Management of adrenal incidentaloma based on published guidelines: Challenging the myths

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Controversias Clinicas en Enfermedades Suprarenales
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Chapter Adrenal Glands: incidentaloma

« Subclinical Cushing’s syndrome»?
« Silent pheochromocytoma »??
« Adrenal cancer »???
Adrenal incidentaloma

DEFINITION

- Clinically silent adrenal mass discovered inadvertently during the investigation of another condition
- Excludes patients undergoing staging and workup for cancer

NIH state-of-science conference statement, July 2002

Adrenal Incidentaloma Epidemics

- Years
  - 1975-79
  - 1980-84
  - 1985-89
  - 1990-94
  - 1995-99
  - 2000-04
  - 2005-09

Number of publications

- "Subclinical Cushing's Syndrome"
- "Adrenal incidentalomas"

So few prospective studies.
Prevalence of Adrenal Incidentalomas

◆ Radiology
  > initial CT: 1 % (0.35-4.36%)
  > recent CT: 4.4 %*

◆ Autopsy:
  > general: 2.1 % (1.4-7.8%)
  > < 30 yo: < 1 %
  > > 70 yo: 6.9 %
  > hypertension: 12.4 %
  > diabetes: 16.5 %

◆ Bilateral: 10-15%

Barzon et al, Heffess NIH conference 2002
### Etiology of adrenal incidentalomas

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenal cortical tumor:</strong></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>36-94%</td>
</tr>
<tr>
<td>Nodular hyperplasia</td>
<td>7-17%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>1.2-11%</td>
</tr>
<tr>
<td><strong>Medullary tumors:</strong></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>1.5-23%</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>0-6%</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>rare</td>
</tr>
<tr>
<td><strong>Other adrenal tumors:</strong></td>
<td></td>
</tr>
<tr>
<td>Myelolipoma, Lipoma, Hamartoma</td>
<td>7-15%</td>
</tr>
</tbody>
</table>

*Barzon et al, NIH conference 2002*
Etiology of adrenal incidentalomas

- **Metastasis:**
  - non oncology patients: 0 - 21 %
  - oncology patients (not incidentaloma): 32-73 %
    (breast, kidney, lung, ovary, melanoma, lymphoma, leukemia)

- **Cysts, pseudocysts:** 4-22 %

- **Hematoma, hemorrhage** 0- 4 %

- **Infections, granulomatosis:** rare

- **Pseudoadrenal mass:** 0-10 %
  (stomach, pancreas, kidney, liver, lymph node, vascular lesion)

*Barzon et al, NIH conference 2002*
Etiologies of adrenal incidentalomas

### TABLE 2a. Frequency of the different types of adrenal incidentaloma in clinical series.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>average (%)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

### TABLE 2b. Frequency of the different types of adrenal incidentaloma in surgical series.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>average (%)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<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>

Terzolo et al Eur J Endocrinol Ahead of print April 2011
Etiology of adrenal incidentalomas

- Primary adrenocortical carcinoma:
  - ≤ 4 cm: 2%
  - 4.1-6 cms: 6%
  - > 6 cm: 25%

*Barzon et al, NIH conference 2002*
Distribution of diagnosis by tumor size at surgery

- Tumor size categories: <2-4 cm, 4.1-6 cm, >6 cm, Total
- Diagnosis categories: Adenoma, Adrenal carcinoma, Pheochromocytoma, Adrenal cyst, Ganglioneuroma, Myelolipoma, Other, Metastases

Etiology of bilateral adrenal incidentalomas

- 10-15% of incidentalomas
  - Metastasis
  - Pheochromocytoma
  - Bilateral macronodular hyperplasia (AIMAH)
  - Cortical adenomas
  - Congenital adrenal hyperplasia
  - ACTH-dependent Cushing's
  - Lymphoma
  - Infection (eg, tuberculosis, fungal)
  - Hemorrhage
  - Amyloidosis
  - Glucocorticoid resistance syndrome

Modified from Young, NEJM, 356: 601, 2007
Hormonal findings in adrenal incidentalomas

- Nonhypersecreting adenoma: 65-90%
- Hypercortisolism: 5-14%
- Hyperaldosteronism: 1-3.3%
- Hyperandrogenism: 0-11%
- Hyperestrogenism: Rare
- Congenital adrenal hyperplasia: Rare
- Pheochromocytoma: 1.5-25%

Barzon et al, NIH conference 2002
Hormonal findings in adrenal incidentalomas

- Italian retrospective study
- 1096 cases
- normal for 1 mg overnight dex: cortisol < 140 nmol/L

Natural history of adrenal incidentalomas

- Adrenocortical cancer:
  - rapid growth
  - 2-year survival: < 50%

- Progression of incidentaloma on follow-up:
  - increase in size by 1 cm: 5 to 25%
  - malignancy if >1 cm increase: 1/1000
  - hormone overproduction: up to 20%
  - hormone excess in lesion < 3 cm: rare

Barzon et al, NIH conference 2002
Evaluation objectives

- Is the lesion of adrenal origin?
- Is the lesion secreting excess hormone: catecholamines, cortisol, aldosterone, androgens?
- Is the lesion malignant?

