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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Abstract

By definition, an adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease. In most cases, adrenal incidentalomas are non-functioning adrenocortical adenomas, but may also represent conditions requiring therapeutic intervention including adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma or metastasis. The purpose of this guideline is to provide clinicians with guidance on clinical management of patients with adrenal incidentalomas. It was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

We predefined four main clinical questions crucial for the management of adrenal incidentaloma patients, addressing those four with systematic literature searches: A) How to assess risk of malignancy?; B) How to define and manage low level autonomous cortisol secretion, the so-called “subclinical” Cushing syndrome?; C) Who should have surgical treatment and how should it be performed?; D) What follow-up is if the adrenal incidentaloma is not surgically removed?

Selected Recommendations: 1) At the time of initial detection of an adrenal mass it should be established whether the mass is benign or malignant to avoid cumbersome and expensive follow-up imaging. 2) To exclude cortisol excess, a 1-mg overnight dexamethasone suppression test should be performed (applying a cutoff value of serum cortisol ≤ 50 nmol/l (1.8 µg/dl)). 3) For patients without clinical signs of overt Cushing's syndrome but serum cortisol levels post 1mg dexamethasone > 140 nmol/l (> 5 µg/dl) we propose the term ‘autonomous cortisol secretion’. For serum cortisol values between 51 and 140 nmol/l (1.9 - 5.0 µg/dl) we propose the term ‘possible autonomous cortisol secretion’. 4) All patients with ‘(possible) autonomous cortisol’ secretion should be screened for arterial hypertension and type 2 diabetes mellitus, to ensure these are appropriately treated. 5) Surgical treatment should be considered in an individualized approach in patients with 'autonomous cortisol secretion' who also have comorbidities that are potentially related to cortisol excess. The appropriateness of surgical intervention should be guided by the likelihood of malignancy, the degree of cortisol excess, age, general health and patient preference. 6) Surgery is not usually indicated in patients with an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on imaging studies. We provide guidance on which surgical approach should be considered for adrenal masses with radiological findings suspicious of malignancy. Furthermore, we offer recommendations for the follow-up of patients with adrenal incidentaloma who do not undergo adrenal surgery, for those with bilateral incidentalomas, for patients with extra-adrenal malignancy and adrenal masses, and for young and elderly patients.

1. Summary of Recommendations*

1.1 General remarks

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 “autonomous cortisol secretion”).
- Evidence of tumor growth during follow-up imaging.
- Adrenal surgery is considered.

1.2 Assessment of the risk of malignancy

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

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 (XOOO). For this purpose, we primarily recommend the use of non-contrast CT (XOOO).

R.2.3 We suggest that if the non-contrast CT is consistent with a benign adrenal mass < 4 cm no further imaging is required (XOOO).

R.2.4 If the adrenal mass is indeterminate on non-contrast CT and the results of the hormonal work-up do not indicate significant hormone excess, there are three options that should be considered by a multidisciplinary team acknowledging the patient’s clinical context: immediate additional imaging, interval imaging in 6 to 12 months (non-contrast CT (or MRI)), or surgery without further delay.

R.2.5 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 (see R6.4).

1.3 Assessment for hormone excess

R.3.1 We recommend that every patient with an adrenal incidentaloma should undergo careful assessment including clinical examination for symptoms and signs of adrenal hormone excess.

R.3.2 We recommend that all patients with adrenal incidentalomas undergo a 1-mg overnight dexamethasone suppression test to exclude cortisol excess (XXOO).

R.3.3 We suggest interpretation of the results of the 1-mg overnight dexamethasone test as a continuous rather than categorical (yes/no) variable (XOOO). However, we recommend using serum cortisol levels post dexamethasone ≤ 50 nmol/l (≤ 1.8 µg/dl) as a diagnostic criterion for the exclusion of autonomous cortisol secretion (XXOO). We suggest that

* The recommendations are worded as *recommend* (strong recommendation) and *suggest* (weak recommendation). The quality of evidence behind the recommendations is classified as low very low (⊕OOO), low (⊕⊕OO), moderate (⊕⊕⊕O) and strong (⊕⊕⊕⊕). See further Section 3.4.

post dexamethasone serum cortisol levels between 51 and 140 nmol/l (1.9 - 5.0 µg/dl) should be described as evidence of 'possible autonomous cortisol secretion' and cortisol levels post dexamethasone > 140 nmol/l (> 5.0 µg/dl) should be taken as evidence of 'autonomous cortisol secretion'.

R.3.4 We recommend against considering 'autonomous cortisol secretion' as a condition with a high risk for the development of overt Cushing's syndrome (XXOO).

R.3.5 We recommend screening patients with '(possible) autonomous cortisol' secretion for arterial hypertension and type 2 diabetes mellitus (XOOO) and suggest offering appropriate treatment of these conditions.

R.3.6 We suggest screening patients with 'autonomous cortisol secretion' for asymptomatic vertebral fractures (XOOO) and to consider appropriate treatment of these conditions (XOOO).

R.3.7 We suggest an individualized approach to consider 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.

R.3.8 We recommend excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrines unless imaging clearly indicates an adenoma.

R.3.9 In patients with concomitant arterial hypertension, we recommend the use of the aldosterone / renin ratio to detect possible cases of primary aldosteronism.

R.3.10 We suggest measurement of sex hormones and steroid precursors in patients with imaging features suggestive of adrenocortical carcinoma.

1.4 Surgical treatment

R.4.1 We recommend adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess.

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 (XOOO).

R.4.3 We suggest performing laparoscopic adrenalectomy in patients with unilateral adrenal masses with radiological findings suspicious of malignancy and a diameter ≤ 6 cm, but without evidence of local invasion (XOOO).

R.4.4 We recommend performing open adrenalectomy for unilateral adrenal masses with radiological findings suspicious of malignancy 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).

R.4.6 We recommend perioperative glucocorticoid treatment at major surgical stress doses as recommended by guidelines, in all patients undergoing surgery for an adrenal tumor where there is evidence of '(possible) autonomous cortisol secretion'.

1.5 Follow-up of patients not undergoing adrenal surgery after initial assessment

R.5.1 We suggest against further imaging for follow-up in patients with an adrenal mass < 4cm with clear benign features on imaging studies (XOOO).

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% (in addition to at least a 5 mm increase in maximum diameter) during this period.

R.5.3. We suggest against repeated hormonal work-up in patients with a normal hormonal work-up at 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 follow-up re-assessment for cortisol excess and careful assessment of comorbidities potentially related to cortisol excess (XOOO). Based on the outcome of this evaluation the potential benefit of surgery should be considered.

1.6 Special circumstances

1.6.1 Patients with bilateral adrenal incidentalomas

R.6.1.1 We recommend that for patients with bilateral adrenal masses each adrenal lesion is assessed at the time of initial detection according to the same imaging protocol as for unilateral adrenal masses to establish if either or both masses are benign or malignant.

R.6.1.2 We recommend that all patients with bilateral adrenal incidentalomas should undergo clinical and hormonal assessment identical to that in patients with unilateral adrenal incidentaloma. The same applies for the assessment of comorbidities that might be related to autonomous cortisol secretion. In addition, 17-hydroxyprogesterone should be measured to exclude congenital adrenal hyperplasia, and testing for adrenal insufficiency should be considered, if suspected on clinical grounds or if imaging suggests bilateral infiltrative disease or hemorrhages.

R.6.1.3 We suggest that for patients with bilateral incidentaloma the same recommendations regarding the indication for surgery and follow-up are used as for patients with unilateral adrenal incidentalomas.

R.6.1.4 We suggest that in patients with bilateral adrenal masses bilateral adrenalectomy is not performed for ACTH-independent 'autonomous cortisol secretion' without clinical

signs of overt Cushing's syndrome. In selected patients a unilateral adrenalectomy of the dominant lesion might be considered using an individualized approach considering age, degree of cortisol excess, general condition, comorbidities and patient preference.

1.6.2 Adrenal incidentalomas in young or elderly patients

R.6.2.1 We recommend urgent assessment of an adrenal mass in children, adolescents, pregnant women and adults < 40 years of age because of a higher likelihood of malignancy.

R.6.2.2 We suggest the use of MRI rather than CT in children, adolescents, pregnant women and adults < 40 years of age if dedicated adrenal imaging is required.

R.6.2.3 We recommend that the management of patients with poor general health and a high degree of frailty be kept in proportion to potential clinical gain.

1.6.3 Patients with a newly diagnosed adrenal mass and a history of extra-adrenal malignancy

R.6.3.1 We recommend measurement of plasma or urinary metanephrines to exclude pheochromocytoma in patients with extra-adrenal malignancy with an indeterminate mass, even if the adrenal mass is likely to be a metastasis. We suggest additional hormonal work-up based on an individualized approach.

R.6.3.2 We suggest that in patients with a history of extra-adrenal malignancy FDG-PET/CT, performed as part of investigations for the underlying malignancy, can replace other adrenal imaging techniques.

R.6.3.3 We recommend that in patients with a history of extra-adrenal malignancy adrenal lesions characterized as benign by non-contrast CT require no further specific adrenal imaging follow-up.

R.6.3.4 For indeterminate lesions in patients with a history of extra-adrenal malignancy, we recommend imaging follow-up assessing the potential growth of the lesion at the same interval as imaging for the primary malignancy. Alternatively, FDG-PET/CT, surgical resection or a biopsy (see also R6.3.5) can be considered.

R.6.3.5 We suggest performing a biopsy of an adrenal mass only if all of the following criteria are fulfilled: (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, and (iii) management would be altered by knowledge of the histology.

R.6.3.6 We recommend assessment of residual adrenal function in patients with large bilateral metastases.

2. Adrenal Incidentaloma – Clinical presentation and terminology

2.1 Definition, etiology and epidemiology of adrenal incidentalomas

An adrenal incidentaloma is an adrenal mass detected on imaging not performed for suspected adrenal disease. By this strict definition, the imaging study is not done for symptoms related to hormone excess (e.g. pheochromocytoma, Cushing's or Conn's syndrome) or an otherwise suspected adrenal mass, but rather for the evaluation of symptoms that are not obviously related to an adrenal problem, such as abdominal or back pain or kidney stones. In addition, adrenal masses discovered on an imaging study performed during tumor evaluation for extra-adrenal malignancies ("tumor staging" or follow-up) do not meet the strict definition of adrenal incidentaloma. However, as this is a clinically frequent scenario, we will address this in a specific chapter (see 5.6.4).

Previous recommendations and reviews (1-13) have not considered adrenal incidentalomas smaller than 1 cm. Although this cut-off is obviously somewhat arbitrary, we agree with this approach and would perform additional diagnostic work-up only in lesions ≥ 1cm unless clinical signs and symptoms suggestive of adrenal hormone excess are present.

The etiology of adrenal incidentalomas varies and includes benign and malignant lesions derived from the adrenal cortex, the medulla or of extra-adrenal origin. The reported frequency varies, depending on the context of the study and inclusion size criteria (see Table 1). Some authors conclude, however, that the prevalence of malignant and functional lesions is likely to be overestimated (3), mainly because the prevalence of malignancy in surgical series is usually higher than in series including all patients presenting with an adrenal mass. There is, however, clear evidence that the vast majority of adrenal incidentalomas are benign adrenocortical adenomas.

The incidence and prevalence of adrenal incidentalomas can only be extrapolated from imaging or autopsy studies. Autopsy studies suggest a prevalence of clinically unapparent adrenal masses of around 2% (range 1.0-8.7%), which increases with age (5-7). Radiological studies report a frequency of around 3% in the age of 50 years, which increases up to 10% in the elderly (2, 5-7, 14-16). In childhood, adrenal incidentalomas are extremely rare.

Table 1: Adrenal incidentalomas - frequency of the different underlying tumor types (adapted according (9))

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

* Data from references: (2, 6, 14)
** Data from references: (2, 3, 6, 7, 10, 14, 17, 18)

2.2. Remarks on terminology

As already discussed above, the term 'adrenal incidentaloma' can be defined by very restrictive criteria, but is sometimes used in a much broader sense, referring to any adrenal mass. Therefore, in the guidelines we frequently speak of adrenal masses or lesions.

