Adrenal Tumors

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Friday, December 13, 2019

Disclosure:

No Conflicts of Interest to Disclose

This presentation is intended for educational purposes only and does not replace independent professional judgment.

I am expressing my own views based on my reading, analysis and interpretation of the scientific information.

I am a member of SPED and a Federal Government employee
but I am **not** speaking in representation of or presenting the views of the Veterans Administration,
Puerto Rican Society of Endocrinology and Diabetes,
State or Federal Government Agency or Department, other Professional Societies, Public or Private Corporation, or Pharmaceutical Company.

Learning Objectives

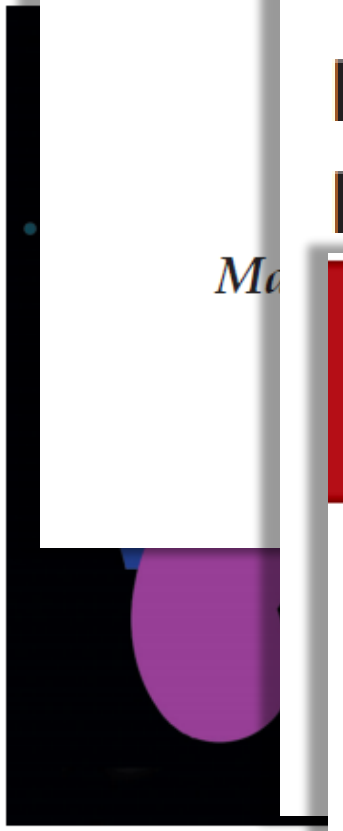
- At the end of this lecture, participants will be able to:
  - Discuss the evaluation and management of adrenal incidentalomas.
  - Recognize the different adrenal imaging ‘phenotypes.’
  - Appreciate the association of mild autonomous cortisol excess (MACE) and increase cardiovascular events, mortality, glucose intolerance and osteoporosis.
  - Reflect in the need to individualize follow up according to imaging phenotype and baseline hormonal profile.

NIH State-of-the-Science Statement on

Management of the Clinically

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS

Management of adrenal incidentalomas:
European Society of Endocrinology Clinical



NIH Consensus and State-

EnM
ENDOCRINOLOGY
AND METABOLISM

Special
Article

Endocrinol Metab 2017;32:200-218
https://doi.org/10.3803/EnM.2017.32.2.200
pISSN 2093-596X · eISSN 2093-5978

Clinical Guidelines for the Management of Adrenal Incidentaloma

Jung-Min Lee[1], Mee Kyoung Kim[2], Seung-Hyun Ko[3], Jung-Min Koh[4], Bo-Yeon Kim[5], Sang Wan Kim[6], Soo-Kyung Kim[7], Hae Jin Kim[8], Ohk-Hyun Ryu[9], Juri Park[10], Jung Soo Lim[11], Seong Yeon Kim[12], Young Kee Shong[4], Soon Jib Yoo[13], the Korean Endocrine Society, Committee for Clinical Practice Guidelines

Adrenal Incidentalomas

- Adrenal incidentalomas (AIs) are adrenal masses discovered serendipitously by radiological evaluation in the absence of clinical features suggestive of adrenal disease. This excludes surveillance in cancer patients and hereditary screening.
- Found in ~3-10% of patients undergoing abdominal imaging
  - Incidence increase with age. Peak prevalence in the 6th and 7th decades of life.
  - **URGENT ASSESSMENT RECOMMENDED IN CHILDREN, ADOLESCENTS OR <40 YEARS OF AGE[1].**
- Evaluation warranted to:
  - Establish secretory status
  - Determine the risk of malignancy
- Noncontrast CT is the cornerstone of imaging
  - Imaging phenotype

The evaluation and management of patients with poor general health and a high degree of frailty must be kept in proportion to the potential clinical gain.

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.
[1]Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

Elhassan YS. ***Ann Intern Med***. 2019;171(2):107
Zeiger MA***. Endocr Pract*** 2009; Suppl1:1
[1]Lee JM. ***Endocrinol Metab*** 2017;32:200

Adrenal Incidentalomas

- Adrenal incidentalomas (AIs) are adrenal masses discovered serendipitously by radiological evaluation in the absence of clinical features suggestive of adrenal diseas[illegible]g.
- Found[illegible]
  - Pea[illegible]
  - **URGENT ASSESSMENT RECOMMENDED IN CHILDREN, ADOLESCENTS OR <40 YEARS OF AGE[1].**
- Evaluation warranted to:
  - Establish secretory status
  - Determine the risk of malignancy
- Noncontrast CT is the cornerstone of imaging
  - Imaging phenotype

Diagnostic work-up is only recommended in lesions ≥1cm unless clinical signs and symptoms suggestive of adrenal hormone excess are present.

The evaluation and management of patients with poor general health and a high degree of frailty must be kept in proportion to the potential clinical gain.

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.
[1]Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

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Most Common Differential Diagnosis of Adrenal Incidentalomas

- Adrenal cortical masses
  - Benign: adenoma, nodular hyperplasia[1], congenital adrenal hyperplasia[1]
  - Malignant: adrenal cell carcinoma
- Adrenal medullary tumors
  - Pheochromocytoma[1], ganglioneuroma, neuroblastoma
- Other adrenal tumors
  - Benign: myelolipoma[1], teratoma, hamartoma, lipoma, hemangioma, lymphangioma, adrenal adenomatoid tumor
  - Malignant: metastasis[1], primary adrenal lymphoma[1], primary adrenal melanoma
- Infections[1]: fungal (histoplasma, coccidioidomycosis, blastomycosis), viral (cytomegalovirus), parasitic (echinococcosis), bacterial (tuberculosis, syphilis)
- Infiltration[1]: sarcoidosis, amyloidosis
- Cysts and pseudocysts
- Hemorrhage[1], hematoma
- Nonadrenal disorders such as schwannoma, leiomyosarcoma, retroperitoneal lipoma

[1]May present as bilateral

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Most Common Differential Diagnosis of Adrenal Incidentalomas

Approximately 15% are Associated with Hormone Excess

	Median	Range
Nonfunctioning cortical adenomas	80%	70%–84%
Mild Autonomous Cortisol Excess (MACE) (Subclinical Cushing syndrome)	12%	1%–29%
Pheochromocytomas	7.0%	1.1%–14%
Primary aldosteronism	2.5%	1.6%–3.3%
Primary adrenocortical carcinomas	2-8%	1.2-11%
Metastases	1-5%	0-18%

CANCER ARE OVERESTIMATED IN SURGICAL SERIES DUE TO SURGICAL BIAS

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.
Zeiger MA***. Endocr Pract*** 2009; Suppl1:1
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Lee JM. ***Endocrinol Metab*** 2017;32:200

Family History is Critical

- Congenital adrenal hyperplasia
- Multiple endocrine neoplasia type 2
- von Hippel-Lindau syndromes
  - Mutation in chromosome 3 (3p25-26) which encodes the VHL tumor suppressor gene
  - **Type 2:** Retina vascular lesions (angiomas) , cysts or solid tumors in the brain or spinal cord (Hemangioblastomas), pancreatic cysts, renal cell CA, epididymal cystadenoma, endolymphatic sac tumors
- Neurofibromatosis type 1
- Carney complex
  - Mucocutaneous spotty pigmentation
  - Myxomas
  - Primary Pigmented Nodular Adrenocortical Disease (PPNAD)
  - Testicular tumors
  - Pit mammosomatotroph tumors
  - Thyroid nodules
  - Psammomatous melanotic schwannoma
- Stratakis-Carney syndrome
  - GI stromal tumor
  - Paraganglioma
- Carney triad
  - Gastric leiomyosarcoma
  - Pulmonary chondroma
  - Extra-Adrenal Pheochromocytoma

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Adrenal Imaging and Images Characteristics "Imaging Phenotype"

Imaging phenotype

- Size
- Lipid content or density
- Heterogeneity
- Areas of necrosis
- Calcifications
- Borders
- Local invasion

Size Does Matter but It is Not the Most Important Thing

- Noncontrast CT is the cornerstone of imaging
- Size
  - The maximum diameter of the mass is predictive of malignancy.
  - The smaller the adrenocortical carcinomas at diagnosis the better is the prognosis
  - There is no safe absolute tumor size cutoff to rule out malignancy

Size	Likelihood Ratio of Adrenal CA
4.0 cm to 5.9 cm	10%
6.0 cm to 7.9 cm	19%
7.0 cm or larger	47%

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Hounsfield Unit

- A relative quantitative measurement of radio density used by radiologists in the interpretation of computed tomography (CT) images.
- The physical density of tissue is proportional to the absorption/attenuation of the X-ray beam.
  - More dense tissue, with greater X-ray beam absorption, has positive values and appears bright.
  - Less dense tissue, with less X-ray beam absorption, has negative values and appears dark.
- Water is arbitrarily defined to be zero Hounsfield Units and air defined as -1000 HU.
  - Adipose tissue -20 to -150 HU
  - Kidney +20 to +150 HU

