Adrenal Mass

CTU Noon Rounds

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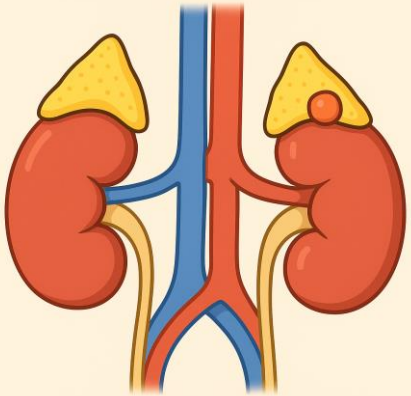


Disclosures

Speaker honoraria

- Abbott
- Dexcom
- Pfizer

Research funding

- Abbott

Consulting honoraria

- Abbott
- Amgen
- Boehringer Ingelheim
- Novo Nordisk
- Pendopharm
- Pfizer

Managing potential bias:

None of these are relevant to the current presentation

Learning Objectives

1. Recognize the epidemiology & clinical significance of adrenal incidentalomas
2. Apply a structured approach to the radiographic & biochemical evaluation of adrenal incidentalomas
3. Differentiate management strategies for benign, indeterminate, & malignant adrenal lesions, incorporating current guideline recommendations
4. Integrate recent evidence & controversies around adrenal masses into clinical decision-making

European Journal of Endocrinology, 2023, **189**, G1–G42
https://doi.org/10.1093/ejendo/lvad066
Advance access publication 15 June 2023
Clinical Practice Guideline

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

Martin Fassnacht,[1,2,*] Stylianos Tsagarakis,[3] Massimo Terzolo,[4] Antoine Tabarin,[5] Anju Sahdev,[6] John Newell-Price,[7,8] Iris Pelsma,[9] Ljiljana Marina,[10] Kerstin Lorenz,[11] Irina Bancos,[12] Wiebke Arlt,[13,14] and Olaf M. Dekkers[9,15]

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 11, 3331–3353
https://doi.org/10.1210/clinem/dgab512
Approach to the Patient

Approach to the Patient

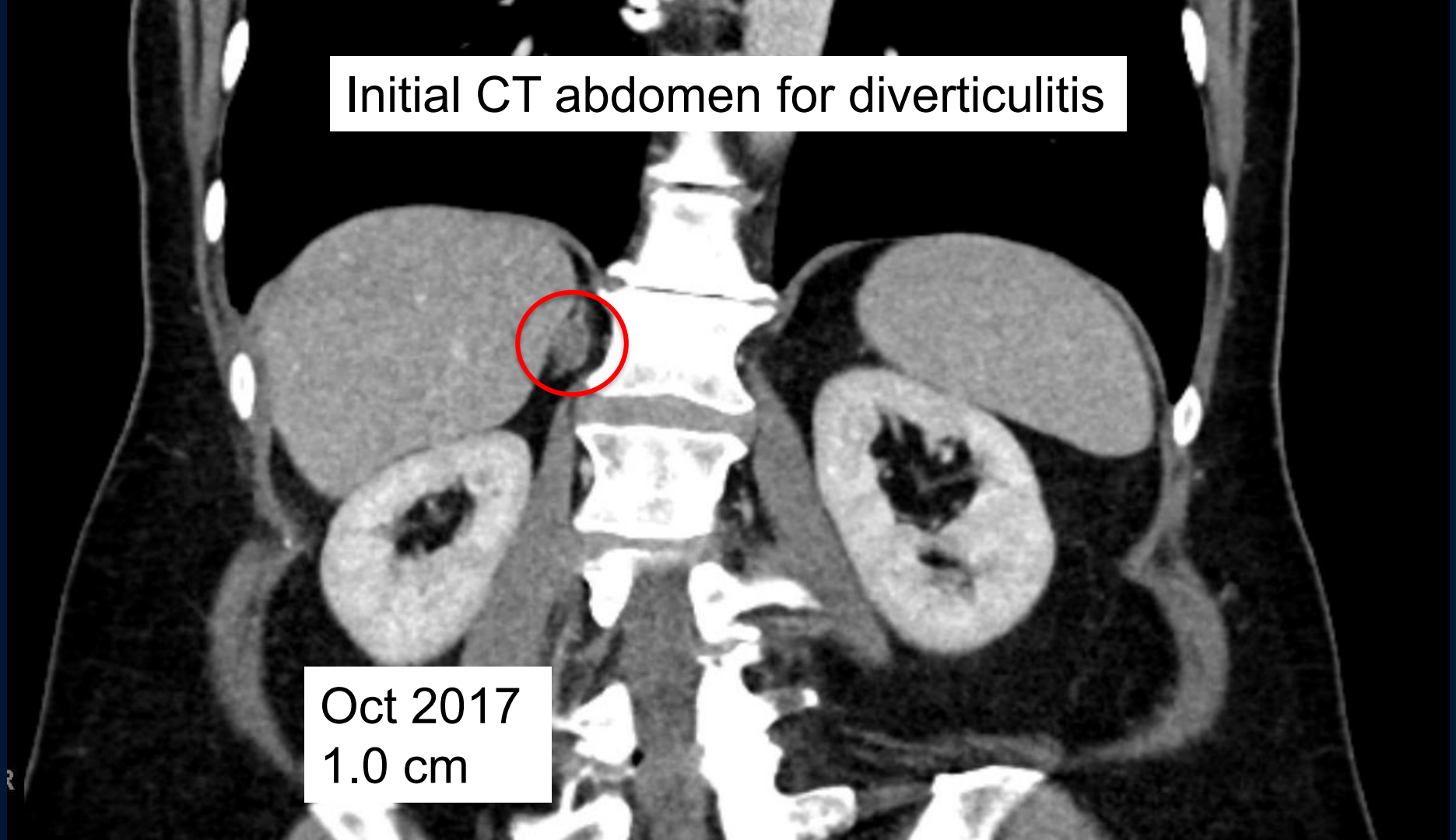
Approach to the Patient With Adrenal Incidentaloma

Irina Bancos,[1,2] and Alessandro Prete[3,4,5]

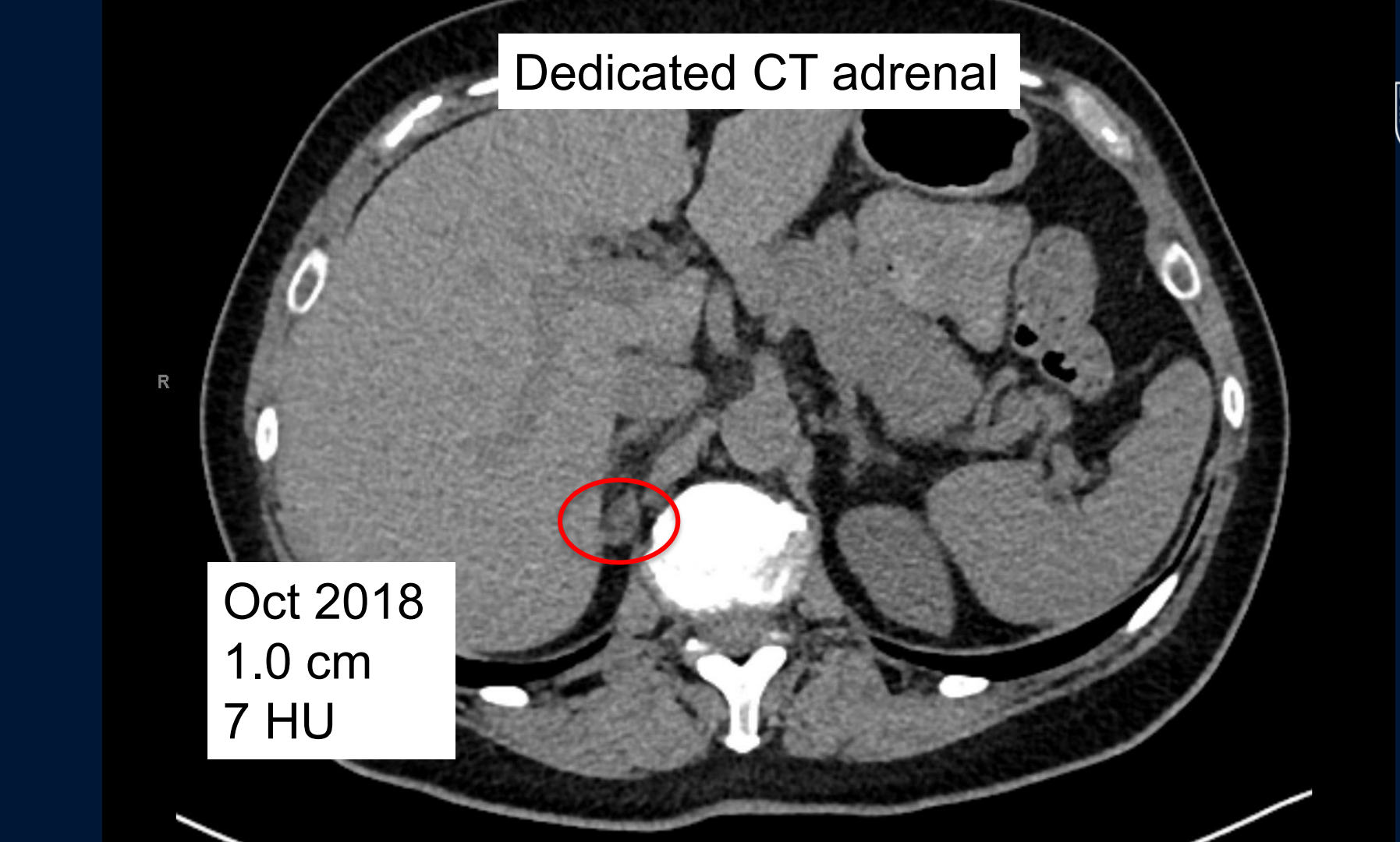
Case 1

- 68 F
- Adrenal mass found on imaging for diverticulitis

- PMHx: diverticulosis, hip OA, GERD
- Meds: none
- Na 140, K 5.4, A1c 5.6, BP 135/78, BMI 27.8