Another term, which is widely used in the literature in the context of adrenal incidentaloma, is ‘subclinical Cushing’s syndrome’ (19). This term aims to define patients with biochemical evidence of cortisol excess, but without specific clinical symptoms of Cushing’s syndrome (mainly the lack of catabolic features, like muscle weakness and skin fragility). There is, however, clear evidence that patients with clinically unapparent cortisol excess very rarely develop Cushing’s syndrome (1, 2, 20-25) and that this condition is different from overt Cushing’s syndrome (including catabolic signs of hypercortisolism like muscle weakness, skin fragility etc.), itself associated with severe morbidity and elevated mortality (26-30). Nevertheless, there is some evidence that this low-grade autonomous cortisol excess might be associated with certain comorbidities (see Table 2). Thus, the panel unanimously decided to avoid the term “subclinical Cushing’s syndrome” and to use instead the term “‘autonomous

cortisol secretion'" in the context of an adrenal incidentaloma throughout the guideline text (for the exact definition see chapter 5.3).

Finally, we wish to address what we mean by the term "laparoscopic adrenalectomy". We recognize that this term is actually reserved for operations that use a transperitoneal approach and should be distinguished from the term retroperitoneoscopic adrenalectomy. However, the term minimally invasive adrenalectomy never gained general acceptance and, therefore, in this guidelines we use the term 'laparoscopic adrenalectomy' to refer to minimally invasive approaches including retroperitoneoscopic surgery.

Table 2: Comorbidities possibly associated with adrenal incidentalomas with 'autonomous cortisol secretion'

Comorbidities	Reference
Arterial hypertension	(23, 31-36)
Glucose intolerance / type 2 diabetes mellitus	(23, 31-39)
Obesity	(23, 31-33)
Dyslipidemia	(23, 31, 32, 36, 40)
Osteoporosis	(35, 38, 41-46)

2.3. Short overview on adrenal imaging

For the differentiation of malignant from benign adrenal tumors, there are three main imaging techniques in current use: computed tomography (CT), magnetic resonanace imaging (MRI), and positron emission tomography with ^{18}F-2-deoxy-D-glucose (mostly combined with CT; FDG-PET/CT). CT and MRI are techniques aiming to maximize sensitivity, making it a usefull tool to exlude an adrenal malignancy (47-50). Conversely, FDG-PET/CT is mainly used for the detection of malignant disease (51-53).

CT has a high spatial and quantitative contrast resolution, which allows assessment of tissue density by measuring X-ray absorption of tissues. This allows calculation of tissue attenuation values, which are measured in Hounsfield units (HU) and quantify X-ray absorption of tissues compared to water, which is conventionally allocated a HU value of 0. For **non-contrast (or 'unenhanced') CT**, 10 HU is the most widely used and accepted threshold attenuation value for the diagnosis of a lipid-rich, benign adrenal adenoma (54). However, on non-contrast CT, up to 30-40% of benign adenomas have an attenuation value of greater than 10 HU and are considered lipid-poor, overlapping in density with malignant lesions and pheochromocytomas, and therefore requiring further work-up (55-57).

Contrast-enhanced washout CT utilizes the unique perfusion pattern of adenomas. Adenomas take up intravenous CT contrast rapidly, but also have a rapid loss of contrast - a phenomenon termed 'contrast enhancement washout'. It is assumed that malignant adrenal lesions usually enhance rapidly but demonstrate a slower washout of contrast medium. This

washout phenomenon can be quantified by 'contrast washout values', which involve lesion attenuation measurements at specific time points acquired in a dedicated adrenal CT: prior to injection of contrast medium (HU_{nativ}), at 60 seconds following injection of contrast medium (HU_{max}) and then at 10 or 15 minutes after contrast injection. This allows calculation of the relative contrast enhancement washout (=100x(HU_{max}-$HU_{10/15min}$)/HU_{max}) and absolute contrast enhancement washout (=100x(HU_{max}-$HU_{10/15min}$)/(HU_{max}-HU_{nativ})). A relative washout > 40% and an absolute washout > 60% is assumed to be suggestive that an adrenal lesion is benign (56, 58-60).

MRI is a non-ionising radiation based imaging modality utilizing weak radio wave signals emitted by body tissues when the body is placed in a strong magnetic field and radio frequency pulses are applied. The major advantages of MRI over CT are its lack of radiation, lack of iodine-based contrast media and its superior tissue contrast resolution. For the differentiation of benign and malignant adrenal masses the MRI technique of **chemical-shift imaging** is used the most (60-65). Chemical shift imaging relies on the fact that, within magnetic fields, protons in water vibrate at a slightly different frequency than protons in lipid. As a result, water and fat protons oscillate in and out of phase with respect to one another. By selecting appropriate sequencing parameters, separate images can be generated with water and fat protons oscillating in-phase or out-of-phase to each other. Adrenal adenomas with a high content of intracellular lipid usually lose signal intensity on out-of-phase images compared to in-phase images, whereas malignant lesions and pheochromocytomas (but also lipid-poor adrenal adenomas) that all lack intracellular lipid remain unchanged (58, 65, 66). Simple visual assessment of signal intensity loss is diagnostic in most cases but quantitative methods may be useful in less clear cut cases. Quantitative analysis can be made using the adrenal-to-spleen signal ratio and the signal intensity index. MR signal intensity units are arbitrary units, unlike CT, and therefore are subject to numerous technical variations.

^{18}F-FDG-PET is a nuclear medicine modality that provides quantitative tomographic images after intravenous injection of a beta-radiation emitting radiotracer (18-Fluorine) used to label 2-deoxy-D-glucose rendering Fluoro-deoxyglucose (^{18}F-FDG)). Both glucose and deoxyglucose enter cells via cell glucose transporters and undergo phosphorylation but while glucose undergoes further enzymatic breakdown, deoxyglucose becomes trapped in intracellular compartments. Cancer cells have an increased requirement for glucose and, therefore, take up more glucose and deoxyglucose than normal cells (67). It must be remembered that ^{18}F-FDG is not a specific marker for cancer cells but a marker only for increased glucose metabolism thus uptake can also be increased in cells with an increased energy requirement due to conditions other than cancer. Quantitative measurement of ^{18}F concentrations within tissues provides the most commonly used clinical measurement index, standard uptake value (SUV), which compares the intensity of uptake of ^{18}F in the adrenal lesion to the average uptake of whole body. SUV values have been utilized to differentiate between benign from malignant adrenal

lesions. FDG-PET has a high sensitivity for detection of metabolic changes but its spatial resolution for anatomical localization is poor. The solution is a hardware fusion between PET and CT (**PET/CT**) allowing simultaneous acquisition of PET and CT data. In clinical practice this involves injecting patients with ^{18}F-FDG tracers at least one hour prior to the start of combined PET/CT. Once post processing is complete, PET and CT data can be viewed separately, side-by-side or as a fused images (68).

2.4. Remarks on the difficulties with hormonal testing

Hormone assessment is crucial in the context of the work-up for an adrenal incidentaloma. However, there are several pitfalls that have to be considered (e.g. daily rhythm, sex-/ age-dependency, limitations of assays, drug interactions). Furthermore, normal ranges vary substantially, depending on the method used, so it is essential to interpret test results in the context of the appropriate reference range. Due to space restrictions we refer to other guidelines that have addressed these issues in more detail (69, 70).

3. Methods

3.1. Guideline working group

This guideline was developed by *The European Society of Endocrinology* (ESE) in collaboration with the European Network for the Study of Adrenal Tumours (ENSAT), supported by CBO (Dutch Institute for health care improvement). The chairs of the working group Martin Fassnacht (clinical) and Olaf Dekkers (methodology) were appointed by the ESE Clinical Committee. The other members were suggested by the chairs and approved by the Clinical Committee of ESE: endocrinologists (Wiebke Arlt (UK), Irina Bancos (USA), John Newell-Price (UK), Antoine Tabarin (France), Massimo Terzolo (Italy), Stylianos Tsagarakis (Greece), a radiologist (Anju Sahdev (UK), and an endocrine surgeon (Henning Dralle (Germany)). Irina Bancos served as representative of the American Endocrine Society. The working group had three in-person meetings (December 2013, October 2014, and June 2015) and communicated by phone and email. Consensus was reached upon discussion; minority positions were taken into account in the rationale behind recommendations. Prior to the process, all participants completed conflict of interest forms.

3.2 Target group

This guideline was developed for healthcare providers of patients with adrenal incidentalomas *ie,* endocrinologists, radiologists, surgeons, and specialists in internal medicine. However, general practitioners might also find the guideline useful, as might our patients. In addition, the guideline document can serve as guidance for patient information leaflets. A draft of the guideline was reviewed by four experts in the field (see “Acknowledgment’ section) and has been submitted for comments by ESE and ENSAT members. All comments and suggestions were then discussed and implemented as appropriate by the panel.

3.3 Aims

The overall purpose of this guideline is to provide clinicians with practical guidance for the management of patients with adrenal incidentalomas.

3.4 Summary of methods used for guideline development

The methods used have been described in more detail previously (71). In short, the guideline used GRADE (Grading of Recommendations Assessment, Development and Evaluation) as a methodological base. The first step was to define clinical question(s) (see section 3.5), the second being a systematic literature search (see Section 3.6). After including relevant articles,

we 1), estimated an average effect for specific outcomes (if possible), and 2), rated the quality of the evidence. The quality of evidence behind the recommendations is classified as low very low (⊕OOO), low (⊕⊕OO), moderate (⊕⊕⊕O) and strong (⊕⊕⊕⊕). Evidence tables are provided in Supplemental file II.

For the recommendations we took into account: 1) quality of the evidence, 2) balance of desirable and undesirable outcomes, 3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc). (72, 73). The recommendations are worded as *recommend* (strong recommendation) and *suggest* (weak recommendation). Formal evidence syntheses were performed and graded only for recommendations addressing our initial questions. Additional recommendations based on good practice were not graded (74). Recommendations were derived from majority consensus of the guideline development committee, but if members had substantive disagreements, this is acknowledged in the manuscript. For transparency, all recommendations provided are accompanied by text explaining why specific recommendations were made.

3.5. Clinical question, eligibility criteria and endpoint definition

At the beginning of the guideline development process, the panel agreed on the four most important clinical questions in the management of patients with adrenal incidentalomas (Table 3), for which a detailed literature search was subsequently performed.

3.6 Description of search and selection of literature

A literature search in electronic medical databases was performed for all four clinical questions separately. Of note, the approach for clinical question 1 (assessment of the risk of malignancy) differed as the search, study selection and also the evidence synthesis was performed in the context of a formal Cochrane Review, which will be published separately from the current guideline. For all four clinical questions details of the yield of the search are shown in Table 3. In summary, we included fifty studies for clinical question 1, twelve studies for clinical question 2a (biochemical profile in adrenal incidentaloma), four studies for clinical question 2b (therapeutic approach in mild glucocorticoid excess), nine studies for clinical question 3 (surgery) and ten studies plus one relevant systematic review for clinical question 4 (follow-up).

