Breaking Boundaries in Adrenal Disorders

ANAH - AFES Joint Symposium 2025

14 – 16 Nov 2025 | Ariyana Convention Center, Da Nang city, Vietnam

Adrenal Incidentalomas: Illustrative Cases of Current Diagnostic Strategies

William F. Young, Jr., MD, MSc
Tyson Family Endocrinology Clinical Professor
Mayo Clinic, Rochester, MN USA

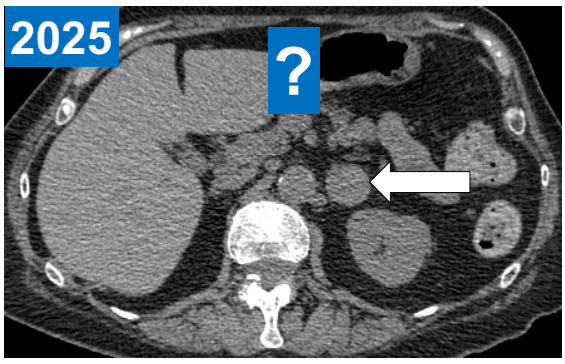
Friday - November 14, 2025 – 1:45 – 2:20 PM – Hall D

1

Adrenal Incidentaloma Definition

- An adrenal mass discovered serendipitously by radiologic examination
- In the absence of symptoms or clinical findings suggestive of adrenal disease
- and ≥ 1-cm in diameter (ie, leaving no question that it really is a mass)

2



3

Adrenal Incidentaloma--Prevalence

- With ↑ing resolution of CT, specific attention from **radiologists**, & more careful prospective studies, the prevalence of adrenal incidentalomas ↑ed from 0.6%* in 1982 to **7.3%** in patients under medical care in 2020**

*Glazer HS, et al., Nonfunctioning adrenal masses: incidental discovery on computed tomography. *AJR* 1982;248:701-704

**Reimondo G, et al. Adrenal Incidentalomas are Tied to Increased Risk of Diabetes: Findings from a Prospective Study. *J Clin Endocrinol Metab*. 2020;105(4):dgz284.

4

Large Cohort in Olmsted County, Minnesota

1050 (**1.5%** of CTs) Olmsted County residents had adrenal incidentaloma:

- **3.3%** were **malignant** (neuroblastoma & adrenocortical cancer [ACC] in children and metastatic disease, lymphoma, & ACC in adults)
- 88% were adrenal adenomas:
  - ✓1.1% had overt hormone excess – Cushing syndrome (CS) & primary aldo
  - ✓8.2% had confirmed subclinical CS
  - ✓12.4% confirmed nonfunctioning adenoma
  - ✓66.4% adrenal adenoma with unknown hormone status
- 0.8% were pheochromocytoma
- 7.8% were other benign tumors (myelolipoma > hematoma > cyst > calcification > ganglioneuroma = schwannoma > hemangioma = lymphangioma)

*Ebbehoj A, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020;8(11):894-902.

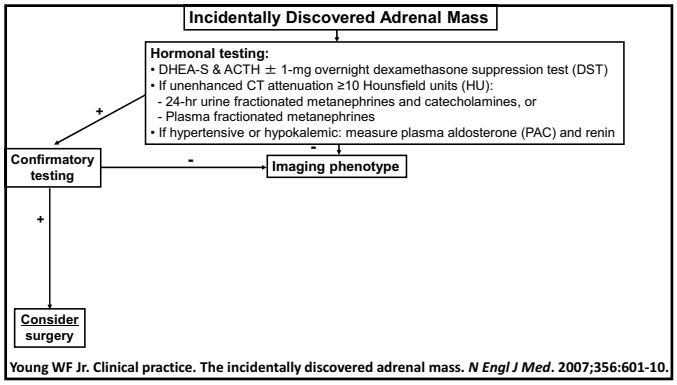
5

Diagnostic Strategy

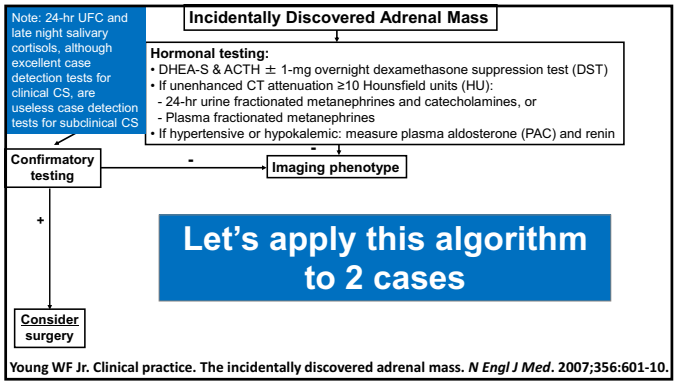
Characterize the mass for:

