Pheochromocytoma

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Nothing to Disclose

Dr. McIntyre does not have any relevant commercial financial relationships to report.
Pheochromocytoma

- When to suspect
- How to screen
- How to localize
- How to treat
Pheochromocytoma

- 2004 WHO classification of endocrine tumors
- Pheochromocytoma: tumor of catecholamine producing chromaffin cells of the adrenal medulla
- Tumors of extra-adrenal sympathetic and parasympathetic paraganglia are classified as paraganglioma
- Parasympathetic tissue (H&N paraganglioma) rarely produce significant catecholamines
Pheochromocytoma

• Frequently sought, rarely found
• When diagnosed and properly treated, it is curable
• When undiagnosed and not properly treated it can be fatal
Pheochromocytoma

Prevalence

- Olmsted County, MN 1-2 / 100,000
- Biochemical screening 2476 people: 1.9%
- Autopsy series Australia 1 / 2301

- Men=Women
- 3rd to 5th decades
- Usually paroxysmal symptoms

Pheochromocytoma

When to suspect

- 5 “Ps” of paroxysm
  - Pressure - HTN
  - Pain - HA
  - Perspiration - profuse
  - Palpitation
  - Pallor

- Diverse manifestations
- Variation in hormones
- Variation in sensitivities
- No correlation between symptoms (even HTN) and levels
- Often not considered
Pheochromocytoma

When to suspect

• HTN
  – Paroxysmal 50%
  – Persistent 30%
  – Normal 20%

• Triad
  – HA, Sweating, Tachycardia in a HTN pt
  – Sensitivity 90.9%
  – Specificity 93.8%

Crout et al J Clin Invest 1964
Pheochromocytoma

When to screen

• Hyperadrenergic spells
• Resistant HTN
• Familial disorder (MEN2, VHL, SDH, NF-I)
• Family History
• Incidentaloma
• Pressor response to anesthesia
• HTN < 20 years old
• Dilated cardiomyopathy
Genetics
5 genes

- MEN 2: Ret proto-oncogene (RET)
- Von Hippel-Lindau (VHL)
- Neurofibromatosis type I (NF I)
- Succinate dehydrogenase
  - Subunits D (SDHD) and B (SHDB)
- SDHC
  - Parasympathetic paragangliomas
## Frequency of Genetic Mutations

### Nonfamilial

<table>
<thead>
<tr>
<th>Gene (%)</th>
<th>Germany and Poland</th>
<th>Holland</th>
<th>France</th>
<th>Spain</th>
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<tr>
<td>VHL</td>
<td>11</td>
<td>4.4</td>
<td>3.5</td>
<td>6</td>
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<tr>
<td>SDHB</td>
<td>4</td>
<td>1.5</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>SDHD</td>
<td>4</td>
<td>1.6</td>
<td>0.8</td>
<td>10</td>
</tr>
<tr>
<td>RET</td>
<td>5</td>
<td>0</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>23</strong></td>
<td><strong>7.5</strong></td>
<td><strong>11.5</strong></td>
<td><strong>27</strong></td>
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</tbody>
</table>
First International Symposium on Pheochromocytoma

• There is now a reasonable argument for more widespread genetic testing,
• It is neither appropriate nor currently cost-effective to test for every disease-causing gene in every patient with a pheochromocytoma or paraganglioma
• The decision to test, and which genes to test, requires judicious consideration of numerous factors
Algorithm for genetic testing for genes associated with pheochromocytoma

First International Symposium on Pheochromocytoma (ISP)
2005, Bethesda, MD, USA
Pheochromocytoma

When to screen

![Graph showing the relationship between suspicion, symptoms, and pretest probability for pheochromocytoma.

- **Suspicion**:
  - High
  - Low

- **Symptoms**:
  - Low HU
  - High HU

- **Pretest Probability**:
  - Pallor spells
  - New HTN
  - Flushing Spells

- Incidentaloma
  - High HU
  - Low HU
Which Test?

• Institutional bias
• Catecholamines can be metabolized within chromaffin cells and released as metanephrines (or normetanephrines) independently of catecholamines which can occur at low rates
Which Test?