Initial CT abdomen for diverticulitis
Oct 2017
1.0 cm

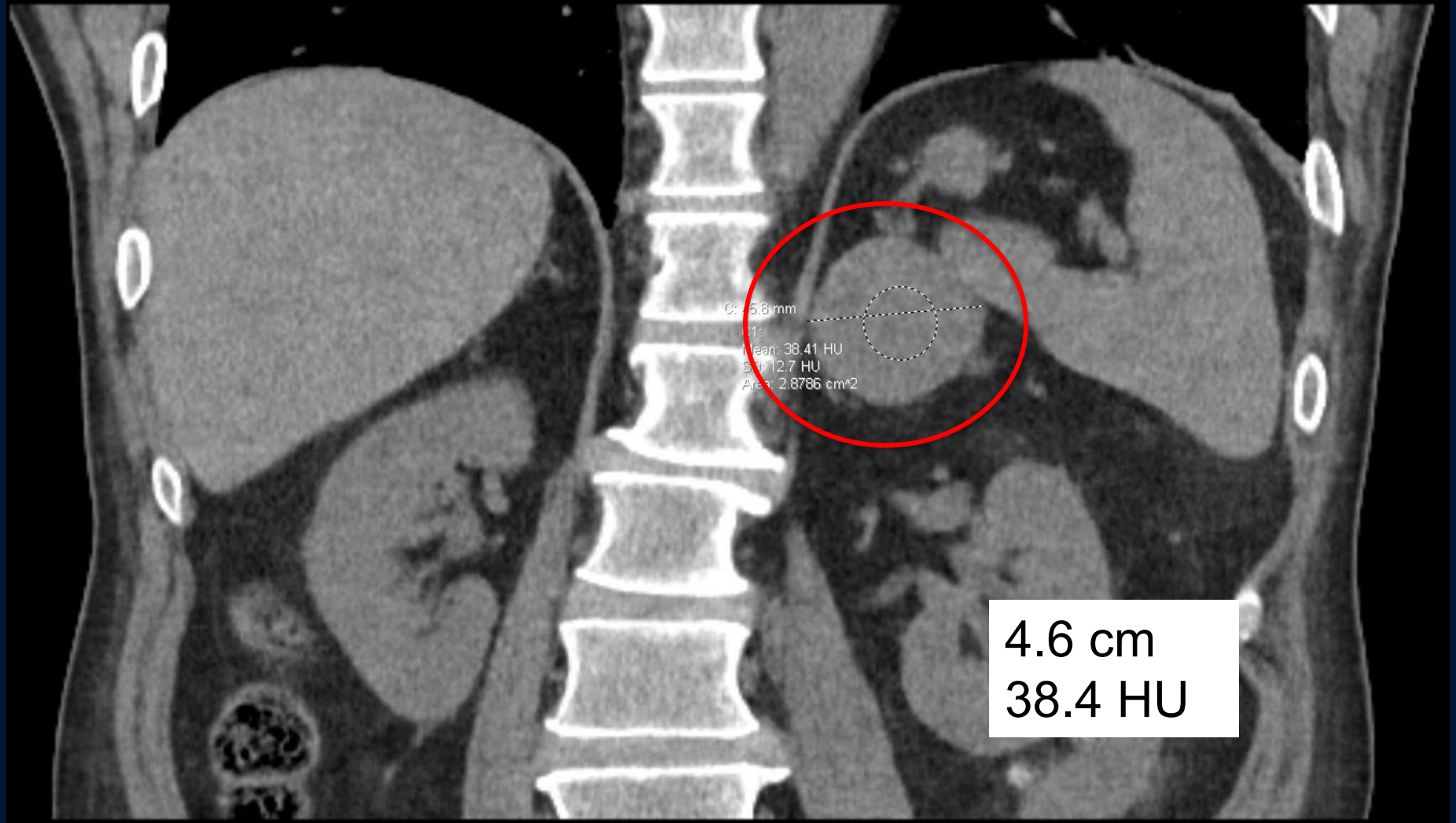
Dedicated CT adrenal



Case 2

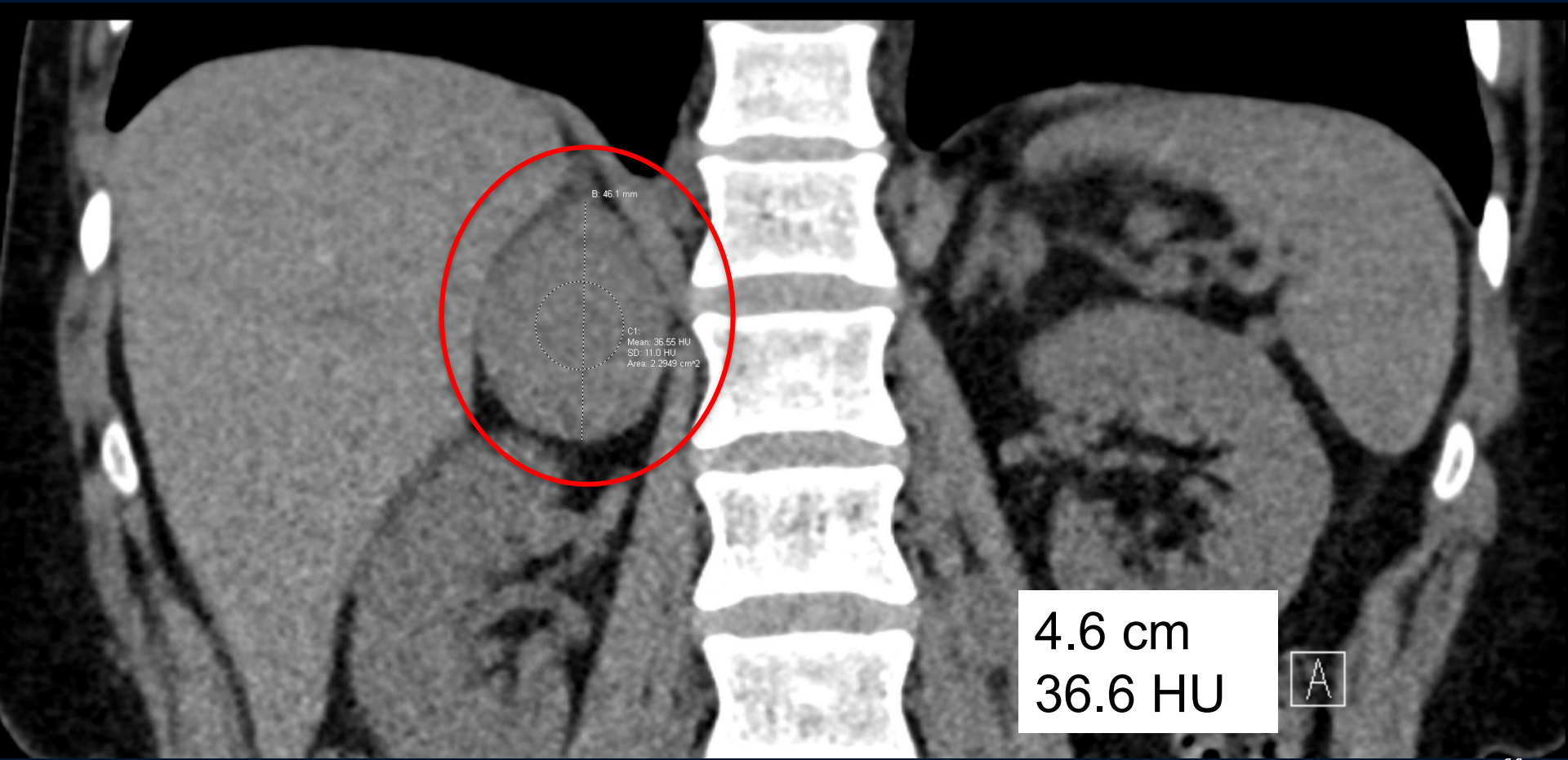
- 63 M
- Presented to hospital with new-onset psychosis & mania

- Had pan-CT done to look for medical etiology
- Found an adrenal mass


Mean: 38.41 HU
Area: 2.8786 cm^2
4.6 cm
38.4 HU

Case 3

- 42 F
- PMHx: NF1, ++neurofibromas, anxiety, migraines
- Meds: bisoprolol, amitriptyline 40 mg/d
- Referred by GP:
  - MRI C, T, and L spine for neurofibroma monitoring
  - Noted to have enlarging adrenal mass


