European Society of Endocrinology Clinical Practice Guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors (ENS@T)

Martin Fassnacht, Irina Bancos, Massimo Terzolo, John Newell-Price, Antoine Tabarin
We have the following potential conflicts of interest to report:

- Research Contracts: M. Fassnacht (Corcept; HRA); I. Bancos (HRA Pharma), M. Terzolo (HRA)
- Consulting: M. Fassnacht (Bayer, HRA), I. Bancos (Corcept, Sparrow, HRA, Recordati), J. Newell-Price (HRA, Recordati); A. Tabarin (HRA, Recordati), M. Terzolo (HRA, Corcept)

- Employment in the Industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Speaker: A. Tabarin (Recordati), M. Terzolo (HRA)
The ESE-ENSAT Guidelines Panel
12 experts from 8 countries

- Irina Bancos, USA
- Olaf Dekkers, The Netherlands
- Martin Fassnacht, Germany
- Kerstin Lorenz, Germany
- John Newell-Price, UK
- Ljiljana Marina Pelsma, The Netherlands
- Anju Sahdev, UK
- Antoine Tabarin, France
- Massimo Terzolo, Italy
- Stelios Tsagarakis, Greece

12 experts from 8 countries.
An adrenal incidentaloma is an adrenal mass detected on imaging not performed for suspected adrenal disease.

Adrenal masses discovered during tumor evaluation for extra-adrenal malignancies do not meet the strict definition of adrenal incidentaloma. However, as this is a clinically frequent scenario, this topic is covered in a specific chapter of the guideline.
Autopsy and radiological studies suggest: prevalence of adrenal incidentaloma 2-3% (range 1.0-10%), which increases with age.
Where did we start?

Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors

Martin Fassnacht1,2, Wiebke Artl3,4, Irina Bancos3,4,5, Henning Dralle6, John Newell-Price2,9, Anju Sahe6v, Antoine Tabarin10, Massimo Terzolo11, Stylianos Tsagarakis12 and Olaf M Dekkers12,14

Eur J Endocrinol. 2016 Aug;175(2):G1-G34

Citations since August 2016: 1318

Citations per year
ESE-ENSAT guidelines 2016

40 recommendations with the main aims:

► to avoid „over-diagnostics“ and „over-treatment“
► without missing relevant diseases (e.g. adrenocortical carcinoma, pheochromocytoma etc.)
► to provide (as much as possible) guidelines based on scientific evidence
GRADE approach

1. Define clinical questions
2. Systematic research
3. Quality of evidence (4 categories)
   Very low < low < moderate < strong
   ⊕ΟΟΟΟ < ⊕⊕ΟΟΟ < ⊕⊕⊕ΟΟ < ⊕⊕⊕⊕Ο

4. Recommendations (2 grades)
   • Strong (`we recommend’)
   • Weak (`we suggest’)

Only for recommendations that based on systematic reviews
Our 4 key research questions

1. How to assess risk of malignancy?

2. How to define and manage mild autonomous cortisol secretion?

3. Who should have surgical treatment and how should it be performed?

4. What follow-up is indicated if the adrenal incidentaloma is not surgically removed?
4 systematic reviews

Overall, 4605 abstracts have been reviewed

- Q1A: Diagnostic accuracy of imaging • 1315 abstracts => 20 studies (12 new)
- Q1B: Diagnostic accuracy of biopsies • 367 abstracts => 11 studies (3 new)
- Q1C: Diagnostic accuracy steroid profiling • 367 abstracts => 2 new studies
- Q2A: Association MACS - comorbidities • 1059 abstracts => 46 studies (34 new)
- Q2B: Therapy for MACS • 291 abstracts => 11 studies (7 new)
- Q3: Surgery: open vs laparoscopic • 690 abstracts => 14 studies (5 new)
- Q4: Optimal follow-up • 516 abstracts => 42 studies (18 new)
Key facts about the revised version

► 20 recommendations are more or less unchanged
► 15 recommendations with some modifications (mainly increase of evidence level and/or strength of recommendation)
► 5 recommendations with major modifications
► 9 new recommendations

=> 49 recommendations
2016: In the absence of strong evidence…

…we can not abstain from guidance because the evidence is not solid
Situation in 2023

The evidence is still not yet solid, but in many aspects better than 2016
Our first recommendation

R.1.1. We recommend that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting, if at least one of the following criteria is met:

- Imaging is not consistent with a benign lesion.
- There is evidence of hormone excess (including mild autonomous cortisol secretion in patients with clinically relevant comorbidities potentially attributable to cortisol).
- Evidence of significant tumor growth during follow-up imaging.
- Adrenal surgery is considered.

