Adrenal Incidentaloma: Work up and Management

Quan-Yang Duh
Professor of Surgery
University of California, San Francisco

UCSF Postgraduate Course in Endocrine & Breast Surgery
March 6, 2015

No Conflicts to Declare

Surgical Approach to Adrenal Incidentalomas: Objectives

- Work up for incidental adrenal tumors
- Evaluating and treating functioning tumors
  - Pheochromocytoma
  - Hypercortisolism and hyperaldosteronism
- Evaluating and treating adrenal malignancy
  - metastasis
  - adrenocortical cancer
- Techniques and results of adrenalectomy

“Incidentaloma”

“Adrenal incidentalomas are tumours of the adrenal gland that are discovered incidentally when imaging studies are done for purpose other than searching for adrenal pathology.”

1-5% of abdominal imaging studies identify unanticipated adrenal tumor

Geelhoed GW, Druy EM. Surgery 92: 866-874, 1982
Duh QY. Br J Surg 89:1347, 2002
Indications for Adrenalectomy

- Hypersecretion of hormones
- Local symptoms
- Cancers or potential cancers
- Uncertain diagnosis

All adrenalectomy can be performed by laparoscopy EXCEPT…

(Relative) Contraindications for Laparoscopic Adrenalectomy

- Large adrenal tumors
  - What is “large”? > 6-15 cm?
  - > 8 cm for right, > 10 cm for left
- Adrenocortical carcinomas
  - Not for obviously invasive cancers.
  - Start laparoscopic then convert as needed?
- Technical limitations
- Risks of inadequate/inappropriate resection (cancer)

500 Laparoscopic Adrenalectomies
UCSF, 1993 to 2009: Diagnoses

- Hyperaldosteronism  N=161  32%
- Pheochromocytoma   N=117  23%
- Cushing            N=82   16%
- Cortical tumors    N=41   8%
- Metastases         N=42   8%
- Others             N=57  11%

Most Adrenal Incidentalomas are Non-functioning Adenomas

- Patient selection (retrospective, prospective, population based) influences prevalence of incidentaloma
  - 1% at age 30, 4% at age 60, 7% at age 70
- Patient selection also influences the prevalence of surgical disease (e.g., functioning or suspicious tumors)
  - 7-30% of operated, 1-10% of pheos or ACC
**Swedish Prospective Multicenter Study for Adrenal Incidentaloma**

- 381 patients, 33 hospitals, 1996-2001
  - 164 men, 217 women, age 64 (18-84), 3 (1-20) cm
- Operative criteria:
  - > 3-4 cm or hypersecreting hormone
- 85/381 (22%) operated
  - 20 (5%) hypersecreting benign tumors (15 pheos)
  - 14 (4%) malignant (10 adrenal cortical ca)
    - 10 (4-16) cm


**Western Sweden Adrenal Study Group Population: Incidentaloma**

- Population 1.7 millions, 18 months, 19 radiology Depts, consecutive, prospective
- 34,044 scans, 534 assessed (1.6 %)
- 226 pts included, 15 operated (6.6%)
  - 3 aldo, 1 pheo, 1 metastasis
  - 10 non-functioning large adenoma (>3 cm)
  - No additional disease diagnosed at 2 yr f/u


**NIH State-of-the-Science Conference on the Clinically Inapparent Adrenal Mass**

- 1-mg Dex suppression
- Plasma free metanephr
- Resect all pheo, clinical Cushing, aldo and others
- Surgery or observation for subclinical Cushing
- Resect > 6 cm
- Observe < 4 cm
- Q 6 m imaging x 2
- Q y hormonal study x 4


**Biochemical Diagnosis of Pheochromocytoma: Which test is best?**

- Plasma metanephrines
  - Best negative predictive v
    - More false positives
    - Screen familial disease
- Urinary metanephrines
  - Best positive predictive v
    - Fewer false positives
    - All other patients
- (CT/MRI characteristics)

