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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1700250> since 2019-04-29T10:47:36Z

Published version:

DOI:10.1530/EJE-16-0467

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

5
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33 **Abstract**

34 By definition, an adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging
35 not performed for suspected adrenal disease. In most cases, adrenal incidentalomas are non-
36 functioning adrenocortical adenomas, but may also represent conditions requiring therapeutic
37 intervention including adrenocortical carcinoma, pheochromocytoma, hormone-producing
38 adenoma or metastasis. The purpose of this guideline is to provide clinicians with best possible
39 evidence-based recommendations for clinical management of patients with adrenal
40 incidentalomas based on the GRADE (Grading of Recommendations Assessment,
41 Development and Evaluation) system.

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

48 **Selected Recommendations:** 1) At the time of initial detection of an adrenal mass
49 establishing whether the mass is benign or malignant is an important aim to avoid cumbersome
50 and expensive follow-up imaging in those with benign disease. 2) To exclude cortisol excess a
51 1-mg overnight dexamethasone suppression test should be performed (applying a cutoff value
52 of serum cortisol ≤ 50 nmol/l (1.8 $\mu\text{g/dl}$)). 3) For patients without clinical signs of overt Cushing's
53 syndrome but serum cortisol levels post 1mg dexamethasone > 140 nmol/l (> 5 $\mu\text{g/dl}$) we
54 propose the term 'autonomous cortisol secretion'. 4) All patients with '(possible) autonomous
55 cortisol' secretion should be screened for hypertension and type 2 diabetes mellitus, to ensure
56 these are appropriately treated. 5) Surgical treatment should be considered in an individualized
57 approach in patients with 'autonomous cortisol secretion' who also have comorbidities that are
58 potentially related to cortisol excess. 6) In principle, the appropriateness of surgical intervention
59 should be guided by the likelihood of malignancy, the presence and degree of hormone excess,
60 age, general health and patient preference. 7) Surgery is not usually indicated in patients with
61 an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on
62 imaging studies. We provide guidance on which surgical approach should be considered for
63 adrenal masses with radiological findings suspicious of malignancy. Furthermore, we offer
64 recommendations for the follow-up of patients with adrenal incidentaloma who do not undergo
65 adrenal surgery, for those with bilateral incidentalomas, for patients with extra-adrenal
66 malignancy and adrenal masses, and for young and elderly patients with adrenal
67 incidentalomas.

68

69 **1. Summary of Recommendations***

70 **1.1 General remarks**

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

- 73 - Imaging is not consistent with a benign lesion.
- 74 - There is evidence of hormone excess (including “autonomous cortisol secretion”).
- 75 - Evidence of significant tumor growth during follow-up imaging.
- 76 - Adrenal surgery is considered.

77 **1.2 Assessment of the risk of malignancy**

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

80 R.2.2 We recommend that all adrenal incidentalomas undergo an imaging procedure to
81 determine if the mass is homogeneous and lipid-rich and therefore benign (XOOO). For
82 this purpose, we primarily recommend the use of non-contrast CT (XOOO).

83 R.2.3 We suggest that if the non-contrast CT is consistent with a benign adrenal mass
84 (Hounsfield units ≤ 10) that is homogeneous and smaller than 4 cm no further imaging is
85 required (XOOO).

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

91 R.2.5 We recommend against the use of an adrenal biopsy in the diagnostic work-up of
92 patients with adrenal masses unless there is a history of extra-adrenal malignancy and
93 additional criteria are fulfilled (see R6.3.5).

94 **1.3 Assessment for hormone excess**

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

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

100 R.3.3 We suggest interpretation of the results of the 1-mg overnight dexamethasone test as a
101 continuous rather than categorical (yes/no) variable (XOOO). However, we recommend

* 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 (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○) and strong (⊕⊕⊕⊕). See further Section 3.4.

102 using serum cortisol levels post dexamethasone ≤ 50 nmol/l (≤ 1.8 $\mu\text{g/dl}$) as a diagnostic
103 criterion for the exclusion of autonomous cortisol secretion (XXOO).

104 R.3.4 We suggest that post dexamethasone serum cortisol levels between 51 and 140 nmol/l
105 (1.9 - 5.0 $\mu\text{g/dl}$) should be considered as evidence of 'possible autonomous cortisol
106 secretion' and cortisol levels post dexamethasone > 140 nmol/l (> 5.0 $\mu\text{g/dl}$) should be
107 taken as evidence of 'autonomous cortisol secretion'. Additional biochemical tests to
108 confirm cortisol secretory autonomy and assess the degree of cortisol secretion might
109 be required. However, for the clinical management the presence of potentially cortisol-
110 related comorbidities and age of the patient are of major importance.

111 R.3.5 We recommend against considering 'autonomous cortisol secretion' as a condition with
112 a high risk for the development of overt Cushing's syndrome (XXOO).

113 R.3.6 We recommend screening patients with 'possible autonomous cortisol secretion' or
114 'autonomous cortisol secretion' for hypertension and type 2 diabetes mellitus (XOOO)
115 and suggest offering appropriate treatment of these conditions.

116 R.3.7 We suggest screening patients with 'autonomous cortisol secretion' for asymptomatic
117 vertebral fractures (XOOO) and to consider appropriate treatment of these conditions
118 (XOOO).

119 R.3.8 We suggest an individualized approach to consider patients with 'autonomous cortisol
120 secretion' due to a benign adrenal adenoma and comorbidities potentially related to
121 cortisol excess for adrenal surgery (XOOO). Age, degree of cortisol excess, general
122 health, comorbidities and patient's preference should be taken into account. In all
123 patients considered for surgery, ACTH-independency of cortisol excess should be
124 confirmed.

125 R.3.9 We recommend excluding pheochromocytoma by measurement of plasma free
126 metanephrines or urinary fractionated metanephrines.

127 R.3.10 In patients with concomitant hypertension or unexplained hypokalemia, we recommend
128 the use of the aldosterone / renin ratio to exclude primary aldosteronism.

129 R.3.11 We suggest measurement of sex hormones and steroid precursors in patients with
130 clinical or imaging features suggestive of adrenocortical carcinoma.

131 **1.4 Surgical treatment**

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

134 R.4.2 We recommend against performing surgery in patients with an asymptomatic, non-
135 functioning unilateral adrenal mass and obvious benign features on imaging studies
136 (XOOO).

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

140 R.4.4 We recommend performing open adrenalectomy for unilateral adrenal masses with
141 radiological findings suspicious of malignancy and signs of local invasion (XOOO).

142 R.4.5 We suggest an individualized approach in patients that do not fall in one of the above-
143 mentioned categories (XOOO).

144 R.4.6 We recommend perioperative glucocorticoid treatment at major surgical stress doses as
145 recommended by guidelines, in all patients undergoing surgery for an adrenal tumor
146 where there is evidence of '(possible) autonomous cortisol secretion', i.e. who do not
147 suppress to <50 nmol/L after 1mg dexamethasone overnight.

148 **1.5 Follow-up of patients not undergoing adrenal surgery after initial** 149 **assessment**

150 R.5.1 We suggest against further imaging for follow-up in patients with an adrenal mass <
151 4cm with clear benign features on imaging studies (XOOO).

152 R.5.2 In patients with an indeterminate adrenal mass (by imaging) opting not to undergo
153 adrenalectomy following initial assessment, we suggest a repeat non-contrast CT or
154 MRI after 6-12 months to exclude significant growth (XOOO). We suggest surgical
155 resection if the lesion enlarges by more than 20% (in addition to at least a 5 mm
156 increase in maximum diameter) during this period. If there is growth of the lesion below
157 this threshold, additional imaging after 6-12 months should be performed.

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

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

165 **1.6 Special circumstances**

166 **1.6.1 Patients with bilateral adrenal incidentalomas**

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

171 R.6.1.2 We recommend that all patients with bilateral adrenal incidentalomas should undergo
172 clinical and hormonal assessment identical to that in patients with unilateral adrenal
173 incidentaloma. The same applies for the assessment of comorbidities that might be
174 related to autonomous cortisol secretion. In addition, 17-hydroxyprogesterone should
175 be measured to exclude congenital adrenal hyperplasia, and testing for adrenal

176 insufficiency should be considered, if suspected on clinical grounds or if imaging
177 suggests bilateral infiltrative disease or hemorrhages.

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

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

187 **1.6.2 Adrenal incidentalomas in young or elderly patients**

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

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

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

195 **1.6.3 Patients with a newly diagnosed adrenal mass and a history of extra- 196 adrenal malignancy**

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

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

204 R.6.3.3 We recommend that in patients with a history of extra-adrenal malignancy adrenal
205 lesions characterized as benign (see also R.2.3) by non-contrast CT require no further
206 specific adrenal imaging follow-up.

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

211 R.6.3.5 We suggest performing a biopsy of an adrenal mass only if all of the following criteria
212 are fulfilled: (i) the lesion is hormonally inactive (in particular, a pheochromocytoma

213 has been excluded), (ii) the lesion has not been conclusively characterized as benign
214 by imaging, and (iii) management would be altered by knowledge of the histology.
215 R.6.3.6 We recommend assessment of residual adrenal function in patients with large bilateral
216 adrenal metastases.

217 **2. Adrenal Incidentaloma – Clinical presentation and terminology**

218 **2.1 Definition, etiology and epidemiology of adrenal incidentalomas**

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

229 Previous recommendations and reviews {Barzon, 1999 #112;Barzon, 2003 #38;Cawood, 2009
230 #35;Favia, 2000 #114;Grumbach, 2003 #39;Kloos, 1995 #36;Mansmann, 2004 #40;Tabarin,
231 2008 #59;Terzolo, 2011 #33;Young, 2007 #43;Zeiger, 2009 #57;Zeiger, 2009 #58;Young, 2000
232 #147} have not considered adrenal incidentalomas smaller than 1 cm. Although this cut-off is
233 obviously somewhat arbitrary, we agree with this approach and would perform additional
234 diagnostic work-up only in lesions ≥ 1 cm unless clinical signs and symptoms suggestive of
235 adrenal hormone excess are present.

236 The etiology of adrenal incidentalomas varies and includes benign and malignant lesions
237 derived from the adrenal cortex, the medulla or of extra-adrenal origin. The reported frequency
238 varies, depending on the context of the study and inclusion size criteria (see Table 1). Some
239 authors conclude, however, that the prevalence of malignant and functional lesions is likely to
240 be overestimated {Cawood, 2009 #35}, mainly because the prevalence of malignancy in
241 surgical series is usually higher than in series including all patients presenting with an adrenal
242 mass. There is, however, clear evidence that the vast majority of adrenal incidentalomas are
243 benign adrenocortical adenomas.

244
245 The incidence and prevalence of adrenal incidentalomas can only be extrapolated from imaging
246 or autopsy studies. Autopsy studies suggest a prevalence of clinically unapparent adrenal
247 masses of around 2% (range 1.0-8.7%), which increases with age {Kloos, 1995
248 #36;Mansmann, 2004 #40;Grumbach, 2003 #39}. Radiological studies report a frequency of
249 around 3% in the age of 50 years, which increases up to 10% in the elderly {Kloos, 1995
250 #36;Mansmann, 2004 #40;Grumbach, 2003 #39;Barzon, 2003 #38;Mantero, 2000 #37;Bovio,
251 2006 #45;Benitah, 2005 #44}. In childhood, adrenal incidentalomas are extremely rare.

252 **Table 1: Adrenal incidentalomas - frequency of the different underlying tumor**
 253 **types (adapted according {Terzolo, 2011 #33})**
 254

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

255
 256 * Data from references: {Barzon, 2003 #38; Kloos, 1995 #36; Mantero, 2000 #37}
 257 ** Data from references: {Barzon, 2003 #38; Kloos, 1995 #36; Mantero, 2000 #37; Bernini, 2002
 258 #41; Cawood, 2009 #35; Lam, 2002 #42; Mansmann, 2004 #40; Young, 2007 #43}
 259 Due to the nature of these studies a selection bias is very probable (the populations studied not reflecting
 260 a random sample of all patients with an adrenal incidentalomas) and most likely leads to an
 261 overestimation of the frequency of some tumor entities.
 262

263 2.2. Remarks on terminology

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

267 Another term, which is widely used in the literature in the context of adrenal incidentaloma, is
 268 'subclinical Cushing's syndrome' {Ross, 1994 #131}. This term aims to define patients with
 269 biochemical evidence of cortisol excess, but without the so-called "specific" clinical signs of
 270 Cushing's syndrome (mainly the lack of catabolic features, like myopathy and skin fragility).
 271 There is, however, clear evidence that patients with clinically unapparent cortisol excess very
 272 rarely develop Cushing's syndrome {Barzon, 1999 #112; Barzon, 2003 #38; Bernini, 2005
 273 #137; Fagour, 2009 #136; Libe, 2002 #123; Terzolo, 2005 #135; Terzolo, 1998 #134; Nieman,
 274 2015 #142} and that this condition is different from overt Cushing's syndrome, which is clearly
 275 associated with severe morbidity and elevated mortality {Dekkers, 2013 #130; Lacroix, 2015

276 #140;Neychev, 2015 #141;Nieman, 2015 #139;Nieman, 2015 #138}. Nevertheless, there is
 277 some evidence that this low-grade autonomous cortisol excess might be associated with
 278 certain comorbidities (see Table 2). Thus, the panel unanimously decided to avoid the term
 279 “subclinical Cushing’s syndrome” and to use instead the term ““autonomous cortisol secretion””
 280 in the context of an adrenal incidentaloma throughout the guideline text (for the exact definition
 281 see chapter 5.3).

282 Although the term “laparoscopic adrenalectomy” is actually reserved for operations that use a
 283 transperitoneal approach and should be distinguished from the term retroperitoneoscopic
 284 adrenalectomy, this never gained general acceptance. Therefore, in this guideline we use the
 285 term “laparoscopic adrenalectomy” to refer to minimally invasive approaches including
 286 retroperitoneoscopic surgery.