*NIH state-of-science conference statement, July 2002*

NIH guideline: initial hormonal testing

- Plasma cortisol at 8-9h00 following 1 mg dexamethasone at midnight: cortisol < 139.75 nmol/L (< 5 µg/dL)
- Plasma free metanephrines (24-hour urinary catecholamines/metanephrines)
- Plasma K⁺, upright plasma aldosterone/renin if HBP (ratio > 30 and aldo > 500 pmol/L are suspicious of primary aldosteronism)

NIH guideline: medical imaging

- Unenhanced CT scan: < 4 cm, homogeneous, < 10 HU: benign
- 4-6 cm, non secreting: uncertain of value of other imaging: simply monitor
- > 6 cm suspicious of malignancy: consider surgery
- MRI as efficient, but not superior to unenhanced CT
- NP-59, MIBG: not widely available, uncertain value
- FDG-PET scan: not enough data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adrenocortical Adenoma</th>
<th>Adrenocortical Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Small, usually ≤3 cm in diameter</td>
<td>Large, usually &gt;4 cm in diameter</td>
<td>Large, usually &gt;3 cm in diameter</td>
<td>Variable, frequently &lt;3 cm</td>
</tr>
<tr>
<td>Shape</td>
<td>Round or oval, with smooth margins</td>
<td>Irregular, with unclear margins</td>
<td>Round or oval, with clear margins</td>
<td>Oval or irregular, with unclear margins</td>
</tr>
<tr>
<td>Texture</td>
<td>Homogeneous</td>
<td>Heterogeneous, with mixed densities</td>
<td>Heterogeneous, with cystic areas</td>
<td>Heterogeneous, with mixed densities</td>
</tr>
<tr>
<td>Laterality</td>
<td>Usually solitary, unilateral</td>
<td>Usually solitary, unilateral</td>
<td>Usually solitary, unilateral</td>
<td>Often bilateral</td>
</tr>
<tr>
<td>Attenuation (density)</td>
<td>≤10 Hounsfield units</td>
<td>&gt;10 Hounsfield units (usually &gt;25)</td>
<td>&gt;10 Hounsfield units (usually &gt;25)</td>
<td>&gt;10 Hounsfield units (usually &gt;25)</td>
</tr>
<tr>
<td>Vascularity on contrast-enhanced CT</td>
<td>Not highly vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
</tr>
<tr>
<td>Rapidity of washout of contrast medium</td>
<td>≥50% at 10 minutes</td>
<td>&lt;50% at 10 minutes</td>
<td>&lt;50% at 10 minutes</td>
<td>&lt;50% at 10 minutes</td>
</tr>
<tr>
<td>Appearance on MRI†</td>
<td>Isointense in relation to liver on T₂-weighted image</td>
<td>Hyperintense in relation to liver on T₂-weighted image</td>
<td>Markedly hyperintense in relation to liver on T₂-weighted image</td>
<td>Hyperintense in relation to liver on T₂-weighted image</td>
</tr>
<tr>
<td>Necrosis, hemorrhage, or calcifications</td>
<td>Rare</td>
<td>Common</td>
<td>Hemorrhage and cystic areas common</td>
<td>Occasional hemorrhage and cystic areas</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Usually stable over time or very slow (&lt;1 cm per year)</td>
<td>Usually rapid (&gt;2 cm per year)</td>
<td>Usually slow (0.5 cm to 1.0 cm per year)</td>
<td>Variable, slow to rapid</td>
</tr>
</tbody>
</table>

NIH guideline: fine needle aspiration biopsy

- Poor sensitivity to distinguish benign from malignant primary adrenal lesions
- Most useful to distinguish non-adrenal (metastasis) from adrenal tissue (lung, breast, kidney)
- Indicated if no other sites of metastasis, heterogenous mass, > 20 HU on CT
- Always eliminate pheochromocytoma first

Integrated PET-CT was used to differentiate adrenal adenomas from malignant lesions.

Using SUV cutoff of 3.1 the sensitivity, specificity, positive predictive, and negative predictive values for malignancies versus adenomas were 100, 98, 97, and 100%.

FDG-PET cannot distinguish between ACC, adrenal metastasis, and pheochromocytoma.

Alternative PET tracers are under study (11C-metomidate which binds to 11 β-hydroxylase and aldosterone synthetase) that might further improve specificity.

## Adrenal incidentaloma

### Summary of current clinical recommendations

<table>
<thead>
<tr>
<th>Publication</th>
<th>Hormonal test</th>
<th>Frequency</th>
<th>Duration</th>
<th>Imaging</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH consensus 2002</td>
<td>1 mg DST, plasma free metanephrines K+, Aldo/renin if HBP</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor those &lt; 4cm; use other criteria in those 4-6 cm</td>
<td>Two CT at least 6 months apart; no repeat if no progression</td>
</tr>
<tr>
<td>Young, NEJM 2007</td>
<td>1 mg DST, urinary metanephrines and catecholamines, K+, aldo/renin if HBP</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor those &lt; 4cm</td>
<td>CT at 6, 12 and 24 months</td>
</tr>
<tr>
<td>Young, Kaplan UpToDate 2010</td>
<td>1 mg DST, urinary metanephrines and catecholamines, K+, aldo/renin if HBP</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor those &lt; 4cm</td>
<td>CT at 6, 12 and 24 months</td>
</tr>
<tr>
<td>SFE 2008</td>
<td>1 mg DST, urinary or plasma free metanephrines, K+, aldo/renin if HBP</td>
<td>6-months, 2 and 5 yrs</td>
<td>5 years</td>
<td>CT scan for those &lt; 4 cm</td>
<td>CT at 6, 24 and 60 months</td>
</tr>
</tbody>
</table>

*Modified from Cawood et al: European Journal of Endocrinology 161 513–527, 2009*
Sub-clinical Cushing’s syndrome

Definition: so variable in literature
Cortisol-secreting adrenal lesion without typical symptoms or signs of Cushing’s syndrome

- **Sub-clinical**: normal UFC but subnormal regulation/suppressibility of cortisol secretion
- **Pre-clinical**: mildly elevated UFC without overt clinical syndrome