Pheochromocytoma: Localizing Studies

CT                    MRI                    MIBG

Best for surgical planning Malignant or metastatic Planning for I131 Tx

Germ-line Mutations are Common
(not a “10% tumor”, 1/3 hereditary)

- If multifocal, 84%
- If < 18 year-old, 59%
- If Extra-adrenal, 93%

66/271 (24%) of non-syndromic pheo
30 VHL, 13 RET, 11 SDHD, 12 SDHB


Pheochromocytoma Crisis Is Not a Surgical Emergency

- 25/137 (18%) UCSF pheo presented in crisis
  - Alpha-adrenergic blockade at least 10 days
  - 10 urgent, 15 elective, no emergency operation
  - No death
- 33/97 pheo crisis pts had emergency operations
  - Death 6/33 vs 0/64 (emergent vs urgent/elective)
  - Intraop complications 80% vs 42%
  - Postop complications 71% vs 33%


Cushing’s Syndrome: Laboratory Diagnosis

- Low-dose dexamethasone suppression
  - 1 mg dexamethasone PO at 11 PM
  - 8 AM plasma cortisol (nl < 5 mcg/dL vs 1.8)
- Mid-night salivary cortisol level
  - normal < 550 ng/dL
  - 24 hr urine free cortisol
  - nl 5-50 mcg/24 hr
- Plasma ACTH
- “Subclinical Cushing’s”
  - Dexamethasone not suppressible
  - Post resection Addisonian crisis

Central obesity
Moon facies
Supraclavicular fat pad
Purple Striae

Incidentaloma with Subclinical Cushing’s 
Resect or Observe?
- Randomized, 45 patients, 7.7 (2-15) years, Padua.
- Incidentaloma < 3.5 cm, no overt disease, but abnormal Dex-suppression.
- 23 Lap adrenalectomy
  - Diabetes: 62.5% (5/8) normalized or improved
  - Hypertension: 67% (12/18)
  - Hyperlipidemia: 37.5% (3/8)
  - Obesity: 50% (3/6)
  - Osteoporosis did not improve.
- 22 Non-surgical: No improvement
  - 3 crossed over to adrenalectomy (tumor grew to > 3.5 cm)


Aldosteronoma: CT scan
- 1-2 cm
- No contralateral abnl
- Adrenal protocol
  - Without and with contrast
  - Thin cut (2.5 mm or less)
- Low Hounsfield U
  - < 10 pre-contrast
- Early washout of contrast

Laboratory Diagnosis: 1° hyperaldo
- High plasma aldosterone (PA)
  - > 20 ng/dL (adenoma), 12-20 (hyperplasia)
  - off meds (spironolactone, diuretic, ACE inhibitors, etc)
  - on high salt diet (>120 mEq/d x 4d)
- Low plasma renin activity (PRA)
  - < 0.5 ng/ml/hr
- High PA/PRA ratio (> 20-30)
  - Adenomas higher (25-100), hyperplasia (15-25)
- Elevated 24 hour urinary aldosterone
  - Less commonly used

Role of Adrenal Vein Sampling
- If relying on CT scan alone
  - 22% would have been exclude for adrenalectomy (bilateral normal or bilateral nodular)
  - 25% would have unnecessary or inappropriate (wrong side) adrenalectomy
- “AVS is an essential diagnostic step in most patients to distinguish between unilateral and bilateral adrenal aldosterone hypersecretion”

WF Young, et al. Surgery 136:1227, 2004
A Clinical Prediction Score to Diagnose Unilateral Primary Aldosteronism

- 100% specific for APA if typical adenoma >0.8 cm and K < 3.5 or Cr Clr >100

**TABLE 3. Clinical prediction score to predict lateralized AVS (higher score indicates higher probability of lateralized AVS)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Conn’s adenoma on imaging</td>
<td>2</td>
</tr>
<tr>
<td>Hypokalemia &lt;3.5 mmmol/L</td>
<td>2</td>
</tr>
<tr>
<td>eGFR (MDRD) (mL/min/1.73 m²)</td>
<td>1</td>
</tr>
<tr>
<td>&lt;80</td>
<td>0</td>
</tr>
<tr>
<td>80 to 100</td>
<td>1</td>
</tr>
<tr>
<td>≥100</td>
<td>2</td>
</tr>
</tbody>
</table>

