ADRENAL INCIDENTALOMAS

Objectives:
Review the prevalence of incidentally identified adrenal masses
Differential diagnosis of an incidentaloma
Functional (biochemical) evaluation of an incidentaloma
Diagnostic Imaging evaluation of an incidentaloma
Follow up and treatment recommendations

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Incidentaloma

• “previously unsuspected adrenal mass that is discovered on an imaging study performed for an unrelated reason.”

• Most times, nonfunctional adrenal cortical adenomas requiring no further treatment, still important clinical concern due to risk of malignancy or hormonal hyperfunction.

Arnaldi G, Endo & Metabolism 2012; 26: 405-419
## Prevalence of incidentalomas by CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Total patients</th>
<th>Scan thickness</th>
<th>Frequency of adrenal mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glazer 1982</td>
<td>2200</td>
<td>NS</td>
<td>0.60%</td>
</tr>
<tr>
<td>Prinz 1982</td>
<td>1423</td>
<td>NS</td>
<td>0.35%</td>
</tr>
<tr>
<td>Abecassis 1985</td>
<td>1459</td>
<td>1-1.5 cm</td>
<td>1.3%</td>
</tr>
<tr>
<td>Belldegrun 1986</td>
<td>12000</td>
<td>1 cm</td>
<td>0.7%</td>
</tr>
<tr>
<td>Kley 1990</td>
<td>2586</td>
<td>NS</td>
<td>0.27%</td>
</tr>
<tr>
<td>Herrera 1991</td>
<td>61054</td>
<td>NS</td>
<td>3.38%</td>
</tr>
<tr>
<td>Bovio 2006</td>
<td>520</td>
<td>0.5 cm</td>
<td>4.4%</td>
</tr>
</tbody>
</table>
Differential Diagnosis:

- Adenoma (functional vs. nonfunctional)
  - Cushing’s (hypercortisolemia - can be subclinical)
  - Conn’s (hyperaldosteronemia)
  - Testosterone secreting
- Pheochromocytoma
- Adrenal cortical carcinoma
- Metastasis from extra-adrenal malignancy
- Myelolipoma/ angiomyelolipoma
- Cyst
- Hematoma
- Ganglioneuroma
Prevalence of incidentaloma in 1004 patients

Non-functional adrenal adenomas (74%)

Functional cortical tumors (11%)

Pheochromocytoma (1.2%)

Adrenal carcinoma (4%)

Other (6%)

Metastasis (0.7%)
Anatomy

**MEDULLA**
- Catecholamines
- Epi and norepi

**CORTEX**
- Mineralocorticoids
- Glucocorticoids
- Androgens
Management of the Clinically Inapparent Adrenal Mass ("Incidentaloma")

Melvin M. Grumbach, MD; Beverly M.K. Biller, MD; Glenn D. Braunstein, MD; Karen K. Campbell; J. Aidan Carney, MD, PhD; Paul A. Godley, MD, MPP; Emily L. Harris, PhD, MPH; Joseph K.T. Lee, MD; Yolanda C. Oertel, MD; Mitchell C. Posner, MD; Janet A. Schlechte, MD; and H. Samuel Wieand, PhD

Table. Take-Home Points

1. All patients with an incidentaloma should have a 1-mg dexamethasone suppression test and measurement of plasma free metanephrines.
2. Patients with hypertension should also undergo measurement of serum potassium and plasma aldosterone concentration/plasma renin activity ratio.
3. A homogeneous mass with a low attenuation value (<10 HU) on computed tomography is suggestive of an adenoma.
4. Surgery should be considered in all patients with functional adrenal cortical tumors that are clinically apparent.
5. All patients with biochemical evidence of phaeochromocytoma should undergo surgery.
6. Corda et al. introduced a non-surgical approach to manage patients with subclinical hyperfunctioning adrenal cortical adenomas.
7. Recommendations for surgery based on tumor size are derived from studies not standardized for inclusion criteria, length of follow-up, or methods of estimating the risk for carcinoma. Nevertheless, patients with tumors >6 cm usually are treated surgically, while those with tumors <4 cm are generally monitored. In patients with tumors between 4 and 6 cm, criteria in addition to size should be considered in the decision to monitor or proceed to adrenalectomy.
INCIDENTALOMA

