ECE 2023
25th European Congress of Endocrinology
13 – 16 May 2023, Istanbul Turkey

European Society of Endocrinology

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

Martin Fassnacht, Irina Bancos, Massimo Terzolo, John Newell-Price, Antoine Tabarin

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CONFLICT OF INTEREST

x **We have the following potential conflicts of interest to report**:

x Research Contracts: M.Fassnacht (Corcept; HRA); I.Bancos (HRA Pharma), M.Terzolo (HRA)

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

☐ Employment in the Industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

x Speaker: A.Tabarin (Recordati). M.Terzolo (HRA)

The ESE-ENSAT Guidelines Panel

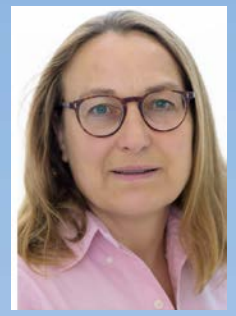
12 experts from 8 countries

Wiebke Arlt
UK

Irina Bancos
USA

Olaf Dekkers
The Netherlands

Martin Fassnacht
Germany

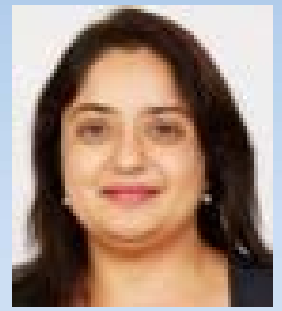


Kerstin Lorenz
Germany

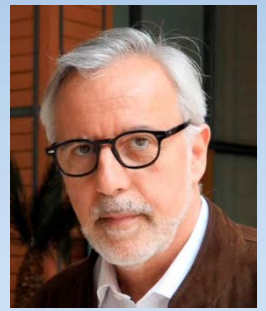
John Newell-Price
UK

Ljiljana Marina
Serbia

Iris Pelsma
The Netherlands



Anju Sahdev
UK



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Italy

Stelios Tsagarakis
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Internal Medicine / Endocrinology

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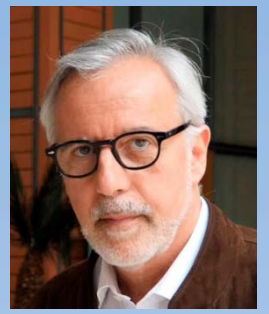

Antoine Tabarin

Massimo Terzolo

Stelios Tsagarakis

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Anju Sahdev

Methodologists

Olaf Dekkers

Iris Pelsma

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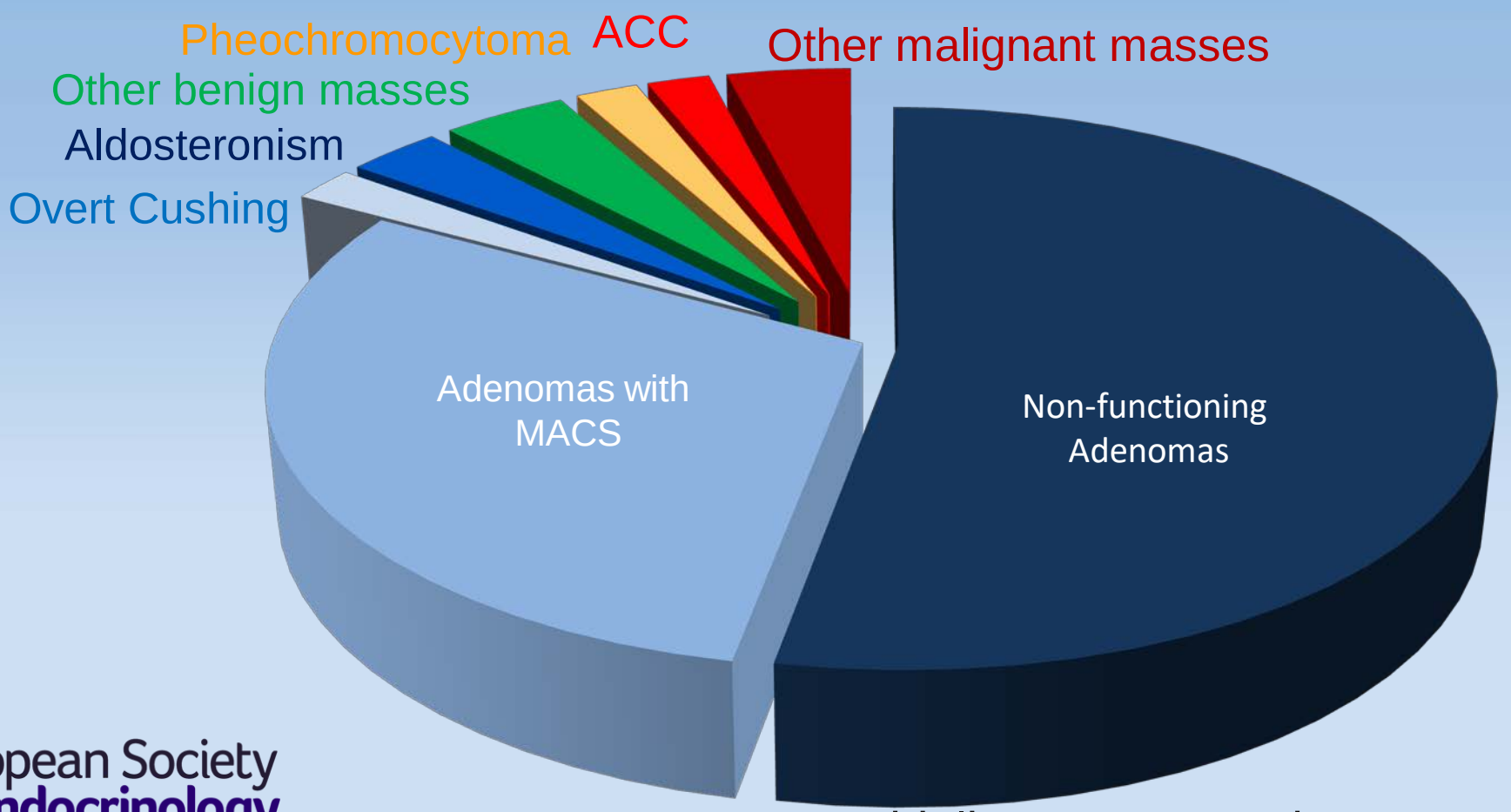
Definition

- An adrenal incidentaloma is an adrenal mass detected on **imaging not performed for suspected adrenal disease**.

- Adrenal masses discovered **during tumor evaluation** for extra-adrenal malignancies **do not meet** the strict definition of adrenal incidentaloma.
  However, as this is a clinically frequent scenario, this topic is covered in a specific chapter of the guideline.

Frequency of adrenal incidentalomas and their etiology

Autopsy and radiological studies suggest: prevalence of adrenal incidentaloma 2-3% (range 1.0-10%), which increases with age.



ESE-ENSAT guidelines EJE 2023 in press

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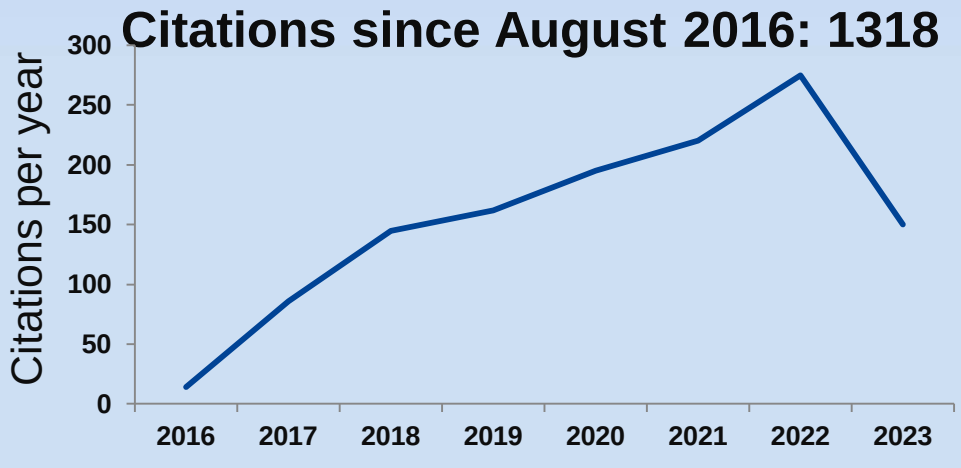
Where did we start?

EJE EUROPEAN JOURNAL OF ENDOCRINOLOGY

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

Martin Fassnacht[1,2], Wiebke Arlt[3,4], Irina Bancos[3,4,5], Henning Dralle[6], John Newell-Price[7,8], Anju Sahdev[9], Antoine Tabarin[10], Massimo Terzolo[11], Stylianos Tsagarakis[12] and Olaf M Dekkers[13,14]

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



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ESE-ENSAT guidelines 2016

40 recommendations with the main aims:

- to avoid „over-diagnostics“ and „over-treatment“
- without missing relevant diseases (e.g. adrenocortical carcinoma, pheochromocytoma etc.)

- to provide (as much as possible) guidelines based on scientific evidence

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GRADE approach

1. Define clinical questions
2. Systematic research
3. Quality of evidence (4 categories)
   Very low < low < moderate < strong
   ⊕OOO < ⊕⊕OO < ⊕⊕⊕O < ⊕⊕⊕⊕
4. Recommendations (2 grades)
   - Strong (‘we **recommend**’)
   - Weak (‘we **suggest**’)

Only for recommendations that based on systematic reviews

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Our 4 key research questions

1. How to assess risk of malignancy?
2. How to define and manage mild autonomous cortisol secretion?
3. Who should have surgical treatment and how should it be performed?
4. What follow-up is indicated if the adrenal incidentaloma is not surgically removed?

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4 systematic reviews

Overall, 4605 abstracts have been reviewed

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

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Key facts about the revised version

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

=> 49 recommendations

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2016: In the absence of strong evidence…

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

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Situation in 2023

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

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Our first recommendation

- R.1.1. We **recommend** that patients with adrenal incidentalomas are discussed in a **multidisciplinary expert team meeting**, if at least one of the following criteria is met:
  - Imaging is not consistent with a benign lesion.
  - There is evidence of hormone excess (including mild autonomous cortisol secretion in patients with clinically relevant comorbidities potentially attributable to cortisol).
  - Evidence of significant tumor growth during follow-up imaging.
  - Adrenal surgery is considered.
- The core multidisciplinary team should consist of a radiologist, an endocrinologist, and a surgeon, all with significant experience in the management of adrenal tumors.

Presentation of the four key questions and the respective recommendations: **Assessment of the risk of malignancy**

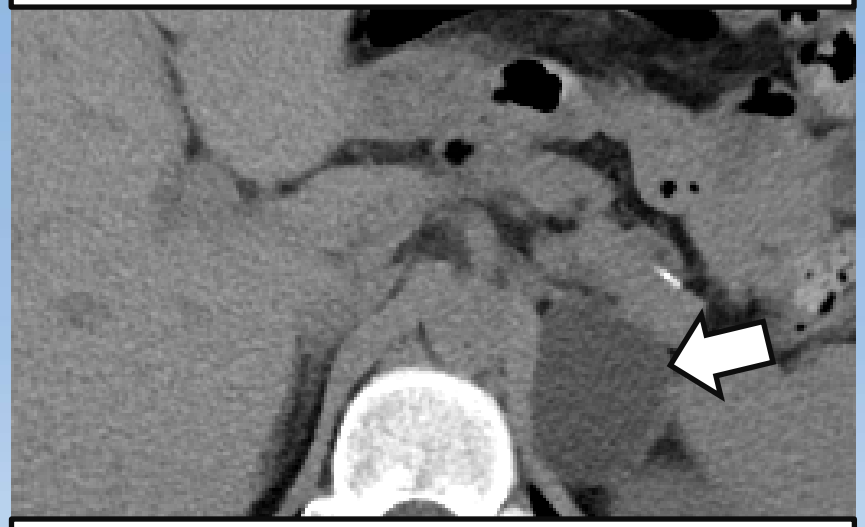
Irina Bancos, USA

Presentation of the four key questions and the respective recommendations: **Assessment of the risk of malignancy**

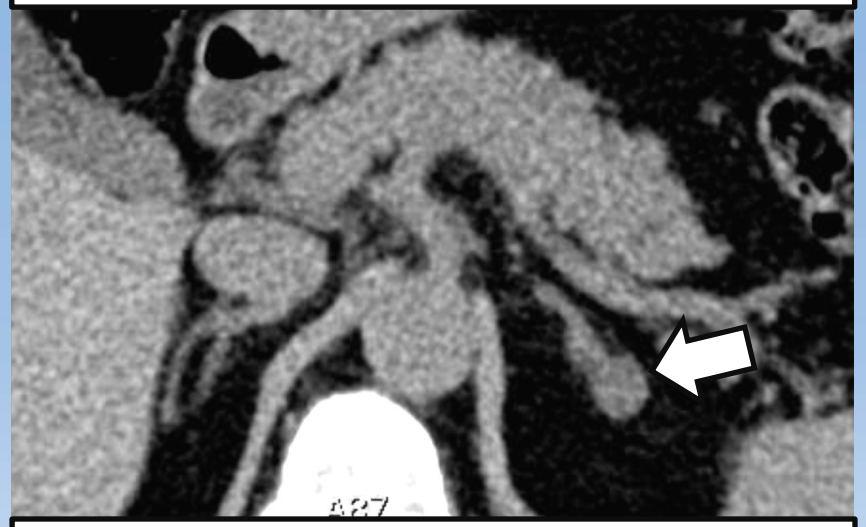
Irina Bancos, USA

Objective: to review recommendations on assessment of the risk of malignancy

42 YO woman: 4.6 cm, HU=6



67 YO man: 1.3 cm, HU=16



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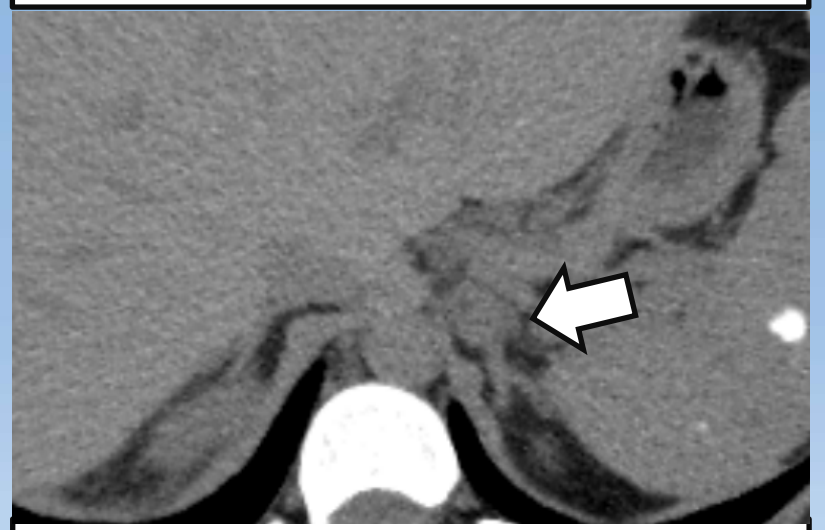
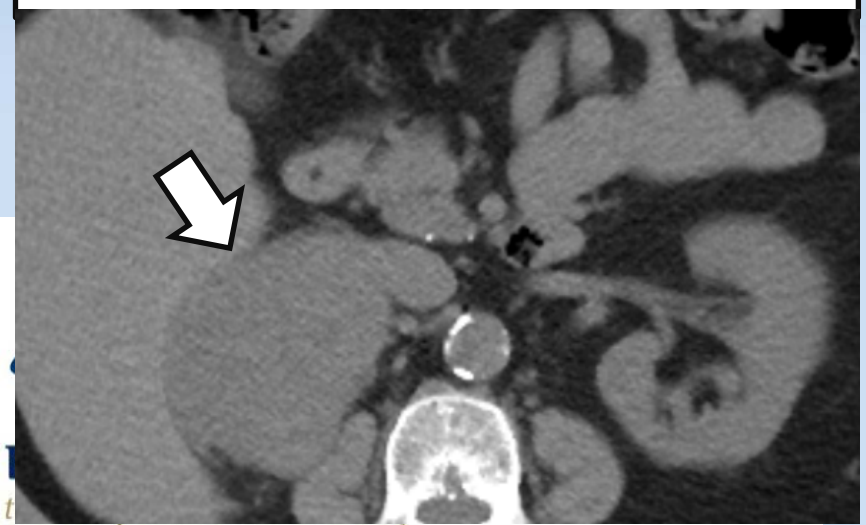


83 YO woman: 7.6 cm, HU=36



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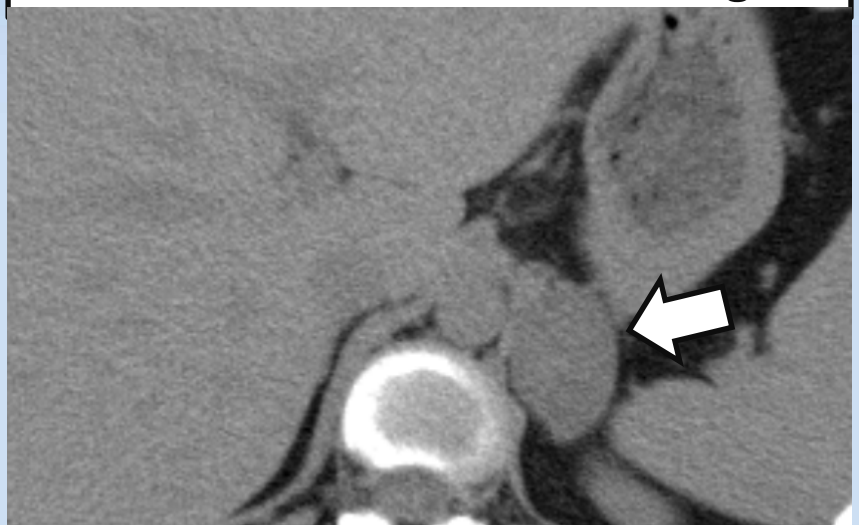

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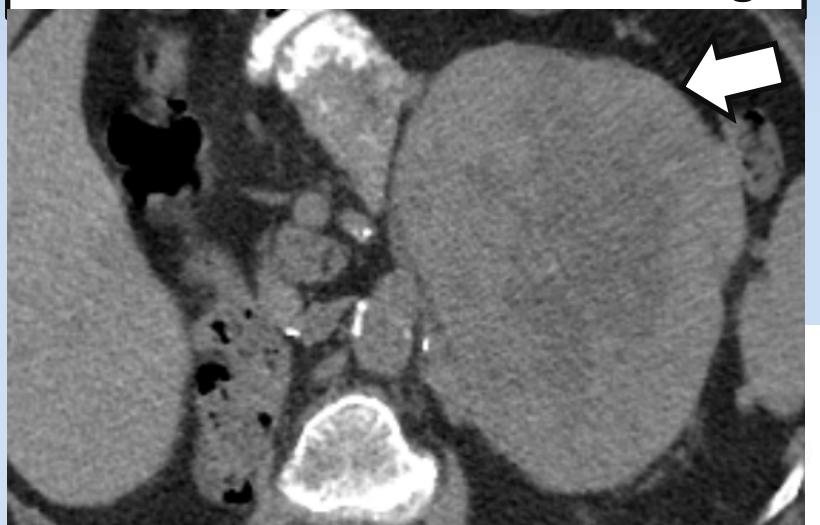
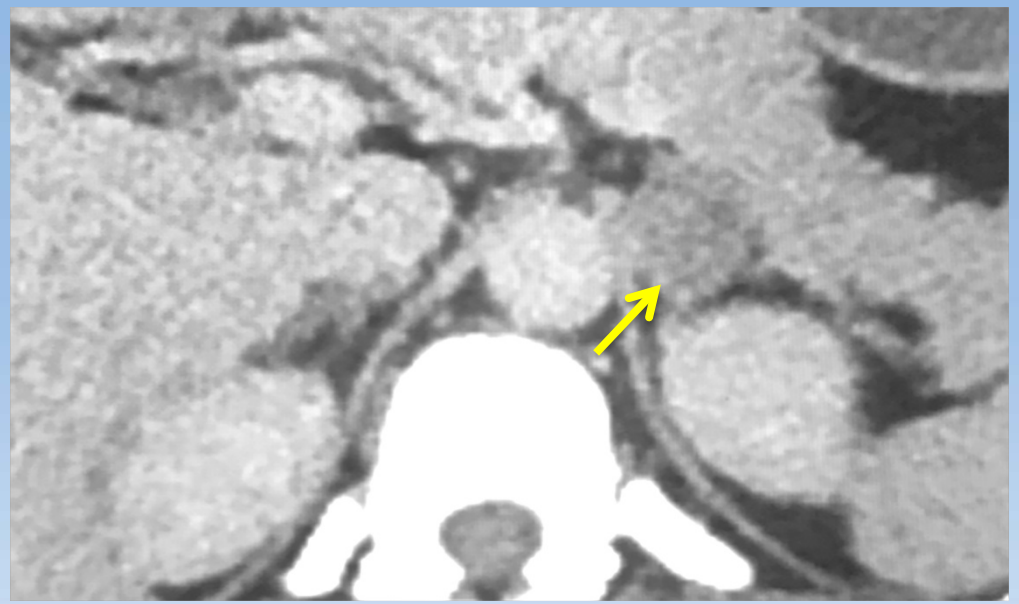


