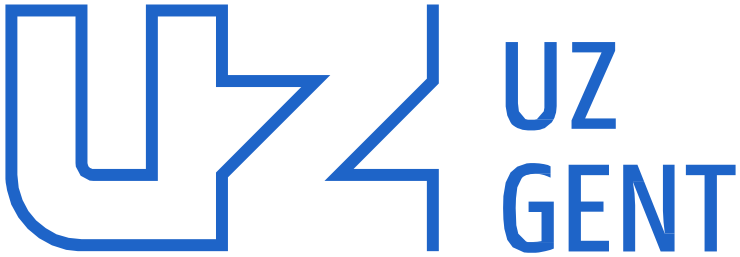
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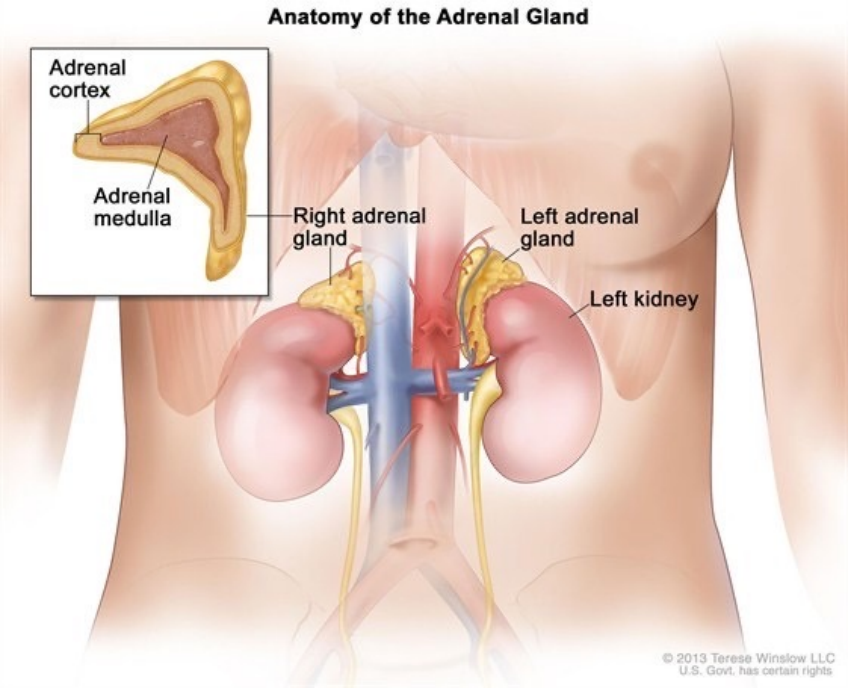
Discovery of an adrenal adenoma : what I have to do

Bruno Lapauw, MD, PhD

November 19th, 2022
De ontmoetingen van endocrinologie – diabetes
Brussel

Outline

- Introduction
- Imaging
- Biochemical work-up
- Special considerations
- Conclusion



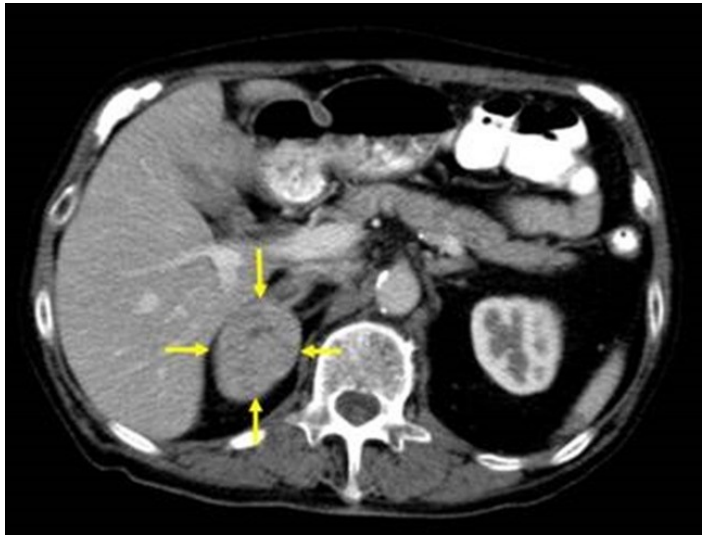
Introduction

- Adrenal incidentaloma

  = an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease

- Prevalence
  - 2 – 8 %; +/- 1% of all CT's
  - Increases with age (0,2 → 10 %)

- Two questions to be answered:
  - Benign or malignant?
    - Adrenocortical carcinoma; metastasis
  - Hormonally active or non-functioning?
    - Pheochromocytoma, aldosteronoma, hypercortisolism



Introduction

- Adrenal incidentaloma: what could it be?

Tumor entity	Median (%)	Range (%)
Series including all patients with an adrenal mass*		
Adenoma	80	33–96
Nonfunctioning	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
Nonfunctioning	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

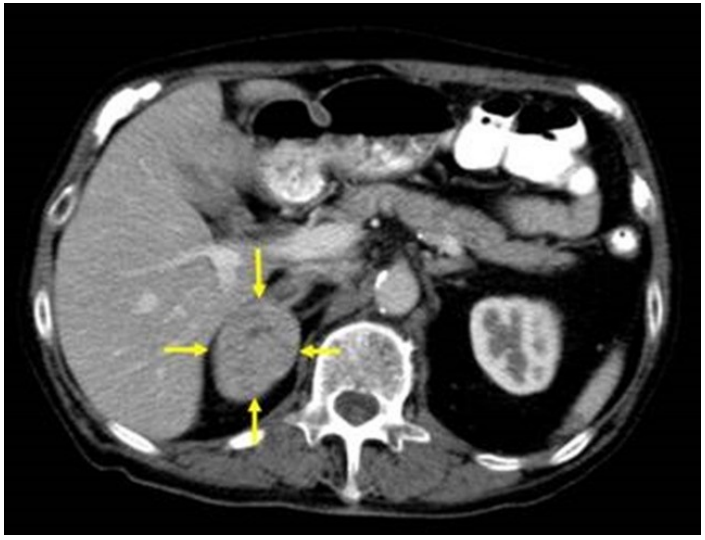


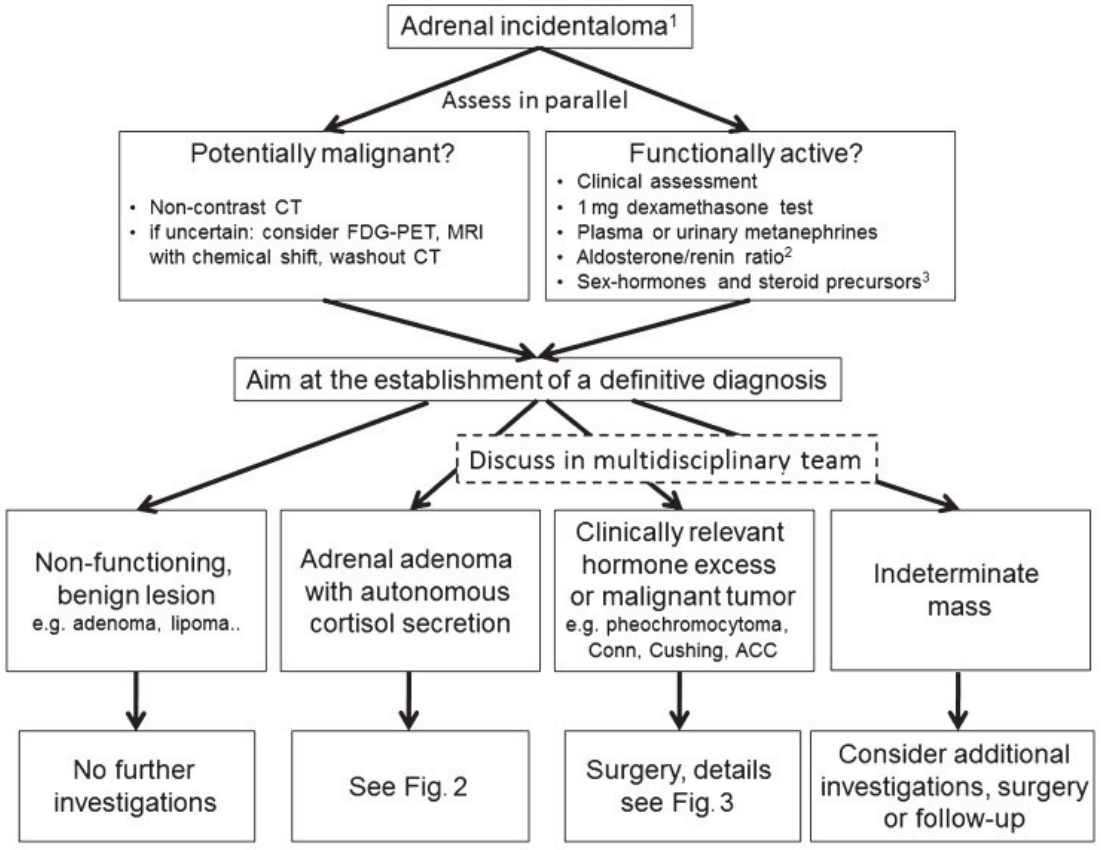
Table 1 Adrenal incidentalomas – frequency of the different underlying tumor types (adapted according (9)). Due to the nature of these studies, a selection bias is very probable (the populations studied not reflecting a random sample of all patients with an adrenal incidentalomas) and most likely leads to an overestimation of the frequency of some tumor entities.

