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

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What is the right balance between ignorance and too much diagnostic and therapeutic action?

Current situation

- No international (general accepted) guidelines are available for adrenal incidentalomas
- In addition to reviews by experts there are only few “guideline-like” papers:
  - NIH state of the art conference 2002 (Grumbach et al., Ann Int Med 2003)
  - Consensus statement of the French Society of Endocrinology 2007-2008 (Tabarin et al., Ann Endocrin 2008)
  - Medical Guidelines of the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (Zeiger et al., Endocr Prac 2009)
  - White Paper of the American Clinical Radiologists (ACR) Incidental Findings Committee (Berland et al. J Am Coll Radiol 2010)
  - Italian Association of Clinical Endocrinologist (AME) (Terzolo et al. Eurp J Endocrinol 2011)

Main Aim

- To avoid “over-diagnostics” and “over-treatment” without missing relevant diseases (e.g. adreno-cortical carcinoma, pheochromocytoma etc.)

- “Philosophy”: try to establish at the time of initial detection of an adrenal mass the “final diagnosis”

Definition

- 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.

Adrenal incidentalomas are frequent

- Autopsy and radiological studies suggest a prevalence of clinically unapparent adrenal masses of around 2-3% (range 1.0-10%), which increases with age.

Tumor entity	Median (%)	Range (%)
Series including all patients with an adrenal mass*		
Adenoma	80	33-96
Non-functioning	75	71-84
Autonomously cortisol-secreting	12	1.0-29
Aldosterone-secreting	2.5	1.6-3.3
Pheochromocytoma	7.0	1.5-14
Adrenocortical carcinoma	8.0	1.2-11
Metastasis	5.0	0-18
Surgical series**		
Adenoma	55	49-69
Non-functioning	69	52-75
Cortisol-secreting	10	1.0-15
Aldosterone-secreting	6.0	2.0-7.0
Pheochromocytoma	10	11-23
Adrenocortical carcinoma	11	1.2-12
Myelolipoma	8.0	7.0-15
Cyst	5.0	4.0-22
Ganglioneuroma	4.0	0-8.0
Metastasis	7.0	0-21

Guideline development process

- October 2013: establishment of the guideline group
- 3 face-to-face meetings
  - Dec 2013 Amsterdam
  - Oct 2014 Frankfurt
  - June 2015 Frankfurt
- Multiple telephone conferences + thousands of emails
- Dec ‘15 – Feb ‘16: Review of the guideline draft by members of ESE, ENSAT, other endocrine societies, and 3 international experts (Andre Lacroix, Canada; Radu Mihai, UK; Paul Stewart, UK)
  - Incorporation of 184 comments and suggestions

GRADE approach: Adrenal incidentaloma

- Diagnostic accuracy imaging
  - Cochrane review: 37 studies included
- Biochemical profiles
  - 353 studies, 16 included
  - Biochemical profiles- different clinical risks?
  - Surgery according to biochemical profile?
- Surgery: open vs laparoscopic
  - 377 studies, 9 included
- Optimal follow-up
  - 133 studies read, 11 included

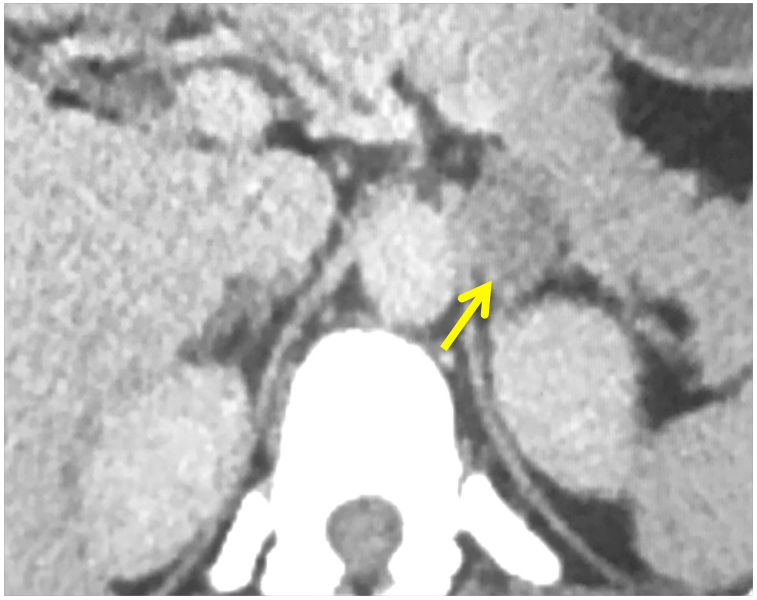
Evidence for adrenal incidentaloma?