Reincke M. *Endocrinol Metab Clin North America* 29, 43, 2000
Spectrum of cortisol secreting tumors

Reincke M. Endocrinol Metab Clin North America 29, 43, 2000
Sub-clinical CS: biochemical testing

**Overnight dexamethasone suppression:**

Plasma cortisol levels:
- < 140 nmol/l: post 1 mg; (NIH 2002, Young 2007, AACE 2008)
- < 80 nmol/l post 3 mg (Reincke et al 2000)
- < 60 nmol/l post 1 mg (Vali et al 2001)
- < 50 nmol/l post 1 mg (Nieman ES consensus 2008, Tabarin SFE 2008)

**Other tests:**
- midnight sleeping plasma cortisol > 50 nmol/L
- elevated evening salivary cortisol not reliable

*(Masserini, Eur J Endocrinol 160:87-92, 2008)*
Sub-clinical CS: biochemical testing

- Low dose 2 mg dexamethasone over 48h:

Plasma cortisol levels at 8 am:

- undetectable: 21%
- 28-138 nmol/L: 67%
- > 138 nmol/L: 12%
- undetectable in all controls

# Sub-clinical hypercortisolism

## TABLE 2. Accuracy of HPA axis secretion parameters in diagnosing SH

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>No. of patients</th>
<th>CCR (SN/SP)</th>
<th>ACTH (SN/SP)</th>
<th>UFC (SN/SP)</th>
<th>DST (SN/SP)</th>
<th>DEX dose, DST cutoff</th>
<th>Gold standard criteria for SH diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantero, 2000 (9)</td>
<td>1004</td>
<td>43/83</td>
<td>79/85</td>
<td>76/88</td>
<td>73/90</td>
<td>1 mg, 5 μg/dl</td>
<td>±2 out of CRH, CCR, ACTH, UFC, DST</td>
</tr>
<tr>
<td>Libè 2002 (52)</td>
<td>64</td>
<td>n.a.</td>
<td>41/96</td>
<td>33/96</td>
<td>91/98</td>
<td>1 mg, 5 μg/dl</td>
<td>±2 out of CRH, CCR, ACTH, UFC, DST</td>
</tr>
<tr>
<td>Masserini, 2009 (32)</td>
<td>103</td>
<td>22.7/87.7</td>
<td>86.4/59.3</td>
<td>31.8/92.6</td>
<td>86.4/96.3</td>
<td>1 mg, 3 μg/dl</td>
<td>±2 out of DST, ACTH, UFC</td>
</tr>
<tr>
<td>Nunes, 2009 (31)</td>
<td>48</td>
<td>77/69*</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1 mg, 2.2 μg/dl</td>
<td>DST plus ACTH or CCR</td>
</tr>
<tr>
<td>Barzon, 2001 (67)</td>
<td>83</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>44/100</td>
<td>1 mg, 5 μg/dl</td>
<td>DST plus ACTH or CCR</td>
</tr>
<tr>
<td>Valli, 2001 (48)</td>
<td>31</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>75/72</td>
<td>1 mg, 1.8 μg/dl</td>
<td>Norcholesterol scintigraphy</td>
</tr>
<tr>
<td>Eller-Vainicher, 2009 (58)</td>
<td>60</td>
<td>64.1/81*</td>
<td>64.1/38</td>
<td>48.7/81</td>
<td>33.3/85.7</td>
<td>1 mg, 5 μg/dl</td>
<td>Postsurgical hypocortisolism</td>
</tr>
<tr>
<td>Morelli, 2010 (59)</td>
<td>231</td>
<td>n.a.</td>
<td>52.4/60.5</td>
<td>42.9/80</td>
<td>59/52.4</td>
<td>1 mg, 3 μg/dl</td>
<td>Postsurgical hypocortisolism</td>
</tr>
<tr>
<td>Eller-Vainicher 2010 (60)</td>
<td>55</td>
<td>65.2/65.6*</td>
<td>n.a.</td>
<td>n.a.</td>
<td>75/48.4</td>
<td>1 mg, 1.8 μg/dl</td>
<td>Prevention of complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.7/96.9</td>
<td>1 mg, 5 μg/dl</td>
<td>Prevention of complications</td>
</tr>
</tbody>
</table>

CRH, Blunted response to CRH; CCR, altered circadian cortisol rhythm (elevated MSeC or MSeC levels); ACTH, low ACTH levels [<10 pg/ml (2.2 pmol/liter)]; UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; DEX, dexamethasone; n.a., data not available; SN, sensitivity (%); SP, specificity (%).

* MSeC levels [cutoff, 1.7 μg/liter (47 nmol/liter)].
* MSeC levels [cutoff, 4.9 μg/dl (135 nmol/liter)].
* MSeC [cutoff, 4.0 μg/dl (110 nmol/liter)].
* MSeC [cutoff, 5.4 μg/dl (149 nmol/liter)].
* Concomitant presence of vertebral fractures, arterial hypertension, and type 2 diabetes mellitus.
* Improvement after surgery of at least two out of the following possible complications of SH: blood pressure, fasting glucose, body weight, and cholesterol levels.
Fig. 3. The spectrum of hypercortisolism.
Fig. 3. The spectrum of hypercortisolism.