Common Clinical Presentations

Most frequent clinical presentation: Single phase Post Contrast CT



Small 1-4 cm unilateral homogenous adrenal mass

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

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

=> Reduces repeated investigations reducing radiation burden, cost, psychological distress

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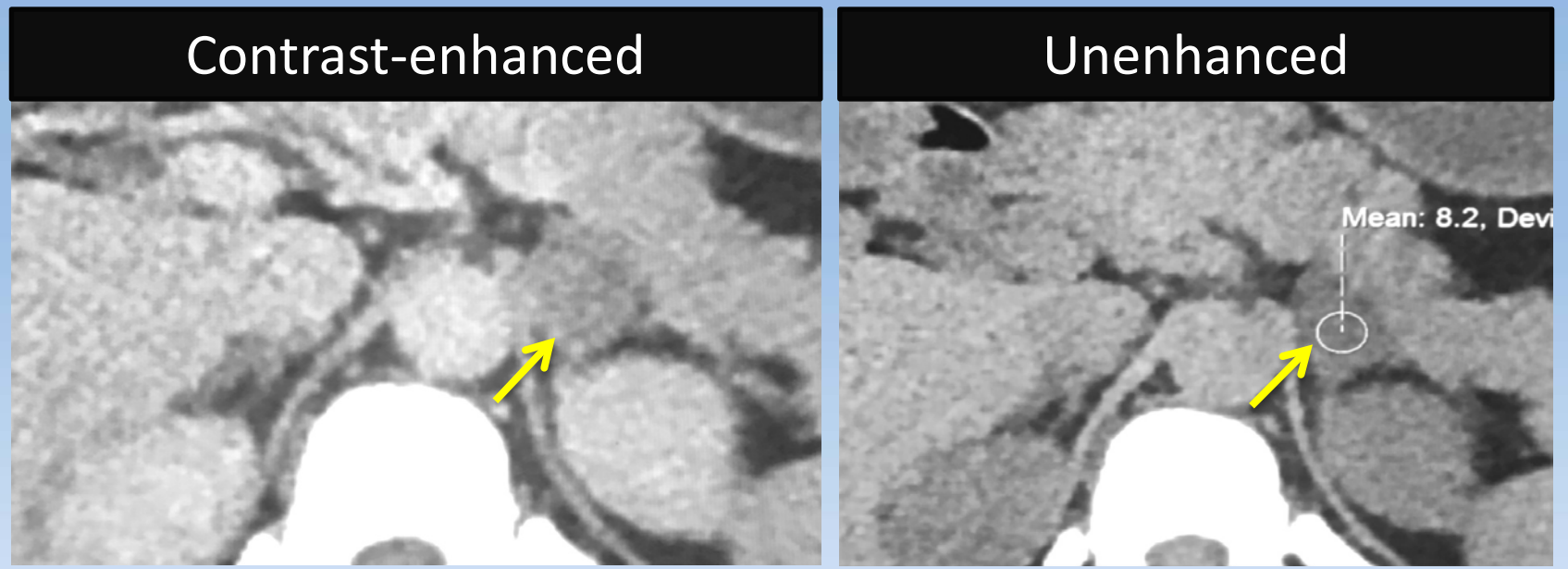
R.2.2. We recommend that all adrenal incidentalomas undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign. For this purpose, we recommend the use of **non-contrast CT** as the first imaging modality if not yet performed.



No further imaging required in around 70% of incidentalomas

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

Rationale

HU cutoff of 10:

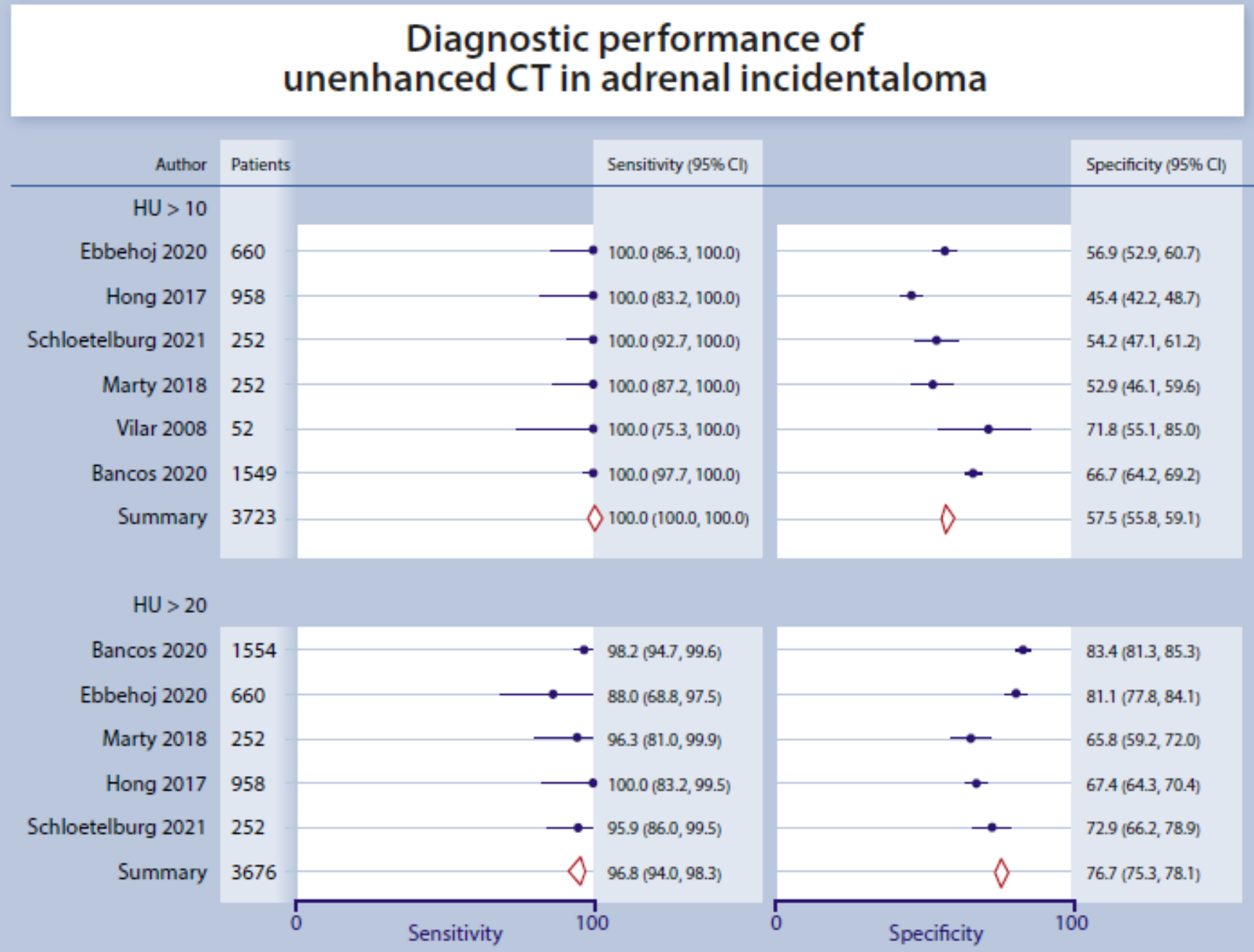
Sensitivity 100%

Specificity 57.5%

HU cutoff of 20

Sensitivity of 96.8%

Specificity of 76.7%



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Options for indeterminate tumors:

*Discussion at MDT

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

Options depend on risk, availability, other factors

- HU: >20 vs 10-20
- Tumor size
- Laterality
- History of cancer
- Hormone excess
- Age

- Homogeneous, HU >10
- Heterogeneous

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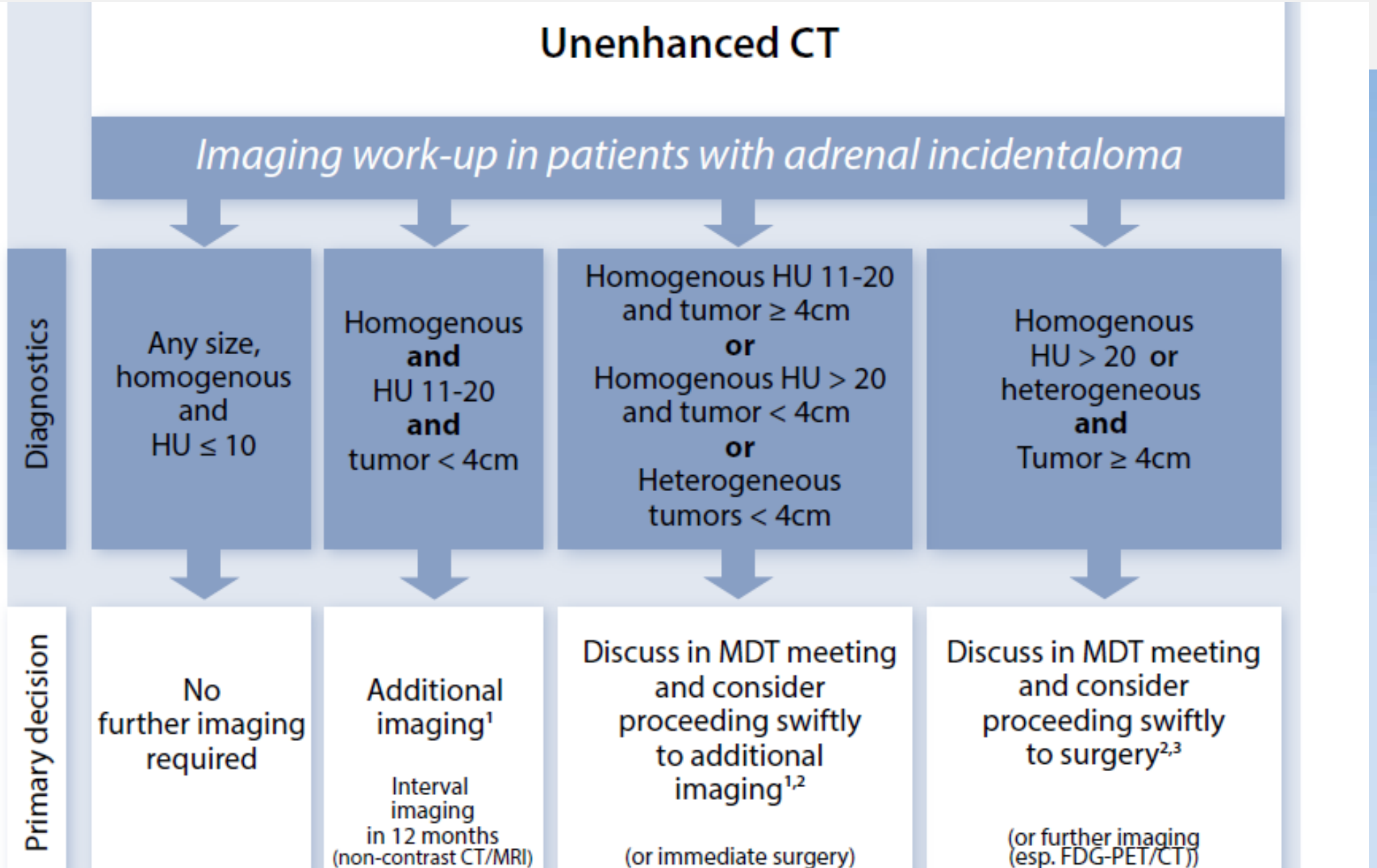
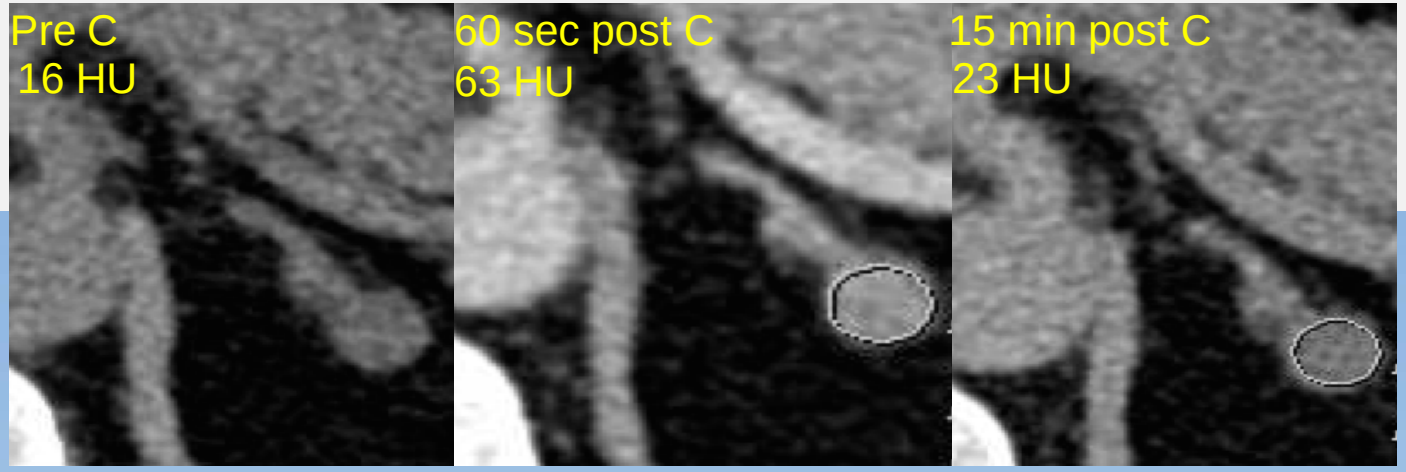
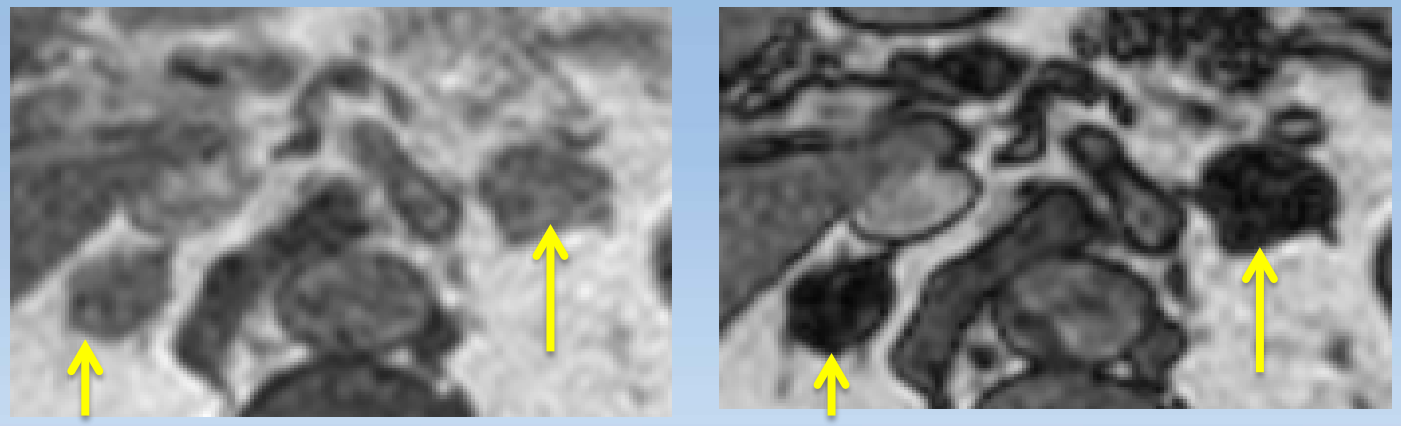
Indeterminate tumors: R2.4, 2.5, 2.6



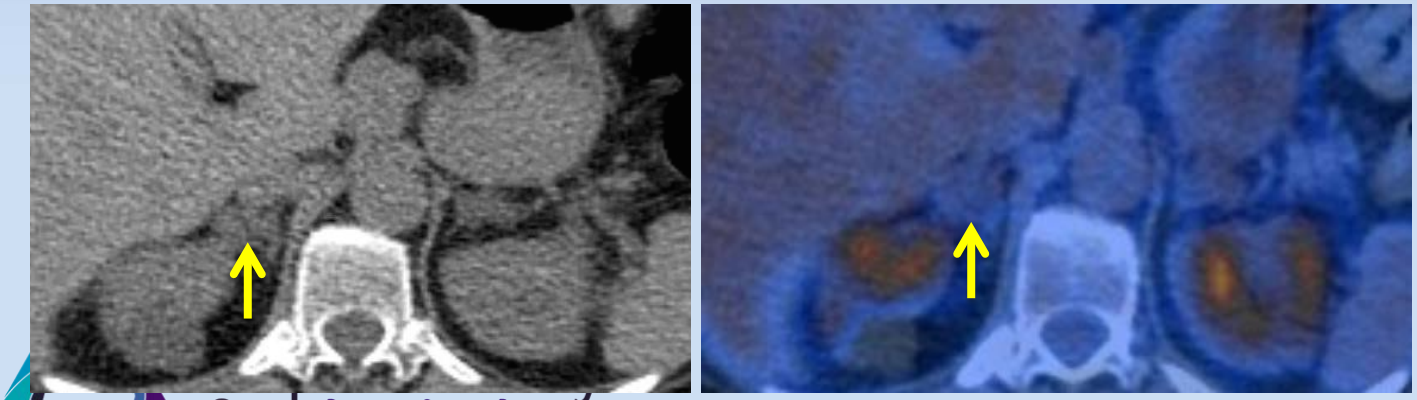


CT with delayed contrast media washout: absolute and relative washout

- weak data
- accuracy of cutoffs challenged



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

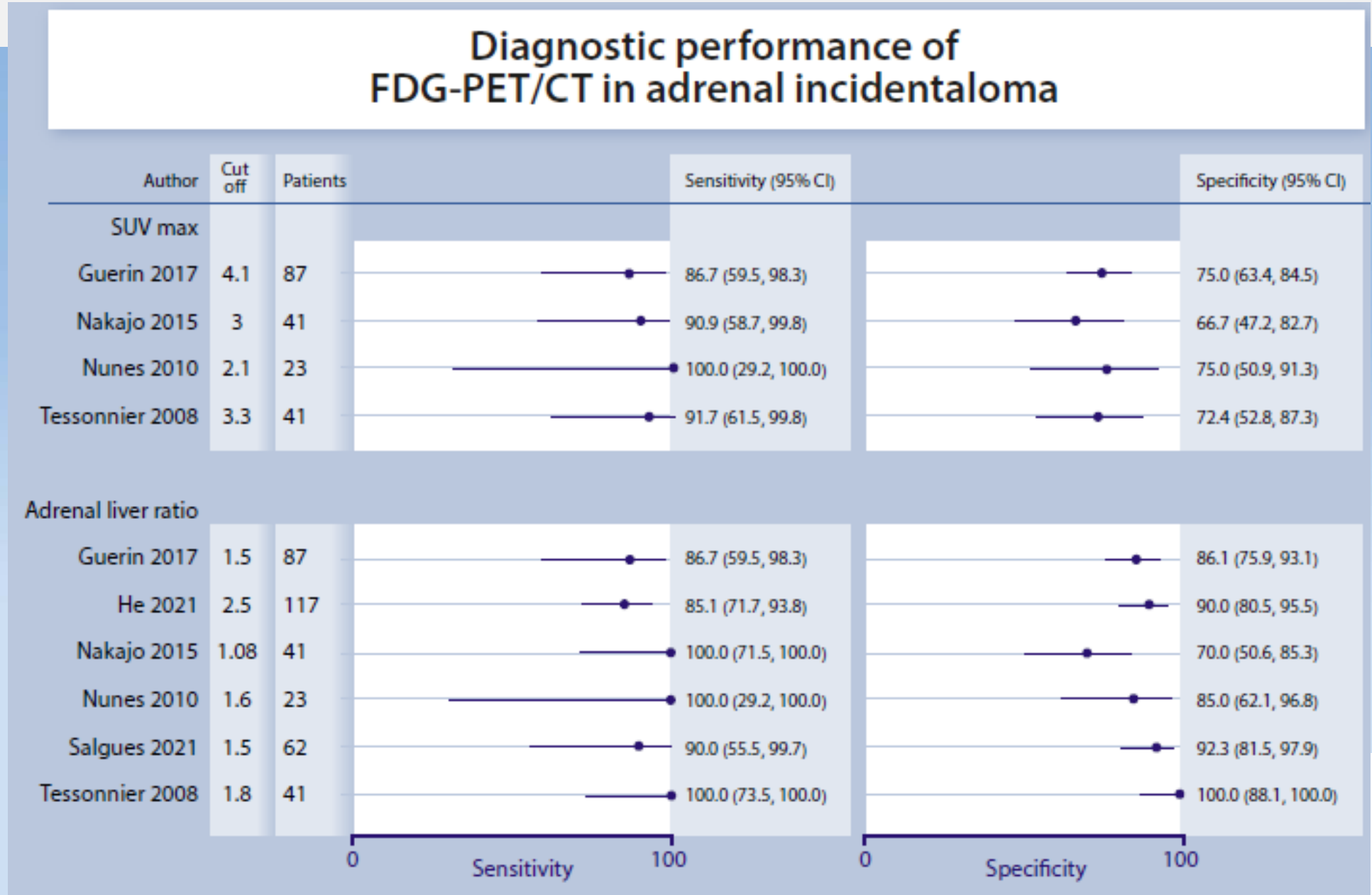


FDG-PET/CT:
Uptake less than liver
=> benign lesion

FDG PET scan

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

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



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Objective: to review recommendations on assessment of the risk of malignancy