BENIGN

FUNCTIONAL

NONFUNCTIONAL

SURGERY

MALIGNANT

SURGERY

OBSERVE
Cushing’s Syndrome in the Incidentaloma

Harvey Cushing (1869-1939)
Cushing’s syndrome = state of hypercortisolemia

Cardinal biochemical features:
- Excess endogenous cortisol secretion
- Loss of feedback of HPA axis
- Disturbed circadian rhythm of cortisol secretion

Causes:
- 18% ACTH-independent
- 70% Pituitary dependent (Cushing’s disease)
- 12% Ectopic Cushing’s syndrome
Cushing’s Syndrome

Symptoms
- Weight gain with central obesity
- Moon facies
- Dorsocervical fat pads
- Easy bruising
- Thin skin
- Poor wound healing
- Purple striae
- Emotional and cognitive changes

Signs
- Hypertension
- Osteopenia
- Osteoporosis
- Fasting hyperglycemia
- Diabetes
- Hypokalemia
- Hyperlipidemia
Tests to work up Cushing’s

- **Low-dose dexamethasone suppression test**
  - 1 mg dex po between 11pm-MN
  - Check between 8 and 9am fasting cortisol

- Serum cortisol >5 ug/ dL (138 nmol/L) diagnostic for overt Cushing’s syndrome

- Pros - patient friendly, Sensitivity of 98%

- Cons- number of medications accelerate hepatic metabolism of dexamethasone (reducing its concentration, allowing false positives)
Tests to work up Cushing’s

- 24 hour Urinary Free Cortisol

**PROS**
- Sensitivity 100%, Specificity of 98%
- Not affected by factors that influence corticosteroid binding globulin levels

**CONS**
- Dependent on renal function
- Need to repeat often due to intermittent hypercortisolism
- Not patient friendly

Mengden T, Clin Investig 1992; 70: 545-548
Cushing’s Syndrome (not disease)

- Confirmation of hypercortisolism
- ACTH suppressed
Groups of people who do not completely suppress Cushing’s Syndrome

Subclinical Cushing’s Syndrome (SCS)

Refers to an autonomous cortisol secretion in patients who do not have typical signs and symptoms of hypercortisolism
What if the low dose suppression test is marginally positive?

Confirmatory tests

- Midnight salivary cortisol measurement
- Formal 2-day dexamethasone suppression test
- ACTH levels
Adrenalectomy?

- Cushing’s syndrome – yes

- Subclinical Cushing’s Syndrome – unclear
  - Consider adrenalectomy for:
    - Younger patients (<40)
    - Those with disorders that are attributable to autonomous cortisol secretion (worsening of HTN, DM, obesity, osteoporosis)
Primary Aldosteronism in the Incidentaloma

1% of adrenal incidentalomas are aldosterone-producing adenomas (APA)

Jerome W. Conn (1907-1994)
Renin-Angiotensin-Aldosterone Pathway

Angiotensinogen → Renin

Angiotensin-I → ACE

Angiotensin-II

Aldosterone

Hypokalemia

K+ excretion → Aldosterone → Na+ reabsorption → Metabolic alkalosis

↑ Blood pressure
Board Review

↑Aldosterone  ↓K+  ↑Na+

Hypertension
(usually multidrug)
Types of primary aldosteronism

- Two most common
  - Aldosterone-producing adenoma (APA)
  - Bilateral idiopathic hyperplasia

Screening test for PA in the Setting of Incidentaloma

- Potassium level is not a reliable source

- Tests of choice: serum aldosterone or SA > 300 pg/ml, plasma renin activity PRA ng/ml/h

  serum aldosterone > 15 ng/dl

Seiler L Euro J Endo, 2004; 150: 329-337.
How do we determine subtype?