The core multidisciplinary team should consist of a radiologist, an endocrinologist, and a surgeon, all with significant experience in the management of adrenal tumors.
Presentation of the four key questions and the respective recommendations:

Assessment of the risk of malignancy

Irina Bancos, USA
Presentation of the four key questions and the respective recommendations:

Assessment of the risk of malignancy

Irina Bancos, USA
Objective: to review recommendations on assessment of the risk of malignancy

- 42 YO woman: 4.6 cm, HU=6
- 67 YO man: 1.3 cm, HU=16
- 26 YO woman: 1.6 cm, HU=23
- 83 YO woman: 7.6 cm, HU=36
- 27 YO man: 3.6 cm, heterog.
- 77 YO woman: 12 cm, heterog.
Most frequent clinical presentation: Single phase Post Contrast CT

Small 1-4 cm unilateral homogenous adrenal mass

This cannot provide a distinction between benign and malignant lesions and provides no indicator of function.

R.2.1. We recommend aiming to establish with the highest possible certainty if an adrenal mass is benign or malignant at the time of initial detection.

=> Reduces repeated investigations reducing radiation burden, cost, psychological distress
R.2.2. We recommend that all adrenal incidentalomas undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign. For this purpose, we recommend the use of non-contrast CT as the first imaging modality if not yet performed.

R.2.3 We recommend that if the non-contrast CT is consistent with a benign adrenal mass (homogenous appearance and Hounsfield units (HU) ≤ 10) no further imaging is required.
## Rationale

**HU cutoff of 10:**
- Sensitivity 100%
- Specificity 57.5%

**HU cutoff of 20**
- Sensitivity of 96.8%
- Specificity of 76.7%

### Diagnostic performance of unenhanced CT in adrenal incidentaloma

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HU &gt; 10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebbehøj 2020</td>
<td>660</td>
<td>100.0 (86.3, 100.0)</td>
<td>56.9 (52.9, 60.7)</td>
</tr>
<tr>
<td>Hong 2017</td>
<td>958</td>
<td>100.0 (83.2, 100.0)</td>
<td>45.4 (42.2, 48.7)</td>
</tr>
<tr>
<td>Schloetlburg 2021</td>
<td>252</td>
<td>100.0 (92.7, 100.0)</td>
<td>54.2 (47.1, 61.2)</td>
</tr>
<tr>
<td>Marty 2018</td>
<td>252</td>
<td>100.0 (87.2, 100.0)</td>
<td>52.9 (46.1, 59.6)</td>
</tr>
<tr>
<td>Vilar 2008</td>
<td>52</td>
<td>100.0 (75.3, 100.0)</td>
<td>71.8 (55.1, 85.0)</td>
</tr>
<tr>
<td>Bancos 2020</td>
<td>1549</td>
<td>100.0 (97.7, 100.0)</td>
<td>66.7 (64.2, 69.2)</td>
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<tr>
<td><strong>Summary</strong></td>
<td>3723</td>
<td>100.0 (100.0, 100.0)</td>
<td>57.5 (55.8, 59.1)</td>
</tr>
<tr>
<td><strong>HU &gt; 20</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bancos 2020</td>
<td>1554</td>
<td>98.2 (94.7, 99.6)</td>
<td>83.4 (81.3, 85.3)</td>
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<tr>
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<td>88.0 (68.8, 97.5)</td>
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<td>Marty 2018</td>
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<td>96.3 (81.0, 99.9)</td>
<td>65.8 (59.2, 72.0)</td>
</tr>
<tr>
<td>Hong 2017</td>
<td>958</td>
<td>100.0 (83.2, 99.5)</td>
<td>67.4 (64.3, 70.4)</td>
</tr>
<tr>
<td>Schloetlburg 2021</td>
<td>252</td>
<td>95.9 (86.0, 99.5)</td>
<td>72.9 (66.2, 78.9)</td>
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<tr>
<td><strong>Summary</strong></td>
<td>3676</td>
<td>96.8 (94.0, 98.3)</td>
<td>76.7 (75.3, 78.1)</td>
</tr>
</tbody>
</table>
Options for indeterminate tumors:

*Discussion at MDT

- Immediate additional imaging
- Follow up imaging (to assess for tumor growth)
- Steroid profiling
- Adrenalectomy

Options depend on risk, availability, other factors
- HU: >20 vs 10-20
- Tumor size
- Laterality
- History of cancer
- Hormone excess
- Age

- Homogeneous, HU >10
- Heterogeneous
Indeterminate tumors: R2.4, 2.5, 2.6

Unenhanced CT

Imaging work-up in patients with adrenal incidentaloma

Diagnoses

- Any size, homogenous and HU ≤ 10
- Homogenous and HU 11-20 and tumor < 4cm
- Homogenous HU 11-20 and tumor ≥ 4cm
  - or
  - Homogenous HU > 20 and tumor < 4cm
  - or
  - Heterogeneous tumors < 4cm
- Homogenous HU > 20 or heterogeneous and Tumor ≥ 4cm