- Fractionated metanephrines
  - Urine (conjugated)
  - or plasma (free)
  - or both (lab expertise)
  - No consensus

- Not rely on binary testing
  - Continuous result
  - Trade off sensitivity and specificity

Pheochromocytoma

Mayo Clinic test stratification

- 24 – hr urine metanephrines & catecholamines
  - Sensitivity 98% (sporadic) 90% (inc syndromic)
  - Specificity 98%
  - Sporadic

- Fractionated plasma free metanephrines
  - Sensitivity 97-100% (inc syndromic)
  - Specificity 85-89%
  - Syndromic

Total met > 1000 mcg
Nmet > 900 mcg, Met > 400 mcg
& or > 2x normal NE, Epi, Dopa

Kudva et al JCEM 2003
Perry et al Clin Endocrinol 2007
Sawka et al JCEM 2003
Lenders et al JAMA 2002
Pheochromocytoma
*Mayo Clinic test stratification*

- 24 hr urine
  - Sporadic
  - Low probability symptoms
  - Older HTN pts

- Plasma free metanephrines
  - Unable to get 24 hr urine
  - 24 hr urine inconclusive
  - High suspicion:
    - PHx/FHx
    - MEN, VHL, SDH, NF-I

Kudva et al JCEM 2003
Pheochromocytoma
*False positive*

- Tricyclic antidepressants
- Levodopa
- Ethanol
- Withdrawl (esp clonidine)
- Antipsychotics
- Major stress
- Sleep apnea
Pheochromocytoma
Pathophysiology Traditional View

• Circulating catecholamines
• Sympathetic nervous system normal or depressed
Pheochromocytoma

Pathophysiology

• However, blood pressure does not correlate with circulating catecholamines
• BP can be normal with high catechol levels
• SNS intact
• Clonidine is effective despite maintaining high circulating levels
Pheochromocytoma
Pathophysiology

Chlorisondamine

Bretylium

Johnson et al J Pharm Exp Ther 1983
Pheochromocytoma
Pathophysiology

Sympathetic Nerve Impulse

Johnson et al J Pharm Exp Ther 1983
## Pathophysiology

<table>
<thead>
<tr>
<th></th>
<th>Control (early)</th>
<th>Pheo (early)</th>
<th>Control (late)</th>
<th>Pheo (late)</th>
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<tr>
<td><strong>Intact anesthetized rats</strong></td>
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<tr>
<td>SBP</td>
<td>106+-5</td>
<td>175+-10*</td>
<td>116+-4</td>
<td>202+-15*δ</td>
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<tr>
<td>DBP</td>
<td>67+-4</td>
<td>93+-9*</td>
<td>70+-3</td>
<td>127+-11*δ</td>
</tr>
<tr>
<td>HR</td>
<td>337+-7</td>
<td>470+-12*</td>
<td>345+-5</td>
<td>510+-13*</td>
</tr>
<tr>
<td><strong>Pithed rats</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>68+-4</td>
<td>114+-5*</td>
<td>73+-2</td>
<td>115+-8*</td>
</tr>
<tr>
<td>DBP</td>
<td>41+-2</td>
<td>42+-2</td>
<td>43+-2</td>
<td>50+-2*δ</td>
</tr>
<tr>
<td>HR</td>
<td>330+-5</td>
<td>466+-7*</td>
<td>336+-6</td>
<td>506+-14*</td>
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<tr>
<td><strong>Pithed rats (after phentolamine)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>67+-2</td>
<td>70+-3</td>
<td>68+-2</td>
<td>74+-4</td>
</tr>
<tr>
<td>DBP</td>
<td>40+-2</td>
<td>31+-1*</td>
<td>42+-2</td>
<td>34+-2*</td>
</tr>
<tr>
<td>HR</td>
<td>328+-12</td>
<td>448+-17</td>
<td>330+-10</td>
<td>487+-19</td>
</tr>
</tbody>
</table>

Tsujimoto et al, Circ Res 1987
Pheochromocytoma

Pathophysiology

- Loading of sympathetic vesicles with catecholamine
- Increase sympathetic neuronal impulse frequency
- Selective desensitization of presynaptic $\alpha_2$ adrenergic receptors which inhibit release of NE