419 **Table 3: Overview of the key clinical questions and predefined outcome parameters**

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Clinical Question	Predefined selection criteria and key outcome parameters*	Metrics of the literature search
Question 1) What is the most accurate diagnostic procedure to determine whether an adrenal mass is benign in patients with unilateral or bilateral adrenal mass(es) on imaging with or without history of other malignant lesions?	• Original studies on imaging in patients with incidentally discovered adrenal mass(es), including those undergoing staging for known extra-adrenal malignancy. • Diagnostic Intervention: CT (non-contrast, contrast-enhanced, washout), MRI, FDG PET(CT) • Reference standard: at least 50% of population had imaging-guided follow-up of > 6 months (for benign adrenal tumors), or histology after surgery or biopsy (for benign or malignant adrenal tumors) • Reporting 2x2 contingency table data or at least two indices of diagnostic accuracy (sensitivity, specificity, negative or positive predictive value) and disease prevalence.	• 4796 abstracts[1] • 621 potentially relevant articles • 50 studies included • Excluded articles were not relevant due to inadequate or unclear reference standard, data collection pre-1990, > 30% pheos, sample size < 10, < 50% histology in malignant group, no differentiation of children versus adults
Question 2a) Are certain biochemical profiles (see 4.2.1) associated with an increased cardiovascular, metabolic and fracture risk in patients with adrenal mass(es), in whom endocrine work-up for glucocorticoid excess was performed? **Question 2b)** Should surgery or a conservative/medical approach be recommended in patients with adrenal mass(es) and with defined biochemistry and cardiovascular, metabolic and fracture risk potentially indicative of mild glucocorticoid excess?	• Original studies on patients with adrenal mass(es), in which endocrine work-up for glucocorticoid excess was performed. Studies independently of their respective definition of 'autonomous cortisol secretion' were eligible. • Comparison between patients based on biochemical profiles (including post-dexamethasone serum cortisol level) (question 2a) • Comparison between surgery and conservative approach (question 2b) • Reporting at least one of the crucial outcome: major cardiovascular events or mortality, vertebral fractures, metabolic profile, cardiovascular profile	Question 2a: • 201 abstracts • 23 potentially relevant articles • 12 studies included Question 2b • 152 abstracts • 18 potentially relevant articles • 4 studies included • Excluded articles were not relevant for outcome parameters (n=17), no relevant design (n=4), overlapping populations (n=2), position paper (n=1), poorly defined patient cohort (n=1)

Question 3) Should laparoscopic (=minimally-invasive) or open surgery be used for patients with non-metastastic adrenal masses suspected to be malignant?	• Original studies on adults with suspected non-metastatic adrenocortical carcinoma • Comparison between laparoscopic versus open surgery • Reporting at least one of the crucial outcomes: perioperative morbidity and mortality; completeness of resection; recurrence-free and overall survival; pain or patient satisfaction • Publications with less than 10 patients per study arm were excluded.	• 377 abstracts • 13 potentially relevant articles • 3 excluded due to samples size < 10 patients per arm, 1 excluded as review • 9 studies included
Question 4) What is the optimal follow-up in patients with an apparently benign adrenal incidentaloma in order to detect malignant transformation and/or development of overt hormone excess?	• Original studies on patients with an adrenal mass without hormone excess and no clear evidence of malignant adrenal tumor at time of primary diagnosis • Reporting at least one of the following outcomes: malignancy in the adrenal (any kind); development of clinically relevant overt hormone excess (Cushing's syndrome, pheochromocytoma, primary hyperaldosteronism)	• 133 abstracts • 19 potentially relevant articles • 9 excluded due to overlapping population (n=3), not relevant to question (n=3), not available in full-text (n=2), unclear methods (n=1) • Included: • 1 systematic review of 14 studies • 10 additional cohort studies

** For each question we searched separately for systematic reviews between 2000 and February 2014 in NHS Economic Evaluation Database (NHSEED), Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects. This revealed no relevant systematic review. Then, we searched for original articles in Medline published between 2000 and July 2014 (Question 3), October 2014 (Question 4), November 2014 (Question 2), and August 2015 (Question 1).* [1] *Summary of separately published meta-analysis (Bancos et al., under submission).*

4. Summary and conclusions from systematic literature reviews

4.1 Assessment of the risk of malignancy (Question 1)

The following paragraph represents a summary of a systematic meta-analysis on the use of imaging for differentiating benign from malignant adrenal incidentalomas (Bancos et al., under submission). Studies were considered eligible for inclusion if: 1) Unselected patients with an adrenal mass were studied; 2) Index imaging test characteristics were reported; 3) at least 50% of patients had an optimal reference standard: availability of histological diagnosis in malignant masses and availability of histology or imaging follow up of at least 6 months in the case of benign adrenal masses.

We included fifty cohort studies. No randomized studies comparing imaging tests were identified. Risk of bias ranged from low to high, with the majority having high risk of bias (mainly due to unclear population selection and flow and timing with resulting concerns of the applicability of results).

Adrenal imaging serves as the initial diagnostic tool to distinguish a malignant adrenal mass ('disease positive') from a benign adrenal mass ('disease negative'): In clinical practice, CT and MRI are aiming at diagnosing an adrenal mass as benign. For this purpose, the test should have a high sensitivity, meaning that a negative test result (for example HU ≤ 10) is truly identifying lesions as benign. This situation is the case when sensitivity for an imaging test is 100%, and thus no malignant tumor is wrongly classified as benign. The other side of the coin is that CT and MR imaging are less equipped to diagnose a malignant adrenal mass (as the specificity is not 100%). In contrast, a test specificity of 100% would indicate that no benign tumor would be wrongly diagnosed as malignant. As FDG-PET/CT has a higher specificity than CT and MRI, it is better suited to detect malignant disease

Non-contrast CT

We identified thirteen eligible studies that had evaluated HU cutoff of ≤ 10 (665 lesions) (52, 61, 75-88). Five studies focused exclusively on patients with current or previous extra-adrenal malignancy (61, 75, 76, 82, 87), only 2 studies clearly reported that population studied represented participants with incidentalomas (83, 88), while the rest of the studies did not clearly report participant characteristics. Based on 2 studies performed mainly (> 50%) in participants with incidentaloma (102 lesions), sensitivity of HU > 10 to diagnose a malignant adrenal mass is 100% (95%CI 71-100%) and specificity is 72% (95%CI 55-85%). In patients with history of extra-adrenal malignancy (5 studies; n=168 lesions), sensitivity is 93% (95%CI 79-98%) and specificity is 71% (95%CI 38-91%).

Contrast-enhanced washout CT

We identified six eligible studies (49, 75, 83, 84, 89, 90) reporting CT washout characteristics. Results are difficult to interpret because of inter-study variability in defined diagnostic cut-offs, mostly with regard to the % washout and the time at which the % washout was recorded. In four studies, no information on participant characteristics was provided. Only one study investigated combined CT washout characteristics in incidentaloma population (50 lesions)(83) (absolute washout of > 60% at 5-15 minutes and relative washout of > 40% at 5-15 minutes). Sensitivity of contrast washout characteristics to diagnose a malignant mass was 96% (95%CI 82-100%) and specificity was 95% (95%CI 77-100%). In one small study including only patients with known extra-adrenal malignancy (75) (40 lesions), sensitivity of absolute contrast washout of > 60% at 15 minutes to diagnose a malignant adrenal mass was unexpectedly poor at only 16% (95%CI 3-40%) while specificity was 86% (95%CI 64-97%). In the same study, sensitivity of relative contrast washout cutoff of > 40% at 15 minutes to diagnose a malignant mass was also 16% (95%CI 3-40%) and specificity was 95% (95%CI 76-100%). This was in contrast to other studies were results could not be interpreted appropriately as population selection was not reported.

MRI chemical shift analysis

We identified seventeen studies (61, 82, 91-106) reporting various MRI characteristics in patients with an adrenal mass. However, few were performed in incidentaloma populations. In 3 studies with > 50% participants with incidentaloma (141 lesions) (94, 101, 103), the sensitivity of signal intensity loss between in and out of phase (MRI with chemical shift) to diagnose a malignant adrenal mass was 90% (95%CI 60-98%) and specificity was 83% (95%CI 74-89%) .

FDG PET

We identified thirteen studies (52, 76, 87, 94, 104, 107-114) investigating FDG PET imaging in adrenal masses. Studies investigated mainly either SUV max of adrenal mass and/or SUV ratio of adrenal mass to liver. In two studies (110, 111) investigating patients with incidentalomas (64 lesions), sensitivity of adrenal/liver ratio (ratios of 1.6-1.8) to diagnose a malignant adrenal mass was 100% (CI 95% 78-100%) and specificity was 96% (95%CI 57-100%). Performance of the adrenal/liver ratio (ratios of 1.53-1.8) was lower in extra-adrenal malignancy (2 studies (104, 108), 117 lesions) with a sensitivity of 82% (95%CI 41-97%) and a specificity of 96% (95%CI 76-99%). Five studies investigated the value of SUV max of adrenal lesion (various cutoffs and populations) and demonstrated lower performance in comparison to adrenal/liver ratio (104, 108, 110, 111, 113).

Adrenal biopsy

In addition to the above mentioned systematic meta-analysis (Bancos et al., under submission), we searched the literature for studies on adrenal biopsies and identified 16 studies with a total of 1470 patients undergoing an adrenal biopsy(4, 79, 82, 115-127). Studies had variable population inclusion criteria, reference standards and biopsy techniques. In studies, in which histology was clearly defined (13 studies, 1073 patients), diagnoses were ACC (n=47), metastasis (n= 455), adenomas and other benign adrenal masses (n=389) and pheochromocytoma (n=25), other (n=157). Complication rate (reported only 10 studies) varied between 0-14%. Rate of non-diagnostic biopsies (reported in 14 studies) was 12% (0-73%). None of the studies reported diagnostic performance of adrenal biopsy in adrenocortical carcinoma separately from other malignancies. Performance of adrenal biopsy to diagnose malignancy (mainly metastasis) varied: sensitivity of 73-100%, specificity of 86-100%, negative predictive value of 58-100%, and positive predictive value of 84-100% reflecting heterogeneous approaches, inclusion/exclusion of non-diagnostic biopsies into the calculation of diagnostic performance and, possibly, variable experience with procedure itself.

4.2.1 Assessment of autonomous cortisol secretion (Question 2a)

Studies were eligible for inclusion independent of the definitions used to define autonomous cortisol secretion. Three different hormonal profiles were distinguished to describe autonomous cortisol secretion associated with adrenal adenomas; Profile 1: serum cortisol > 1.8 µg/dl (50 nmol/l) after 1-mg, 2-mg, or 8-mg overnight dexamethasone suppression test, or 2-day low dose dexamethasone test, and ONE of the following additional endocrine alterations: increased 24-h urinary free cortisol (UFC), low plasma ACTH, elevated midnight serum or salivary cortisol; Profile 2: serum cortisol > 3.0 µg/dl (83 nmol/l) after 1-mg overnight dexamethasone test and ONE additional endocrine alteration (same as above); Profile 3: cortisol > 5 µg/dl (140 nmol/l) after 1-mg overnight dexamethasone test as sole criterion. The defined profiles do not fit completely with the specific criteria used in all of the studies included. Virtually all diagnostic algorithms are, however, variations of these profiles.

In total, twelve studies were included: seven cross-sectional studies (38, 42, 43, 45, 128-130) and five cohort studies (40, 46, 131-133). Only two studies are prospective (40, 46). In eight studies, a comparison was made between patients with elevated (group 1) or normal (group 2) cortisol levels after 1-mg dexamethasone test. Two studies used the biochemical profile 1 and four studies used the biochemical profile 2 with a variation since the post-

dexamethasone serum cortisol cutoff was not a mandatory criterion. Three studies identified 3 subgroups of patients (38, 131, 132), normal, intermediate and frankly altered cortisol suppression corresponding to cortisol levels after 1-mg dexamethasone of < 1.8 µg/dl (83 mmol/l), between 1.8 µg/dl to 5.0 µg/dl, and > 5.0 µg/dl (140 nmol/l), respectively.

In the cross-sectional studies, the risk of bias is estimated as high, given the inability to assess causality. For the cohort studies risk of bias ranged from low to high.

Outcome measures

Change in biochemical profile

In three studies no patient progressed to overt Cushing's syndrome during follow-up (40, 132, 133).

Change in metabolic and cardiovascular profile

The risk of type 2 diabetes was higher in patients with impaired cortisol suppression after 1-mg dexamethasone test and increased further during follow-up (38, 132, 133). Also, the risk of hypertension was higher in patients with altered cortisol suppression and increased further with follow-up (38, 128, 130, 133). However, a smaller study did not confirm the increase in diabetes and hypertension with time (40).