Fassnacht *et al.*, EJE 2016

Introduction

- Adrenal incidentaloma
  - Large majority of lesions is benign & non-functioning
  - Higher chance of metastatic lesions in case of known extra-adrenal malignancy
- Differentiation of benign vs. malignant lesion virtually always possible using imaging characteristics
  - Rarely need for biopsy
  - Pheochromocytoma needs to be excluded before biopsy!
- Evaluation of functionality?
  - No contribution of imaging
  - Based on anamnesis, clinical features & hormonal evaluation

Imaging



[1]For patients with history of extra-adrenal malignancy, see special section 5.6.4.
[2]Only in patients with concomitant hypertension and/or hypokalemia.
[3]Only in patients with clinical or imaging features suggestive of adrenocortical carcinoma.

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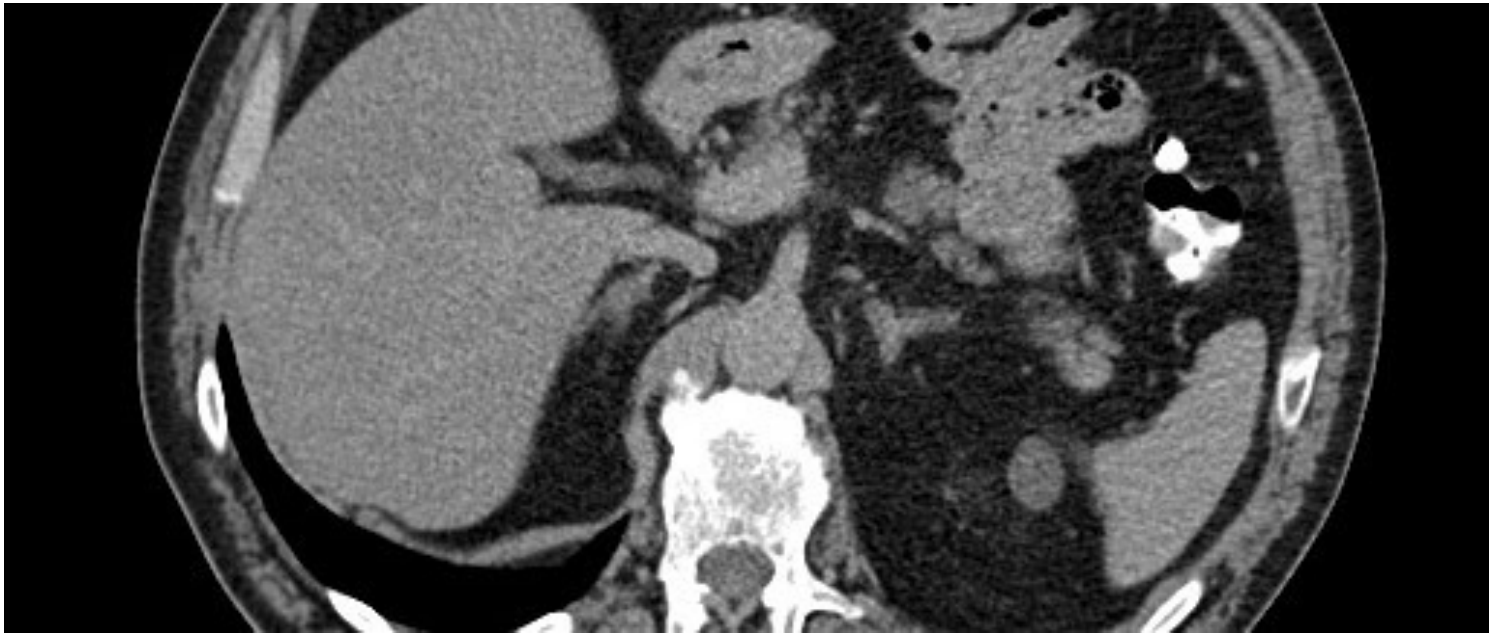
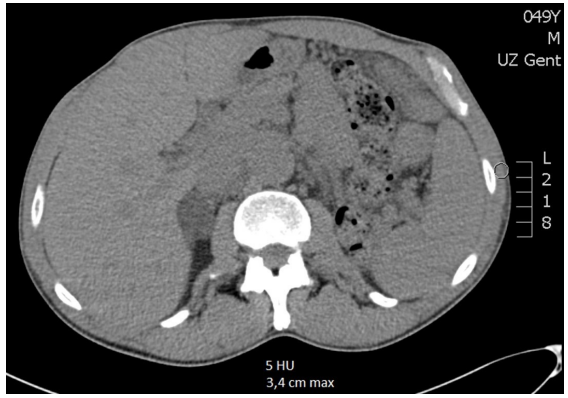
Imaging

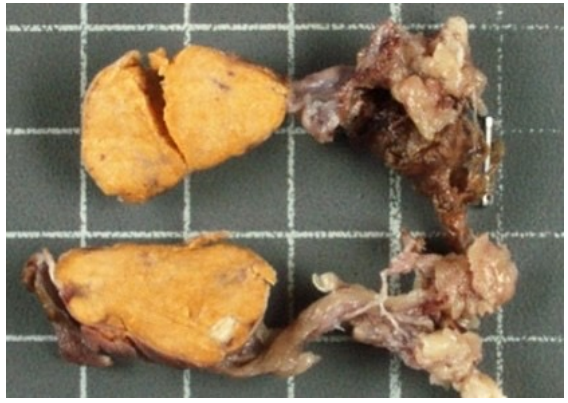
- Normal adrenals

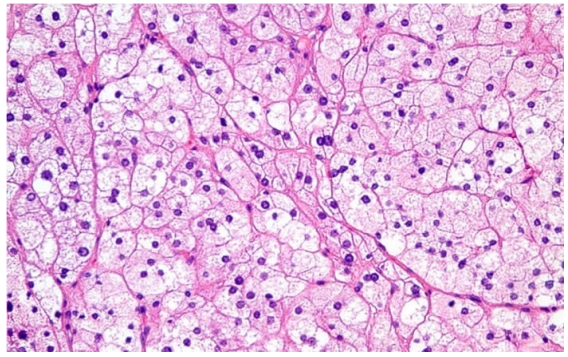


Imaging

- How does an adrenal adenoma look like?
  - Small, mostly < 3 cm
  - Round or oval shape
  - Homogenous composition, well demarcated
  - Stable size (or only slow growth)
- Macroscopically
  - Non-adherent, tender
- Microscopically
  - 70% are lipid-rich (intracellularly)
  - 30% lipid-poor