Langer et al Hypertension 1980
Pheochromocytoma

Pathophysiology

• Direct or reflexive stimuli of SNS activity releases excessive NE stores causing hypertensive crisis.
Pheochromocytoma
Pathophysiology

• Other mediators
  – Neuropeptide Y
    • Indirect cardiovascular effects = potentiates NE action
    • Direct effects = vasoconstriction, resistant to α blockade
Pheochromocytoma

**Pathophysiology**

- Catecholamines may be high or low and BP does not correlate
- SNS hyper-reactive leading to spells
- Other mediators
Surgical Endocrinology

- Never do a localization study before a biochemical diagnosis
Pheochromocytoma Localization

• Adrenal and abdominal imaging (MRI = or > CTS, institutional bias) is first test

• Paragangliomas
  – Superior abdominal para-aortic (46%)
  – Inferior abdominal para-aortic (39%)
  – Bladder (10%)
  – Thorax (10%)
  – H & N (3%)
  – Pelvis (2%)

Whalen et al J Urol 1992; Erickson et al 2001
Pheochromocytoma

Localization

- Unilateral adrenal pheochromocytoma
  - No need for $^{123}$I MIBG

- Paraganglioma
  - $^{123}$I MIBG

- Negative abdominal imaging
  - H&N and chest imaging
    - $^{123}$I MIBG

- SRS Indium 111 pentreotide

- FDG-PET
**Pheochromocytoma Algorithm**

1. Discontinue interfering medications
   - Clinical suspicion (Pretest probability)
     - High: 24-h urine Fractionated metanephrines
     - Low: 24-h urine Fractionated metanephrines
2. Normal: Recheck during a spell
   - Normal: Investigate other causes of spells
3. >2-fold elevation above upper limit of nl in urine catecholamines or ↑ urine metanephrines (Nmet >900 µg or Met >400 µg) or "significant increase" in fractionated plasma mets
   - Normal: Localization: Adrenal/abdominal MRI or CT scan
     - Typical adrenal or para-aortic mass
     - ¹²³I-MIBG scan if:
       - >10-cm adrenal mass
       - Paraganglioma
4. Reassess the diagnosis
   - Consider:
     - ¹²³I-MIBG scan
     - In-III pentetetide scan
     - Whole body MRI scan
     - PET scan
   - Tumor found
   - Consider genetic testing
     - Preoperative α- & β-adrenergic blockade
     - Surgical resection
Pheochromocytoma

Preoperative Blockade

• Manage hypertension
• Control cardiac symptoms
• Decrease perioperative morbidity and mortality
• Phenoxybenzamine – nonspecific α blockade
• Hypertensive crisis occur with or without α blockade
Pheochromocytoma

Preoperative Preparation

- 113 patients Cleveland Clinic 1977 to 1994
- 92 adrenal and 21 extra-adrenal tumors
- 12 syndromic
- Saline expansion 3 hours before surgery

Urlacher et al J Urol 1999
## Preoperative Preparation

<table>
<thead>
<tr>
<th>Preoperative antihypertensive medications</th>
<th>Overall %</th>
<th>1990-1994 %</th>
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<tbody>
<tr>
<td>Ca channel blockade</td>
<td>26</td>
<td>45</td>
</tr>
<tr>
<td>Selective α blockade*</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>β blockers**</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>10</td>
<td>5</td>
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<tr>
<td>No medications</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

*(prazosin, doxazosin, terazosin)

Urlacher et al J Urol 1999
## Pheochromocytoma

*Preparation v No preparation*

<table>
<thead>
<tr>
<th></th>
<th>No Medications</th>
<th>Medications</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Systolic max. (mm. Hg)</td>
<td>198</td>
<td>192</td>
<td>0.40</td>
</tr>
<tr>
<td>Systolic min. (mm. Hg)</td>
<td>99</td>
<td>102</td>
<td>0.39</td>
</tr>
<tr>
<td>Diastolic max. (mm. Hg)</td>
<td>104</td>
<td>106</td>
<td>0.62</td>
</tr>
<tr>
<td>Diastolic min. (mm. Hg)</td>
<td>56</td>
<td>58</td>
<td>0.45</td>
</tr>
<tr>
<td>Intraop. fluids (cc)</td>
<td>5,536</td>
<td>6,492</td>
<td>0.08</td>
</tr>
<tr>
<td>Postop. day 1 fluids (cc)</td>
<td>3,387</td>
<td>3,866</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Urlscher et al J Urol 1999
Pheochromocytoma: State of the Art

- These studies suggest that the need for the use of POB or other drugs that produce profound and long-lasting blockade in preparing pheochromocytoma patients for the surgical removal of the tumor is no longer necessary.