B: 46.1 mm
C1:
Mean: 36.55 HU
SD: 11.0 HU
Area: 2.2949 cm^2
4.6 cm
36.6 HU
A

Cases

1. Homogeneous, 1.0 cm, 7 HU, stable 1yr apart

2. Homogeneous, 5.1 cm, 40 HU

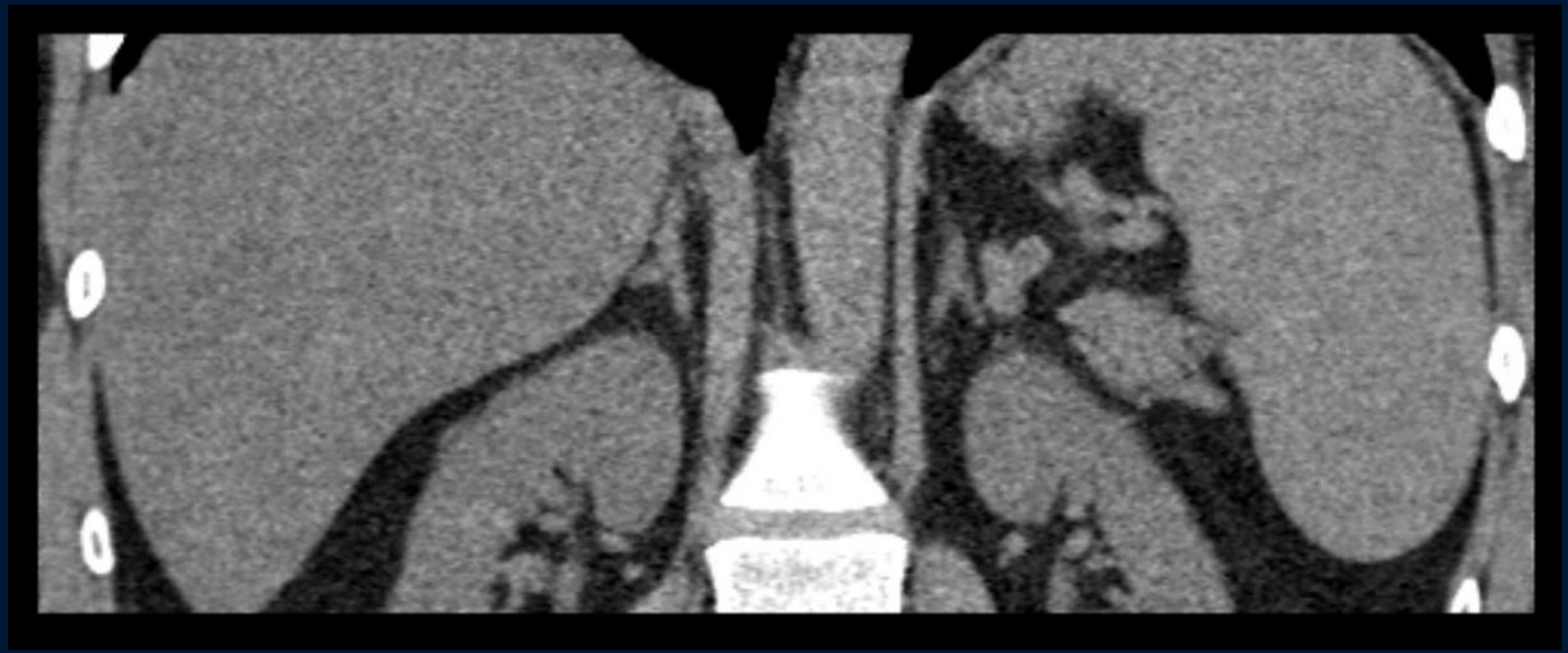
3. Homogeneous, 5.0 cm, 37 HU, growth 0.6–0.7 cm/yr

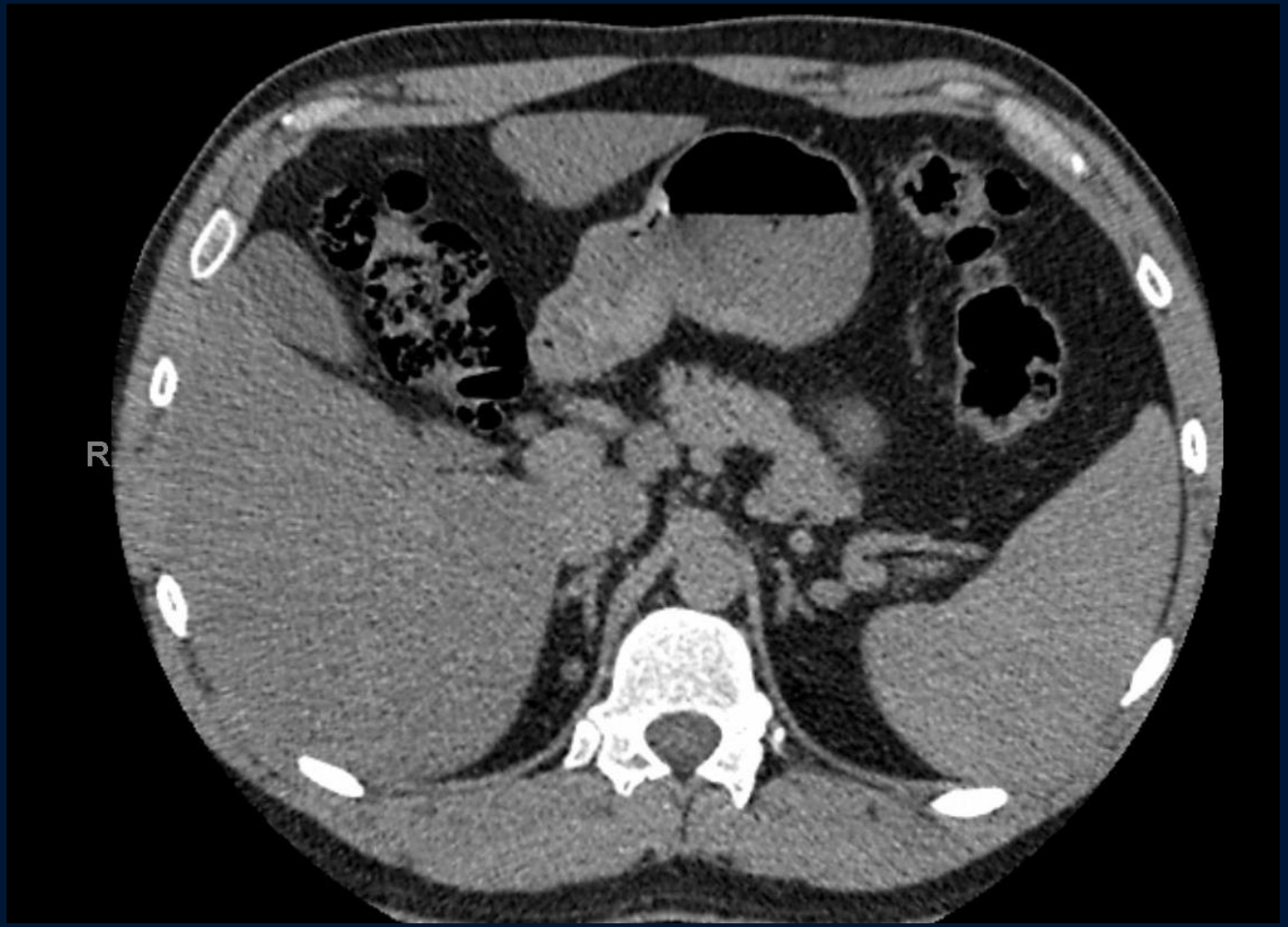
Definitions

- Adrenal incidentaloma:
  - Adrenal mass found on imaging
  - No suspected adrenal dz
  - Generally use threshold of ≥1 cm (somewhat arbritary)

- MACS
  - Mild Autonomous Cortisol Secretion
  - Previously called “subclinical Cushing syndrome”

Normal Adrenal Glands

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Epidemiology

- Adrenal incidentalomas are common
- Prevalence 1–10% (median 3%) in autopsy series
- Prevalence 1–5% (median 2%) in radiology series
  - ~3% in adults over 50 yr
  - Up to 10% in those >80 yr

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Types of Adrenal Masses

- 80–90% benign adenoma
- 3–8% other benign (myelolipoma, cyst, etc)

- 3–8% malignant (mostly metastases)
  - Series from referral centres → higher rates
  - Incidentaloma series ~3%
- 1–2% pheochromocytoma
- 0.3–1% adrenocortical carcinoma (ACC)

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Etiology	Prevalence of the different entities among adrenal incidentalomas
Adrenocortical adenoma or macronodular bilateral adrenal hyperplasia	80%-85%
• Nonfunctioning	40%-70%
• Mild autonomous cortisol secretion (MACS)	20%-50%
• Primary aldosteronism	2%-5%
• Overt Cushing's syndrome	1%-4%
Other benign mass	
• Myelolipoma	3%-6%
• Cyst and pseudocyst	1%
• Ganglioneuroma	1%
• Schwannoma	<1%
• Hemorrhage	<1%
Pheochromocytoma	1%-5%
Adrenocortical carcinoma (ACC)	0.4%-4%
Other malignant mass (mostly adrenal metastases)	3%-7%

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Signs & Symptoms

- “Incidentaloma” implies no adrenal SSx
- But should look for signs of hormone excess
  - Cushing’s: striae, fat pads, ecchymoses, myopathy
  - Hyperaldo: hypertension, hypokalemia
  - Pheo: spells, palpitations, HTN, headache, orthostasis
- Rarely have signs of mass effect (malignancy)
- Most don’t have any specific features
  - Even most pheos are picked up incidentally these days

Clinical Approach

1. Risk of malignancy
    - Imaging phenotype – typically CT

2. Functional (endocrine) status
    - Clinical
    - Biochemistry
        - 1 mg dex suppression test (+/- ACTH, DHEAS)
        - Aldosterone & renin
        - Metanephrines (urine or plasma)

Imaging

- For most situations: CT > MRI
  - Prefer MRI in younger pts esp if screening in genetic dz
- Characteristics of importance
  - Size
  - Heterogeneity
  - Attenuation on unenhanced CT (Hounsfield units)
  - Contrast washout
  - Growth rate (if available)
  - Chemical-shift imaging (if using MRI)