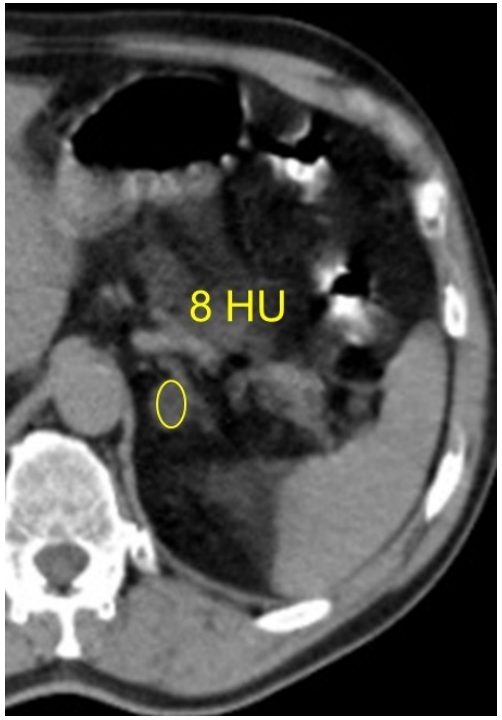




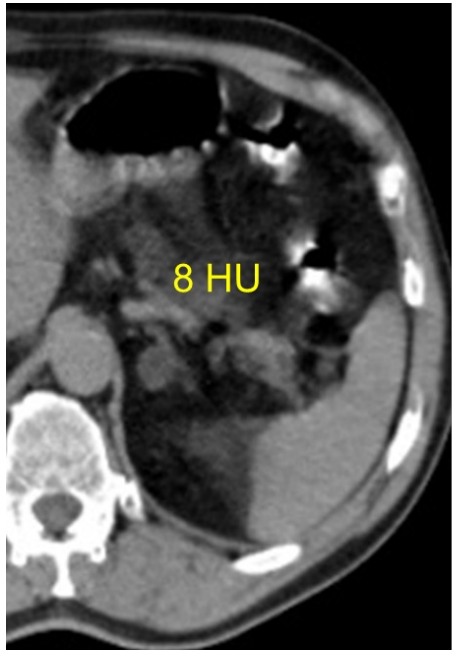
Imaging

- Density on non-enhanced CT 0-10 Hounsfield units = adenoma

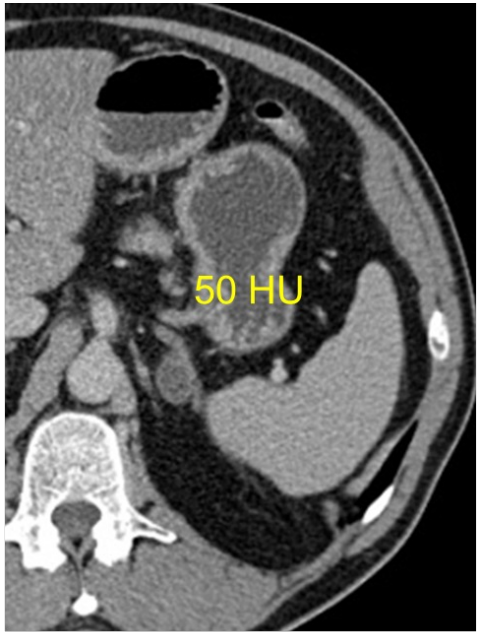
- Density on non-enhanced CT > 10 Hounsfield units = can still be a (lipid-poor) adenoma
- Further differentiation (adenoma vs. metastasis / pheochromocytoma / ACC) based on contrast enhancement and washout; MRI characteristics



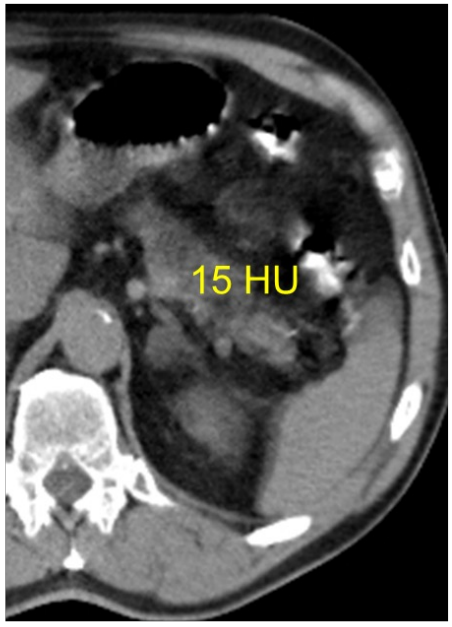
Imaging



Unenhanced



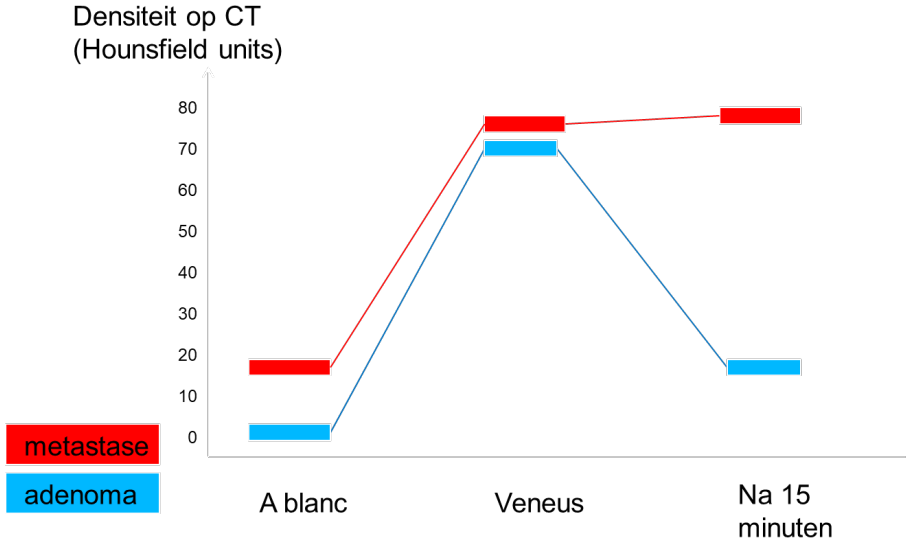
Early venous phase (70 sec)



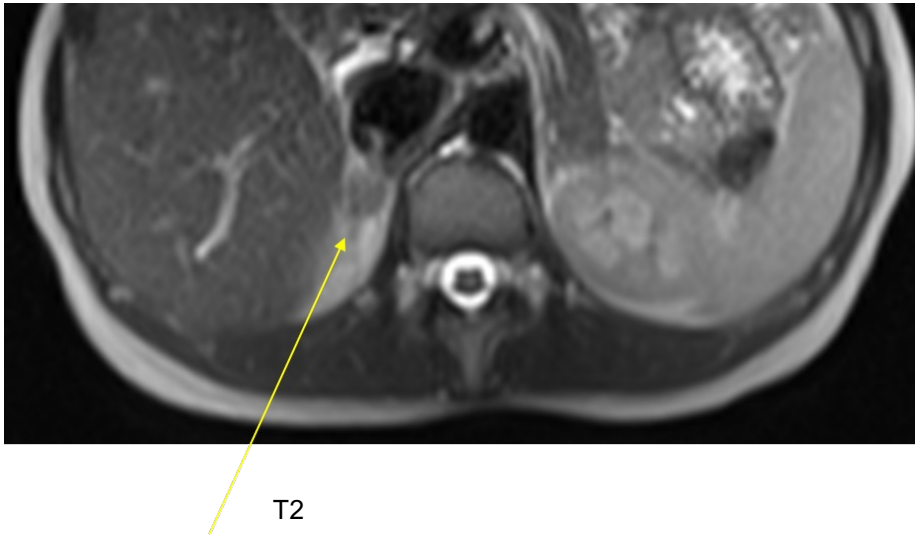
Delayed venous phase (15 min)