- This is, in large part, attributable to advances in anesthetic and monitoring techniques and the availability of fast-acting drugs capable of correcting sudden changes in cardiovascular hemodynamics.

Bravo and Tagle JCEM 2003
Pheochromocytoma

Preoperative Blockade

• First International Symposium on Pheochromocytoma
  – all patients should receive appropriate preoperative medical management to block the effects of released catecholamines
  – Wide-ranging practices, international differences in available or approved therapies, and a scarcity of evidence-based studies comparing different therapies leads to a lack of consensus regarding the recommended drugs for preoperative blockade.

Pheochromocytoma

Preoperative Blockade

• $\alpha$-adrenoceptor antagonists, calcium channel blockers, or angiotensin receptor blockers

• For tachyarrhythmias, $\beta$-adrenoceptor or calcium channel blockers.

• $\beta$-adrenoeceptor blockers should be used only after adequate pretreatment with $\alpha$-adrenoceptor antagonists to avoid hypertensive crisis from unopposed $\alpha$-adrenoceptor overstimulation.

Pheochromocytoma

**Preoperative Preparation**

- 105 patients 1991 2002 at Lille's University Hospital
- Oral nicardipine (20–60 mg.day$^{-1}$ as TID). Preparation 3 days in normotensive vs 7-10 days in others
- 1 hour preop oral dose 20 mg
- OR: infusion of nicardipine at 0.5–2.0 μg.kg$^{-1}$.min$^{-1}$

Lebuffe et al Anaesthesia 2005
<table>
<thead>
<tr>
<th>Peri-operative complications</th>
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<tbody>
<tr>
<td>Transient hypertension</td>
<td>65 (61.9)</td>
</tr>
<tr>
<td>SBP &gt; 160 mmHg</td>
<td>65 (61.9)</td>
</tr>
<tr>
<td>SBP &gt; 180 mmHg</td>
<td>47 (44.8)</td>
</tr>
<tr>
<td>SBP &gt; 200 mmHg</td>
<td>27 (25.7)</td>
</tr>
<tr>
<td>SBP &gt; 220 mmHg</td>
<td>14 (13.3)</td>
</tr>
<tr>
<td>Persistent hypertension</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Tachycardia event</td>
<td>30 (28.5)</td>
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<tr>
<td>Sustained hypotension</td>
<td>13 (12.4)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.9)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative complications</th>
<th>9.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Prolonged mechanical ventilation</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Non septic hyperthermia</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>ICU; days Median (range)</td>
<td>1 (0–7)</td>
</tr>
<tr>
<td>Hosp LOS Median (range)</td>
<td>10 (2–35)</td>
</tr>
</tbody>
</table>

Lebuffe et al Anaesthesia 2005
Pheochromocytoma

Hemodynamic Instability during Surgery

73 patients Erasmus Medical Center 1995-2007
Pretreatment $\alpha$ blockade (PXB or DOX)
48 of 73 (66%) MAP $\leq$ 100 mm Hg
39 of 48 (81%) BP $\leq$ 130/85 mm Hg
25 of 73 (34%) MAP $>$ 100 mm Hg
Adequate BP achieved 55% (PXB) and 53% (DOX) of patients

Bruynzeel et al JCEM 2010
Pheochromocytoma

Hemodynamic Instability during Surgery

Intraoperative time SBP above 160 mm Hg
MAP response to blockade
plasma norepinephrine levels \(r = 0.23; P < 0.05\),
tumor diameter \(r = 0.36; P < 0.01\),
postural BP fall \(r = 0.30; P < 0.05\)

