SEDUTA MULTIDISCIPLINARE

INQUADRAMENTO CLINICO DELL’INCIDENTALOMA SURRENALICO

Marta Bondanelli
Sezione di Endocrinologia
Dip. di Scienze Mediche
Università degli Studi di Ferrara
ADRENAL INCIDENTALOMA (AI)

A previously unsuspected 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)
CAUSES OF ADRENAL INCIDENTALOMA (AI)

- Medullary
  - Phaeochromocytoma
  - Ganglioneuroma
  - Ganglioneuroblastoma
  - Neuroblastoma
  - Carcinoma

- Cortical
  - Myelolipoma
  - Lipoma
  - Lymphoma
  - Haemangioma
  - Angiomyolipoma
  - Adenoma
  - Nodular Hyperplasia
  - Carcinoma

- 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Average (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>80</td>
<td>33–96</td>
</tr>
<tr>
<td>Non-functioning</td>
<td>75</td>
<td>71–84</td>
</tr>
<tr>
<td>Cortisol secreting</td>
<td>12</td>
<td>1.0–29</td>
</tr>
<tr>
<td>Aldosterone secreting</td>
<td>2.5</td>
<td>1.6–3.3</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>7.0</td>
<td>1.5–14</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>8.0</td>
<td>1.2–11</td>
</tr>
<tr>
<td>Metastasis</td>
<td>5.0</td>
<td>0–18</td>
</tr>
<tr>
<td><strong>Surgical studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>55</td>
<td>49–69</td>
</tr>
<tr>
<td>Non-functioning</td>
<td>69</td>
<td>52–75</td>
</tr>
<tr>
<td>Cortisol secreting</td>
<td>10</td>
<td>1.0–15</td>
</tr>
<tr>
<td>Aldosterone secreting</td>
<td>6.0</td>
<td>2.0–7.0</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>10</td>
<td>11–23</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>11</td>
<td>1.2–12</td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>8.0</td>
<td>7.0–15</td>
</tr>
<tr>
<td>Cyst</td>
<td>5.0</td>
<td>4.0–22</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>4.0</td>
<td>0–8.0</td>
</tr>
<tr>
<td>Metastasis</td>
<td>7.0</td>
<td>0–21</td>
</tr>
</tbody>
</table>

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

**Bilateral masses in 10-15% of cases**

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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 (tuberculosis, fungal), hemorrhage
- Pheochromocytoma

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 mass in 0.2%
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

<table>
<thead>
<tr>
<th>SIZE</th>
<th>Risk of ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 cm</td>
<td>&lt;2 %</td>
</tr>
<tr>
<td>&gt;4 &lt;6 cm</td>
<td>6%</td>
</tr>
<tr>
<td>≥6 cm</td>
<td>25%</td>
</tr>
</tbody>
</table>

NIH Conference 2003

4 cm cut-off

93% sensitivity, 76% sensibility

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)

Change in size over time

growth > 1 cm/year
(ACC rapid growth >2 cm/yr)

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**Evaluation for malignancy**

- **CT scan (noncontrast)**: excluded non adenomatous lesions
  - HU ≤20 and tumor size ≤4 cm
  - Homogeneous lesion with a smooth border
  - 96-100% sensitivity; 50-100% specificity

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

- **MRI**: can distinguish adenomas from malignancy and pheochromocytoma
  - Isointensity with liver on both T1 and T2 weighted sequences
  - Chemical shift evidence of lipid
  - High signal intensity on T2 weighted MRI (pheochromocytoma)
  - 84-100% sensitivity; 92-100% specificity

- **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% (varying 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**

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-functioning adenoma</strong></td>
<td>80% (50-95)</td>
</tr>
<tr>
<td><strong>Functioning adenoma</strong></td>
<td>10-15%</td>
</tr>
<tr>
<td>Cortisol-secreting</td>
<td>10-15% (1-48)</td>
</tr>
<tr>
<td>Aldosterone-secreting</td>
<td>2% (1.5-7)</td>
</tr>
<tr>
<td>Androgen or estrogen-secreting</td>
<td>0-11%</td>
</tr>
<tr>
<td><strong>Pheochromocytoma</strong></td>
<td>4-7% (1-20)</td>
</tr>
</tbody>
</table>


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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.

**All patients with adrenal incidentaloma should undergo biochemical testing for pheochromocytoma**

Even when clinically silent, this tumor can be lethal.

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

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Screening for pheochromocytoma

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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-free metanephrines</td>
<td>99%</td>
<td>89%</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td>Urinary catecholamines</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>Urinary-fractionated metanephrines</td>
<td>97%</td>
<td>69%</td>
</tr>
<tr>
<td>Urinary total metanephrines</td>
<td>77%</td>
<td>93%</td>
</tr>
<tr>
<td>VMA</td>
<td>64%</td>
<td>95%</td>
</tr>
</tbody>
</table>

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.