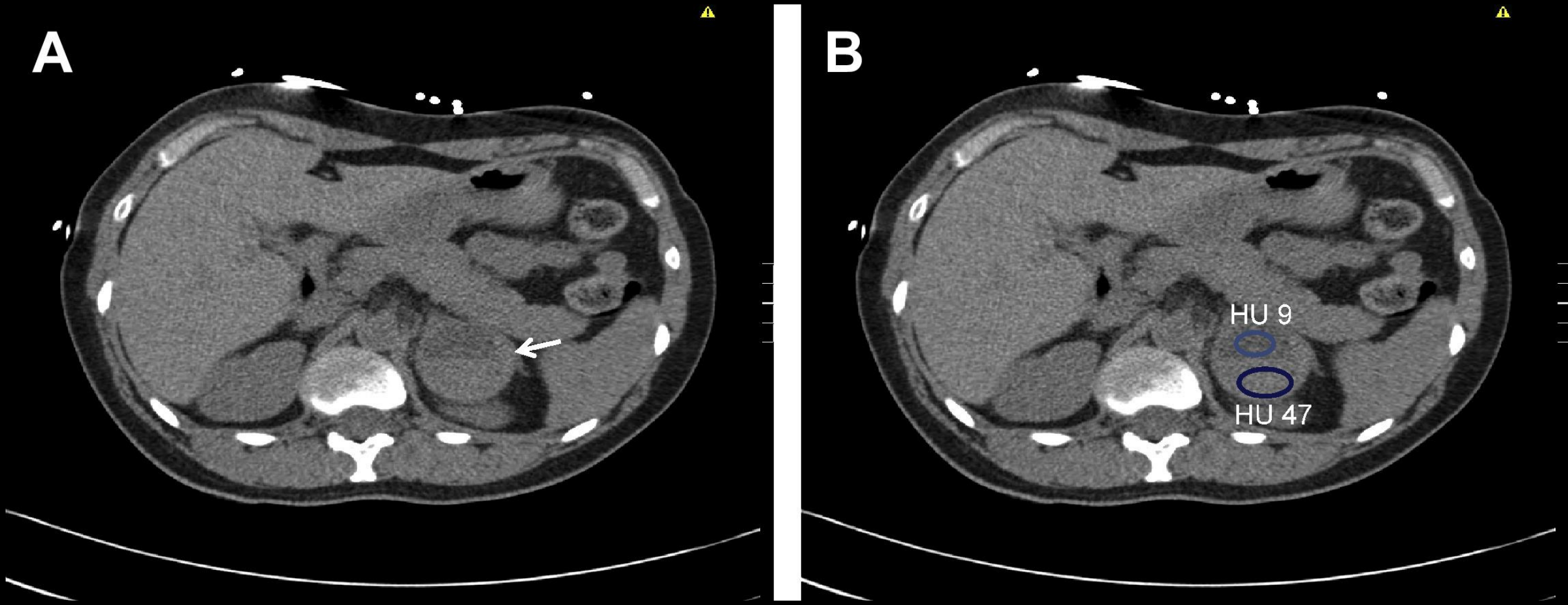
Sir Godfrey Hounsfield
Nobel in Physiology/Medicine in 1979

CT Scan
Hounsfield Unit Determination

- The region of interest during measurement of attenuation value should encompass **one half to two-thirds** of the surface area of the mass and should avoid boundaries to prevent volume averaging with tissue outside the nodule.
- Only homogeneous regions of the tumor should be selected, avoiding with cystic or calcified areas and necrotic changes.
- The highest CT attenuation values in mixed tumors should be used for clinical decision making

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.
Garrett RW. ***AJR*** 2016;206:1170

Final Pathology: Pheochromocytoma



Heterogeneous left adrenal mass

Variable CT attenuation HU

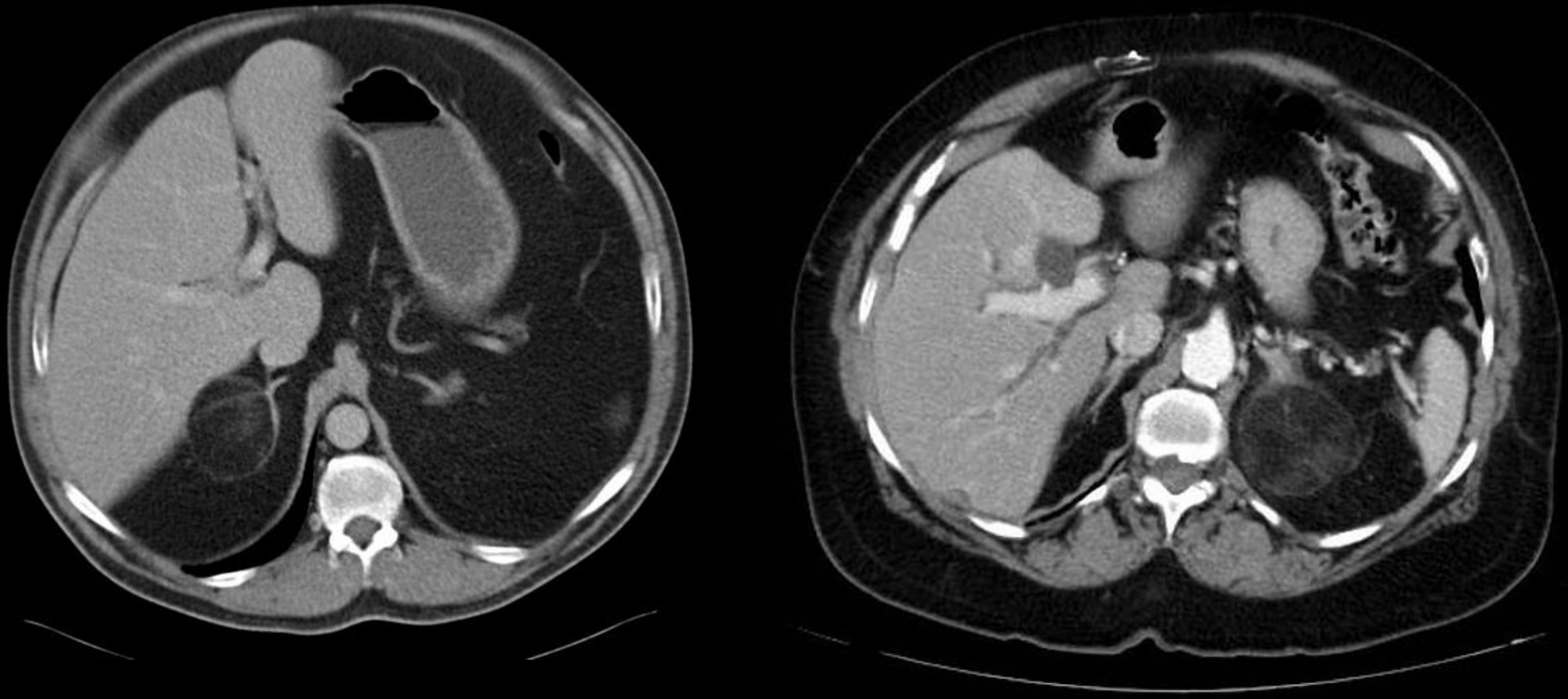
CT Scan

- **Myelolipomas** are characterized by attenuation of less than -20 HU.
  - Image attenuation does not distinguish from liposarcomas.
- **AN ADRENAL MASS WITH HU UNDER 10 ON UNENHANCED CT IS ALMOST LIKELY TO BE BENIGN.**
  - Low attenuation is 2^{ry} to high fat concentration in sterol producing tissue
  - Lipid-rich adenomas
- Approximately **30% of benign adenomas do not contain large amount of lipid** and are undistinguishable from nonadenomas adrenal masses in unenhanced CT scans.
  - Consider adrenal contrast-enhanced CT or MRI with CSI
- The unenhanced CT attenuation value is a better predictor of benign tumors than adrenal tumor size.
  SIZE DOES MATTER BUT IT IS NOT THE MOST IMPORTANT THING

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

Adrenal Myelolipoma



Unenhanced CT: Hounsfield Units

Adrenal	Hounsfield Units
Adenomas/hyperplasia	16.2
Carcinomas	36.9
Metastasis	39.2
Pheochromocytomas	38.6

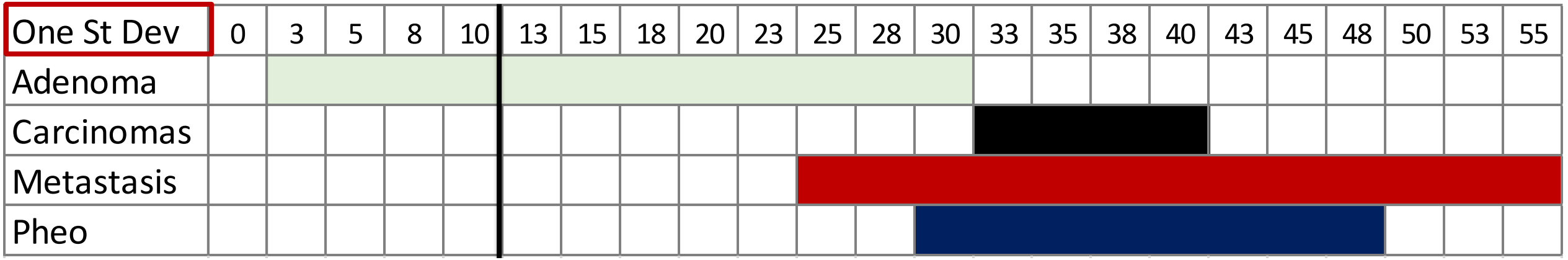
Hamrahian AH. ***J Clin Endocrinol Metab*** 2005;90:871