Adrenal vein sampling

Cortisol adrenal

Cortisol cava

A/C left A/C right

Results of Bilateral Adrenal Venous Sampling

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldosterone (A), ng/dL</th>
<th>Cortisol (C), µg/dL</th>
<th>A/C ratio</th>
<th>Aldosterone ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>R adrenal vein</td>
<td>1,538</td>
<td>940</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>L adrenal vein</td>
<td>8,925</td>
<td>760</td>
<td>11.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>210</td>
<td>37</td>
<td>5.7</td>
<td></td>
</tr>
</tbody>
</table>

*L adrenal vein A/C ratio divided by R adrenal vein A/C ratio.
Adrenal Vein Sampling (AVS) versus CT

Nwariaku et al

- 41 patients with CT and AVS
- AVS successful in 95%
- Concordance between CVS and CT 54%
- CT-based approach would have led to inappropriate therapy in 45% of patients

Downsides?

Androgen secreting tumors
Testosterone biosynthesis

- Cholesterol
  - → Pregnenolone
  - → Progesterone
  - → 17OH-Pregnenolone
  - → 17OH-Progesterone
  - → 11-deoxycortisol
  - → Cortisol

- 17,20-Lyase
  - → Dehydroepiandrosterone
  - → Androstenedione
  - → Testosterone

(occurs outside of the adrenal)
Androgen-secreting tumors

- 3 categories of symptoms:
  - Hirsutism
    - Excessive hair growth in androgen-sensitive body areas (upper lip, chin, chest, areola, linea alba, buttocks, lower back, thighs, genitalia)
  - Virilization
    - Clitoral enlargement, deepening of voice, hair loss, development of masculine somatic characteristics
  - Disruption of normal menstrual cycles

Symptomatology depends on sex and age of presentation
Pheochromocytoma

• Biochemical eval is imperative for all patients with adrenal incidentaloma
  – Even in absence of signs of symptoms
Pheochromocytoma

**Symptoms**
- Palpitations/Forceful heartbeat
- Anxiety
- Sweating
- Sudden onset of headaches
- Pale skin
- Abdominal pain
- Feeling of extreme fright

**Signs**
- Tachycardia
- Severe hypertension/crisis but can also be normotensive or paroxysmal
- Cardiac arrhythmias

Screening

- Either 24hr fractionated catecholamines and urine total metanephrines levels
- OR plasma fractionated metanephrines and normets

- Plasma levels are easier to obtain and are sensitive
  - Levels of 3-4 times normal are diagnostic for pheo

Important!

• Do not biopsy/ perform surgery on an adrenal mass until pheochromocytoma is ruled out

• If pheo is suspected/ confirmed, achieve alpha and beta blockade prior to any procedure
  – Do not biopsy
Adrenal Cortical Carcinoma

- Rare!
- Should be suspected in any pt with large adrenal mass (>6cm) or virilizing features
- Approx 5% of pts with incidentaloma may harbor ACC, true incidence is unclear since abdominal, back or flank pain is indication for imaging in first place

Adrenal Cortical Carcinoma

• Usually 40-50 yrs old
• Present with large abdominal mass
• Poor prognosis
• Should undergo complete biochemical screening since approx. 50% of these lesions are functional
  – Hypercortisolism seen most frequently
  – Can secrete multiple hormones

Nonfunctioning Benign Adrenal Mass

MAJORITY of adrenal incidentalomas
• Adenoma
• Adrenal cyst
• Ganglioneuroma
• Myelolipoma/ angiomyelolipoma

• An asymptomatic, nonfunc, benign-appearing, unilateral adrenal incidentaloma (<4cm) that does not enlarge significantly over time can be followed safely with physical and radiologic examinations.