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.

Eisenhofer 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.

<table>
<thead>
<tr>
<th>Sawka AM, JCEM 2003</th>
<th>Sensibility</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma fractionated metanephrines *</td>
<td>97 %</td>
<td>85%</td>
</tr>
<tr>
<td>24-h urinary metanephrines and catecholamines (both elevated)</td>
<td>90 %</td>
<td>98%</td>
</tr>
</tbody>
</table>
Screening for pheochromocytoma in patients with adrenal 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](http://www.uptodate.com)
Screening for pheochromocytoma in patients with adrenal 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)

<table>
<thead>
<tr>
<th>Nature of Interference</th>
<th>Analytical methods</th>
<th>Pharmacodynamic or pharmacokinetic interference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ticlopidine and antidepressants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenothiazines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norepinephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levodopa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>alpha-Methyltyrosine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strobe Intaquim</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sympathomimetics (e.g., amphetamines, ephedrine)</td>
</tr>
</tbody>
</table>

*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 Guidelines 2009
Cawood J et al. EJE 2009
**Raccomandation for ARR measurement**

- **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**
Evaluation for hormonal hypersecretion

**Screening of primary aldosteronism**

**In patients with HIGH ARR**
- PA (ng/dl) / PRA (ng/ml/h) > 30-50
- PA (ng/dl) / DRC (mIU/l) > 3.7

**CONFIRMATORY 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 Guidelines 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*
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.

- Sensitivity: 73-100%
- Specificity: 90%

Cut-off levels:
- 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

References:

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

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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 interfering 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 (hypertriglyceridemia, 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)

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**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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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)

After adrenalectomy → significant IMPROVEMENT in quality of life

Iacobone M et al. Surgery 2012
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.
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.

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

Removal of adrenal mass in patients with NFAI

is associated with

IMPROVEMENT of Metabolic Syndrome Features

or

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

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)

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

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

### Table: Non-hypersecreting vs Subclinical Cushing's syndrome

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

Mantero et al. 2000

Peppa M et al. J Int Med 2010
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

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

No significant differences for prevalence of metabolic complications 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)
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.

<table>
<thead>
<tr>
<th></th>
<th>Operated</th>
<th>Not-operated</th>
<th>Operated</th>
<th>Not-operated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTH (pg/ml)</strong></td>
<td>5.9±7.2</td>
<td>26.15±9.9 +</td>
<td>9.12±10.5</td>
<td>12.67±10.3</td>
</tr>
<tr>
<td><strong>Morning Cortisol (µg/dl)</strong></td>
<td>17.68±3.9</td>
<td>15.77±3.6</td>
<td>18.99±7.5</td>
<td>19.02±9.3</td>
</tr>
<tr>
<td><strong>Cortisol after DXT (µg/dl)</strong></td>
<td>7.84±5.4</td>
<td>1.02±0.3 +</td>
<td>3.63±1.4</td>
<td>3.22±1.1</td>
</tr>
<tr>
<td><strong>UFC (µg/24h)</strong></td>
<td>220.17±110.1</td>
<td>119.01±45.1 +</td>
<td>106.8±87.9</td>
<td>150.51±69.2 +</td>
</tr>
</tbody>
</table>

**P<0.05**

**P<0.001**
**Clinical characteristics of Subclinical Cushing Syndrome (SCS) patients who underwent surgery compared with not-operated SCS patients,**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Operated</th>
<th>Not-operated</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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.

**EFE 2010**

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.
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**

- **NFAI**
  - Autonomous cortisol secretion may be the only abnormality

- **Subclinical CS**
  - Autonomous cortisol secretion along with other HPA axis abnormalities (↑ UFC, ↓ ACTH)

- **Overt CS**
  - Unequivocal evidence of increased cortisol secretion

**Adrenal incidentaloma**

**Metabolic syndrome**

- Hypertension, obesity, dyslipidemia, abnormalities in carbohydrate metabolism, endothelial dysfunction
- Osteoporosis
- ? Hepatic steatosis
The risk of progression from non-functioning adenoma (NFAI) to subclinical Cushing’s syndrome (SCS) to overt Cushing’s syndrome is MINIMAL (<1%).

Terzolo M et al. Clin Endocrinol 2012
De Leo M et al Best Pract Clin Endocrinol 2012
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

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)

<table>
<thead>
<tr>
<th>Developed overt CS (%)</th>
<th>mean</th>
<th>range</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed SCS (%)</td>
<td>0.3</td>
<td>0-2.7</td>
<td>0</td>
</tr>
<tr>
<td>Developed pheochromocytoma (%)</td>
<td>0.2</td>
<td>0-1.3</td>
<td>0</td>
</tr>
<tr>
<td>Developed aldosteronoma (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Cawood TJ et al Eur J Endocrinol 2009
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.