287

288 **Table 2: Comorbidities possibly associated with adrenal incidentalomas with**
 289 **‘autonomous cortisol secretion’**

Comorbidities	Reference
Hypertension	{Terzolo, 2005 #146;Terzolo, 2005 #135;Tauchmanova, 2002 #143;Emral, 2003 #144;Bernini, 2003 #164;Morelli, 2010 #163;Rossi, 2000 #162}
Glucose intolerance / type 2 diabetes mellitus	{Terzolo, 2005 #146;Terzolo, 2005 #135;Tauchmanova, 2002 #143;Emral, 2003 #144;Reincke, 1996 #166;Bernini, 2003 #164;Di Dalmazi, 2012 #12;Fernandez-Real, 1998 #165;Morelli, 2010 #163;Rossi, 2000 #162}
Obesity	{Terzolo, 2005 #146;Terzolo, 2005 #135;Tauchmanova, 2002 #143;Emral, 2003 #144}
Dyslipidemia	{Terzolo, 2005 #146;Terzolo, 2005 #135;Tauchmanova, 2002 #143;Giordano, 2010 #6;Rossi, 2000 #162}
Osteoporosis	{Hadjidakis, 2003 #145;Chiodini, 2004 #18;Chiodini, 2009 #53;Chiodini, 2010}

290

291

292 **2.3. Short overview on adrenal imaging**

293 For the differentiation of malignant from benign adrenal tumors, there are three main imaging
294 techniques in current use: computed tomography (CT), magnetic resonance imaging (MRI),
295 and positron emission tomography with ¹⁸F-2-deoxy-D-glucose (mostly combined with CT;
296 FDG-PET/CT). CT and MRI are techniques mainly aiming to identify benign lesions, therefore
297 representing tools designed for the exclusion of adrenal malignancy {Peppercorn, 1998
298 #168;Caoili, 2002 #80;Blake, 2006 #93;Ilias, 2007 #167}. Conversely, FDG-PET/CT is mainly
299 used for the detection of malignant disease {Mackie, 2006 #185;Groussin, 2009
300 #100;Deandreis, 2011 #184}.

301 CT has a high spatial and quantitative contrast resolution, which allows assessment of tissue
302 density by measuring X-ray absorption of tissues. This allows calculation of tissue attenuation
303 or tissue density values, which are measured in Hounsfield units (HU) and quantify X-ray
304 absorption of tissues compared to water, which is conventionally allocated a HU value of 0. For
305 **non-contrast (or 'unenhanced') CT**, HU of ≤ 10 is the most widely used threshold attenuation
306 value for the diagnosis of a lipid-rich, benign adrenal adenoma {Boland, 1998 #201}. However,
307 on non-contrast CT, some 30% of benign adenomas have an attenuation value of > 10 HU and
308 are considered lipid-poor, overlapping in density with malignant lesions and
309 pheochromocytomas {Caoili, 2000 #202;Pena, 2000 #171;Zhang, 2012 #183}.

310 **Contrast-enhanced washout CT** utilizes the unique perfusion pattern of adenomas.
311 Adenomas take up intravenous CT contrast rapidly, but also have a rapid loss of contrast - a
312 phenomenon termed 'contrast enhancement washout'. It is assumed that malignant adrenal
313 lesions usually enhance rapidly but demonstrate a slower washout of contrast medium. This
314 washout phenomenon can be quantified by 'contrast washout values', which involve lesion
315 attenuation measurements at specific time points acquired in a dedicated adrenal CT: prior to
316 injection of contrast medium (HU_{nativ}), at 60 seconds following injection of contrast medium
317 (HU_{max}) and then at 10 or 15 minutes after contrast injection. This allows calculation of the
318 relative contrast enhancement washout ($=100 \times (HU_{\text{max}} - HU_{10/15\text{min}}) / HU_{\text{max}}$) and absolute contrast
319 enhancement washout ($=100 \times (HU_{\text{max}} - HU_{10/15\text{min}}) / (HU_{\text{max}} - HU_{\text{nativ}})$). A relative washout $> 40\%$ and
320 an absolute washout $> 60\%$ is assumed to suggest that an adrenal lesion is benign {Pena,
321 2000 #171;Dunnick, 2002 #205;Szolar, 1998 #174;Young, 2011 #182}.

322 **MRI** is a non-ionising radiation based imaging modality utilizing weak radio wave signals
323 emitted by body tissues when the body is placed in a strong magnetic field and radio frequency
324 pulses are applied. The advantages of MRI over CT are its lack of radiation exposure, lack of

325 iodine-based contrast media and its superior tissue contrast resolution. For the differentiation of
326 benign and malignant adrenal masses the MRI technique of **chemical-shift imaging** is most
327 commonly used {McNicholas, 1995 #68;Sahdev, 2004 #175;Korobkin, 1996 #177;Korobkin,
328 1996 #178;Haider, 2004 #181;Young, 2011 #182}. Chemical shift imaging relies on the fact
329 that, within magnetic fields, protons in water vibrate at a slightly different frequency than
330 protons in lipid. As a result, water and fat protons oscillate in and out of phase with respect to
331 one another. By selecting appropriate sequencing parameters, separate images can be
332 generated with water and fat protons oscillating in-phase or out-of-phase to each other. Adrenal
333 adenomas with a high content of intracellular lipid usually lose signal intensity on out-of-phase
334 images compared to in-phase images, whereas malignant lesions and pheochromocytomas
335 (but also lipid-poor adrenal adenomas) that all lack intracellular lipid remain unchanged {Haider,
336 2004 #181;Dunnick, 2002 #205;Bharwani, 2011 #212}. Simple visual assessment of signal
337 intensity loss is diagnostic in most cases but quantitative methods may be useful in less clear
338 cut cases. Quantitative analysis can be made using the adrenal-to-spleen signal ratio and the
339 signal intensity index. MR signal intensity units are arbitrary units, unlike CT, and therefore are
340 subject to numerous technical variations.

341 **¹⁸F-FDG-PET** is a nuclear medicine modality that provides quantitative tomographic images
342 after intravenous injection of a beta-radiation emitting radiotracer (18-Fluorine) used to label 2-
343 deoxy-D-glucose rendering Fluoro-deoxyglucose (¹⁸F-FDG). Both glucose and deoxyglucose
344 enter cells via cell glucose transporters and undergo phosphorylation but while glucose
345 undergoes further enzymatic breakdown, deoxyglucose becomes trapped in intracellular
346 compartments. Cancer cells have an increased requirement for glucose and, therefore, take up
347 more glucose and deoxyglucose than normal cells {Becherer, 2001 #188}. However, ¹⁸F-FDG
348 is not a specific marker for cancer cells but a marker only for increased glucose metabolism
349 thus uptake can also be increased in cells with an increased energy requirement due to
350 conditions other than cancer. Quantitative measurement of ¹⁸F concentrations within tissues
351 provides the most commonly used clinical measurement index, standard uptake value (SUV),
352 which compares the intensity of uptake of ¹⁸F in the adrenal lesion to the average uptake of
353 whole body. SUV values have been utilized to differentiate between benign from malignant
354 adrenal lesions. FDG-PET has a high sensitivity for detection of metabolic changes but its
355 spatial resolution for anatomical localization is poor. The solution is a hardware fusion between
356 PET and CT (PET/CT) allowing simultaneous acquisition of PET and CT data. In clinical
357 practice this involves injecting patients with ¹⁸F-FDG tracers at least one hour prior to the start
358 of combined PET/CT. Once post processing is complete, PET and CT data can be viewed
359 separately, side-by-side or as a fused images {Vogel, 2004 #214}.

360 Other potentially emerging imaging techniques (e.g. metomidate-based adrenal imaging) are
361 not yet clinically widely available and, therefore, will not be discussed in this guideline.

362

363 **2.4. Remarks on the difficulties with hormonal testing**

364 Hormone assessment is crucial in the context of the work-up for an adrenal incidentaloma.
365 However, there are several pitfalls that have to be considered (e.g. daily rhythm, sex-/ age-
366 dependency, limitations of assays, drug interactions). Furthermore, normal ranges vary
367 substantially, depending on the method used, so it is essential to interpret test results in the
368 context of the appropriate reference range. Due to space restrictions we refer to other
369 guidelines that have addressed these issues in more detail {Nieman, 2008 #47;Lenders, 2014
370 #48}.

371 **3. Methods**

372 **3.1. Guideline working group**

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

386

387

388 **3.2 Target group**

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

396

397

398 **3.3 Aims**

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

401

402

403 **3.4 Summary of methods used for guideline development**

404 The methods used have been described in more detail previously {Bollerslev, 2015 #46}. In
405 short, the guideline used GRADE (Grading of Recommendations Assessment, Development
406 and Evaluation) as a methodological base. The first step was to define clinical question(s) (see
407 section 3.5), the second being a systematic literature search (see Section 3.6). After including

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

412 For the recommendations we took into account: 1) quality of the evidence, 2) balance of
413 desirable and undesirable outcomes, 3) values and preferences (patient preferences, goals for
414 health, costs, management inconvenience, feasibility of implementation, etc). {Hammarstedt,
415 2010 #126;Andrews, 2013 #133}. The recommendations are worded as *recommend* (strong
416 recommendation) and *suggest* (weak recommendation). Formal evidence syntheses were
417 performed and graded only for recommendations addressing our initial questions. Additional
418 recommendations based on good practice were not graded {Ferreira, 2005 #128}.
419 Recommendations were derived from majority consensus of the guideline development
420 committee, but if members had substantive disagreements, this is acknowledged in the
421 manuscript. For transparency, all recommendations provided are accompanied by text
422 explaining why specific recommendations were made.

423

424

425 **3.5. Clinical question, eligibility criteria and endpoint definition**

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

429

430

431 **3.6 Description of search and selection of literature**

432 A literature search in electronic medical databases was performed for all four clinical questions
433 separately. Of note, the approach for clinical question 1 (assessment of the risk of malignancy)
434 differed as the search, study selection and also the evidence synthesis was performed in the
435 context of a formal systematic review and meta-analysis published separately from the current
436 guideline. For all four clinical questions details of the yield of the search are shown in Table 3.
437 In summary, we included 37 studies for clinical question 1 (with 18 fulfilling the criteria for
438 inclusion in the meta-analysis), twelve studies for clinical question 2a (biochemical profile in
439 adrenal incidentaloma), four studies for clinical question 2b (therapeutic approach in mild
440 glucocorticoid excess), nine studies for clinical question 3 (surgery) and ten studies plus one
441 relevant systematic review for clinical question 4 (follow-up).

442

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

Clinical Question	Predefined selection criteria and key outcome parameters ¹	Metrics of the literature search
<p>Question 1a) What is the most accurate diagnostic imaging 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?</p>	<ul style="list-style-type: none"> • 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 any duration (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. 	<ul style="list-style-type: none"> • 5496 abstracts² • 525 potentially relevant articles • 37 studies included in systematic review, 18 in meta-analysis • Major reasons for exclusion of articles were lack of test accuracy data, inadequate or unclear reference standard and ineligible populations. Other reasons for exclusion data collection pre-1990, sample size <10, < 50% histology in malignant group, >30% pheochromocytomas in malignant group, >10% pheochromocytomas in benign group, no differentiation of children versus adults
<p>Question 1b) What is the diagnostic accuracy of adrenal biopsy?</p>	<ul style="list-style-type: none"> • Original studies on patients with adrenal masses undergoing an adrenal biopsy procedure • Outcomes: non-diagnostic rate, diagnostic accuracy data, complication rate • For studies included in the diagnostic accuracy analysis: 1) Reference standard: at least 50% of population either histology from adrenalectomy or autopsy, imaging follow up 3-12 months or clinical follow up of 2 years and 2) Reporting 2x2 contingency table data or at least two indices of diagnostic accuracy (sensitivity, specificity, negative or positive predictive value) and disease prevalence. 	<ul style="list-style-type: none"> • 175 abstracts³ • 80 potentially relevant articles • 32 studies included in systematic review of at least one outcome. • Diagnostic accuracy data included from 8 studies • Major reasons for exclusion overall were: no outcomes of interest, fewer than 10 patients, abstract only, patient overlap. • Major exclusions from diagnostic accuracy analysis were: suboptimal reference standard and >30% non-adenomas

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?

Question 3)

Should laparoscopic (=minimally-invasive) or open surgery be used for patients with non-metastatic adrenal masses suspected to be malignant?

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 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
- 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.
- 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,

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)

• 377 abstracts

- 13 potentially relevant articles
- 3 excluded due to samples size < 10 patients per arm, 1 excluded as review
- 9 studies included

• 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:

pheochromocytoma, primary
hyperaldosteronism)

- 1 systematic review of 14 studies
 - 10 additional cohort studies
-

444

445 ¹ For each question we searched separately for systematic reviews between 2000 and February 2014 in NHS Economic Evaluation Database (NHSEED),
446 Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects. This revealed no relevant systematic review. Then, we
447 searched for original articles in Medline published between 2000 and July 2014 (Question 3), October 2014 (Question 4), November 2014 (Question 2), and
448 August 2015 (Question 1).

449 ² Summary of separately published meta-analysis {Dinnes, 2016 #246}.

450 ³ Summary of separately published meta-analysis {Tamhane, 2016 #248}

451

452 **4. Summary and conclusions from systematic literature reviews**

453

454 4.1 Assessment of the risk of malignancy (Question 1)

455 4.1.1 Assessment of the risk of malignancy by imaging (Question 1a)

456 The following paragraph represents a summary of a recent meta-analysis on the use of
457 imaging for differentiating benign from malignant adrenal incidentalomas carried out with
458 involvement of some of the guideline panel members {Dinnes, 2016 #246}. Studies were
459 considered all studies of CT, MRI or FDG-PET in adults eligible if: 1) included patients
460 underwent imaging for any indications other than investigation of suspected adrenal mass; 2)
461 index imaging test characteristics were reported; 3) at least 50% of patients had an optimal
462 reference standard: histological diagnosis in malignant masses and availability of histology or
463 imaging follow up of any duration in the case of benign adrenal masses. Exclusion criteria
464 are summarized in Table 3. The review looked separately at patients with true adrenal
465 incidentaloma and patients with adrenal mass and a history of extra-adrenal malignancy.

466 We identified 37 studies for inclusion in the systematic review {Angelelli, 2013 #218;Marin,
467 2012 #224;Maurea, 2004 #88;Nunes, 2010 #101;Sandrasegaran, 2011 #105;Tessonier,
468 2008 #97;Vilar, 2008 #98;Burt, 1994 #63;Choi, 2013 #109;Frilling, 2004 #87;Lang, 2015
469 #120;McNicholas, 1995 #68;Porte, 1999 #76;Ream, 2015 #111;Schwartz, 1995
470 #69;Uemura, 2013 #111;Kunikowska, 2014 #121;Villar Del Moral, 2010 #104;Aksakal, 2013
471 #108;Bilbey, 1995 #131;Blake, 2006 #93;Boraschi, 1999 #74;Chung, 2001 #77;Groussin,
472 2009 #100;Gust, 2012 #106;Ichikawa, 1993 #61;Kamiyama, 2009 #219;Kebapci, 2003
473 #84;Launay, 2015 #226;Mayo-Smith, 1995 #67;Nwariaku, 2001 #79;Park, 2015 #115;Park,
474 2007 #96;Petersenn, 2015 #220;Remer, 2006 #94;Zettinig, 2004 #90;Zielonko, 2008 #99},
475 with only 18 of them fulfilling the criteria for inclusion in the actual meta-analysis {Angelelli,
476 2013 #218;Marin, 2012 #224;Maurea, 2004 #88;Nunes, 2010 #101;Sandrasegaran, 2011
477 #105;Tessonier, 2008 #97;Vilar, 2008 #98;Burt, 1994 #63;Choi, 2013 #109;Frilling, 2004
478 #87;Lang, 2015 #120;McNicholas, 1995 #68;Porte, 1999 #76;Ream, 2015 #111;Schwartz,
479 1995 #69;Uemura, 2013 #111;Kunikowska, 2014 #121;Villar Del Moral, 2010 #104}. No
480 randomized studies comparing imaging tests were identified. Risk of bias ranged from low to
481 high, with the majority having unclear or high risk of bias (mainly due to unclear population
482 selection, retrospective selection of the diagnostic threshold and inadequate reference
483 standards with resulting concerns of the applicability of results).