- Functional Status:
  - ✓ History and physical exam
  - ✓ Hormonal assessment
- Malignant Potential:
  - ✓ Imaging Phenotype
  - ✓ Size, growth, and history of extra-adrenal malignancy

6



7



8

Case #1: 71-Year-Old Man

- 7 months ago: contrast-enhanced abdominal CT done for non-adrenal reasons
- Incidentally discovered 2.4-cm right adrenal mass
- Normotensive, weight stable, no adrenal-related symptoms
- Meds: aspirin, rosuvastatin, coenzyme Q10
- Exam: BP 110/69 mmHg, HR 85 bpm, BMI 30.9 kg/m^2; appears well
- Lab: serum K^+ = 4.4 mmol/L (normal, 3.6 – 5.2)

9

Labs

Subclinical CS (SCS) Scree

- DHEA-S = 86 mcg/dL (2.33 µmol/L) (normal, 12-227 mcg/dL; 0.33-6.15 µmol/L)

If DHEA-S is <40 mcg/dL (<1.1 µmol/L) it is suspicious for SCS. If DHEA-S is >100 mcg/dL (>2.7 µmol/L), SCS is unlikely*

*Carafone LE, et al. Diagnostic Accuracy of Dehydroepiandrosterone Sulfate and Corticotropin in Autonomous Cortisol Secretion. *Biomedicines*. 2021;9(7):741.

10

Labs

Subclinical CS (SCS) Screen:

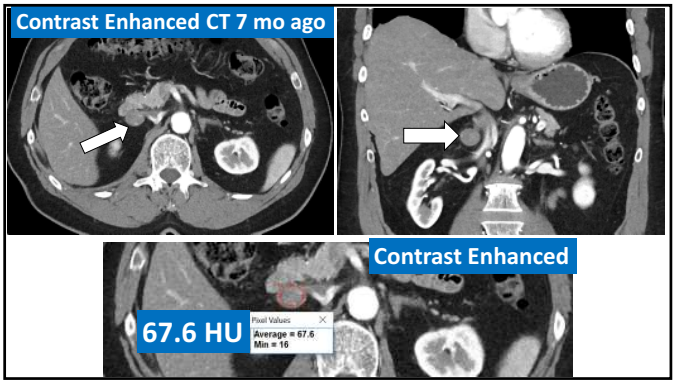
- DHEA-S = 86 mcg/dL (2.33 µmol/L) (normal, 12-227 mcg/dL; 0.33-6.15 µmol/L)
- 2-mg Overnight DST = 1.3 mcg/dL (35.9 nmol/L) (normal, <1.8 mcg/dL; <49.7 nmol/L)

Pheochromocytoma Screen:

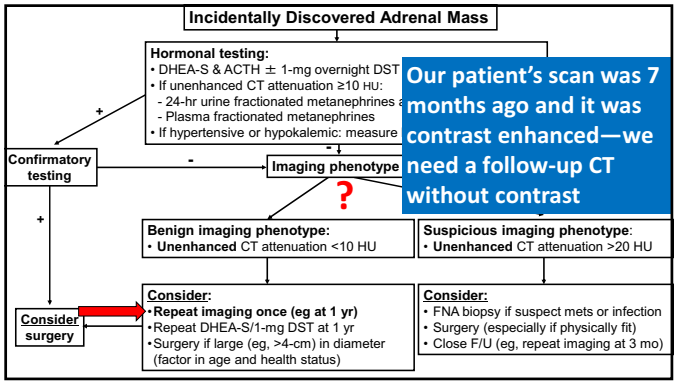
- Plasma fractionated metanephrines – normal

Primary aldosteronism screen – not needed (normal BP and normal K^+)