Fig. 3. The spectrum of hypercortisolism.
The clarity of evaluations for sub-clinical CS
Prevalence of sub-clinical CS in incidentalomas


<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>No. of patients</th>
<th>F/M ratio</th>
<th>Mean age (years)</th>
<th>Subclinical Cushing’s syndrome (%)</th>
<th>Pheochromocytoma (%)</th>
<th>Aldosterone-producing adenoma (%)</th>
<th>Adrenocortical cancer (%)</th>
<th>Metastatic cancer (%)</th>
<th>Apparent non-functioning adenoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosi et al. 1995 (51)</td>
<td>32</td>
<td>2.5</td>
<td>55</td>
<td>12.2</td>
<td>0</td>
<td>0</td>
<td>3.13</td>
<td>0</td>
<td>73.1</td>
</tr>
<tr>
<td>Aso &amp; Homma 1992 (16)</td>
<td>210</td>
<td>0.7</td>
<td>53</td>
<td>4.9</td>
<td>3.3</td>
<td>23.3</td>
<td>3.3</td>
<td>4.29</td>
<td>1.4</td>
</tr>
<tr>
<td>Bardet et al. 1996 (52)</td>
<td>46</td>
<td>NR</td>
<td>NR</td>
<td>2.6</td>
<td>6.5</td>
<td>4.4</td>
<td>0</td>
<td>4.35</td>
<td>2.2</td>
</tr>
<tr>
<td>Barzon et al. 2002 (53)</td>
<td>284</td>
<td>1.5</td>
<td>56</td>
<td>3.6</td>
<td>11.3</td>
<td>5.9</td>
<td>2.1</td>
<td>8.80</td>
<td>2.8</td>
</tr>
<tr>
<td>Bastouins et al. 1997 (54)</td>
<td>86</td>
<td>1.5</td>
<td>61</td>
<td>4.1</td>
<td>3.5</td>
<td>2.33</td>
<td>0</td>
<td>1.16</td>
<td>2.3</td>
</tr>
<tr>
<td>Benosk et al. 1995 (55)</td>
<td>63</td>
<td>1.1</td>
<td>27–85</td>
<td>2.5–1.4</td>
<td>20.6</td>
<td>0</td>
<td>0</td>
<td>1.59</td>
<td>11.1</td>
</tr>
<tr>
<td>Bondanelli et al. 1997 (56)</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>2.6</td>
<td>10.5</td>
<td>5.3</td>
<td>0</td>
<td>2.63</td>
<td>0</td>
</tr>
<tr>
<td>Bulow &amp; Ahren 2002 (57)</td>
<td>381</td>
<td>1.3</td>
<td>64</td>
<td>3.0</td>
<td>1.0</td>
<td>3.9</td>
<td>0.5</td>
<td>2.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Caplan et al. 1994 (21)</td>
<td>26</td>
<td>1.9</td>
<td>66</td>
<td>NR</td>
<td>11.5</td>
<td>0</td>
<td>3.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Favia et al. 2000 (58)</td>
<td>158</td>
<td>1.2</td>
<td>58</td>
<td>4.4</td>
<td>5.1</td>
<td>2.5</td>
<td>3.8</td>
<td>9.49</td>
<td>1.9</td>
</tr>
<tr>
<td>Flechta et al. 1995 (59)</td>
<td>32</td>
<td>1.3</td>
<td>57</td>
<td>3.7</td>
<td>21.9</td>
<td>0</td>
<td>0</td>
<td>6.25</td>
<td>6.2</td>
</tr>
<tr>
<td>Herrera et al. 1991 (20)</td>
<td>342</td>
<td>1.5</td>
<td>82</td>
<td>2.5</td>
<td>0.6</td>
<td>1.5</td>
<td>0</td>
<td>1.17</td>
<td>0.3</td>
</tr>
<tr>
<td>Kasperlik-Zaluska et al. 1997 (60)</td>
<td>208</td>
<td>2.5</td>
<td>52</td>
<td>NR</td>
<td>2.9</td>
<td>9.1</td>
<td>0</td>
<td>8.65</td>
<td>9.1</td>
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<td>Lins et al. 1996 (61)</td>
<td>57</td>
<td>1.3</td>
<td>49</td>
<td>5.9</td>
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<td>7.0</td>
<td>0</td>
<td>3.51</td>
<td>3.5</td>
</tr>
<tr>
<td>Mantermo &amp; Arnold 2000 (62)</td>
<td>208</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>13.9</td>
<td>3.4</td>
<td>1.0</td>
<td>0.96</td>
<td>1.0</td>
</tr>
<tr>
<td>Munti et al. 1999 (63)</td>
<td>59</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.7</td>
<td>18.6</td>
<td>1.7</td>
<td>5.08</td>
<td>0</td>
</tr>
<tr>
<td>Oseir et al. 1994 (64)</td>
<td>45</td>
<td>1.4</td>
<td>55</td>
<td>3</td>
<td>15.6</td>
<td>4.4</td>
<td>0</td>
<td>6.67</td>
<td>2.2</td>
</tr>
<tr>
<td>Proye et al. 1988 (65)</td>
<td>103</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>14.6</td>
<td>4.8</td>
<td>4.85</td>
<td>3.9</td>
</tr>
<tr>
<td>Riehlke et al. 1992 (66)</td>
<td>66</td>
<td>1.6</td>
<td>59</td>
<td>3.2</td>
<td>11.8</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ross et al. 2000 (67)</td>
<td>65</td>
<td>1.7</td>
<td>54</td>
<td>3.3</td>
<td>18.5</td>
<td>7.7</td>
<td>0</td>
<td>3.08</td>
<td>3.1</td>
</tr>
<tr>
<td>Seppel &amp; Schlaghecke 1994 (68)</td>
<td>52</td>
<td>1.7</td>
<td>56</td>
<td>3</td>
<td>1.9</td>
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</tr>
<tr>
<td>Mantermo et al. 2000 (69)</td>
<td>1004</td>
<td>1.4</td>
<td>58</td>
<td>3</td>
<td>9.2</td>
<td>4.2</td>
<td>1.6</td>
<td>4.68</td>
<td>1.2</td>
</tr>
<tr>
<td>Tanabe et al. 2001 (70)</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>47.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Terzolo et al. 1997 (71)</td>
<td>210</td>
<td>1.5</td>
<td>55</td>
<td>3.1</td>
<td>14.3</td>
<td>4.8</td>
<td>0.5</td>
<td>7.14</td>
<td>0.9</td>
</tr>
<tr>
<td>Tutuncu &amp; Gekk 1999 (72)</td>
<td>33</td>
<td>1.2</td>
<td>51</td>
<td>5.1</td>
<td>6.1</td>
<td>18.2</td>
<td>0</td>
<td>6.06</td>
<td>6.1</td>
</tr>
<tr>
<td>Virkate et al. 1989 (73)</td>
<td>20</td>
<td>1.4</td>
<td>59</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>3868</td>
<td></td>
<td></td>
<td></td>
<td>217 (5.6%)</td>
<td>48 (1.2%)</td>
<td>170 (4.4%)</td>
<td>81 (2.1%)</td>
<td>2781 (71.2%)</td>
</tr>
</tbody>
</table>