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)

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>range</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased in size (%)</td>
<td>14.7</td>
<td>0-41.5</td>
<td>14.1</td>
</tr>
<tr>
<td>Decreased in size (%)</td>
<td>7.0</td>
<td>0-44</td>
<td>0</td>
</tr>
<tr>
<td>Became malignant (%)</td>
<td>0.2</td>
<td>0-1.6</td>
<td>0</td>
</tr>
<tr>
<td>Developed ACC (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Developed metastases (%)</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The risk of developing malignancy is minimal

Adapted from Cawood TJ et al Eur J Endocrinol 2009
Long term follow-up is needed for all patients with adrenal incidentalomas.

The majority of apparently benign adrenal incidentalomas with no hyperfunction at diagnosis remain unchanged over time functionally and morphologically.

Even if...
### Management strategy for patients with adrenal incidentaloma

<table>
<thead>
<tr>
<th>Experts opinion</th>
<th>Endocrine tests</th>
<th>Tests and frequency</th>
<th>Duration</th>
<th>Imaging</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Consensus statement 2002(^1)</td>
<td>1 mg DST, plasma free metanephrines, K and PRA/aldosterone in hypertensive patients</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor mass &lt;4 cm. In addition to size use additional criteria if size 4-6 cm</td>
<td>Two CTs, at least 6 months apart, no data to support continued imaging if size remains stable</td>
</tr>
<tr>
<td>Young, 2007(^1)</td>
<td>1 mg DST, urinary metanephrines and catecholamines, K and PRA/aldosterone in hypertensive patients</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor mass &lt;4 cm</td>
<td>CT at 6, 12 and 24 months</td>
</tr>
<tr>
<td>French Society of Endocrinology Consensus, 2008(^2)</td>
<td>1 mg DST, glycemia, plasma and urinary metanephrines, K and PRA/aldosterone in hypertensive patients</td>
<td>1 mg DST, plasma and urinary metanephrines at 6 months then 1 mg DST at 2 and 5 years</td>
<td>5 years</td>
<td>Monitor mass &lt;4 cm</td>
<td>CT at 6 months and then at 2 and 5 years</td>
</tr>
<tr>
<td>AACE/AES Medical Guidelines, 2009(^3)</td>
<td>1 mg DST, plasma and urinary metanephrines/catecholamines and PRA/aldosterone in hypertensive patients</td>
<td>Annual</td>
<td>5 years</td>
<td>Monitor mass &lt;4 cm</td>
<td>Imaging reevaluation at 3-6 months and then annually for 1-2 years. Imaging reevaluation at 1-2 years (or more) and for intermediate mass at 3-12 months. CT or MRI at 3-6 months. No further imaging if mass is &lt;2 cm with clear benign features. If mass &gt;2 cm judge on individual basis.</td>
</tr>
<tr>
<td>Nieman, 2010(^4)</td>
<td>1 mg DST or late-night cortisol test, plasma and urinary metanephrines/catecholamines and PRA/aldosterone in hypertensive patients</td>
<td>Annual No repeat screening for aldosteronism if previously excluded</td>
<td>4 years if mass &lt;3 cm, nonfunctional and benign at imaging 1-2 years (or more)</td>
<td>Monitor mass &lt;4 cm, in addition to size use additional criteria</td>
<td>imaging</td>
</tr>
<tr>
<td>AME Position(^5) 2011</td>
<td>1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldosterone in hypertensive and/or hypokalemic patients</td>
<td>To be judged on individual basis after clinical monitoring</td>
<td>To be judged on individual basis after clinical monitoring</td>
<td>Monitor 2-4 cm mass in addition to size use additional criteria</td>
<td>imaging</td>
</tr>
<tr>
<td>Arnaldi, 2012</td>
<td>1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldosterone in hypertensive patients</td>
<td>Annual No repeat screening for aldosteronism if previously excluded</td>
<td>5 years</td>
<td>Monitor mass &lt;4 cm; in addition to size use additional criteria</td>
<td>imaging</td>
</tr>
</tbody>
</table>

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

EFE 2013
An abdominal CT scan is estimated to cause one cancer-related death for every

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

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

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

Negative results

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

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

Consider:
- Repeat 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 *

Consider:
- SURGERY

Autonomous hormonal secretion

Mass > 4 cm

Growth ≥ 1 cm

* To be judged on individual basis after clinical monitoring

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