Major cardiovascular incidents

In two cohort studies (132, 133), the incidence of cardiovascular events was higher in patients with altered cortisol suppression.

Mortality

Two studies reported on mortality (131, 132) and found an increased mortality risk in patients with higher cortisol levels after 1-mg dexamethasone. However, the results were adjusted for other prognostic factors only in the first study.

Risk of vertebral fractures

Four studies reported a higher prevalence of vertebral fractures (38, 42, 43, 45) in patients with impaired cortisol suppression. In a cohort study (46), the incidence of new vertebral fractures was higher in patients with higher cortisol levels after 1-mg dexamethasone. However, most of the detected vertebral fractures were minor and have questionable clinical impact.

4.2.2. Surgery vs. conservative management in patients with autonomous cortisol secretion (Question 2b)

For question 2b, four studies were included in which surgery was compared to a conservative approach: one randomized controlled trial and three observational studies. The randomized trial (134) reported on patients with autonomous cortisol secretion who underwent surgery (n=23) or were treated by a conservative approach (n=22). The mean follow up was 7.7 years and the results were only a qualitative description of changes in hypertension, diabetes mellitus or dyslipidemia.

Tsuiki et al. included patients with autonomous cortisol secretion and compared a group treated by surgery (n=10) and a group treated conservatively (n=10) (135). Follow up was 7-19 months. Sereg et al. compared surgery (n=43) with a conservative approach (n=70) in patients with non-functioning adenomas (136). Median follow up was 9.1 years (range 5-16). Outcome measures were the number of patients with dyslipidemia, diabetes, or hypertension. The third observational study included both patients with non-functioning adenomas (30 treated by surgery, 37 conservatively treated) and patients with autonomous cortisol secretion (25 treated by surgery and 16 conservatively treated) (44). Outcome measures included: proportion of patients with steady, improved, or worsened blood pressure, fasting glucose or LDL cholesterol.

The quality of evidence from these studies is low to very low, mainly due to confounding factors. Only one study was randomized, and none of the studies reported blinded outcome assessment. Most studies were also downgraded for imprecision, due to low number of patients and / or events.

Outcome measures

Change in metabolic and cardiovascular profiles in patients with non-functioning adenomas

A higher percentage of patients who underwent adrenalectomy showed improvement in fasting glucose, blood pressure and LDL levels compared to patients managed conservatively (44). At variance, another study did not find any difference between patients who underwent adrenalectomy and those who did not (136).

Change in metabolic and cardiovascular profile in patients with autonomous cortisol secretion

In the randomized trial, in 62% of patients with type 2 diabetes mellitus had improved glycemic control after surgery (134), compared to none in the conservative group. The two cohort studies (44, 135) reported an improvement in impaired glucose tolerance in 40% of patients after surgery. In the conservatively treated groups, none of the patients improved.

The cohort studies (44, 135) reported an improvement in hypertension and dyslipidemia in some patients after surgery. In the conservatively managed group, none of the patients improved.

Risk of vertebral fractures

None of the included studies reported on the risk of vertebral fractures.

Major cardiovascular incidents and mortality

None of the included studies reported on the risk of major cardiovascular events or mortality.

4.3 Surgical approach: open vs. minimally-invasive adrenalectomy

Nine observational studies on the surgical treatment of patients with non-metastatic adrenocortical carcinoma were included (137-145). In eight studies data were retrieved from hospital databases or registries, in one study the results were based on a survey (141). Only three studies reported on the subgroups of patients in whom complete resection of the tumor was achieved (139, 141, 145).

The quality of evidence from these observational studies is very low (see Appendix), mainly because patient groups were not comparable at baseline with regard to important prognostic characteristics, such tumor stage or size. Tumor stage was, on average, lower in patients with laparoscopic surgery as compared to open surgery. In few studies (137, 144), treatment effects were adjusted for differences in tumor stage. Mostly, however, only uncorrected estimates of recurrence-free and overall survival were reported. Moreover, most studies had a small sample size with associated imprecision of the estimated effect.

Outcome measures

Perioperative mortality and morbidity

One study reported on perioperative mortality (137). In this study, none of the 152 patients died perioperatively. Three studies reported on intraoperative or postoperative complications (140, 141, 144). Major postoperative complications (according to Clavien-classification score 3-5) occurred in 19.5% of open surgeries and 8.6% of laparoscopic surgeries (RR 0.43 (0.12 to 1.62), but these estimates are imprecise due to low numbers of events. Furthermore, one study (139) reported a significant shorter hospital stay in the laparoscopy group (7 vs. 9 days).

Completeness of resection

In five studies the completeness of resection was reported (137, 138, 140, 142, 144). The pooled estimate of these five studies indicated no difference in complete resection between surgical approaches (RR 0.99 (95% CI 0.83 to 1.17)). The results of these studies, however, were inconsistent, leading to much uncertainty regarding this conclusion.

Recurrence-free and overall survival

Eight studies reported on recurrence after surgery, but differed in the presentation of these data. These studies also provided data on overall or disease-specific survival (137-141, 143-145). There is no evidence that one of the approaches (laparoscopic or open adrenalectomy) is superior with regard to time to recurrence and/or survival in patients with adrenocortical carcinoma. Yet again, however, the studies have significant limitations, inconsistencies and imprecision precluding reliance on this conclusion.

Pain / patient satisfaction

None of the studies reported on pain or patient satisfaction.

4.4 Follow-up

On systematic review of fourteen studies reporting the natural course of 1410 patients with apparently benign, non-functioning adrenal incidentalomas (3) and ten additional cohort studies were included (40, 44, 46, 128, 133, 146-154). The systematic review included studies reporting the follow up of adrenal incidentaloma patients, published between 1980 and 2008, including publications that reported more than 20 patients, and in which the majority were referred to an endocrinologist (excluding oncology series). The additional ten studies, published between 2005 and 2014, included 1131 incidentaloma patients with apparently benign non-functioning tumors or with autonomous cortisol secretion.

The quality of evidence from these studies was judged moderate or low. Selection criteria were often not reported, the duration of follow-up was heterogeneous across studies (medians ranging from 19 to 90 months) and the completeness of follow-up was difficult to assess. Information on the protocol of biochemical or radiological re-evaluation was not always provided. In addition, biological criteria for the development of hormonal excess were heterogeneous across studies.

Outcome measures

Malignancy

The estimated pooled risk for developing malignancy in the systematic review was 0.2% (95%CI 0.0 to 0.4) (3). In two of the 14 cohort studies, one case of malignancy was found: one patient with adrenal non-Hodgkin lymphoma and one patient with renal cancer metastasis. In the first case, the imaging characteristics of the adrenal incidentaloma at the first evaluation were not consistent with benign characteristics and the lymphoma may have been misdiagnosed initially (22). The second case had a history of renal cell carcinoma and it is unclear whether the adrenal mass was found incidentally or during the follow-up the cancer (155). No case of malignancy was reported in the other 904 patients included in the additional observational studies. Importantly, no malignant transformation of a benign incidentaloma was reported in the studies.

Development of clinically overt hormone excess

The risk of developing overt Cushing' syndrome in the individual studies ranged from 0% to 4.2%, with a pooled risk 0.27% (total number of included patients: 2225). The risk of developing an aldosterone-producing adenoma in the individual studies ranged from 0% to 1.6%, with pooled risk of developing an aldosteronoma of 0.06% (total number of included patients: 1794). The risk of developing a pheochromocytoma ranged from 0% to 2.6%, with a pooled risk of 0.38% (total number of included patients: 2003).

5. Recommendations, Rationale for the Recommendations

5.1. General remarks

The main part of these guidelines addresses the management of patients who fulfill the definition of adrenal incidentaloma (section 2.1). In addition, we discuss specific situations separately: bilateral adrenal masses (5.6.1), patients who are young or elderly and frail (5.6.2+3), and adrenal masses detected during evaluation for extra-adrenal malignancy (5.6.4).

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 (Figure 1):

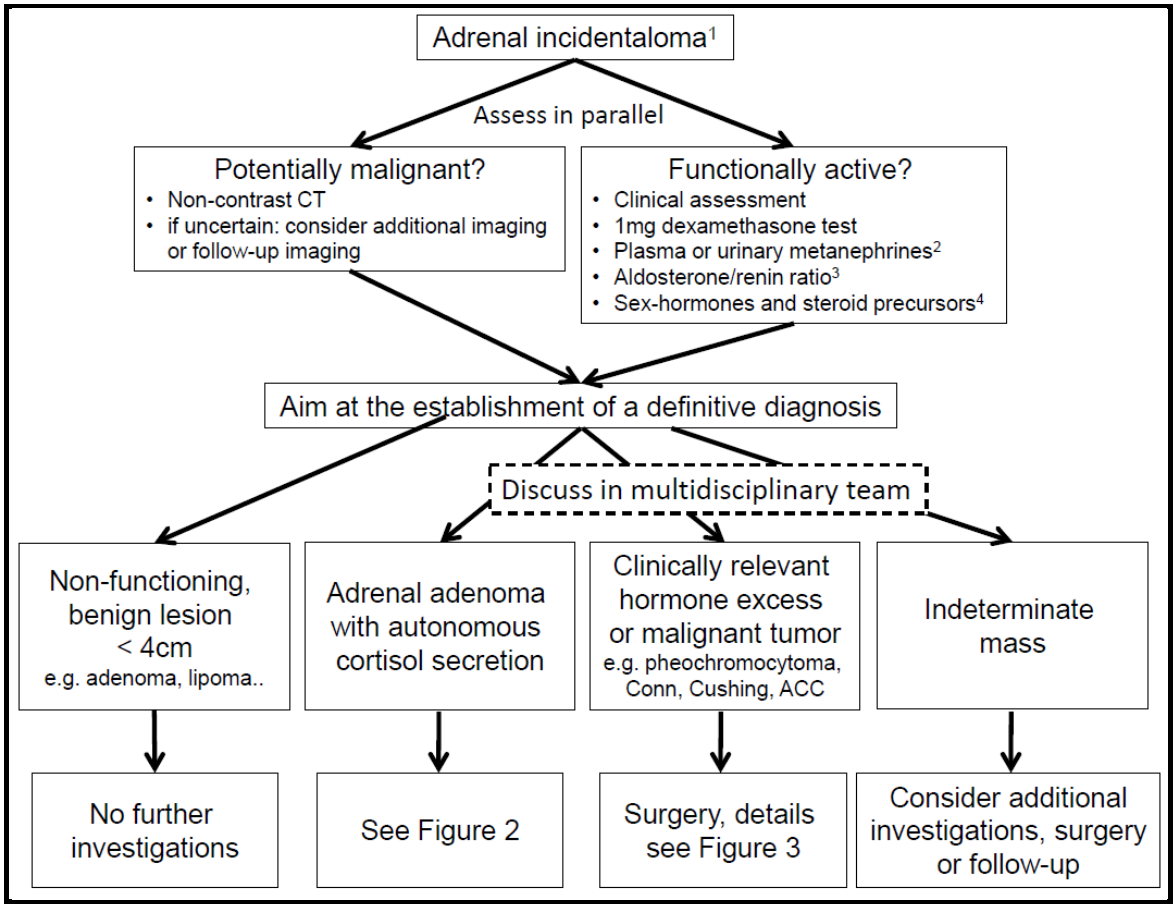
- **Imaging is not consistent with a benign lesion.**
- **There is evidence of hormone excess (including 'autonomous cortisol secretion').**
- **Evidence of tumor growth during follow-up imaging.**
- **Adrenal surgery is considered.**

Reasoning:

Although we believe that the ideal would be for all patients with adrenal incidentalomas to be managed by an expert multidisciplinary team, in many health care settings this is an unrealistic aspiration. Despite lack of compelling evidence, we aimed at identifying subgroups of patients that would be most likely to benefit from multidisciplinary team discussion, and that these discussions occur quickly for patients that meet the criteria above. The core multidisciplinary team should consist of at least a radiologist, an endocrinologist, and a surgeon, all with significant experience in adrenal tumors. Furthermore, this team should have access to anesthetists and an endocrine pathologist, who are experienced in adrenal tumors.