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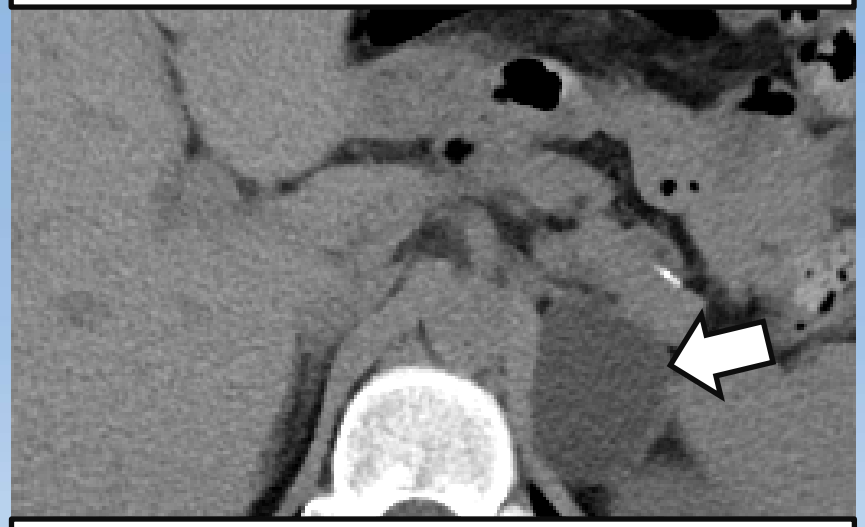

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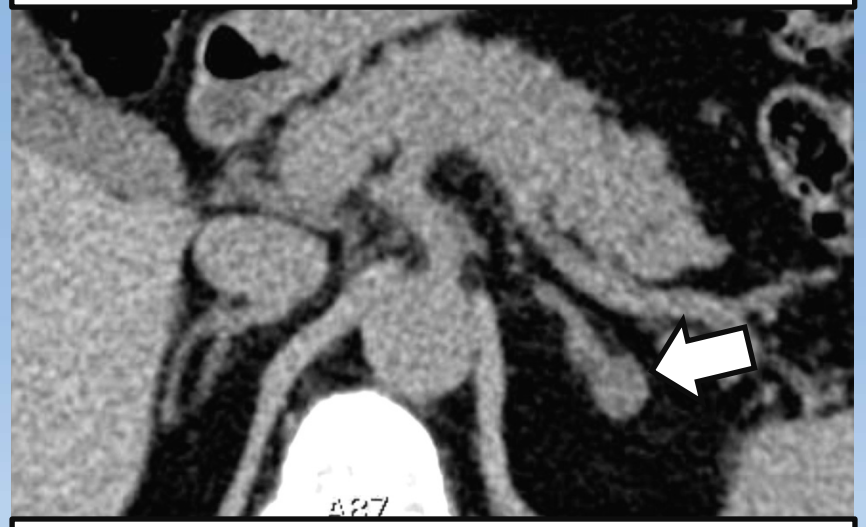

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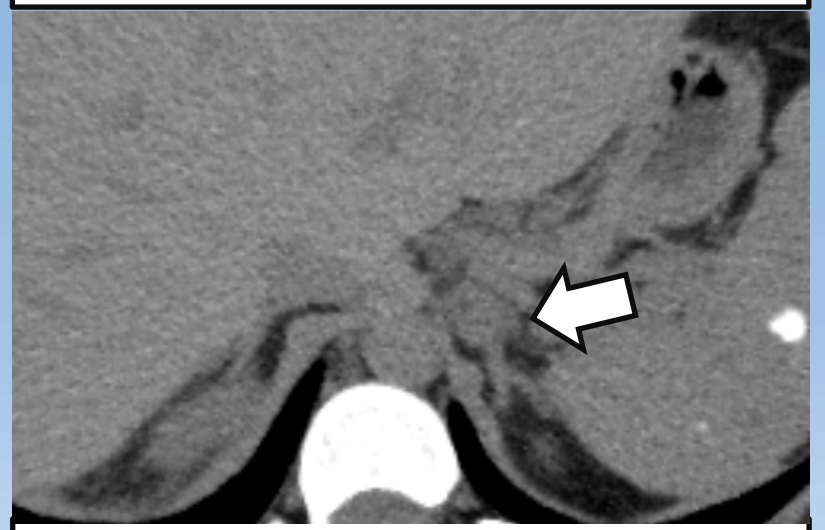

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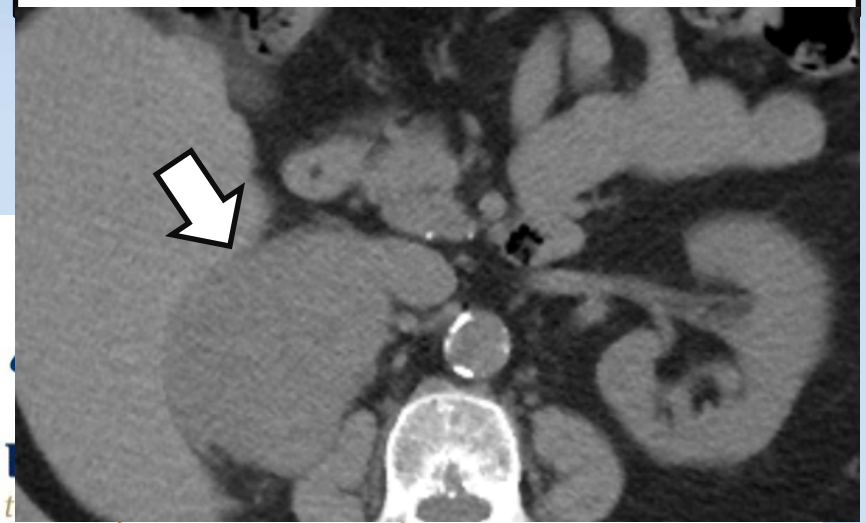

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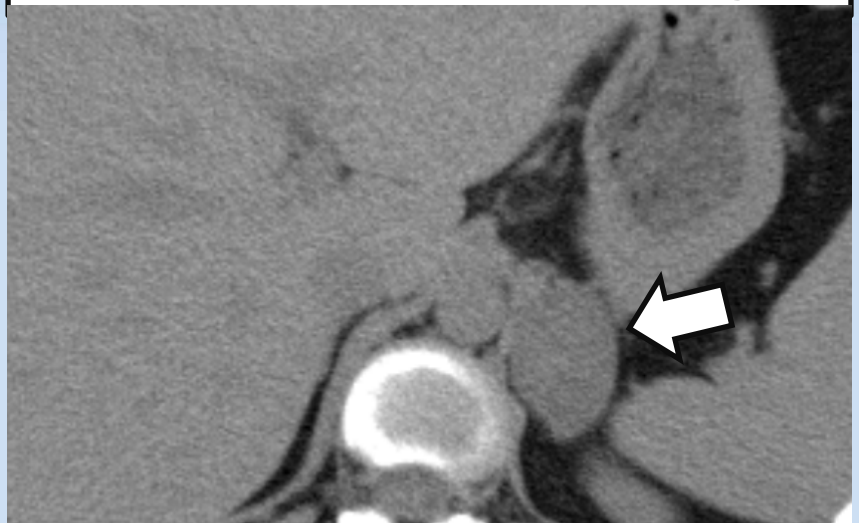

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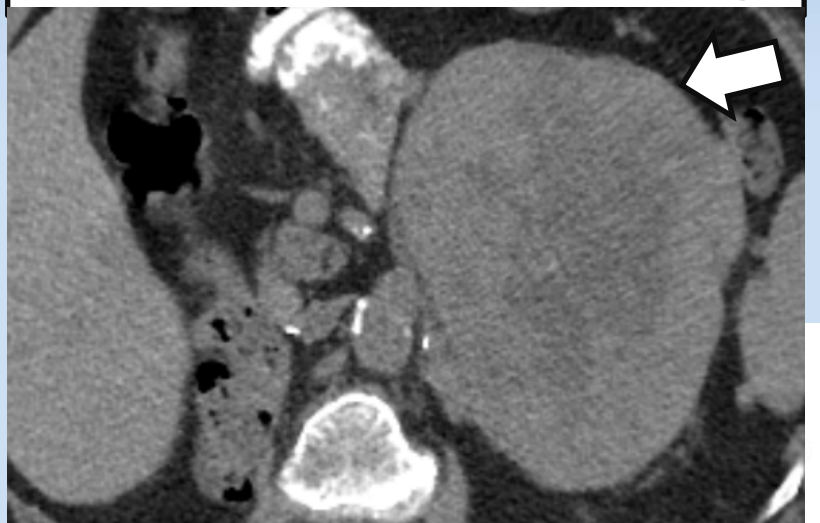
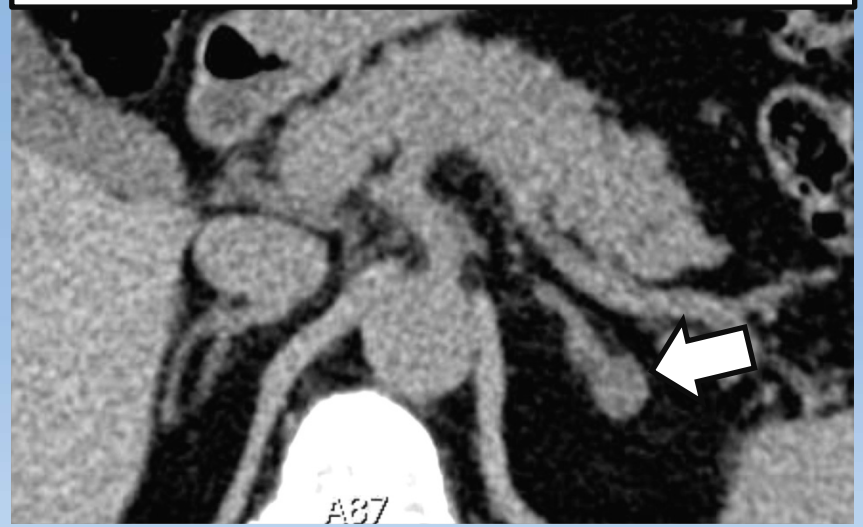


Indeterminate tumors: R 2.4

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

67 YO man: 1.3 cm, HU=16



Imaging 12 months later – no change in tumor size

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

Objective: to review recommendations on assessment of the risk of malignancy

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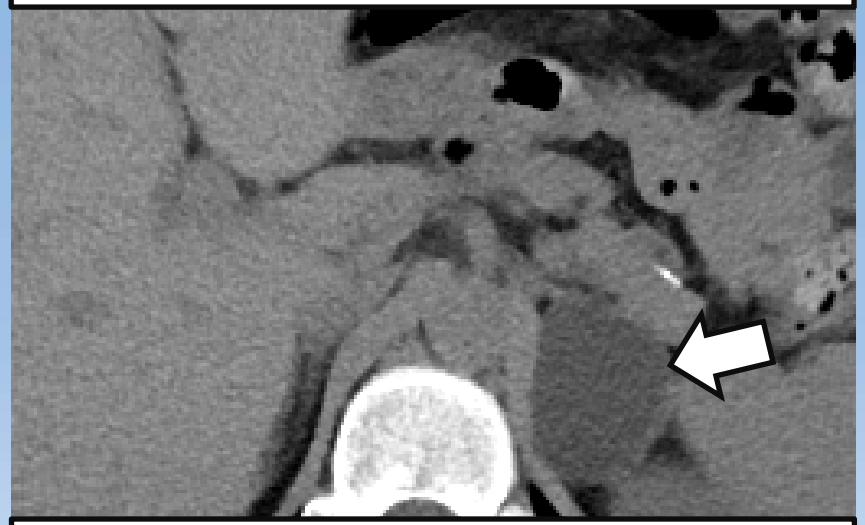

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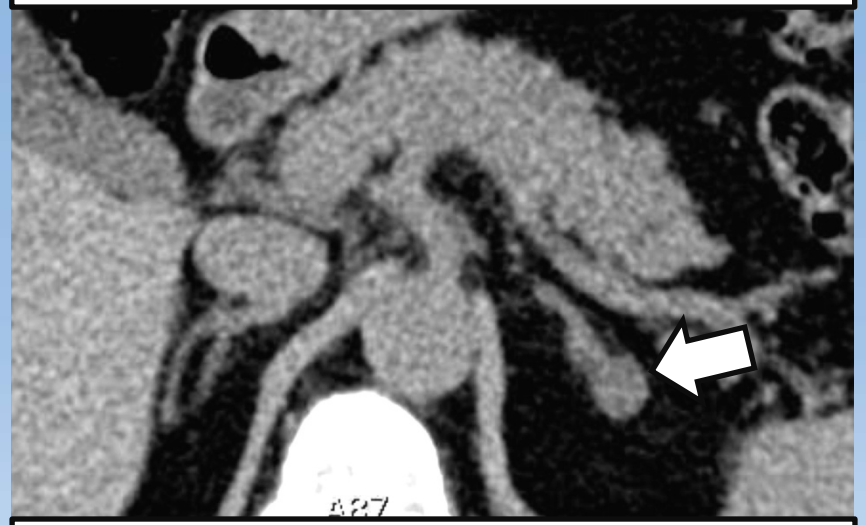

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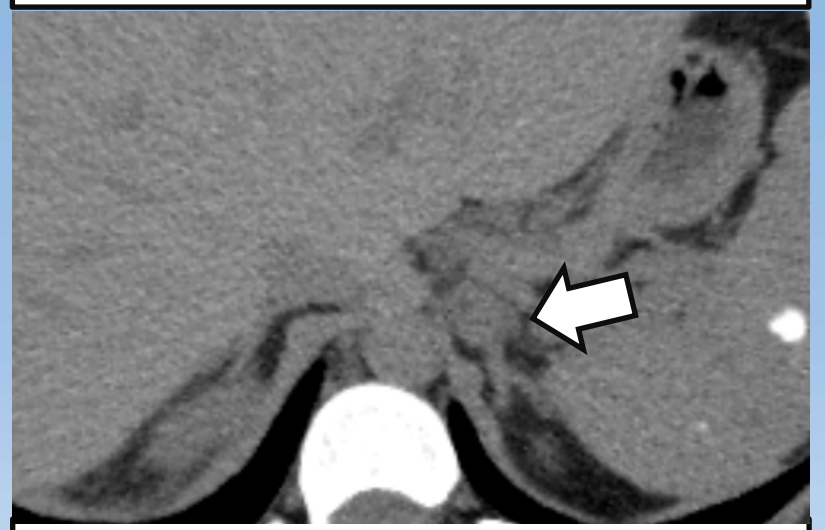

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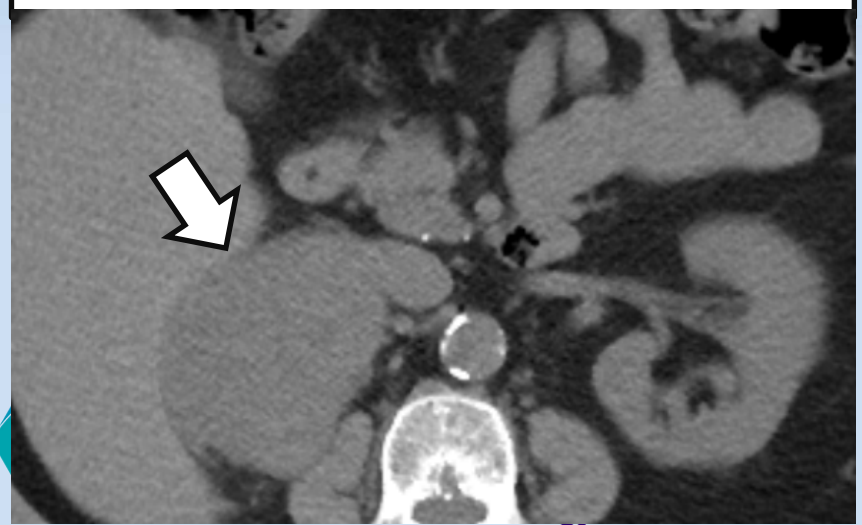

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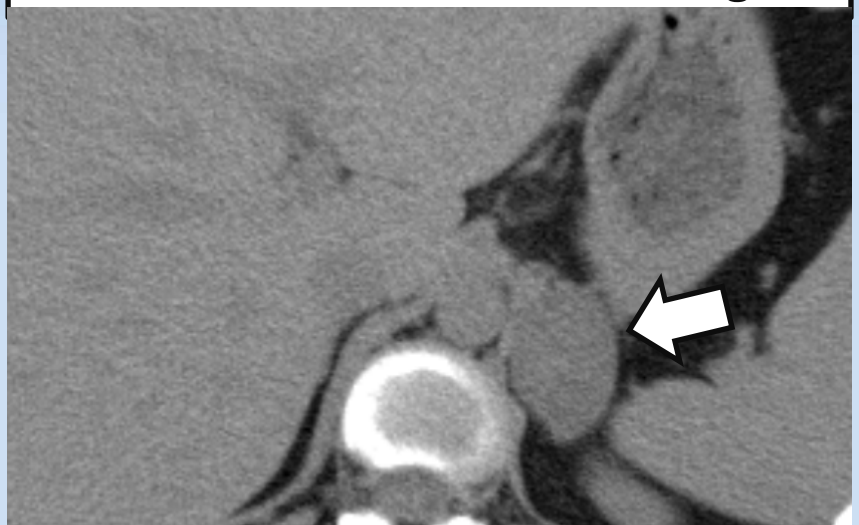