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Size

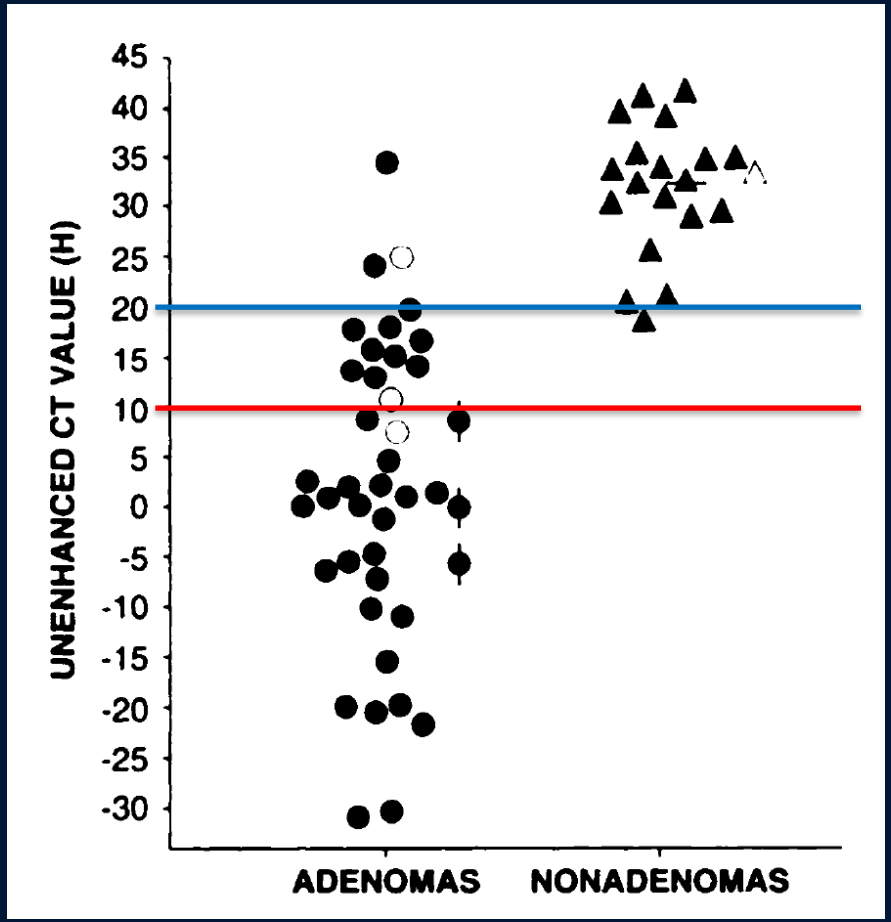
- Most benign masses are small
- ↑size → ↑risk of malignancy
  - <2 cm → 6% are malignant
  - 2–4 cm → 9% are malignant
  - >4 cm → 34% are malignant (sens 77%, spec 90%)
- Large masses can still be benign
  - eg, 5 cm mass but HU<10 & homogeneous → benign
  - Myelolipomas (benign) can be very large
- Malignant lesions start out as small masses

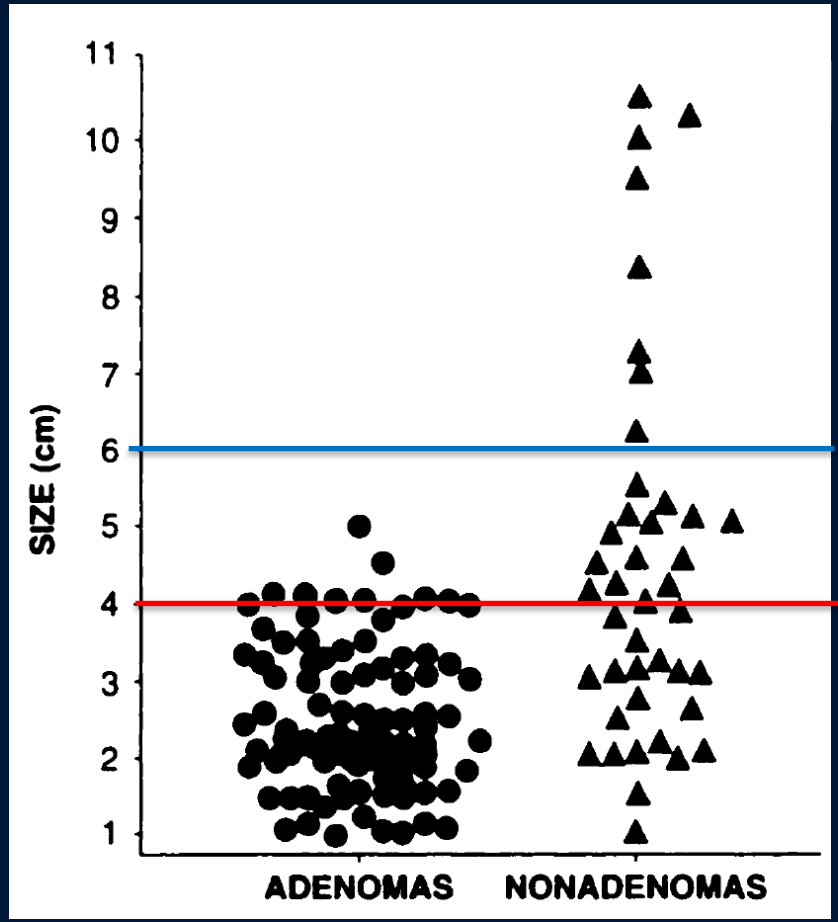
Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42. Bancos et al. JCEM. 2021 Oct;106(11):3331-3353.

CT Attenuation

- Quantified using Hounsfield units (HU)
- Benign adrenal masses have high lipid content
- Low HU is very accurate in ruling out malignancy
  - HU<10 has sensitivity 54%, specificity 100%
  - HU<20 has sensitivity 77%, specificity 90%
- High HU can still be benign, but Dx of exclusion
- MRI with chemical-shift imaging for lipid content
  - Sensitivity 86–90%, specificity 85%

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42. Bancos et al. JCEM. 2021 Oct;106(11):3331-3353.





Korobkin et al. Am J Roentgenol. 1996 Mar;166(3):531-536.

Contrast Washout

- In general:
  - Benign masses have rapid washout of contrast
  - Malignant masses have slow washout of contrast

Washout	Calculation	Reassuring
Absolute	$\frac{Enhanced-Delayed}{Enhanced-Nonenhanced}$	>60% at 10-15min
Relative	$\frac{Enhanced-Delayed}{Enhanced}$	>40% at 10-15min

VGH:
Precontrast
1min post
15min post

- In reality, there is significant overlap
  - Absolute washout >60% → sensitivity 64%, specificity 78%
  - Relative washout >40% → sensitivity 69%, specificity 92%
  - vs HU<10 → sensitivity 54%, specificity 100%

Schloetelburg et al. Eur J Endocrinol. 2021 Dec;186(2):183-193.

Growth Rate

- Benign masses can grow, but slowly
- Malignant masses grow quickly
- Pheo growth rate in between (unless malignant)
- No clear cut-offs but some general principles:
  - ≥1 cm/yr → concerning
  - ≤1–2 mm/yr → reassuring (mean is 2 mm over 4–5 yr)
  - 3–7 mm/yr → typical growth rate for pheo
  - Consider surgery if growth >20% & ≥5mm

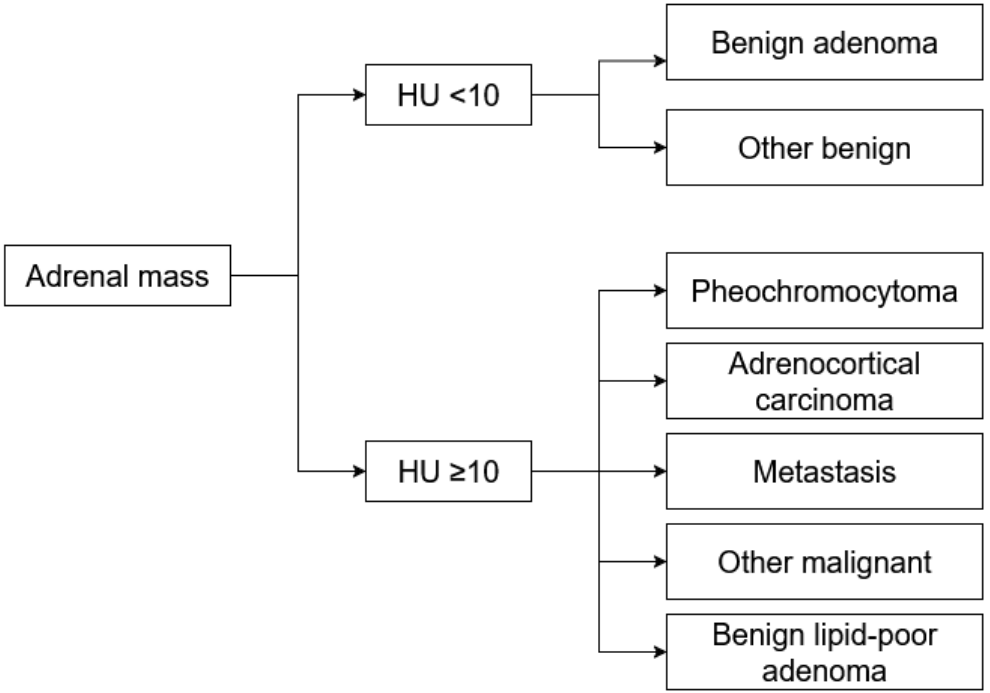
Bancos et al. JCEM. 2021 Oct;106(11):3331-3353.