There is sufficient evidence that higher surgical volume correlates with better outcome, however, for the time being no specific numbers of operations per year that result in this favorable outcome can be recommended (138, 156-158).

Figure 1: Flow-chart on the management of patients with adrenal incidentalomas (overview)



[1] For patients with history of extra-adrenal malignancy, see special section 5.6.4
[2] unless imaging clearly indicated an adenoma
[3] only in patients with concomitant arterial hypertension
[4] only in patients with imaging feature suggestive of adrenocortical carcinoma

5.2. Assessment of the risk of malignancy

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

Reasoning

It is critical to know if an adrenal mass is malignant or benign as clinical management is dependent on establishing this fact, regardless of whether the mass is functioning or not. Malignant lesions may need urgent surgical intervention and other therapies, and delay may cause harm.

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 (XOOO). For this purpose, we primarily recommend the use of non-contrast CT (XOOO)

R.2.3 We suggest that if the non-contrast CT is consistent with a benign adrenal mass < 4cm no further imaging is required (XOOO).

Reasoning

In patients with no known extra-adrenal malignancy adrenal incidentalomas are likely to be benign. The non-contrast CT value is reflective of tissue density. Benign lesions including lipid rich adenoma, myelolipoma, fluid-filled homogenous cysts, and other soft tissue tumors (ganglioneuromas, some schwanomas) have low CT density ≤ 10 HU. In our literature search (which included mainly populations at risk, such as oncological patients and patients ultimately undergoing biopsy and / or adrenalectomy) of the 665 lesions, 273 were malignant (of which 88 were ACCs and 158 were metastases) and 392 were benign. In 199 lesions with HU ≤ 10, 10 (5%) were malignant (false positives), 9 representing metastases in patients with known malignancy and one was ACC in a patient presenting with glucocorticoid and androgen excess (NPV of 95%). In 423 lesions with HU > 10, 230 (54%) were benign (PPV 56%), reflective of the poor performance of CT to determine a lesion a malignant with certainty.

Similar to CT, the results of MRI with chemical shift imaging are based on the lipid content of masses (159, 160). Our literature search identified 7 studies with 706 patients that reported results on MRI with chemical shift. Sensitivity and specificity to diagnose a malignant adrenal lesion was 95% and 70%, respectively. However, focusing only on patients with incidentally discovered masses, loss of signal intensity was noted in 74 lesions, 5 of which were malignant (NPV 93%). In 50 lesions where loss of signal intensity was not observed, 18 were benign (PPV of 64%). However, the quantitative assessment of loss of signal intensity is not

well standardized between the different studies and, therefore, the interpretation of the images might be more dependent on the experience of the radiologist than for CT assessment.

However, it should be acknowledged that the Hounsfield units in non-contrast CT and the loss of signal intensity in chemical shift MRI are continuous (rather than categorical) variables.

In conclusion, the panel felt - despite the limited evidence - confident about the negative predictive value of non-contrast CT to recommend that additional imaging was not necessary when benign characteristics were found in an adrenal mass < 4 cm, especially as additional imaging may also risk false positive results and significant psychological and financial burden for patients and the health system, respectively. MRI with chemical shift has an even poorer evidence base with regard to its diagnostic value in excluding malignancy and therefore should be first choice only where a CT is less desirable (pregnancy, children). However, if an MRI with chemical shift is already performed and the results are unambiguous, a multidisciplinary expert team might judge this as sufficient for an individual patient.

R.2.4 If the adrenal mass is indeterminate on non-contrast CT and the results of the hormonal work-up do not indicate significant hormone excess, there are three options that should be considered by a multidisciplinary team considering the patient's clinical context: immediate additional imaging, interval imaging in 6 to 12 months (non-contrast CT (or MRI)), or surgery without further delay.

Reasoning

Evidence of targeted evaluation for "second or third-line" imaging in patients with indeterminate adrenal mass is very poor (see section 4.1 for details). However, the panel considered it important to provide some guidance for daily clinical practice (Table 4), although consensus was not reached other than agreeing that such discussions needed to be individualized and should take place within a multidisciplinary team meeting.

The advantages and limitations of MRI with chemical shift are already discussed at R 2.3.

Contrast washout CT has very limited and low quality evidence from studies (Bancos et al., under submission). Absolute contrast washout of > 60% was noted in 33/38 adrenal adenomas with HU > 10 (48, 89). It should be noted, however, that approximately 5/63 malignant lesions (especially lymphoma and metastases), were falsely characterized as 'benign" on contrast washout CT (48, 89). CT washout is widely available but there is huge

variability in the protocols applied and therefore poor comparability between studies and centers.

FDG-PET/CT has the advantage that the risk of false negative results is quite low, and this refers mainly to a few subtypes of extra-adrenal malignancies with low uptake (e.g. in metastases renal cell cancer or low-grade lymphoma)(161-163). This procedure is, however, more expensive, is not always easily available, and has the disadvantage that several benign adrenal tumors (e.g. functional adenomas or pheochromocytoma) may be FDG-positive (164).

Table 4: Imaging criteria suggesting a benign adrenal mass[1]

Non-contrast CT	**≤ 10 HU**
MRI - chemical shift[2]	Loss of signal intensity on out-phase imaging consistent with lipid-rich adenoma
CT with delayed contrast media washout[2, 3]	Absolute washout > 60% Relative washout > 40%
18F-FDG-PET[2]	Absence of FDG uptake or uptake less than the liver[4]

[1] these criteria applies only for masses with homogenous appearance, or masses that have other clear characteristics consistent with benign disease, e.g. myelolipoma (see text)
[2] Evidence is weak for FDG-PET and MRI with chemical shift and very weak for CT with contrast washout and no comparative studies on "second line imaging" are available.
[3] There is no clear evidence about the best time interval. We recommend 10 or 15 min.
[4] Certain metastasis (e.g. from kidney cancer or low grade lymphoma) may be FDG negative

Whilst the panel was in favor of attempts to fully characterize the adrenal mass on imaging, due to the limitations summarized above, it considered that in patients with indeterminate results on non-contrast CT one of the above discussed imaging methods could be arranged. Although no direct comparison is available the panel clearly judged the published evidence for FDG-PET as better than for the other methods. However, we acknowledge that FDG-PET might be less widely available and more expensive. Alternatively, in patients without a strong suspicion of malignancy and older patients, follow-up imaging 6-12 months after the initial scan could be undertaken. The rationale for a follow-up scan at 6-12 months is based on the principle that either primary adrenal malignancies or adrenal metastases are likely to increase in size over this time period; lack of growth may be taken as an indicator of benign disease in radiologically indeterminate lesions. There are no published size or volume cut-

offs commonly agreed or with evidence base to support that they indicate growth suggestive of malignancy; the expert panel agreed that an increase in > 20% of the largest tumor diameter together with an at least 5 mm increase in this diameter should be considered as suspicious.

R.2.5 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 (see R6.4).

Reasoning

Adrenal biopsy has a limited role in evaluation of adrenal masses – mainly in diagnosis of extra/adrenal malignancy, lymphoma, infiltrative or infectious process. Even in such situations, adrenal biopsy should be performed only by experienced radiologist and when it will help guide further care. We particularly recommend against an adrenal biopsy if an adrenal mass is likely to be an adrenocortical carcinoma, because a biopsy of such a tumor runs the risk of tumor dissemination precluding an R0 resection. The only exception might be if a formal confirmation of the diagnosis is needed in an inoperable tumor to inform oncological management or as part of a clinical trial.

5.3 Assessment for hormone excess

R.3.1 We recommend that every patient with an adrenal incidentaloma should undergo careful assessment including clinical examination for symptoms and signs of adrenal hormone excess.

Reasoning

For the clinical assessment for Cushing's syndrome, primary aldosteronism, and pheochromocytoma, we refer to guidelines of other societies (69, 70, 165).

Rapidly developed hirsutism or virilization is a clinical indicator for an androgen-producing tumor, and should be addressed by measuring testosterone and androgen precursors, whereas recent onset of gynecomastia should trigger measurement of estradiol (166-169) (see also R.3.10).

R.3.2 We recommend that all patients with adrenal incidentalomas undergo a 1-mg overnight dexamethasone suppression test to exclude cortisol excess (XXOO).

R.3.3 We suggest interpretation of the results of the 1-mg overnight dexamethasone test as a continuous rather than categorical (yes/no) variable (XOOO). However, we recommend using serum cortisol levels post dexamethasone ≤ 50 nmol/l (≤ 1.8 µg/dl) as a diagnostic criterion for the exclusion of autonomous cortisol secretion (XXOO). We suggest that post dexamethasone serum cortisol levels between 51 and 140 nmol/l (1.9 - 5.0 µg/dl) should be described as evidence of 'possible autonomous cortisol secretion' and cortisol levels post dexamethasone > 140 nmol/l (> 5.0 µg/dl) should be taken as evidence of 'autonomous cortisol secretion' (Figure 2).

Reasoning

A variety of diagnostic algorithms have been used to exclude cortisol excess or to define so-called 'subclinical hypercortisolism', but in the literature there are no head to head comparisons between tests (or different criteria to define a test positive, or different diagnostic algorithms) to assess their diagnostic performance (see section 4.2.1). Moreover, patient inclusion criteria were heterogeneous across studies adding another source of bias in their comparative assessment. Furthermore, the lack of a definitive clinical phenotype precludes ascertainment of a true positive test.

Nevertheless, the panel recommends the use of the overnight 1-mg dexamethasone test based on pathophysiological reasoning, simplicity, and the fact that the test was incorporated

in the diagnostic algorithms of most studies. It is important to consider drugs or conditions that interfere with this test (see Appendix Table A3).

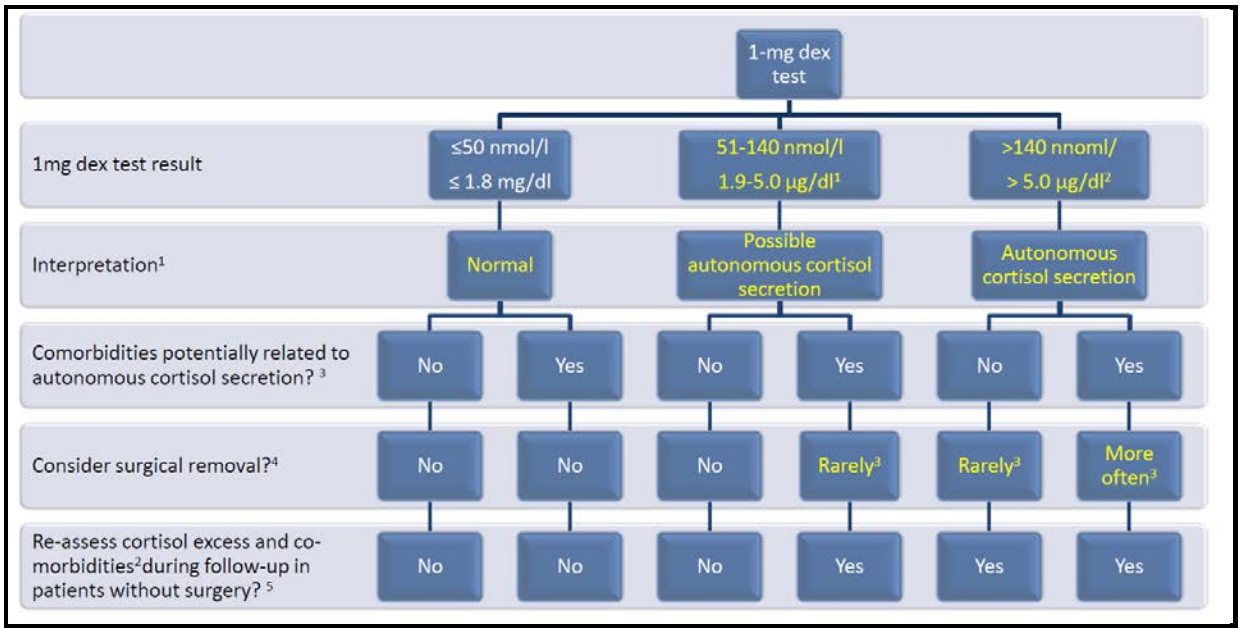
Although the overnight 1-mg dexamethasone test has been the most widely used test in the diagnostic approach in adrenal incidentalomas, there is no consensus on the cutoff value to consider the test as positive. The traditional threshold of 5 µg/dl (140 nmol/l) to define adequate suppression has been proposed by the NIH state-of-the-science conference (5) and the AACE/AAES Medical Guidelines for the management of adrenal incidentalomas (12). However, the French Society of Endocrinology recommended a cutoff at 1.8 µg/dl (50 nmol/l) to increase detection of cortisol excess following the recommendations for screening of overt Cushing's syndrome (8). Specificity is an issue when such post-dexamethasone serum cortisol values are used, with more false-positive test results. Therefore, several studies have used post dexamethasone cortisol values in between these two thresholds and/or required further tests to secure the diagnosis of 'autonomous cortisol secretion'. However, in none of these additional tests was the performance was convincing enough to ultimately decide on diagnostic criteria.