- Evidence for all clinical questions: very low

- *No evidence* based on RCTs for
  - Optimal treatment (type of surgery, indication for surgery)
  - Optimal screenings-algorithm
  - Optimal follow-up algorithm

Common Clinical Presentations

Most frequent Clinical presentation: Single phase CT image



Small 1-4cm unilateral homogenous adrenal mass

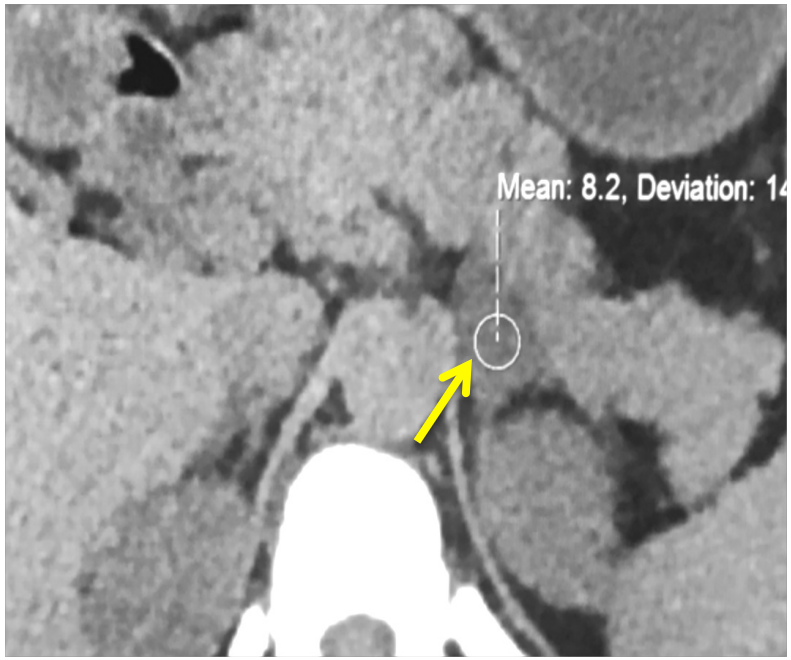
This cannot provide a distinction between benign and malignant lesions and provides no indicator of function

Recommendation 2.1

Aim to establish an adrenal mass as benign or malignant at initial detection => Reduces repeated investigations reducing radiation burden, cost, psychological distress

Recommendation 2.2 and 2.3

- All incidentalomas should undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign.
- For this purpose, we primarily recommend the use of non-contrast CT as the first line imaging investigation.



Homogenous ≤4cm Masses:

↓

Re-image with a Non contrast CT

Non contrast CT value ≤10HU

↓

No further imaging follow up
(70% of incidentalomas)

Rationale

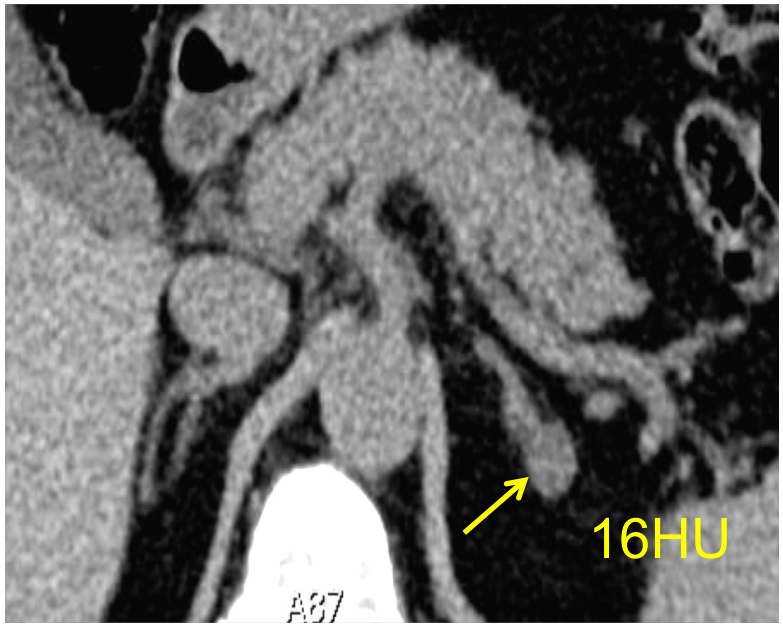
Systematic review and meta-analysis indicated:

- Quality of available studies is lower than expected
- Best data available for non-contrast CT
- In “true incidentalomas”: If Hounsfield Units > 10, sensitivity to detect a malignant tumor: 100 % (95 CI: 91 – 100%)

Dinnes et al. submitted

In addition:

- Low dose techniques can limit radiation exposure
- Cheap and universally available
- Simple, no training requirements



Homogenous Masses:

↓

Re image with a Non contrast CT

↓

Non contrast CT value **>10HU**

MDT discussion

Recommendation 2.4

Depending on the clinical context, 3 options should be considered:

1. Immediate additional imaging with another modality
2. Interval imaging in 6 to 12 months (non-contrast CT or MRI)
3. Surgery without further delay.