Unenhanced CT: Hounsfield Units

Adrenal	Hounsfield Units	Variability	Range ± 1 SD
Adenomas/hyperplasia	16.2	± 13.6	2.6-29.8
Carcinomas	36.9	± 4.1	32.8-41.0
Metastasis	39.2	± 15.2	24.0-54.4
Pheochromocytomas	38.6	± 8.2	30.4-46.8

Hamrahian AH. ***J Clin Endocrinol Metab*** 2005;90:871

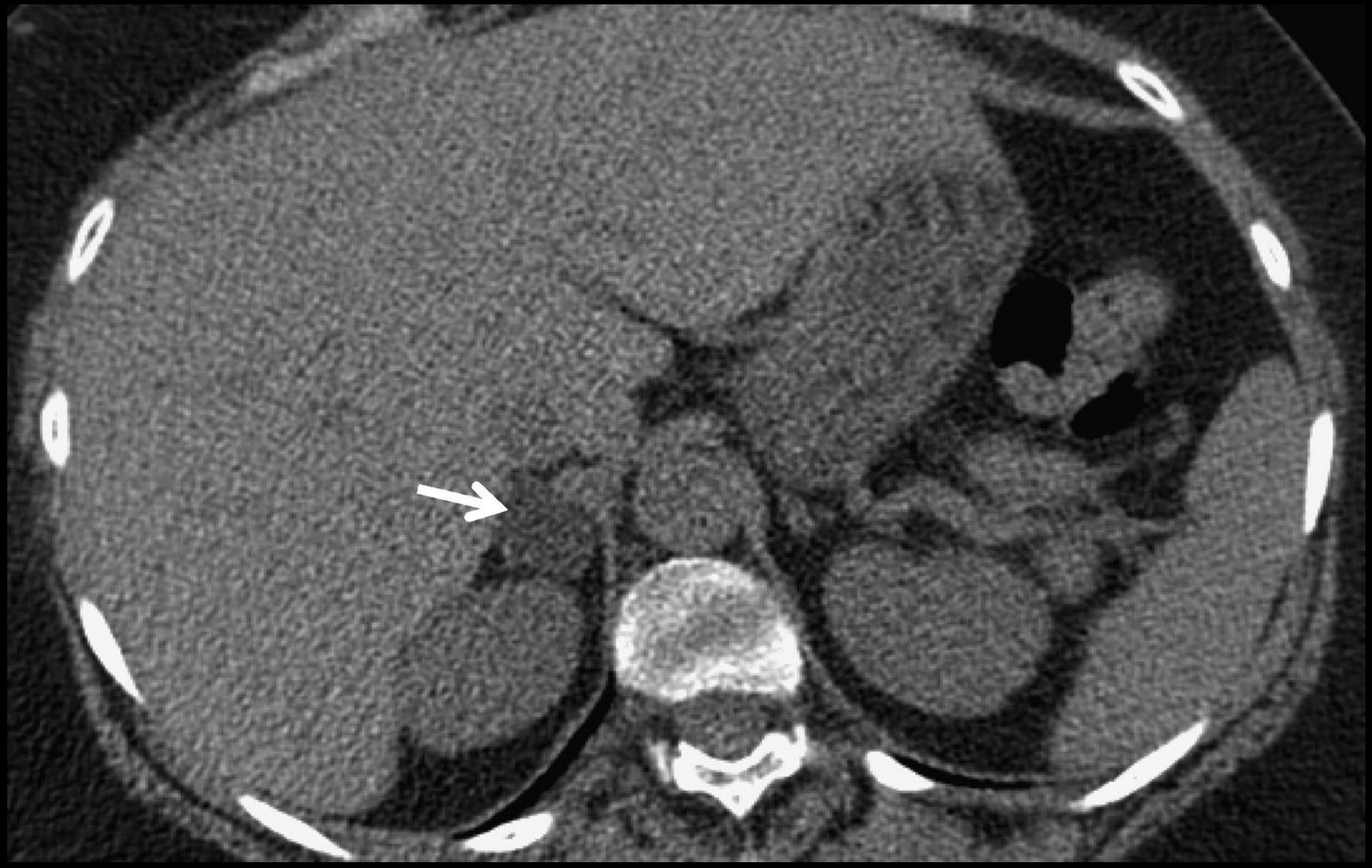
Unenhanced CT: Hounsfield Units



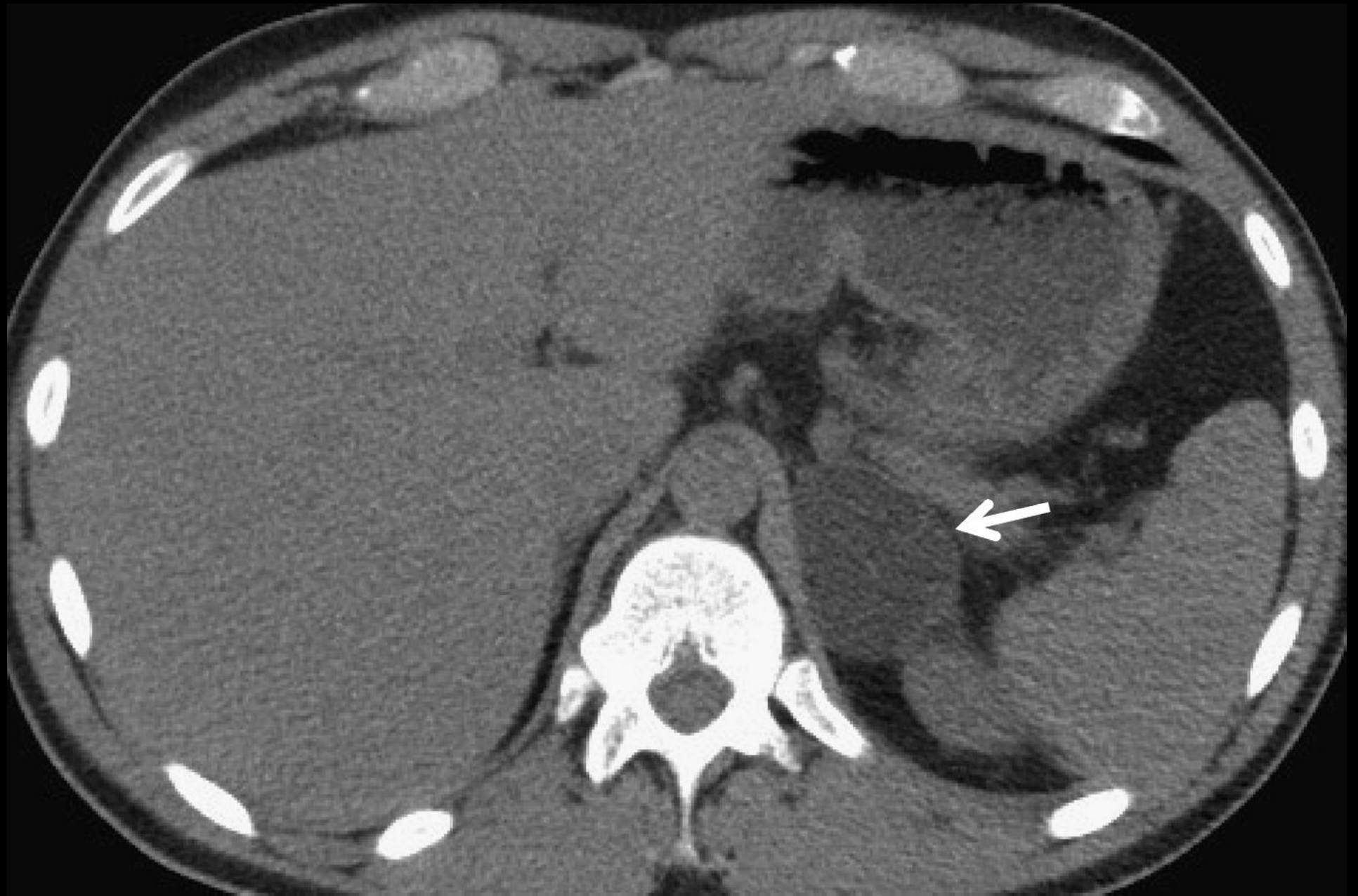
Hamrahian AH. **J Clin Endocrinol Metab** 2005;90:871