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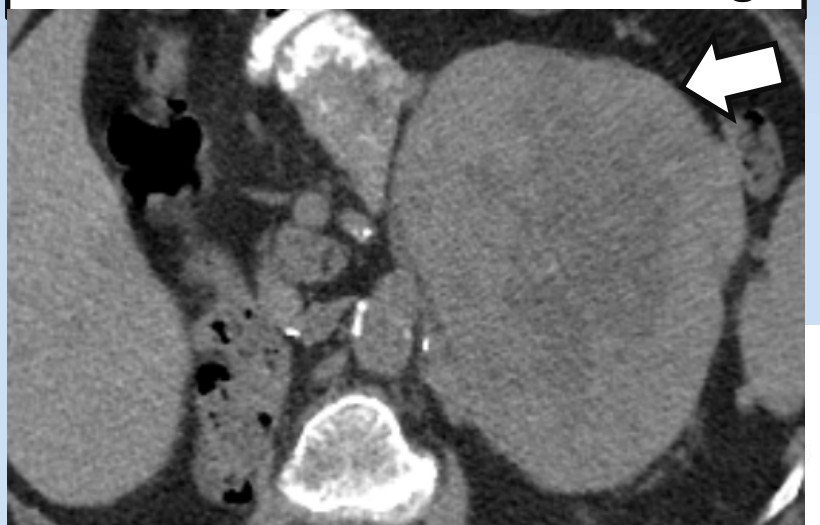

Indeterminate tumors: R 2.5

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

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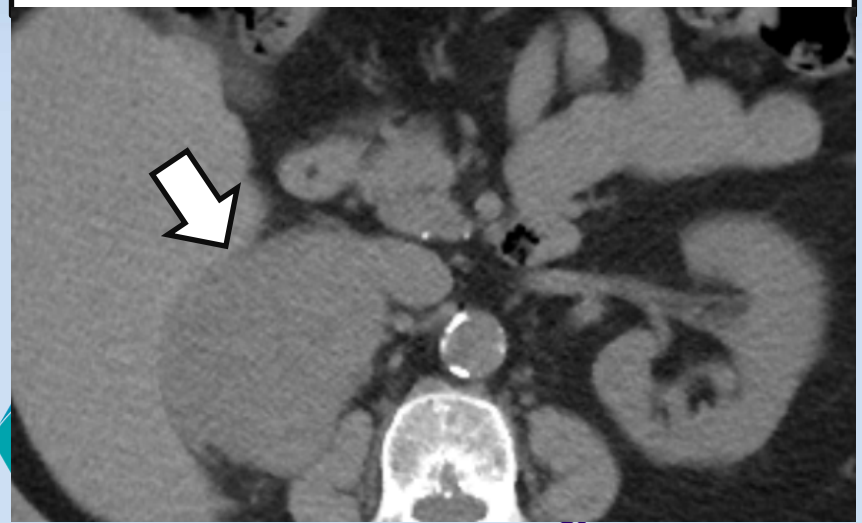

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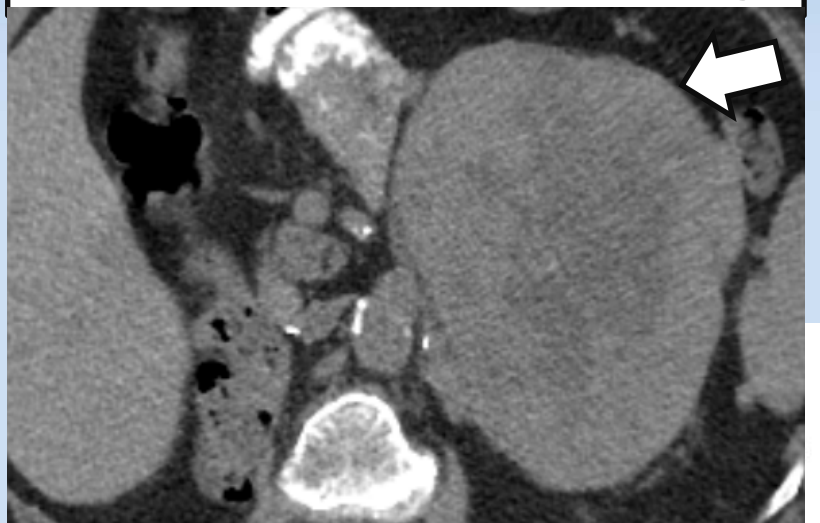

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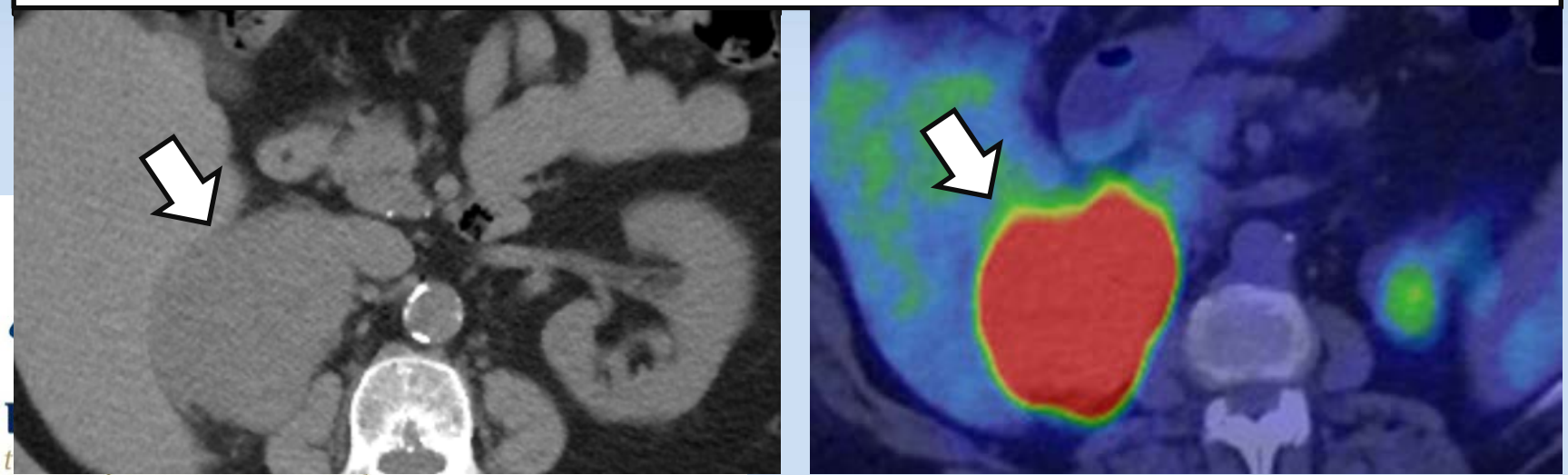
83 YO woman: 7.6 cm, HU=36, **SUV max of 40.9**



Adrenalectomy:
Adrenocortical carcinoma

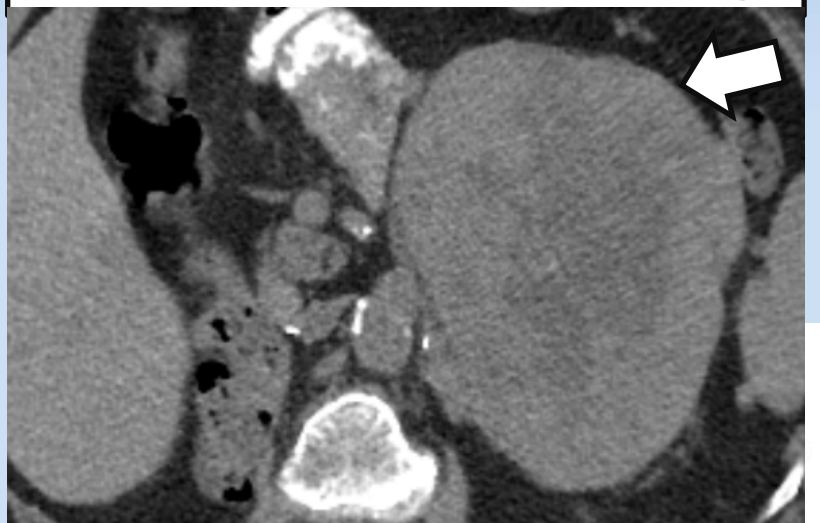
Adrenal biopsy

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

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

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

77 YO woman: 12 cm, heterog.



Biopsy: Renal cell carcinoma

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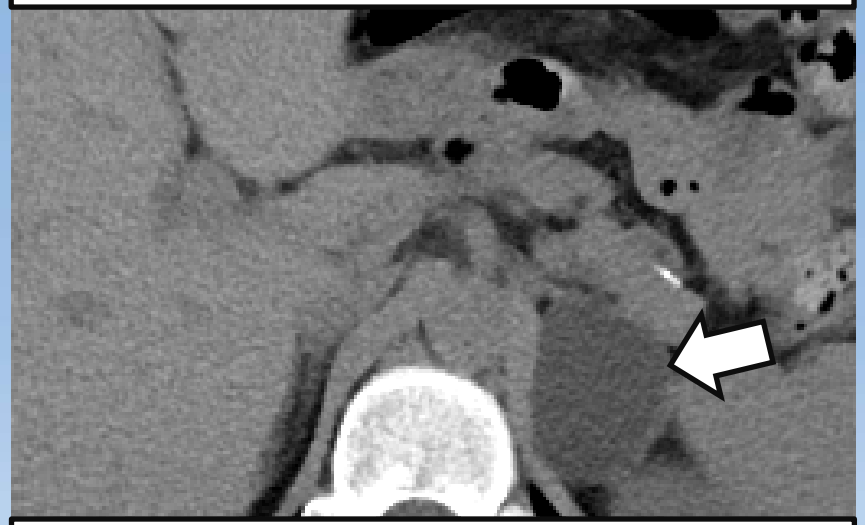
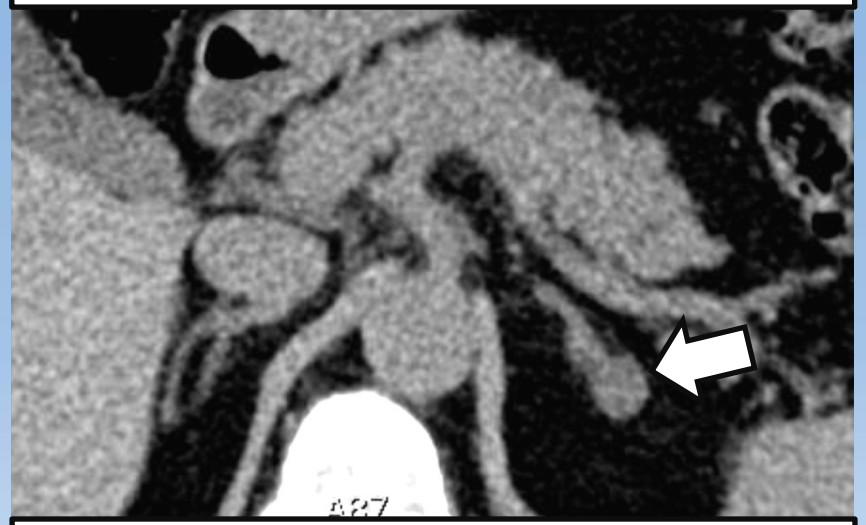
Objective: to review recommendations on assessment of the risk of malignancy

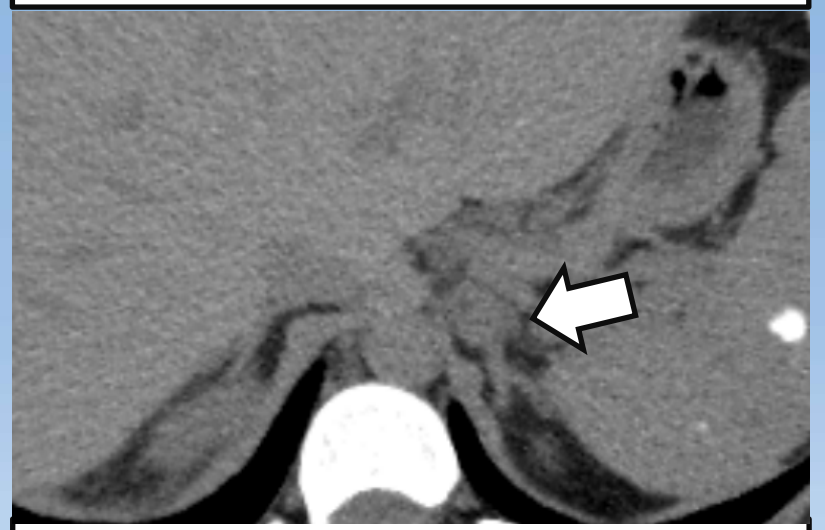
42 YO woman: 4.6 cm, HU=6



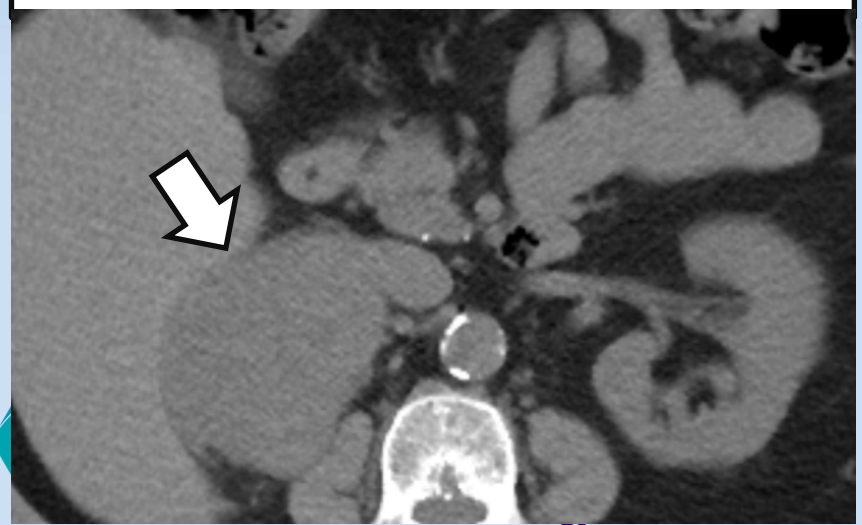
67 YO man: 1.3 cm, HU=16



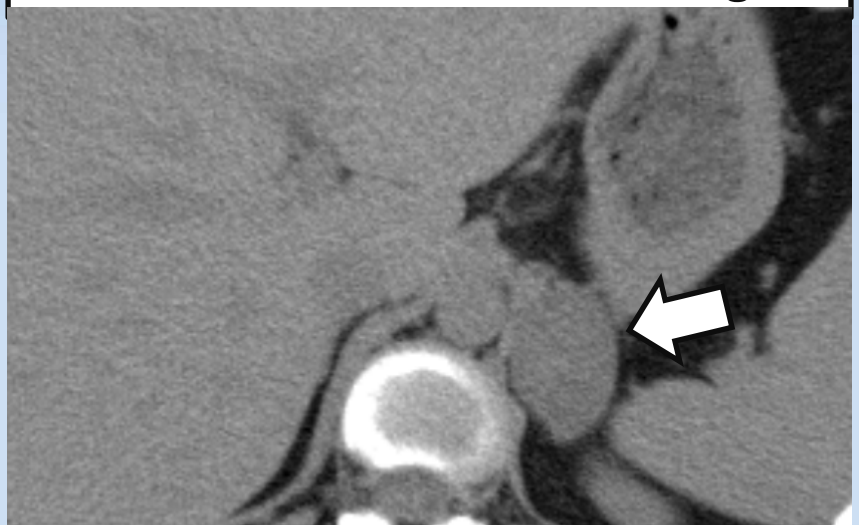
26 YO woman: 1.6 cm, HU=23



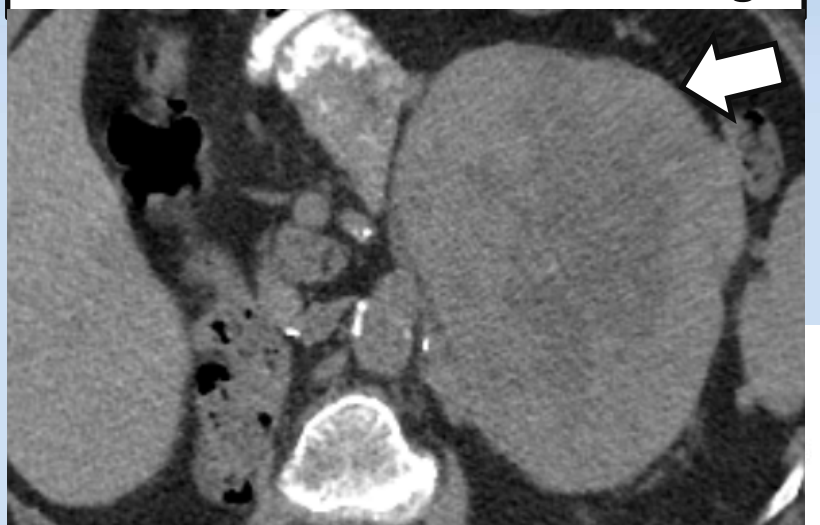
83 YO woman: 7.6 cm, HU=36



27 YO man: 3.6 cm, heterog.



77 YO woman: 12 cm, heterog.



Indeterminate tumors: R 2.6

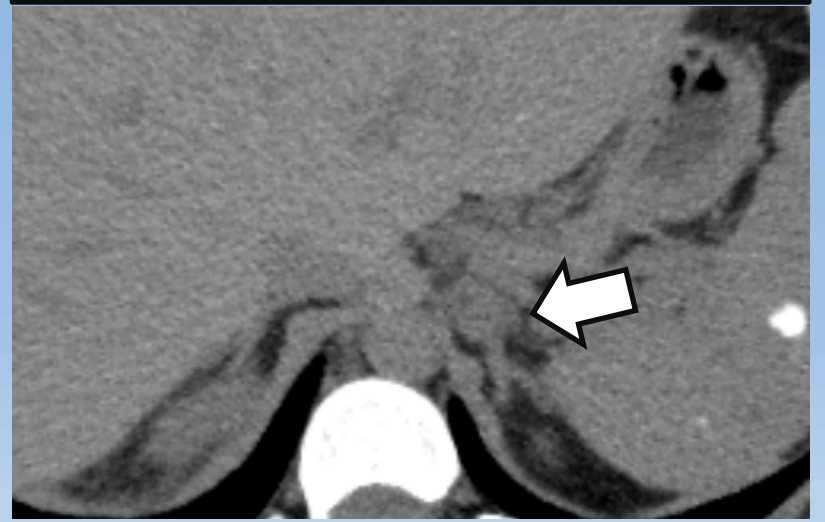
Homogenous HU 11-20
and tumor ≥ 4cm
or
Homogenous HU > 20
and tumor < 4cm
or
Heterogeneous
tumors < 4cm

Discuss in MDT meeting
and consider
proceeding swiftly
to additional
imaging[1,2]

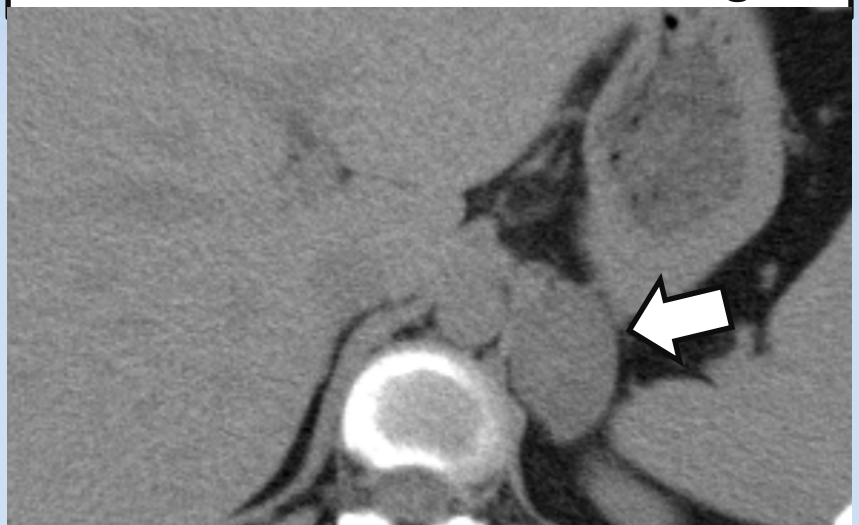
(or immediate surgery)