NR: not reported.
Endocrine activity in incidentalomas

Allolio 2001
Endocrine activity in incidentalomas

Allolio 2001
Sub-clinical CS: clinical presentation

- Subtle signs of hormone excess
  - weight gain (28%)
  - hypertension (42%)
  - diabetes (10%)

887 patients in Italian study group

Angeli et al Hormone Res 1997

- Other findings
  - increased markers of bone turnover
  - reduced osteocalcin levels

Ambrosi et al Eur J Endocrinol 1995
## Sub-clinical CS and metabolic syndrome

**Controls:** 41 Multi-nodular goiter.

<table>
<thead>
<tr>
<th></th>
<th>Silent</th>
<th>Subclinical CS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose/75g Glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1 mmol/l</td>
<td>7.02 mmol/l</td>
<td>8.72 mmol/l</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.08 mmol/l</td>
<td>1.06 mmol/l</td>
<td>1.73 mmol/l</td>
</tr>
<tr>
<td><strong>BP syst / BP diast.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125/75</td>
<td>132/82</td>
<td>139/84</td>
</tr>
</tbody>
</table>

*Terzolo JCEM, 87(3): 998-1003 2002*
**Table 2.** Characteristics of the metabolic syndrome described in patients with clinically inapparent adrenal adenoma (highlighted in bold).

<table>
<thead>
<tr>
<th>Systolic and diastolic hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperinsulinemia / Insulin resistance</td>
</tr>
<tr>
<td>Endotelial dysfunction</td>
</tr>
<tr>
<td><strong>Low HDL cholesterol</strong></td>
</tr>
<tr>
<td><strong>Elevated triglycerides</strong></td>
</tr>
<tr>
<td>LDL remnants</td>
</tr>
<tr>
<td><strong>Elevated fibrinogen</strong></td>
</tr>
<tr>
<td><strong>Hypercoagulability</strong></td>
</tr>
<tr>
<td>Increase of PCR and other inflammatory markers</td>
</tr>
<tr>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Non-dipping BP pattern</td>
</tr>
<tr>
<td>Increase of uric acid</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td><strong>Accelerated atherosclerosis</strong></td>
</tr>
</tbody>
</table>
# TABLE 3.
Studies investigating the prevalence of SH and its origin in type 2 diabetic and osteoporotic patients

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>Population (n)</th>
<th>Screening test</th>
<th>Cutoff</th>
<th>Overall prevalence (%)</th>
<th>Adrenal origin (%)</th>
<th>Pituitary origin (%)</th>
<th>Other origin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leibowitz, 1996 (63)</td>
<td>Type 2 diabetics (90)</td>
<td>1-mg DST</td>
<td>5.1 µg/dl</td>
<td>3.3</td>
<td>33.3</td>
<td>66.6</td>
<td>0</td>
</tr>
<tr>
<td>Contreras 2000 (81)</td>
<td>Type 2 diabetics (48)</td>
<td>UFC</td>
<td>112 µg/24 h</td>
<td>2.1</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Kann, 2001 (90)</td>
<td>Osteoporotics (78)</td>
<td>3-mg DST</td>
<td>1.8 µg/dl</td>
<td>3.8</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Catargi, 2003 (82)</td>
<td>Type 2 diabetics (200)</td>
<td>1-mg DST</td>
<td>2.1 µg/dl</td>
<td>5.5</td>
<td>72.3</td>
<td>27.3</td>
<td>0</td>
</tr>
<tr>
<td>Chiodini, 2005 (83)</td>
<td>Type 2 diabetics (294)</td>
<td>1-mg DST</td>
<td>1.8 µg/dl</td>
<td>10.8</td>
<td>66.6</td>
<td>13</td>
<td>20.4</td>
</tr>
<tr>
<td>Liu, 2005 (88)</td>
<td>Type 2 diabetics (154)</td>
<td>MSaC</td>
<td>0.15 µg/dl</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reimondo, 2007 (85)</td>
<td>Type 2 diabetics (100)</td>
<td>1-mg DST</td>
<td>3.6 µg/dl</td>
<td>1</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Chiodini, 2007 (91)</td>
<td>Osteoporotics (147)</td>
<td>1-mg DST</td>
<td>1.8 µg/dl</td>
<td>4.8</td>
<td>85.4</td>
<td>14.6</td>
<td>0</td>
</tr>
<tr>
<td>Newsome, 2008 (86)</td>
<td>Type 2 diabetics (178)</td>
<td>1-mg DST</td>
<td>1.8 µg/dl</td>
<td>1</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Taniguchi, 2008 (84)</td>
<td>Type 2 diabetics (77)</td>
<td>MSaC</td>
<td>5.0 µg/dl</td>
<td>2.6</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Mullan, 2010 (87)</td>
<td>Type 2 diabetics (201)</td>
<td>MSaC</td>
<td>0.4 µg/dl</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