Primary decision

- No further imaging required
- Additional imaging¹
  - Interval imaging in 12 months (non-contrast CT/MRI)
- Discuss in MDT meeting and consider proceeding swiftly to additional imaging¹,²
- Discuss in MDT meeting and consider proceeding swiftly to surgery²,³
  - (or further imaging (esp. FDG-PET/CT))
CT with delayed contrast media washout: absolute and relative washout
- weak data
- accuracy of cutoffs challenged

Chemical shift MRI:
Loss of signal intensity on out-phase imaging => benign lesion

FDG-PET/CT:
Uptake less than liver => benign lesion
FDG PET scan

**SUV max:**
Sensitivity 87-100%
Specificity 67-75%

**Adrenal liver ratio**
Sensitivity 85-100%
Specificity 85-100%

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*European Society of Endocrinology*
*The voice for endocrinology*
Objective: to review recommendations on assessment of the risk of malignancy

- 42 YO woman: 4.6 cm, HU=6
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- 26 YO woman: 1.6 cm, HU=23
- 83 YO woman: 7.6 cm, HU=36
- 27 YO man: 3.6 cm, heterog.
- 77 YO woman: 12 cm, heterog.
Indeterminate tumors: R 2.4

- No symptoms
- Non-functioning
- No history of cancer

If CT demonstrates a homogeneous adrenal mass with unenhanced HU between 11 and 20 and a tumor size < 4cm ... we suggest an immediate additional imaging. Alternatively, interval imaging in 12 months by non-contrast CT (or MRI) could be performed.

67 YO man: 1.3 cm, HU=16

R.2.4. If CT demonstrates a homogeneous adrenal mass with unenhanced HU between 11 and 20 and a tumor size < 4cm ... we suggest an immediate additional imaging. Alternatively, interval imaging in 12 months by non-contrast CT (or MRI) could be performed.

Imaging 12 months later – no change in tumor size
Objective: to review recommendations on assessment of the risk of malignancy

42 YO woman: 4.6 cm, HU=6
67 YO man: 1.3 cm, HU=16
26 YO woman: 1.6 cm, HU=23

83 YO woman: 7.6 cm, HU=36
27 YO man: 3.6 cm, heterog.
77 YO woman: 12 cm, heterog.
R.2.5 If the adrenal mass is ≥ 4cm and heterogeneous or has unenhanced HU > 20, we suggest discussing such cases in a multidisciplinary team meeting. In most cases, immediate surgery will be the management of choice, but in some patients, additional imaging might be an option.
Indeterminate tumors: R 2.5

R.2.5 If the adrenal mass is ≥ 4cm and heterogeneous or has unenhanced HU > 20, we suggest discussing such cases in a multidisciplinary team meeting. In most cases, immediate surgery will be the management of choice, but in some patients, additional imaging might be an option.

83 YO woman: 7.6 cm, HU=36, SUV max of 40.9

Adrenalectomy: Adrenocortical carcinoma
R.2.7. We recommend **against** the use of an adrenal biopsy in the diagnostic work-up of patients with adrenal masses unless there is a history of extra-adrenal malignancy.

1. Lesion is hormonally inactive (pheochromocytoma has been excluded),
2. Lesion has not been conclusively characterized as benign by diagnostic imaging
3. Management would be altered by the knowledge of histology

- No symptoms
- History of renal cell carcinoma 12 years prior, treated with right nephrectomy and right adrenalectomy
- Hormonal work up: negative for catecholamine excess, dexamethasone suppression test – negative, however positive for subclinical primary adrenal insufficiency.

**Biopsy: Renal cell carcinoma**
Objective: to review recommendations on assessment of the risk of malignancy

42 YO woman: 4.6 cm, HU=6

67 YO man: 1.3 cm, HU=16

26 YO woman: 1.6 cm, HU=23

83 YO woman: 7.6 cm, HU=36

27 YO man: 3.6 cm, heterog.

77 YO woman: 12 cm, heterog.
Indeterminate tumors: \textbf{R 2.6}

- Homogenous HU 11-20 and tumor $\geq$ 4cm
- Homogenous HU $> 20$ and tumor $< 4$cm
- Heterogeneous tumors $< 4$cm

\textbf{R.2.6} In adrenal masses that do not fall in one of the categories above we suggest an individualized approach with discussion in a multidisciplinary team meeting.

26 YO woman: 1.6 cm, HU=23

27 YO man: 3.6 cm, heterog.
R.2.6 In adrenal masses that do not fall in one of the categories above we suggest an individualized approach with discussion in a multidisciplinary team meeting.