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

26 YO woman: 1.6 cm, HU=23



27 YO man: 3.6 cm, heterog.



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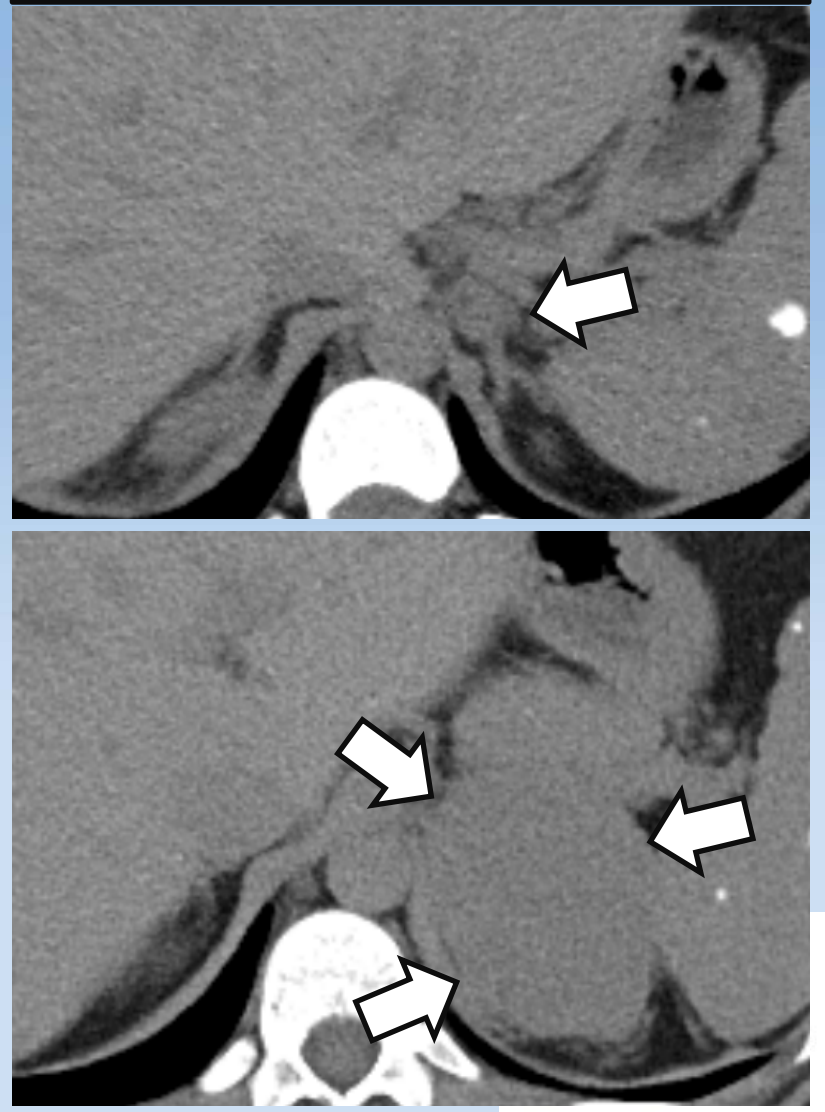
Discuss in MDT meeting
and consider
proceeding swiftly
to additional
imaging[1,2]

(or immediate surgery)

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

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

26 YO woman: 1.6 cm, HU=23



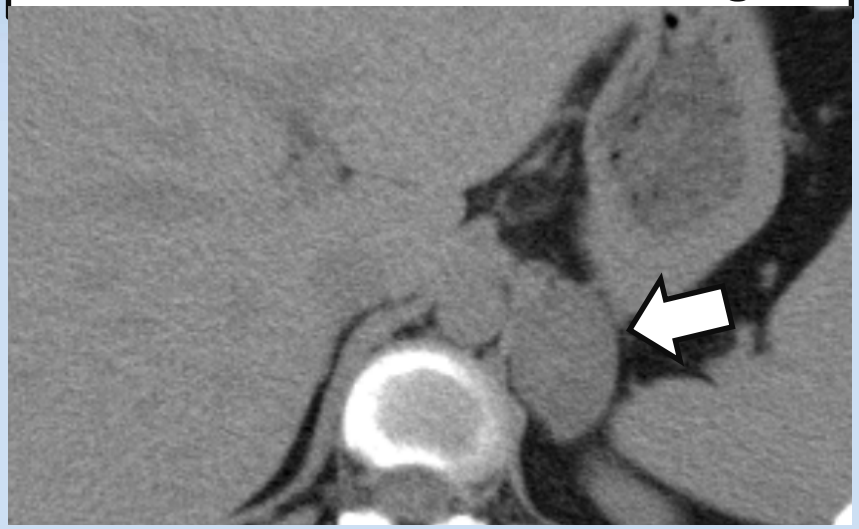
Steroid profiling

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

Lipid poor adenoma OR adrenocortical carcinoma?

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

27 YO man: 3.6 cm, heterog.



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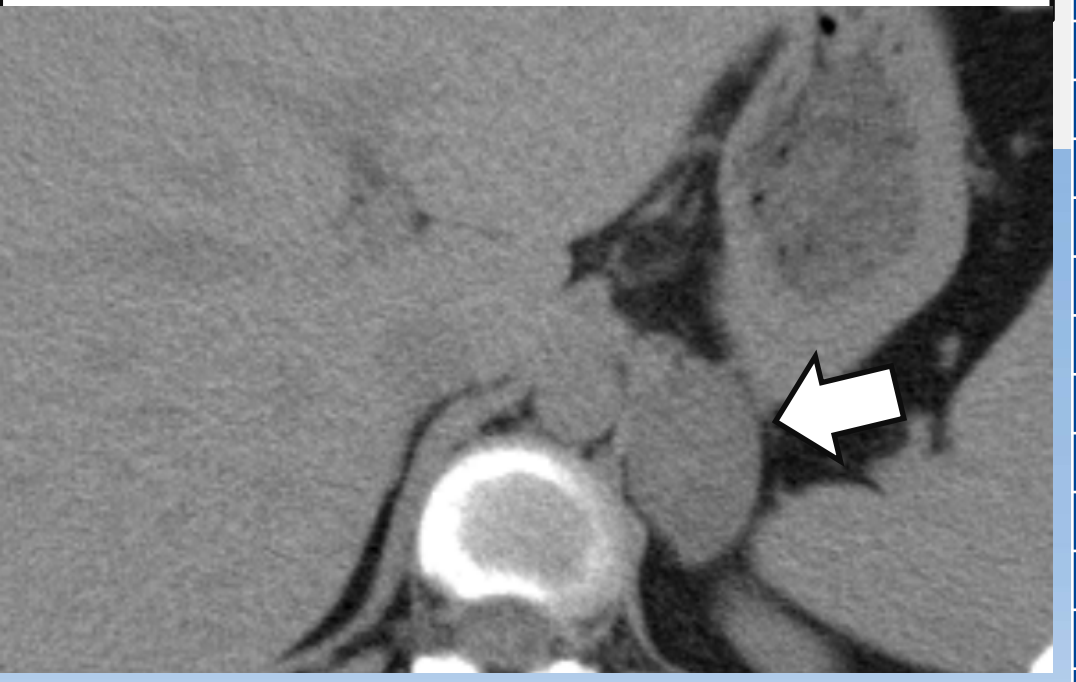
27 YO man: 3.6 cm, heterog.



Steroid profiling:

adrenocortical carcinoma

Analyte	Full name of steroid	Z score
An	Androsterone	0.3
Etio	Etiocholanolone	2.2
DHEA	Dehydroepiandrosterone	-0.5
16a-DHEA	16α-hydroxy-Dehydroepiandrosterone	-0.8
5PT	**Pregnenetriol**	**16**
5PD	Pregnenediol	-0.2
THB	Tetrahydrocorticosterone	-1.7
THDOC	Tetrahydrodeoxycorticosterone	2.8
PD	Pregnanediol	-0.2
PT	Pregnanetriol	12
17HP	17α-Hydroxypregnanolone	1.8
PTONE	Pregnanetriolone	0.5
THS	**Tetrahydrodeoxycortisol**	**284**
Cortisol	Cortisol	0.2
Cortisone	Cortisone	0.6
6B-OH-Cortisol	6β-Hydroxycortisol	3.5
11B-OH-AN	11β-Hydroxyandrosterone	-0.5
11-OXO-ET	11-Oxoetiocholanolone	1.7
B-Cortol	β-Cortol	0.6
a-Cortolone	α-Cortolone	2.9
B-Cortolone	β-Cortolone	1.9
5a-THF	5α-Tetrahydrocortisol	0.9
THF	Tetrahydrocortisol	2.3
THE	Tetrahydrocortisone	2.6

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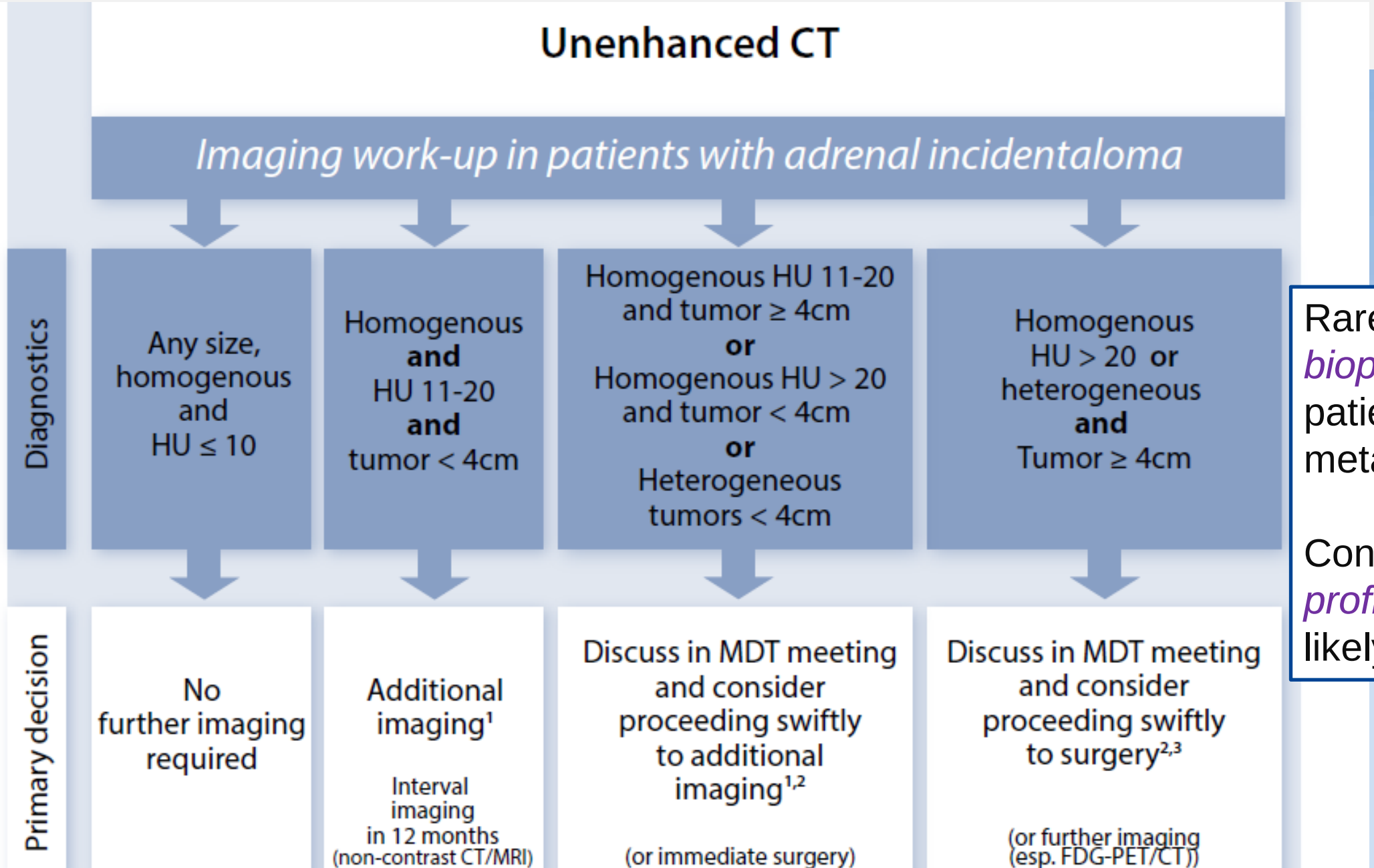
SUMMARY



Rarely consider *biopsy* in selected patients likely to have metastasis

Consider *steroid profiling* in patients likely to have ACC

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Presentation of the four key questions and the respective recommendations: **Assessment of hormone excess**

Massimo Terzolo, Italy

Hormone excess (cortisol)

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

A major change in terminology

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

- In 2023, the panel introduced the term **“mild autonomous cortisol secretion (MACS)**, due to the fact that ACS may include also patients with overt Cushing syndrome.

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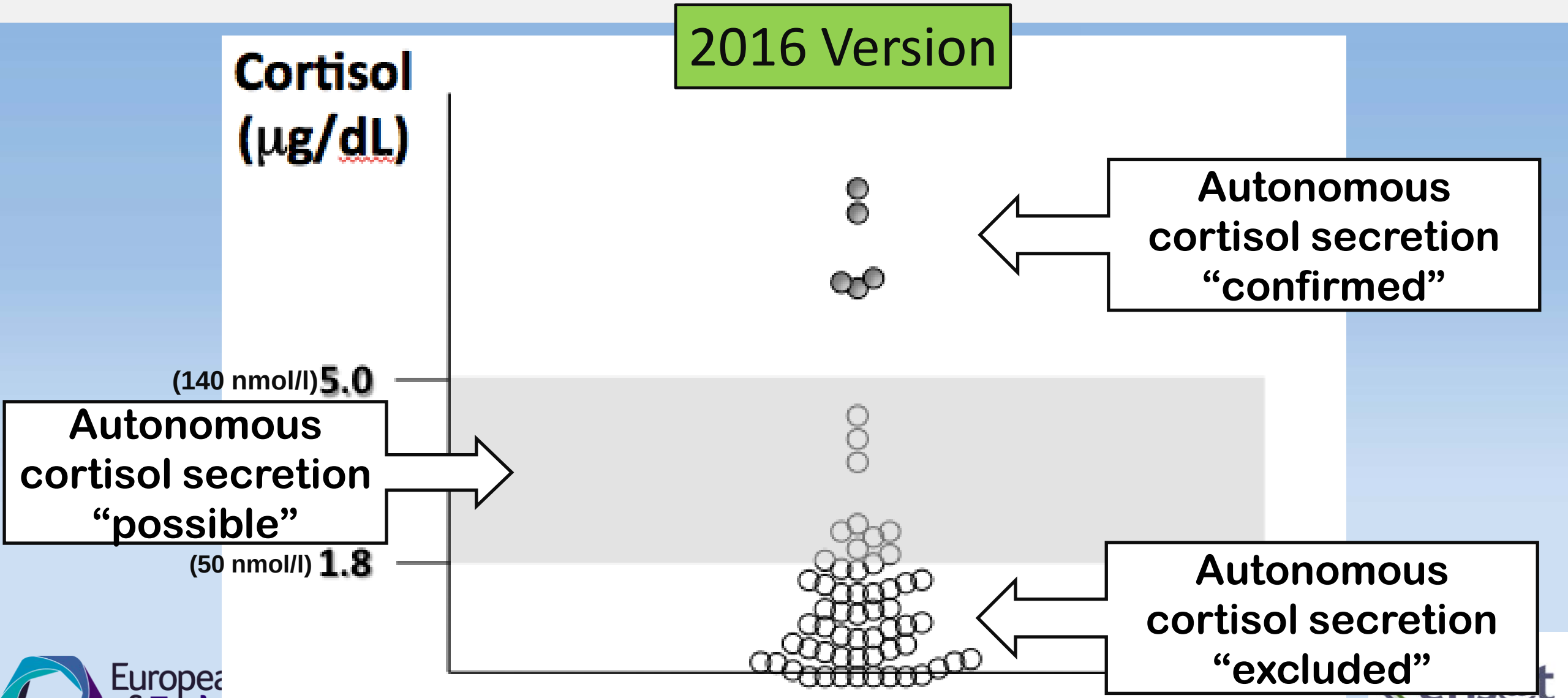
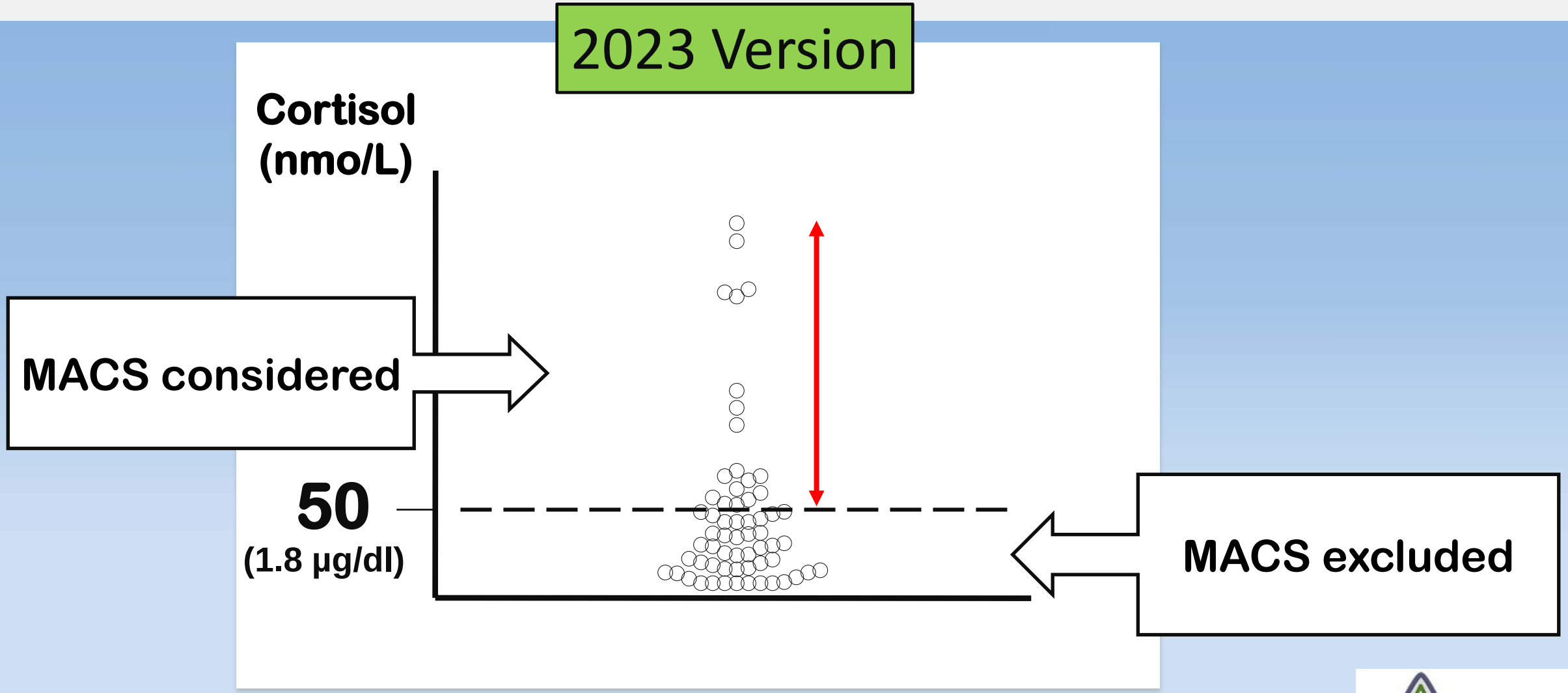
A major change in the interpretation of DST