Table 4. Imaging criteria to discriminate benign from malignant adrenal masses.[a]

Method	Criteria favoring a benign mass	Strength of evidence[b]
Noncontrast CT	≤ 10 HU[c]	⊕⊕⊕◯
FDG-PET/CT	Absence of FDG uptake or uptake less than the liver[d]	⊕◯◯◯
MRI—chemical shift	Loss of signal intensity on out-phase imaging consistent with lipid-rich adenoma	⊕◯◯◯
CT with delayed contrast media washout[e]	Relative washout > 58%[f]	⊕◯◯◯

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Approach



Homogeneous
Generally <4cm
Generally rapid washout

Heterogeneous
Higher risk if >4cm
Generally slow washout

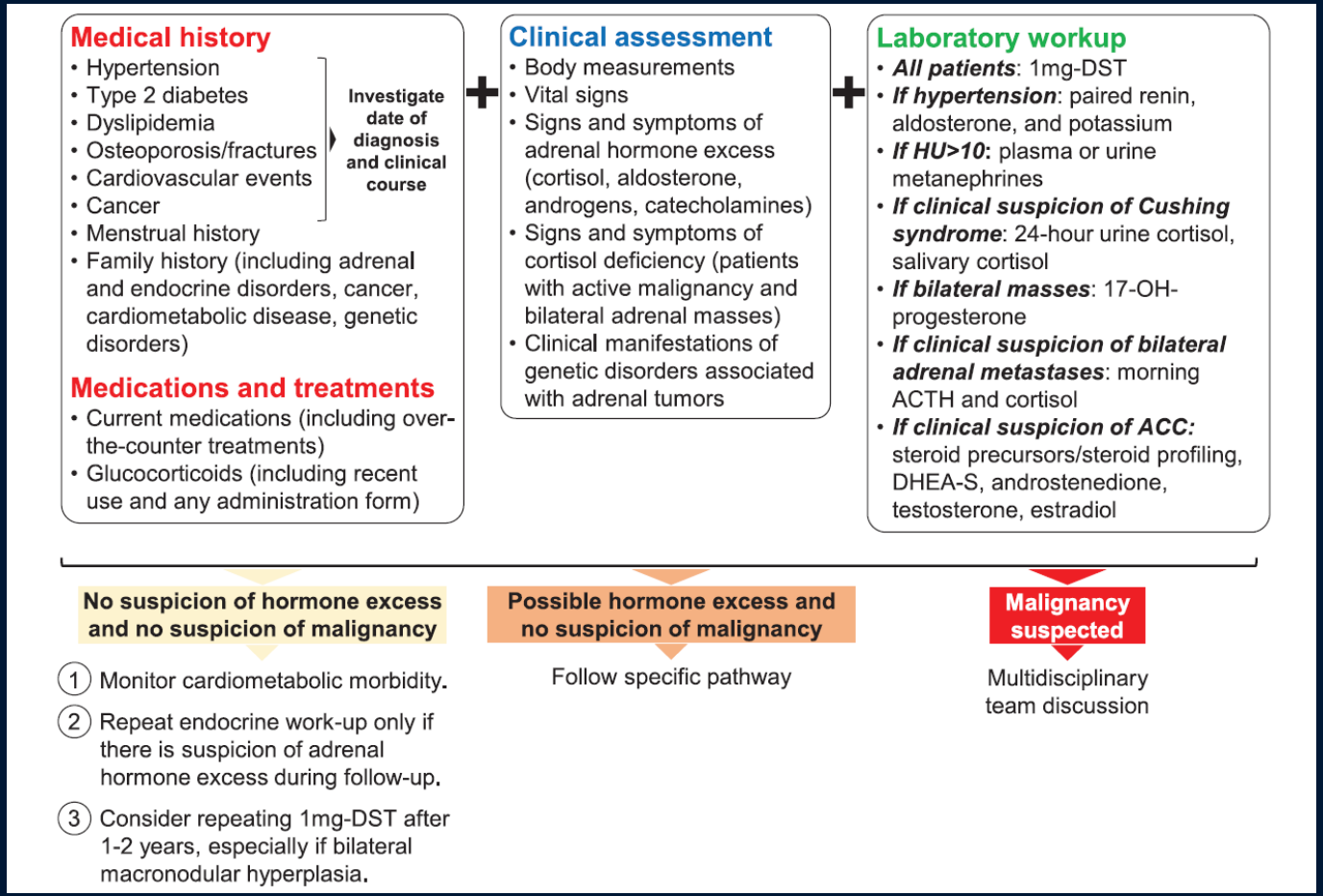
(30–40% of adenomas)

Biochemistry

- All incidentalomas should have endocrine testing

1. Test all for cortisol excess – usually 1mg DST
   - Rule out pheo before giving dexamethasone
2. Aldosterone & renin if hypertension or hypokalemia
3. Metanephrines if HU≥10

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.



Bancos et al. JCEM. 2021 Oct;106(11):3331-3353.

MACS

- Mild autonomous cortisol secretion (MACS)
  - Older term (subclinical Cushing syndrome) not preferred
  - No features of Cushing syndrome on exam
- Associated with T2DM, HTN, DL, Op, ↑mortality
- General approach
  - 1 mg dex suppression test, +/- repeat (+/- dex level)
  - ACTH, DHEAS (should be low)
  - +/- 24 hr urine cortisol or late-night salivary cortisol
  - +/- 8 mg dex suppression test

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Testing In Hospital

- Generally, workup should be deferred to outpt
  - Cortisol & catecholamines normally ↑ in hospital pts
  - Thus many false positives if perform testing in hospital

- Except if suspect pheo, malignancy, Cushings
  - Urine cortisol or metanephrines >3–5x ULN can be useful

Kline et al. Am J Med. 2021 Aug;134(8):1039-1046.

Biopsy

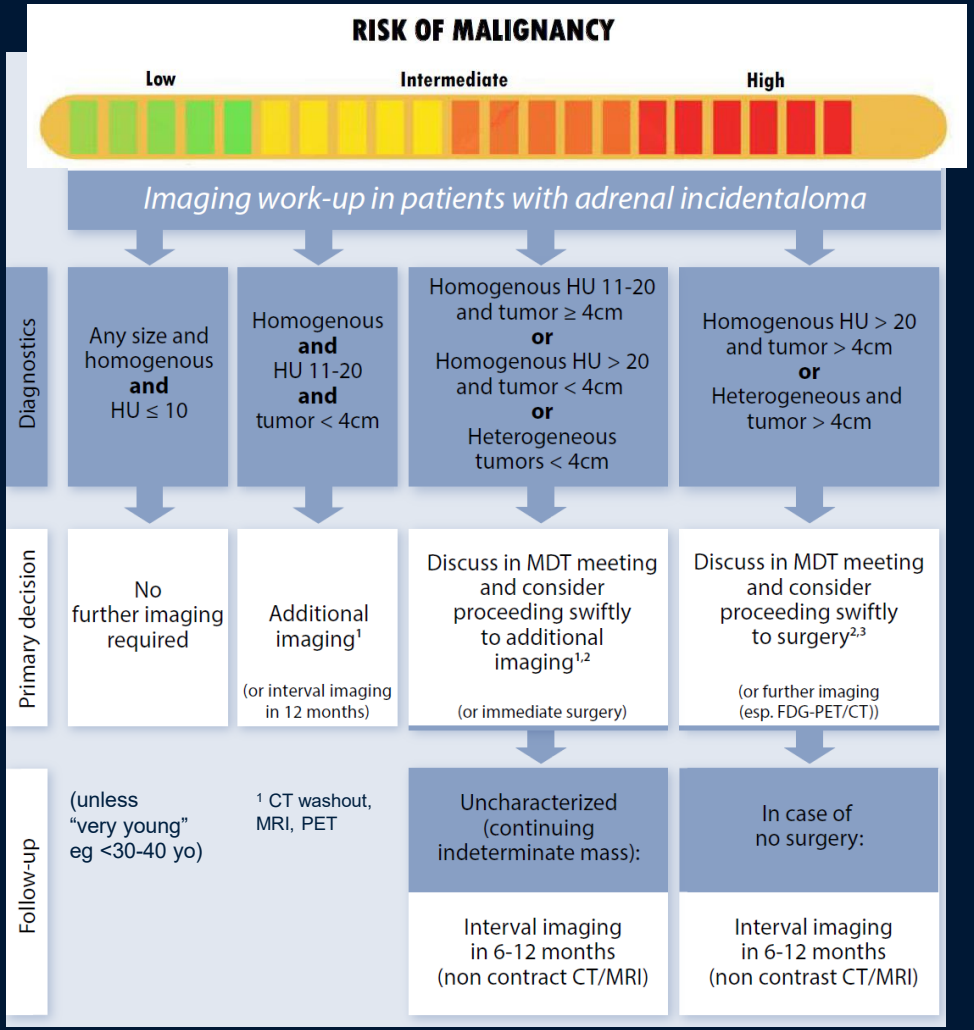
- Generally, adrenal biopsy is NOT useful
  - Cannot distinguish benign vs malignant adrenal neoplasm
  - If cancer → biopsy may seed
- May be considered in specific situations
  - Metastases, lymphoma, sarcoma, infiltrative, infectious
  - Only if management would be altered by biopsy results
  - Must rule out pheo first (biopsy can precipitate crisis)
- Accurate & safe if performed correctly & appropriately
  - Diagnostic in >90%, complications in only ~2%

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Follow-up

- Imaging
  - Benign (HU<10) → no further imaging needed (+/- 1yr if young)
  - Indeterminate (HU 10–20) → image in 6–12 mo (or surgery)
  - Concerning (HU>20) → surgery or image in 3–6 months
- Biochemistry
  - Generally do not repeat pheo or aldo screen
    - Unless HU>10 (pheo) or become hypertensive (aldo)
  - ? Repeat 1 mg dex vs monitor comorbidities only
    - 4–5% develop MACS over time

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42. Elhassan et al. Ann Intern Med. 2019 Jul;171(2):107-116.



Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42. Vassiliadi et al. JCEM. 2024 Jul;109(8):2136-2148.

Bilateral Adrenal Masses

- Evaluate imaging phenotype of each mass independently
- Specific Dx to consider:
  - Bilateral metastases
  - Bilateral pheochromocytoma (remember genetics)
  - Bilateral infiltrative, infectious, hemorrhage
  - Bilateral hyperplasia
    - ACTH-dependent Cushing syndrome
    - CAH (congenital adrenal hyperplasia)
    - BMAH (bilateral macronodular adrenal hyperplasia)
- Risk of adrenal insufficiency (~12%) esp with mets/infiltrative

Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

Known Extra-Adrenal Malignancy

- "Incidentaloma" often found during staging workup

- Apply similar principles for imaging phenotype
  - High HU → can be mets, but must rule out pheo still
  - Benign imaging (HU<10) → benign (despite known cancer)

- If Dx is not clear → PET, surgery, or biopsy
  - High FDG avidity in most mets (except renal cancer)

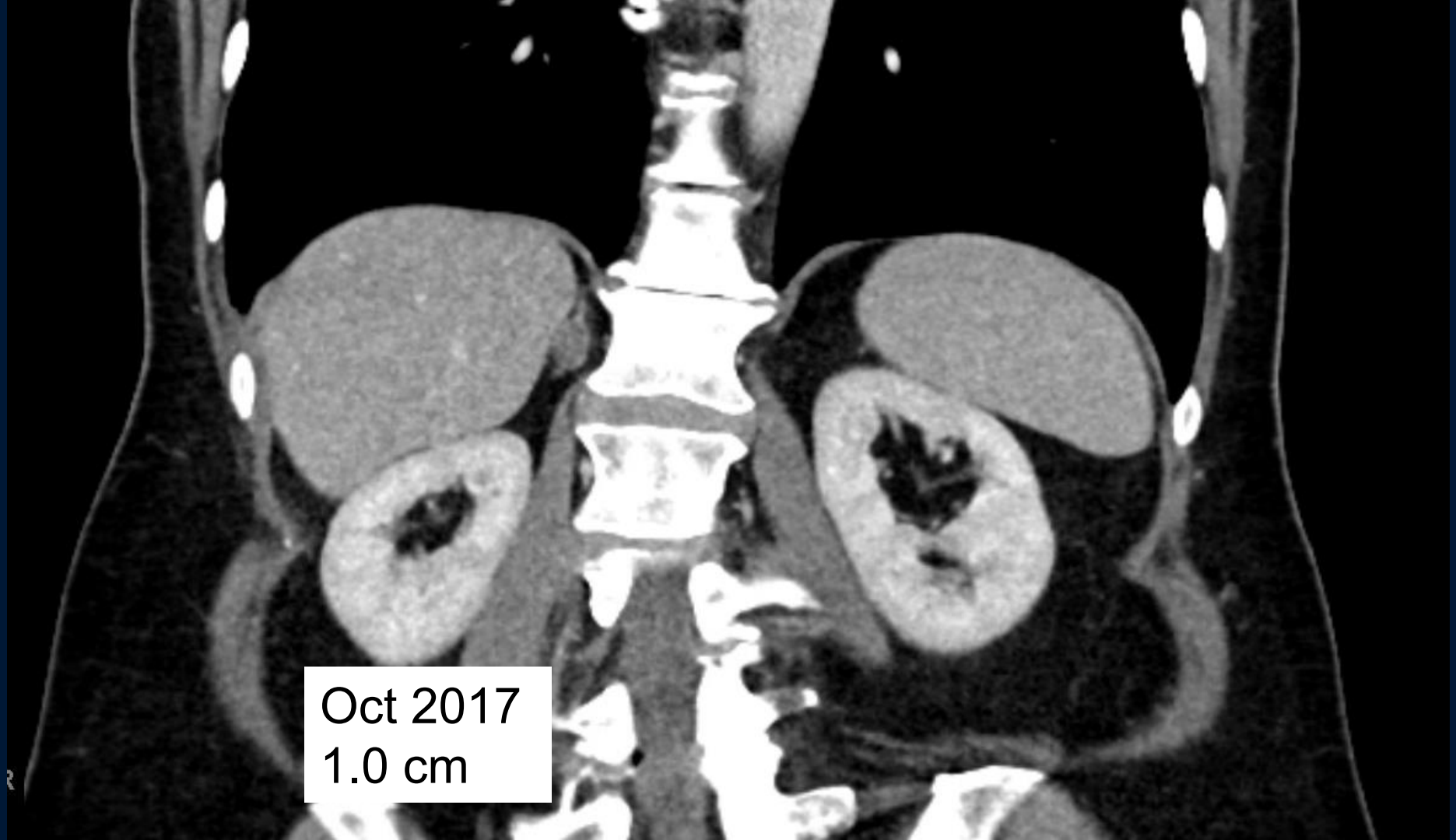
Fassnacht et al. Eur J Endocrinol. 2023 Jul;20(1):G1-G42.

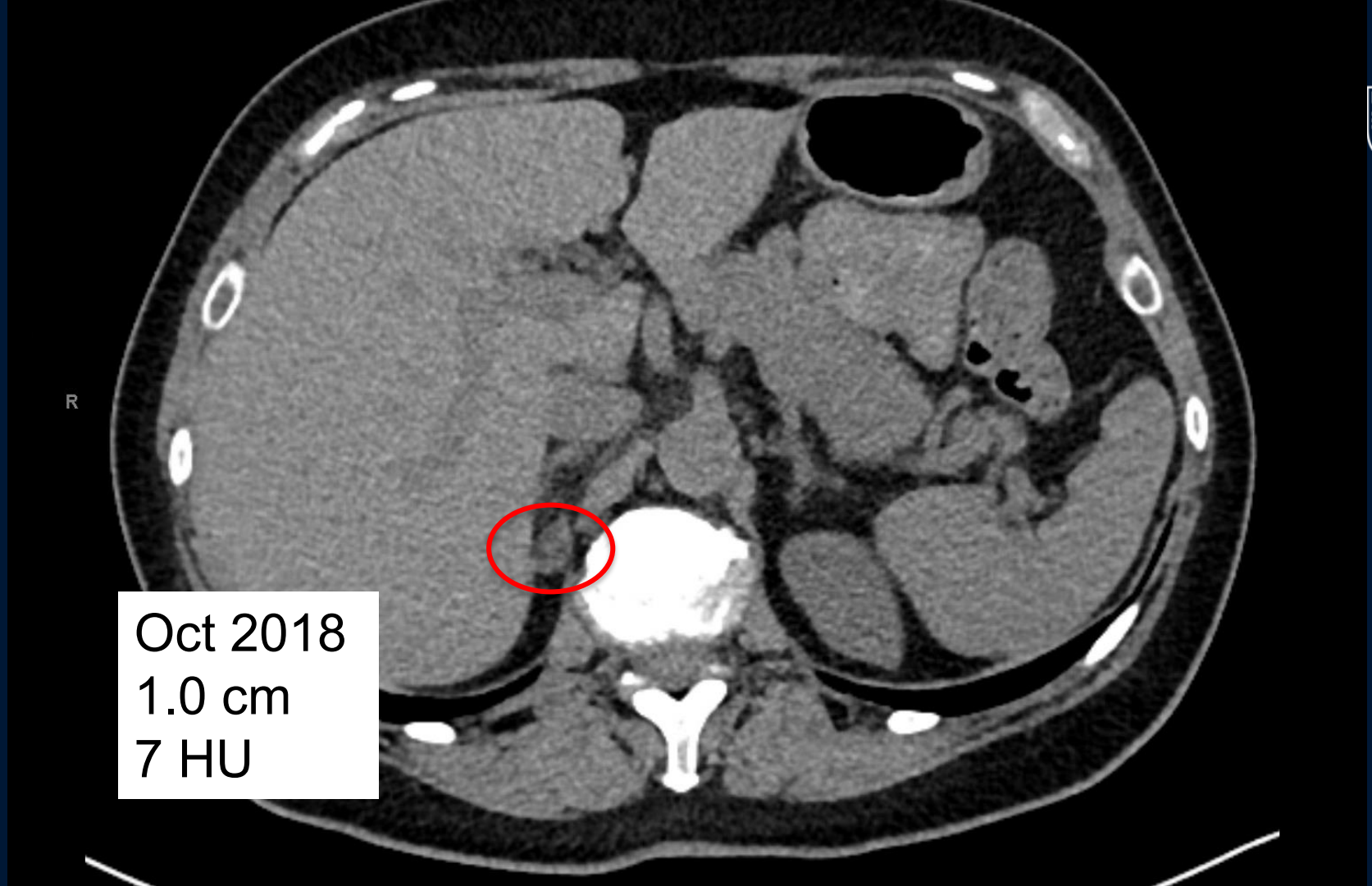
- Back to our cases

Case 1

- 68 F
- Adrenal mass found on imaging for diverticulitis

- PMHx: diverticulosis, hip OA, GERD
- Meds: none
- Na 140, K 5.4, A1c 5.6, BP 135/78, BMI 27.8


Oct 2017
1.0 cm


R
Oct 2018
1.0 cm
7 HU

Adrenal/Pituitary Function

Dexamethasone Challenge

Cortisol Post Dose Dexamethasone	41 Patient on dexamethasone	<130	nmol/L

Adrenal/Pituitary Function

Adrenocorticotropic Hormone (ACTH)