Imaging

		Wash out values	
Percentage washout	Formula	Adenoma	Malignancy
Absolute PW	(E-D)/(E-U) x 100 *Wash-out/wash-in*	>60%	<60%
Relative PW	(E-D)/E x 100	>40%	<40%
U: unenhanced attenuation value, E: enhanced (venous) attenuation value, D: delayed (15min) enhanced value			

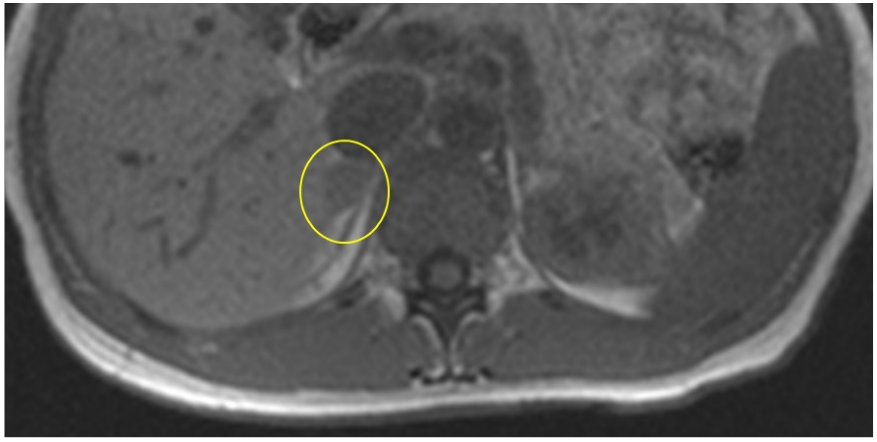


Imaging

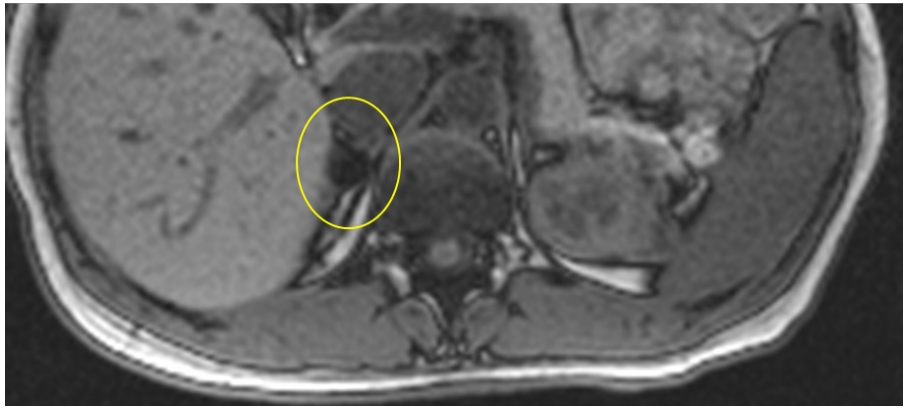


T2

Lipid-rich adenoma on MRI: chemical shift artefact → loss of signal on out of phase sequences



T1 in phase



T1 out of phase

Imaging

- CT vs. MRI?

Managing Incidental Findings on Abdominal CT: White Paper of the ACR Incidental Findings Committee

Lincoln L. Berland, MD[a], Stuart G. Silverman, MD[b], Richard M. Gore, MD[c], William W. Mayo-Smith, MD[d], Alec J. Megibow, MD, MPH[e], Judy Yee, MD[f], James A. Brink, MD[g], Mark E. Baker, MD[h], Michael P. Federle, MD[i], W. Dennis Foley, MD[j], Isaac R. Francis, MD[k], Brian R. Herts, MD[h], Gary M. Israel, MD[g], Glenn Krinsky, MD[l], Joel F. Platt, MD[k], William P. Shuman, MD[m], Andrew J. Taylor, MD[n]

J Am Coll Radiol 2010;7:754-773.

Last review date: 2012

American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Incidentally Discovered Adrenal Mass**

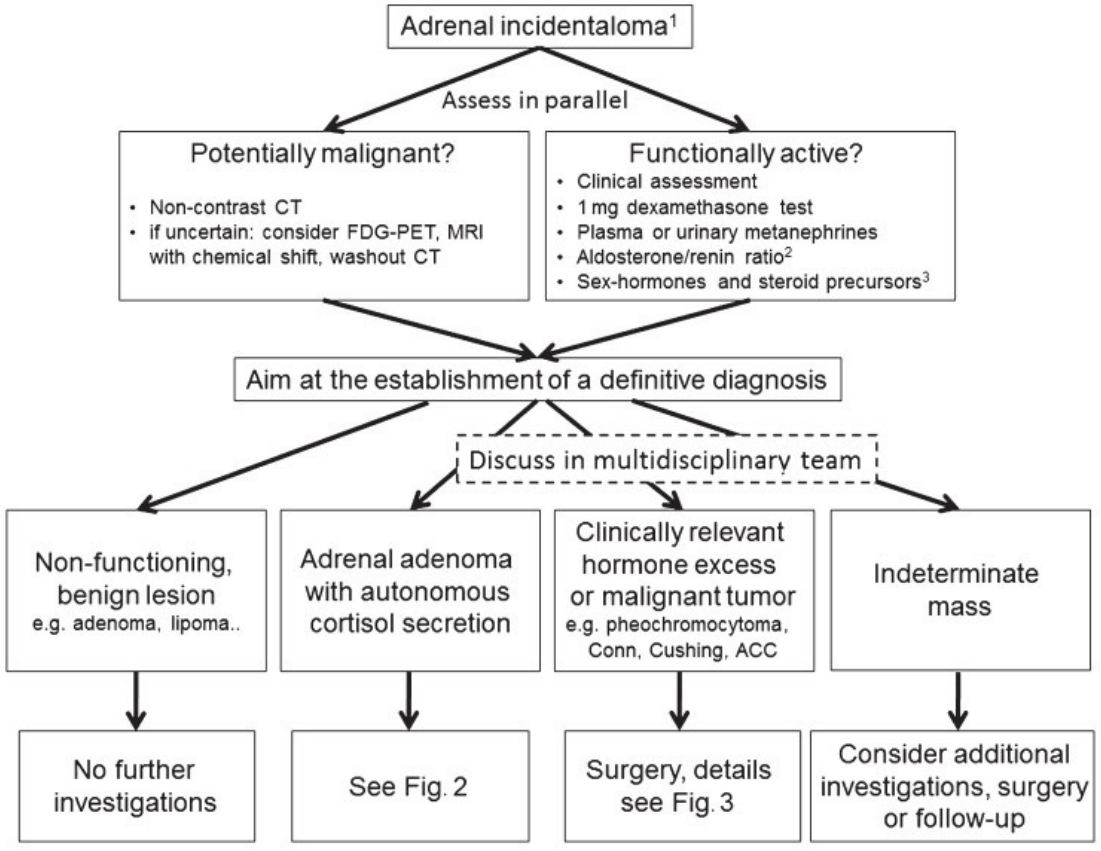
Variant 1: **No history of malignancy; mass 1-4 cm in diameter. Initial evaluation.**

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen without IV contrast	8	Presumes that a noncontrast CT has not already been performed and that there are no suspicious imaging features. Should be evaluated by radiologist to determine if contrast administration is needed.	☢☢☢
CT abdomen without and with IV contrast	8	Indicated if noncontrast CT is not diagnostic or if there are concerning imaging features of malignancy. Delayed imaging obtained to calculate washout.	☢☢☢☢
MRI abdomen without IV contrast	8	May be helpful when nonenhanced CT is equivocal or if there is suspicious imaging features. Appropriate for patient with iodinated contrast allergy.	O
MIBG	2	Only for suspicion of pheochromocytoma.	☢☢☢
MRI abdomen without and with IV contrast	2		O
US adrenal gland	1		O
Biopsy adrenal gland	1		Varies
CT abdomen with IV contrast	1		☢☢☢
X-ray abdomen	1		☢☢
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	1		☢☢☢☢

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate — *Relative Radiation Level