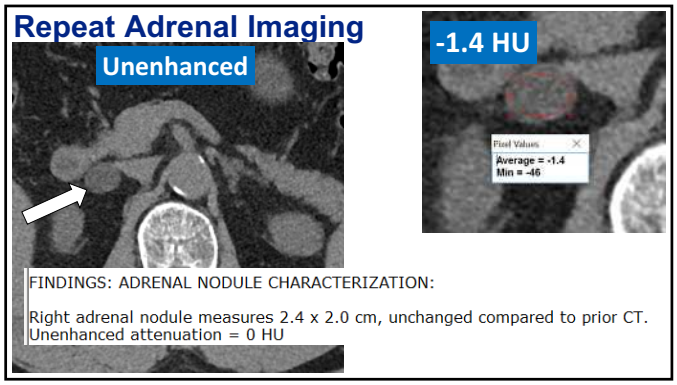
11



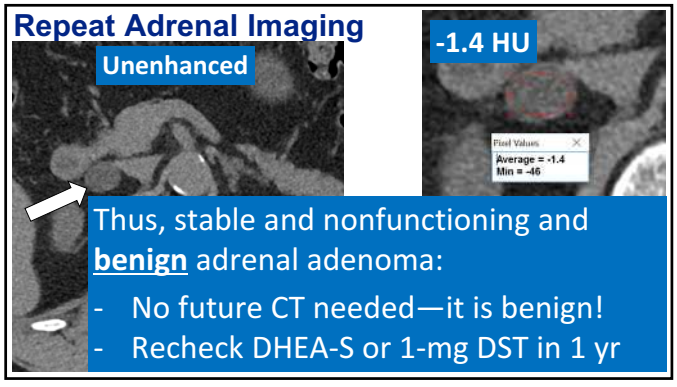
12


Incidentally Discovered Adrenal Mass
Hormonal testing:
• DHEA-S & ACTH ± 1-mg overnight DST
• If unenhanced CT attenuation ≥10 HU:
- 24-hr urine fractionated metanephrines a
- Plasma fractionated metanephrines
• If hypertensive or hypokalemic: measure
Our patient's scan was 7 months ago and it was contrast enhanced—we need a follow-up CT without contrast
Confirmatory testing
Imaging phenotype
?
Benign imaging phenotype:
• Unenhanced CT attenuation <10 HU
Suspicious imaging phenotype:
• Unenhanced CT attenuation >20 HU
Consider surgery
Consider:
•Repeat imaging once (eg at 1 yr)
•Repeat DHEA-S/1-mg DST at 1 yr
•Surgery if large (eg, >4-cm) in diameter (factor in age and health status)
Consider:
• FNA biopsy if suspect mets or infection
• Surgery (especially if physically fit)
• Close F/U (eg, repeat imaging at 3 mo)

13


Repeat Adrenal Imaging
Unenhanced
-1.4 HU
Pixel Values
Average = -1.4
Min = -46
FINDINGS: ADRENAL NODULE CHARACTERIZATION:
Right adrenal nodule measures 2.4 x 2.0 cm, unchanged compared to prior CT.
Unenhanced attenuation = 0 HU

14

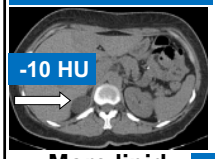

Repeat Adrenal Imaging
Unenhanced
-1.4 HU
Pixel Values
Average = -1.4
Min = -46
Thus, stable and nonfunctioning and benign adrenal adenoma:
- No future CT needed—it is benign!
- Recheck DHEA-S or 1-mg DST in 1 yr

15

"Imaging Phenotype"

CT attenuation measured in Hounsfield Units (HU)

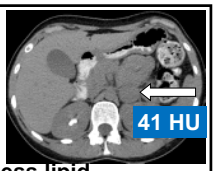
Unenhanced CT attenuation <10 HU



More lipid
Benign

+60 HU

-20 HU



Less lipid
ACC
Met
Pheo
Lipid-poor adenoma

Unenhanced CT attenuation >20 HU

NOTE: Washout CT has limited utility in evaluating incidental adrenal nodules in patients without known malignancy.
Corwin MT, et al. *AJR Am J Roentgenol*. 2022;219(5):804-812.

16

CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma

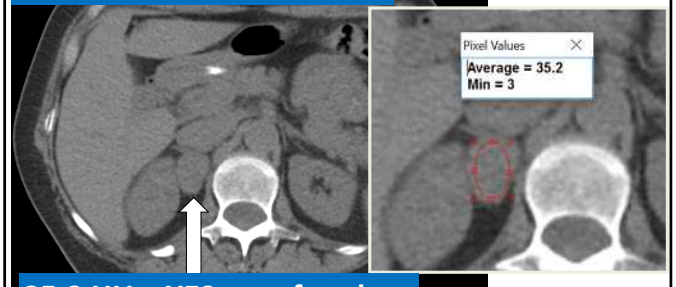
Letizia Canu,[1,2] Janna A. W. Van Hemert,[1] Michiel N. Kerstens,[3] Robert P. Hartman,[4] Aakanksha Khanna,[5] Ivana Kraljevic,[6] Darko Kastelan,[6] Corin Badiu,[7] Urszula Ambroziak,[8] Antoine Tabarin,[9] Magalie Haissaguerre,[9] Edward Buitenwerf,[3] Anneke Visser,[10] Massimo Mannelli,[2] Wiebke Arlt,[11] Vasileios Chortis,[11] Isabelle Bourdeau,[12] Nadia Gagnon,[12] Marie Buchy,[13] Francoise Borson-Chazot,[13] Timo Deutschbein,[14] Martin Fassnacht,[14,15] Alicja Hubalewska-Dydejczyk,[16] Marcin Motyka,[16] Ewelina Rzepka,[16] Ruth T. Casey,[17] Benjamin G. Challis,[17] Marcus Quinkler,[18] Laurent Vroonen,[19] Ariadni Spyroglou,[20,21] Felix Beuschlein,[20,21] Cristina Lamas,[22] William F. Young,[9] Irina Bancos,[9] and Henri J. L. M. Timmers[1]