UFC, 24-h UFC. SI conversion factor: cortisol × 27.56.
Natural history of sub-clinical CS

- Limited number of long-term follow-up studies
- Follow-up of 75 “non-functioning” incidentalomas (60 uni/15 bilateral) for up to 9 years
  - 9/75 mass enlargement: 12%
  - 2/75 new contralateral mass: 2.6%
  - 5/75 progression to sub-clinical: 6.6%
  - 2/75 progression to overt CS: 2.6%
  - risk factors: size > 3cm, NP-59 unilateral uptake

Barzon et al JCEM, 83: 55, 1998
## Outcome of adrenalectomy

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Operate D Patients with SCS (n)</th>
<th>Operate D Patients without SCS (n)</th>
<th>Definition of SCS</th>
<th>Study Type</th>
<th>Median Follow-up (mos)</th>
<th>Control Group of Non-Operated Pts</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi '00</td>
<td>5</td>
<td>13</td>
<td>LDDST (F&gt;5.0 (\mu)g/dl) + 1 test</td>
<td>Prospective</td>
<td>26</td>
<td>7 pts with SCS, 25 pts without SCS</td>
<td>ADX improved BP, glucose and lipids vs. no change in non-operated pts</td>
</tr>
<tr>
<td>Midorikawa '01</td>
<td>4</td>
<td>8</td>
<td>LDDST (F&gt;3.0 (\mu)g/dl) or HDDST (F&gt;1 (\mu)g/dl)</td>
<td>Prospective</td>
<td>1</td>
<td>NA</td>
<td>ADX reduced insulin resistance and HTN</td>
</tr>
<tr>
<td>Bemini '03</td>
<td>6</td>
<td>9</td>
<td>LDDST (F&gt;5.0 (\mu)g/dl)</td>
<td>Prospective</td>
<td>1</td>
<td>NA</td>
<td>ADX reduced BP, BW and FG</td>
</tr>
<tr>
<td>Erbil '06</td>
<td>11</td>
<td>-</td>
<td>LDDST and HDDST (F&gt;3.0 (\mu)g/dl)</td>
<td>Retrospective</td>
<td>1</td>
<td>NA</td>
<td>HTN improved in 71% and T2DM in 33% of pts after ADX</td>
</tr>
<tr>
<td>Tsuiki '08</td>
<td>10</td>
<td>-</td>
<td>LDDST (F&gt;3.0 (\mu)g/dl) and HDDST (F&gt;1 (\mu)g/dl)</td>
<td>Retrospective</td>
<td>27.3</td>
<td>10 pts with SCS</td>
<td>Improvement in HTN or T2DM or DL in 80% of pts after ADX vs. worsening in 60% of non-operated pts</td>
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<tr>
<td>Toniato '09</td>
<td>23</td>
<td>-</td>
<td>LDDST (F&gt;3.0 (\mu)g/dl) + 1 test</td>
<td>Prospective, randomized</td>
<td>91</td>
<td>22 pts with SCS</td>
<td>Improvement in HTN and T2DM in 38% of pts after ADX vs. worsening in about 30% of non-operated pts</td>
</tr>
<tr>
<td>Sereg '09</td>
<td>5</td>
<td>42</td>
<td>F24&gt;5.0 (\mu)g/dl or LDDST (F&gt;3.6 (\mu)g/dl)</td>
<td>Retrospective</td>
<td>109</td>
<td>8 pts with SCS, 70 pts without SCS</td>
<td>No difference in the frequency of HTN, T2DM, DL, obesity at the last visit between operated and non-operated pts</td>
</tr>
<tr>
<td>Chiodini '10</td>
<td>25</td>
<td>30</td>
<td>Two altered tests</td>
<td>Retrospective</td>
<td>36</td>
<td>16 pts with SCS, 37 pts without SCS</td>
<td>ADX improved BP and FG in pts with or without SCS vs. non-operated pts</td>
</tr>
</tbody>
</table>
Adrenal incidentaloma

Summary of current clinical recommendations

- 1 mg DST: cortisol < 5 µg/dL
- Midnight salivary cortisol*
- UFC*
- 2 mg dexa x 48 h*
  * For high suspicion or confirmation

Evaluate all cases for pheochromocytoma
Aldosterone/renin ratio if hypertension

Imaging 3-6 months and after 1 or 2 years
Hormonal evaluation yearly for 5 years

Endocr Pract. 15 Suppl 1:1-20 and 15:450-3 2009
AME Position Statement on Adrenal Incidentaloma.

Authors
M. Terzolo¹, A. Stigliano², I. Chiodini³, P. Loli⁴, L. Furlani⁵, G. Arnaldi⁶, G. Reimondo¹, A. Pia¹, V. Toscano², M. Zini⁷, G. Borretta⁸, E. Papini⁹, P. Garofalo¹⁰

Reviewers
B. Allolio¹¹, B. Dupas¹², F. Mantero¹³, A. Tabarin¹⁴

Accepted Preprint first posted on 6 April 2011 as Manuscript EJE-10-1147
1. We recommend ruling out pheochromocytoma in all patients with adrenal incidentalomas. 1ennifer

2. We recommend ruling out primary aldosteronism in all hypertensive and/or hypokalemic patients with adrenal incidentalomas. 1ennifer

3. We recommend ruling out overt Cushing’s syndrome in all patients with adrenal incidentalomas. 1ennifer

4. We recommend the 1-mg overnight DST for screening of subclinical Cushing’s syndrome. 1ennifer

5. We suggest to not proceed with further testing in patients suppressing cortisol below 1.8 μg/dl (50 nmol/l) after DST. 2ennifer

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. 2ennifer

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.
Clinical recommendation on the management of adrenal incidentalomas.