Evidence for washout CT, MRI and FDG-PET is all equally weak not permitting a strong individual recommendation in favor of any one modality.

"Poor evidence but good clinical experience"

Other Considerations when selecting second line imaging:

1. Radiation exposure and age
2. Cost and MRI/PET availability with potential diversion of limited resources to a mostly a benign disease
3. Pre test probability of malignancy
4. Local availability and expertise

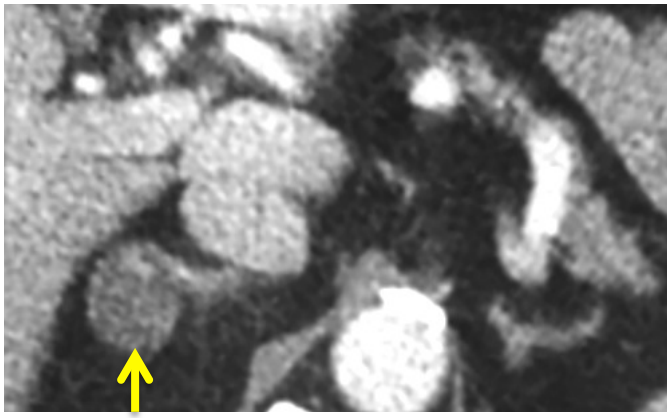
Role of adrenal biopsy

R.2.5 We recommend against adrenal biopsy in the diagnostic work-up unless there is a history of extra-adrenal malignancy and all the following additional criteria are fulfilled:

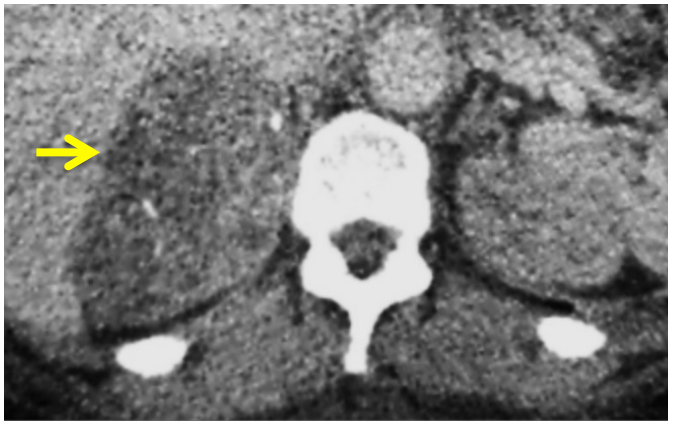
1. Lesion is hormonally inactive (pheochromocytoma has been excluded),
2. Lesion has not been conclusively characterized as benign by diagnostic imaging
3. Management would be altered by the knowledge of histology

Common Clinical Presentations

Heterogeneous adrenal mass: NC-CT, CT contrast washout and MRI should NOT be used to characterize heterogeneous masses



Heterogeneous mass erroneously called an adenoma

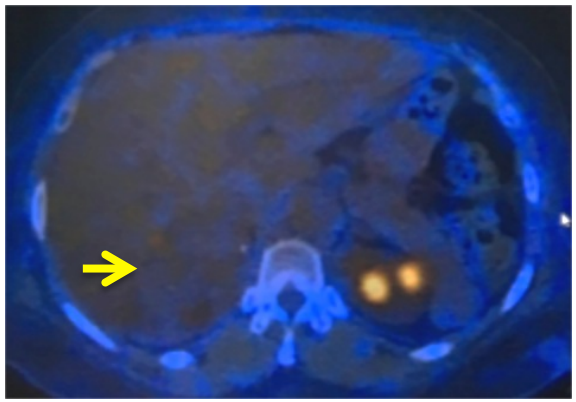


3 years later, ACC on histology, -ve PET

No imaging modality can confirm benignity in a heterogeneous mass irrespective of size