- Multicenter retrospective study of 533 patients with 548 histologically confirmed pheos
- Among the 376 pheos for which **unenhanced** CT attenuation data were available, 374 had an attenuation of >10 HU (99.5%)
- In the 2 exceptions (0.5%), the unenhanced CT attenuation was exactly 10 HU

Canu L, et al. CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma. *J Clin Endocrinol Metab*. 2019;104(2):312-18

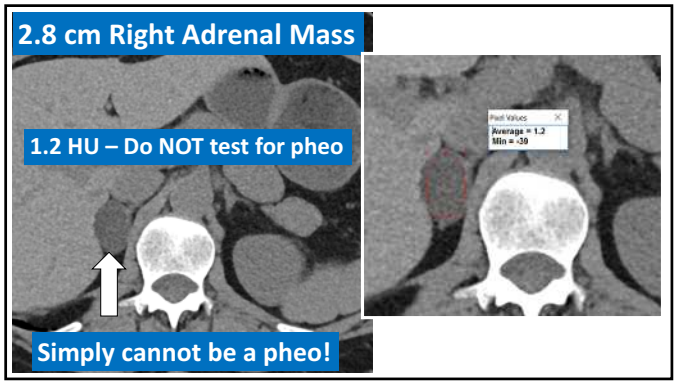
17

2.8 cm Right Adrenal Mass

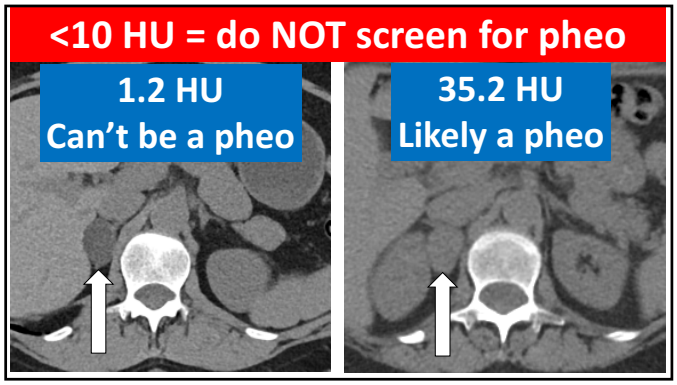


35.2 HU – YES, test for pheo

18



19

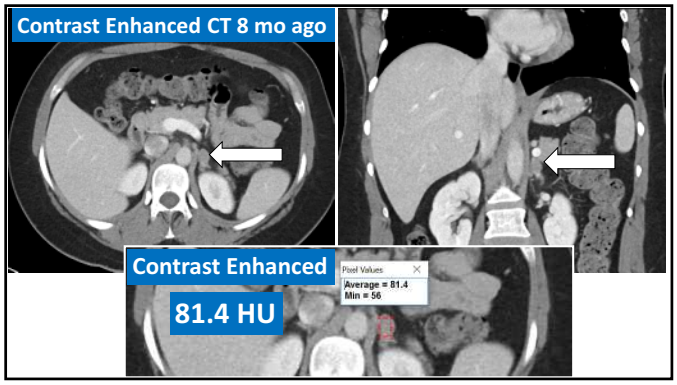


20

Case #2: 39-Year-Old Woman

- 8 months ago: contrast-enhanced abdominal CT done for abdominal pain
- Incidentally discovered 1.3-cm left adrenal mass
- Normotensive, weight stable, no adrenal-related symptoms; diagnosed in past with PCOS and ADD
- Meds: metformin 1000 mg/d; oral contraceptive pill; methylphenidate LA 20 mg daily
- Exam: BP 106/79 mmHg, HR 64 bpm, BMI 31.8 kg/m^2; appears well
- Lab: serum K^+ = 4.5 mmol/L (normal, 3.6 – 5.2)

21



22

Screen for Subclinical Cushing Syndrome (SCS)

DHEA-S = 146 mcg/dL (3.96 µmol/L)
(normal, 31-228 mcg/dL; 0.84-6.18 µmol/L)

With a DHEA-S >100 mcg/dL (2.71 µmol/L) overnight DST is not needed to exclude SCS*

*Carafone LE, et al. Diagnostic Accuracy of Dehydroepiandrosterone Sulfate and Corticotropin in Autonomous Cortisol Secretion. *Biomedicines*. 2021;9(7):741.