Biochemical work-up

- Indicated for every lesion > 1 cm



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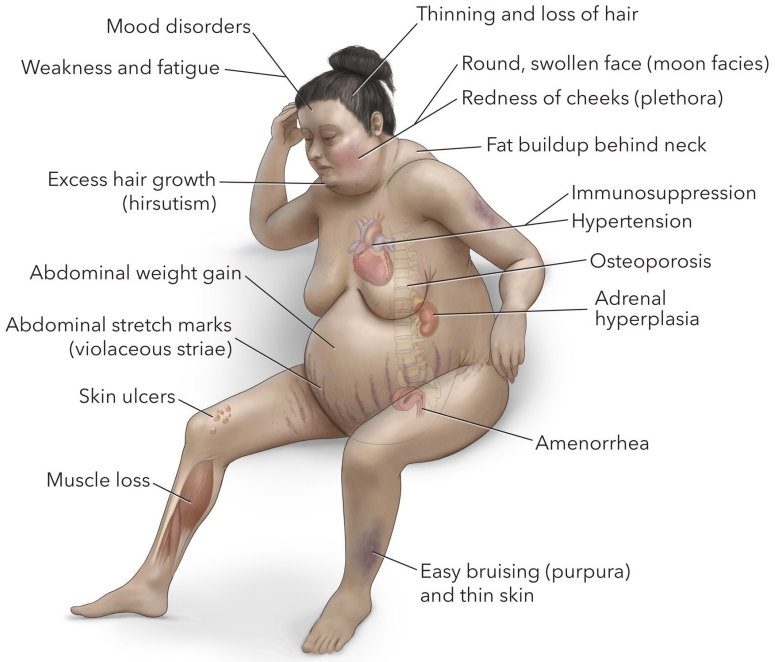
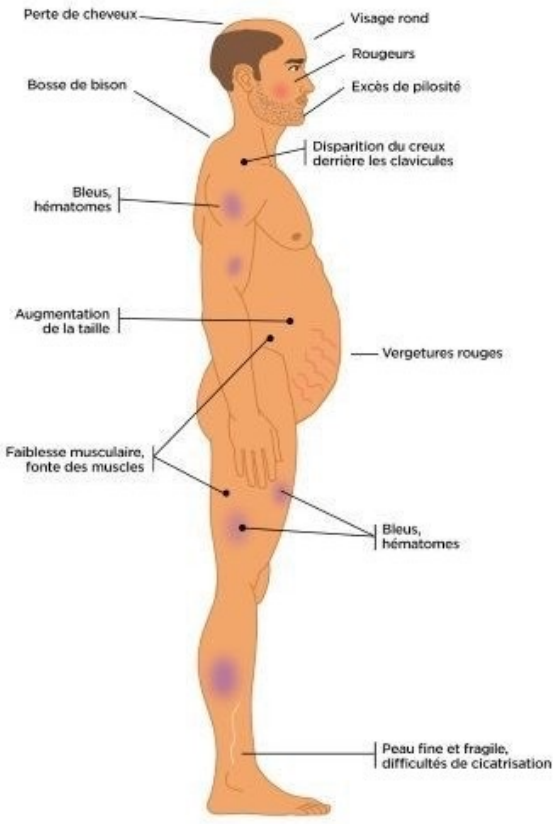
Fassnacht *et al.*, EJE 2016

Biochemical work-up

- Clinical assessment





Biochemical work-up

- Screening for hypercortisolism
  - No value in morning cortisol measurements
  - Screening tests based on:
    - Disrupted circadian rhythm: late night salivary cortisol (LNSC)
    - Autonomous cortisol secretion: overnight dexamethasone suppression test (DST)
    - Increased cortisol exposure: 24-h urinary cortisol

- CAVE:
  - Suboptimal sensitivity & specificity < false positive & false negative results
  - 2/3 tests positive = confirmation of disease

Table 1. SE, SP, LR^{neg}, LR^{pos}, AUC, and Respective 95% CI of Each Test Used for the Diagnosis of CS

Non-CS (n = 99) vs CS (n = 38)

Test	Cutoff	SE, % (95% CI)	SP, % (95% CI)	LR^{neg} (95% CI)[a]	LR^{pos} (95% CI)	AUC (95% CI)
1-mg DST	50 nmol/L	100 (90.8–100)	91.9 (84.9–95.9)		12.37 (6.37–24.05)	98.9 (97.5–100)
	138 nmol/L	86.8 (72.7–94.2)	96.7 (91.5–99)	0.14 (0.06–0.31)	28.66 (9.34–87.9)	
LNSC	14.46 nmol/L	84.2 (69.6–92.6)	88.9 (81.2–93.7)	0.18 (0.09–0.37)	7.58 (4.27–13.45)	95.8 (92.5–99.1)
UFC	170 nmol per 24 h	97.4 (86.5–99.5)	90.9 (83.6–95.1)	0.03 (0.01–0.2)	10.71 (5.73–20)	97.7 (94.6–100)

[a] LR^{neg} not computable if SE = 100%.

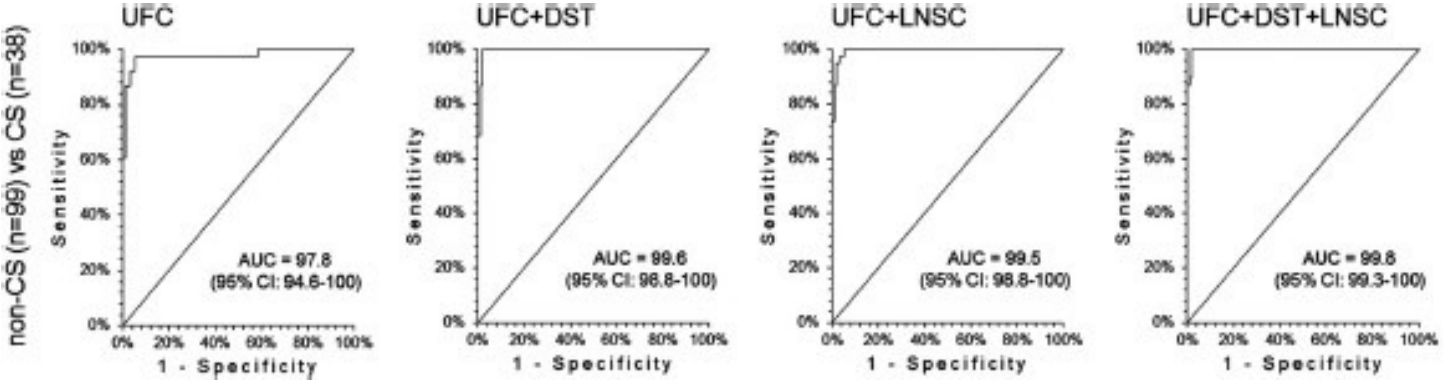


Table 3. Number and Percentage of False-Negative (FN) and False Positive (FP) Test Results

	1-mg DST 50 nmol/L n/Total, %	1-mg DST 138 nmol/L n/Total, %	LNSC 14.46 nmol/L n/Total, %	UFC 170 nmol per 24 h n/Total, %
CS	FN 0/38	FN 5/38 (13%)	FN 6/38 (16%)	FN 1/38 (3%)
Non-CS	FP 9/99 (9%)	FP 3/99 (3%)	FP 11/99 (11%)	FP 9/99 (9%)

Ceccato, JCEM 2015

Biochemical work-up

- CAVEATS:
  - Total cortisol not interpretable in case of exogenous estrogen exposure → use LNSC, 24-h cortisoluria
  - LNSC not representative in case of disrupted circadian rhythm
  - Pseudo-cushing: functional hypercortisolism in alcohol abuse, depression, …
  - Pharmacokinetic interactions with dexamethasone

