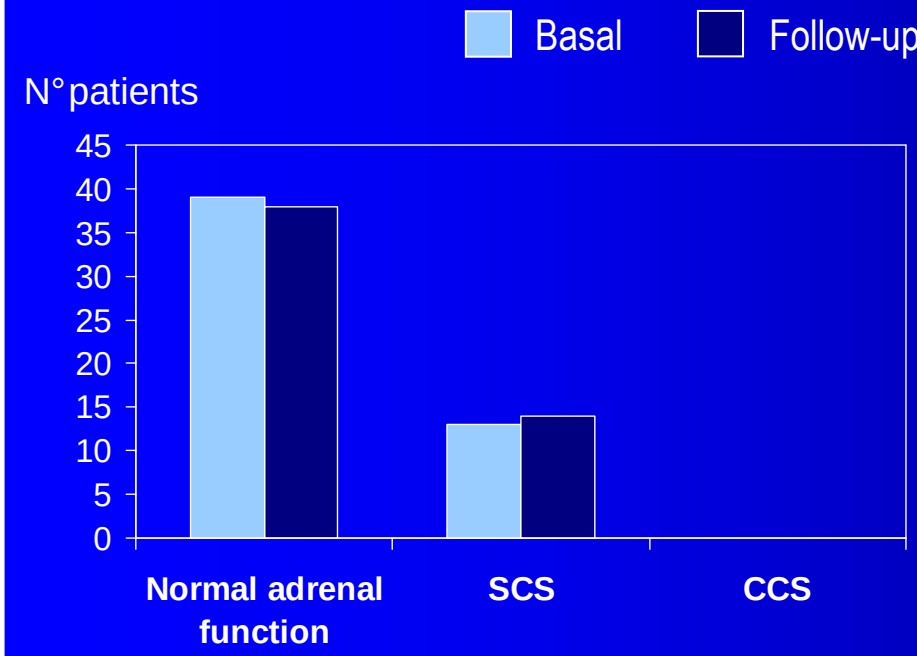




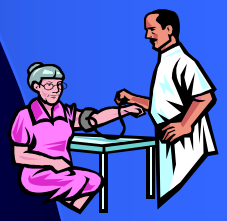
Bondanelli et al. JEI 2010 (abstract)

ADRENAL INCIDENTALOMA: CLINICAL AND METABOLIC ASPECTS DURING LONG-TERM FOLLOW-UP

Changes in adrenal function in 52 not-operated patients during 48-148 months follow-up



- Only one patient (1.9%) with normal adrenal function developed Subclinical Cushing's Syndrome (SCS)
- No patients with SCS developed Clinical Cushing's Syndrome (CSC)