23

Screen for Pheochromocytoma

Plasma:

- Metanephrine = 0.44 nmol/L (normal <0.5)
- Normetanephrine = 0.82 nmol/L (normal <0.9)

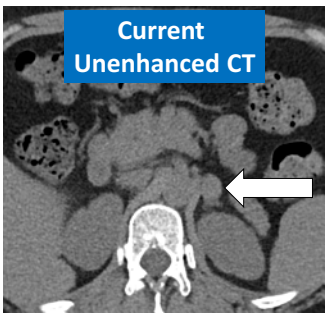
24-hr Urine:

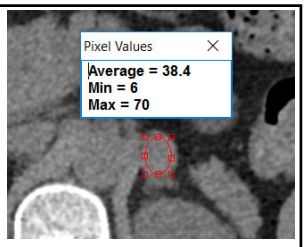
All Normal!

- Metanephrine = 325 mcg (1648 nmol)
  normal = <400 mcg (<2028 nmol)
- Normetanephrine = 557 mcg (3041 nmol)
  normal = <900 mcg (<4814 nmol)
- NE = 29 mcg (172 nmol) normal = <80 mcg (<473 nmol)
- EPI = 8.6 mcg (47 nmol) normal = <21 mcg (<115 nmol)
- DA = 222 mcg (1448 nmol) normal = <400 mcg (<2610 nmol)

24

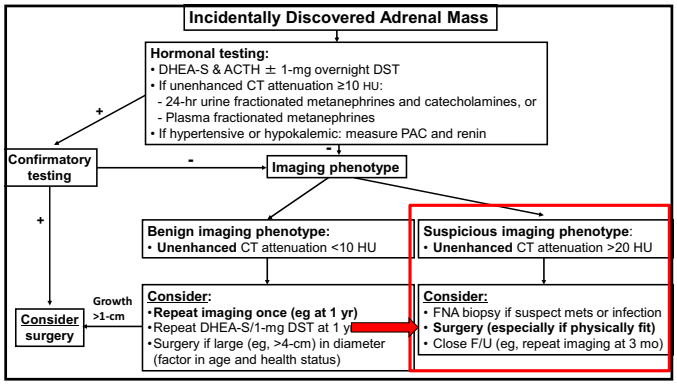
Repeat Adrenal Imaging





1.9 x 1.3 cm lipid poor left adrenal mass—increased in size from 1.3 x 1.1 cm at 8 months ago

25



26

Consider Surgical Resection

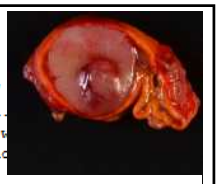
IMPRESSION/REPORT/PLAN

#1 Lipid poor left adrenal mass--suspect pheochromocytoma

Dr. [redacted] obtained a DHEA sulfate, and it was normal at 146 mcg/dL. I added plasma metanephrines and a 24-hour urine for metanephrines and catecholamines. I will review those results when they become available. I shared with the patient and her mother today that I suspect she may have a pheochromocytoma based on the imaging phenotype and the fact that her plasma metanephrine was close to being abnormal when checked back in May. We will go ahead and start her on doxazosin 1 mg at bedtime. We will get preoperative testing next week and introduce her to an endocrine surgeon the week of January 9. If this proves to be a lipid poor adenoma, I think it still should be resected. She is only 39 years old, and this nodule has grown over a fairly short period of time. Patient understands and recognizes the rationale behind this recommendation. I have shared with her an article on adrenal incidentalomas and given her an education brochure on pheochromocytoma.

27

Consider Surgical Resection



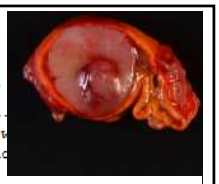
GROSS DESCRIPTION:
A. Received fresh labeled "left adrenal gland"
1.4 x 1.2 cm adrenal gland with a 2.0 x 1.4 x 1.
gray to red, firm mass located in the medulla, w
beyond the adrenal gland. Representative sectio

DIAGNOSIS:
A. Adrenal gland, left, adrenalectomy: Pheochromocytoma.