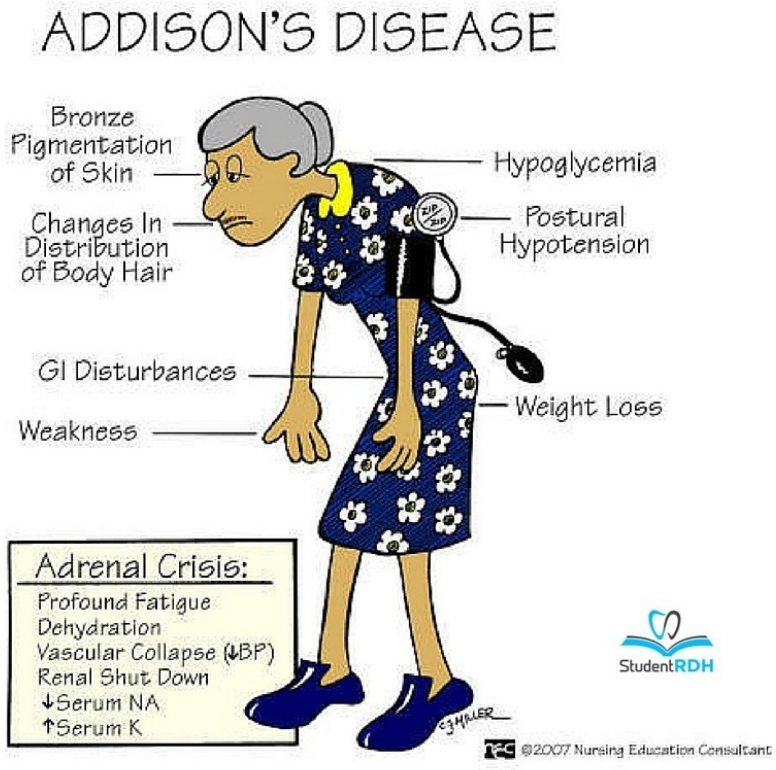
TABLE 3. Selected drugs that may interfere with the evaluation of tests for the diagnosis of Cushing's syndrome[a]

Drugs
Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
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
Drugs that increase UFC results
Carbamazepine (increase)
Fenofibrate (increase if measured by HPLC)
Some synthetic glucocorticoids (immunoassays)
Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)

Fassnacht *et al.*, EJE 2016

Biochemical work-up

- Screening for hypocortisolism
  - Only indicated if suspicion for (bilateral) infiltrative disease



Biochemical work-up

- Screening for hyperaldosteronism
  - Only indicated if known arterial hypertension / hypokalemia
    - Hypertension appears similar to that of primary (essential) hypertension
    - Pts with PA rarely have edema
    - Majority of pts with PA are normokalemic without alkalosis!
  - Screening using aldosterone / renin ratio
  - Beware of pre-analytical conditions!

TABLE 4. Factors that may affect the ARR and thus lead to false-positive or false-negative results

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
β-Adrenergic blockers	↓	↓ ↓	↑ (FP)
Central α-2 agonists (*e.g.* clonidine and α-methyldopa)	↓	↓ ↓	↑ (FP)
NSAIDs	↓	↓ ↓	↑ (FP)
K^+-wasting diuretics	→↑	↑ ↑	↓ (FN)
K^+-sparing diuretics	↑	↑ ↑	↓ (FN)
ACE inhibitors	↓	↑ ↑	↓ (FN)
ARBs	↓	↑ ↑	↓ (FN)
Ca^{2+} blockers (DHPs)	→↓	↑	↓ (FN)
Renin inhibitors	↓	↓ ↑[a]	↑ (FP)[a] ↓ (FN)[a]
Potassium status			
Hypokalemia	↓	→↑	↓ (FN)
Potassium loading	↑	→↓	↑ (FP)
Dietary sodium			
Sodium restricted	↑	↑ ↑	↓ (FN)
Sodium loaded	↓	↓ ↓	↑ (FP)
Advancing age	↓	↓ ↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2	→	↓	↑ (FP)
Pregnancy	↑	↑ ↑	↓ (FN)
Renovascular HT	↑	↑ ↑	↓ (FN)
Malignant HT	↑	↑ ↑	↓ (FN)

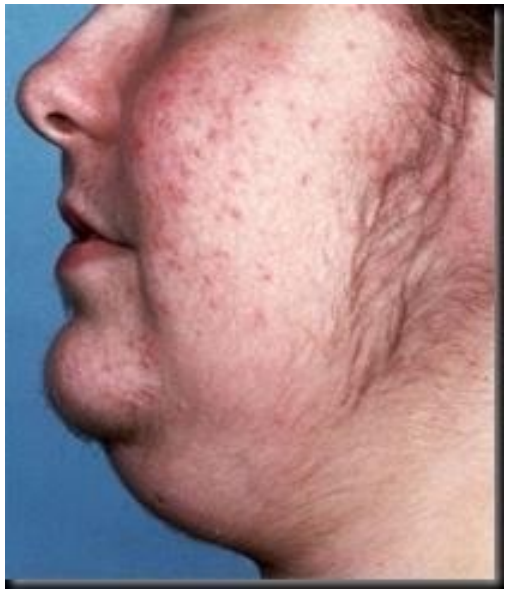
ACE, Angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; DHP, dihydropyridine; FP, false positive; FN, false negative; HT, hypertension; NSAID, nonsteroidal antiinflammatory drug; PHA-2, pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate).

[a] Renin inhibitors lower PRA but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC.

Biochemical work-up

- Screening for adrenocortical carcinoma
  - Measurement of sex steroids / steroid precursors
  - Only if (rapid development of)signs of virilization and/or high suspicion for ACC

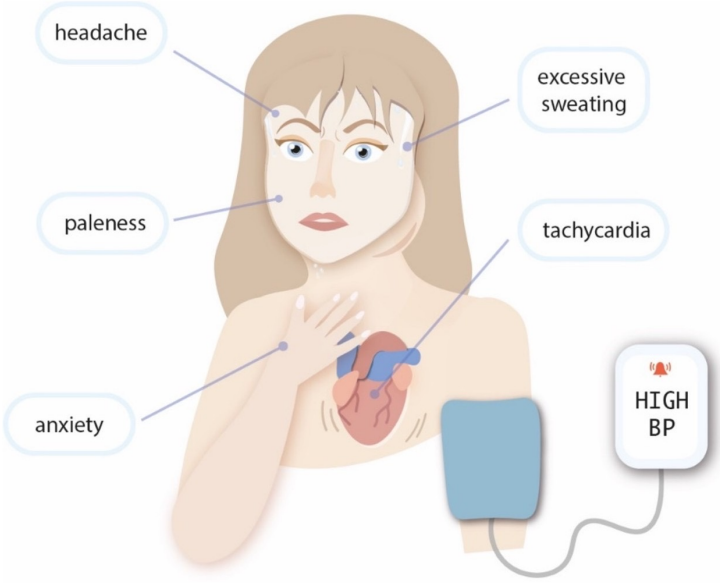
  - Most often accompanying features on imaging are present
  - Plus: other clinical signs and symptoms