The panel appreciated that this ongoing debate reflects a biological continuum with no clear separation between non-functioning adenomas and functioning adenomas associated with some degree of cortisol excess. Therefore, the panel recommended considering that the probability of clinically relevant cortisol excess increases the higher the post- dexamethasone serum cortisol value. Although there is debate on the precise post- dexamethasone serum cortisol value that indicates cortisol excess, a value of < 1.8 µg/dl (50 nmol/l) may be regarded as normal, excluding cortisol excess. Furthermore, studies have found that patients with post dexamethasone cortisol values > 1.8 µg/dl (50 nmol/l) have an increased morbidity or mortality (131, 132),

Following much debate the panel proposes that the following terminology be used on biochemical grounds, but clearly indicates that for the clinical management the presence of potentially related comorbidities (Table 2) is of major importance (Figure 2). For patients without overt Cushing's syndrome and a serum cortisol post dexamethasone between 51 and 140 nmol/l we propose the term 'possible autonomous cortisol secretion' and for higher values the term "autonomous cortisol secretion".

Furthermore, the majority of panel members (but not all) preferred additional biochemical tests to better judge the degree of cortisol secretion. In patients with 'possible autonomous cortisol secretion' and comorbidities, we suggest measurement of basal morning plasma ACTH and to repeat the dexamethasone test after 3-12 months. In patients with 'autonomous cortisol secretion' we suggest the additional measurement of 24-h urinary free cortisol.

Figure 2: Assessment and management of 'autonomous cortisol secretion' in patients with adrenal incidentalomas



[1] The majority of but not all panel members preferred additional biochemical tests to better judge the degree of cortisol secretion. In patients with comorbidities, we suggest to measure plasma ACTH and to repeat the dexamethasone test in 3-12 months.
[2] We suggest additional biochemical tests to better judge the degree of cortisol secretion: plasma ACTH, 24-h urinary free cortisol and repetition of the dexamethasone test in 3-12 months.
[3] See Table 2 for potentially related comorbidities.
[4] Choice for surgery should always be individualized
[5] Need of follow-up by an endocrinologist

R.3.4 We recommend against considering 'autonomous cortisol secretion' as a condition with a high risk for the development of overt Cushing's syndrome (XXOO).

Reasoning

Studies reporting on follow-up of patients with adrenal incidentalomas have uniformly found a very low percentage (< 1%) of patients with 'autonomous cortisol secretion' progressing to overt Cushing (1-3, 20-25).

R.3.5 We recommend screening patients with '(possible) autonomous cortisol secretion' for arterial hypertension and type 2 diabetes mellitus (XOOO) and suggest offering appropriate treatment of these conditions.

Reasoning

Studies from different research groups have consistently demonstrated an association between cortisol excess and arterial hypertension and hyperglycemia (23, 31-39). The association with dyslipidemia is less proven, although biologically plausible. There is also evidence that patients with cortisol excess are at increased risk of cardiovascular events and excess mortality (131, 132).

Therefore, the panel recommended screening for these conditions, which are well known independent cardiovascular risk factors and which may be driven by cortisol excess, and to treat them according to current guidelines.

R.3.6 We suggest screening patients with 'autonomous cortisol secretion' for asymptomatic vertebral fractures (XOOO) and to consider appropriate treatment of these conditions (XOOO).

Reasoning

Several studies, although mainly from a single research group, have demonstrated an association between autonomous cortisol secretion and an increased risk of vertebral fractures (41-46). Although most of the fractures are asymptomatic, the panel suggests screening patients with 'autonomous cortisol secretion' for vertebral fractures at least once at the time of diagnosis. This may be done by re-evaluating the available images (if a CT was performed), by plain X-ray or bone mineral density (DXA). If osteoporosis is present, active treatment should be considered. If there is no other likely explanation for the osteoporosis, removal of the adrenal adenoma might be considered (see R3.7).

R.3.7 We suggest an individualized approach to consider patients with (possible) '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.

Reasoning

Due to the limitations of current literature, especially the lack of randomized trials, the panel could not reach consensus on the exact indication for surgery for 'autonomous cortisol secretion'. The panel appreciated that there is some evidence of improvement of

hypertension, hyperglycemia and dyslipidemia with surgery but this is based on low quality data. However, no data are available on clinically relevant endpoints (e.g. mortality or major cardiovascular events). Thus, the decision to undertake surgery should be individualized taking into account factors that are linked to surgical outcome, such as patient's age, duration and evolution of comorbidities and their degree of control, and presence and extent of end organ damage. Because it is not possible to be sure that surgical intervention will normalize or improve the clinical phenotype of an individual patient, there was no complete agreement within the panel with regard to the optimal management of these patients. Approaches varied between the two ends of the spectrum. Overall, the group agreed that there is an indication of surgery in a patient with post dexamethasone cortisol > 5 µg/dl and the presence of at least two comorbidities potentially related to cortisol excess (e.g. type 2 diabetes, hypertension, obesity, osteoporosis), of which at least one is poorly controlled by medical measures. Conversely, there is no reason for surgery, when serum cortisol post dexamethasone is < 140 nmol/l and no comorbidities are present. However, some panel members favor a more proactive approach, for example considering surgical intervention, especially in younger patients with 'possible autonomous cortisol' secretion and less comorbidities potentially related to cortisol excess, even if controlled by medical therapy.
However, there was consensus that when surgery is considered due to 'autonomous cortisol secretion', ACTH-independency has to be proven by a suppressed or low basal morning plasma ACTH. If not, other reasons of cortisol excess have to be considered.

R.3.8 We recommend excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrines unless imaging clearly indicates an adenoma.

Reasoning:

For details we refer to the most recent guidelines of other societies (e.g. (70)). However, few retrospective studies suggest that metanephrines may be normal in up to 25% of patients with normotensive incidentally discovered pheochromocytomas (170). Importantly, these clinically silent tumors may be responsible for hemodynamic instability during surgical excision (171). In adrenal lesions with imaging criteria of an adenoma the likelihood of a pheochromocytoma is extremely low (172).

R.3.9 In patients with concomitant arterial hypertension, we recommend the use of the aldosterone / renin ratio to detect possible cases of primary aldosteronism.

Reasoning:

For details we refer to the most recent guidelines of other societies (e.g. (165)).

R.3.10 We suggest measurement of sex hormones and steroid precursors in patients with imaging features suggestive of adrenocortical carcinoma.

Reasoning:

Adrenocortical carcinoma is associated in more than half of cases with elevated sex hormones and steroid precursors (168, 169, 173, 174). The panel does not recommend measurement of these hormones in patients with adrenal incidentalomas on a routine basis, but in cases with indeterminate adrenal mass by imaging, significantly increased sex hormones or precursors might clearly point towards adrenocortical carcinoma. Thus, measurement of serum DHEA-S, androstenedione, 17-OH progesterone as well as testosterone in women and estradiol in men and postmenopausal women can prove the adrenocortical nature of the adrenal mass. However, the panel acknowledges that the published evidence for this suggestion is very low (174, 175). A very promising new tool to discriminate benign from malignant adrenocortical tumors appears the analysis of a comprehensive urinary steroid profile measured by GC-MS or LC-MS (175).

5.4. Surgical treatment

R.4.1 We recommend adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess.

Reasoning:

As covered by several other guidelines, there is consensus that adrenal tumors leading to clinically significant hormone excess (e.g. primary aldosteronism, Cushing syndrome or pheochromocytoma) should be surgically removed (30, 70, 165). The guideline group is convinced that for these tumors the same rules regarding the surgical approach should apply as for endocrine inactive tumors (see below). There are no substantiated reasons why the surgical approach for hormone-producing tumors should differ from that in endocrine inactive tumors (R4.3, R4.4, R4.5).

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 (Table 4) (XOOO).

Reasoning:

Most adrenal incidentalomas are non-functioning benign lesions (e.g. adenomas, myelolipomas) that do not cause harm. Therefore, there is broad consensus that the majority of these adrenal masses do not require surgery. The guideline group defined two criteria that need to be fulfilled to allow characterization of a unilateral adrenal lesion as not harmful: (i) imaging criteria indicating a benign lesion (see section 5.2, Table 4) (ii) no relevant endocrine activity (see section 5.3).

There was considerable discussion by the group if a certain cutoff of size should be a factor to consider surgery. There was consensus that a tumor with a diameter of ≤ 4 cm with benign imaging features does not require surgery, accepting that this size cutoff is arbitrary. However, due to the paucity of follow-up data on the natural history of large apparently benign adrenal incidentalomas the panel was divided on the approach to the management of patients with larger lesions. One approach is to rely on imaging criteria only to determine if a lesion is benign irrespective of size. Alternatively, because of clinician or patient uncertainty about the potential behavior of the adrenal mass, surgery may be considered in lesions > 4 cm even if imaging characteristics suggest a benign nature of the mass, allowing for an individualized approach.

R.4.3 We suggest performing laparoscopic adrenalectomy in patients with unilateral adrenal masses with radiological findings suspicious of malignancy and a diameter ≤ 6 cm, but without evidence of local invasion (XOOO).

R.4.4 We recommend performing open adrenalectomy for unilateral adrenal masses with radiological findings suspicious of malignancy 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).

Reasoning:

The main threat of a unilateral adrenal mass, which is suspected to be malignant, is adrenocortical carcinoma. For adrenocortical carcinoma without metastases, surgery is the most important single therapeutic measure. As summarized above (section 4.1.3) there are nine cohort studies on surgery for localized adrenocortical carcinoma comparing laparoscopic versus open adrenalectomy, each with more than ten patients per group (137-145), but these studies are, however, hampered by methodological flaws, and importantly none was randomized. Nevertheless, based on these data and the clinical experience of the guideline group members, it was judged that laparoscopic adrenalectomy may be justified for tumors with radiological signs of malignancy but only where there was no evidence of local invasion. For this approach the group arbitrarily chose a cut-off size for the adrenal tumor of ≤ 6 cm, because for this size it is believed that laparoscopic adrenalectomy is feasible without rupture of tumor capsule (a major risk factor for recurrence), and where it is beneficial for the patient (e.g. less pain, shorter hospital stay). However, with increasing tumor size risk of tumor capsule rupture may increase. If during surgery there is a risk of tumor capsule rupture conversion to open procedure should be performed. We acknowledge that the cutoff of 6 cm for laparoscopic vs. open adrenalectomy is not based on good evidence from clinical studies, and we recognize that laparoscopic adrenalectomy for tumors < 6 cm is common practice in most centers. However, this cutoff by no means indicates that every tumor smaller than 6 cm has to undergo laparoscopic adrenalectomy and every tumor larger than 6 cm open adrenalectomy. We are convinced that in many cases an individualized decision process is required to find the best surgical approach for a given patient. This is also true for all patients that do not fall in one of the categories described in R.4.2 - 4.4.