Immunoperoxidase studies were performed on paraffin sections using antibodies directed against the following antigens: Chromogranin, Synaptophysin, Keratin OSCAR, and S-100.
The neoplastic cells are positive for Chromogranin and Synaptophysin. S-100 highlights sustentacular cells. Keratin OSCAR is negative.

28

Consider Surgical Resection



Screen for Pheochromocytoma

Plasma:
- Metanephrine = 0.44 nmol/L (normal <0.5)
- Normetanephrine = 0.82 nmol/L (normal <0.9)

24-hr Urine:
- Metanephrine = 325 mcg (1648 nmol)
  normal = <400 mcg (<2028 nmol)
- Normetanephrine = 557 mcg (3041 nmol)
  normal = <900 mcg (<4814 nmol)
- NE = 29 mcg (172 nmol) normal = <80 mcg (<473 nmol)
- EPI = 8.6 mcg (47 nmol) normal = <21 mcg (<115 nmol)

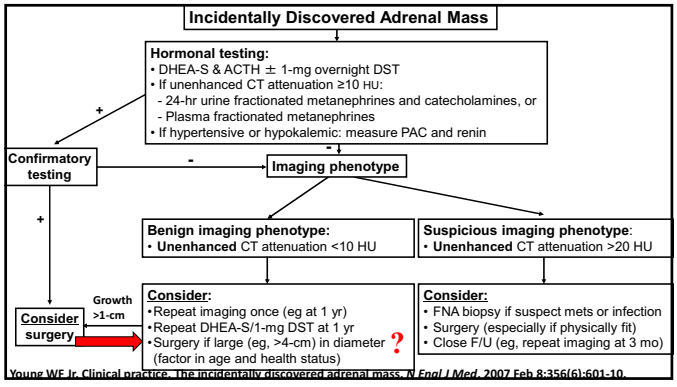
All Normal!

gland"
..4 x 1.
ulla, w
sectio

Pheochromocytoma

Clinical Pearl: when pheochromocytomas are small (eg, <1.5-2.0 cm), the factory is not big enough to be biochemically detectable—know the pheo imaging phenotype!

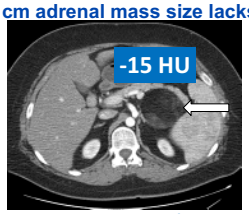
29

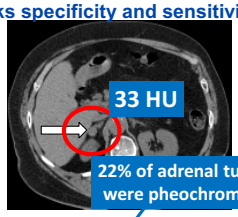


Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med*. 2007 Feb 8;356(6):601-10.

30

But >4 cm adrenal mass size lacks specificity and sensitivity!





22% of adrenal tumors ≥4 cm were pheochromocytomas

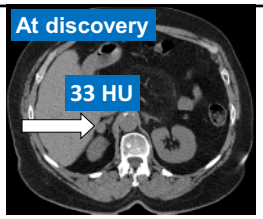
So, if >4-cm half are either malignant or pheo!

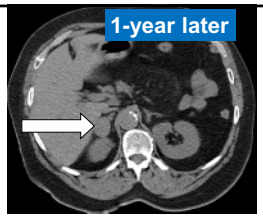
Mayo series: years 2000-2014:*

- 4085 patients with adrenal tumors were evaluated (pheos w
- 17% had adrenal tumors ≥4 cm—**31% were malignant:**
  - ✓58% non-adrenal (mets): unenhanced CT attenuation = 14-56 HU
  - ✓42% ACC: unenhanced CT attenuation = 18-75.5 HU

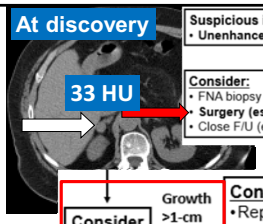
*Iñiguez-Ariza N, et al. Clinical, Biochemical, and Radiological Characteristics of a Single-Center Retrospective Cohort of 705 Large Adrenal Tumors. *Mayo Clin Proc Innov Qual Outcomes*. 2(1):30-39.