↓

MDT discussion



Multidisciplinary Team Discussion: R 1.1

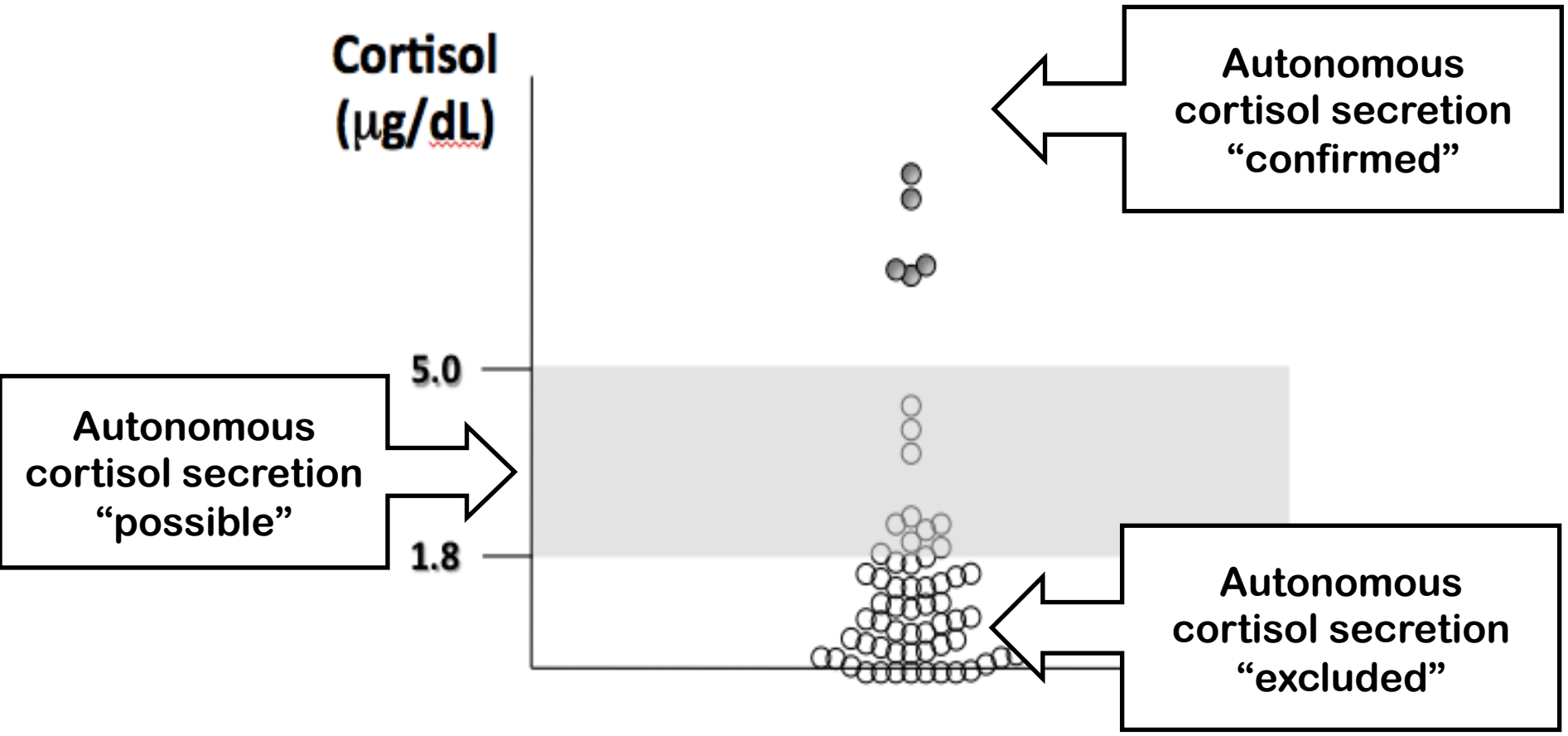
We recommend that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting, if at least one of the following criteria is met

1. Imaging is not conclusive of a benign lesion (indeterminate mass)
2. There is evidence of hormone excess (including ‘autonomous cortisol secretion’)
3. Evidence of significant tumor growth during follow-up imaging
4. Adrenal surgery is considered