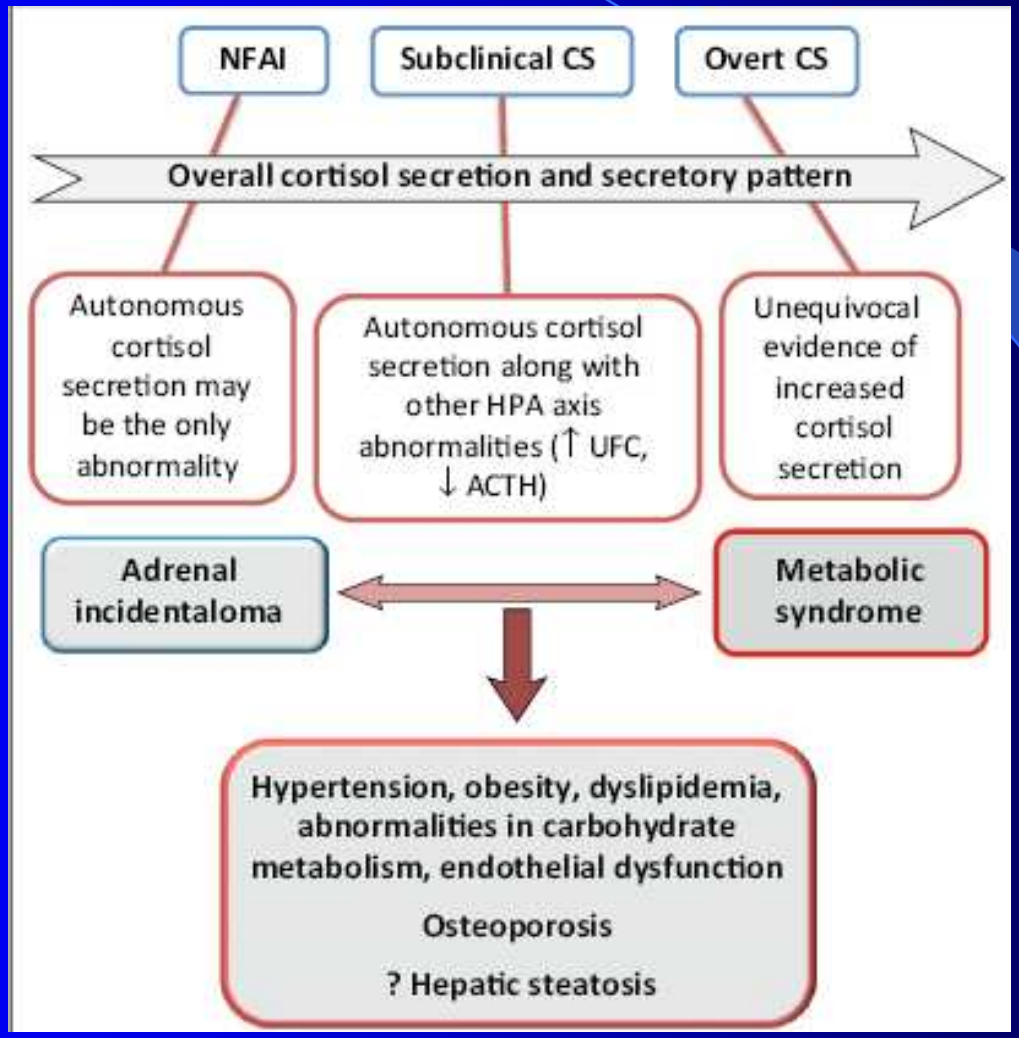
No significant increase in average mass diameter :

- Significant increase (≥1 cm) in 3 cases (5.7%) with no signs of malignancy
- Slight increase (<1 cm) in 11 cases (21%)
- Decrease in 4 cases (7.7%)

Bondanelli et al. JEI 2010 (abstract)

Inquadramento Clinico dell'Incidentaloma Surrenalico

Natural history of AI



Kaltsas G et al Trends Endocrinol Metab 2012

Inquadramento Clinico dell'Incidentaloma Surrenalico

Natural history of AI

The risk of progression

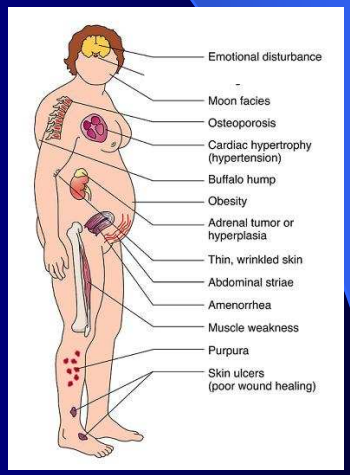
from non functioning adenoma (NFAI)

to

from subclinical Cushing's syndrome (SCS)

to

overt Cushing's syndrome



is MINIMAL (< 1%)