484 Five commonly used diagnostic thresholds were studied: (1) tumor density >10HU on non-
485 contrast CT; (2) CT with delayed contrast media washout: absolute percentage washout
486 and/or relative percentage washout at any washout percentage % or delay time on enhanced
487 CT; (3) MRI chemical shift analysis: loss of signal intensity between in and out of phase

488 images (including both qualitative and quantitative estimates of signal loss); and, for FDG-
489 PET or PET-CT, (4) the maximum standardized uptake value (SUVmax), and (5) the ratio of
490 SUVmax in the adrenal gland compared to the liver (adrenal liver ratio).

491 The 37 studies included were generally small with a median sample size of 45 (range 12 to
492 181). Of the 18 studies included in the formal meta-analysis, 7 addressed purely incidental
493 adrenal masses and 11 studies focused on patients with known extra-adrenal malignancy.

494 Limited data (two studies with 102 true incidentalomas) suggest that CT density >10 HU has
495 a high sensitivity for detection of adrenal malignancy (100%, 95% confidence interval 91-
496 100%); meaning that adrenal masses with a density of ≤10 HU are unlikely to be malignant.
497 In patients with a history of extra-adrenal malignancy five studies evaluating the >10 HU cut-
498 off as indicative of malignancy showed high sensitivity (93%) for detection of malignancy but
499 variable specificity; this means that 7% of adrenal metastases were found to have a tumor
500 density of ≤10 HU.

501 Disappointingly, all other estimates of test performance are based on small numbers of
502 studies with very few patients and accompanying wide 95% confidence intervals, indicating
503 much uncertainty in test performance for all other imaging markers. For true adrenal
504 incidentalomas, two of three MRI studies reported slightly lower sensitivity and specificity
505 than CT for measures of adrenal-liver and adrenal-spleen ratios and loss of signal intensity.
506 The performance of PET for adrenal liver ratio and SUVmax measures in the two included
507 studies was not clearly better than CT. In patients with a history of extra-adrenal malignancy,
508 only one study reported on CT contrast-enhanced washout tests, which showed very low
509 sensitivity (16%). Four of the five studies of MRI used 1.5 Tesla machines and reported high
510 sensitivity (89%-99%) for measures of adrenal-liver, adrenal-spleen, adrenal-muscle ratios
511 and loss of signal intensity. Specificity varied (60%-93%) but was high for most MRI
512 measures. The performance of PET was similar to MRI for ALR and max SUV measures.
513 Although more studies had evaluated CT, MRI and PET in the pathway for follow-up of
514 known extra-adrenal malignancy than for incidentally discovered adrenal lesions, estimates
515 of test performance are still based on too small numbers of studies to be able to discern
516 whether any test performs adequately or better than alternative tests from the available data.

517

518 4.1.2 Value of an adrenal biopsy (Question 1b)

519 The following paragraph represents a summary of a recent systematic review carried out with
520 involvement of some of the guideline panel members on published experience with adrenal
521 biopsy and its outcomes {Tamhane, 2016 #248}. Inclusion criteria and definition of reference
522 standard differed from the imaging meta-analysis mainly in population selection criteria (as
523 adrenal biopsy is not indicated in incidentaloma population but rather in patients at high risk
524 for malignancy) and in reference standard (where we accepted imaging and clinical follow up

525 in addition to histopathology as most metastases would not undergo adrenalectomy). We
526 identified 32 studies {Deville, 2002 #13484;Macaskill P, #13485;Moher, 2009
527 #13486;Silverman, 1993 #237;Puri, 2015 #13487;Martinez, 2014 #13488;Welch, 1994
528 #240;Rana, 2012 #13489;Mody, 1995 #172;Hussain, 1996 #13490;Wu, 1998 #72;Schwartz,
529 1998 #73;Porte, 1999 #76;de Agustin, 1999 #67;Lumachi, 2001 #231;Lumachi, 2003
530 #85;Paulsen, 2004 #230;Kocijancic, 2004 #13493;Lucchi, 2005 #13494;Lumachi, 2007
531 #95;Quayle, 2007 #236;Tsitouridis, 2008 #142;Osman, 2010 #13496;Mazzaglia, 2009
532 #13451;Bodtger, 2009 #13497;Eloubeidi, 2010 #13498;Schuurbiens, 2011 #13499;Tyng,
533 2012 #13500;Tirabassi, 2012 #14;Rana, 2012 #13489;Martinez, 2014 #13390;Puri, 2015
534 #13487} with a total of 2174 patients which reported at least one outcome of interest
535 (complication rate, non-diagnostic rate, diagnostic accuracy parameters). Of these, only 8
536 studies{Porte, 1999 #76;Lumachi, 2001 #231;Lumachi, 2003 #85;Lucchi, 2005
537 #13494;Lumachi, 2007 #95;Quayle, 2007 #236;Tsitouridis, 2008 #142;Tirabassi, 2012 #14}
538 were included for the diagnostic accuracy analysis, reasons for exclusion being lack of any or
539 optimal reference standard for at least 50% patients (n=20) and more than 30% patients with
540 non-adenomas in benign cohort (n=4). Included studies were assessed to be at a moderate
541 risk for bias, most limitations relating to patient selection, assessment of outcome and
542 adequacy of follow up of the study population.

543 Studies had diverse population inclusion criteria, reference standards and biopsy techniques.
544 Pathology of adrenal lesion was reported only for 1600/2207 cases. Out of these 819 were
545 malignant (703 metastases, 67 ACCs, 49 other malignancies or not specified), 690 were
546 benign and 91 were various other non-malignant lesions (36 pheochromocytomas, 29
547 granulomas, 16 other). Pooled non-diagnostic rate derived from 30 studies (2030 adrenal
548 biopsy procedures) was 8.6% (CI 6.1%-11%; I² = 84%, p<0.001). Pooled overall
549 complication rate derived from studies (1356 biopsies) was 2.4% (CI 1.5%-3.3%; I² = 21%,
550 p=0.175), though likely under-represented due to differences in both assessment and
551 reporting of complication as well as retrospective nature of the studies. The diagnostic
552 performance of adrenal biopsy was calculated using the data from the 8 studies (323 adrenal
553 biopsy procedures) meeting pre-established eligibility criteria. Performance of adrenal biopsy
554 in the diagnosis of malignancy overall was: sensitivity 87% (CI95% of 78-93%), specificity
555 100% (CI95% of 76-100%), positive likelihood ratio of 229 (CI95% of 2.9-18145) and
556 negative likelihood ratio of 0.13 (CI95% of 0.07-0.23). Performance was lower (and with even
557 wide 95%CIs) for ACC: sensitivity 70% (CI95% of 42-88%), specificity 98% (CI95% of 86-
558 100%), positive likelihood ratio of 100.43 (CI95% of 8-1245) and negative likelihood ratio of
559 30.9 (CI95% of 4.16-229).

560

561

562 4.2 Assessment of autonomous cortisol secretion in adrenal incidentalomas
563 4.2.1 Assessment of autonomous cortisol secretion in relation to clinical outcomes
564 (Question 2a, Appendices I and II)

565 Studies were eligible for inclusion independent of the criteria used to define autonomous
566 cortisol secretion. Three different hormonal profiles were distinguished to describe
567 autonomous cortisol secretion associated with adrenal adenomas; Profile 1: serum cortisol >
568 50 nmol/l (>1.8 µg/dl) after 1-mg, 2-mg, or 8-mg overnight dexamethasone suppression
569 tests, or 2-day low dose dexamethasone test, and one of the following additional endocrine
570 alterations: increased 24-h urinary free cortisol (UFC), low plasma ACTH, elevated midnight
571 serum or salivary cortisol; Profile 2: serum cortisol > 83nmol/l (>3.0 µg/dl) after 1-mg
572 overnight dexamethasone test and one additional endocrine alteration (same as above);
573 Profile 3: cortisol > 140 nmol/l (>5 µg/dl) after 1-mg overnight dexamethasone test as sole
574 criterion. The defined profiles do not fit completely with the specific criteria used in all of the
575 studies included. Virtually all diagnostic algorithms are, however, variations of these profiles.

576
577 In total, twelve studies were included: seven cross-sectional studies {Chiodini, 2004
578 #18;Chiodini, 2009 #53;Di Dalmazi, 2012 #12;Eller-Vainicher, 2012 #13;Androulakis, 2014
579 #17;Olsen, 2012 #15;Vassilatou, 2014 #243} and five cohort studies {Debono, 2014 #19;Di
580 Dalmazi, 2014 #20;Giordano, 2010 #6;Morelli, 2011 #14;Morelli, 2014 #8}. In eight studies, a
581 comparison was made between patients with elevated (group 1) or normal (group 2) cortisol
582 levels after a 1-mg dexamethasone test. Two studies used the biochemical profile 1 and four
583 studies used the biochemical profile 2 with a variation since the post-dexamethasone serum
584 cortisol cutoff was not a mandatory criterion. Three studies identified 3 subgroups of patients
585 {Debono, 2014 #19;Di Dalmazi, 2014 #20;Di Dalmazi, 2012 #12}, normal, intermediate and
586 frankly altered cortisol suppression corresponding to cortisol levels after 1-mg
587 dexamethasone of < 50 nmol/l (< 1.8 µg/dl), between 50 to 140 nmol/l (1.8 µg/dl - 5.0 µg/dl),
588 and > 140 nmol/l (> 5.0 µg/dl), respectively.

589 In the cross-sectional studies, the risk of bias is estimated as high, given the inability to
590 assess causality and the potential for residual confounding factors, and these issues hamper
591 the ability to make firm conclusions from these studies. Differences in diagnostic protocols,
592 definitions of outcome, and duration of follow-up were associated with considerable
593 heterogeneity between and within studies.

594

595 **Outcome measures**

596 *Change in biochemical profile*

597 In three studies with a median follow-up of 3, 6.9, and 7.5 years no patient progressed to
598 overt Cushing's syndrome during follow-up {Di Dalmazi, 2014 #20;Giordano, 2010 #6;Morelli,
599 2014 #8}.

600

601 *Change in metabolic and cardiovascular profile*

602 The risk of type 2 diabetes was higher in patients with impaired cortisol suppression after 1-
603 mg dexamethasone test and increased further during follow-up {Di Dalmazi, 2014 #20;Di
604 Dalmazi, 2012 #12;Morelli, 2014 #8}. Also, the risk of hypertension was higher in patients
605 with impaired cortisol suppression and increased further with follow-up {Di Dalmazi, 2012
606 #12;Morelli, 2014 #8;Olsen, 2012 #15;Vassilatou, 2009 #10}. A smaller study did not confirm
607 the increase in diabetes and hypertension with time {Giordano, 2010 #6}.

608

609 *Major cardiovascular incidents*

610 In two cohort studies {Di Dalmazi, 2014 #20;Morelli, 2014 #8}, the incidence of
611 cardiovascular events was higher in patients with altered cortisol suppression.

612

613 *Mortality*

614 Two studies reported on mortality {Debono, 2014 #19;Di Dalmazi, 2014 #20} and found an
615 increased mortality risk in patients with higher cortisol levels after 1-mg dexamethasone.
616 However, the results were adjusted for other prognostic factors only in the first study, and
617 effect estimates were uncertain due to low number of events.

618

619 *Risk of vertebral fractures*

620 Four studies reported a higher prevalence of vertebral fractures {Chiodini, 2004 #18;Chiodini,
621 2009 #53;Di Dalmazi, 2012 #12;Eller-Vainicher, 2012 #13} in patients with impaired cortisol
622 suppression. In a cohort study {Morelli, 2011 #14}, the incidence of new vertebral fractures
623 was higher in patients with impaired cortisol suppression. However, most of the detected
624 vertebral fractures were minor and of uncertain clinical impact.

625

626

627 4.2.2. Surgery vs. conservative management in patients with autonomous cortisol 628 secretion (Question 2b, Appendices III and IV)

629 For question 2b, four studies were included in which surgery was compared to a
630 conservative approach: one randomized controlled trial and three observational studies. The
631 randomized trial {Toniato, 2009 #22} reported on patients with autonomous cortisol secretion
632 who underwent surgery (n=23) or were treated by a conservative approach (n=22). The

633 mean follow up was 7.7 years and the results were only a qualitative description of changes
634 in hypertension, diabetes mellitus or dyslipidemia.

635 Tsuiki et al. included patients with autonomous cortisol secretion and compared a group
636 treated by surgery (n=10) and a group treated conservatively (n=10) {Tsuiki, 2008 #23}.
637 Follow up was 7-19 months. The second cohort study included 41 patients with autonomous
638 cortisol secretion (25 treated by surgery and 16 conservatively treated) {Chiodini, 2010 #11}.
639 Outcome measures included: proportion of patients with steady, improved, or worsened
640 blood pressure, fasting glucose or LDL cholesterol. In the third study by Iacobone et al, 372
641 patients with autonomous cortisol secretion (20 treated by surgery and 15 conservatively
642 treated) {Iacobone, 2012 #244}. Outcomes were blood pressure, glucose and cholesterol.
643 The quality of evidence from these studies is low to very low, mainly due to confounding
644 factors. Only one study was randomized, and none of the studies reported blinded outcome
645 assessment. Most studies were also downgraded for imprecision, due to low number of
646 events. Differences in diagnostic protocols, definitions of outcome, and duration of follow-up
647 were associated with considerable heterogeneity between and within studies.

648

649

650 **Outcome measures**

651

652 *Change in metabolic and cardiovascular profile in patients with autonomous cortisol*
653 *secretion*

654 In the randomized trial, 25% of patients with type 2 diabetes mellitus had normalized
655 glycemic control after surgery {Toninato, 2009 #22}, compared to none in the conservative
656 group. The cohort studies {Chiodini, 2010 #11;Tsuiki, 2008 #23;Iacobone, 2012 #244}
657 reported an improvement in glucose levels in 10-48% of patients after surgery. In the
658 conservatively treated groups, none of the patients improved.