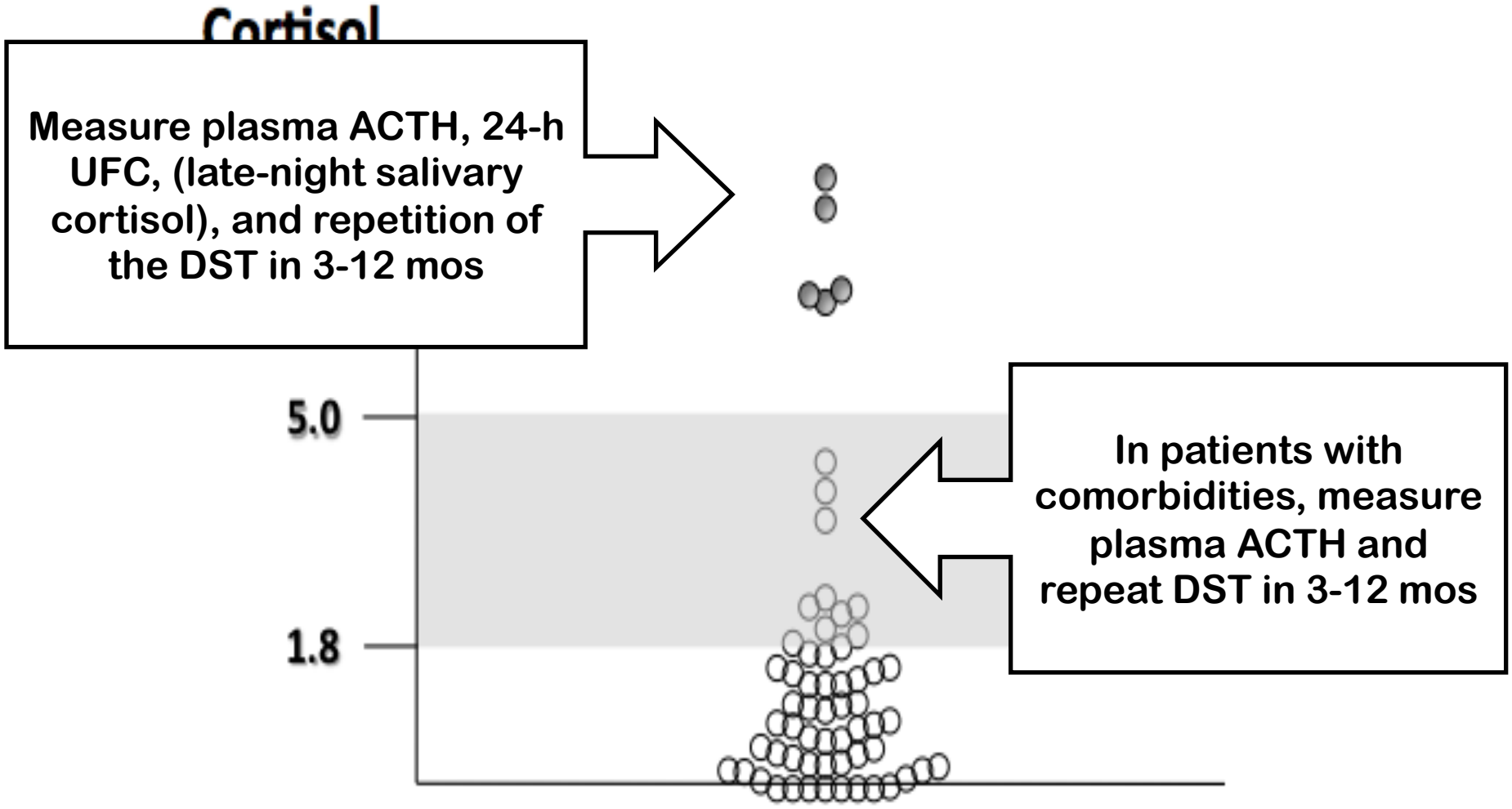
Endocrine work-up (cortisol secretion)

- **The panel the panel unanimously decided to avoid the term "subclinical Cushing's syndrome" and to use instead the term "autonomous cortisol secretion".**
- R.3.2 We recommend that all patients with AI undergo a **1-mg overnight DST** to exclude cortisol excess (XXOO).
- R.3.3 We suggest interpretation of the results of the 1-mg DST as a **continuous rather than categorical (yes/no) variable** (XOOO).