1. We recommend surgery for any adrenal mass with radiological aspects compatible with malignancy. The threshold for a mass size clearly indicative of malignancy is unknown. 1★★★★

2. We recommend surgery in all patients with functional adrenal tumors causing overt steroid hormone or catecholamine excess. 1★★★★

3. We recommend surgery in all patients with pheochromocytoma. 1★★★★

4. Data are insufficient to make any recommendation for or against surgery in patients with subclinical Cushing’s syndrome.

5. We suggest postoperative glucocorticoid replacement in all patients who undergo surgery for a presumed cortical adenoma. Replacement is mandatory in patients with subclinical Cushing’s syndrome and in patients without pre-operative testing. 2★★★★
6. Data are insufficient to make firm recommendations on endocrine and radiologic follow-up.

7. We suggest to repeat imaging (CT or MRI) 3-6 months after discovery of an adrenal incidentaloma to recognize early a rapidly growing mass, except when the adrenal mass is small (≤2 cm) with clear benign features (density ≤10 HU). If an adrenal mass has clear features of myelolipoma or cyst no additional follow-up is needed. 2⊕ΟΟΟ

8. We suggest careful clinical monitoring of patients at high cardiovascular risk and to treat adequately associated diseases according to the specific guidelines (i.e., hypertension, diabetes). 2⊕ΟΟΟ

9. We suggest considering adrenalectomy if the mass enlarges by 1 cm or more and/or changes its appearance during observation. 2⊕ΟΟΟ

10. We suggest considering adrenalectomy in patients with subclinical Cushing’s syndrome when an adequate medical therapy does not reach the treatment goals of associated diseases potentially linked to hypercortisolism. 2⊕ΟΟΟ

11. We recommend laparoscopic adrenalectomy in all patients with presumably benign tumors who are submitted to surgery. 1⊕⊕⊕⊕
The myths of the recommendations

• Literature review 1980-2008
• 828 papers on adrenal incidentaloma
• 110 English language with more than 20 cases reviewed
• 20 met criteria of original studies excluding surgical series

Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink?

T J Cawood, P J Hunt, D O’Shea¹, D Cole and S Soule

Department of Endocrinology, Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand and ¹Department of Endocrinology, St Vincent’s University Hospital, Dublin, Ireland

(Correspondence should be addressed to T J Cawood: Email: tom.cawood@cdhb.govt.nz)
# Revised etiology of adrenal incidentaloma

<table>
<thead>
<tr>
<th>Condition</th>
<th>Previous reviews</th>
<th>Cawood 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal cancer</td>
<td>4.4-4.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Metastasis</td>
<td>2.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>5.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Sub-clinical CS</td>
<td>6.4%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

Risk of radiation exposure with repeated imaging

- Radiation with abdominal CT: 10 mSv (3.9-30)
- Equal to 3.3 years of natural background exposure
- Twice for delayed contrast washout CT
- Estimated cancer death for each 10 mSv: 0.048%
- 1 cancer death for every 1000-2000 abdominal CT
- 1 cancer death / 5000 abdominal CT if patient > 30 yo
- Low risk, but not zero

Economic cost of evaluation of incidentaloma

- Hormonal evaluation if HBP: ~ US 120 $
- Further hormonal evaluation: ~ US 200 $
- CT scan: ~ US 500 $
- Total initial cost: ~ 620-820 $
- 1388 lesions between 1-2 cms: US 1 million $
- Cost financial and psychological to patient !!!

Applying the current recommendations to evaluate adrenal incidentaloma

<table>
<thead>
<tr>
<th>Approximate risk of event during 2-year radiological follow-up and 4-year biochemical follow-up of an adrenal incidentaloma initially thought to be benign and non-functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate financial cost of tests</td>
</tr>
<tr>
<td>Radiation exposure from CT imaging during follow-up</td>
</tr>
<tr>
<td>Risk of inducing fatal cancer from radiation exposure during follow-up CT imaging</td>
</tr>
<tr>
<td>Risk of detecting cancer during follow-up</td>
</tr>
<tr>
<td>Risk of detecting non-metastatic cancer during follow-up</td>
</tr>
<tr>
<td>Risk of false-positive diagnosis/suspicion of malignancy during CT imaging</td>
</tr>
<tr>
<td>Risk of false-positive diagnosis of subclinical Cushing’s syndrome</td>
</tr>
<tr>
<td>Risk of true-positive diagnosis of subclinical Cushing’s syndrome</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on risk of causing fatal cancer of between 1 in 1000 and 1 in 50000 CT scans, and 2.3 CT scans occurring during follow-up.

<sup>b</sup>Approximately, half of tumours detected will be metastases, and so diagnosis unlikely to affect outcome.

<sup>c</sup>Based on specificity of CT of 95% for malignancy, see Table 6.

<sup>d</sup>Based on specificity of 1 mg DXT of 90% and four annual follow-up tests.

<sup>e</sup>Based on 2 cases per 1000 developing over 2 years of follow-up, see Table 6.

What size of adrenal incidentalomas justifies investigation and follow-up?

