## Types: Endometrial Cancers

<table>
<thead>
<tr>
<th>Feature</th>
<th>Endometrioid</th>
<th>Non-Endometrioid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histotype</strong></td>
<td><strong>Endometrioid, Secretory, Squamous</strong></td>
<td><strong>Serous, Clear cell, Carcinosarcoma</strong></td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td><strong>Indolent</strong></td>
<td><strong>Aggressive</strong></td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td><strong>Hormonal</strong></td>
<td><strong>None</strong></td>
</tr>
<tr>
<td><strong>Precursor</strong></td>
<td>“Hyperplasia”</td>
<td><strong>Serous EIC</strong></td>
</tr>
</tbody>
</table>
Retrospective Studies (Hertig, 1949)

Time from old biopsies to CA Interval Finding

> 15 yr Normal
> 6 yr Cystic hyperplasia
< 5 yr Adenomatous/Atyp hyperplasia CIS
Endometrial Hyperplasia
Common terms

- Simple v. Complex v. Atypia
- Cystic atrophy v. Hyperplasia
- Disordered prolif v Simple hyperplasia
- Mild, Mod, Marked (3Ms)
  - with/without Atypia
- Adenomatous, Anaplasia & CIS
WHO94 Endometrial Hyperplasia System

Criteria

Glandular complexity
Nuclear atypicality
WHO94 Endometrial Hyperplasia System

ARCHITECTURE

Simple → No atypia

Complex → No atypia

With atypia

With atypia
<table>
<thead>
<tr>
<th>Cytology</th>
<th>No atypia</th>
<th>Atypia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td></td>
<td>Simple</td>
</tr>
<tr>
<td>Complex</td>
<td></td>
<td>Complex</td>
</tr>
</tbody>
</table>
**Progression to cancer**

**Nested case control (2008)**

<table>
<thead>
<tr>
<th>Hyperplasia</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>2.0</td>
</tr>
<tr>
<td>Complex</td>
<td>2.8</td>
</tr>
<tr>
<td>Atypical</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Lacey 2008
Problems in diagnosis: GOG experience

Community cases submitted as atypical hyperplasia

40% Benign/Hyper
30% Atyp Hyper
30% Cancer

Trimble, Gyn Onc 2004
Problems in diagnosis:
GOG experience

Expert gynecologic pathologists disagree among themselves

60% disagreement

Zaino, USCAP 2004
EIN: Endometrial Intraepithelial Neoplasia

Conceptual shift in thinking
EIN – Conceptual Import

- Genetic changes key, not estrogen
- Computer measurable (Reproducible)
- Weeds out cases that otherwise might likely be treated
- May identify latent cases
Geometry of Benign, Premalignant, and Malignant lesions

<table>
<thead>
<tr>
<th>Benign</th>
<th>Premalignant</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repair</td>
<td>Unopposed E2</td>
<td>EIN</td>
</tr>
</tbody>
</table>

Surface Repair

Localized

Estrogen

Random Fieldwide

Mutation→Clonal

Localized

Aggressive

Localized
Monoclonal Origin

- Point origin and expansile growth
  Select relevant fields
  Size changes over time
- Lesion contrasts with normal
  Compare internally
Key features

• Ratio glands to stroma
  – Volume % glands

• Length of basement membrane
  – ‘Outer surface density’ of glands

• Nuclear pleomorphism
  – Std deviation of shortest nuclear diameter
EIN

• Excessive glands (glands > stroma)
• Abnormal architecture
  – Excessive branching, out- or inward complexity & papillary snouts
• Cytologic atypia
  – Nuclei pleomorphic, dyspolarized, irregularly stratified
  – Nucleoli uniformly prominent
  – Cytoplasm eosinophilic
D-Score

\[ + 0.0439 \times \text{(Volume } \% \text{ Stroma)} \]
\[ - 0.1592 \times \text{(Outer Surface Density glands)} \]
\[ - 3.9934 \times \ln \text{(Std Dev Shortest Nuclear Axis)} \]
\[ + 0.6229 \]

Progression risk

40-60\% \hspace{1cm} 25-30\% \hspace{1cm} \sim 0\%

Frequency:

15-25\% \hspace{1cm} 5\% \hspace{1cm} 65\%

Baak 1988
Contribution to D-Score

- Volume % Glands 65%
- Perimeter Basement Membr 25%
- Standard Deviation Shortest Nuclear Axis 10%