659 The cohort studies {Chiodini, 2010 #11;Tsuiki, 2008 #23;Iacobone, 2012 #244} reported an
660 improvement in hypertension and dyslipidemia in some patients after surgery. In the
661 conservatively managed group, none of the patients improved.

662

663 *Risk of vertebral fractures*

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

665

666 *Major cardiovascular incidents and mortality*

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

668

669

670 4.3 Surgical approach: open vs. minimally-invasive adrenalectomy (Question 3,
671 Appendices V and VI)

672 As adrenocortical carcinoma is the main threat for an adverse outcome in patients with
673 adrenal incidentaloma undergoing surgery, we focused our efforts with regards to surgery on
674 the management of adrenocortical carcinoma. Nine cohort studies on the surgical treatment
675 of patients with non-metastatic adrenocortical carcinoma were included {Brix, 2010
676 #24;Cooper, 2013 #25;Donatini, 2014 #26;Fossa, 2013 #27;Lombardi, 2012 #28;Miller, 2010
677 #29;Miller, 2012 #30;Mir, 2013 #31;Porpiglia, 2010 #32}. Three studies reported on the
678 patients in whom complete resection of the tumor was achieved {Donatini, 2014
679 #26;Lombardi, 2012 #28;Porpiglia, 2010 #32}.

680
681 The quality of evidence from these observational studies is very low, mainly because patient
682 groups were not comparable at baseline with regard to important prognostic characteristics,
683 such tumor stage or size. Tumor stage was, on average, lower in patients with laparoscopic
684 surgery as compared to open surgery. In few studies {Brix, 2010 #24;Mir, 2013 #31},
685 treatment effects were adjusted for differences in tumor stage. Mostly, however, only
686 uncorrected estimates of recurrence-free and overall survival were reported. Moreover, most
687 studies had imprecise effect estimates.

688
689 **Outcome measures**

690 *Perioperative mortality and morbidity*

691 One study reported on perioperative mortality {Brix, 2010 #24}. In this study, none of the 152
692 patients died perioperatively. Three studies reported on intraoperative or postoperative
693 complications {Fossa, 2013 #27;Lombardi, 2012 #28;Mir, 2013 #31}. Major postoperative
694 complications (Clavien-classification score 3-5) occurred more often in open surgeries
695 compared to laparoscopic surgeries (RR 1.7, 95% CI 0.5-6.2) but these estimates are
696 imprecise due to low numbers of events.

697
698
699 *Completeness of resection*

700 In five studies the completeness of resection was reported {Brix, 2010 #24;Cooper, 2013
701 #25;Fossa, 2013 #27;Miller, 2010 #29;Mir, 2013 #31}. The pooled estimate of these five
702 studies indicated no clear difference in complete resection between surgical approaches (RR
703 0.8 (95% CI 0.6 to 1.1)). The results of these studies were inconsistent, leading to much
704 uncertainty regarding this conclusion.

705
706 *Recurrence-free and overall survival*

707 Eight studies reported on recurrence after surgery, but differed in the presentation of these
708 data. These studies also provided data on overall or disease-specific survival {Brix, 2010
709 #24;Cooper, 2013 #25;Donatini, 2014 #26;Fossa, 2013 #27;Lombardi, 2012 #28;Miller, 2012
710 #30;Mir, 2013 #31;Porpiglia, 2010 #32}. There is no compelling evidence that one of the
711 approaches (laparoscopic or open adrenalectomy) is superior with regard to time to
712 recurrence and/or survival in patients with adrenocortical carcinoma, provided that rupture of
713 tumor capsule is excluded. However, the studies have significant limitations, inconsistencies
714 and imprecision precluding reliance on this conclusion.

715

716 *Pain / patient satisfaction*

717 None of the studies reported on pain or patient satisfaction.

718

719 4.4 Natural course of apparently benign adrenal incidentaloma (risk of malignancy 720 or development of hormone excess) (Question 4, Appendix VII and VIII)

721 A systematic review of fourteen studies assessing the natural course of 1410 patients with
722 apparently benign, non-functioning adrenal incidentalomas {Cawood, 2009 #35} and ten
723 additional cohort studies were included {Chiodini, 2010 #11;Cho, 2013 #3;Comlekci, 2010
724 #4;Debono, 2013 #117;Fagour, 2009 #5;Giordano, 2010 #6;Kim, 2005 #7;Morelli, 2011
725 #14;Morelli, 2014 #8;Muth, 2011 #9;Muth, 2013 #119;Song, 2008 #262;Vassilatou, 2009
726 #10;Yener, 2009 #121}. The systematic review included studies reporting the follow up of
727 adrenal incidentaloma patients, published between 1980 and 2008, including publications
728 that reported more than 20 patients, and in which the majority were referred to an
729 endocrinologist (excluding oncology series). The additional ten studies, published between
730 2005 and 2014, included 1131 incidentaloma patients with apparently benign non-functioning
731 tumors or with autonomous cortisol secretion.

732

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

739

740 **Outcome measures**

741 *Malignancy*

742 The estimated pooled risk for developing malignancy in the systematic review was 0.2%
743 (95%CI 0.0 to 0.4) {Cawood, 2009 #35}. In two cohort studies, one case of malignancy was

744 found: one patient with adrenal non-Hodgkin lymphoma and one patient with renal cancer
745 metastasis. In the first case, the imaging characteristics of the adrenal incidentaloma at the
746 first evaluation were not consistent with benign characteristics and the lymphoma may have
747 been misdiagnosed initially {Libe, 2002 #123}. The second case had a history of renal cell
748 carcinoma and it is unclear whether the adrenal mass was found incidentally or during the
749 follow-up for cancer {Tsvetov, 2007 #122}. No case of malignancy was reported in the other
750 904 patients included in the cohort studies. Importantly, no malignant transformation of a
751 presumably benign incidentaloma was reported.

752

753 *Development of clinically overt hormone excess*

754 The risk of developing overt Cushing' syndrome in patients without clinical signs of Cushing's
755 syndrome at the time of initial assessment ranged in the individual studies from 0% to 4%,
756 whereas the risk of developing autonomous cortisol secretion in the absence of clinically
757 overt Cushing's syndrome was low, with a pooled estimate from a systematic review of 0.3%
758 {Cawood, 2009 #35}. The risk of developing an aldosterone-producing adenoma in the
759 individual studies ranged from 0% to 2%.The risk of developing a pheochromocytoma ranged
760 from 0% to 2% but it is unclear whether an accurate initial imaging and biochemical
761 screening was performed.

762 **5. Recommendations, Rationale for the Recommendations**

763 **5.1. General remarks**

764 The main part of this guideline addresses the management of patients who fulfill the
765 definition of adrenal incidentaloma (section 2.1). In addition, we discuss specific situations
766 separately: bilateral adrenal masses (5.6.1), patients who are young or elderly and frail
767 (5.6.2), and adrenal masses detected during evaluation for extra-adrenal malignancy (5.6.3).

768

769 **R.1.1 We recommend that patients with adrenal incidentalomas are discussed in a**
770 **multidisciplinary expert team meeting, if at least one of the following criteria is**
771 **met (Figure 1):**

- 772 - **Imaging is not consistent with a benign lesion.**
- 773 - **There is evidence of hormone excess (including ‘autonomous cortisol**
774 **secretion’).**
- 775 - **Evidence of significant tumor growth during follow-up imaging.**
- 776 - **Adrenal surgery is considered.**

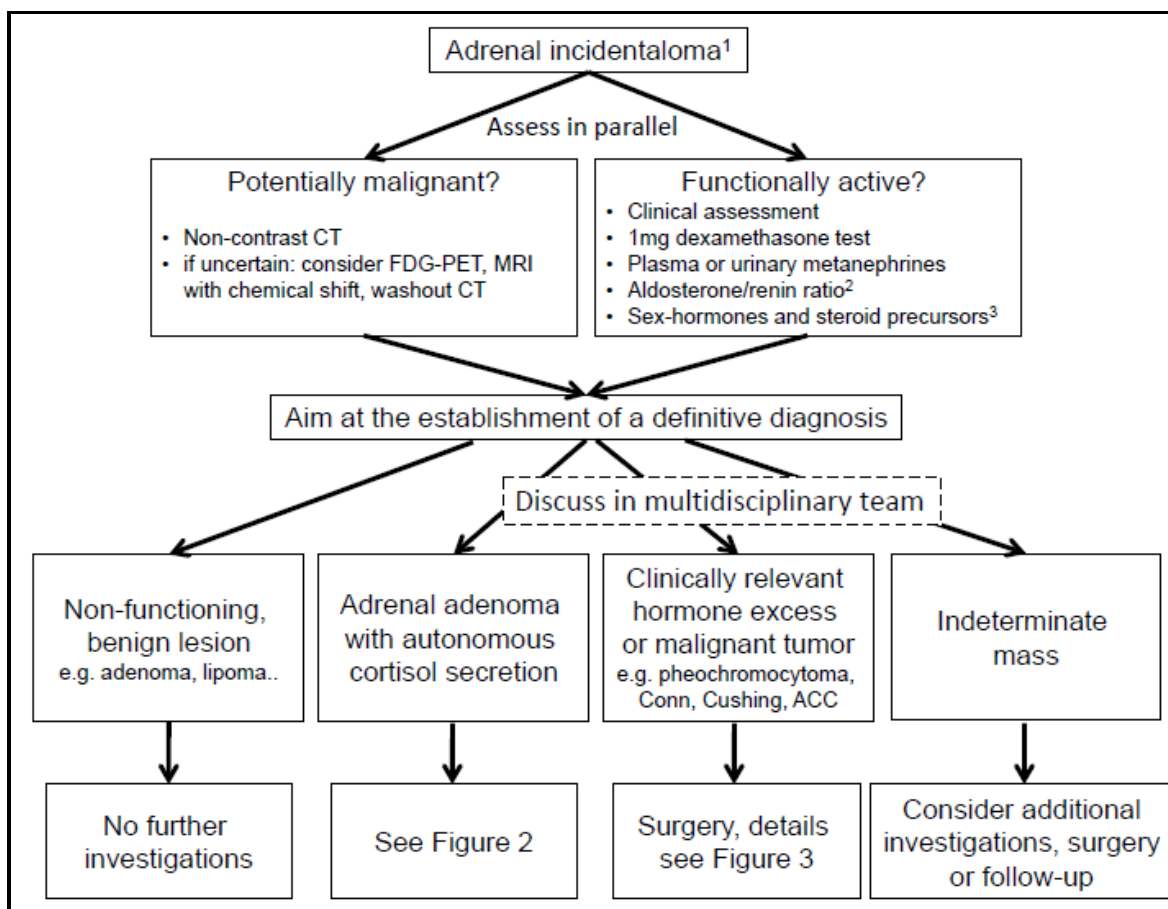
777

778 Reasoning:

779 Although we believe that the ideal would be for all patients with adrenal incidentalomas to be
780 managed by an expert multidisciplinary team, in many health care settings this is an
781 unrealistic aspiration. Despite lack of compelling evidence, we aimed at identifying
782 subgroups of patients that would be most likely to benefit from multidisciplinary team
783 discussion, and that these discussions occur quickly for patients that meet the criteria above.
784 The core multidisciplinary team should consist of at least a radiologist, an endocrinologist,
785 and a surgeon, all with significant experience in adrenal tumors. Furthermore, this team
786 should have access to anesthetists and an endocrine pathologist, who are experienced in
787 adrenal tumors. Although it is beyond the scope of this guideline, the use of a standardized
788 pathology report is highly recommended.

789 There is sufficient evidence that higher surgical volume correlates with better outcome,
790 however, for the time being no specific numbers of operations per year that result in this
791 favorable outcome can be recommended {Park, 2009 #50;Kerkhofs, 2013 #51;Lombardi,
792 2012 #52;Cooper, 2013 #25}.

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



795

796 ¹ For patients with history of extra-adrenal malignancy, see special section 5.6.4

797 ² only in patients with concomitant hypertension and /or hypokalemia

798 ³ only in patients with clinical or imaging features suggestive of adrenocortical carcinoma

799

800 **5.2. Assessment of the risk of malignancy**

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

803 Reasoning

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

808

809 **R.2.2 We recommend that all adrenal incidentalomas undergo an imaging procedure**
810 **to determine if the mass is homogeneous and lipid-rich and therefore benign**
811 **(XOOO). For this purpose, we primarily recommend the use of non-contrast CT**
812 **(XOOO)**

813

814 **R.2.3 We suggest that if the non-contrast CT is consistent with a benign adrenal**
815 **mass (Hounsfield units ≤ 10) that is homogeneous and smaller than 4 cm no**
816 **further imaging is required (XOOO).**

817

818 Reasoning

819 In patients with no known extra-adrenal malignancy adrenal incidentalomas are likely to be
820 benign. The non-contrast CT value is reflective of tissue density. Benign lesions including
821 lipid rich adenoma, myelolipoma, fluid-filled homogenous cysts, and other soft tissue tumors
822 (ganglioneuromas, some schwannomas) have low CT density ≤ 10 HU. Based on the
823 systematic review and meta-analysis {Dinnes, 2016 #246}, in patients presenting without
824 known malignancy a non-contrast CT with HU of ≤ 10 was only found in those with benign
825 disease, whereas in patients with extra-adrenal malignancy 7% of cases with non-contrast
826 HU ≤ 10 turned out to be malignant.

827 Similar to CT, the results of MRI with chemical shift imaging are based on the lipid content of
828 masses {Rodacki, 2014 #268; Seo, 2014 #269}. Unlike CT (or FDG-PET) MRI has the
829 advantage of avoiding ionizing radiation and its attendant risks to the patient. However, the
830 quantitative assessment of loss in signal intensity is not well standardized between the
831 different studies and, therefore, evidence base for performance of MRI in the diagnosis of
832 malignancy is insufficient to make strong recommendations. Moreover, the interpretation of
833 the images might be more dependent on the experience of the radiologist than for CT
834 assessment. In addition, the meta-analysis was not able to determine the diagnostic value of
835 MRI due to the low number and quality of eligible studies.

836

837 In conclusion, the panel felt - despite the limited evidence - confident about the negative
838 predictive value of non-contrast CT to recommend that additional imaging was not necessary
839 when benign characteristics were found in an adrenal mass < 4 cm, especially as additional
840 imaging may also risk false positive results and significant psychological and financial burden
841 for patients and the health system, respectively. We acknowledge that the cutoff of 4 cm is
842 not based on good evidence from clinical studies, but the panel felt it is necessary to provide
843 clear guidance based on clinical experience.