A major change in the interpretation of DST



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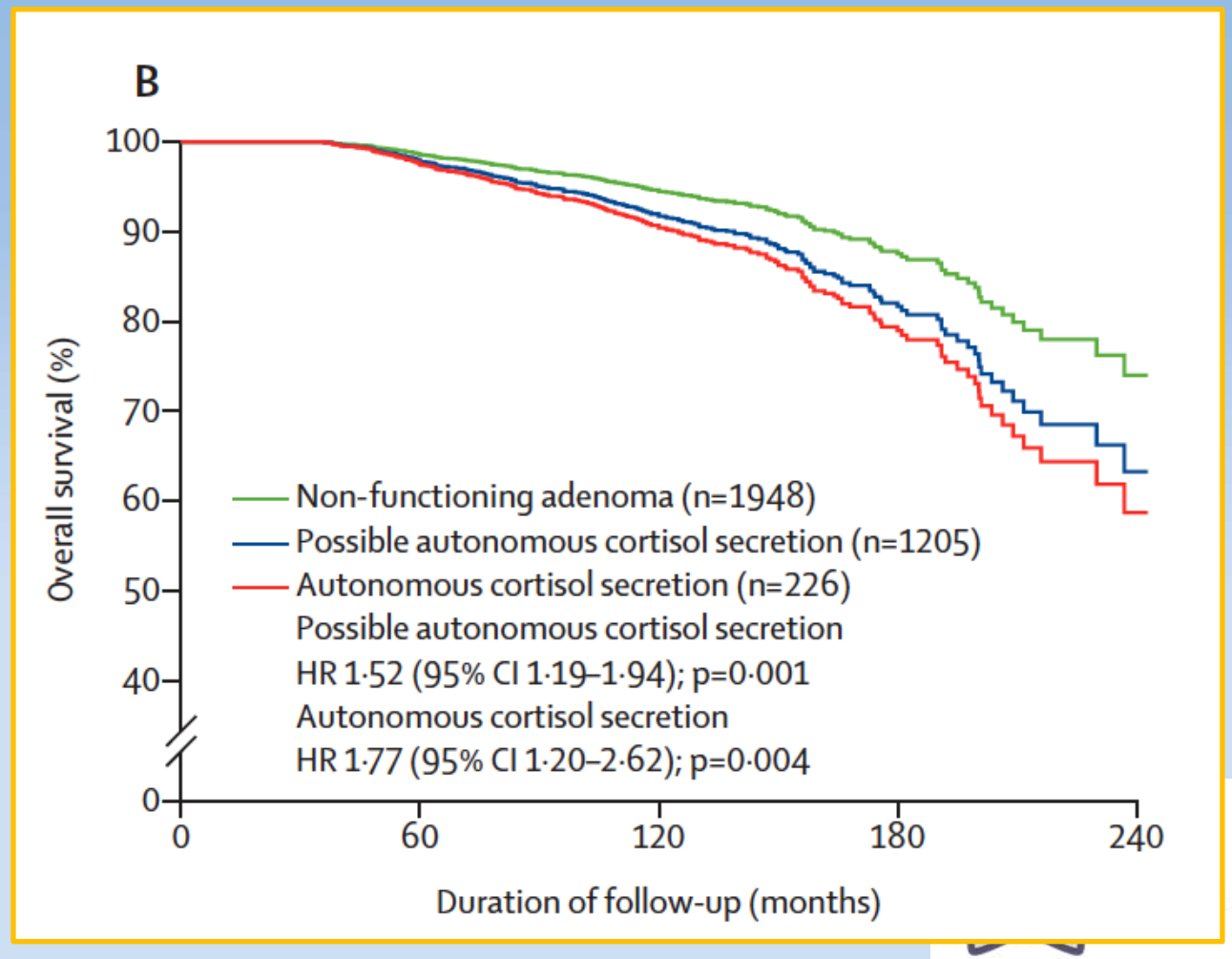
Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study

Lancet Diabetes Endocrinology, 2022

Timo Deutschbein*, Giuseppe Reimondo*, Guido Di Dalmazi, Irina Bancos, Jekaterina Patrova, Dimitra Argyro Vassiliadi, Anja Barač Nekić, Miguel Debono, Pina Lardo, Filippo Ceccato, Luigi Petramala, Alessandro Prete, Iacopo Chiodini, Miomira Ivović, Kalliopi Pazaitou-Panayiotou, Krystallenia I Alexandraki, Felicia Alexandra Hanzu, Paola Loli, Serkan Yener, Katharina Langton, Ariadni Spyroglou, Tomaz Kocjan, Sabina Zacharieva, Nuria Valdés, Urszula Ambroziak, Mari Suzuki, Mario Detomas, Soraya Puglisi, Lorenzo Tucci, Danae Anastasia Delivanis, Dimitris Margaritopoulos, Tina Dusek, Roberta Maggio, Carla Scaroni, Antonio Concistrè, Cristina Lucia Ronchi, Barbara Altieri, Cristina Mosconi, Aristidis Diamantopoulos, Nicole Marie Iñiguez-Ariza, Valentina Vicennati, Anna Pia, Matthias Kroiss, Gregory Kaltsas, Alexandra Chrisoulidou, Ljiljana V Marina, Valentina Morelli, Wiebke Arlt, Claudio Letizia, Marco Boscaro, Antonio Stigliano, Darko Kastelan, Stylianos Tsagarakis, Shobana Athimulam, Uberto Pagotto, Uwe Maeder, Henrik Falhammar, John Newell-Price, Massimo Terzolo†, Martin Fassnacht†

OVERALL SURVIVAL



The larger difference in mortality is between NFA and Possible ACS

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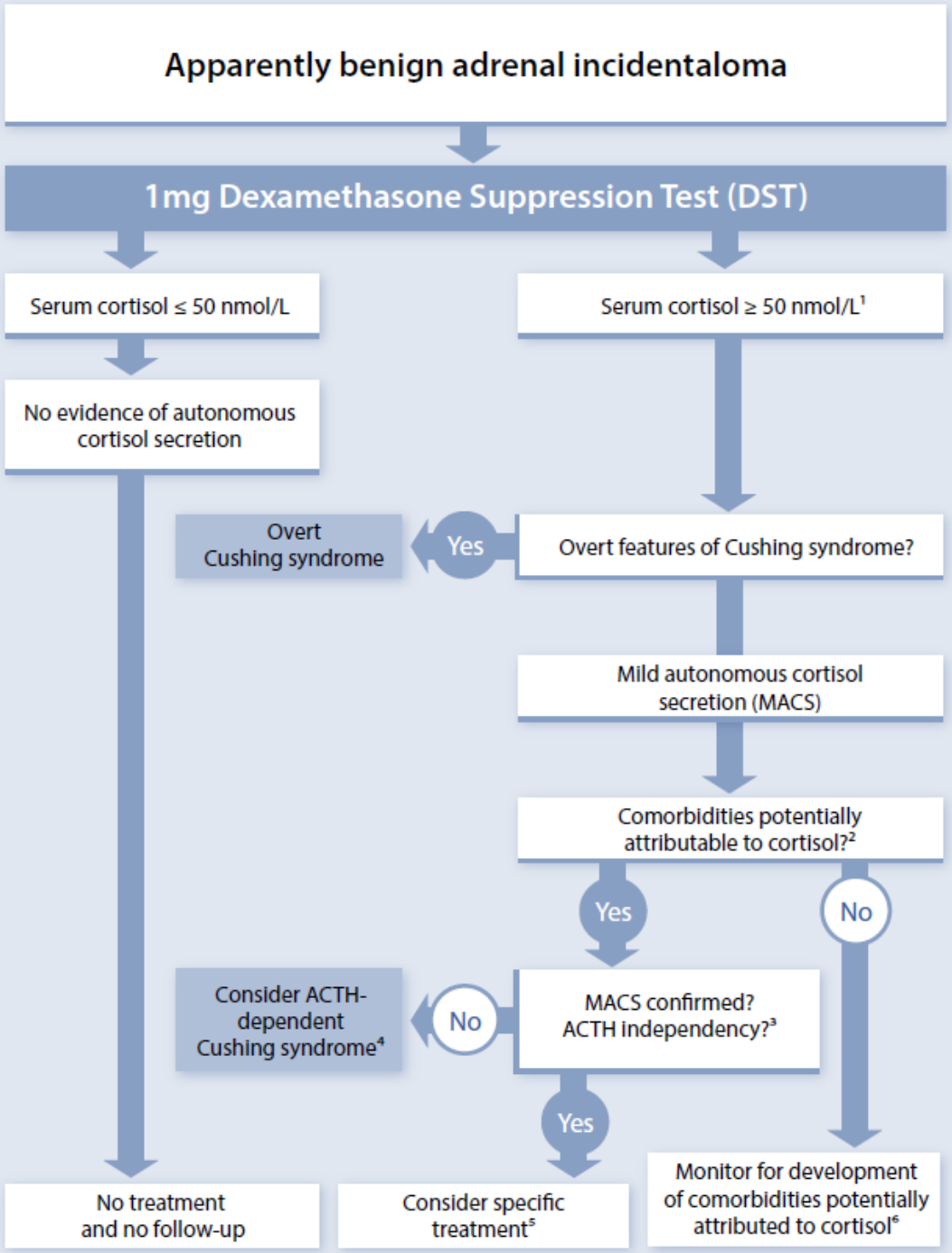
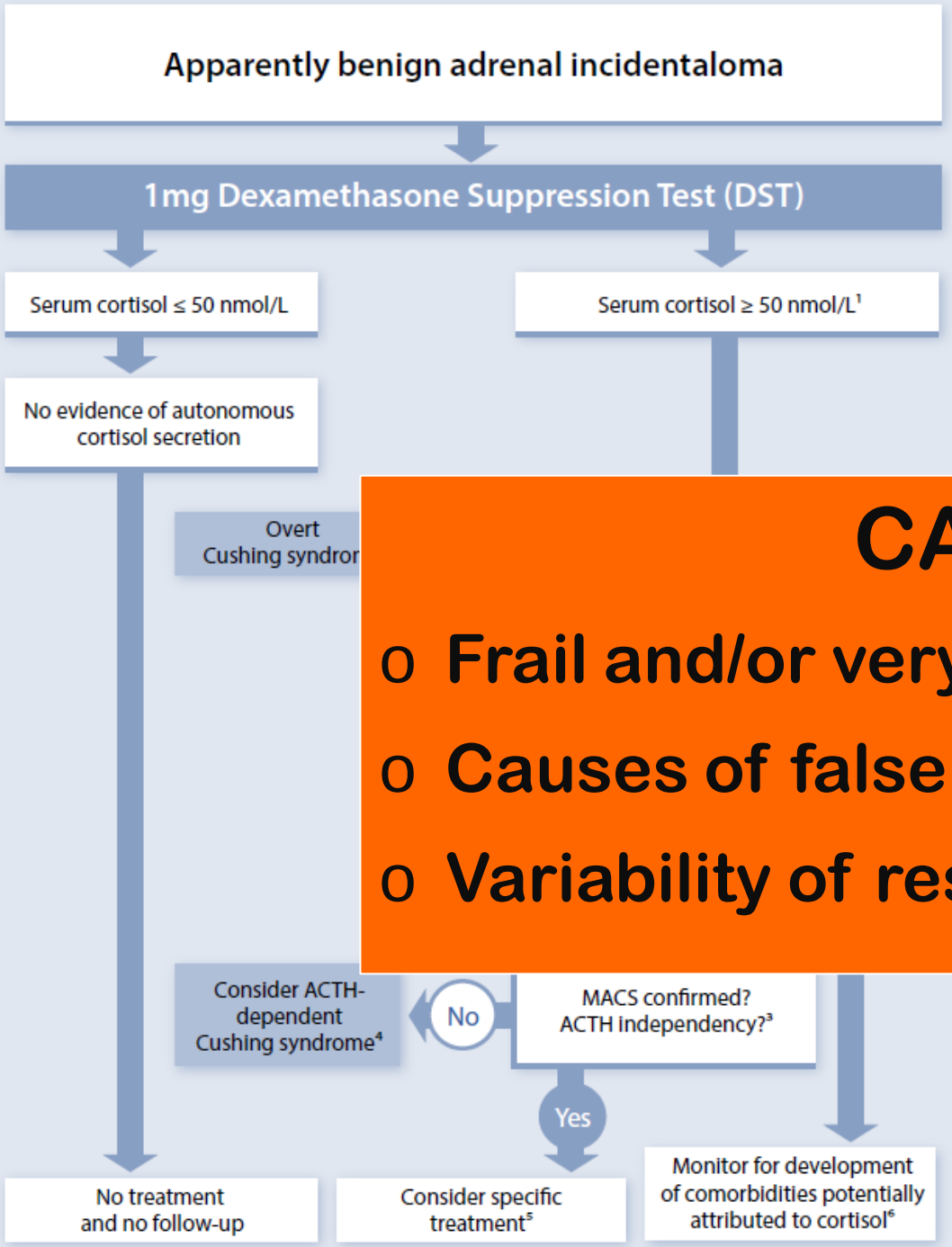


How to diagnose MACS?

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

- **Look for comorbidities**

How to diagnose MACS?



- Accurate physical examination to exclude Cushing
- Ascertain ACTH independency
- y be useful
- firm MACS

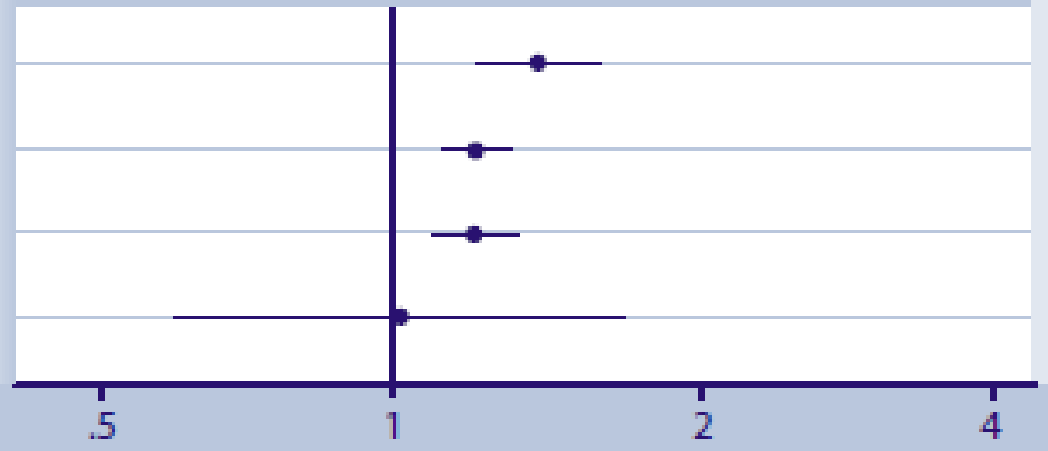
dities

CAVEATS

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

Morbidity[1] in patients with mild autonomous cortisol secretion (MACS[2])

Outcome	Cut off	Number of studies	Number of patients	Relative Risk (95% CI)
Diabetes	>1.8µg/dL	14	9375	1.44 (1.23, 1.69)
Hypertension	>1.8µg/dL	18	10031	1.24 (1.16, 1.32)
Dyslipidemia	>1.8µg/dL	12	7769	1.23 (1.13, 1.34)
Vertebral fractures[3,4]	>1.8µg/dL	3	637	1.08 (0.68, 1.71)



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Details see Pelsma et al. Eur J Endocrinol submitted

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Surgical treatment of MACS

New recommendation:

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

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Surgical treatment of MACS

New recommendation:

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The decision for surgery should be individualized !

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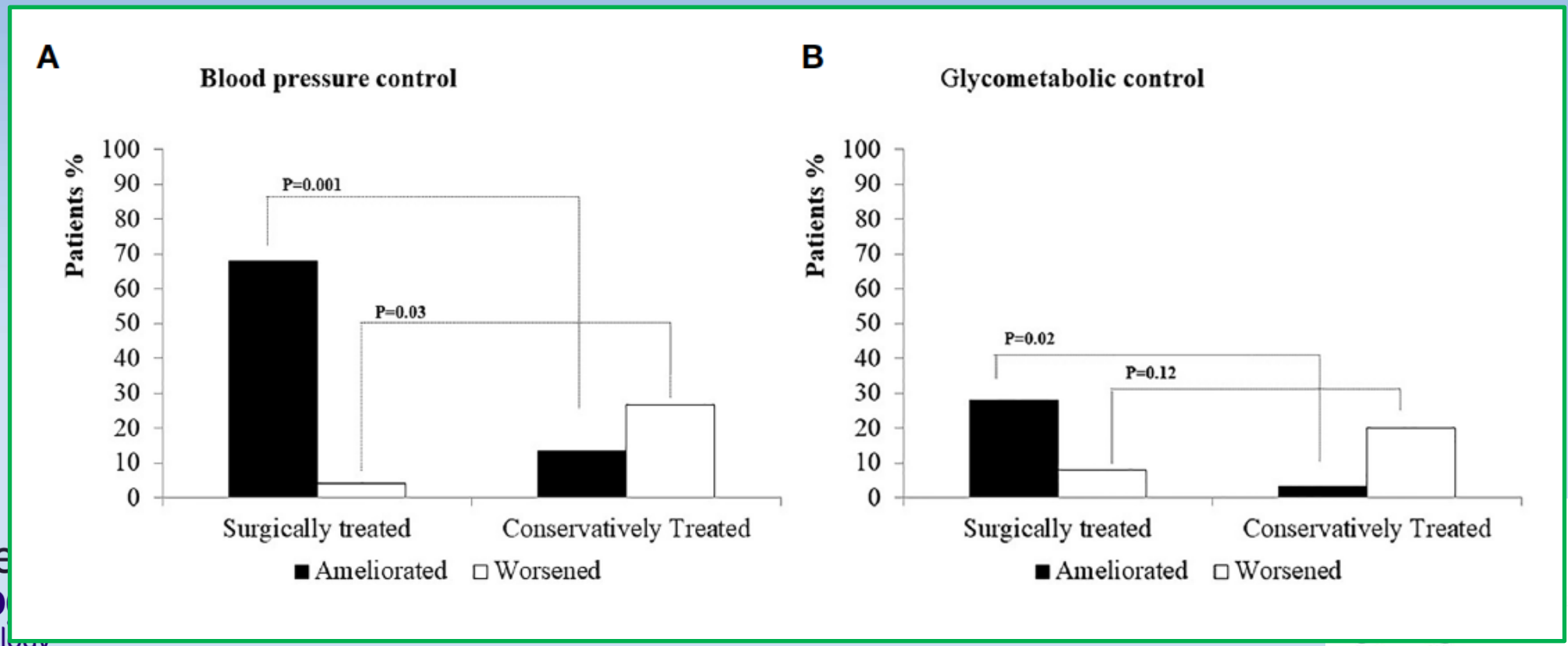
Adrenalectomy Improves Blood Pressure and Metabolic Control in Patients With Possible Autonomous Cortisol Secretion: Results of a RCT

Valentina Morelli[1†], Sofia Frigerio[2,3], Carmen Aresta[1], Elena Passeri[4], Flavia Pugliese[5], Massimilano Copetti[6], Anna Maria Barbieri[2,3], Silvia Fustinoni[3,7], Elisa Polledri[3], Sabrina Corbetta[4,8], Maura Arosio[2,3], Alfredo Scillitani[5] and Iacopo Chiodini[1,9†]*

Frontiers in Endocrinology, 2022

55 pts with PACS randomized between ADX or surveillance



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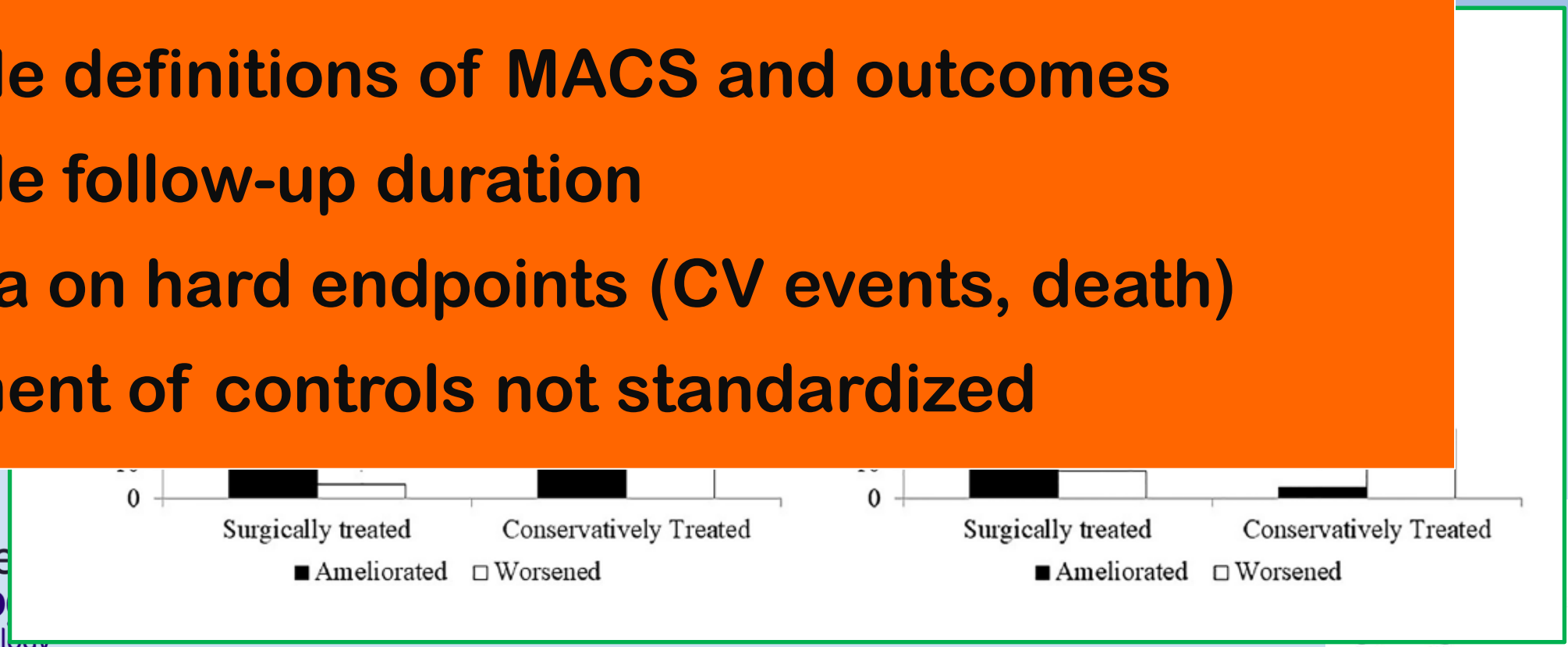
55 pts with PACS randomized between ADX or surveillance

Limits of available literature

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



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Endocrine work-up

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

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

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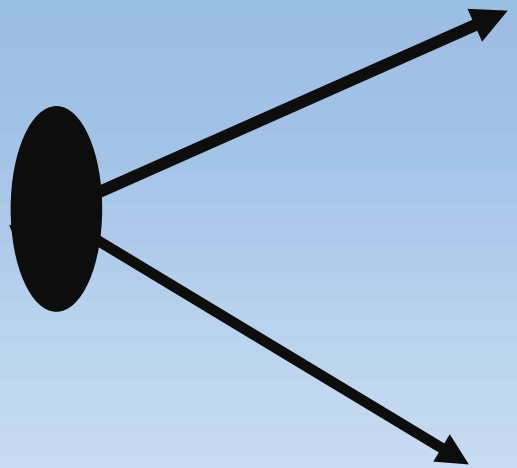
Presentation of the four key questions and the respective recommendations: **Surgical treatment**

John Newell-Price, UK

Surgery – Key questions



Who should *NOT* have an operation?