Bruynzeel et al JCEM 2010
Pheochromocytoma

Hemodynamic Instability during Surgery

- Postoperative MAP was significantly higher PXB vs DOX ($P < 0.01$).
- No relation between the PXB or DOX dosage and intraoperative BP fluctuations or postoperative hypotension.
- The doses of esmolol (25 patients) were significantly higher in the PXB group compared with the DOX group (314.5 mg, 25.0–5520; vs. 95.0 mg, 0.06–2500 mg; $P < 0.05$).
- Other vasoactive drugs as phenylephrine ($n = 15$), nitroglycerine ($n = 24$), NE ($n = 36$), and phentolamine ($n = 28$) did not differ between both groups.

Bruynzeel et al JCEM 2010
Comparison of Two Preoperative Strategies

- Retrospective chart review of 50 Mayo Clinic patients and 37 Cleveland Clinic patients
- Mayo Clinic predominantly used the long-lasting nonselective $\alpha_{1,2}$ antagonist phenoxybenzamine, and Cleveland Clinic predominately used selective $\alpha_1$ blockade.

Weingarten et al Urology 2010
Comparison of Two Preoperative Strategies

<table>
<thead>
<tr>
<th></th>
<th>Mayo Clinic (50)</th>
<th>Cleveland Clinic (37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoxybenzamine</td>
<td>98</td>
<td>16</td>
</tr>
<tr>
<td>β blockade</td>
<td>78</td>
<td>46</td>
</tr>
<tr>
<td>CCB</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>$\alpha_1$ Adrenergic blockade</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Metyrosine</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Oral NaCl</td>
<td>60</td>
<td>89</td>
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<tr>
<td>IV Hydration</td>
<td>8</td>
<td>0</td>
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</table>

Weingarten et al Urology 2010
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mayo Clinic (50)</th>
<th>Cleveland Clinic (37)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Anesthetic (min)</td>
<td>201 ± 43</td>
<td>306 ± 185</td>
<td>&lt;.001</td>
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<tr>
<td>Arterial line</td>
<td>50 (100.0)</td>
<td>37 (100.0)</td>
<td>.425</td>
</tr>
<tr>
<td><strong>Central line</strong></td>
<td><strong>15 (30.0)</strong></td>
<td><strong>22 (59.5)</strong></td>
<td><strong>.008</strong></td>
</tr>
<tr>
<td>PAC</td>
<td>4 (8.0)</td>
<td>9 (24.3)</td>
<td>.065</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>31 (62.0)</td>
<td>25 (67.6)</td>
<td>.592</td>
</tr>
<tr>
<td><strong>Nitroglycerin</strong></td>
<td><strong>1 (2.0)</strong></td>
<td><strong>17 (46.0)</strong></td>
<td><strong>&lt;.001</strong></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>26 (52.0)</td>
<td>10 (27.0)</td>
<td>.027</td>
</tr>
<tr>
<td>α/β-Blocker (labetalol)</td>
<td>12 (24.0)</td>
<td>15 (40.5)</td>
<td>.109</td>
</tr>
<tr>
<td>CCB</td>
<td>0 (0.0)</td>
<td>3 (8.1)</td>
<td>.073</td>
</tr>
<tr>
<td><strong>Phenylephrine</strong></td>
<td><strong>28 (56.0)</strong></td>
<td><strong>10 (27.0)</strong></td>
<td><strong>.009</strong></td>
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<tr>
<td>Dopamine</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td>1.00</td>
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<tr>
<td>Epinephrine</td>
<td>2 (4.0)</td>
<td>1 (2.7)</td>
<td>1.00</td>
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<tr>
<td>Norepinephrine</td>
<td>1 (2.0)</td>
<td>1 (2.7)</td>
<td>1.00</td>
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Weingarten et al. Urology 2010
<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Mayo Clinic (50)</th>
<th>Cleveland Clinic (37)</th>
<th>P Value</th>
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<tr>
<td>Greatest BP</td>
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<tr>
<td>Systolic BP</td>
<td>187 ± 30</td>
<td>209 ± 44</td>
<td>.011</td>
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<tr>
<td>Mean BP</td>
<td>136 ± 20</td>
<td>151 ± 30</td>
<td>.004</td>
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<tr>
<td>Diastolic BP</td>
<td>109 ± 18</td>
<td>114 ± 26</td>
<td>.294</td>
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<tr>
<td>Systolic BP ≥30% baseline (min)</td>
<td>2 (0–11)</td>
<td>5 (0–22)</td>
<td>.119</td>
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<tr>
<td>Systolic BP ≥200 mm Hg (min)</td>
<td>0 (0–2)</td>
<td>0 (0–7)</td>
<td>.071</td>
</tr>
<tr>
<td>Lowest BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>73 ± 14</td>
<td>78 ± 15</td>
<td>.159</td>
</tr>
<tr>
<td>Mean BP</td>
<td>55 ± 11</td>
<td>56 ± 10</td>
<td>.870</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>46 ± 9</td>
<td>43 ± 9</td>
<td>.191</td>
</tr>
<tr>
<td>Systolic BP ≤30% baseline, min</td>
<td>28 (6–62)</td>
<td>13 (3–49)</td>
<td>.114</td>
</tr>
<tr>
<td><strong>Systolic BP ≤30% baseline (% anesthesia time)</strong></td>
<td><strong>15.7 (3.3–24.9)</strong></td>
<td><strong>5.1 (0.9–16.0)</strong></td>
<td><strong>.026</strong></td>
</tr>
</tbody>
</table>
Comparison of Two Preoperative Strategies