- No plan was made for adrenal incidentaloma
- 3 years later: CT scan demonstrated the adrenal mass is now 7.3 cm
- Work up: abnormal DST and high DHEAS
- Adrenalectomy: ACC

Homogenous HU 11-20 and tumor ≥ 4 cm or Homogenous HU > 20 and tumor < 4 cm or Heterogeneous tumors < 4 cm

Discuss in MDT meeting and consider proceeding swiftly to additional imaging or immediate surgery

26 YO woman: 1.6 cm, HU=23
Steroid profiling

R.2.8. We suggest measurement of sex steroids and precursors of steroidogenesis (ideally using **multi-steroid profiling** by tandem mass spectrometry) in patients in whom by imaging or clinical features an adrenocortical carcinoma is suspected.

- No symptoms
- No past medical history
- Indeterminate adrenal mass
- Younger age
- Overnight dexamethasone suppression test - abnormal

Lipid poor adenoma OR adrenocortical carcinoma?
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Full name of steroid</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>An</td>
<td>Androsterone</td>
<td>0.3</td>
</tr>
<tr>
<td>Etio</td>
<td>Etiocholanolone</td>
<td>2.2</td>
</tr>
<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
<td>-0.5</td>
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<tr>
<td>16a-DHEA</td>
<td>16α-hydroxy-Dehydroepiandrosterone</td>
<td>-0.8</td>
</tr>
<tr>
<td>5PT</td>
<td>Pregnenetriol</td>
<td>16</td>
</tr>
<tr>
<td>5PD</td>
<td>Pregnenediol</td>
<td>-0.2</td>
</tr>
<tr>
<td>THB</td>
<td>Tetrahydrocorticosterone</td>
<td>-1.7</td>
</tr>
<tr>
<td>THDOC</td>
<td>Tetrahydrodeoxycorticosterone</td>
<td>2.8</td>
</tr>
<tr>
<td>PD</td>
<td>Pregnanediol</td>
<td>-0.2</td>
</tr>
<tr>
<td>PT</td>
<td>Pregnanetriol</td>
<td>12</td>
</tr>
<tr>
<td>17HP</td>
<td>17α-Hydroxypregnanolone</td>
<td>1.8</td>
</tr>
<tr>
<td>PTONE</td>
<td>Pregnanetriolone</td>
<td>0.5</td>
</tr>
<tr>
<td>THS</td>
<td>Tetrahydrodeoxycortisol</td>
<td>284</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Cortisol</td>
<td>0.2</td>
</tr>
<tr>
<td>Cortisone</td>
<td>Cortisone</td>
<td>0.6</td>
</tr>
<tr>
<td>6B-OH-Cortisol</td>
<td>6β-Hydroxycortisol</td>
<td>3.5</td>
</tr>
<tr>
<td>11B-OH-AN</td>
<td>11β-Hydroxyandrosterone</td>
<td>-0.5</td>
</tr>
<tr>
<td>11-OXO-ET</td>
<td>11-Oxoetiocholanolone</td>
<td>1.7</td>
</tr>
<tr>
<td>B-Cortol</td>
<td>β-Cortol</td>
<td>0.6</td>
</tr>
<tr>
<td>a-Cortolone</td>
<td>α-Cortolone</td>
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</tr>
<tr>
<td>B-Cortolone</td>
<td>β-Cortolone</td>
<td>1.9</td>
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<tr>
<td>5a-THF</td>
<td>5α-Tetrahydrocortisol</td>
<td>0.9</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrocortisol</td>
<td>2.3</td>
</tr>
<tr>
<td>THE</td>
<td>Tetrahydrocortisone</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Steroid profiling: adrenocortical carcinoma

27 YO man: 3.6 cm, heterog.

adrenocortical carcinoma
SUMMARY

Rarely consider biopsy in selected patients likely to have metastasis.

Consider steroid profiling in patients likely to have ACC.
Presentation of the four key questions and the respective recommendations:
Assessment of hormone excess

Massimo Terzolo, Italy
Hormone excess (cortisol)

- Is glucocorticoid excess associated with an increased cardiovascular, metabolic and fracture risk in patients with adrenal mass(es)?
- Should surgery or a conservative/medical approach be recommended in patients with adrenal mass(es) and mild glucocorticoid excess?
A major change in terminology

- In 2016, the panel unanimously decided to avoid the term “subclinical Cushing’s syndrome” and to use instead the term “autonomous cortisol secretion”.

- In 2023, the panel introduced the term “mild autonomous cortisol secretion (MACS),” due to the fact that ACS may include also patients with overt Cushing syndrome.
A major change in the interpretation of DST

2016 Version

Autonomous cortisol secretion
- "possible" (140 nmol/l)
- "confirmed" (50 nmol/l)

Autonomous cortisol secretion
- "excluded"
A major change in the interpretation of DST

- Cortisol (nmol/L)
  - MACS considered
  - 50 (1.8 µg/dl)
  - MACS excluded

2023 Version
Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study

Lancet Diabetes Endocrinology, 2022

The larger difference in mortality is between NFA and Possible ACS
How to diagnose MACS?