Adrenocorticotropic Hormone (ACTH)	5.2	1.6-13.9	pmol/L

Dehydroepiandrosterone Sulfate

Dehydroepiandrosterone Sulfate	1.4	<6.7	umol/L

Mineral and Water Balance

Aldosterone	740	90-1000	pmol/L
Renin	19.1	5-75	ng/L
Aldosterone/Renin	39 Aldosteronism is unlikely when the Aldosterone/Renin Ratio (ARR) is less than 50.	<50	

Urine Chemistry

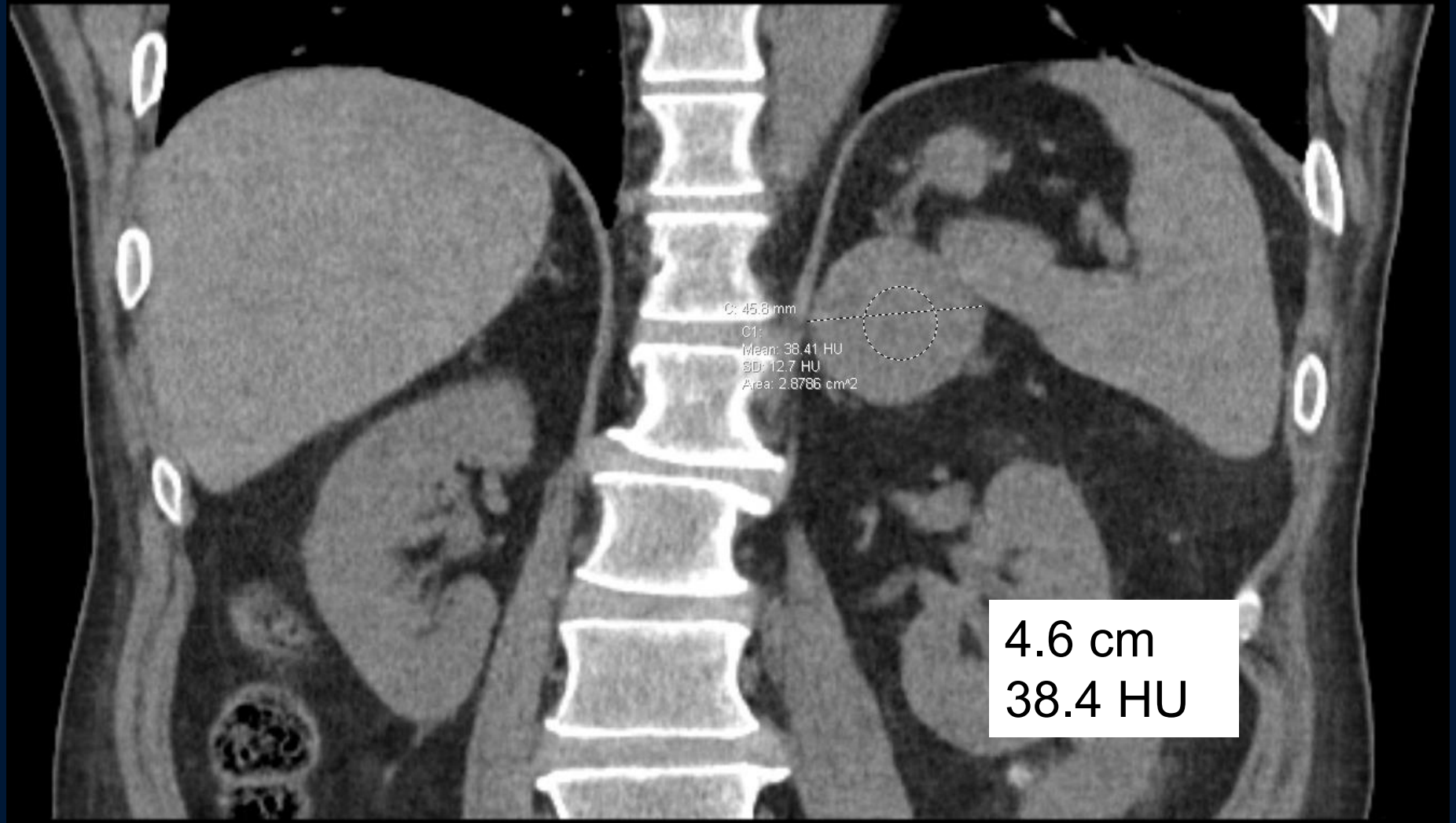
Creatinine; Urine; 24h			
	Urine volume: 2400		
Creatinine; Urine; 24h	10.5	5.0-16.0	mmol/d
Catecholamines; Urine; 24h			
Dopamine; Urine; 24h	783	400-3300	nmol/d
Epinephrine; Urine; 24h			nmol/d
	Epinephrine less than 19 nmol/L		
Norepinephrine; Urine; 24h	128	<650	nmol/d
Metanephrine Free & Normetanephrine Free; Urine			
Metanephrines Free; Urine; 24h			umol/d
	Metanephrine less than 0.041 umol/L		
Normetanephrine Free; Urine; 24h			umol/d
	Normetanephrine less than 0.064 umol/L		
Cortisol Free; Urine; 24h			
Cortisol Free; Urine; 24h	47	8-119	nmol/d

- Conclusion:
- Lipid-rich adenoma
- No further testing or imaging required
  - +/- testing for MACS

Case 2

- 63 M
- Presented to hospital with new-onset psychosis & mania (no psych history)

- Had pan-CT done to look for medical etiology
- Found an adrenal mass


C: 45.8 mm
C1:
Mean: 38.41 HU
SD: 12.7 HU
Area: 2.8786 cm^2
4.6 cm
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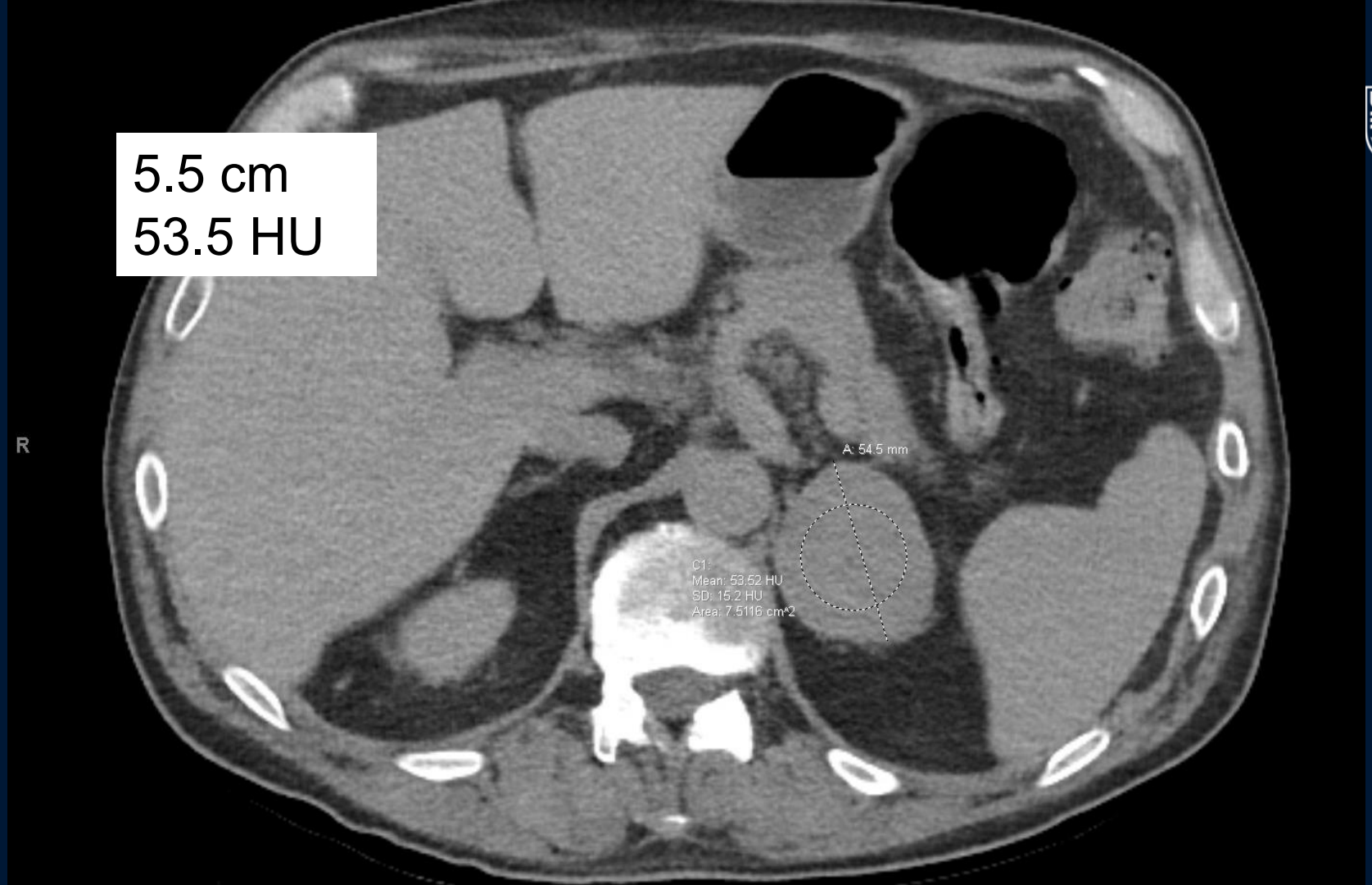
5.5 cm
53.5 HU
R
A: 54.5 mm
C1:
Mean: 53.52 HU
SD: 15.2 HU
Area: 7.5116 cm^2

CT Abdomen Report

No intrathoracic abnormality.