Endocrine work-up: how to interpret DST results



Endocrine work-up

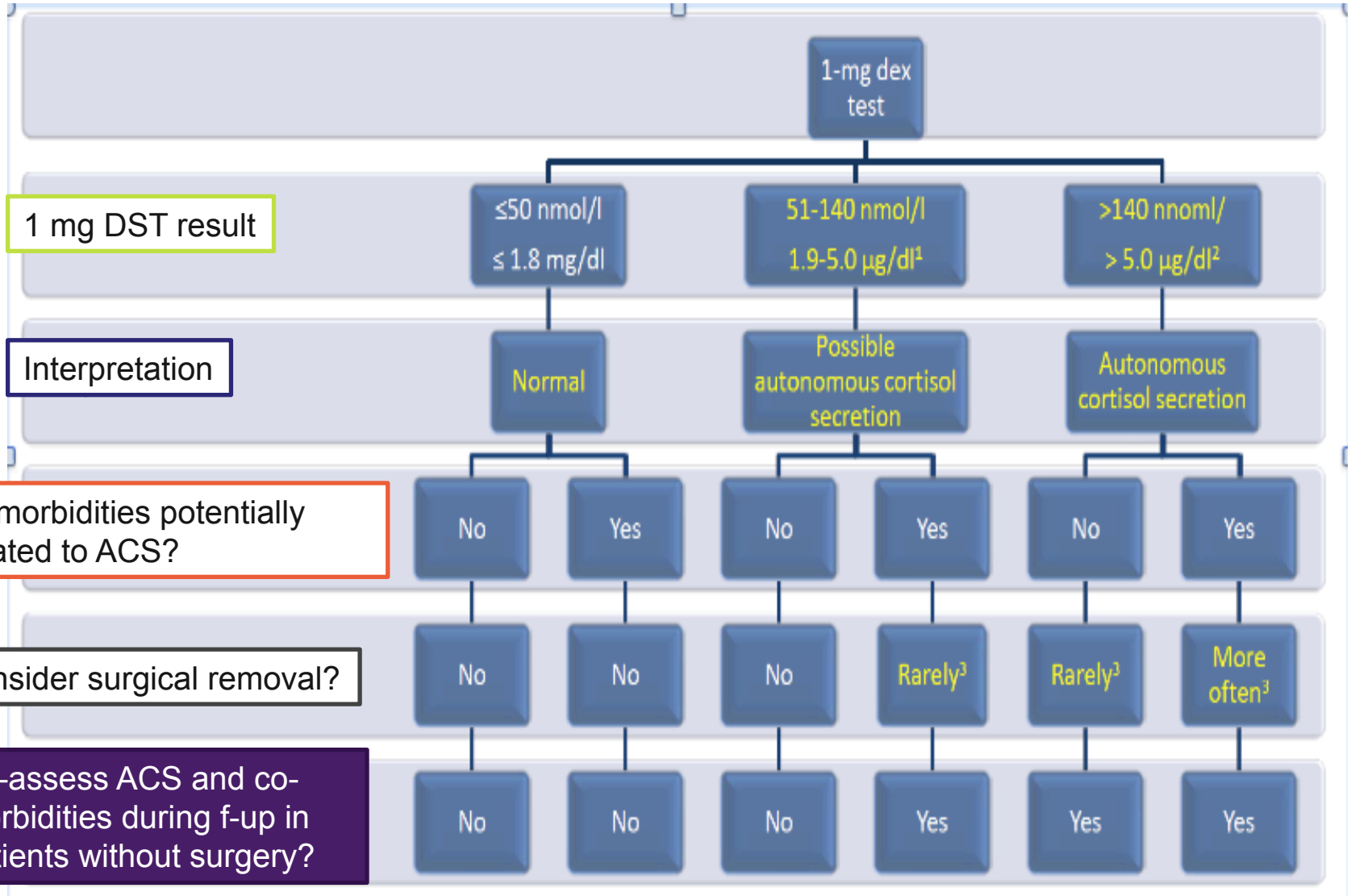


Comorbidities potentially associated with adrenal incidentalomas with "autonomous cortisol secretion"

- Hypertension
- Glucose intolerance or type 2 diabetes mellitus
- Obesity
- Dyslipidemia
- Osteoporosis

For the clinical management, the presence of potentially related comorbidities and age of the patient are of major relevance

Endocrine work-up & management



Endocrine work-up & management

- R.3.8 We suggest an **individualized approach** in patients with “autonomous cortisol secretion” due to a benign adrenal adenoma and comorbidities potentially related to cortisol excess for adrenal surgery (XOOO).
- Age, degree of cortisol excess, general health, comorbidities and patient’s preference should be taken into account.
- In all patients considered for surgery, ACTH-independency of cortisol excess should be confirmed.

Endocrine work-up

- R.3.9 We recommend excluding pheochromocytoma by measurement of **plasma free metanephrines** or **urinary fractionated metanephrines**.
- R.3.10 In patients with concomitant hypertension or unexplained hypokalemia, we recommend the use of the **aldosterone / renin ratio** to exclude primary aldosteronism.
- R.3.11 We suggest measurement of **sex hormones and steroid precursors** in patients with clinical or imaging features suggestive of adrenocortical carcinoma.

Surgery: Central questions

- Which patients / tumors require surgery?
- And when surgery is performed, should it be done as open or minimal invasive (= “laparoscopic”) adrenalectomy?

Surgery - Yes and No ?

- R.4.1 We recommend **adrenalectomy** for unilateral adrenal tumors **with clinically significant hormone excess**.
  - General consensus as indicated by several other guidelines for aldosteronism, Cushing's syndrome and pheochromocytoma

Surgery - Yes and No ?