- Accurate physical examination to exclude Cushing
- Ascertain ACTH independency
- Additional tests may be useful
- Repeat DST to confirm MACS
- Look for comorbidities

1. Apparently benign adrenal incidentaloma
   - 1mg Dexamethasone Suppression Test (DST)
     - Serum cortisol ≤ 50 nmol/L
       - No evidence of autonomous cortisol secretion
       - No treatment and no follow-up
     - Serum cortisol ≥ 50 nmol/L
       - Overt Cushing syndrome
         - Overt features of Cushing syndrome?
           - Yes
             - Mild autonomous cortisol secretion (MACS)
               - Comorbidities potentially attributable to cortisol?
                 - Yes
                   - Consider ACTH-dependent Cushing syndrome
                     - No treatment and no follow-up
                 - No
                   - MACS confirmed? ACTH independency?
                     - Yes
                       - Monitor for development of comorbidities potentially attributable to cortisol
                     - No
                       - Consider specific treatment
How to diagnose MACS?

- Accurate physical examination to exclude Cushing
- Ascertain ACTH independency may be useful
- Additional tests may be useful to confirm MACS
- Repeat DST to confirm MACS
- Look for comorbidities

CAVEATS

- Frail and/or very old patients
- Causes of false positive results of DST
- Variability of results in repeated tests

Apparently benign adrenal incidentaloma

1mg Dexamethasone Suppression Test (DST)

Serum cortisol ≤ 50 nmol/L

No evidence of autonomous cortisol secretion

Overt Cushing syndrome

Consider ACTH-dependent Cushing syndrome

MACS confirmed? ACTH independency?

No

No treatment and no follow-up

Yes

Monitor for development of comorbidities potentially attributed to cortisol

Consider specific treatment
Morbidity in patients with mild autonomous cortisol secretion (MACS²)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cut off</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>&gt;1.8µg/dL</td>
<td>14</td>
<td>9375</td>
<td>1.44 (1.23, 1.69)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;1.8µg/dL</td>
<td>18</td>
<td>10031</td>
<td>1.24 (1.16, 1.32)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>&gt;1.8µg/dL</td>
<td>12</td>
<td>7769</td>
<td>1.23 (1.13, 1.34)</td>
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<tr>
<td>Vertebral fractures³⁴</td>
<td>&gt;1.8µg/dL</td>
<td>3</td>
<td>637</td>
<td>1.08 (0.68, 1.71)</td>
</tr>
</tbody>
</table>

Details see Pelsma et al. Eur J Endocrinol submitted
New recommendation:

R.3.8 We recommend discussing the option of surgery with the patient with MACS and relevant comorbidities and a unilateral mass (⊕ΟΟΟ). Age, sex, general health, degree and persistence of non-suppressible cortisol after DST, severity of comorbidities and patient’s preference should be taken into account (⊕ΟΟΟ).
New recommendation:

- R.3.8 We recommend discussing the option of surgery with the patient with MACS and relevant comorbidities and a unilateral mass (⊕ΟΟΟ). Age, Sex, Overall health, degree and persistence of non-suppressible cortisol after DST, severity of comorbidities and patient’s preference should be taken into account (⊕ΟΟΟ).

The decision for surgery should be individualized!
Adrenalectomy Improves Blood Pressure and Metabolic Control in Patients With Possible Autonomous Cortisol Secretion: Results of a RCT

Valentina Morelli1, Sofia Frigerio2,3, Carmen Aresta1, Elena Passeri1, Flavia Pugliese5, Massimiliano Copetti6, Anna Maria Barbieri2,3, Silvia Fustinoni3,7, Elisa Polledri3, Sabrina Corbetta4,8, Maura Arosio2,3, Alfredo Scillitani5 and Iacopo Chiodini1,8

Frontiers in Endocrinology, 2022

55 pts with PACS randomized between ADX or surveillance
Adrenalectomy Improves Blood Pressure and Metabolic Control in Patients With Possible Autonomous Cortisol Secretion: Results of a RCT

Valentina Morelli1, Sofia Frigerio2, Carmen Aresta1, Elena Passeri4, Flavia Pugliese5, Massimilano Copetti6, Anna Maria Barbieri2,3, Silvia Fustinoni3,7, Elisa Polledri3, Sabrina Corbetta4,8, Maura Arosio2,3, Alfredo Scillitani3 and Iacopo Chiodini1,8

55 pts with PACS randomized between ADX or surveillance.