- NIH consensus: no size mentioned!
- Young, NEJM, 2007 and UpToDate: 1 cm
- Tabarin, French Consensus 2008: 1 cm
- Cawood 2009: definition size: 1 cm

QUESTION

Should all patients with adrenal incidentalomas undergo the same initial investigation regardless of size of incidentaloma?
Same need for investigation and follow-up?

- 54 yo woman with 1.1 cm thickening of inner leaflet of left adrenal, 4 HU, normal weight and blood pressure
- 54 yo woman with 3.5 cm left adrenal nodule, 8 HU, BMI of 28, normal blood pressure
- 54 yo woman with 1.8 cm left adrenal nodule, 15 HU, BMI of 26, high blood pressure

What should I do!
Exclude silent pheochromocytoma

- YES for lesions > 2cms?
- YES for patients with hypertension
- YES for lesions > 10 HU
- NIH consensus to use plasma free metanephrines is costly, not widely available and not clearly superior to urinary fractionnated catecholamines / metanephrines (95% sensitivity and specificity)
- plasma metanephrines (98% sensitivity, 89% specificity) reserved for patients with high index of suspicion of pheochromocytoma
Screen for excess cortisol production

- No evidence-based recommendations
- Restrict to lesions > 2 cms or HBP, diabetes
- Use 1 mg dexamethasone overnight screening
  - < 50 nmol/L: non cortisol secreting, no follow-up unless clinical changes
  - 50-139 nmol/L: cortisol secreting lesion, evaluate for metabolic risks, repeat one year if imaging non suspicious of ACC
  - > 140 nmol/L: do further endocrine evaluation
  - Inexpensive, 73-100% sensitivity, 90% specificity
Evaluation of cortisol production in adrenal incidentalomas

Detailed clinical history and physical examination
(consider: presence of progressive CS predictive features and diagnosis of diabetes, osteoporosis or hypertension)
1-mg overnight DST: a.m. cortisol < 1.8 µg/dl (50 nmol/L)
(consider: drug interactions as interference on dexamethasone metabolism or increasing of CBG levels by estrogens)

Normal suppression

Non-functioning adrenal mass

Unilateral

Bilateral

ACTH-stimulation test (cortisol and 17-OH progesterone)

> 4cm < 4cm

Surgery Follow-up

Normal Abnormal

Screening for late-onset congenital adrenal hyperplasia

Further CS investigation
(24-hUFC, ACTH/DHEA-S; confirmatory DST, late-night cortisol)

Abnormal (but normal 24hUFC)

Subclinical CS

Consider:
• Degree of hypercortisolism
• Protocol for aberrant receptors

Unilateral

Bilateral

> 4cm < 4cm

Normal Abnormal

Surgery

Follow-up or Treatment
Decisions must be individualized
• If progressive or decompensating subclinical CS, consider unilateral adrenalectomy.
• If aberrant hormone receptors, consider specific pharmacological treatment

Mazzuco, Bourdeau, Lacroix Cur Opin Endo & Dia, 16:203 2009
Additional hormonal testing

- plasma ACTH, UFC and higher dose oral or IV dexamethasone if plasma cortisol $>$ 50 nmole/L post 1 mg at midnight
- primary aldosteronism confirmation tests if elevated aldo/PRA ratio (Funder, Endo Society 2009)
- ACTH 250 µg test if bilateral lesions
- 17-OH-progesterone if hirsutism or family history of CAH; ACTH 250 µg stimulation test
- testosterone, DHEAS if hirsutism or virilization
- estradiol if gynecomastia
Need a consensus on definitions of sub-clinical CS

- Primary adrenal Cushing’s syndrome
  - Elevated UFC and suppressed ACTH with clinical signs of CS
  - Elevated UFC and suppressed ACTH without clinical signs of CS

- Partially ACTH-independent cortisol secretion (former sub-clinical CS):
  - Normal UFC but cortisol incompletely suppressible by dexamethasone
  - Variable degree of HPA axis suppression and clinical effects of cortisol excess
Revise the guidelines for adrenal incidentaloma

- Exclude functionality and malignancy on initial evaluation of lesions either > 2cm*, or accompanied by risk factors such as morphology, clinical signs, HBP, diabetes, osteoporosis
- No imaging or biochemical follow-up for lesions not suspicious and with normal evaluation
- Repeat imaging at 3-6 months only in larger or suspicious lesions; use PET-CT for suspicious lesions*
- Further hormonal evaluation only if clinical progression

Incidentaloma : surgical indication

- Functional tumor
  - Pheochromocytoma: yes
  - Overt Cushing’s tumor: yes
  - AIMA: aberrant receptor: medical Rx
  - Aldosteronoma: surgery vs medical Rx
  - Idiopathic aldosteronism: medical
  - Androgen secretion: yes

- Sub-clinical Cushing’s syndrome if elevated UFC, suppressed ACTH, HBP, diabetes, osteoporosis (cortisol replacement)
Incidentaloma: surgical indication

- Suspicion of adrenal cancer (radiology, hormonal profile, PET-scan)
- Unilateral Lesion
  - > 6 cm: higher risk: yes
  - 4-6 cm: individualize (morphology, patient)
  - < 4 cm: lower risk: follow-up
- Isolated metastasis (rarely)
Surgical approach

- Laparoscopic
  - Benign lesion
  - Experienced surgeon and team
  - Less morbidity
- Open surgery
  - Malignant lesion
  - Extensive previous abdominal surgery
  - Surgeon’s expertise for size of lesion
- Glucocorticoid replacement in cortisol secreting lesions
Thank you: Questions

Spring time in my Montreal garden