- R.4.1 We recommend **adrenalectomy** for unilateral adrenal tumors **with clinically significant hormone excess**.
  - General consensus as indicated by several other guidelines for aldosteronism, overt Cushing syndrome and pheochromocytoma
- R.4.2 We recommend **against** surgery for asymptomatic, **non-functioning** unilateral adrenal mass **with obvious benign features** on imaging studies (XOOO).
  - Consensus that this is the best approach for ALL these tumors ≤ 4 cm (= majority of incidentalomas)
  - However, **in tumors > 4cm surgery may be considered**

Unilateral adrenal mass
Radiological suspicion of malignancy?
No
Yes
Relevant hormone excess?
No
Yes
No Surgery
Laparoscopic adrenalectomy

Key question: open or laparoscopic surgery?

- Main threat for patients: adrenocortical carcinoma (ACC)
- Surgery is the most important single therapeutic measure for ACC => high expertise of the surgeon is crucial
- Systematic review for the following question:
  - Should laparoscopic or open surgery be used for patients with non-metastastic adrenal masses suspected to be malignant?

Key question: open or laparoscopic surgery?

- Systematic review:
  - Of 377 abstracts only 9 retrospective studies with ≥ 10 patients per arm could be identified (LA:223 vs. OA 767)
  - Quality of evidence was in general very low (e.g. baseline characteristics were not identical between groups)

⇒No evidence that one of the approaches is superior with regard to time to recurrence and/or survival

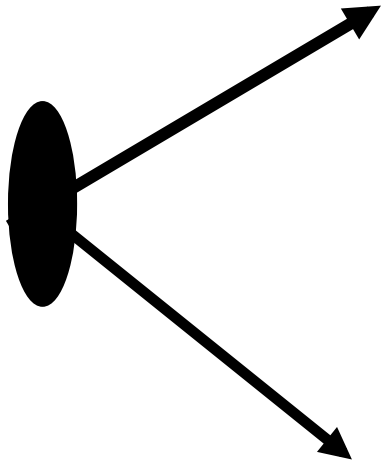
⇒Perioperative morbidity seems to be slightly higher in open adrenalectomy

Key question: open or laparoscopic surgery?

- R.4.3 We suggest **laparoscopic adrenalectomy** for radiologically suspicious masses and a diameter **≤ 6 cm**, but **without** evidence of **local invasion** (XOOO).
- R.4.4 We recommend **open adrenalectomy** for radiologically suspicious masses **and signs of local invasion** (XOOO).
- R.4.5 We suggest an **individualized approach** in patients that do not fall in one of the above- mentioned categories (XOOO).

Unilateral adrenal mass
Radiological suspicion of malignancy?
No
Relevant hormone excess?
Yes
Local invasion ?
No
Yes
Diameter ≤ 6 cm ?
No
Yes
Yes
No
No Surgery
Laparoscopic adrenalectomy
Individualized surgical approach
Open Adrenalectomy

Follow-Up : Aims



Malignant transformation

Hormonal Hyperactivity

Heterogeneity of previous recommendations

	NIH 2003	French Endocr 2008	AACE/AAES 2009	Italian Endocr 2011
CT	6 Mo - 1 y	6 Mo - 2 y - 5 y	3~6 Mo - 1y - 2y	3~6 Mo if > 2 cm
Biology	DST + UMN 1y-2y-3y-4y	DST + UMN 6 Mo 1mg DST 2y-5y	1y-2y-3y-4y-5 y	Mostly clinical Discuss DST

Literature review

- **One systematic review of 14 studies in an „endocrinology setting“** : natural course of **1410 patients** with apparently benign, non functional AI
  - ***Cawood et al. EJE 2009***
- **10 aditional studies:** follow-up of **1131 patients** with apparently benign, non functional AI or mild autonomous cortisol secretion
  - ***Anagnostis (2010), Cho (2013),***
  - ***Comlekci (2010), DiDalmazi (2014),***
  - ***Fagour (2009), Giordano (2010),***
  - ***Kim (2005), Morelli (2014),***
  - ***Muth (2011), Vassilatou (2009)***

Malignancy : evidence

- **Systematic review : a pooled risk of 0.2% (95%CI 0.0 to 0.4) of developing malignancy : in 2 of the 14 included studies, one case of malignancy was found**