Limits of available literature

- Variable definitions of MACS and outcomes
- Variable follow-up duration
- No data on hard endpoints (CV events, death)
- Treatment of controls not standardized

![Graph showing comparison between surgically treated and conservatively treated groups, with 'Ameliorated' and 'Worsened' outcomes depicted.](image-url)
Endocrine work-up

R.3.9 We recommend excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrines in all patients with adrenal lesions with features not typical for a benign adenoma.

R.3.10 In patients with concomitant hypertension or unexplained hypokalemia, we recommend use of the aldosterone / renin ratio to evaluate primary aldosteronism.
Presentation of the four key questions and the respective recommendations:

Surgical treatment

John Newell-Price, UK
Surgery – Key questions

Who should **NOT** have an operation?

What surgical approaches should be used?
Who should NOT have an operation?

R.4.2 We recommend against performing surgery in patients with an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on imaging studies (⊕⊕ΟΟ).
R.4.3 If surgery is indicated for a benign adrenal mass causing hormone excess (including MACS), we recommend that a **minimally invasive approach** is used (⊕ΟΟΟ). **(New recommendation)**

Emphasis on ‘Expert High Volume Surgeon’ for **ALL** surgical procedures!
Surgical pathway Flow

Unilateral adrenal mass

Radiological suspicion of malignancy?

No

Relevant hormone excess?

No

Yes

No surgery

Minimally invasive adrenalectomy
Surgical pathway Flow

Unilateral adrenal mass

Radiological suspicion of malignancy?

No

Relevant hormone excess?

No

No surgery

Yes

Minimally invasive adrenalectomy

Local invasion?

No

Individualized surgical approach

Yes

Open adrenalectomy

Yes

Diameter ≤ 6cm?
R.4.7 We recommend **perioperative glucocorticoid treatment** at surgical stress doses in all patients undergoing surgery and a preoperative morning serum cortisol $>50 \text{ nmol/L (1.8ugi/dL)}$ after a 1mg overnight dexamethasone test.
R.4.8 We suggest that patients with MACS that underwent surgery should be followed by an endocrinologist until recovery of hypothalamic-pituitary-adrenal axis function has been documented. (New advice)
R.4.8 We suggest that patients with MACS that underwent surgery should be followed by an endocrinologist until recovery of hypothalamic-pituitary-adrenal axis function has been documented. (New advice)

**Why?**

MACS may lead to adrenal insufficiency

Some patients may experience ‘glucocorticoid withdrawal’
Presentation of the four key questions and the respective recommendations:

Follow-up of patients not undergoing adrenal surgery

Antoine Tabarin, France
Follow-Up: Aims

- Malignant transformation?
- Hormonal Hyperactivity?
2016. Systematic review of series including ≈ 2300 patients: only 2 cases of development of malignancy (with ambiguous/unclear characteristics at initial imaging).

R.5.1 **We suggest** against further imaging during follow-up in patients with an adrenal mass < 4cm with clear benign features on imaging studies (⊕ΟΟΟ).
Malignancy: evidence in 2023

- Five additional follow-up studies including 853 patients

- No occurrence of an adrenal malignancy in AI with **benign features** at imaging **regardless of their size**

*Hong AR et al. EJE 2017*
R.5.1 We **recommend against** further imaging during follow-up in patients with an adrenal lesion with clear benign features on imaging studies (⊕⊕⊕⊕). 

The **cutoff** for tumor size of **4 cm** that was included in the recommendation of 2016 is removed.
Follow Up for malignancy: 2023 guidelines

Unenhanced CT

Imaging work-up in patients with adrenal incidentaloma

- Any size, homogenous and HU ≤ 10
  - No further imaging required

- Homogenous and HU 11-20 and tumor < 4 cm
  - Additional imaging:
    - Interval imaging in 12 months (non-contrast CT/MRI)

- Homogenous HU 11-20 and tumor ≥ 4 cm or Homogenous HU > 20 and tumor < 4 cm or Heterogeneous tumors < 4 cm
  - Discuss in MDT meeting and consider proceeding swiftly to additional imaging (or immediate surgery)

- Homogenous HU > 20 or heterogeneous and Tumor ≥ 4 cm
  - Discuss in MDT meeting and consider proceeding swiftly to surgery

Follow-up

- Uncharacterized (continuing indeterminate mass):
  - Interval imaging in 6-12 months (non-contrast CT/MRI)

- In case of no surgery:
  - Interval imaging in 6-12 months (non-contrast CT/MRI)
In patients with an indeterminate adrenal mass by imaging opting not to undergo adrenalectomy following initial assessment, we suggest a repeat non-contrast CT or MRI after 6-12 months to exclude significant growth (⊕OOO).