Total score (maximum 7)


Incidentaloma: Avoid FNA

- 14 complications
- 6 hematoma
- 5 incorrect dx
- 2 recurrences

Vanderveen KA, et al (Thompson GB), Surgery; 2009; 146:1158-66

Adrenal Incidentaloma as Presentation of Unknown Primary Cancer is very Rare

- Retrospective review 1715 patients referred for evaluation of suspected unknown primary cancer, 1639 had cancer.
- Adrenal involved at presentation in 95 (5.8%).
- Involved only adrenal in 4 patients (0.2%).
- All large (> 6 cm), symptomatic, 3/4 bilateral.
- NO TURE INCIDENTALOMA


Resection for Isolated Adrenal Metastasis

- MSK 1995-2006
- Median survival 30 months
- 17% local recurrence
- 31 lap vs. 63 open
  - Op time: 175 min vs. 208 min
  - EBL: 106 ml vs 749 ml
  - Hosp: 2.8 d vs. 8.0 d
  - Fewer complications

Duh QY. Ann Surg Oncol 14:3288, 2007
Adrenocortical Carcinoma: Imaging
- Central necrosis
- Irregularity
- HU > 20
- Invasion (liver, IVC)

Is size the best Predictor for the risk of Adrenal Cortical Cancer?
- CT findings
- Cortical adenoma
  - Homogeneous
  - Pre-contrast < 10 HU
  - Rapid wash-out
- Carcinoma, mets, pheochromocytoma
  - Heterogeneous
  - Pre-contrast > 20 HU
  - Slow wash-out


Laparoscopic compared to Open Adrenalectomy: more positive margin and tumor rupture, earlier recurrence

<table>
<thead>
<tr>
<th></th>
<th>Open (71 patients)</th>
<th>Laparoscopic (17 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall recurrence—any site*</td>
<td>65%</td>
<td>63%</td>
</tr>
<tr>
<td>Local/Tumor bed</td>
<td>20%</td>
<td>25% (p = 0.23)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>11%</td>
<td>18% (p = 0.22)</td>
</tr>
<tr>
<td>Distant</td>
<td>49%</td>
<td>24% (p = 0.03)</td>
</tr>
<tr>
<td>% Positive margins or intraoperative tumor rupture</td>
<td>18%</td>
<td>50% (p = 0.01)</td>
</tr>
<tr>
<td>Time to local recurrence (mos)</td>
<td>19.2 (±37.5)</td>
<td>9.6 (±14) (p &lt; 0.005)</td>
</tr>
<tr>
<td>Additional surgery performed for recurrence</td>
<td>31%</td>
<td>29.4%</td>
</tr>
</tbody>
</table>


Laparoscopic Adrenalectomy: Size Matters (UCSF, 1993-2011)
- 523 patients, 563 adrenalectomies
  - Aldo180, pheo 123, Cushing 85, mets 44, others 91
- Smaller (< 3 cm) vs Larger (≥ 3 cm) tumors
  - op time 2.29 hr vs 3.07 hr
  - EBL 44 ml vs 97 ml
  - Intraop complication 2% vs 10%
  - Postop complications 14% vs 24 %
  - Hospital stay 1.6 days vs 2.5 days
Bilateral Incidentalomas

- 15-20% of incidentalomas
- 4 times more likely to have subclinical Cushing
- 4 times less likely to have Pheos


Management of Adrenal Incidentalomas

- Work up of adrenal tumors
  - R/O pheo (metanephrines), Cushing (Dex-sup.)
  - no FNA
- When to operate
  - Functioning tumors, isolated metastases
  - Large (> 5-6 cm) and increased risk of cancer
- How to operate
  - Laparoscopic (retroperitoneal vs transabdominal)
  - Open resection for cancer