5 cm left adrenal mass suspicious for a neoplasm.

Correlation with serum hormone and catecholamine levels recommended.

The lesion is amenable to CT-guided biopsy.

Thoughts?

CT Adrenal Report

There is a homogeneous soft tissue mass arising from the left adrenal gland. It measures **5.1 x 4.6 x 4.3 cm.** The average density is **40 Hounsfield units** which increases to 72.5 Hounsfield units on the portal venous phase and reduces to 52.1 on the 15 minute delayed phase. This gives an overall washout of 63% which is suggestive of a benign lesion.

CONCLUSION:
The adrenal **washout of 63% is highly suggestive of an adrenal adenoma**.
In view of this a 6 month follow-up is suggested to monitor interval change.

Thoughts?

Mineral and Water Balance

Aldosterone					
Aldosterone	231			pmol/L	18/Jul/2024 16:43
	Reference intervals for aldosterone are: upright: 70 to 660 pmol/L and supine: 30 to 415 pmol/L.				
	The screen for primary aldosteronism is negative.				
	Dr. Andre Mattman, MD				
Aldosterone/Renin	436		<1500		18/Jul/2024 16:43
Renin	0.53			ng/L/s	18/Jul/2024 16:43
	Reference intervals for plasma renin activity are: upright: 0.10 to 1.10 ng/L/s and supine: <0.45 ng/L/s.				

Urine Chemistry

Collection Information; 24h				
Collection Duration; Urine	24			h
Specimen Volume; Urine; 24h	**3.000**	**H**	0.600-2.400	L
Creatinine; Urine; 24h	11.3		8.4-22.0	mmol/d
Metanephrine and Catecholamine Excretion Panel				
Metanephrine; Urine; 24h	Below analytical limits		<250	nmol/d
Normetanephrine; Urine; 24h	81		<281	nmol/d
3-Methoxytyramine; Urine; 24h	126		<524	nmol/d
Epinephrine; Urine; 24h	24		<85	nmol/d
Norepinephrine; Urine; 24h	228		<473	nmol/d
Dopamine; Urine; 24h	1275		<2660	nmol/d

Cortisol Free; Urine; 24h	**549**	**A**	12-166	nmol/d

Adrenocorticotropic Hormone (ACTH)	**<0.6**	**A**	1.6-13.9	pmol/L

- Thoughts?

- Has core biopsy:

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OPINION>>::
S24-1053 (procedure date: 12/MAR/2024)
LEFT ADRENAL TUMOUR, CORE BIOPSY:
     -     ONCOCYTIC ADRENOCORTICAL NEOPLASM (SEE COMMENT).
```

- What to do next?

- Final histopathology:

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FINAL DIAGNOSIS>>::
VS24-18235 - Procedure date: May 1, 2024
LEFT ADRENAL GLAND, ADRENALECTOMY:
     -     ADRENOCORTICAL CARCINOMA, ONCOCYTIC TYPE, LOW GRADE.
-     See Comment for further details and sinusoidal invasion.
```
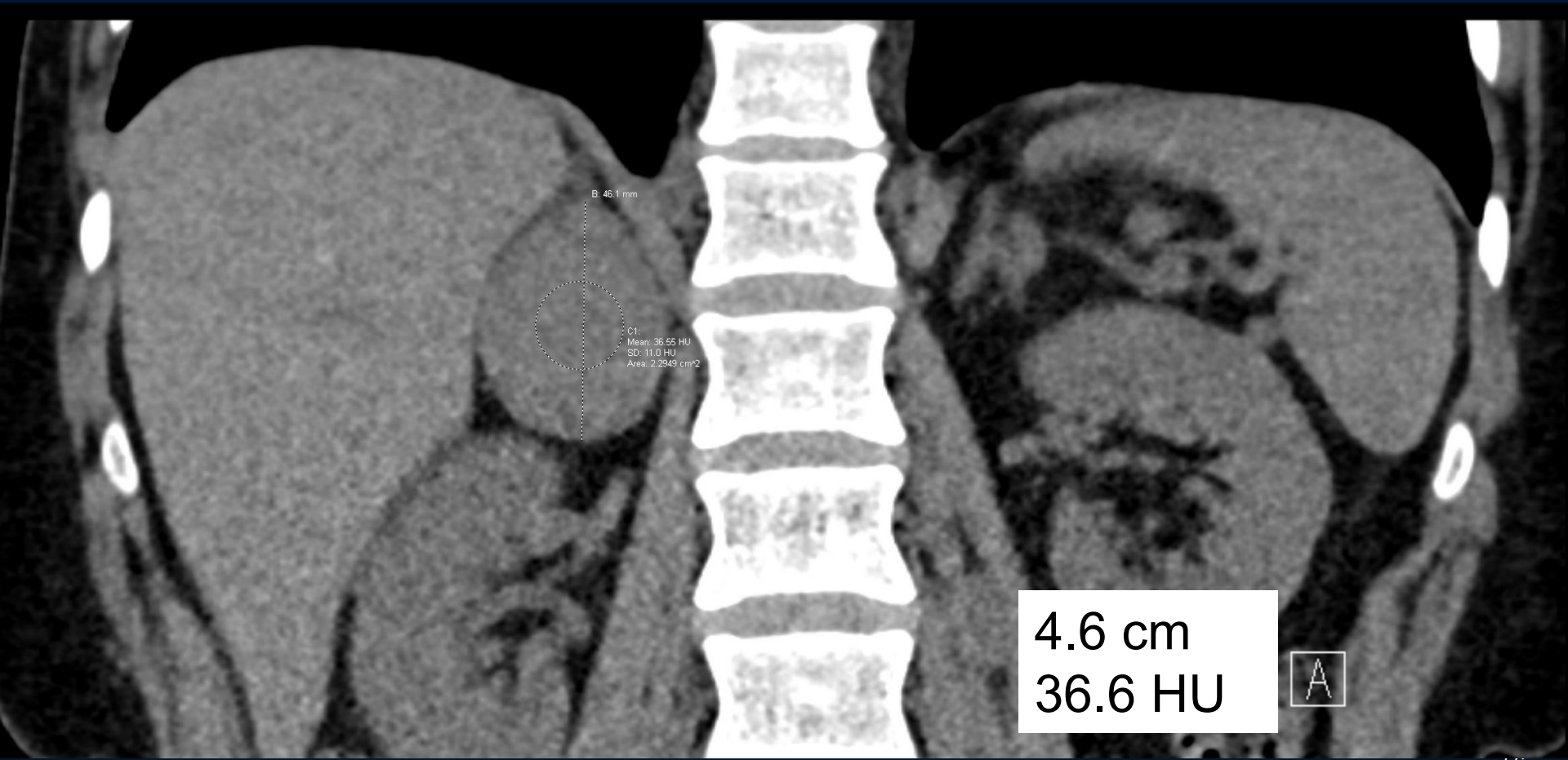

Case 3

- 42 F
- PMHx: NF1, ++neurofibromas, anxiety, migraines
- Meds: bisoprolol, amitriptyline 40 mg/d
- Referred by GP:
  - MRI C, T, and L spine for neurofibroma monitoring
  - Noted to have enlarging adrenal mass

Case 3 cont

- Endorsed years of “spells” → dizziness, nausea, palpitations, sweating, headache
  - Dx with POTS
- Smokes 1 ppd
- Was given req for 24hr urine metanephrines
  - Pt was told she had to stop smoking & d/c amitriptyline
  - Thus patient never completed testing


B: 46.1 mm
C1:
Mean: 36.55 HU
SD: 11.0 HU
Area: 2.2949 cm^2
4.6 cm
36.6 HU
A

Date	MRI
May 2014	R adrenal mass 2.6 x 1.6 x 2.5 cm
June 2018	R adrenal mass 3.8 x 2.5 x 3.9 cm (growth 0.7 cm/yr)
July 2020	R adrenal mass 5.0 x 2.9 x 4.5 cm (growth 0.6 cm/yr)

Urine Chemistry

Catecholamines; Urine; 24h

Dopamine; Urine; 24h	**9345**	2.8x	**A**	400-3300	nmol/d
Epinephrine; Urine; 24h	**663**	7.4x	**A**	<90	nmol/d
Norepinephrine; Urine; 24h	**882**	1.4x	**A**	<650	nmol/d

Metanephrine Free & Normetanephrine Free; Urine

Metanephrines Free; Urine; 24h	**1.63**	8.2x	**A**	<0.20	umol/d
Normetanephrine Free; Urine; 24h	**2.62**	6.6x	**A**	<0.40	umol/d

Final Diagnosis ::

Right adrenal gland, adrenalectomy:

- Pheochromocytoma
- Tumor size 5.5 cm
- Clear surgical margins
- No evidence of extra-adrenal and lymphovascular invasion
- Mitotic activity: 0 per 10 hpf x40 magnification (0.62 mm field diameter)
- Biomarkers: Tumor cells are positive with synaptophysin and chromogranin, sustentacular cells are positive with S100 antibodies, as expected

Take Home Points

- Adrenal incidentalomas are common, ~95% are benign
- Imaging phenotype is very important, esp HU
- Lipid-rich (HU<10) masses are not concerning
- **Lipid-poor (HU>10 but esp HU>20)** or >4cm or heterogeneous → *concerning & need to be followed*
- Perform endocrine testing in all adrenal masses
- Limited role for adrenal biopsy (r/o pheo first)
- Ask your endocrinology friends if in doubt!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