We suggest surgical resection if the lesion enlarges by more than 20% and ≥5 mm increase in maximum diameter. If there is growth of the lesion below this threshold, additional imaging again after 6-12 months might be performed (⊕OOO).
## Follow Up for hormonal excess

<table>
<thead>
<tr>
<th>2016</th>
<th>2023 FUp in ≥ 3000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldosteronoma (N = 1794)</strong></td>
<td><strong>Aldosteronoma</strong></td>
</tr>
<tr>
<td>0% to 1.6%</td>
<td>0.0% to 1.6%</td>
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<tr>
<td><strong>Pheochromocytoma (N = 2003)</strong></td>
<td><strong>Pheochromocytoma</strong></td>
</tr>
<tr>
<td>0% to 2.6%</td>
<td>0.0% to 2.1%</td>
</tr>
<tr>
<td><strong>Overt hypercortisolism (N = 2225)</strong></td>
<td><strong>Overt hypercortisolism</strong></td>
</tr>
<tr>
<td>0% to 4.2%</td>
<td>0.0% to 0.6%</td>
</tr>
</tbody>
</table>
Follow Up for development of MACS
Follow Up for hormonal excess

2016

- R.5.3. We **suggest against** repeated hormonal work-up in patients with a normal hormonal initial evaluation unless new clinical signs of endocrine activity appear or there is worsening of comorbidities (e.g. hypertension and type 2 diabetes) (⊕ΟΟΟ).

2023  FUp in ≥ 3000 patients

- R.5.3 We **recommend against** repeated hormonal work-up in patients with hormonal work-up results within the reference range at initial evaluation unless new clinical signs of endocrine activity appear or there is worsening of comorbidities (e.g. hypertension, type 2 diabetes) (⊕⊕ΟΟΟ).
Follow Up of non-operated patients with MACS

Reasoning

Very low-risk of developing overt hypercortisolism

R.5.4 We recommend **only annual re-assessment of comorbidities** potentially attributable to cortisol (⊕⊕ΟΟ). For this purpose, we **suggest** that **discharge from specialized endocrine** follow-up be considered and that monitoring of comorbidities … by primary health care providers… (⊕ΟΟΟ). **If these comorbidities develop or worsen, referral to an endocrinologist is suggested** to reassess the endocrine status and reconsider the potential benefit of intervention.
Presentation of the four key questions and the respective recommendations:

Special circumstances

Martin Fassnacht, Germany
Bilateral adrenal incidentalomas

► R.6.1.1 We **recommend** that … **each adrenal lesion** is assessed **individually** … according to the same imaging protocol as for unilateral adrenal masses...

► R.6.1.2 We **recommend** … **clinical and hormonal assessment identical** to that in patients with unilateral adrenal incidentaloma.

Bilateral hyperplasia

Bilateral adenomas

2 similar, non-adenoma lesions

2 different masses
Bilateral hyperplasia or bilateral adenomas

- **Without MACS**: Exclude congenital adrenal hyperplasia: 17-OH progesterone
- **With MACS**: Assess comorbidities
  Treatment has to be individualized
- We suggest **against** bilateral ADX in patients without overt Cushing
Suspected bilateral malignant disease

- R.6.1.6 In patients with bilateral metastases, lymphoma, infiltrative inflammatory disease and hemorrhages, we recommend assessment for adrenal insufficiency.
Adrenal mass and history of extra-adrenal malignancy

Adrenal mass in a patient with extra-adrenal malignancy\(^1\)

Benign radiological features

- Yes
- Relevant hormone excess?
  - Yes
  - Consider individualized treatment
  - No
  - Management as for primary malignancy
- No
- Exclude pheochromocytoma, other test individualized\(^2\)
  - Would the result of pathological assessment alter clinical management?\(^3\)
    - Yes
    - Adrenal biopsy, FDG-PET/CT or resection
    - No
    - Management as for primary malignancy
Adrenal incidentalomas in young or elderly patients

R.6.2.1 We recommend **urgent assessment** of an adrenal mass in pregnant women and individuals < 40 years ... (higher likelihood of malignancy and significant hormone excess).

R.6.2.2 We suggest the use of MRI rather than CT in children, adolescents, and pregnant women.

R.6.2.3 We **suggest surgical resection if an adrenal mass is indeterminate on imaging** in children, adolescents, pregnant women and adults < 40 years of age.

R.6.2.4 We recommend that investigation and management of patients with poor general health and a high degree of frailty be kept in proportion to potential clinical gain.
1) “Second-line imaging methods”
2) Real-world data on steroid profiling
3) Prospective studies on MACS with 'hard' endpoints
4) Randomized studies on the best therapy for MACS
5) Association between MACS and osteoporosis
6) Studies with repeated DST
7) New biomarkers to identify patients with clinically relevant cortisol excess
8) Prospective study on the best surgical approach
9) Long-term study on follow-up
10) Studies on quality of life, mental health, cognition, and frailty
Information for individuals with adrenal incidentalomas

Background
You are recently diagnosed as having an adrenal incidentaloma. The adrenal glands are small, pyramid shaped organs sitting on top of the kidneys (see Figure 1), that produce a variety of hormones. An adrenal incidentaloma is a mass (tumor) in these adrenal glands, incidentally found on radiological imaging which was originally performed for another reason than searching for adrenal disease (for instance, a CT scan of the abdomen, performed to look for appendicitis or causes of back pain). About 2% of adults have an adrenal incidentaloma, increasing to 10% in the elderly, which does not cause relevant health issues in the majority of cases. This patient leaflet is specifically designed to inform you how an adrenal incidentaloma is evaluated and managed based on the current guideline.