Right Adrenal Mass, Typical Adenoma: Less than 10 HU

Small
Homogeneous
Smooth borders



Left Adrenal Mass: 4.7 cm with Less than 10 HU

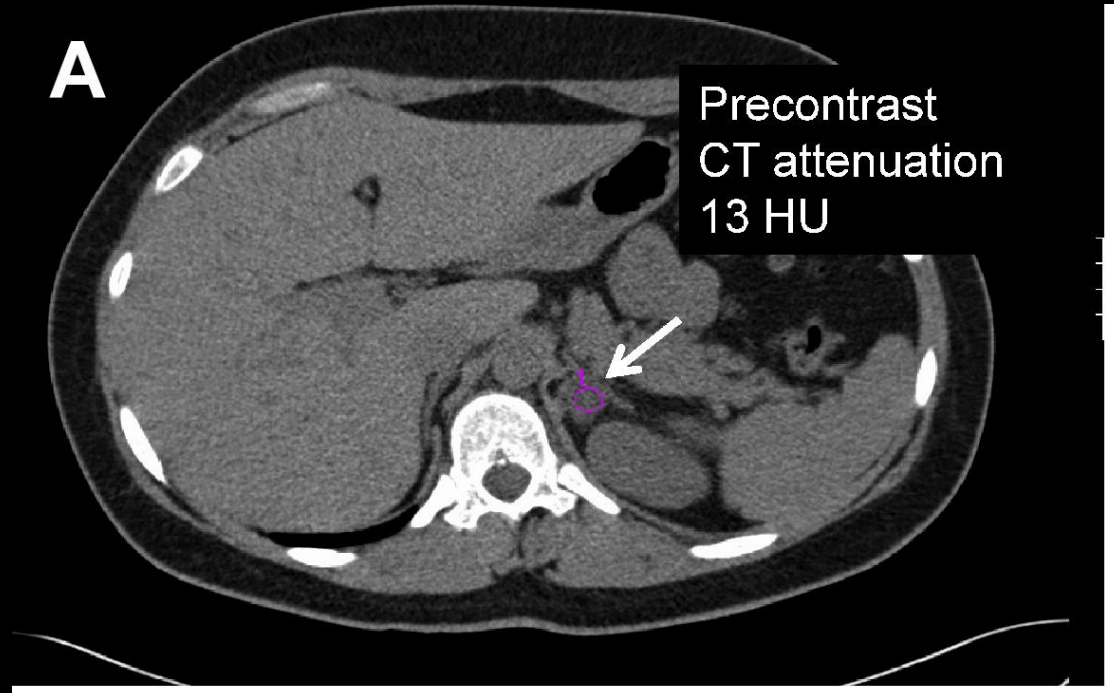


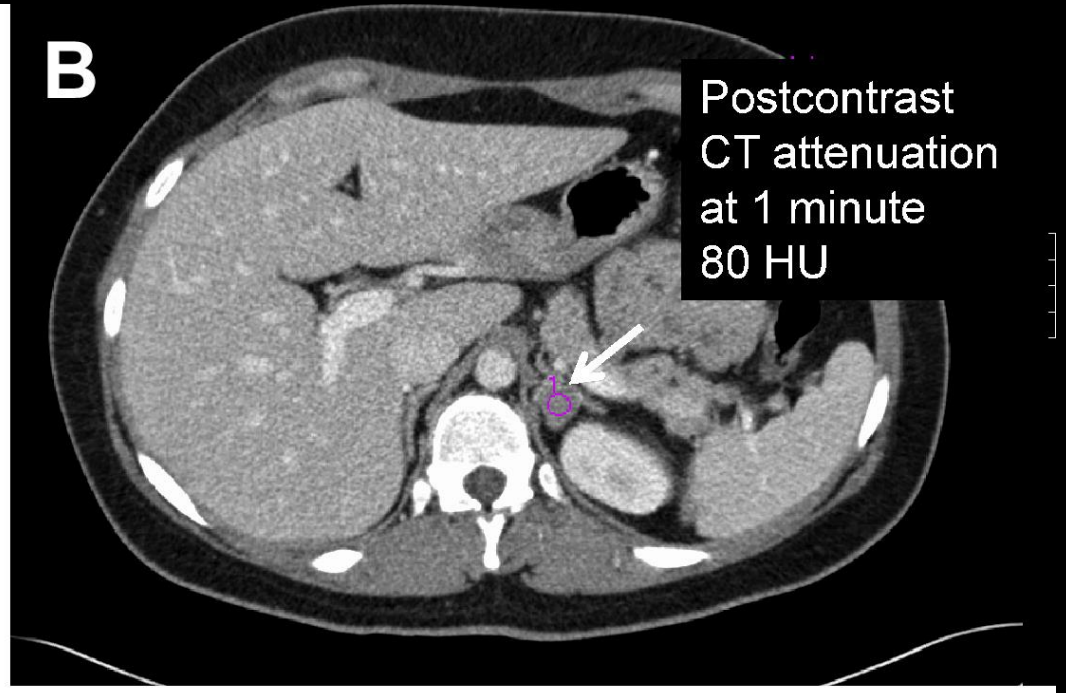
Large
Homogeneous
Smooth borders

Contrast Enhanced Adrenal CT Indicated if HU are More than 10

- Contrast medium washout
  - 10-15 mins after administration of contrast and absolute washout of 50% or more has been reported to be 100% sensitive and specific for adenoma
    - Postcontrast images should be done 1 and 15 minutes
  - Enhancement Washout[1]:
    - Absolute: (1min – 15min)/(1min-Pre Contrast)
    - Relative: (1min – 15min)/1min (Used when unenhanced CT is not available)
- Adenomas
  - Rapid contrast medium washout
    - Commonly enhance up to 80-90 HU and have an **Absolute** percentage washout > 60% or **Relative** percentage washout > 40%.
- Nonadenomas
  - Enhance rapidly but demonstrate a slower washout of contrast medium

Caoili EM. ***American Journal of Roentgenology***. 2000;175: 1411 Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1



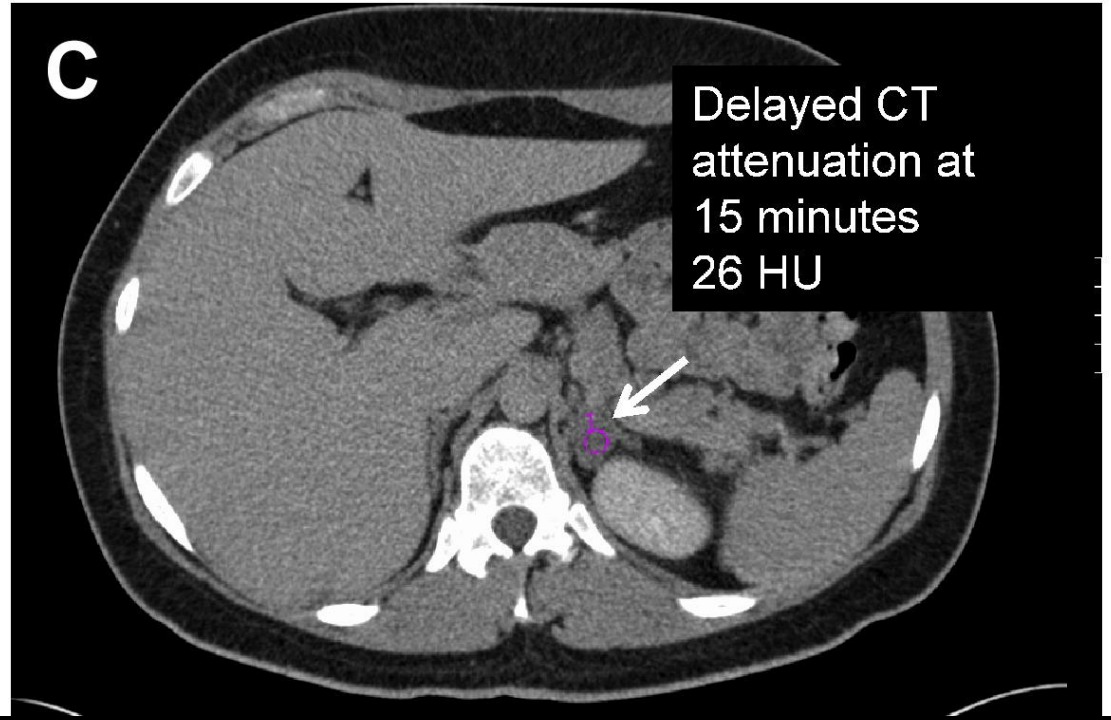


Enhancement:

67 = [80 - 13]

Washout:

54 = [80 - 26]



***Absolute* WOut:**

81% = [54/67]