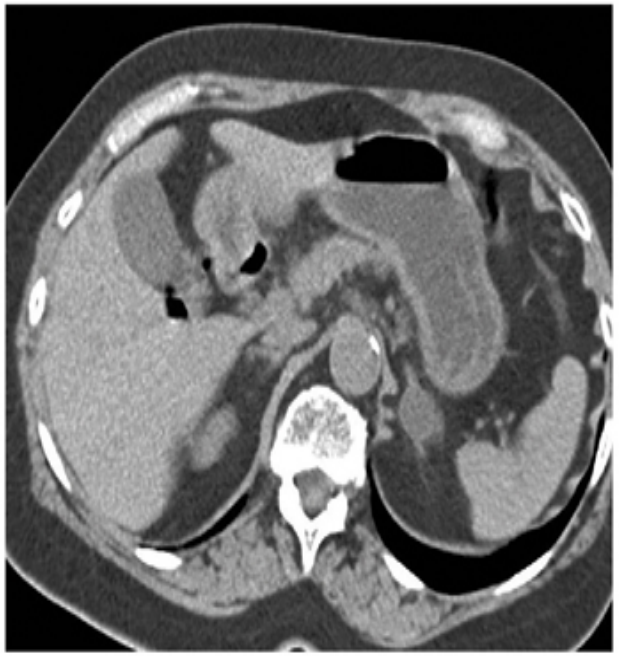
- **Additional observational studies ?**

  No case of malignancy (904 patients)

Malignancy : evidence

- **Malignant transformation of a benign AI towards a *adrenal carcinoma (ACC) ?***

No case described



Malignancy : recommendations

- **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 (XOOO).**

Malignancy : recommendations

- **R.5.2**
  - **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 (XOOO).**
  - ***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.**

Development of hormonal excess : Evidence

Aldosteronoma

- the risk of developing an aldosteronoma : 0% to 1.6%. Weighted **mean risk of 0.06%** (*N = 1794 p*).

Pheochromocytoma

- the risk of developing a pheochromocytoma : 0% to 2.6%. Weighted **mean risk of 0.38%** (*N = 2003 p*).

Development of hormonal excess : Evidence

- **Cushing's syndrome**

  The risk of developing **overt Cushing' syndrome :** 0% to 4.2%. Weighted **mean risk of 0.27%** (*N* = *2225 p*).

- **Autonomous cortisol secretion**

  Occurrence in 8 to 18 % of non-functioning adrenal incidentalomas but ***many caveats***

Development of hormonal excess : recommendations

- 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) (XOOO).
- R.5.4 In patients with autonomous cortisol secretion without signs of overt Cushing's syndrome, *we* *suggest* annual **clinical re-assessment** for cortisol excess and comorbidities potentially related to cortisol excess (XOOO). Based on the outcome of this evaluation the potential benefit of surgery should be considered.

R 1.6 Three main ‘Special Circumstances’

- R1.6.1 - Patients with bilateral incidentaloma
- R1.6.2 - Adrenal incidentaloma in the young or elderly
- R1.6.3 - Patients with a newly diagnosed adrenal mass and a history of extra adrenal malignancy

1.6.2 Adrenal incidentalomas in young or elderly patients

Recommend:

- Urgent assessment in children, adolescents, pregnant women and adults < 40 years of age because of a higher likelihood of malignancy.
- Management of patients with poor general health and a high degree of frailty be kept in proportion to potential clinical gain

Suggest:

- MRI rather than CT in children, adolescents, pregnant women and adults < 40 years of age if dedicated adrenal imaging is required.

R1.6.3 - Patients with a newly diagnosed adrenal mass and a history of extra adrenal malignancy

Recommend

- For indeterminate lesions in patients with a history of extra-adrenal malignancy potential growth of the lesion should be assessed at the same interval as imaging for the primary malignancy. Alternatively, FDG-PET/CT, surgical resection or a biopsy can be considered.

R1.6.3 - Patients with a newly diagnosed adrenal mass and a history of extra adrenal malignancy

Suggest

Biopsy of an adrenal mass only if *ALL* of the following:

- (i) the lesion is hormonally inactive (in particular, a pheochromocytoma has been excluded)
- (ii) the lesion has not been conclusively characterized as benign by imaging
- (iii) management would be altered by knowledge of the histology.

R1.6.3 - Patients with a newly diagnosed adrenal mass and a history of extra adrenal malignancy

Suggest

- FDG-PET/CT, performed as part of investigations for the underlying malignancy, can replace other adrenal imaging techniques

Συμπεράσματα

- Οι κατευθυντήριες οδηγίες των ESE/ENS@T είναι οι πρώτες που παρέχουν με συστηματικό τρόπο συστάσεις βασισμένες σε αποδείξεις (evidence-based)
- Δίνουν έμφαση στην αναγκαιότητα προσέγγισης των ασθενών από ομάδα ειδικών και επιπλέον παρέχουν συστάσεις για ειδικές ομάδες ασθενών.
- Αν και τα δεδομένα βασίζονται σε χαμηλής ποιότητας μελέτες αναμένεται ότι η προσπάθεια αυτή θα αποτελέσει τη βάση για ενσωμάτωση νέων γνώσεων από ποιοτικότερες μελέτες που θα επιτρέψει την δημιουργία εγκυρότερων συστασεων στο μέλλον.