Evaluation
Once an adrenal incidentaloma is found, you will be referred to a hormone specialist (endocrinologist), to determine if:
1. The mass is producing any hormones
   The adrenal glands produce a variety of hormones, such as adrenaline, aldosterone, and cortisol. These hormones are involved in several important processes in your body, such as regulation of blood pressure, metabolism, and the immune system, and can also affect your mental health. To assess if the adrenal incidentaloma overproduces one or more of these hormones, your doctor will search for any signs or symptoms of hormonal overproduction and perform blood as well as urine tests if required.
2. The mass is benign or malignant
   Fortunately, over 90% of adrenal incidentalomas are benign (meaning, they are not cancerous). The most reliable first-line imaging method to assess if a mass is benign or malignant is a computed tomography (CT) scan without use of contrast media, which is reviewed by a radiologist. A CT scan combines a series of X-ray images taken from different angles around your body to produce “slices”. Other imaging modalities which can be used are MRI scan (using magnetic fields to make images of your body) and PET scan (using a radioactive drug tracer).
to show both normal and abnormal metabolic activity).

Management
The result of imaging and blood and/or urine tests will usually guide the management of an adrenal incidentaloma. When the adrenal incidentaloma appears to be benign and not producing an excess of hormones, no further investigation or follow-up is needed. In the event the adrenal incidentaloma is producing excess hormone or showing some unusual or concerning features, a discussion by the multidisciplinary team (MDT) is usually needed to agree on the most appropriate approach to deal with the condition. An MDT usually consists of several experts in adrenal tumours, such as an endocrinologist, surgeon, radiologist and specialist nurse. When there is evidence of overproduction of hormones or the mass appears to be malignant, surgical removal of the adrenal gland containing the incidentaloma (called an adrenalectomy) is usually the preferred treatment. Whether or not you will undergo surgery may also be influenced by other individual factors, such as your physical condition or age.

In some cases, a "wait-and-see policy" may be advised: you will need follow-up with your endocrinology team with repeat imaging and/or blood/urine tests. Further management will depend on the results of repeated testing.

Q & A
Q1: I have incidentalomas in both adrenal glands, or multiple incidentalomas in one adrenal gland; does the information in this leaflet apply to me?
A1: Yes, you will undergo the same evaluation of imaging and blood and/or urine tests. However, since the underlying causes may be slightly different from those who have a single, one-sided adrenal incidentaloma, your doctor may consider some additional tests.

Q2: If no surgery is performed, is it helpful/necessary to perform a biopsy to secure the correct diagnosis?
A2: No, a biopsy generally has no role in evaluation of an adrenal mass. It will only be considered under special circumstances, for instance when malignant disease outside of the adrenals is already present, or when there is suspicion of an infectious disease.

Q3: My adrenal incidentaloma causes 'mild autonomous cortisol secretion'. What does this mean?
A3: Cortisol is one of the hormones which can be overproduced by an adrenal incidentaloma. When cortisol overproduction is evident and accompanied by typical features like fat accumulation in the abdominal area, easy bruising or muscle weakness, this is called Cushing's syndrome. When such features are absent, this is called 'mild autonomous cortisol secretion'. This mild overproduction of cortisol can have undesirable effects such as hypertension, type 2 diabetes or bone fragility. Your doctor will carefully examine you for these undesirable effects and if present, discuss appropriate treatment options.

Q4: My adrenal mass was detected during an evaluation due to a malignant disease. Does this mean that my adrenal mass is a metastasis of this other tumour?
A4: No, that doesn't have to be the case – the risk is, amongst others, dependent on the type of underlying malignant disease. If the mass appears benign on a CT scan without intravenous contrast media, a metastasis is unlikely and no further specific imaging of the adrenals is needed. In other cases, additional investigations like a PET scan or biopsy may be considered. In all cases, you and your doctor will discuss which (hormonal) evaluation and management options will fit you best, based on individual factors like the stage of the underlying malignancy and quality of life.

Q5: Where can I get more information and support?
A5: You can find more information through the following website: www.esse-hormones.org/for-patients/patient-advocacy-groups
• Patient leaflets accessible via ESE website:

https://www.ese-hormones.org/