There are no sufficiently powered data published on the approach to patients with stage III adrenocortical carcinoma (local invasion, lymph nodes metastases, or tumor thrombus in the

renal vein or vena cava). However, the guideline group unanimously voted for open adrenalectomy as standard procedure for this stage of disease.

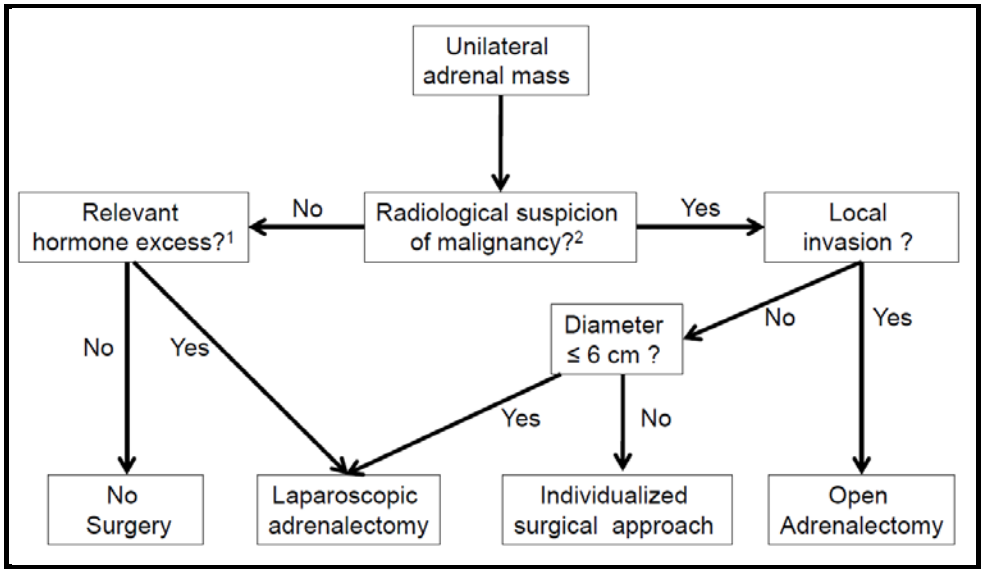
There is weak evidence that locoregional lymph node dissection not only improves the diagnostic accuracy but also the clinical outcome (176). We suggest, therefore, that this procedure is considered in all patients with strong pre- and intraoperative evidence for adrenocortical carcinoma, in particular when local invasion is present.

R.4.6 We recommend perioperative glucocorticoid treatment at major surgical stress doses, as recommended by guidelines, in all patients undergoing surgery for an adrenal tumor where there is evidence of '(possible) autonomous cortisol secretion'.

Reasoning:

Autonomous cortisol may lead to adrenal insufficiency after removal of the adrenal source of cortisol. Therefore, the group unanimously recommends peri- and post-operative glucocorticoid replacement, preferably by hydrocortisone in patients with an adrenal tumor and evidence for '(possible) autonomous cortisol secretion' (post dexamethasone cortisol > 50 nmol/l (> 1.8 µg/dl)) even if there are no clinical sign of cortisol excess. This should follow the suggestions for major stress dose replacement as per a recent international guideline (177). Postoperatively, the glucocorticoid dose should be tapered individually by a physician experienced in this clinical scenario.

Figure 3: Flow-chart on the management of adrenal masses considered for surgery



[1] 'autonomous cortisol secretion' is not automatically judged as clinically relevant (see section 5.3 for details).
[2] in tumors with benign radiological features and a tumor size > 4 cm, surgery might also be individually considered (see text)

5.5. Follow-up of patients not undergoing adrenal surgery after initial assessment

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).

Reasoning

Amongst more than 2300 patients included in published follow-up studies (3, 9) there is no report of occurrence of adrenal malignancy in adrenal incidentalomas displaying typical features of adrenocortical adenomas at initial imaging studies. Therefore, the panel does not support repeating imaging investigations if the initial work-up is unequivocally consistent with a benign lesion. However, many patients with adrenal incidentalomas > 4 cm in diameter have undergone adrenalectomy in the past and the literature on follow-up of non-operated large adrenal incidentalomas is scarce. Thus, and similar to the discussion on the surgical treatment (R.4.2), some panel members argued that one follow-up imaging (non-contrast CT or MRI) after 6-12 months might be considered in lesions > 4 cm.

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% (in addition to at least a 5 mm increase in maximum diameter) during this period.

Reasoning

Contrary to benign adrenal tumors that may exhibit a slow growth tendency with time, malignant adrenal lesions (mostly adrenocortical carcinoma and metastases) are almost invariably characterized by a rapid growth within months (169, 173, 174). Consequently, the panel recommends performing follow-up imaging studies in adrenal incidentaloma, in which the benign nature cannot be established with certainty at initial evaluation, in order to recognize early a rapidly growing mass. Many clinicians would opt for surgical removal if the mass is of larger size and cannot be determined as benign with certainty.

Lack of growth of an adrenal mass over a period of 6-12 months makes a malignant mass highly unlikely while surgery is recommended if significant rapid growth is observed. There is no generally accepted definition of significant growth of an adrenal tumor. However, the panel proposes an adaptation of the RECIST 1.1 criteria (178). These criteria, which are

used in most oncological trials, define progress by an increase of 20% of the largest diameter. Although RECIST 1.1 criteria are not validated for the differentiation between benign and malignant adrenal tumors, the 20% cut-off together with an absolute increase of at least 5 mm in diameter may serve as warning for significant growth and reconsideration then given for surgical excision.

The panel is aware that there are exceptional cases of malignant adrenal tumor without significant growth for several years (179, 180). However, this can be considered a very rare exception and does not justify following all patients with an adrenal mass with repeated imaging over years.

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

Reasoning

The pooled risk of developing clinically relevant hormonal excess (e.g. primary aldosteronism, Cushing's syndrome and pheochromocytoma) is below 0.3% in patients with initial hormonal work-up consistent with a non-functioning lesion (3, 9).

Development of 'autonomous cortisol secretion' without signs of overt Cushing's syndrome is the most frequently reported event during the follow-up and may occur in 8 to 14% of patients with non-functioning adrenal incidentalomas. Owing the risk of false positive results (181) the panel does not recommend systematic follow-up hormonal investigations in patients with non-functioning adrenal incidentalomas at initial evaluation.

R.5.4 In patients with 'autonomous cortisol secretion' without signs of overt Cushing's syndrome (see Figure 2), we suggest annual follow-up with re-assessment for cortisol excess and careful assessment of comorbidities potentially related to cortisol excess (XOOO). Based on the outcome of this evaluation the potential benefit of surgery should be considered.

Reasoning

As discussed above, it is extremely rare that patients will develop overt Cushing's syndrome during follow-up. However, as elaborated in section 5.3, the panel considers 'autonomous cortisol secretion' as a condition associated with several comorbidities (Table 2). Therefore,

the panel recommends annual clinical follow-up in patients with ‘autonomous cortisol secretion’ and in patients with both ‘possible autonomous cortisol secretion’ and potentially associated comorbidities, in whom an initial decision against surgery was made (Figure 2). Clinical follow-up should include evaluation of potentially cortisol excess-related comorbidities. The presence or worsening of these conditions should prompt hormonal re-evaluation at any time during follow-up. Appropriate symptomatic treatment and reconsideration of surgical removal of the adrenal mass is recommended, in line with the observed changes in the clinical and hormonal status of the patient.

In the absence of evidence, we suggest that follow-up by an endocrinologist beyond 2-4 years is not needed in patients with no relevant change during this time.

5.6. Special circumstances

5.6.1. Patients with bilateral adrenal incidentalomas

R.6.1.1 We recommend that for patients with bilateral adrenal masses each adrenal lesion is assessed at the time of initial detection according to the same imaging protocol as for unilateral adrenal masses to establish if either or both lesions are benign or malignant.

Reasoning:

In most cases bilateral adrenal masses represent benign bilateral adrenocortical disease: either bilateral adenomas, macronodular hyperplasia, or distinct bilateral nodules with normal or atrophic cortex intervening. The possibility of metastases (especially in patients with known malignancy), adrenal lymphoma or bilateral pheochromocytomas should also be considered. Moreover, bilateral adrenal masses may represent co-occurrence of different entities, such as adenoma, pheochromocytoma, cyst, myelolipoma, adrenocortical carcinoma, etc. Therefore the best approach is to separately characterize each lesion following the recommendations in R.2.2. and R.2.3 .

R.6.1.2 We recommend that all patients with bilateral adrenal incidentalomas should undergo clinical and hormonal assessment identical to that in patients with unilateral adrenal incidentaloma. The same applies for the assessment of comorbidities that might be related to 'autonomous cortisol secretion' (Table 2). In addition, 17-hydroxy progesterone should be measured to exclude congenital adrenal hyperplasia, and testing for adrenal insufficiency should be considered if suspected on clinical grounds or if imaging suggests bilateral infiltrative disease or hemorrhages.

Reasoning:

Hormonal excess in patients with bilateral adrenal masses may originate either from one of the lesions or bilaterally. Cushing's syndrome, primary aldosteronism, and pheochromocytoma(s) may all be encountered. For the clinical assessment of these entities we refer to guidelines of other societies (69, 70, 165). As for unilateral lesions, subtle autonomous cortisol secretion is the most common secretory abnormality and, therefore, requires a full assessment of related comorbidities. Occasionally, bilateral adrenal enlargement is due to congenital adrenal hyperplasia and therefore the additional

measurement of 17-OH progesterone should be performed (182).However, the measurement of 17-OH progesterone to identify the most common cause of congenital adrenal hyperplasia, 21-hydroxylase deficiency, as the cause of bilateral adrenal hyperplasia should be interpreted with caution. In some cases increased levels of 17-OH progesterone may represent increased secretion of steroid precursors from the lesion(s) (183) especially in malignant tumors or in massive macronodular adrenal hyperplasia. In these cases low/suppressed ACTH levels may argue against congenital adrenal hyperplasia. Bilateral adrenal enlargement due to metastatic disease rarely causes adrenal insufficiency (for details see R.6.3.6).

R.6.1.3 We suggest that for patients with bilateral incidentaloma the same recommendations regarding the indication of surgery and follow-up are used as for patients with unilateral adrenal incidentalomas.

Reasoning:

'Autonomous cortisol secretion' is more frequently encountered in patients with bilateral adrenal incidentalomas, compared to those with unilateral lesions, but there is no published evidence that they should be managed differently. However, in the few cases, in whom bilateral surgery is potentially indicated (e.g. bilateral pheochromocytomas), one should consider adrenal-sparing surgery (184).

R.6.1.4 We suggest that in patients with bilateral adrenal masses bilateral adrenalectomy is not performed for ACTH-independent 'autonomous cortisol secretion' without clinical signs of overt Cushing's syndrome. In selected patients a unilateral adrenalectomy of the dominant lesion might be considered using an individualized approach considering age, degree of cortisol excess, general condition, comorbidities and patient preference.

Reasoning:

Surgery is a complex decision for patients with bilateral adrenal incidentalomas. This is because, in the absence of clinical signs of overt Cushing's syndrome, the clinical situation may not be severe enough to prompt surgical management. Moreover, bilateral adrenalectomy is associated with higher morbidity compared to unilateral surgery, the patient is dependent lifelong on adrenal replacement therapy and at risk for life-threatening adrenal crisis. In addition, glucocorticoid replacement is frequently sub-optimal and cannot mimic the

diurnal profile of endogenous cortisol, and may result in persisting exposure to subtle cortisol excess. In macronodular adrenal hyperplasia there is limited evidence of beneficial effects of unilateral adrenalectomy (185). In most published studies excision of the largest lesion was performed, based on observations that the size of the adrenal lesion correlates with the degree of cortisol excess (185). Adrenal venous sampling may aid in the lateralization of cortisol excess but the data are very weak (186). Due to the limited available evidence, an individualized approach, considering age, degree of cortisol excess, general condition, comorbidity status and patient's preference is suggested. However, when bilateral surgery is potentially indicated, again selective adenomectomy with preservation of the normal cortex might be considered (187).