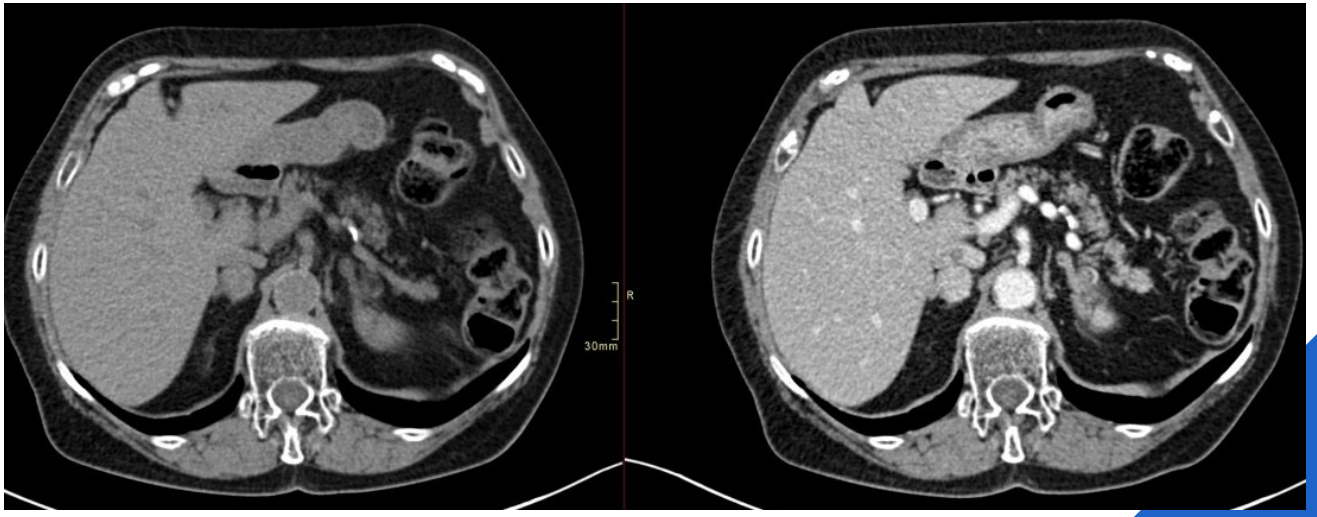


Biochemical work-up

- Screening for pheochromocytoma

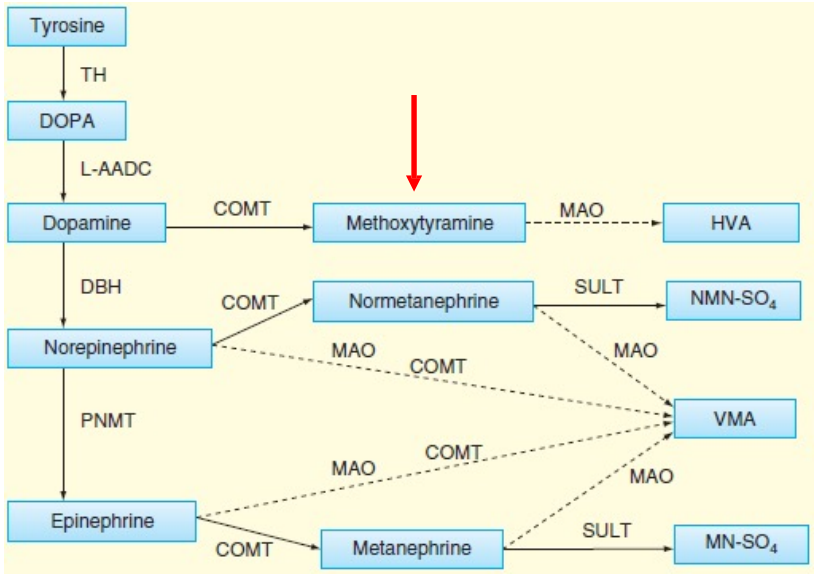
- 5 P’s
  - Pain (headache)
  - Pressure (hypertension)
  - Palpitations
  - Perspiration
  - Pallor

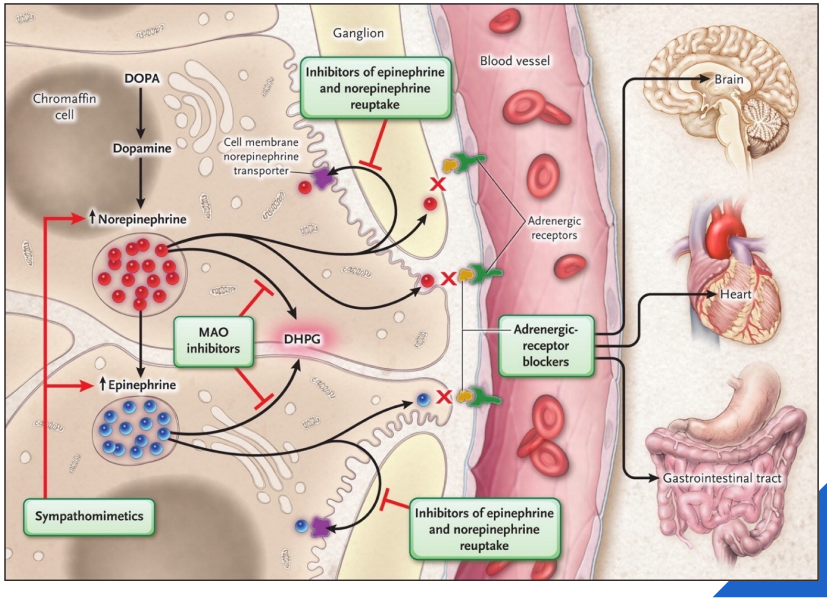




Biochemical work-up

- Pheochromocytoma
  - About 40% of patients are asymptomatic
  - Screening using plasma or urinary (nor)metanephrines
  - No need for adrenalin or noradrenalin measurements
  - Beware of test interference!





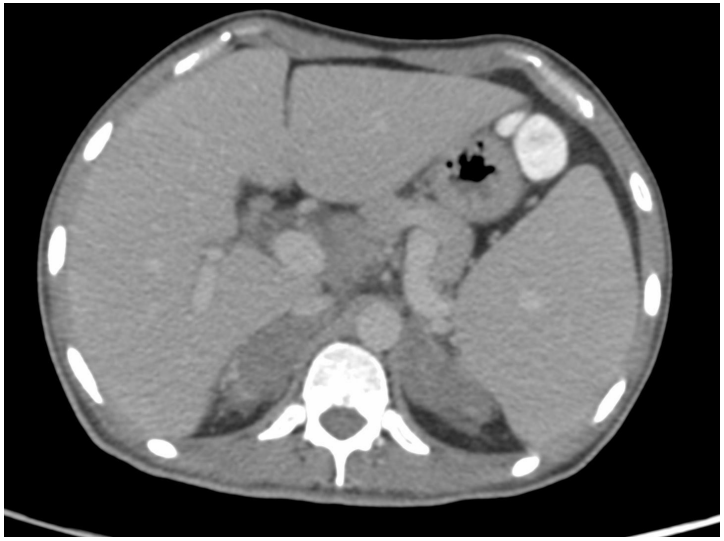
Biochemical work-up

- Pheochromocytoma

PREANALYTISCHE FACTOREN	
Inspanning, lichaamshouding, hypoglykemie, emotionele stress, leeftijd, roken vs. stress ikv rookstop	
Fysieke stress of ziekte: cerebrovasculair accident, myocardinfarct, congestief hartfalen, AHT, OSAS	
Chronische nierinsufficiëntie, vooral bij dialysepatiënten	
Slechte bloedafnametechniek*	
Voeding rijk aan biogene aminen: fruit, noten	
MEDICAMENTEUZE INTERACTIES	
Medicatie met analytische invloed op HPLC-ECD	Paracetamol, labetalol, buspiron, mesalazine, sulfasalazine
Sympathicomimetische agentia	Efedrine, amfetamine, cocaïne, cafeïne, nicotine
Noradrenalineheropnameremmers	Noradrenaline- en serotonineheropnameremmers (venlafaxine) Selectieve serotonineheropnameremmers (SSRI's) Tricyclische antidepressiva (TCA's)
Antihypertensieve medicatie	Vasodilatoren (dihydropyridine-calciumantagonisten) Fenoxybenzamine, betablokkers
Andere	Monoamineoxidaseremmers Levodopa quetiapine
Rebound-effect van medicatie/drugs	Clonidine, alcohol