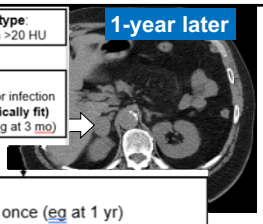
31





32





Suspicious imaging phenotype:
- **Unenhanced** CT attenuation >20 HU

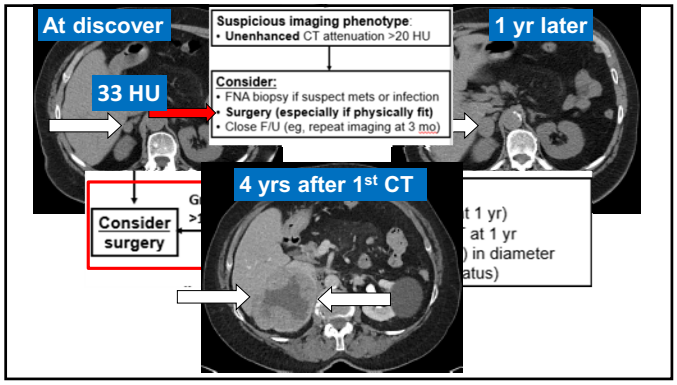
Consider:
- FNA biopsy if suspect mets or infection
- **Surgery (especially if physically fit)**
- Close F/U (eg, repeat imaging at 3 mo)

Growth >1-cm

Consider surgery

Consider:
- Repeat imaging once (eg at 1 yr)
- Repeat DHEA-S/1-mg DST at 1 yr
- Surgery if large (eg, >4-cm) in diameter (factor in age and health status)

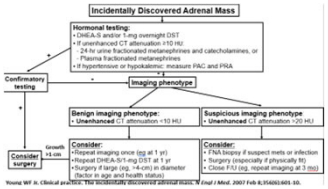
33



34

The Problem with Algorithms

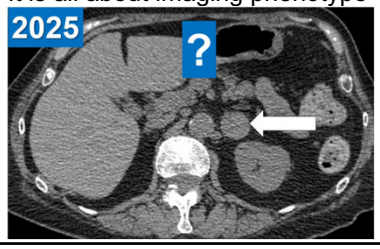
- No algorithm is perfect
- Common sense should prevail
- Not a substitute for good clinical judgment!
- Consider patient age and clinical circumstances



35

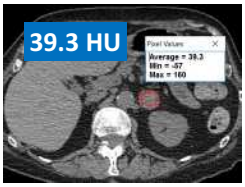
Final Thoughts:

✓95% of incidentally discovered adrenal tumors are benign
✓85% are nonfunctioning cortical adenomas
✓It is all about imaging phenotype



36

1.What is the unenhanced CT attenuation?



Clinical context:
72-yr-old healthy woman with longstanding hypertension
Rx with metoprolol 25 mg/d

2.What are the results for biochemical testing for pheo?

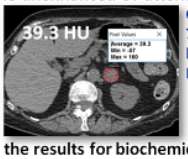
24-hr urine: Metanephrine = 335 mcg (N <400)
Normetanephrine = 556 mcg (N <900 mcg)

3.What are: DHEA-S, 1-mg DST, and PAC & PRA?

DHEA-S = 65 mcg/dL (N, 5.3-124 mcg/dL); 1 mg DST <1 mcg/dL (<28 nmol/L) (N <1.8 mcg/dL; <50 nmol/L) PAC = 6.6 ng/dL (183 pmol/L) & PRA 1.4 ng/mL/hr

37

1.What is the unenhanced CT attenuation?



Clinical context:
72-yr-old healthy woman with longstanding hypertension
Rx with metoprolol 25 mg/d

2.What are the results for biochemical testing for pheo?

24-hr urine: Metanephrine = 335 mcg (N <400)
Normetanephrine = 556 mcg (N <900 mcg)

3.What are: DHEA-S, 1-mg DST, and PAC & PRA?

DHEA-S = 65 mcg/dL (N, 5.3-124 mcg/dL); 1 mg DST <1 mcg/dL (<28 nmol/L (N <1.8 mcg/dL; <50 nmol/L) PAC = 6.6 ng/dL (183 pmol/L) & PRA 1.4 ng/mL/hr

1. Surgery vs. 2. Observation

Stable in size on follow-up CTs at ½ yr & 1.5 yrs after discovery
→dismissed from care; 3 yrs after discovery she comes to Mayo Clinic

38

My clinic note at 3 yrs after discovery

Chief Complaint: Mrs. [redacted]s a 72-yr-old woman from [redacted], seen in consultation today at the request of Dr. [redacted] for further evaluation and treatment of a left adrenal pheochromocytoma.