In cases of bilateral macronodular hyperplasia, especially in younger patients or those with relevant family history, genetic testing (e.g. ARMC5) can be considered (188).

A number of patients will have evidence of the presence of aberrant receptors, but routine assessment by the complex testing (27, 189-195) that is needed to establish the presence of these receptors is hard to justify based on the fact that in the majority of patients long-term management will not be based on knowledge of receptor activity, and therefore we suggest that these tests should be confined to clinical studies.

5.6.2 Adrenal incidentalomas in young or elderly patients

R.6.2.1 We recommend urgent assessment of an adrenal mass in children, adolescents, pregnant women and adults < 40 years of age because of a higher likelihood of malignancy.

R.6.2.2 We suggest the use of MRI rather than CT in children, adolescents, pregnant women and adults < 40 years of age if dedicated adrenal imaging is required.

R.6.2.3 We recommend that the management of patients with poor general health and a high degree of frailty be kept in proportion to potential clinical gain.

Reasoning

The incidence of adrenal incidentaloma shows clear variation with age, with the majority of patients presenting in the 5th to 7th decade of life. Overall incidence of adrenal incidentaloma in a population undergoing routine imaging not related to suspected adrenal disease is reported as 1-4 % (15, 72, 74, 196). While 10 % or more of individuals older than 70 years harbor an adrenal mass detectable upon imaging or autopsy, adrenal nodules in individuals < 40 years are much less prevalent and are a rarity in children and young adults. Consequently, work-up in young patients including pregnant women has to be pursued with urgency as the risk of malignancy in this cohort is much higher. Conversely, a smaller

adrenal incidentaloma in an elderly patient can be assumed to have a very low pre-test probability of malignancy. Thus work-up in elderly patients only needs to be expedited if there are clear signs of suspicion of malignancy and the extent of imaging work-up should be kept in proportion to the clinical performance status of the individual and the expected clinical gain of further work-up in an affected patient.

5.6.3 Patients with a newly diagnosed adrenal mass and a history of extra-adrenal malignancy (Figure 4)

General remarks:

In principle, for adrenal masses in patients with known extra-adrenal malignancy the same recommendations apply as described above. However, in this situation it is particularly important to consider the different pre-test probabilities and the life expectancy of the patient.

In patients with underlying extra-adrenal malignancy and an indeterminate adrenal mass, studies revealed a high rate of malignancy, up to 70%. Although age specific subgroup analysis is not available, it can be assumed that older patients have a higher likelihood of co-existent benign adenomas. Conversely younger patients with an underlying malignancy are more likely to have a metastasis.

R.6.3.1 We recommend measurement of plasma or urinary metanephrines to exclude pheochromocytoma in patients with extra-adrenal malignancy with an indeterminate mass, even if the adrenal mass is likely to be a metastasis. We suggest additional hormonal work-up based on an individualized approach.

Reasoning

Pheochromocytomas are almost impossible to distinguish from metastasis by conventional imaging (including FDG-PET/CT). Furthermore, pheochromocytomas can lead to life-threatening complications, especially in the context of medical interventions (surgery, biopsies etc.) (70, 197, 198). Additional hormonal work-up should depend on the stage of the extra-adrenal malignancy and life expectancy. Evidence of adrenal hormone excess indicating that the mass is a primary adrenal lesion can influence management of the extra-adrenal malignancy.

R.6.3.2 We suggest that in patients with a history of extra-adrenal malignancy FDG-PET/CT, performed as part of investigations for the underlying malignancy, can replace other adrenal imaging techniques.

Reasoning:

^{18}FDG-PETCT can add additional value in the assessment of an indeterminate adrenal mass. Both qualitative and quantitative interpretations of ^{18}FDG-PETCT imaging have been studied, but these vary considerably. An adrenal lesion / liver ratio of 1.53-1.8 were investigated in patients with history of extra-adrenal malignancy (2 studies (104, 108), 117 lesions) and found to have sensitivity of 82% (95%CI 41-97%) and specificity of 96% (95%CI 76-99%).

R.6.3.3 We recommend that in patients with a history of extra-adrenal malignancy adrenal lesions characterized as benign by non-contrast CT require no further specific adrenal imaging follow-up.

Reasoning

See details R2.2-4

R.6.3.4 For indeterminate lesions in patients with a history of extra-adrenal malignancy, we recommend imaging follow-up assessing the potential growth of the lesion at the same interval as imaging for the primary malignancy. Alternatively, FDG-PET/CT, surgical resection or a biopsy (see also R.6.3.5) can be considered.

Reasoning:

In many patients with advanced extra-adrenal malignancy (e.g. with multiple metastases) the knowledge of the origin of the adrenal mass will not alter the clinical management of the patient. If, however, clinical management would be altered by the demonstration that a primary adrenal lesion is a metastasis, then every effort should be made to allow this discrimination. If the adrenal mass is potentially the only metastasis and if resection of single metastasis seems to be reasonable from an oncological point of view, then surgery should be considered. Regarding biopsy, we recommend applying the criteria provided in R.6.3.5.

R.6.3.5 We suggest performing a biopsy of an adrenal mass only if all of the following criteria are fulfilled: (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, and (iii) management would be altered by knowledge of the histology.

Reasoning:

Adrenal biopsy has significant procedural risk. Biopsy is only recommended for masses not characterized as benign on cross-sectional imaging and where a biopsy result would affect clinical treatment decisions. Adrenal biopsy does not have a clinically useful accuracy in distinguishing between adenomas and primary adrenocortical carcinoma and therefore is not recommended in this setting.

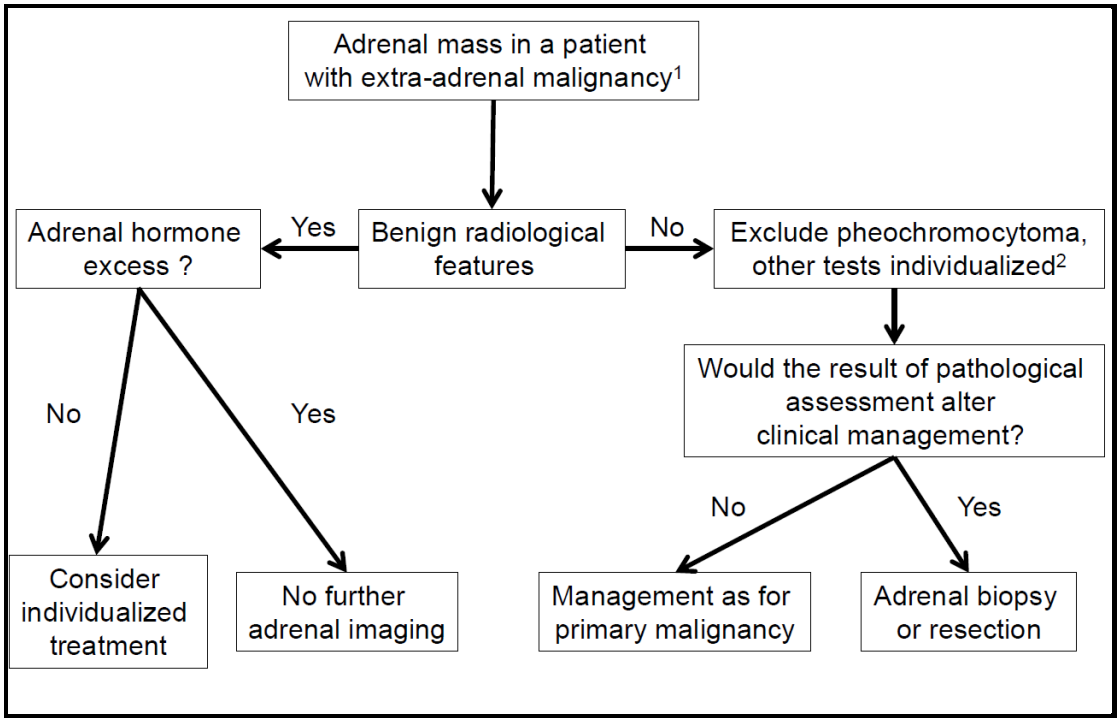
R.6.3.6 We recommend assessment of residual adrenal function in patients with large bilateral metastases.

Reasoning

In rare cases, bilateral adrenal metastases can lead to adrenal insufficiency. Thus, in all patients with potentially bilateral metastases, adrenal insufficiency should be considered and clinically evaluated. If adrenal insufficiency seems to be possible, we recommend first to measure a morning serum cortisol and plasma ACTH. In case of adrenal insufficiency, plasma ACTH is clearly elevated in parallel to low cortisol. In uncertain cases, a synacthen test should be performed (177).

If only one adrenal metastasis is present, adrenal insufficiency is extremely unlikely and we recommend no specific measures.

Figure 4: Evaluation of patients with adrenal mass and known extra-adrenal malignancy



[1] Always take life expectancy in consideration
[2] If there is hormone excess, treat individualized

6. Future directions and recommended research

The NIH conference on the management of the clinically unapparent adrenal mass in 2002 formulated several research questions for future studies (5). Although some of these issues have been addressed, only few questions have been conclusively answered. From the current perspective we see need for clinical trials in all four areas particularly addressed in the guideline (see section 3.5).

Among many important research questions, we selected five as particularly important. All of them can only be answered in a collaborative interdisciplinary manner.

1) Large, cohort study in patients with an adrenal mass > 2 cm to investigate the most suitable imaging methods to determine if an adrenal mass is benign or not. It will be crucial to establish a definitive diagnosis either by histopathology or by long-term follow-up (> 2 years).

2) Large, long-term study to define whether or not ‘autonomous cortisol secretion’ is associated with increased mortality and other hard clinical endpoints (e.g. myocardial infarction or stroke). Such a study will also provide evidence for a suitable biochemical definition of ‘autonomous cortisol secretion’.

3) Randomized trial on the potential benefit of surgery in patients with "autonomous cortisol secretion". To make such a trial feasible it is probably wise to define a surrogate endpoint (e.g. hypertension or type 2 diabetes) that can be well controlled (including standardized treatment regimens) throughout the study. A similar trial could evaluate the value of drugs targeting the cortisol excess.

4) Prospective study (laparoscopic vs. open surgery) in patients with potentially malignant adrenal mass (<10 cm) without pre-operative evidence of local invasion and metastases to learn which surgical approach is the most suitable one for this patient cohort.

5) In addition we propose a long-term study with annual biochemical work-up of patients with adrenal incidentalomas to clarify if such a long-term hormonal assessment is justified.

Several other research questions deserve future research. Of particular importance seems to us the establishment of biomarkers to determine non-invasively the origin of the adrenal mass (adrenal cortex, medulla, extra-adrenal) and whether or not the mass is malignant. Currently, urine steroidobolomics (175) and the combination of functional imaging methods (e.g. metomidate-based imaging and FDG-PET/CT) are the most promising tools that should be further investigated. Similarly, for patients with ‘autonomous cortisol secretion’ new methods to stratify on an individual basis to intervention (or observation) are needed.

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Declaration of interest

The guideline was developed in collaboration with CBO – Dutch Institute for Health Care Improvement.

Appendix

Table A1: Description of analyzed studies

Table A2: Results of the GRADE analyses

Table A3: Selected drugs that may interfere with results of the dexamethasone test* (adapted according (69))

Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Mitotane
Rifapentine
Ethosuximide
Pioglitazone
Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine
Drugs that increase CBG and may falsely elevate cortisol results
Estrogens
Mitotane

- * This should not be considered a complete list of potential drug interactions.
- Data regarding CYP3A4 obtained from http://medicine.iupui.edu/flockhart/table.htm.

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