ARCHITECTURAL FEATURES MORE IMPORTANT THAN CYTONUCLEAR FEATURES
Normal Gland

EIN Gland

Hyperplasia

Basal Membrane = Outer Surface Density

Increases from Normal † Hyperplasia † EIN
Clinical Outcome of 176 WHO “Hyperplasias”

Followup, Months

Outcome
- Cancer
- No Cancer

Mutter, 2002
Clinical Outcome of 176 “Hyperplasias” Rediagnosed by EIN Criteria

Mutter 2002
Timing - a critical flaw

Concurrent
Appears in 1\textsuperscript{st} year

Progression
Appears in 2\textsuperscript{nd} or later years
Concept of Progression

• **Concurrent:**
  Tumor appears in 1\textsuperscript{st} year, i.e., < 1 yr follow-up
  197 women

• **Progression:**
  Appears > 1 year
  477 women (median 48 mo, max 22 yrs)
Progression – WHO 94

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;1 yr</th>
<th>&gt;1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>CH</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>SAH</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>CAH</td>
<td>53</td>
<td>20</td>
</tr>
<tr>
<td>Score</td>
<td>&lt;1 yr</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>&lt;1</td>
<td>41</td>
<td>29</td>
</tr>
<tr>
<td>&gt;1</td>
<td>0</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Cancer Outcomes in 477 “Hyperplasias” restrapified by EIN

Follow-up Time (> 12 mo)
From Baak, Mutter, Robboy et al, Cancer June 2005
Endometrial Intraepithelial Neoplasia

Baak et al 2005
2 of every 3 “hyperplasia” cases are benign
EIN: ICD-9

As of January 1, 2010

621.34
Benign endometrial hyperplasia

621.35
Endometrial intraepithelial neoplasia [EIN]
EIN Reproducibility

Usubutum A et al

Modern Pathol 25: 877-884, 2012
Questionnaire, 20 reviewers

Terminology preferred  WHO 80%
Read Robboy’s PFRT  Yes 90%
Visit EM.org Website  Yes 90%
EIN system easy to learn  Yes 85%
Easy to apply  Yes 70%
Community: "Expert"
EIN Diagnostic Reproducibility

Expert
Consensus
kappa=0.74

Community-Expert:
20 pathologists
79% agree w expert.
Community to expert
kappas= 0.72 (.45-.84)

Usubutun et al, 2012
## Discordant Cases

**Defines Pathologist Style**

<table>
<thead>
<tr>
<th>Ref Dx</th>
<th>Red</th>
<th>Green</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OverDx</strong></td>
<td><strong>UnderDx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIN</td>
<td>EIN</td>
<td>B9</td>
<td>Small focus, EIN in anov Polyp; Loose, Subtle</td>
</tr>
<tr>
<td>B9</td>
<td>EIN</td>
<td>B9</td>
<td>Fragment, Shattered, Thick</td>
</tr>
</tbody>
</table>
PTEN & mutations
PAX2 (10q24)

• Transcription factor
• Embryonic expression required for:
  Kidney
  Mesonephric structures
  Paramesonephric ducts
• 5-fold reduced in endometrial Ca
PAX2 knockout leads to Mullerian and renal atresia
Coinactivated PAX2 & PTEN in EIN

Mutter, 2010
## PAX2 & PTEN null rates by dx

<table>
<thead>
<tr>
<th></th>
<th>PE (normal)</th>
<th>EIN</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX2 null</td>
<td>36%</td>
<td>71%</td>
<td>77%</td>
</tr>
<tr>
<td>PTEN null</td>
<td>49%</td>
<td>44%</td>
<td>68%</td>
</tr>
<tr>
<td>Both express</td>
<td>36%</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Mutter, 2010
Atypical Hyperplasia

$kappa = 0.34-0.47$

True Precancer Target

$EIN$

$kappa = 0.54-0.62$

Interobserver Reproducibility Improved
WHO-2014 (New) Endometrial Hyperplasia System

Benign
Hyperplasia without atypica

Precancer
Atypical hyperplasia /
Endometrioid Intraepithelial Hyperplasia
Acknowledgements

• Jan Baak, MD, Professor of Pathology
  Stavanger University Hospital, Norway
  University of Munich, Germany

• George Mutter, MD, Professor of Pathology
  Brigham & Womens’ Hospital
  Harvard University Medical School
  Also see www.endometrium.org