844 MRI with chemical shift has an even poorer evidence base with regard to its diagnostic value
845 in excluding malignancy and therefore should be first choice only where a CT is less
846 desirable (e.g. pregnancy, children). However, if an MRI with chemical shift is already
847 performed and the results are unambiguous, a multidisciplinary expert team might judge this
848 as sufficient for an individual patient.

849

850

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

857

858 Reasoning

859 Evidence of targeted evaluation for "second or third-line" imaging in patients with
860 indeterminate adrenal mass is very poor (see section 4.1 and {Dinnes, 2016 #246} for
861 details). However, the panel considered it important to provide some guidance for daily
862 clinical practice (Table 4), although consensus was not reached other than agreeing that
863 such discussions needed to be individualized and should take place within a multidisciplinary
864 team meeting.

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

866 Contrast washout CT has very limited and low quality evidence from studies {Dinnes, 2016
867 #246}. CT washout is widely available but there is huge variability in the protocols applied
868 and therefore poor comparability between studies and centers; in addition, the meta-analysis
869 could only identify a single eligible study reporting CT washout study results, carried out in
870 patients without a history of extra-adrenal malignancy.

871 FDG-PET/CT has the advantage that the risk of false negative results (namely missing a
872 malignant adrenal tumor) is quite low, and this refers mainly to a few subtypes of extra-
873 adrenal malignancies with low uptake {Karam, 2006 #207;Tsukamoto, 2007

874 #206;Zukotynski, 2012 #272;Ansquer, 2010 #273}. This procedure is, however, more
 875 expensive, not always easily available, and has the disadvantage that several benign adrenal
 876 tumors (e.g. functional adenomas or benign pheochromocytoma) may be FDG-positive
 877 {Timmers, 2009 #209;Alencar, 2011 #212}.

878
 879

880 **Table 4: Imaging criteria suggesting a benign adrenal mass¹**

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

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¹ these criteria apply only for masses with homogenous appearance, or masses that have other clear characteristics consistent with benign disease, e.g. myelolipoma. A homogeneous mass is defined as a lesion with uniform density or signal intensity throughout. The measurements/region of interest (ROI) should include at least 75% of a lesion without contamination by tissues outside the adrenal lesion. Inhomogeneous lesions should not be subjected to MRI or washout CT for further characterization.
² Evidence is weak for MRI, CT with contrast washout, and FDG-PET and no comparative studies on "second line imaging" are available. Thus, in this guideline we clearly recommend non-contrast CT as imaging procedure of choice.
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

893 Whilst the panel was in favor of attempts to fully characterize the adrenal mass on imaging,
 894 due to the limitations summarized above, it considered that in patients with indeterminate
 895 results on non-contrast CT further imaging by one of the modalities detailed above should be
 896 arranged. Due to the lack of evidence and studies reporting direct comparison the panel was
 897 not able to clearly judge one method over another. Alternatively, in patients without a strong
 898 suspicion of malignancy and older patients, follow-up imaging 6-12 months after the initial
 899 scan could be undertaken. The rationale for a follow-up scan at 6-12 months is based on the
 900 principle that either primary adrenal malignancies or adrenal metastases are likely to
 901 increase in size over this time period; lack of growth may be taken as an indicator of benign
 902 disease in radiologically indeterminate lesions. The exact timing of this imaging should be
 903 individualized. However, especially in cases with a low likelihood of a malignant tumor the
 904 panel favors a time interval of 12 months. There are no published size or volume cut-offs
 905 commonly agreed or with evidence base to support that they indicate growth suggestive of
 906 malignancy; the expert panel agreed that an increase in > 20% of the largest tumor diameter
 907 together with an at least 5 mm increase in this diameter should be considered as suspicious.
 908

909

910 **R.2.5 We recommend against the use of an adrenal biopsy in the diagnostic work-up**
911 **of patients with adrenal masses unless there is a history of extra-adrenal**
912 **malignancy (see R6.3.5).**

913

914 Reasoning

915 Adrenal biopsy has a limited role in evaluation of adrenal masses – mainly in diagnosis of
916 extra/adrenal malignancy, lymphoma, infiltrative or infectious process. Even in such
917 situations, adrenal biopsy should only be performed by an experienced radiologist and when
918 it is required to guide further care. We particularly recommend against an adrenal biopsy if
919 an adrenal mass is likely to be an adrenocortical carcinoma, because a biopsy of such a
920 tumor runs the risk of tumor dissemination precluding an R0 resection (although this risk
921 seems to be low {Williams, 2014 #152}). The only exception might be if a formal confirmation
922 of the diagnosis is needed in an inoperable tumor to inform oncological management or as
923 part of a clinical trial.

924 **5.3. Assessment for hormone excess**

925

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

929

930 Reasoning

931 All patients should undergo a careful evaluation with detailed history and physical
932 examination since a second round evaluation may detect clues of overt hormone excess that
933 were overlooked initially. For the clinical assessment and subsequent diagnostic procedures
934 for Cushing's syndrome, primary aldosteronism, and pheochromocytoma, we refer to
935 guidelines of other societies {Nieman, 2008 #47;Lenders, 2014 #48;Funder, 2008 #276}.

936 Rapidly developing hirsutism or virilization is a clinical indicator for an androgen-producing
937 tumor, and should be addressed by measuring testosterone and androgen precursors,
938 whereas recent onset of gynecomastia should trigger measurement of estradiol {Fassnacht,
939 2009 #149;Fassnacht, 2004 #148;Libe, 2007 #157;Else, 2014 #153} (see also R.3.10).

940

941

942

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

945 **R.3.3 We suggest interpretation of the results of the 1-mg overnight dexamethasone**
946 **test as a continuous rather than categorical (yes/no) variable (XOOO). However,**
947 **we recommend using serum cortisol levels post dexamethasone ≤ 50 nmol/l (\leq**
948 **1.8 $\mu\text{g/dl}$) as a diagnostic criterion for the exclusion of autonomous cortisol**
949 **secretion (XXOO).**

950 **R.3.4 We suggest that post dexamethasone serum cortisol levels between 51 and 140**
951 **nmol/l (1.9 - 5.0 $\mu\text{g/dl}$) should be considered as evidence of 'possible**
952 **autonomous cortisol secretion' and cortisol levels post dexamethasone > 140**
953 **nmol/l (> 5.0 $\mu\text{g/dl}$) should be taken as evidence of 'autonomous cortisol**
954 **secretion'. Additional biochemical tests to confirm cortisol secretory autonomy**
955 **and assess the degree of cortisol secretion might be required (Figure 2).**
956 **However, for the clinical management the presence of potentially cortisol-**
957 **related comorbidities (Table 2) and age of the patient are of major importance**
958 **(Figure 2).**

959

960

961 Reasoning

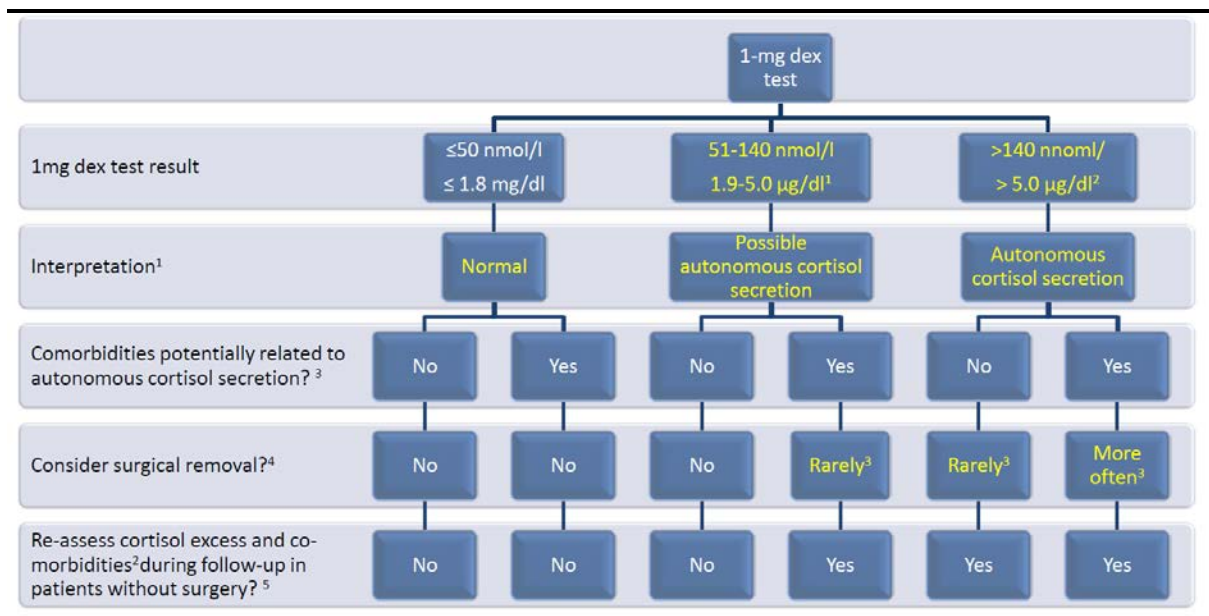
962 A variety of diagnostic algorithms have been used to exclude cortisol excess or to define so-
963 called 'subclinical hypercortisolism', but in the literature there are no head to head
964 comparisons between tests to assess their diagnostic performance (see section 4.2.1).
965 However, the panel recommends the use of the 1-mg overnight dexamethasone test based
966 on pathophysiological reasoning, simplicity, and the fact that the test was incorporated in the
967 diagnostic algorithms of most studies. It is important to consider drugs or conditions that
968 interfere with this test (see Appendix Table A3). In published guidelines and reviews variable
969 thresholds have been recommended {Grumbach, 2003 #39;Young, 2007 #43;Terzolo, 2011
970 #33;Tabarin, 2008 #59}. Several studies have used post dexamethasone serum cortisol
971 values between 50 and 140 nmol/l (1.8 - 5.0 µg/dl) and/or required further tests to secure the
972 diagnosis of 'autonomous cortisol secretion'. However, in none of these additional tests was
973 the performance convincing enough to ultimately establish diagnostic criteria.

974 The panel appreciated that this ongoing debate reflects a biological continuum with no clear
975 separation between non-functioning adenomas and functioning adenomas associated with
976 some degree of cortisol excess. However, a value of ≤ 50 nmol/l (≤ 1.8 µg/dl) may be
977 regarded as normal, excluding cortisol excess. This cut-off is supported by studies
978 demonstrating that patients with post dexamethasone cortisol values > 50 nmol/l (> 1.8 µg/dl)
979 have an increased morbidity or mortality {Debono, 2014 #19;Di Dalmazi, 2014 #20}. Since
980 the probability of clinically relevant cortisol excess increases the higher the post-
981 dexamethasone serum cortisol value and that the principle of dexamethasone testing is
982 based on pharmacological suppression of ACTH secretion, we propose the following
983 terminology be used on biochemical grounds. For patients without overt Cushing's syndrome
984 and a serum cortisol post dexamethasone between 51 and 140 nmol/l we propose the term
985 'possible autonomous cortisol secretion' and for higher values the term "autonomous cortisol
986 secretion". However, for the clinical management, the presence of potentially related
987 comorbidities (Table 2) and age of the patient are of major relevance (Figure 2).

988 The majority of panel members (but not all) preferred additional biochemical tests to confirm
989 cortisol secretory autonomy and assess the degree of cortisol secretion. However, we
990 acknowledge that use of several tests may be associated with an increased likelihood of at
991 least one being a false positive result Nevertheless, we suggest measurement of basal
992 morning plasma ACTH and to repeat the dexamethasone test after 3-12 months in all
993 patients with 'possible autonomous cortisol secretion' and comorbidities. In patients with
994 'autonomous cortisol secretion' we suggest the additional measurement of 24-h urinary free
995 cortisol and/or late-night salivary cortisol (although few studies suggest a poor performance
996 of this parameter in patients with incidentaloma). Following the concept that cortisol secretion
997 in patients with 'autonomous cortisol secretion' is independent of ACTH, a higher dose of

998 dexamethasone (e.g. 3mg, 2x2mg, or 8mg) might also be reasonable as additional test.
 999 However, the published literature is too limited and controversial to make a clear statement
 1000 on these tests.

1001
 1002 **Figure 2: Assessment and management of ‘autonomous cortisol secretion’ in patients**
 1003 **with adrenal incidentalomas**



1004
 1005
 1006 ¹ The majority of but not all panel members preferred additional biochemical tests to better judge the degree of
 1007 cortisol secretion. In patients with comorbidities, we suggest to measure plasma ACTH and to repeat the
 1008 dexamethasone test in 3-12 months.
 1009 ² We suggest additional biochemical tests to better judge the degree of cortisol secretion: plasma ACTH, 24-h
 1010 urinary free cortisol, (and/or late-night salivary cortisol), and repetition of the dexamethasone test in 3-12
 1011 months.
 1012 ³ See Table 2 for potentially cortisol-related comorbidities.
 1013 ⁴ Choice for surgery should always be individualized.
 1014 ⁵ Need of follow-up by an endocrinologist
 1015

1016
 1017 **R.3.5 We recommend against considering ‘autonomous cortisol secretion’ as a**
 1018 **condition with a high risk for the development of overt Cushing’s syndrome**
 1019 **(XXOO).**

1020
 1021 Reasoning
 1022 Studies reporting on follow-up of patients with adrenal incidentalomas have uniformly found a
 1023 very low percentage (< 1%) of patients with ‘autonomous cortisol secretion’ progressing to
 1024 overt Cushing’s syndrome {Cawood, 2009 #35;Barzon, 1999 #112;Barzon, 2003 #38;Bernini,
 1025 2005 #137;Fagour, 2009 #136;Libe, 2002 #123;Terzolo, 2005 #135;Terzolo, 1998
 1026 #134;Nieman, 2015 #142}.

1027
 1028

1029 **R.3.6 We recommend screening patients with ‘possible autonomous cortisol**
1030 **secretion’ or ‘autonomous cortisol secretion’ for hypertension and type 2**
1031 **diabetes mellitus (XOOO) and suggest offering appropriate treatment of these**
1032 **conditions.**

1033

1034 Reasoning

1035 Studies from different research groups have consistently demonstrated an association
1036 between cortisol excess and hypertension and hyperglycemia {Terzolo, 2005 #146;Terzolo,
1037 2005 #135;Tauchmanova, 2002 #143;Emral, 2003 #144;Reincke, 1996 #166;Bernini, 2003
1038 #164;Di Dalmazi, 2012 #12;Fernandez-Real, 1998 #165;Morelli, 2010 #163;Rossi, 2000
1039 #162}. The association with dyslipidemia is less proven, although biologically plausible.
1040 There is also evidence that patients with cortisol excess are at increased risk of
1041 cardiovascular events and excess mortality {Debono, 2014 #19;Di Dalmazi, 2014 #20}.
1042 Therefore, the panel recommended screening for these conditions, which are well known
1043 independent cardiovascular risk factors and which may be driven by cortisol excess, and to
1044 treat them according to current guidelines.