<table>
<thead>
<tr>
<th>%</th>
<th>Mayo Clinic (50)</th>
<th>Cleveland Clinic (37)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>EBL (mL)</td>
<td>75 (25–150)</td>
<td>100 (82–250)</td>
<td>.010</td>
</tr>
<tr>
<td>Intraoperative crystalloid (L)</td>
<td>3.0 (2.0–3.1)</td>
<td>5.0 (3.4–6.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intraoperative colloid (L)</td>
<td>0 (0–0)</td>
<td>1.00 (0.5–1.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Weingarten et al Urology 2010
Comparison of Two Preoperative Strategies

- Noncompetitive α-adrenergic antagonist phenoxybenzamine appeared to produce better attenuation of intraoperative hypertension
- But at the cost of longer lasting intraoperative hypotension that required a greater use of vasopressors.
Adrenalectomy

- Open anterior
- Thoraco-abdominal
- Flank
- Posterior
- Laparoscopic
- Retroperitoneoscopic
### Open v Laparoscopy
**PRT University of Brescia**

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with hypertensive peaks</td>
<td>3/9</td>
</tr>
<tr>
<td>Hypertensive peaks/pts</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Blood loss, cc</strong></td>
<td><strong>164 ± 94</strong></td>
</tr>
<tr>
<td>Mean operative time, min (range)</td>
<td>180 (120–230)</td>
</tr>
<tr>
<td><strong>Mean hospital stay, days</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

Tiberio et al Surg Endosc 2008
## Open v Laparoscopy

*Mt Sinai New York*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laparoscopic (11)</th>
<th>Open(11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative Hypertension</td>
<td>11</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative Hypotension</td>
<td>4</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Duration</td>
<td>146±36</td>
<td>153±55</td>
<td>NS</td>
</tr>
<tr>
<td>LOS</td>
<td>5.5±2.2</td>
<td>6.1±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Complications</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Inabnet et al W J Surg 2000
Surgical Technique

• Type
• Size
• Site
• Hereditary

• Adrenal cortex sparing
  • Prevent permanent glucocorticoid deficiency
  • Risk of tumor recurrence
Pathology

- 2004 WHO defines malignancy as metastasis not invasion
- Invasion is poor predictor of metastasis
- Lack of invasion does not preclude metastasis
- Several scoring systems
- No consensus
Pathology

- Extra-adrenal
- Course nodularity
- Confluent necrosis
- Hyaline globules
- Size