***Relative* WOut:**

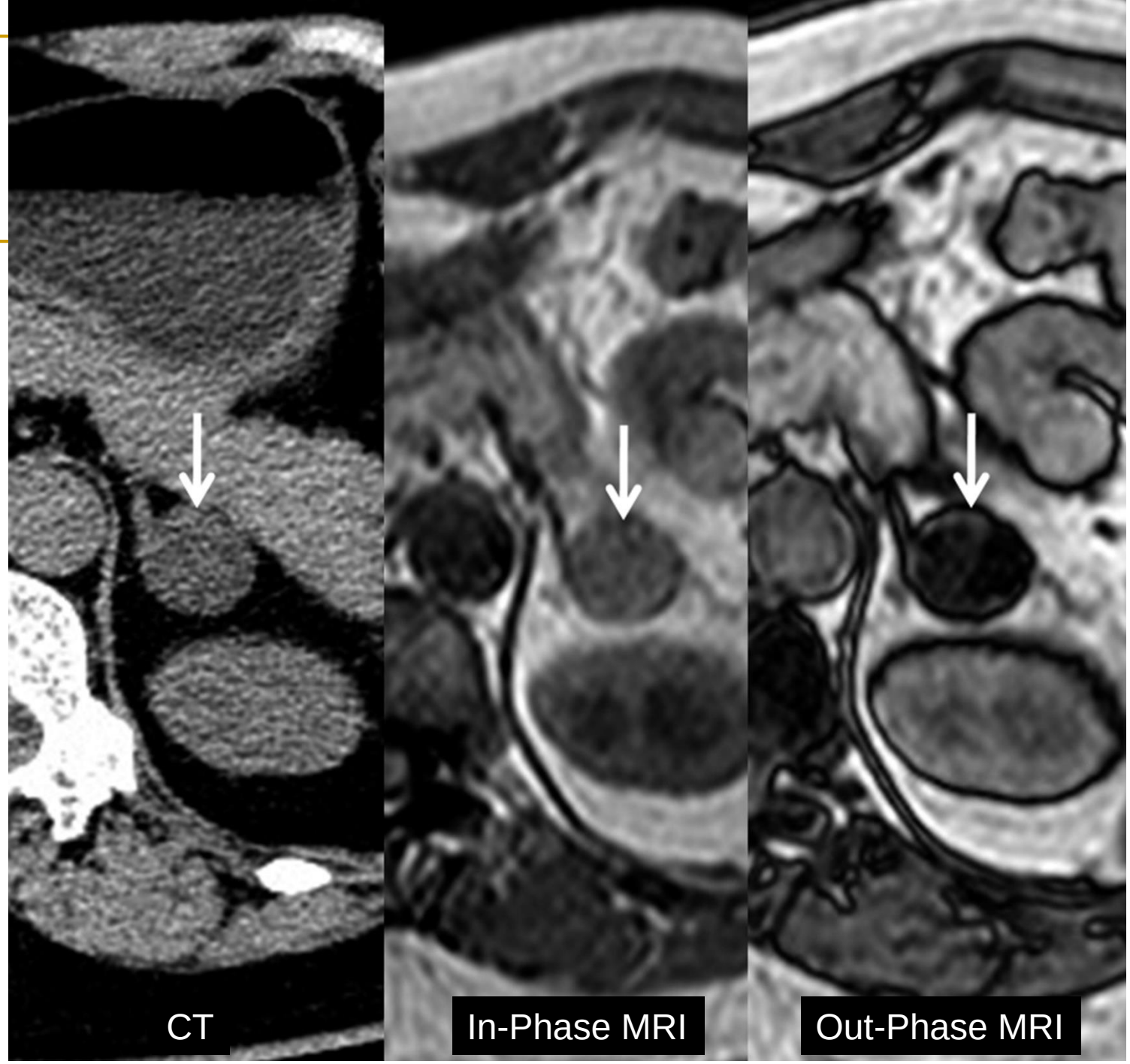
33% = [54/80]

Magnetic Resonance Imaging: MRI

- **Conventional spin-echo MRI**
  - T1 and T2 images
  - Adenomas are isointense with liver on T1 and T2 weighted sequences
  - Pheochromocytomas have high signal in T2 weighted MRI
    - 35% are not light-bulb bright on T2 weighted MRI
  - Adrenal carcinoma are hypointense on T1 and intermediate/high in T2 weighted MRI.
  - Metastasis are Iso/Hypointese on T1 and intermediate/high in T2 weighted MRI.
- **Gadolinium**-diethylene triamine pentaacetic acid (DTPA) enhanced MRI
  - Rapid washout favors adenomas
- **Chemical shift imaging (CSI)**
  - Hydrogen protons in lipid and water resonate at different frequencies (‘chemical shift’)
  - Adenomas lose signal on out-of-phase images; bright on in-phase images
  - Malignant lesions, pheochromocytomas and lipid-poor adenomas remain unchanged
  - Although there is debate, it considered less accurate than CT

Chemical-Shift MRI

- CT: 5 HU
- **In-Phase**
  - Homogeneous
  - Hyperintense
- **Out-Phase**
  - Homogeneous
  - Hypointense, lose signal
- Quantitative parameters have been suggested
  - Adrenal-to-spleen Ratio
  - Signal Intensity Index



Park JJ. ***Br J Radiol*** 2016;89:20151018

Functional Imaging

Usual Indications for PET/CT Scan:
- **enlarging adrenal mass**
- **indeterminate adrenal mass on CT**
- **adrenal mass ≥4 cm**

- Study relies on trapping of the material by metabolically active cells
- Iodine-meta-iodobenzylguanidine (^{123}I-MIBG)
- ^{131}I-6b-iodomethyl-19-norcholesterol (NP-59)
  - Seems better for hyperfunctioning lesions but has limited clinical availability
- **PET**
  - ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG)
  - ^{18}F-3,4-dihydroxyphenylalanine (^{18}F-DOPA)
  - ^{18}F-fluorodopamine (^{18}F-FDA)
  - PET is considered superior to MIBG.

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Positron Emission Tomography: PET Scan

- **Fludeoxyglucose F18 (FDG)**
  - Cancer cells have an increased requirement for glucose and, therefore, take up more glucose and deoxyglucose than normal cells
  - Both glucose and deoxyglucose enter cells via cell glucose transporters and undergo phosphorylation, but while glucose undergoes further enzymatic breakdown deoxyglucose becomes trapped in intracellular compartments.
  - ^{18}F-FDG is not a specific marker for cancer cells but a marker only for increased glucose metabolism
    - **Up to 5% of adenomas may be hypermetabolic on PET/CT**.
    - Adrenal metastasis and pheochromocytomas have PET uptake.
  - Standard uptake value (SUV), which compares the intensity of uptake of 18F in the adrenal lesion to the average uptake of whole body
- **11C-metomidate (MTO)**

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Imaging Phenotypes of Most Common Adrenal Masses

Type	Size (cm)	Nonenhanced Attenuation	CT Washout >60% Absolute	MRI with CSI Loss of Signal on T1 Out of Phase MRI
Adenoma	<4 cm	< 10 HU	Yes	Yes
1ry Carcinoma	> 4 cm	> 30 HU	No	No
Metastasis	Variable	> 10 HU	No, except renal cell and Hepato Cel CA	No, except renal cell and Hepato Cel CA
Pheo	> 3 cm	> 17 HU	Variable washout Enhancement >100 HU	No

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

European Society of Endocrinology Clinical Practice Guideline How to assess risk of malignancy?

- **R 2.3.** We suggest that if the noncontrast CT is consistent with a benign adrenal mass (Hounsfield units ≤10) that is homogeneous and smaller than 4cm, no further imaging is required
- **R 2.4.**If the adrenal mass is indeterminate on noncontrast CT and the results of the hormonal work-up do not indicate significant hormone excess, three options should be considered by a multidisciplinary team acknowledging the patient's clinical context: immediate additional imaging with another modality, interval imaging in 6–12 months (noncontrast CT or MRI), or surgery without further delay.
- **2.5**.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 and additional criteria are fulfilled

Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

Fine-Needle Aspiration Biopsy

- Cannot distinguish benign from primary adrenal carcinoma
- Can help to distinguish adrenal tumor from metastasis
- Mainly used for diagnosis of extra/adrenal malignancy, lymphoma, infiltrative or infectious process
- Violation of the tumor capsule may promote needle track metastasis.

European Guideline[1]:

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

Fassnacht M ***J Clin Endocrinol Metab*** 2013;98:4551

[1]Fassnacht M. ***Eur J Endocrinol*** 2016; 175, G1

Biochemical Evaluation in Adrenal Incidentalomas

Biochemical Evaluation

- Screening for subclinical excess is indicated in all patients with an adrenal incidentaloma
  - Mild Autonomous Cortisol Excess (MACE) or Subclinical Cushing Syndrome
    - 1mg-dexamethasone overnight test preferred over Urinary Free Cortisol
  - Pheochromocytoma
    - Some recommend only if HU > 10.
  - Primary aldosteronism
    - If hypertensive or hypokalemic
  - Virilization or hyperandrogenism
- **EXCEPTION: IF IT IS AN OBVIOUS MYELOLIPOMA. ADRENAL MYELOLIPOMAS HAVE A LOW CT ATTENUATION DUE TO FAT CONTENT (-10 TO -20 HOUNSFIELD UNITS)**

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.
Zeiger MA***. Endocr Pract*** 2009; Suppl1:1

Mild Autonomous Cortisol Excess (MACE)

Subclinical Cushing Syndrome
Mild Autonomous Cortisol Excess (MACE)

- Subtle autonomous production of cortisol from an adrenal mass, with suppression of cortisol production from the contralateral gland, but no over clinical features of Cushing syndrome. Very rarely (<1%) develop overt Cushing's syndrome.
- Prevalence of up to 20-30% in adrenal incidentalomas has been reported.
- Retrospective studies have indicated these patients have an increase in cardiovascular events and mortality.
- The European Society of Endocrinology guidelines suggest that adrenalectomy may be performed in patients with unilateral adenomas and at least 2 comorbidities potentially related to hypercortisolism.
  - Overall, the quality of evidence supporting adrenalectomy in SH was very low.

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

Zavattta G. ***Endo and Metab Clinics*** 2018;47:375

Subclinical Cushing Syndrome
Mild Autonomous Cortisol Excess (MACE)

- 1-mg Dexamethasone test
  - **Normal** Response: Cortisol under 1.9 µg/dL
  - **Possible** Excess: Cortisol 1.9 to 5 µg/dL
  - **Subclinical Excess**: Cortisol greater than 5.0 µg/dL
- **For Possible or Subclinical Excess:**
  - Request late night salivary cortisol, DHEAs, or androgens by mass spectrometry
    - Low DHEAs level (less than 40 µg/dL) suggest contralateral suppression
  - ACTH & UFC seems less helpful
    - Urinary free cortisol has low sensitivity in mild cortisol excess. Therefore, rarely recommended.
    - New determination by mass spectrometry may changes this
      - Mass spectrometry is superior to immunometric assays.