1045

1046

1047 **R.3.7 We suggest screening patients with ‘autonomous cortisol secretion’ for**
1048 **asymptomatic vertebral fractures (XOOO) and to consider appropriate**
1049 **treatment of these conditions (XOOO).**

1050

1051 Reasoning

1052 Several studies, although mainly from a single research group, have demonstrated an
1053 association between autonomous cortisol secretion and an increased risk of vertebral
1054 fractures {Hadjidakis, 2003 #145;Chiodini, 2004 #18;Chiodini, 2009 #53;Chiodini, 2010
1055 #11;Eller-Vainicher, 2012 #13;Morelli, 2011 #14}. Although most of the fractures are
1056 asymptomatic, the panel suggests screening patients with ‘autonomous cortisol secretion’ for
1057 vertebral fractures at least once at the time of diagnosis. This may be done by re-evaluating
1058 the available images (if a CT was performed) or by plain X-ray. The panel did not reach
1059 consensus on recommending assessment of bone mineral density by dual-energy x-ray
1060 absorptiometry (DXA). If osteoporosis is present, active treatment should be considered. If
1061 there is no other likely explanation for the osteoporosis, removal of the adrenal adenoma
1062 might be considered (see R3.8).

1063

1064

1065 **R.3.8 We suggest an individualized approach in patients with ‘autonomous cortisol**
1066 **secretion’ due to a benign adrenal adenoma and comorbidities potentially**
1067 **related to cortisol excess for adrenal surgery (X000). Age, degree of cortisol**
1068 **excess, general health, comorbidities and patient’s preference should be taken**
1069 **into account. In all patients considered for surgery, ACTH-independency of**
1070 **cortisol excess should be confirmed.**

1071

1072 Reasoning

1073 Due to the limitations of current literature, especially the lack of high-quality randomized
1074 trials, the panel could not reach consensus on the exact indication for surgery for
1075 ‘autonomous cortisol secretion’. The panel appreciated that there is some evidence of
1076 improvement of hypertension, hyperglycemia and dyslipidemia with surgery but this is based
1077 on low quality data. However, no data are available on clinically relevant endpoints (e.g.
1078 mortality or major cardiovascular events). Thus, the decision to undertake surgery should be
1079 individualized taking into account factors that are linked to surgical outcome, such as
1080 patient’s age, duration and evolution of comorbidities and their degree of control, and
1081 presence and extent of end organ damage. Because it is not possible to be sure that surgical
1082 intervention will normalize or improve the clinical phenotype of an individual patient, there
1083 was no complete agreement within the panel with regard to the optimal management of
1084 these patients. Approaches varied between two ends of the spectrum. Overall, the group
1085 agreed that there is an indication of surgery in a patient with post dexamethasone cortisol >
1086 140 nmol/l (> 5 µg/dl) and the presence of at least two comorbidities potentially related to
1087 cortisol excess (e.g. type 2 diabetes, hypertension, obesity, osteoporosis), of which at least
1088 one is poorly controlled by medical measures. Conversely, there is no reason for surgery,
1089 when serum cortisol post dexamethasone is < 140 nmol/l (< 5 µg/dl) and no comorbidities
1090 are present. However, some panel members favor a more proactive approach, for example
1091 considering surgical intervention, especially in younger patients with ‘possible autonomous
1092 cortisol’ secretion and less comorbidities potentially related to cortisol excess, even if
1093 controlled by medical therapy.

1094 However, there was consensus that when surgery is considered due to ‘autonomous cortisol
1095 secretion’, ACTH-independency has to be proven by a suppressed or low basal morning
1096 plasma ACTH. If not, other reasons of cortisol excess have to be considered.

1097

1098

1099 **R.3.9 We recommend excluding pheochromocytoma by measurement of plasma free**
1100 **metanephrines or urinary fractionated metanephrines.**

1101

1102 Reasoning:

1103 For details we refer to the most recent guidelines of other societies (e.g. {Lenders, 2014
1104 #48}). Of note, there are clinically silent pheochromocytomas {Haissaguerre, 2013
1105 #150;Erickson, 2001 #241;Kopetschke, 2009 #242} that might lead to hemodynamic
1106 instability during surgical excision {Lafont, 2015 #151}. Thus, metanephrines should be
1107 measured in normotensive patients and the diagnosis of pheochromocytoma should be
1108 considered in patients with borderline values of metanephrines and indeterminate imaging
1109 features on CT.

1110 In adrenal lesions with imaging criteria of an adenoma the likelihood of a pheochromocytoma
1111 is extremely low {Sane, 2012 #210;Schalin-Jantti, 2015 #217}. Thus, it seems to be
1112 reasonable to avoid measuring metanephrines in patients with clear evidence of an adrenal
1113 adenoma, but definitive data in this area are lacking.

1114

1115

1116 **R.3.10 In patients with concomitant hypertension or unexplained hypokalemia, we**
1117 **recommend the use of the aldosterone / renin ratio to exclude primary**
1118 **aldosteronism.**

1119

1120 Reasoning:

1121 For details we refer to the most recent guidelines of other societies (e.g. {Funder, 2008
1122 #276}).

1123

1124

1125 **R.3.11 We suggest measurement of sex hormones and steroid precursors in patients**
1126 **with imaging or clinical features suggestive of adrenocortical carcinoma.**

1127

1128 Reasoning:

1129 Adrenocortical carcinoma is associated in more than half of cases with elevated sex
1130 hormones and steroid precursors {Berruti, 2012 #156;Fassnacht, 2013 #54;Libe, 2007
1131 #157;Else, 2014 #153}. The panel does not recommend measurement of these hormones in
1132 patients with adrenal incidentalomas on a routine basis, but in cases with indeterminate
1133 adrenal mass by imaging or clinical signs for androgen excess, significantly increased sex
1134 hormones or precursors might clearly point towards adrenocortical carcinoma. Thus,
1135 measurement of serum DHEA-S, androstenedione, 17-hydroxyprogesterone as well as
1136 testosterone in women and estradiol in men and postmenopausal women can prove the
1137 adrenocortical nature of the adrenal mass. However, the panel acknowledges that the
1138 published evidence for this suggestion is very low {Arlt, 2011 #34;Fassnacht, 2013 #54}. A

1139 very promising new tool to discriminate benign from malignant adrenocortical tumors appears
1140 the analysis of a comprehensive urinary steroid profile measured by GC-MS or LC-MS {Arlt,
1141 2011 #34;Kerkhofs, 2015 #216}.

1142 **5.4. Surgical treatment**

1143

1144 **R.4.1 We recommend adrenalectomy as the standard of care for unilateral adrenal**
1145 **tumors with clinically significant hormone excess.**

1146

1147 *Reasoning:*

1148 As covered by several other guidelines, there is consensus that adrenal tumors leading to
1149 clinically significant hormone excess (e.g. primary aldosteronism, Cushing syndrome or
1150 pheochromocytoma) should be surgically removed {Lenders, 2014 #48;Funder, 2008
1151 #276;Nieman, 2015 #138}. The guideline group is convinced that for these tumors the same
1152 rules regarding the surgical approach should apply as for endocrine inactive tumors (see
1153 below). There are no substantiated reasons why the surgical approach for hormone-
1154 producing tumors should differ from that in endocrine inactive tumors (R4.3-5).

1155

1156

1157 **R.4.2 We recommend against performing surgery in patients with an asymptomatic,**
1158 **non-functioning unilateral adrenal mass and obvious benign features on**
1159 **imaging studies (XOOO).**

1160

1161 *Reasoning:*

1162 Most adrenal incidentalomas are non-functioning benign lesions (e.g. adenomas,
1163 myelolipomas) that do not cause harm. Therefore, there is broad consensus that the majority
1164 of these adrenal masses do not require surgery. The guideline group defined two criteria that
1165 need to be fulfilled to allow characterization of a unilateral adrenal lesion as not harmful: (i)
1166 imaging criteria indicating a benign lesion (see section 5.2, Table 4) (ii) no relevant endocrine
1167 activity (see section 5.3).

1168 There was considerable discussion by the group if a certain cutoff of size should be a factor
1169 to consider surgery. There was consensus that a tumor with a diameter of ≤ 4 cm with benign
1170 imaging features does not require surgery, accepting that this size cutoff is arbitrary.
1171 However, due to the paucity of follow-up data on the natural history of large apparently
1172 benign adrenal incidentalomas the panel was divided on the approach to the management of
1173 patients with larger lesions. One approach is to rely on imaging criteria only to determine if a
1174 lesion is benign irrespective of size. Alternatively, because of clinician or patient uncertainty
1175 about the increasing incidence of malignancy the larger is size, surgery may be considered in
1176 larger lesions (e.g. > 4 cm) even if imaging characteristics suggest a benign nature of the
1177 mass, allowing for an individualized approach. We voted against a certain cutoff which
1178 indicates that surgery has to be performed. However, we acknowledge that with a larger

1179 tumor size patients and clinicians might feel increasingly uncomfortable, but again an
1180 individualized approach was deemed most appropriate.

1181

1182

1183 **R.4.3 We suggest performing laparoscopic adrenalectomy in patients with unilateral**
1184 **adrenal masses with radiological findings suspicious of malignancy and a**
1185 **diameter \leq 6 cm, but without evidence of local invasion (XOOO).**

1186 **R.4.4 We recommend performing open adrenalectomy for unilateral adrenal masses**
1187 **with radiological findings suspicious of malignancy and signs of local invasion**
1188 **(XOOO).**

1189 **R.4.5 We suggest an individualized approach in patients that do not fall in one of the**
1190 **above mentioned categories (XOOO).**

1191

1192 Reasoning:

1193 The main threat of a unilateral adrenal mass, which is suspected to be malignant, is
1194 adrenocortical carcinoma. For adrenocortical carcinoma without metastases, surgery is the
1195 most important single therapeutic measure. Thus, the high expertise of the surgeon is of
1196 major importance. Although we cannot provide a specific number of required operations per
1197 year, we have no doubts that surgical volume correlates with better outcome. As summarized
1198 above (section 4.1.3) there are nine cohort studies on surgery for localized adrenocortical
1199 carcinoma comparing laparoscopic versus open adrenalectomy, each with more than ten
1200 patients per group {Brix, 2010 #24;Cooper, 2013 #25;Donatini, 2014 #26;Fossa, 2013
1201 #27;Lombardi, 2012 #28;Miller, 2010 #29;Miller, 2012 #30;Mir, 2013 #31;Porpiglia, 2010
1202 #32}, but these studies are, however, hampered by methodological flaws, and importantly
1203 none was randomized. Nevertheless, based on these data and the clinical experience of the
1204 guideline group members, it was judged that laparoscopic adrenalectomy may be justified for
1205 tumors with radiological signs of malignancy but only where there was no evidence of local
1206 invasion. For this approach the group arbitrarily chose a cut-off size for the adrenal tumor of
1207 \leq 6 cm, because for this size it is believed that laparoscopic adrenalectomy is feasible
1208 without rupture of tumor capsule (a major risk factor for recurrence), and is beneficial for the
1209 patient (e.g. less pain, shorter hospital stay). However, with increasing tumor size risk of
1210 tumor capsule rupture may increase. If during surgery there is a risk of tumor capsule
1211 rupture, conversion to open procedure should be performed. We acknowledge that the cutoff
1212 of 6 cm for laparoscopic vs. open adrenalectomy is not based on good evidence from clinical
1213 studies, and we recognize that laparoscopic adrenalectomy for tumors $<$ 6 cm is common
1214 practice in most centers. However, this cutoff by no means indicates that every tumor smaller
1215 than 6 cm has to undergo laparoscopic adrenalectomy and every tumor larger than 6 cm

1216 open adrenalectomy. We are convinced that in many cases an individualized decision
1217 process is required to find the best surgical approach for a given patient. This is also true for
1218 all patients that do not fall in one of the categories described in R.4.2 - 4.4.

1219

1220 There are no sufficiently powered studies published on the approach to patients with stage III
1221 adrenocortical carcinoma (local invasion, lymph nodes metastases, or tumor thrombus in the
1222 renal vein or vena cava). However, the guideline group unanimously voted for open
1223 adrenalectomy as standard procedure for this stage of disease.

1224

1225

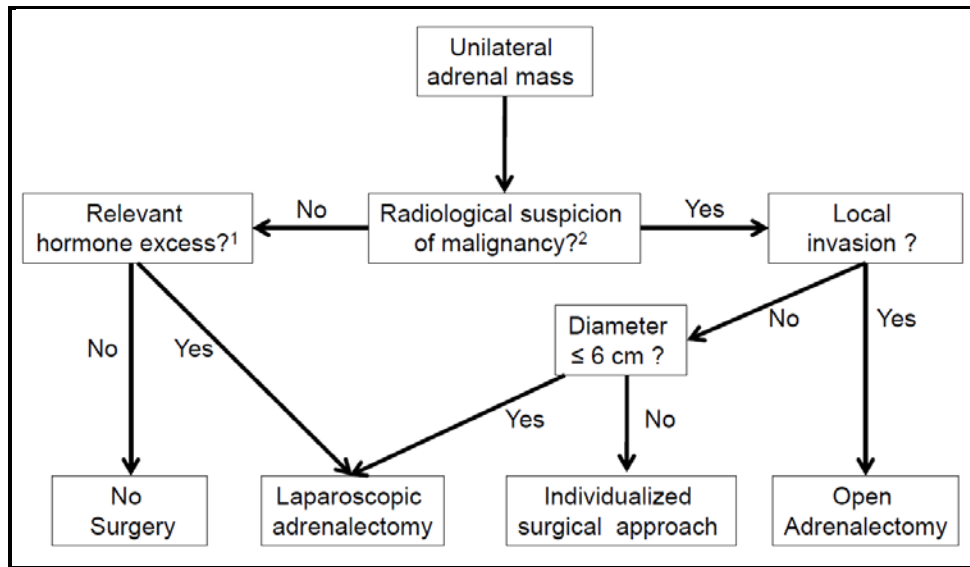
1226 **R.4.6 We recommend perioperative glucocorticoid treatment at major surgical stress**
1227 **doses, as recommended by guidelines, in all patients undergoing surgery for**
1228 **an adrenal tumor where there is evidence of ‘possible autonomous cortisol**
1229 **secretion’ or ‘autonomous cortisol secretion’.**

1230

1231 Reasoning:

1232 Autonomous cortisol secretion may lead to adrenal insufficiency after removal of the adrenal
1233 source of cortisol (even in patients with incompletely suppressed ACTH {Eller-Vainicher,
1234 2010 #214}). Therefore, the group unanimously recommends intra- and post-operative
1235 glucocorticoid replacement, preferably by hydrocortisone in patients with an adrenal tumor
1236 and evidence for ‘(possible) autonomous cortisol secretion’ (post dexamethasone cortisol >
1237 50 nmol/l (> 1.8 µg/dl)) even if there are no clinical sign of cortisol excess. This should follow
1238 the suggestions for major stress dose replacement as per a recent international guideline
1239 {Bornstein, 2016 #211}. Postoperatively, the glucocorticoid dose should be tapered
1240 individually by a physician experienced in this clinical scenario.