AACE and AAES guidelines:

- Biochemical screening annually for 2 years
- Repeat CT at 6 and 12mo after detection and then annually for 1-2 years (D/C if the lesion does not increase in size)

- Another recent review suggests that radiologic f/u is not needed when and incidentaloma is Dx as myelolipoma or nonfunc. cyst
- Stable adrenal mass (growth <1cm/year) makes a benign dx very likely

- Adrenalectomy is advised if the mass enlarges by 1cm or more or if autonomous hormonal secretion develops during follow-up
Imaging Evaluation

- Does the patient have old radiographic studies for which to compare???
- CT Scan (enhanced and unenhanced)
  - Myelolipomas- macroscopic fat
  - Hematomas- high density
  - Cysts- fluid density
  - Infectious- coarse calcification
  - ACC- large (>6cm), heterogeneous, sometimes calcs, tumor necrosis, irregular boarders
    - Washout <40%
  - Mets- higher in attenuation, may have irregular borders, other areas of disease
  - Adrenal cortical adenomas contain significant intracellular lipids
    - A signal intensity <10HU on unenhanced imaging is highly indicative
    - Homogenous
    - Washout >40%

Imaging Evaluation

• MRI (with chemical shift sequence)
  – Useful if the lesion type remains indeterminate
  – Benign lesions have greater lipid component than malignant
    • Show loss of signal intensity
    • Malignant lesions maintain similar signal intensities on both imaging sequences

Aid in operative panning when tissue planes are delineated

Imaging Evaluation

• PET/CT
  – Despite lipid-sensitive CT and washout tests, and/or MRI, a small portion of adrenal incidentalomas will remain indeterminate
  – ?Hx of another malignancy, consider PET
  – Some benign lesions show mild FDG avidity so it is not completely discriminatory

Role of Percutaneous Adrenal Biopsy

• Limited
• May result in complications that could increase difficulty of operation
• If malignant, it could seed tumor cells
• If pheo- could ppt a HTN crisis

• Useful if suspected infection or adrenal mets in the setting of other extra-adrenal metastatic disease

When to resect?

• Biochemically functioning tumor
• Lesions that are atypical for benign mass on imaging
  – Larger than 4-5 cm
• Pain/ symptom related

• Most can be resected laparoscopically
  – Absolute contraindication is presence of locally invasive tumor since resection of contiguous structures would be required
  – Consider open approach for any larger primary adrenal cortical tumor (>6cm) given high likelihood of malignancy
    • Avoid tumor spillage

Operative Approach

• Open
• Transabdominal lateral flank laparoscopic
• Retroperitoneoscopic
• Robotic Assisted

• Adherence to oncologic principles is paramount
Retroperitoneoscopic Adrenalectomy

Positioning and Technique

- Ventral rectangular support
- Allow for abdomen to hang freely
Retroperitoneoscopic Adrenalectomy Technique
(Right Posterior Approach)

- CO$_2$ pressure of 24-30 mmHg
- 30° scope placed through medial port
- Dissection proceeds using blunt dissection and harmonic scalpel
Retroperitoneoscopic Adrenalectomy
Evaluation of an incidental adrenal mass

**Imaging (CT) demonstrates isolated adrenal mass**

Evaluate for hormone production
- 24-hr urine collection for VMA, metanephrines, and catecholamines
- 1mg overnight dexamethasone suppression test
- Serum K⁺

Hormonally inactive tumor

Consider enhanced CT/ MRI

Imaging suggests benign

Small tumor (< 4 cm)

Significant comorbidity

Observe

Hormonally active tumor

Imaging suggests malignant or is indeterminate

Large tumor (≥ 4 cm)

No significant comorbidity

Resect
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3. A homogeneous mass with a low attenuation value (<10 HU) on computed tomography is probably a benign adenoma.

4. Surgery should be considered in all patients with functional adrenal cortical tumors that are clinically apparent.

5. All patients with biochemical evidence of pheochromocytoma should undergo surgery.

6. Data are insufficient to indicate the superiority of a surgical or nonsurgical approach to manage patients with subclinical hyperfunctioning adrenal cortical adenomas.

7. Recommendations for surgery based on tumor size are derived from studies not standardized for inclusion criteria, length of follow-up, or methods of estimating the risk for carcinoma. Nevertheless, patients with tumors >6 cm usually are treated surgically, while those with tumors <4 cm are generally monitored. In patients with tumors between 4 and 6 cm, criteria in addition to size should be considered in the decision to monitor or proceed to adrenalectomy.