What surgical approaches should be used?

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Who should NOT have an operation?

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

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MACS

- R.4.3 If surgery is indicated for a benign adrenal mass causing hormone excess (including MACS), we recommend that a **minimally invasive approach** is used **(⊕OOO)**. **(New recommendation)**

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

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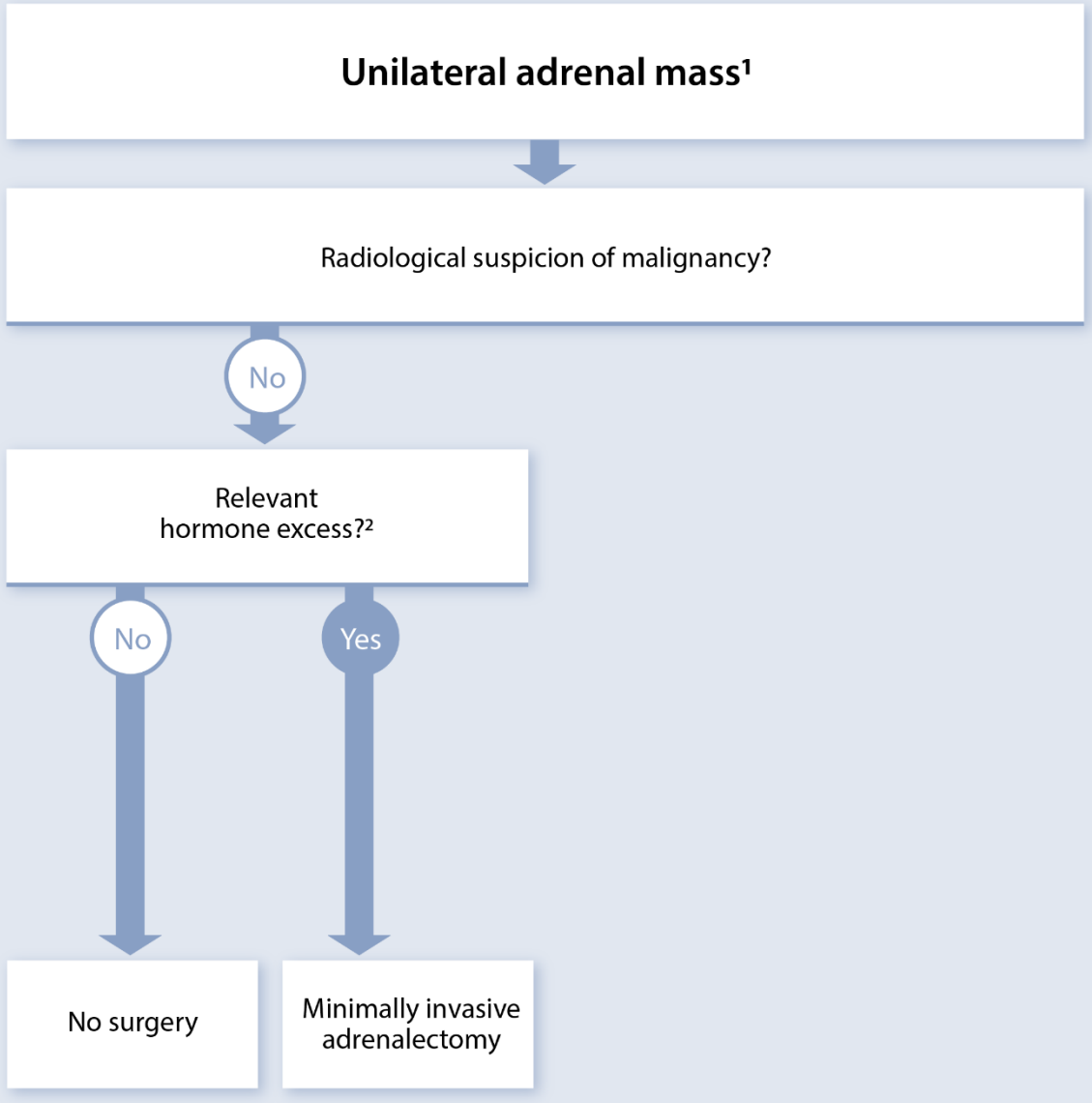
Surgical pathway Flow



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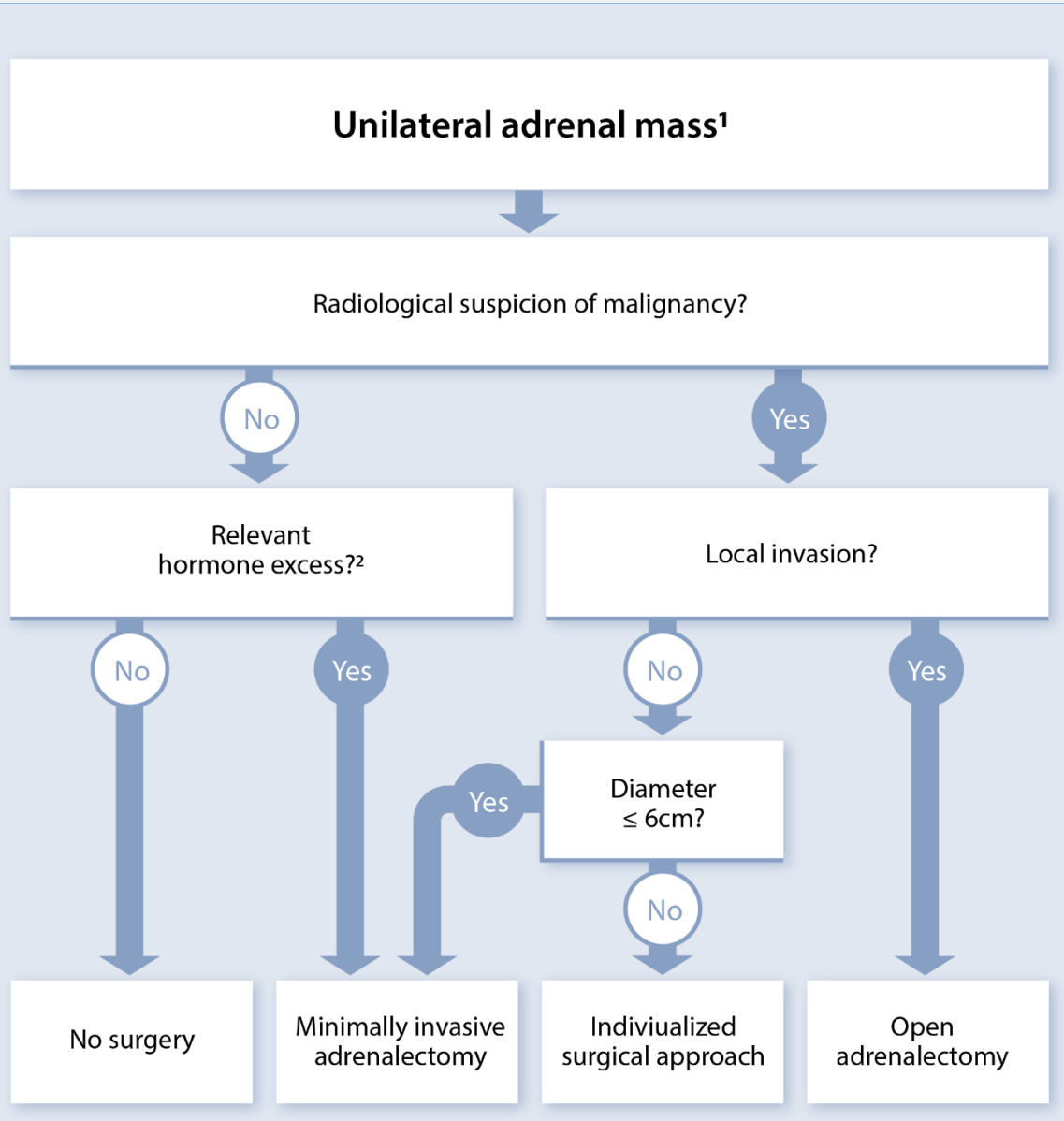
Surgical pathway Flow



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Involvement of Endocrinologist

- R.4.7 We recommend **perioperative glucocorticoid treatment** at surgical stress doses in all patients undergoing surgery and a preoperative morning serum cortisol >50 nmol/L (1.8ug/dL) after a 1mg overnight dexamethasone test

Involvement of Endocrinologist

- R.4.8 We suggest that patients with **MACS** that underwent surgery should be **followed by an endocrinologist until recovery** of hypothalamic-pituitary-adrenal axis function has been documented. **(New advice)**

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Involvement of Endocrinologist

- R.4.8 We suggest that patients with **MACS** that underwent surgery should be **followed by an endocrinologist until recovery** of hypothalamic-pituitary-adrenal axis function has been documented. **(New advice)**

Why?

MACS may lead to adrenal insufficiency

Some patients may experience ‘glucocorticoid withdrawal’

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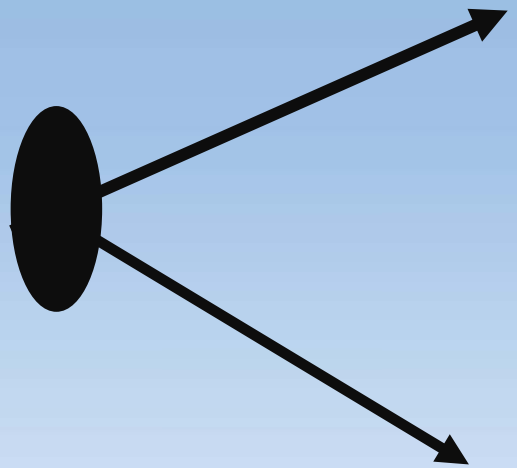
Presentation of the four key questions and the respective recommendations:
Follow-up of patients not undergoing adrenal surgery

Antoine Tabarin, France

Follow-Up : Aims



Malignant transformation?

Hormonal Hyperactivity?

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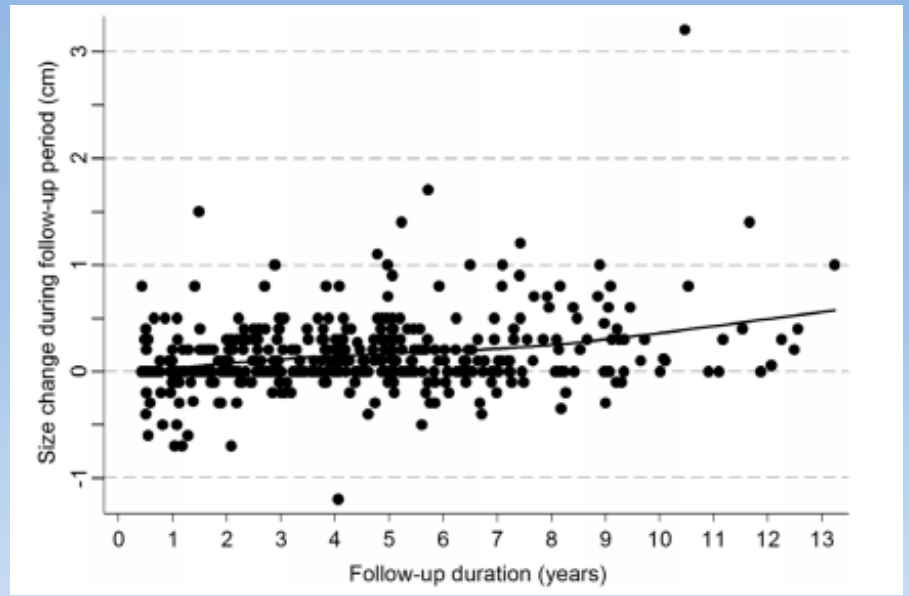
Malignancy : evidence in 2016

- 2016. Systematic review of series including ≈ 2300 patients : **only 2 cases of development of malignancy (with ambiguous/unclear characteristics at initial imaging).**
- R.5.1 **We suggest** against further imaging during follow-up in patients with an adrenal mass **< 4cm** with clear benign features on imaging studies (⊕OOO) .

Malignancy : evidence in 2023

- Five additional follow-up studies including 853 patients



Hong AR et al. EJE 2017

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

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Follow Up for malignancy : 2023 guidelines

- R.5.1 We **recommend against** further imaging during follow-up in patients with an adrenal lesion with clear benign features on imaging studies **(⊕⊕⊕O).**

- The **cutoff** for tumor size of **4 cm** that was included in the recommendation of 2016 **is removed**

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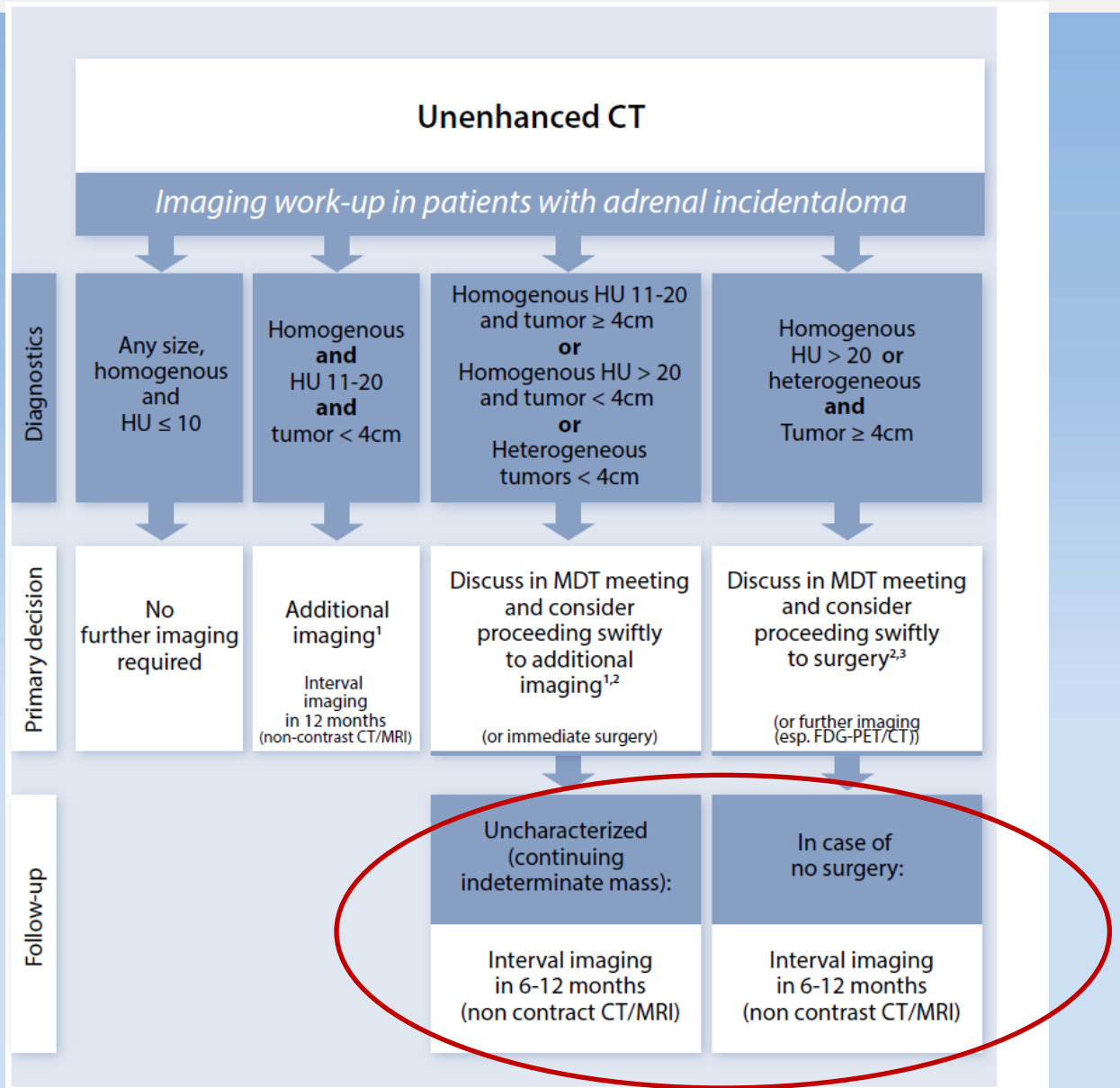
Follow Up for malignancy : 2023 guidelines



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No change in the 2023 recommendations

- R.5.2
  - In patients with an indeterminate adrenal mass by imaging opting not to undergo adrenalectomy following initial assessment, *we suggest* a repeat non-contrast CT or MRI after 6-12 months to exclude significant growth (⊕OOO).

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

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Follow Up for hormonal excess

2016

Aldosteronoma (*N = 1794*)

0% to 1.6%.

Pheochromocytoma (*N = 2003*)

0% to 2.6%.