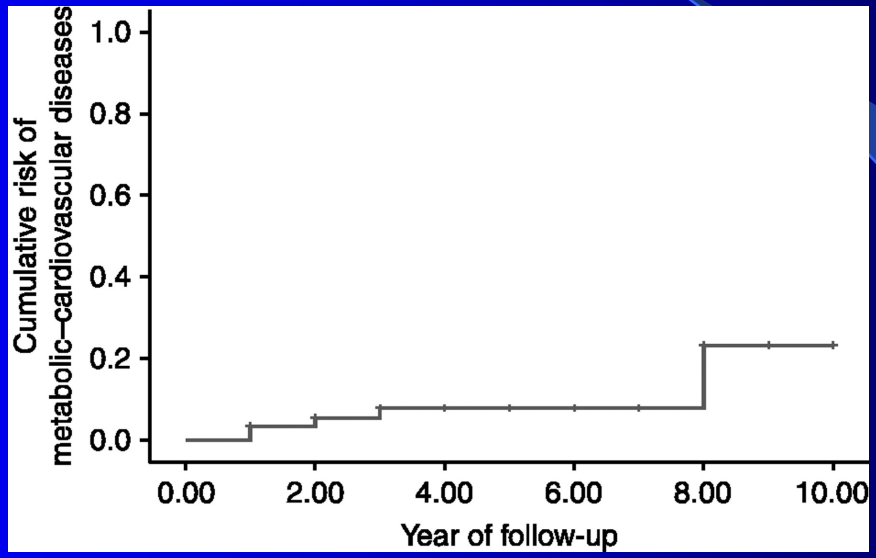
Terzolo M et al. Clin Endocrinl 2012
De Leo M et al Best Pract Clin Endocrinol 2012
Cawood TJ et al. Eur J Endocrinol 2009

Inquadramento Clinico dell'Incidentaloma Surrenalico

Natural history of AI

Estimated cumulative risk of developing metabolic-cardiovascular disease overtime in patients with adrenal incidentalomas (n=118)

102 NFAI - 16 SCS



The cumulative risk of developing metabolic-cardiovascular abnormalities was globally low (22%), but progressive up to 8 years

New diseases were recorded only in the group of NFAI
(3 dyslipidemia, 4 impaired fasting glucose/impaired glucose tolerance, 3 diabetes mellitus)

None of NF patients developed subclinical or overt endocrine disease
None of SCS patients shifted to overt Cushing's syndrome

EFE 2013

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

Inquadramento Clinico dell'Incidentaloma Surrenalico

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)

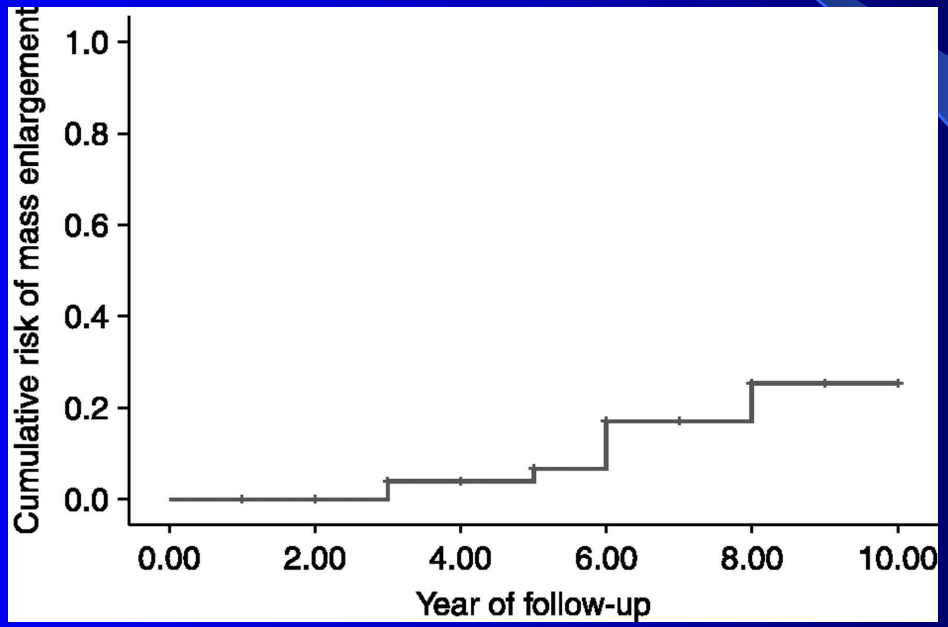
	mean	range	median
Became functional (%)	**0.9**	**0-8**	**0**
			0
- Developed overt CS (%)	**0.3**	**0-2.7**	**0**
- Developed SCS (%)	**0.3**	**0-4**	**0**
- Developed pheochromocytoma (%)	**0.2**	**0-1.3**	**0**
- Developed aldosteronoma (%)	**0**	**0**	**0**