Stevens & T'Sjoen, TVG 2015

Special considerations

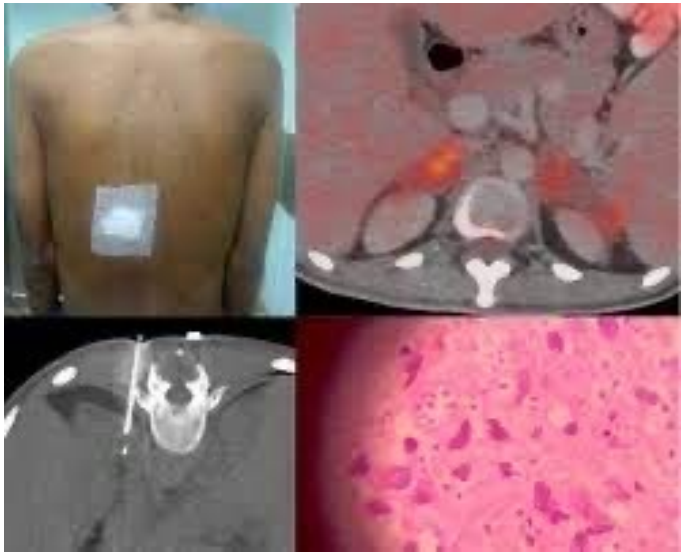


- Bilateral adenomas / hyperplasia
  - Mostly benign disease
  - DD:
    - Bilateral hyperplasia
    - Metastases, adrenal lymphoma
    - Bilateral pheochromocytoma
  - Work-up similar as for unilateral adenoma
    - Plus:
      - 17-OH-progesterone to screen for congenital adrenal hyperplasia
      - Morning serum cortisol to exclude adrenal insufficiency < metastases, infiltrative disease (TBC, sarcoidosis, …), hemorrhage

Special considerations

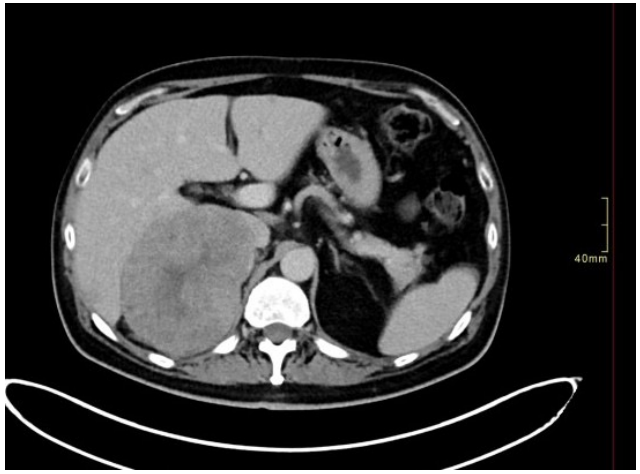
- Tissue is the issue?
  - ESE guideline recommend against the use of adrenal biopsy

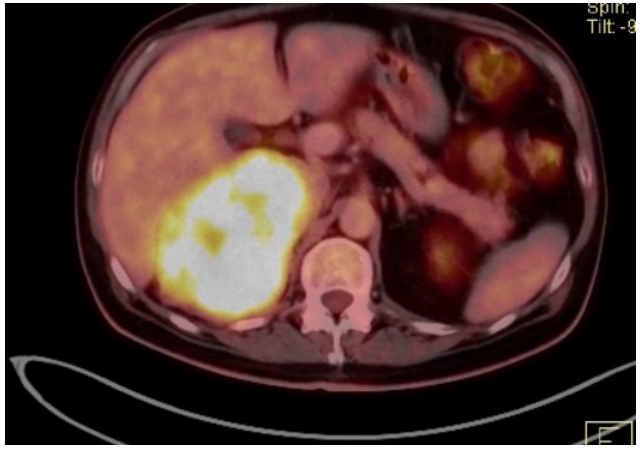
- Except if (all criteria should be fulfilled):
  - History of extra-adrenal malignancy.
  - Hormonally inactive (in particular pheochromocytoma has been excluded).
  - No conclusively benign features on imaging.
  - Management would be altered by knowledge of the histology.



Special considerations

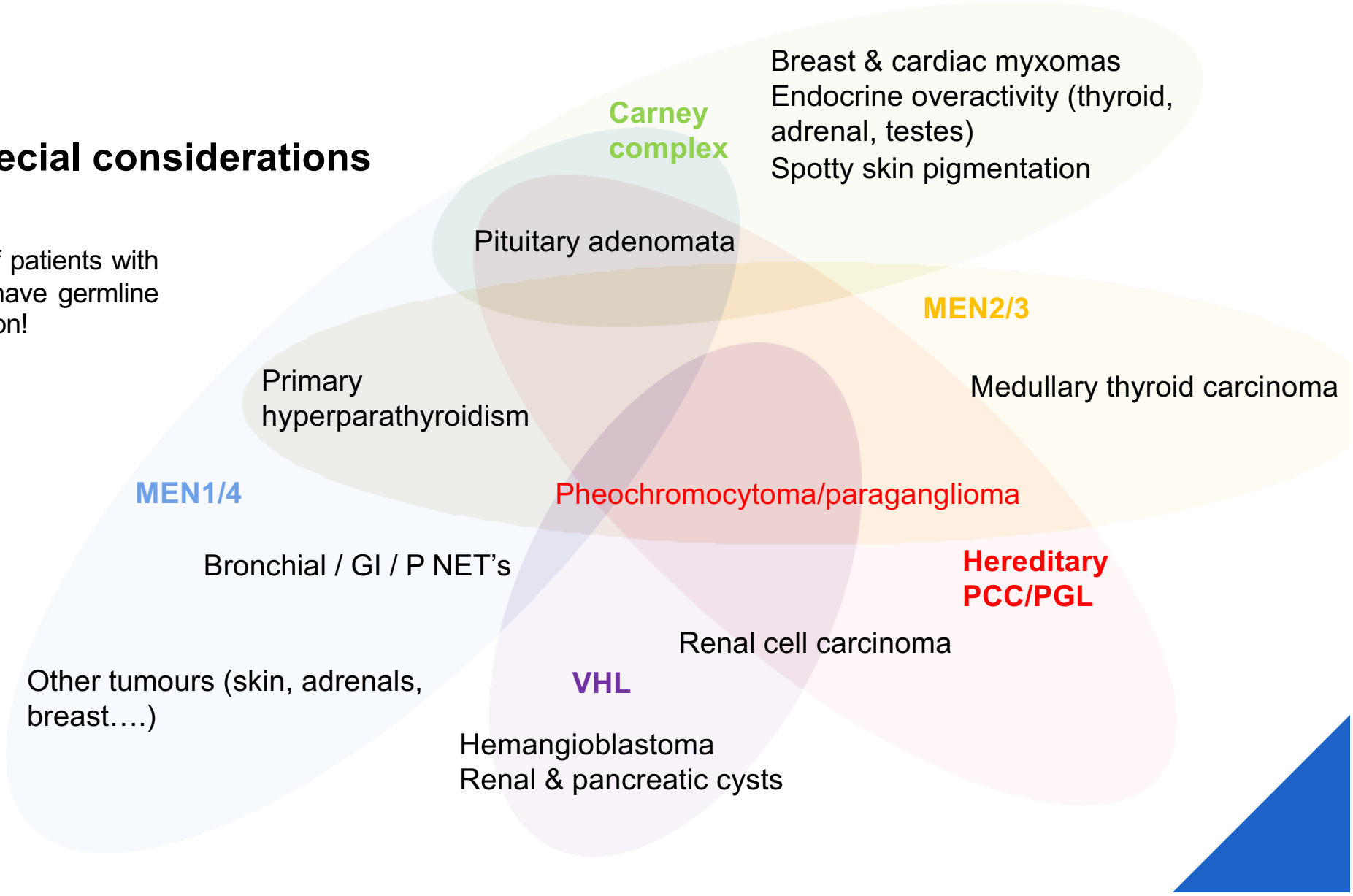
- Adrenocortical carcinoma
  - Rare
  - Rapid progressive disease
  - 50% are hormonally active
  - Variable imaging characteristics
    - heterogenous, necrotic, irregular borders, calcifications, FDG-avid
  - Complete surgical removal = only curative option





Special considerations

- 40% of patients with pheo have germline mutation!



Conclusions

- Adrenal lesions are relatively common
  - 1% of CT's
- Most are benign & non-functional but there are some not to miss lesions
- Imaging can help you a lot
  - Look at the scans
  - Talk to your radiologist!
- Don't forget the hormonal work-up!
  - Choose your test wisely
  - Beware of specificities & limitations
  - Talk to your hormonology lab!

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