Overt hypercortisolism (*N = 2225*)

0% to 4.2%

2023 FUp in ≥ 3000 patients

Aldosteronoma

0.0% to 1.6%

Pheochromocytoma

0.0% to 2.1%

Overt hypercortisolism

0.0% to 0.6%

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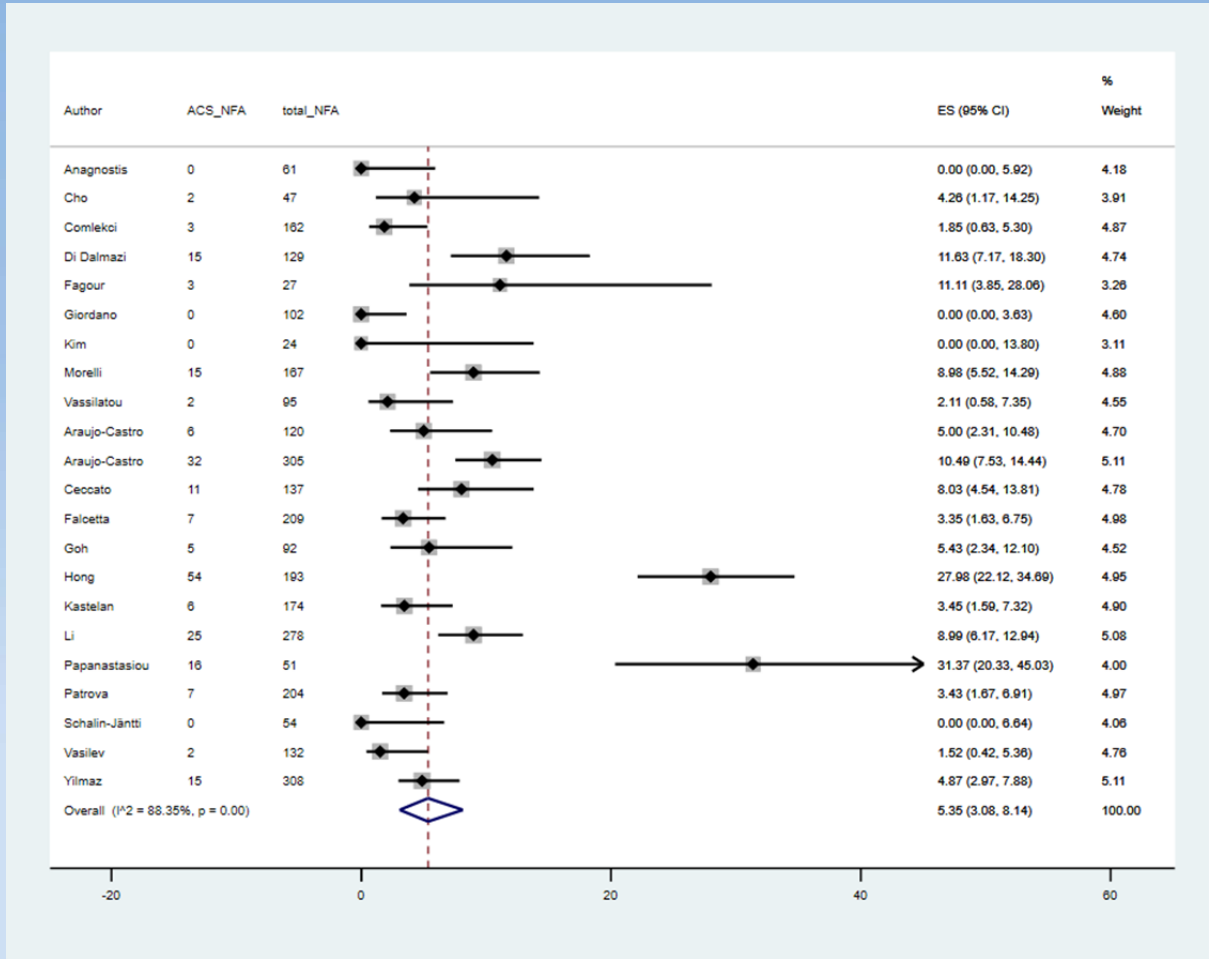
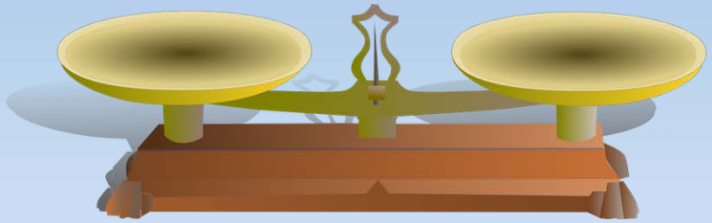
Follow Up for development of MACS



Low probability of developing MACS ≈ 5%

Risk of false positive of the 1 mg DST



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Follow Up for hormonal excess

2016

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

2023 FUp in ≥ 3000 patients

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

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Follow Up of non-operated patients with MACS

Reasoning

+

+

Very low-risk of developing overt hypercortisolism

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

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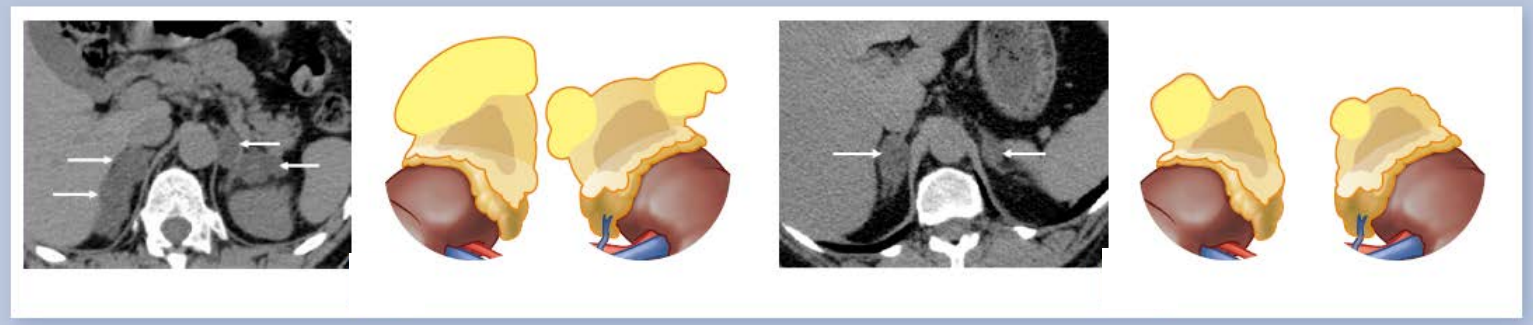
Presentation of the four key questions and the respective recommendations:
Special circumstances

Martin Fassnacht, Germany

Bilateral adrenal incidentalomas

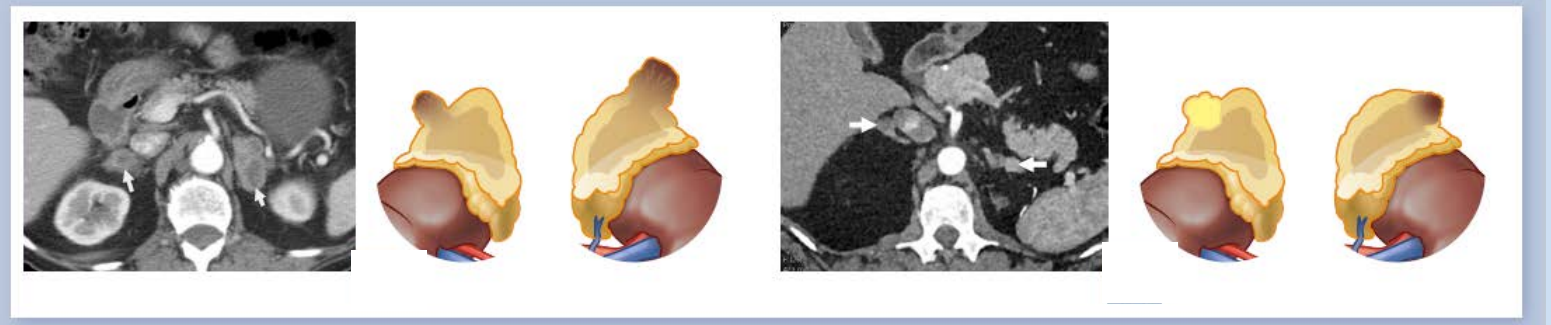
- R.6.1.1 We **recommend** that … **each adrenal lesion** is assessed **individually** … according to the same imaging protocol as for unilateral adrenal masses...
- R.6.1.2 We **recommend** … **clinical and hormonal assessment identical** to that in patients with unilateral adrenal incidentaloma.

Bilateral hyperplasia



Bilateral adenomas

2 similar, non-adenoma lesions



2 different masses

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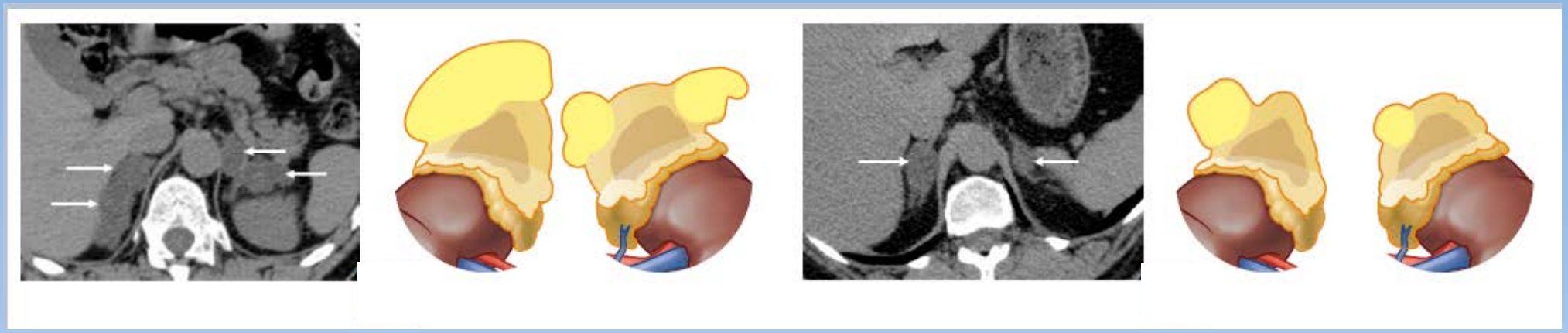
Bilateral hyperplasia or bilateral adenomas



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

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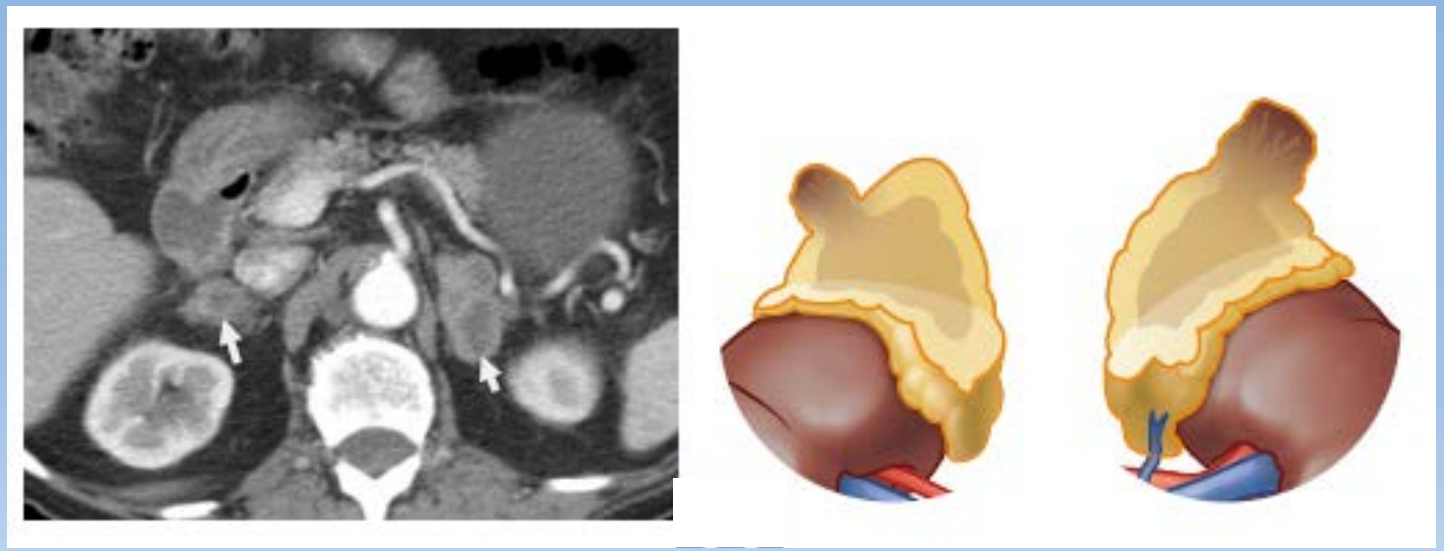
Suspected bilateral malignant disease



- R.6.1.6 In patients with bilateral metastases, lymphoma, infiltrative inflammatory disease and hemorrhages, **we recommend assessment for adrenal insufficiency**.

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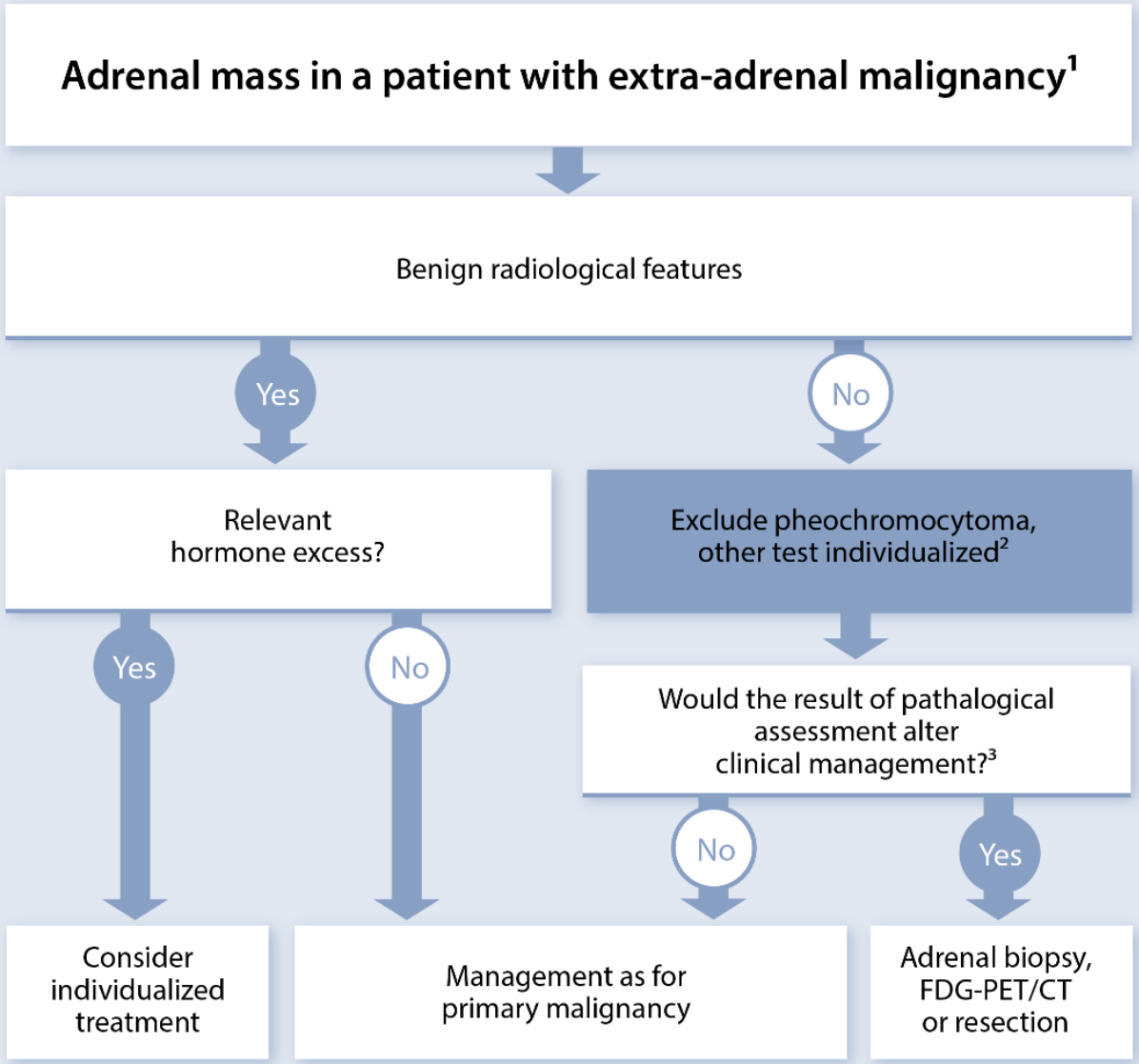
Adrenal mass and history of extra-adrenal malignancy



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Adrenal incidentalomas in young or elderly patients

- R.6.2.1 We recommend **urgent assessment** of an adrenal mass in **pregnant women and individuals < 40 years** … (higher likelihood of malignancy and significant hormone excess).
- R.6.2.2 We suggest the use of MRI rather than CT in children, adolescents, and pregnant women.
- R.6.2.3 We **suggest surgical resection if an adrenal mass is indeterminate on imaging** in children, adolescents, pregnant women and adults < 40 years of age.
- R.6.2.4 We recommend that investigation and management of patients with poor general health and a high degree of frailty be kept in proportion to potential clinical gain.

Future research questions

1) “Second-line imaging methods”
2) Real-world data on steroid profiling
3) Prospective studies on MACS with 'hard' endpoints
4) Randomized studies on the best therapy for MACS
5) Association between MACS and osteoporosis
6) Studies with repeated DST
7) New biomarkers to identify patients with clinically relevant cortisol excess
8) Prospective study on the best surgical approach
9) Long-term study on follow-up
10) Studies on quality of life, mental health, cognition, and frailty

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Information for individuals with adrenal incidentalomas

This patient leaflet is based on the European Society of Endocrinology Clinical Guideline on the management of adrenal incidentalomas in collaboration with the European Network for the Study of Adrenal Tumors, written by an expert pan-European Endocrine team. The aim of this guideline is to help clinicians managing patients who have an adrenal incidentaloma, and is published in the *European Journal of Endocrinology* (2023) xxxxxx. The information in this leaflet is not intended to replace your doctor's advice.

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Background

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

Evaluation

Once an adrenal incidentaloma is found, you will be referred to a hormone specialist (endocrinologist), to determine if:

1. The mass is producing any hormones

The adrenal glands produce a variety of hormones, such as adrenaline, aldosterone, and cortisol. These hormones are involved in several important processes in your body, such as regulation of blood pressure, metabolism and the immune system, and can also affect your mental health. To assess if the adrenal incidentaloma overproduces one (or more) of these hormones, your doctor will search for any signs or symptoms of hormonal overproduction and perform blood as well as urine tests if required.

2. The mass is benign or malignant

Fortunately, over 90% of adrenal incidentalomas are benign (meaning, they are not cancerous). The most reliable first-line imaging method to assess if a mass is benign or malignant is a computed tomography (CT) scan without use of contrast media, which is reviewed by a radiologist. A CT scan combines a series of X-ray images taken from different angles around your body to produce "slices". Other imaging modalities which can be used are MRI scan (using magnetic fields to make images of your body) or PET scan (using a radioactive drug (tracer)

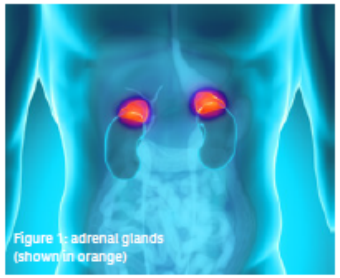

Figure 1: adrenal glands (shown in orange)

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to show both normal and abnormal metabolic activity).

Management

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

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

Q & A

Q1: I have incidentalomas in both adrenal glands, or multiple incidentalomas in one adrenal gland; does the information in this leaflet apply to me?

A1: Yes, you will undergo the same evaluation of imaging and blood and/or urine tests. However, since the underlying causes may be slightly different from those who have a single, one-sided adrenal incidentaloma, your doctor may consider some additional tests.

Q2: If no surgery is performed, is it helpful/necessary to perform a biopsy to secure the correct diagnosis?

A2: No, a biopsy generally has no role in evaluation of an adrenal mass. It will only be considered under special circumstances, for instance when malignant disease outside of the adrenals is already present, or when there is suspicion of an infectious disease.

Q3: My adrenal incidentaloma causes 'mild autonomous cortisol secretion', what does this mean?

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

Q4: My adrenal mass was detected during an evaluation due to a malignant disease. Does this mean that my adrenal mass is a metastasis of this other tumour?

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

Q5: Where can I get more information and support?

A5: You can find more information through the following website: www.ese-hormones.org/for-patients/patient-advocacy-groups

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