1241 **Figure 3: Flow-chart on the management of adrenal masses considered for**
 1242 **surgery**



1243

1244

1245 ¹ 'autonomous cortisol secretion' is not automatically judged as clinically relevant (see section 5.3 for details).

1246 ² in tumors with benign radiological features and a tumor size > 4 cm, surgery might also be individually
 1247 considered (see text)

1248 **5.5 Follow-up of patients not undergoing adrenal surgery after initial**
1249 **assessment**

1250

1251 **R.5.1 We suggest against further imaging during follow-up in patients with an adrenal**
1252 **mass < 4cm with clear benign features on imaging studies (XOOO).**

1253

1254 Reasoning

1255 Amongst more than 2300 patients included in published follow-up studies {Cawood, 2009
1256 #35;Terzolo, 2011 #33} there is no report of occurrence of adrenal malignancy in adrenal
1257 incidentalomas displaying typical features of adrenocortical adenomas at initial imaging
1258 studies. Therefore, the panel does not support repeating imaging investigations if the initial
1259 work-up is unequivocally consistent with a benign lesion. However, many patients with
1260 adrenal incidentalomas > 4 cm in diameter have undergone adrenalectomy in the past and
1261 the literature on follow-up of non-operated large adrenal incidentalomas is scarce. Thus, and
1262 similar to the discussion on the surgical treatment (R.4.2), some panel members argued that
1263 one follow-up imaging (non-contrast CT or MRI) after 6-12 months might be considered in
1264 lesions > 4 cm.

1265

1266

1267 **R.5.2 In patients with an indeterminate adrenal mass (by imaging), opting not to**
1268 **undergo adrenalectomy following initial assessment, we suggest a repeat non-**
1269 **contrast CT or MRI after 6-12 months to exclude significant growth (XOOO). We**
1270 **suggest surgical resection if the lesion enlarges by more than 20% (in addition**
1271 **to at least a 5 mm increase in maximum diameter) during this period. If there is**
1272 **growth of the lesion below this threshold, additional imaging again after 6-12**
1273 **months might be performed.**

1274

1275 Reasoning

1276 Contrary to benign adrenal tumors that may exhibit a slow growth tendency with time,
1277 malignant adrenal lesions (mostly adrenocortical carcinoma and metastases) are almost
1278 invariably characterized by a rapid growth within months {Else, 2014 #153;Fassnacht, 2013
1279 #54;Berruti, 2012 #156}. Consequently, the panel recommends performing follow-up imaging
1280 studies in adrenal incidentaloma, in which the benign nature cannot be established with
1281 certainty at initial evaluation, in order to recognize early a rapidly growing mass. Many
1282 clinicians would opt for surgical removal if the mass is of larger size and cannot be
1283 determined as benign with certainty.

1284 Lack of growth of an adrenal mass over a period of 6-12 months makes a malignant mass
1285 highly unlikely while surgery is recommended if significant rapid growth is observed. There is
1286 no generally accepted definition of significant growth of an adrenal tumor. However, the
1287 panel proposes an adaptation of the RECIST 1.1 criteria {Eisenhauer, 2009 #56}. These
1288 criteria, which are used in most oncological trials, define progress by an increase of 20% of
1289 the largest diameter. Although RECIST 1.1 criteria are not validated for the differentiation
1290 between benign and malignant adrenal tumors, the 20% cut-off together with an absolute
1291 increase of at least 5 mm in diameter may serve as warning for significant growth and
1292 reconsideration then given for surgical excision.

1293 The panel is aware that there are exceptional cases of malignant adrenal tumor without
1294 significant growth for several years {Nogueira, 2015 #55;Ozsari, 2015 #158}. However, this
1295 can be considered a very rare exception and does not justify following all patients with an
1296 adrenal mass with repeated imaging over years. However, in case there is some measurable
1297 growth (10-20%) that does not qualify for the above-mentioned criteria, additional follow-up
1298 imaging should be considered.

1299

1300

1301 **R.5.3 We suggest against repeated hormonal work-up in patients with a normal**
1302 **hormonal work-up at initial evaluation unless new clinical signs of endocrine**
1303 **activity appear or there is worsening of comorbidities (e.g. hypertension and**
1304 **type 2 diabetes) (XOOO).**

1305

1306 Reasoning

1307 The pooled risk of developing clinically relevant hormonal excess (e.g. primary
1308 aldosteronism, Cushing's syndrome and pheochromocytoma) is below 0.3% in patients with
1309 initial hormonal work-up consistent with a non-functioning lesion {Cawood, 2009 #35;Terzolo,
1310 2011 #33}.

1311 Development of 'autonomous cortisol secretion' without signs of overt Cushing's syndrome is
1312 the most frequently reported event during the follow-up and may occur in 8 to 14% of
1313 patients with non-functioning adrenal incidentalomas. Owing to the risk of false positive
1314 results {Elamin, 2008 #159} the panel does not recommend systematic follow-up hormonal
1315 investigations in patients with non-functioning adrenal incidentalomas at initial evaluation (ie
1316 cortisol \leq 50 nmol/l (\leq 1.8 μ g/dl) post 1-mg overnight dexamethasone test).

1317

1318

1319 **R.5.4 In patients with 'autonomous cortisol secretion' without signs of overt**
1320 **Cushing's syndrome (see Figure 2), we suggest annual follow-up with re-**

1321 **assessment for cortisol excess and careful assessment of comorbidities**
1322 **potentially related to cortisol excess (X000). Based on the outcome of this**
1323 **evaluation the potential benefit of surgery should be considered.**

1324

1325 Reasoning

1326 As discussed above, it is extremely rare that patients will develop overt Cushing's syndrome
1327 during follow-up. However, as elaborated in section 5.3, the panel considers 'autonomous
1328 cortisol secretion' as a condition associated with several comorbidities (Table 2). Therefore,
1329 the panel recommends annual clinical follow-up in patients with 'autonomous cortisol
1330 secretion' and in patients with both 'possible autonomous cortisol secretion' and potentially
1331 associated comorbidities, in whom an initial decision against surgery was made (Figure 2).
1332 Clinical follow-up should include evaluation of potentially cortisol excess-related
1333 comorbidities. The presence or worsening of these conditions should prompt hormonal re-
1334 evaluation at any time during follow-up. Appropriate symptomatic treatment and
1335 reconsideration of surgical removal of the adrenal mass is recommended, in line with the
1336 observed changes in the clinical and hormonal status of the patient.

1337 In the absence of evidence, we suggest that follow-up by an endocrinologist beyond 2-4
1338 years is not needed in patients with no relevant change during this time.

1339 **5.6. Special circumstances**

1340

1341 **5.6.1 Patients with bilateral adrenal incidentalomas**

1342 **R.6.1.1 We recommend that for patients with bilateral adrenal masses each adrenal**
1343 **lesion is assessed at the time of initial detection according to the same**
1344 **imaging protocol as for unilateral adrenal masses to establish if either or both**
1345 **lesions are benign or malignant.**

1346

1347 Reasoning:

1348 In most cases bilateral adrenal masses represent benign bilateral adrenocortical disease:
1349 either bilateral adenomas, macronodular hyperplasia, or distinct bilateral nodules with normal
1350 or atrophic cortex intervening. The possibility of metastases (especially in patients with
1351 known malignancy), adrenal lymphoma or bilateral pheochromocytomas should also be
1352 considered. Moreover, bilateral adrenal masses may represent co-occurrence of different
1353 entities, such as adenoma, pheochromocytoma, cyst, myelolipoma, adrenocortical
1354 carcinoma, etc. Therefore the best approach is to separately characterize each lesion
1355 following the recommendations in R.2.2 and R.2.3.

1356

1357

1358 **R.6.1.2 We recommend that all patients with bilateral adrenal incidentalomas should**
1359 **undergo clinical and hormonal assessment identical to that in patients with**
1360 **unilateral adrenal incidentaloma. The same applies for the assessment of**
1361 **comorbidities that might be related to ‘autonomous cortisol secretion’ (Table**
1362 **2). In addition, 17-hydroxyprogesterone should be measured to exclude**
1363 **congenital adrenal hyperplasia, and testing for adrenal insufficiency should**
1364 **be considered if suspected on clinical grounds or if imaging suggests**
1365 **bilateral infiltrative disease or hemorrhages.**

1366

1367 Reasoning:

1368 Hormonal excess in patients with bilateral adrenal masses may originate either from one of
1369 the lesions or bilaterally. Cushing's syndrome, primary aldosteronism, and
1370 pheochromocytoma(s) may all be encountered. For the clinical assessment of these entities
1371 we refer to guidelines of other societies {Nieman, 2008 #47;Lenders, 2014 #48;Funder, 2008
1372 #276}. As for unilateral lesions, subtle autonomous cortisol secretion is the most common
1373 secretory abnormality and, therefore, requires a full assessment of related comorbidities.
1374 Occasionally, bilateral adrenal enlargement is due to congenital adrenal hyperplasia and

1375 therefore the additional measurement of 17-hydroxyprogesterone should be performed
1376 {Jaresch, 1992 #190}. However, the measurement of 17-hydroxyprogesterone to identify the
1377 most common cause of congenital adrenal hyperplasia, 21-hydroxylase deficiency, as the
1378 cause of bilateral adrenal hyperplasia should be interpreted with caution. In some cases
1379 increased levels of 17-hydroxyprogesterone may represent increased secretion of steroid
1380 precursors from the lesion(s) {Del Monte, 1995 #191} especially in malignant tumors or in
1381 bilateral macronodular adrenal hyperplasia. In these cases low/suppressed ACTH levels may
1382 argue against congenital adrenal hyperplasia. Bilateral adrenal enlargement due to
1383 metastatic disease rarely causes adrenal insufficiency (for details see R.6.3.6).

1384

1385

1386 **R.6.1.3 We suggest that for patients with bilateral incidentaloma the same**
1387 **recommendations regarding the indication of surgery and follow-up are used**
1388 **as for patients with unilateral adrenal incidentalomas.**

1389

1390 Reasoning:

1391 'Autonomous cortisol secretion' is more frequently encountered in patients with bilateral
1392 adrenal incidentalomas, compared to those with unilateral lesions, but there is no published
1393 evidence that they should be managed differently. However, in the few cases, in whom
1394 bilateral surgery is potentially indicated (e.g. bilateral pheochromocytomas), one can
1395 consider adrenal-sparing surgery {Castinetti, 2015 #192}.

1396

1397

1398 **R.6.1.4 We suggest that in patients with bilateral adrenal masses bilateral**
1399 **adrenalectomy is not performed for 'autonomous cortisol secretion' without**
1400 **clinical signs of overt Cushing's syndrome. In selected patients a unilateral**
1401 **adrenalectomy of the dominant lesion might be considered using an**
1402 **individualized approach considering age, degree of cortisol excess, general**
1403 **condition, comorbidities and patient preference.**

1404

1405 Reasoning:

1406 Surgery is a complex decision for patients with bilateral adrenal incidentalomas. This is
1407 because, in the absence of clinical signs of overt Cushing's syndrome, the clinical situation
1408 may not be severe enough to prompt surgical management. Moreover, bilateral
1409 adrenalectomy is associated with higher morbidity compared to unilateral surgery, the patient
1410 is dependent lifelong on adrenal replacement therapy and at risk for life-threatening adrenal
1411 crisis. In addition, glucocorticoid replacement is frequently sub-optimal and cannot mimic the

1412 diurnal profile of endogenous cortisol, and may result in persisting exposure to subtle cortisol
1413 excess. In bilateral macronodular adrenal hyperplasia there is limited evidence of beneficial
1414 effects of unilateral adrenalectomy {Debillon, 2015 #129;Perogamvros, 2015 #213}. In most
1415 published studies excision of the largest lesion was performed, based on observations that
1416 the size of the adrenal lesion correlates with the degree of cortisol excess {Debillon, 2015
1417 #129}. Adrenal venous sampling may aid in the lateralization of cortisol excess but the data
1418 are very weak {Young, 2008 #302}. Due to the limited available evidence, an individualized
1419 approach, considering age, degree of cortisol excess, general condition, comorbidity status
1420 and patient's preference is suggested. However, when bilateral surgery is potentially
1421 indicated, cortical sparing adrenalectomy might be considered {Vassiliadi, 2011 #195}.
1422 In cases of bilateral macronodular hyperplasia, especially in younger patients or those with
1423 relevant family history, family screening with 1 mg dexamethasone test can be considered.
1424 A number of patients will have evidence of the presence of aberrant receptors, but routine
1425 assessment by the complex testing {Vassiliadi, 2011 #197;Bourdeau, 2001 #201;Lacroix,
1426 2009 #199;Lacroix, 2004 #200;Lacroix, 2010 #198;Lacroix, 2001 #202;Libe, 2010
1427 #203;Lacroix, 2015 #140} that is needed to establish the presence of these receptors is hard
1428 to justify based on the fact that in the majority of patients long-term management will not be
1429 based on knowledge of receptor activity, and therefore we suggest that these tests should be
1430 confined to clinical studies.