Adapted from Cawood TJ et al Eur J Endocrinol 2009

Inquadramento Clinico dell'Incidentaloma Surrenalico

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

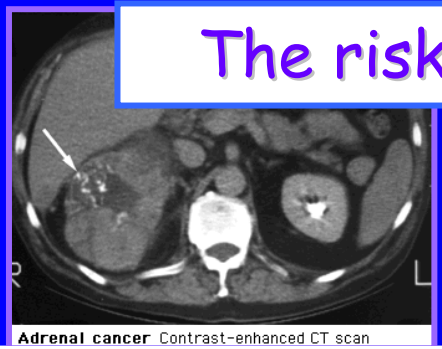
Inquadramento Clinico dell'Incidentaloma Surrenalico

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**


Adrenal cancer Contrast-enhanced CT scan

The risk of developing malignancy is minimal

Adapted from Cawood TJ et al Eur J Endocrinol 2009

Inquadramento Clinico dell'Incidentaloma Surrenalico

Natural history of AI

Even if

The majority of
apparently benign adrenal incidentalomas
with no hyperfunction at diagnosis

remain

functionally

morphologically

unchanged
over time

**Long term follow-up
is needed
for all patients with adrenal incidentalomas**

Inquadramento Clinico dell'Incidentaloma Surrenalico

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] 2011	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

Inquadramento Clinico dell'Incidentaloma Surrenalico

Epidemiological evidence from human populations
demonstrated that
acute exposure to ionizing radiation at doses of 10–50 mSv
(i.e. the organ dose range typically delivered by two or three CT scans)
increases the risk of some cancers

Brenner DJ et al. 2003

An abdominal CT scan is estimated to cause

one cancer-related death for every

⇨ 1000 (http://www.nap.edu/catalog/11340.htm)

⇨ 2000 (http://www.icrp.org/docs/Rad_for_GP_for_web.pdf)

abdominal CT scans

Cawood J et al. EJE 2009

Management strategy for patients with adrenal incidentaloma

History and physical examination
Hormonal testing:
- Overnight dexamethasone (1 mg) suppression test
- Fractionated metanephrines and catecholamines in a 24-hr urinary specimen

If hypertension and/or hypokaliemia,
plasma aldosterone and plasma renin activity (or direct renin) measurement

Positive results

Confirmatory testing

Confirmation of autonomous secretion of cortisol, aldosterone, or catecholamines

Consider:
SURGERY

Mass > 4 cm
Growth ≥ 1 cm

Autonomous hormonal sectretioN

Lack of autonomous secretion of cortisol, aldosterone, or catecholamines

Negative results

Imaging phenotype

Benign appearance: ≤4 cm
Unenhanced CT attenuation ≤10 HU
CT-contrast-medium: rapid washout
(APW>60%, RPW>40%)

Consider :
Repeating imaging at 6 mo (before if suspected, later if <2 cm benign at imaging), at 1- 2 yr, and at 5 yr *
Hormonal testing annually for 5 yr *

Suspiciuos appearance: >4 cm
Unenhanced CT attenuation >10 HU
CT-contrast-medium: slow washout
(APW<60%, RPW <40%)

Consider: FDG-PET
- Fine-needle aspiration biopsy if metastatic disease or infection suspected
- Surgery
- Close follow-up (e.g. repeating imaging at 3 mo)

* To be jdged on individual basis after clinical momitoring

GRAZIE PER L'ATTENZIONE