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335. Zavattta G. ***Endo and Metab Clinics*** 2018;47:375

European Society of Endocrinology Clinical Practice Guideline
How to define and manage low-level autonomous cortisol secretion

- **3.2.**We recommend that all patients with adrenal incidentalomas undergo a 1mg overnight dexamethasone suppression test to exclude cortisol excess
- **3.3.**We suggest interpretation of the results of the 1mg overnight dexamethasone test as a continuous rather than categorical (yes/no) variable.

  However, we recommend using serum cortisol levels post dexamethasone ≤1.8µg/dL as a diagnostic criterion for the exclusion of autonomous cortisol secretion
  - 1.9–5.0 µg/dL : 'possible autonomous cortisol secretion'
  - >5.0 µg/dL : 'autonomous cortisol secretion'
- Individualized approach according to the screening of HTN, T2DM or vertebral Fx

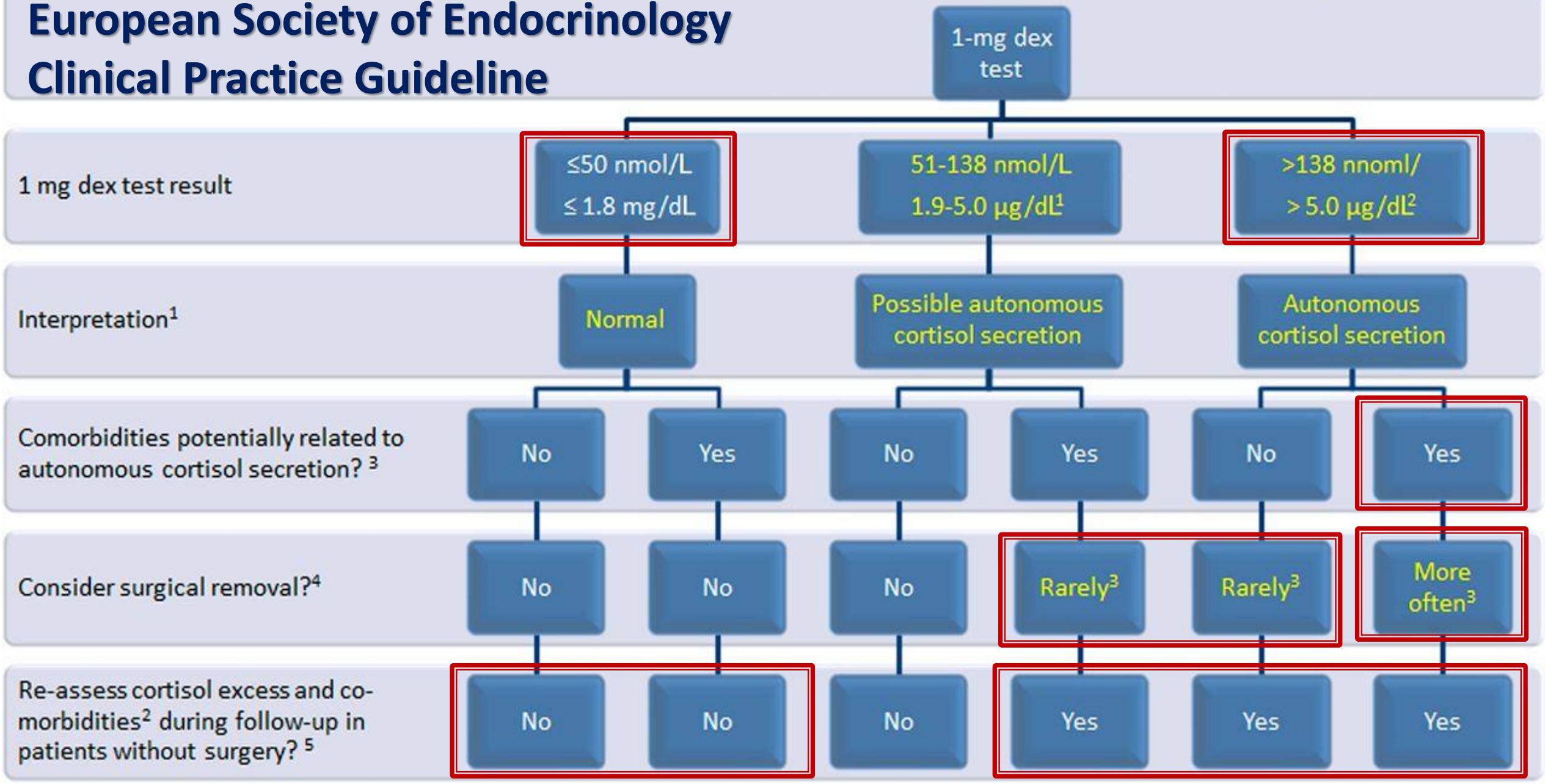
Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

AACE Guideline

- **R5.** A diagnosis of **subclinical Cushing syndrome (SCS)** is made if the serum cortisol level is **more than 5.0 mg/dL** after a 1-mg dexamethasone suppression test, in a patient with an adrenal adenoma and absence of typical physical stigmas of hypercortisolism.
- **R6.** In patients with SCS, until further evidence is available regarding the long-term benefits of adrenalectomy, surgical resection should be reserved for those with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis

Zeiger MA. ***Endocr Pract*** 2009; Suppl1:1

European Society of Endocrinology Clinical Practice Guideline



Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

Natural History of Adrenal Incidentalomas
A Systematic Review and Meta-analysis

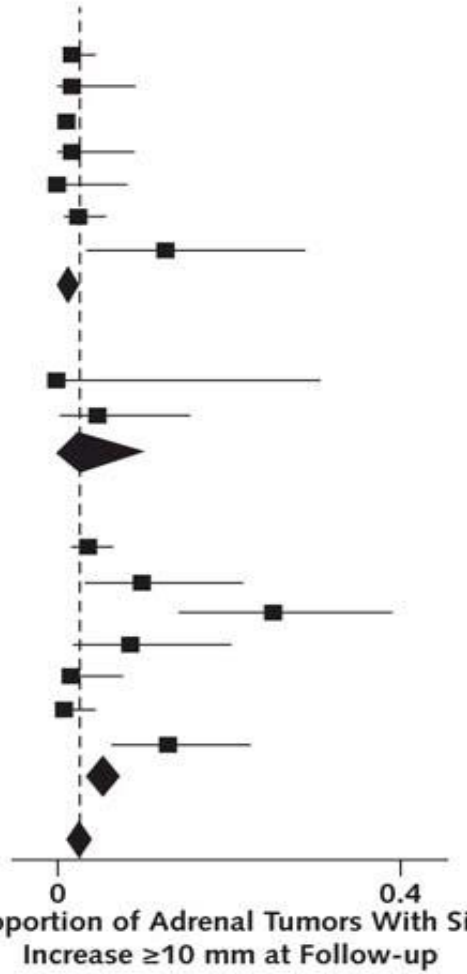
- Summary of available literature of the natural history of non-functional adrenal tumors (NFAT) and mild autonomous cortisol excess adenomas (MACE). Specifically during follow up in:
  - Changes in size & hormone production
  - Prevalence of hypertension, obesity, dyslipidemia, T2DM and cardiovascular events
  - Incidence all-cause and cardiovascular mortality
- Studies between Jan 1990 and Feb 2019
  - 32 studies included: 17 retro- and 15 prospective
  - 4,121 patients with mean follow up of 50 months (range, 1 to 320 months)
    - 2873 NFAT: Non-Functional Adrenal Tumor
    - 784 MACE: Mild Cortisol Autonomous Excess
    - 464 Could not be disaggregated to the presence of absence of MACE

Elhassan YS ***Ann Intern Med.*** 2019;171:107

Increased in Size ≥10 mm During Follow-Up

- 2.5% of adrenal incidentalomas grew by > 10 mm over a mean follow-up of 41.5 months.
- The mean increase in adenoma size in all patients was negligible at 2.0 mm.

Study, Year (Reference)	Mean Follow-up, *mo*	Follow-up Range, *mo*	Events, *n/N*	Proportion (95% CI)
NFAT				
Barry et al, 1998 (23)	49	1 to 123	4/231	0.017 (0.005 to 0.044)
Bastounis et al, 1997 (25)	–	–	1/60	0.017 (0.000 to 0.089)
Hong et al, 2017 (13)	48	36 to 216	4/449	0.009 (0.002 to 0.023)
Ng et al, 2010 (39)	30.2	–	1/61	0.016 (0.000 to 0.088)
Terzolo et al, 1998 (45)	–	–	0/43	0.000 (0.000 to 0.082)
Yener et al, 2010 (47)	24	6 to 159	5/212	0.024 (0.008 to 0.054)
Yilmaz et al, 2009 (49)	24	18 to 60	4/32	0.125 (0.035 to 0.290)
Subtotal	35.1	1 to 216	19/1088	0.012 (0.005 to 0.020)
MACE				
Terzolo et al, 1998 (45)	–	–	0/10	0.000 (0.000 to 0.308)
Yener et al, 2010 (47)	17	6 to 187	2/45	0.044 (0.005 to 0.151)
Subtotal	17	6 to 187	2/55	0.024 (0.000 to 0.096)
NFAT and MACE				
Comlekci et al, 2010 (29)	24	7 to 103	10/293	0.034 (0.016 to 0.062)
Fagour et al, 2009 (31)	51.6	–	5/51	0.098 (0.033 to 0.214)
Libè et al, 2002 (36)	25.5	12 to 120	13/52	0.250 (0.140 to 0.389)
Morelli et al, 2014 (38)	72.3	60 to 186	17/206	0.083 (0.049 to 0.129)
Papanastasiou et al, 2017 (14)	66.5	36 to 120	1/71	0.014 (0.000 to 0.076)
Ruiz et al, 2019 (42)	48	–	1/130	0.008 (0.000 to 0.042)
Vassilatou et al, 2009 (12)	60	12 to 154	10/77	0.130 (0.064 to 0.226)
Subtotal	49.7	12 to 186	57/880	0.053 (0.038 to 0.069)
Overall	41.5	1 to 216	78/2023	0.025 (0.018 to 0.033)