1431

1432

1433 **5.6.2 Adrenal incidentalomas in young or elderly patients**

1434 **R.6.2.1 We recommend urgent assessment of an adrenal mass in children,**
1435 **adolescents, pregnant women and adults < 40 years of age because of a**
1436 **higher likelihood of malignancy.**

1437 **R.6.2.2 We suggest the use of MRI rather than CT in children, adolescents, pregnant**
1438 **women and adults < 40 years of age if dedicated adrenal imaging is required.**

1439 **R.6.2.3 We recommend that the management of patients with poor general health and**
1440 **a high degree of frailty be kept in proportion to potential clinical gain.**

1441

1442 Reasoning

1443 The incidence of adrenal incidentaloma shows clear variation with age, with the majority of
1444 patients presenting in the 5th to 7th decade of life. Overall incidence of adrenal incidentaloma
1445 in a population undergoing routine imaging not related to suspected adrenal disease is
1446 reported as 1-4 % {Ferreira, 2005 #128;Bovio, 2006 #45;Hammarstedt, 2010
1447 #126;Davenport, 2011 #125}. While 10 % or more of individuals older than 70 years harbor
1448 an adrenal mass detectable upon imaging or autopsy, adrenal nodules in individuals < 40

1449 years are much less prevalent and are a rarity in children and young adults. Consequently,
1450 work-up in young patients including pregnant women has to be pursued with urgency as the
1451 risk of malignancy in this cohort is much higher. Conversely, a smaller adrenal incidentaloma
1452 in an elderly patient can be assumed to have a very low pre-test probability of malignancy.
1453 Thus work-up in elderly patients only needs to be expedited if there are clear signs of
1454 suspicion of malignancy and the extent of imaging work-up should be kept in proportion to
1455 the clinical performance status of the individual and the expected clinical gain of further work-
1456 up in an affected patient.

1457 As radiation safety is even more important in the young patient, we suggest MRI as the
1458 preferred imaging technique. However, adapted low-dose unenhanced CT protocols can
1459 limited radiation exposure and can be considered as an alternative (especially if the
1460 availability of MRI is limited).

1461

1462

1463 **5.6.3 Patients with a newly diagnosed adrenal mass and a history of extra-** 1464 **adrenal malignancy (Figure 4)**

1465

1466 General remarks:

1467 In principle, for adrenal masses in patients with known extra-adrenal malignancy the same
1468 recommendations apply as described above. However, in this situation it is particularly
1469 important to consider the different pre-test probabilities and the life expectancy of the patient.
1470 In patients with underlying extra-adrenal malignancy and an indeterminate adrenal mass,
1471 studies revealed a high rate of malignancy, up to 70%. Although age specific subgroup
1472 analysis is not available, it can be assumed that older patients have a higher likelihood of co-
1473 existent benign adenomas. Conversely younger patients with an underlying malignancy are
1474 more likely to have a metastasis.

1475

1476

1477 **R.6.3.1 We recommend measurement of plasma or urinary metanephrines to exclude**
1478 **pheochromocytoma in patients with extra-adrenal malignancy with an**
1479 **indeterminate mass, even if the adrenal mass is likely to be a metastasis. We**
1480 **suggest additional hormonal work-up based on an individualized approach.**

1481

1482 Reasoning

1483 Pheochromocytomas are almost impossible to distinguish from metastasis by conventional
1484 imaging (including FDG-PET/CT). Furthermore, pheochromocytomas can lead to life-
1485 threatening complications, especially in the context of medical interventions (surgery,

1486 biopsies etc.) {Mannelli, 2012 #161;Stolk, 2013 #160;Lenders, 2014 #48}. Additional
1487 hormonal work-up should depend on the stage of the extra-adrenal malignancy and life
1488 expectancy. Evidence of adrenal hormone excess indicating that the mass is a primary
1489 adrenal lesion can influence management of the extra-adrenal malignancy.

1490

1491 **R.6.3.2 We suggest that in patients with a history of extra-adrenal malignancy FDG-**
1492 **PET/CT, performed as part of investigations for the underlying malignancy,**
1493 **can replace other adrenal imaging techniques.**

1494

1495 Reasoning:

1496 ¹⁸FDG-PETCT may add additional value in the assessment of an indeterminate adrenal
1497 mass, however, the evidence base is insufficient to make strong recommendations {Dinnes,
1498 2016 #246}. Both qualitative and quantitative interpretations of ¹⁸FDG-PETCT imaging have
1499 been studied, but these vary considerably. An adrenal lesion / liver ratio of 1.53-1.8 were
1500 investigated in patients with history of extra-adrenal malignancy (2 studies {Kunikowska,
1501 2014 #121;Villar Del Moral, 2010 #104}, 117 lesions) and found to have sensitivity of 82%
1502 (95%CI 41-97%) and specificity of 96% (95%CI 76-99%) to detect malignant disease.

1503

1504

1505 **R.6.3.3 We recommend that in patients with a history of extra-adrenal malignancy**
1506 **adrenal lesions characterized as benign by non-contrast CT require no further**
1507 **specific adrenal imaging follow-up.**

1508

1509 Reasoning

1510 See details R2.2-4. However, we acknowledge that the currently available data suggest a
1511 false negative rate of 7% in this population.

1512

1513

1514 **R.6.3.4 For indeterminate lesions in patients with a history of extra-adrenal**
1515 **malignancy, we recommend imaging follow-up assessing the potential growth**
1516 **of the lesion at the same interval as imaging for the primary malignancy.**
1517 **Alternatively, FDG-PET/CT, surgical resection or a biopsy (see also R.6.3.5)**
1518 **can be considered.**

1519

1520 Reasoning:

1521 In many patients with advanced extra-adrenal malignancy (e.g. with multiple metastases) the
1522 knowledge of the origin of the adrenal mass will not alter the clinical management of the

1523 patient. If, however, clinical management would be altered by the demonstration that the
1524 adrenal lesion is a metastasis, then every effort should be made to allow this discrimination.
1525 If the adrenal mass is potentially the only metastasis and if resection of this metastasis
1526 seems to be reasonable from an oncological point of view, then surgery should be
1527 considered. Regarding biopsy, we recommend applying the criteria provided in R.6.3.5.

1528

1529

1530 **R.6.3.5 We suggest performing a biopsy of an adrenal mass only if all of the following**
1531 **criteria are fulfilled: (i) the lesion is hormonally inactive (in particular, a**
1532 **pheochromocytoma has been excluded), (ii) the lesion has not been**
1533 **conclusively characterized as benign by imaging, and (iii) management would**
1534 **be altered by knowledge of the histology.**

1535

1536 Reasoning:

1537 Adrenal biopsy may present with a significant non-diagnostic rate and a potential for
1538 complications {Tamhane, 2016 #248}. Biopsy is only recommended for masses not
1539 characterized as benign on cross-sectional imaging and where a biopsy result would affect
1540 clinical treatment decisions. In patients with no other obvious metastatic lesions and when
1541 surgical removal of the lesion is an option, FDG-PET/CT should be considered in order to
1542 exclude metastases outside the adrenal that were not visualized by CT or MRI. Adrenal
1543 biopsy presents with lower diagnostic performance for ACC and therefore is not
1544 recommended in this setting {Tamhane, 2016 #248}.

1545

1546

1547 **R.6.3.6 We recommend assessment of residual adrenal function in patients with large**
1548 **bilateral metastases.**

1549

1550 Reasoning

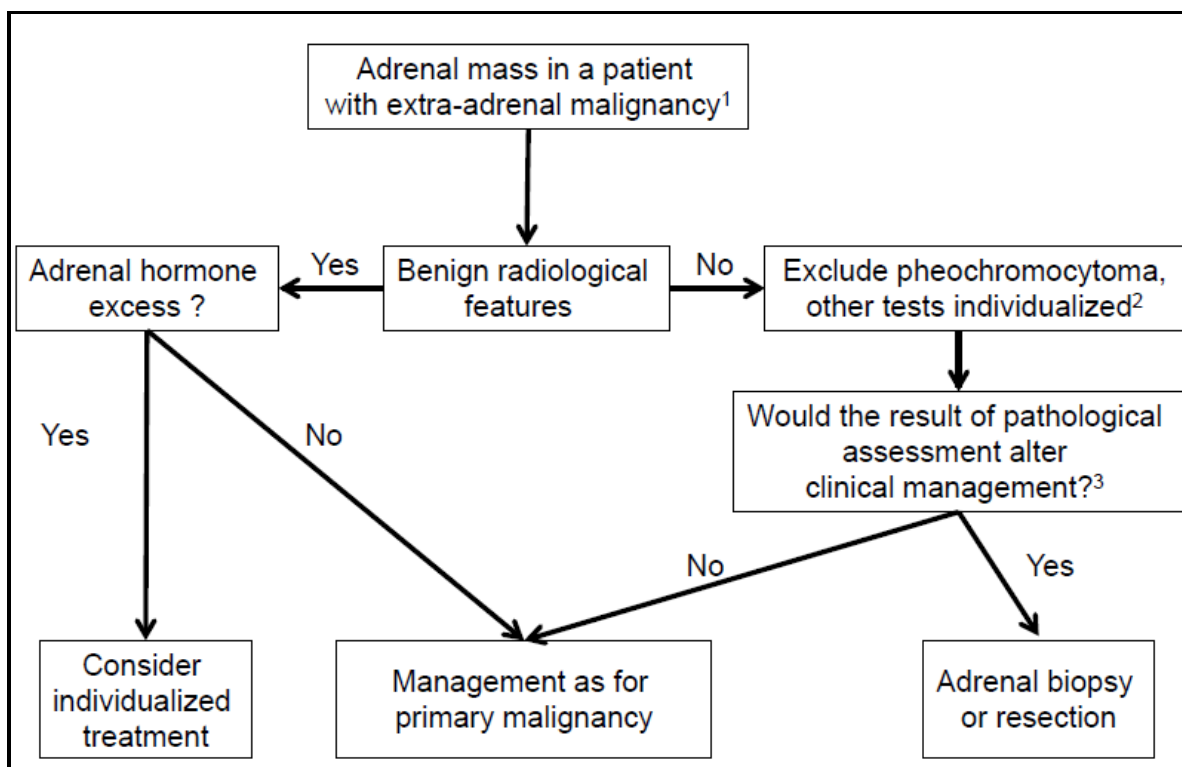
1551 In rare cases, bilateral adrenal metastases can lead to adrenal insufficiency. Thus, in all
1552 patients with potentially bilateral metastases, adrenal insufficiency should be considered and
1553 clinically evaluated. If adrenal insufficiency seems to be possible, we recommend first to
1554 measure a morning serum cortisol and plasma ACTH. In case of adrenal insufficiency,
1555 plasma ACTH is clearly elevated in parallel to low cortisol. In uncertain cases, a synacthen
1556 test should be performed {Bornstein, 2016 #211}.

1557 If only one adrenal metastasis is present, adrenal insufficiency is extremely unlikely and we
1558 recommend no specific assessment of adrenal reserve.

1559

1560
1561

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



1562
1563
1564
1565
1566
1567

¹ Always take life expectancy in consideration.

² If there is hormone excess, treat individualized.

³ FDG-PET/CT should be considered to exclude other metastatic deposits in patients with no other obvious metastatic lesions for whom surgical removal of the lesion is an option.

1568 **6. Future directions and recommended research**

1569

1570 The NIH conference on the management of the clinically unapparent adrenal mass in 2002
1571 formulated several research questions for future studies {Grumbach, 2003 #39}. Although
1572 some of these issues have been addressed, only few questions have been conclusively
1573 answered. From the current perspective we see need for clinical trials in all four areas
1574 particularly addressed in the guideline (see section 3.5). Given that most recommendations
1575 in this guideline are based on weak evidence, there is clearly room for studies aiming to
1576 improve the evidence base of management of adrenal incidentalomas.

1577 Among many important research questions, we selected five as particularly important. All of
1578 them can only be answered in a collaborative interdisciplinary manner.

1579 1) Large, cohort study in patients with an adrenal mass > 2 cm to investigate the most
1580 suitable imaging methods to determine if an adrenal mass is benign or not. It will be crucial to
1581 establish a definitive diagnosis either by histopathology or by long-term follow-up (> 2 years).

1582 2) Large, long-term study to define whether or not 'autonomous cortisol secretion' is
1583 associated with increased mortality and other hard clinical endpoints (e.g. myocardial
1584 infarction or stroke). Such a study will also provide evidence for a suitable biochemical
1585 definition of 'autonomous cortisol secretion'.

1586 3) Randomized trial on the potential benefit of surgery in patients with "autonomous cortisol
1587 secretion". To make such a trial feasible it is probably wise to define a surrogate endpoint
1588 (e.g. hypertension or type 2 diabetes) that can be well controlled (including standardized
1589 treatment regimens) throughout the study. A similar trial could evaluate the value of drugs
1590 targeting the cortisol excess.

1591 4) Prospective study (laparoscopic vs. open surgery) in patients with potentially malignant
1592 adrenal mass (<10 cm) without pre-operative evidence of local invasion and metastases to
1593 learn which surgical approach is the most suitable one for this patient cohort.

1594 5) We propose a long-term study with annual biochemical work-up of patients with adrenal
1595 incidentalomas to clarify if such a long-term hormonal assessment is justified. This study
1596 should also help to define the true incidence of relevant diseases like adrenocortical
1597 carcinoma and pheochromocytoma among incidentalomas.

1598

1599 Several other research questions deserve future research. Of particular importance seems to
1600 us the establishment of biomarkers to determine non-invasively the origin of the adrenal
1601 mass (adrenal cortex, medulla, extra-adrenal) and whether or not the mass is malignant.
1602 Currently, urine steroid metabolomics for non-invasive and radiation free detection of a
1603 malignant 'steroid fingerprint' in adrenocortical carcinoma patients {Arlt, 2011 #34} and the
1604 combination of functional imaging methods (e.g. metomidate-based imaging and FDG-

1605 PET/CT) are the most promising tools that should be further investigated. Similarly, for
1606 patients with 'autonomous cortisol secretion' new methods to stratify on an individual basis to
1607 intervention (or observation) are needed.

1608 **Acknowledgement**

1609 The authors of the guideline would like to thank and acknowledge Andre Lacroix, Radu
1610 Mihai, and Paul Stewart for their expert review and additional 28 members of the European
1611 Society of Endocrinology, the European Network for the Study of Adrenal Tumors or
1612 representatives of national endocrine societies for valuable and critical comments.
1613 Furthermore, we thank two patient representatives who provided valuable feedback for the
1614 guideline. **The comments of the reviewers as well as our responses are available until**
1615 **December 2016 at XXXX (website of ESE).**

1616

1617 **Funding**

1618 This guideline was sponsored by the European Society of Endocrinology with support by the
1619 European Network for the Study of Adrenal Tumors (via the European Science Foundation).

1620

1621 **Declaration of interest**

1622 The guideline was developed in collaboration with CBO – Dutch Institute for Health Care
1623 Improvement.

1624 **Appendix**

1625 **Table A1: Description of analyzed studies**

1626 **Table A2: Results of the GRADE analyses**

1627

1628 **Table A3: Selected drugs that may interfere with results of the dexamethasone**
1629 **test* (adapted according {Nieman, 2008 #47})**

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

1630

- *This should not be considered a complete list of potential drug interactions.

1631

- Data regarding CYP3A4 obtained from <http://medicine.iupui.edu/flockhart/table.htm>.

1632 **References**

1633