History of Present Illness:
#1 Pheochromocytoma Benign Left--2.6 cm
On August 16th of this year this patient was undergoing laparoscopic cholecystectomy and with anesthesia induction her blood pressure went to 250/130 mm Hg. The surgery was completed but that episode triggered an evaluation for pheochromocytoma. Plasma fractionated metanephrines have been measured on 3 occasions and normetanephrine has been 799, 905, and 1234 with an upper all normal of 145. Metanephrine levels have been 298, 200, and 157 with an upper limit of normal of 62. Subsequent 24 urine normetanephrine was 1829 mcg and metanephrine 606 mcg. In 2016 the 24 urine showed metanephrines 335 mcg and normetanephrine 556 mcg. It

39

Op Note by [redacted]

Author: [redacted] Service: GNS General Surgery
Filed: 1[redacted]PM Date of Service: [redacted]
Editor: [redacted]

FULL OP NOTE

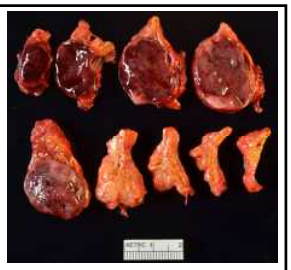
Procedure(s) (LRB):
LAPAROSCOPIC ADRENALECTOMY, ANTERIOR. (Left)

Surgeon(s) and Role:
- [redacted]

Anesthesia Type
General

Pre-operative Diagnosis
Pheochromocytoma Benign Personal History

FINAL DIAGNOSIS
A. Adrenal gland, left, adrenalectomy: Pheochromocytoma, forming a 2.8 cm mass. See Comment.
COMMENT
Immunohistochemical stains performed at Mayo Clinic (block A1) show synaptophysin and chromogranin staining in the tumor cells with sustentacular cells being positive for S100, supporting the above diagnosis.



40

Adrenal Incidentaloma—Final Thoughts:

- ✓ 95% of incidentally discovered tumors are benign
- ✓ 85% are nonfunctioning cortical adenomas
- ✓ **It is all about imaging phenotype**
- ✓ DHEA-S and/or 1-mg DST for subclinical CS (“MACS”)
- ✓ If CT ≥10 HU, exclude pheochromocytoma (≈1-2% of all adrenal incidentalomas & 60% of all pheos are discovered as adrenal incidentalomas!)
- ✓ When pheos are small the factory is not big enough to be biochemically detectable—rely on imaging phenotype!
- ✓ Exclude PA in hypertensive or hypokalemic patients
- ✓ All patients should have at least one F/U image
- ✓ Consider surgery in patients with lipid-poor “adenomas”

41

Breaking Boundaries in Adrenal Disorders
ANAH - AFES Joint Symposium 2025
14 - 16 Nov 2025 | Ariyana Convention Center, Da Nang city, Vietnam

Adrenal Incidentalomas: Illustrative Cases of Current Diagnostic Strategies

William F. Young, Jr., MD, MSc
Tyson Family Endocrinology Clinical Professor
Mayo Clinic, Rochester, MN USA

Friday - November 14, 2025 – 1:45 – 2:20 PM – Hall D

42

References

Canu L, et al. CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma. *J Clin Endocrinol Metab*. 2019;104(2):312-18

Carafone LE, et al. Diagnostic Accuracy of Dehydroepiandrosterone Sulfate and Corticotropin in Autonomous Cortisol Secretion. *Biomedicines*. 2021;9(7):741.

Corwin MT, et al. Incidental Adrenal Nodules in Patients Without Known Malignancy: Prevalence of Malignancy and Utility of Washout CT for Characterization-A Multiinstitutional Study. *AJR* 2022;219(5):804-812.

Ebbehoj A, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020;8(11):894-902.

Gandhi MM, Young WF, Williams PN, Watto MF. "#377 Adrenal Incidentalomas with Dr. William Young". *The Curbsiders Internal Medicine Podcast*. https://thecurbsiders.com/episode-list January 16, 2023.

Glazer HS, et al., Nonfunctioning adrenal masses: incidental discovery on computed tomography. *AJR* 1982;248:701-704.

Iñiguez-Ariza N, et al. Clinical, Biochemical, and Radiological Characteristics of a Single-Center Retrospective Cohort of 705 Large Adrenal Tumors. *Mayo Clin Proc Innov Qual Outcomes*. 2(1):30-39.

Jing Y, et al. Prevalence and Characteristics of Adrenal Tumors in an Unselected Screening Population : A Cross-Sectional Study. *Ann Intern Med*. 2022;175(10):1383-1391.

Reimondo G, et al. Adrenal Incidentalomas are Tied to Increased Risk of Diabetes: Findings from a Prospective Study. *J Clin Endocrinol Metab*. 2020;105(4):dgz284.

Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *NEJM* 2007;356:601-10.

43