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Mean Difference in Adenoma Size (in mm) Between Baseline and End of Follow-Up in Patients with NFAT or MACE

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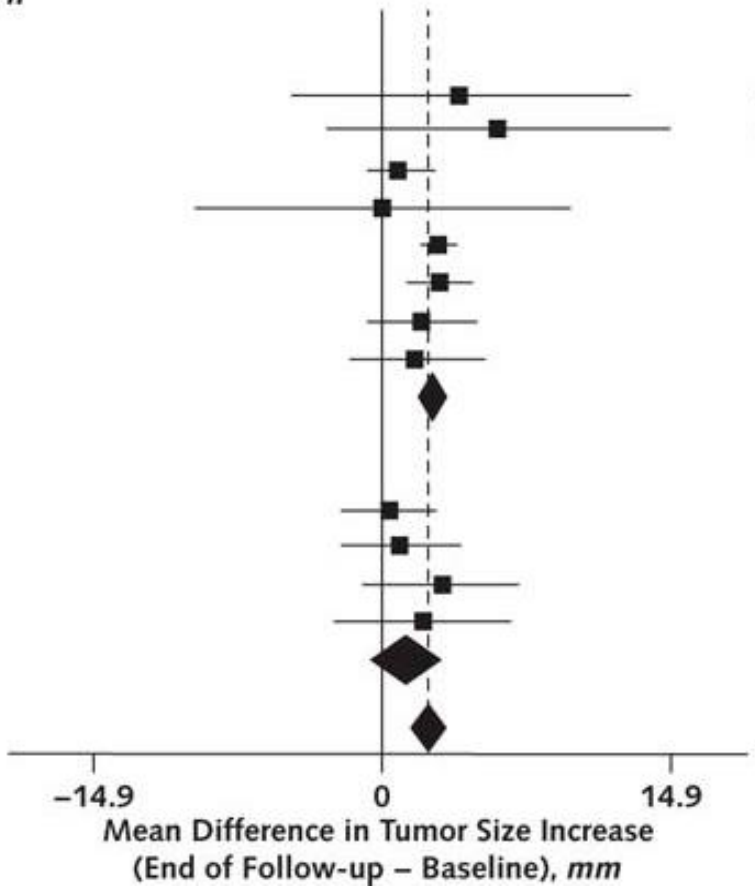
Study, Year (Reference)	Tumor Type	Mean Follow-up, *mo*	Follow-up Range, *mo*	Total Patients, *n*	Tumor Size Increase (95% CI), *mm*
Tumor size at baseline <25 mm					
Chiodini et al, 2001 (28)	NFAT	31.6	12 to 61	17	4.000 (–4.765 to 12.765)
Chiodini et al, 2001 (28)	MACE	24.8	19 to 33	7	6.000 (–2.920 to 14.920)
Di Dalmazi et al, 2014 (30)	NFAT	94.8	–	129	0.800 (–0.957 to 2.557)
Giordano et al, 2010 (32)	MACE	36	12 to 120	10	0.000 (–9.701 to 9.701)
Hong et al, 2017 (13)	NFAT	51.7	23 to 72	449	2.900 (2.006 to 3.794)
Morelli et al, 2014 (38)	NFAT	82.5	60 to 186	167	3.000 (1.271 to 4.729)
Papanastasiou et al, 2017 (14)	NFAT	66.5	36 to 120	51	2.000 (–0.917 to 4.917)
Yilmaz et al, 2009 (49)	NFAT	24	18 to 60	32	1.690 (–1.877 to 5.257)
Subtotal (I^2 = 0.0%; P = 0.55)	–	48.4	12 to 186	862	2.515 (1.831 to 3.198)
Tumor size at baseline ≥25 mm					
Bernini et al, 2005 (26)	NFAT	48	12 to 84	115	0.300 (–2.195 to 2.795)
Di Dalmazi et al, 2014 (30)	MACE	82.8	–	69	0.796 (–2.457 to 4.050)
Morelli et al, 2014 (38)	MACE	82.5	60 to 186	39	3.000 (–1.222 to 7.222)
Papanastasiou et al, 2017 (14)	MACE	66.5	36 to 120	20	2.000 (–2.659 to 6.659)
Subtotal (I^2 = 0.0%; P = 0.72)	–	60.8	12 to 186	243	1.074 (–0.599 to 2.747)
Overall (I^2 = 0.0%; P = 0.55)	–	52.8	12 to 186	1105	2.309 (1.676 to 2.941)



Risk of Adrenal Carcinoma and Hormonal Production

- In 26 studies involving 2,854 patients, **none** of the adrenal tumors initially determined to be benign NFAT or MACE transformed into an adrenocortical carcinoma.

  IS REPEATED RADIOLOGIC FOLLOW-UP NECESSARY?

- Overall, 23 studies involving 2,745 patients assessed changes in hormone production by adrenal tumors initially diagnosed as NFAT or MACE
  - 6 patients (within 2 studies) developed overt Cushing syndrome
    - 5 initially classified as NFAT and 1 as MACE
  - 3 patients (within 2 studies) developed pheochromocytoma
  - None primary aldosteronism

  THEREFORE, OVERT HORMONE SECRETION ALMOST NEVER OCCURRED (0.1 to 0.2%)

- Nineteen studies involving 2083 patients with NFAT assessed development of MACE, which was observed in only 4.3% (CI, 3.4% to 5.3%)

Elhassan YS ***Ann Intern Med.*** 2019;171:107

Cardiometabolic Comorbid Conditions

- Comorbid Conditions were more frequently found in MACE vs NFAT:
  - Hypertension at baseline and follow up
  - Worsening of hypertension
  - Gain weight during follow up
  - Dyslipidemia worsening
  - T2DM at baseline
  - Worsening of T2DM
  - Cardiovascular events
    - Twice as likely in MACE
- Mortality, all cause and cardiovascular was similar between NFAT & MACE

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Table. Summary of the Meta-analysis of the Cardiometabolic Comorbid Conditions*

Comorbid Condition	Studies, *n*	Participants at Baseline, *n*	Pooled Mean Duration of Follow-up (Range), *mo*	Patients With Comorbid Condition at Baseline		Patients With Newly Developing Comorbid Condition		Patients With Worsening Comorbid Condition	
				Patients, *n*	Prevalence (95% CI), %	Patients, *n*	Proportion (95% CI), %	Patients, *n*	Proportion (95% CI), %
Hypertension									
All patients	15	1389	57.9 (12-277.2)	823	60.0 (56.8-62.1)	86	5.6 (4.2-7.2)	92	5.7 (3.9-7.6)
NFAT	9	952	59.1 (12-277.2)	553	58.2 (55.0-61.4)	51	5.2 (3.7-6.9)	52	4.8 (2.9-7.0)
MACE	10	296	59.8 (12-204)	188	64.0 (58.2-69.6)	23	8.4 (4.6-13.0)	40	13.4 (8.9-18.7)
Mixed group of NFAT and MACE	2	141	44.1 (12-154)	82	58.2 (49.9-66.3)	12	8.4 (4.2-13.7)	0	0.0 (0.0-5.6)
Obesity/weight gain									
All patients	7	566	51.3 (12-186)	240	42.0 (37.9-46.2)	78	9.2 (6.7-11.9)	–	–
NFAT	3	301	52.4 (12-186)	118	38.8 (33.3-44.4)	40	8.7 (5.6-12.3)	–	–
MACE	4	124	53.2 (12-178)	51	41.0 (32.1-50.1)	28	21.0 (13.8-29.0)	–	–
Mixed group of NFAT and MACE	2	141	44.1 (12-154)	71	50.3 (42.0-58.6)	10	4.1 (1.2-8.2)	–	–
Dyslipidemia									
All patients	11	1101	58.6 (12-277.2)	382	33.7 (30.8-36.6)	72	6.0 (4.4-7.9)	39	4.8 (2.8-7.1)
NFAT	7	805	66.8 (12-277.2)	278	33.8 (30.5-37.2)	52	6.9 (5.0-9.1)	20	4.3 (2.1-7.1)
MACE	10	296	59.8 (12-204)	104	34.1 (28.5-39.9)	20	5.7 (2.6-9.7)	19	6.8 (3.3-11.3)
Mixed group of NFAT and MACE	–	–	–	–	–	–	–	–	–
Type 2 diabetes									
All patients	11	1151	62.7 (12-277.2)	226	18.1 (15.8-20.4)	55	4.8 (3.3-6.4)	18	1.6 (0.3-3.5)
NFAT	6	733	68.1 (12-277.2)	113	14.4 (11.9-17.1)	34	5.3 (3.5-7.3)	0	0.0 (0.0-1.0)
MACE	8	277	62.8 (12-204)	82	28.1 (22.8-33.8)	13	4.7 (1.8-8.5)	18	9.2 (4.6-14.8)
Mixed group of NFAT and MACE	2	141	44.1 (12-154)	31	22.0 (15.4-29.3)	8	5.0 (1.8-9.5)	0	0.0 (0.0-5.6)
Prediabetes									
All patients	3	390	70.5 (12-277.2)	48	8.8 (6.1-12.0)	36	8.6 (5.8-11.7)	–	–
NFAT	2	293	76.4 (36-277.2)	38	11.5 (8.0-15.4)	31	10.3 (7.0-14.1)	–	–
MACE	1	20	66.5 (36-120)	10	50.0 (27.2-72.8)	1	5.0 (0.1-24.9)	–	–
Mixed group of NFAT and MACE	1	77	62.7 (12-154)	0	0.0 (0.0-4.7)	4	5.2 (1.4-12.8)	–	–
Composite diabetes									
All patients	5	495	52.2 (12-277.2)	130	25.1 (21.2-29.3)	52	7.9 (5.4-10.6)	–	–
NFAT	4	461	48.8 (12-277.2)	119	25.4 (21.4-29.5)	43	8.6 (6.1-11.5)	–	–
MACE	3	34	55.6 (12-120)	11	32.0 (16.5-49.6)	9	9.5 (2.8-18.6)	–	–
Mixed group of NFAT and MACE	–	–	–	–	–	–	–	–	–
Cardiovascular events									
All patients	7	835	63.5 (12-320)	82	7.8 (5.9-9.9)	82	8.2 (6.3-10.3)	–	–
NFAT	5	613	69.7 (18-320)	61	8.7 (6.5-11.2)	42	6.4 (4.5-8.6)	–	–
MACE	6	222	58.2 (12-320)	21	6.3 (3.1-10.3)	40	15.5 (10.7-20.8)	–	–
Mixed group of NFAT and MACE	–	–	–	–	–	–	–	–	–