Linnoila et al. Hum Pathol 1990
Kimura et al. Endocr Pathol 2005
Pheochromocytoma of the Adrenal Gland Scaled Score (PASS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score if present (no. of points assigned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large nests or diffuse growth</td>
<td>2</td>
</tr>
<tr>
<td>(&gt;10% of tumor volume)</td>
<td></td>
</tr>
<tr>
<td>Central (middle of large nests)</td>
<td>2</td>
</tr>
<tr>
<td>or confluent tumor necrosis</td>
<td></td>
</tr>
<tr>
<td>(not degenerative change)</td>
<td></td>
</tr>
<tr>
<td>High cellularity</td>
<td>2</td>
</tr>
<tr>
<td>Cellular monotony</td>
<td>2</td>
</tr>
<tr>
<td>Tumor cel spindling (even if focal)</td>
<td>2</td>
</tr>
<tr>
<td>Mitotic figures &gt;3/10 HPF</td>
<td>2</td>
</tr>
<tr>
<td>Atypical mitotic figure(s)</td>
<td>2</td>
</tr>
<tr>
<td>Extension into adipose tissue</td>
<td>2</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>1</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>1</td>
</tr>
<tr>
<td>Profound nuclear pleomorphism</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear hyperchromasia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

HPF = high-power field.

- PASS of >=4 correctly identified all tumors that were histologically malignant,
- 17 of the 50 patients did not develop malignant clinical behavior.
- All of the patients who had clinically aggressive neoplasms were identified by a PASS of >=4.

Sensitive but not specific
Immunohistochemistry

nuclear pleomorphism

Spindle cell

Ki67 immunohistochemistry
Risk of Recurrence

Hôpital Européen Georges Pompidou, Paris, France
1975-2003

29/176 at risk = 16% over 9 years

Amar et al JCEM 2005
### Hazard ratios for the risk of recurrence

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>P value</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, per yr</strong></td>
<td>–0.008</td>
<td>0.015</td>
<td>0.602</td>
<td>0.992</td>
<td>0.963–1.022</td>
</tr>
<tr>
<td>Familial vs. sporadic</td>
<td>1.235</td>
<td>0.523</td>
<td>0.018</td>
<td>3.437</td>
<td>1.234–9.584</td>
</tr>
<tr>
<td>Bilateral vs. left adrenal</td>
<td>0.351</td>
<td>1.152</td>
<td>0.760</td>
<td>1.421</td>
<td>0.149–13.58</td>
</tr>
<tr>
<td>Right vs. left adrenal</td>
<td>1.127</td>
<td>0.760</td>
<td>0.138</td>
<td>3.085</td>
<td>0.696–13.69</td>
</tr>
<tr>
<td>Extraadrenal vs. left adrenal</td>
<td>2.420</td>
<td>0.828</td>
<td>0.003</td>
<td>11.24</td>
<td>2.219–56.99</td>
</tr>
<tr>
<td>Tumor diameter, per cm</td>
<td>0.140</td>
<td>0.058</td>
<td>0.015</td>
<td>1.150</td>
<td>1.027–1.289</td>
</tr>
</tbody>
</table>

Amar et al JCEM 2005
Follow up testing

• No consensus

• Yearly
Metastatic Pheochromocytoma

- Options limited, no cure
- Debulking palliates symptoms but no survival advantage
- RFA lesions
- EBRT: bone metastasis
Metastatic Pheochromocytoma

- Chemotherapy: cyclophosphamide, vincristin, dacarbazine (CVD)
  - 50% tumor shrinkage = improved symptoms
  - Short lived, no survival advantage
- \( ^{131}I \) Labeled MIBG

Huang et al. Cancer 2008
Targeted Therapies

- Vascular endothelial growth factor (VEGF),
- Endothelin receptor type A and B,
- Telomerase complex,
- Heat shock protein 90 (HSP90)
- Cyclo-oxygenase and
- N-cadherin

- VEGF-inhibitor
  - thalidomide with temozolomide
- Tyrosine kinase inhibitors
  - Sunitinib
  - Sorafenib
  - Imatinib mesylate
- mTOR
  - Everolimus
Future Direction

• Distinct
  – Phenotypes
  – Neurochemistry
  – Histopathology

Eisenhofer et al Endocrine-Related Cancer 2004
Chris Raeburn
Proteomic Hypothesis:

• Distinct phenotypic profiles of patients with pheochromocytoma derive from distinct pathogenesis due to protein expression

• Distinct tumors arise from different cell origins
Questions?