MACE = mild autonomous cortisol excess; NFAT = nonfunctioning adrenal tumor.
* This is reported as pooled meta-analysis for all patients with NFAT and MACE. Further subgroup analysis was done for patients with NFAT, patients with MACE, and a group with NFAT/MACE for whom it was not possible to disaggregate the outcome data by presence or absence of MACE. Composite diabetes represents the combination of the type 2 diabetes and prediabetes groups.

Follow-Up in Adrenal Incidentalomas: An Italian Multicenter Study

- **Retrospective analysis** of 1,120 adrenal incidentalomas referred between 1996-2012
  - 206 in the cohort follow-up 5 years or more
    - Between 1cm and 6 cm
    - Homogeneous texture
    - Below 10 Hounsfield units
    - Regular and smooth margins
- Baseline and end of follow-up:
  - 8AM Cortisol after 1mg DM
  - 24-hr urinary free cortisol
  - ACTH
- At baseline:
  - 24 patients had SH [11.6%]
  - 182 patients did not have SH – [88.3%]

Criteria for **Subclinical Hypercortisolism (SH)**:

- 1mg DST Cortisol > 5ug/dL

OR

- Two of the following:
  - ACTH < 10 pg/mL
  - Increase UFC
  - 1mg DST Cortisol >3.0 ug/dL

Morelli V. ***J Clin Endocrinol Metab.*** 2014;99:827

Follow-Up in Adrenal Incidentalomas: An Italian Multicenter Study

- At baseline subclinical hypercortisolism (SH) patients were older (62 vs 59) and showed higher of T2DM (33% vs 17%) and cardiovascular events (21% vs 6%).
- Mean follow up of 82.5 ± 32 months
  - Diameter increased ~ 0.3cm over time
    - 1 cm of more growth was seen in 8.3% of the patients
    - 2.5 cm growth was observed in 2.4% of the patients
  - 15 patients developed SH during follow up. None showed normalization over time.
    - **2.4cm or larger was predictive of SH development**
  - SH patient had higher:
    - New CV events (21% vs. 8.4%)
    - New CV events in CV negative at baseline (10% vs. 6.7%)
    - Increased body weight
    - Worsened BP, glycemic control, and LDL-cholesterol

Morelli V. ***J Clin Endocrinol Metab.*** 2014;99:827

If Surgery is Recommended . . .

European Society of Endocrinology Clinical Practice Guideline
Who should have surgical treatment and how?

- **R 4.1.** We recommend adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess.
- **R 4.2.** We recommend against performing surgery in patients with an asymptomatic, nonfunctioning unilateral adrenal mass and obvious benign features on imaging studies
  - May consider surgery if 4cm or larger, even with benign imaging.
- **R 4.3.** We suggest performing laparoscopic adrenalectomy in patients with unilateral adrenal masses with radiological findings suspicious of malignancy and a diameter **≤6cm**, but without evidence of local invasion
- **R 4.4**. We recommend performing open adrenalectomy for unilateral adrenal masses with radiological findings suspicious of malignancy and signs of local invasion.

Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

AACE Guideline

- **R21.** Open adrenalectomy should be performed if adrenocortical carcinoma (ACC) is suspected

Zeiger MA. ***Endocr Pract*** 2009; Suppl1:1

Follow Up

European Society of Endocrinology Clinical Practice Guideline Indicated Follow-Up if the Adrenal incidentaloma is not Removed?

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

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

Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

Other Guideline

[1]Zeiger MA. ***Endocr Pract*** 2009; Suppl1:1

[2]Lee JM. ***Endocrinol Metab*** 2017;32:200.

- **AACE Guideline**[1]
  - **R2.** Patients with adrenal incidentalomas who do not fulfill the criteria for surgical resection need to have **radiographic reevaluation** at 3 to 6 months and then annually for 1 to 2 years. For all adrenal tumors, **hormonal evaluation** should be performed at the time of diagnosis and then annually for 5 years
- **The Korean Endocrine Society**[2]
  - **R16.** (C) We recommend annual hormone tests for 4 to 5 years to check the functionality of the tumor.
  - **R17.** (C) Follow-up imaging studies to differentiate malignancy are recommended 3 to 6 months after the initial study and continuing for 1 to 2 years. Considering adrenalectomy if the mass enlarges by 1 cm or more and/ or changes its appearance during observation.
    - **When the tumor is less than 2 cm and ≤10 HU, if the tumor does not change in size over a period of more than 1 year, we recommend no further follow-up.**

European Society of Endocrinology Clinical Practice Guideline Indicated Follow-Up if the Adrenal incidentaloma is not Removed?

- **R 5.1**.We suggest **against** further imaging for follow-up in patients with an adrenal mass <4cm with clear benign features on imaging studies
- **R 5.2**.In patients with an **indeterminate** adrenal mass (by imaging) opting not to undergo adrenalectomy following initial assessment, we suggest a repeat noncontrast CT or MRI after **6–12months** to exclude significant growth (⊕OOO).
  - Surgical resection if enlarges >20% & at least a 5mm in maximum diameter
- **R 5.3**.We suggest **against** repeated hormonal work-up in patients with a normal hormonal work-up at initial evaluation unless new clinical signs of endocrine activity appear or there is worsening of comorbidities (e.g. hypertension and type 2 diabetes)
- **R 5.4.** In patients with '**autonomous cortisol secretion**' without signs of overt Cushing's syndrome, we suggest annual clinical reassessment for cortisol excess and comorbidities potentially related to cortisol excess

Fassnacht-M. ***Eur J Endocrinol*** 2016; 175, G1

Pheochromocytoma

Pheochromocytoma

- Prevalence of Pheo in adrenal incidentalomas is ~ 3% (1.1%-11%)
- Evaluation is recommended regardless of normal BP
  - Fifty percent of incidentally discovered pheochromocytoma are normotensive.
- Some authors do not recommend evaluation for PHEO in adrenal incidentalomas if a noncontrast CT attenuation less than or equal to 10 HU[2].
- Pheochromocytomas with HU of 17 and less than 10 have been reported. These are rare exceptions.
  - One was a tumor of 1.5cm, another had medullary hyperplasia in pathology.
  - Measurement technique has been questioned.
- Modest plasma and urine normetanephrine level increases (<4-fold above upper normal limit) in adrenal masses greater than 5 cm are almost always false-positive.

Ioachimescu AG ***Endo and Metab Clinics*** 2015;44:335.

[2]Sane T. ***J Clin Endocrinol Metab.*** 2012; 97: 2077
Hamrahian AH. ***J Clin Endocrinol Metab*** 2005;90:871

Summary/Conclusions

- The incidence of AI is expected to increase because of improved resolution of CT imaging and its use for nonspecific symptoms.
- Noncontrast CT attenuation characteristics of AIs is the most important radiological characteristic to differentiate between benign adenomas, hyperplasia, or cysts and malignant adrenal tumors
- Screening for mild autonomous cortisol excess (subclinical **cortisol)** is indicated in all patients with AIs who do not have typical characteristics of myelolipoma.
  - Catecholamine excess measurement if HU > 10
  - Aldosterone/PRA if hypertension or hypokalemia
- Imaging and biochemical follow up will depend on the imaging phenotype and baseline hormonal determinations.
  - Patient with MACE require further follow especially in the presence of HTN, dysglycemia or vertebral fractures.