Endometrial Hyperplasia and Malignancy

- Jacqueline Morgan
- July, 2016
Not Addressing

- Non endometrioid tumors
- Uterine sarcomas
- Cervical tumors
- Lynch (HNPCC) in detail
Endometrial Cancer

- Approx 44,000 cases a year
- 7,000 attributable deaths
- 4\textsuperscript{th} most common malignancy in women
- 7\textsuperscript{th} most common cancer death

- 25% in peri or premenopausal women
- Seeing increasing incidence in young obese women.
### Endometrial cancer risk factors

<table>
<thead>
<tr>
<th>Trait</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>30lb overweight</td>
<td>3</td>
</tr>
<tr>
<td>50lb overweight</td>
<td>10</td>
</tr>
<tr>
<td>200lb overweight</td>
<td>+++</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>2</td>
</tr>
<tr>
<td>Late menopause</td>
<td>2.5</td>
</tr>
<tr>
<td>Type II DM</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5</td>
</tr>
<tr>
<td>Unopposed estrogen therapy</td>
<td>9.5</td>
</tr>
<tr>
<td>Complex atypical hyperplasia</td>
<td>29</td>
</tr>
<tr>
<td>Lynch mutation</td>
<td></td>
</tr>
</tbody>
</table>
Endometrial Hyperplasia

- WHO schema
- 4 groups, less reproducible

<table>
<thead>
<tr>
<th>% progressing to malignancy</th>
<th>Simple hyperplasia</th>
<th>Complex hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No atypia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>With atypia</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>
International Endometrial Collaborative Group

- Benign Endometrial Hyperplasia
- Endometrial Intraepithelial Neoplasia
- Endometrioid adenocarcinoma, well differentiated
## Endometrial Classification

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Distribution</th>
<th>Functional Label</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign endometrial hyperplasia</td>
<td>Diffuse</td>
<td>Prolonged estrogen effect</td>
<td>Hormonal Rx</td>
</tr>
<tr>
<td>Endometrial intraepithelial neoplasia</td>
<td>Focal initially</td>
<td>Precancerous</td>
<td>Surgery or Hormonal Rx if not surgery candidate</td>
</tr>
<tr>
<td>Well differentiated endometrioid adenocarcinoma</td>
<td>Focal initially</td>
<td>Malignant</td>
<td>Surgical staging</td>
</tr>
</tbody>
</table>
Diagnosis

- History- Abnormal uterine bleeding
- Endometrial sampling
- Pelvic U/S
Endometrial sampling

- Endometrial biopsy
  - In office, samples the least endometrial
  - Difficult if uterine mass lesion
  - Quick to get result

- D&C with hysteroscopy
  - Still samples <50% of endometrium in most cases

- Directed endometrial biopsy
  - Most accurate if focal lesion
Pelvic U/S

- Useful to assess uterine size in the well insulated patient
- If endometrial thickness <4mm in postmenopausal pt, may consider avoiding sampling due to lower risk of malignancy
- Does not provide diagnosis in itself
- Isolated endometrial thickening in absence of other symptoms of uncertain significance
Screening

- Lynch- “Consider” serial EMBx
  - Evidence very weak
- Poorly tolerated
- In absence of desire to preserve fertility, recommend risk reduction with hysterectomy
Benign endometrial hyperplasia

- Risk factor modification
- Hormonal therapy
  - Megestrol
    - 40-80mg PO BID
  - Medroxyprogesterone
    - 10-20mg daily, continuous or cyclic
    - Depot 150mg IM q 3 monthly
  - Levonorgestrel IUD
Hormonal Therapy Complications

- Poor compliance
- Appetite stimulation
- Weight gain
- Edema
- Thrombosis
- Disease progression
Endometrial Intraepithelial Neoplasia

- EIN on endometrial sampling = 40% risk of carcinoma at time of hysterectomy

- Typically low grade, early stage malignancy
Hysterectomy recommended unless
- Pt unfit for surgery
- Desires future fertility and no contraindication to pregnancy
Any method of hysterectomy acceptable
- Remove uterus intact
- Salpingectomy
- Oophorectomy not required in premenopausal patients
  - Balance risks of premature menopause against risk of occult disease spread or future mass or symptoms resulting in need for further surgery
EIN

- If invasive malignancy evident at time of surgery, >2cm tumor, 50% myometrial invasion, recommend surgical staging.

- Do not routinely stage all EIN cases- excessive morbidity
EIN Hormonal therapy

- Options as for benign hyperplasia
- Repeat sampling 3-6 monthly
- Once resolved- achieve pregnancy ASAP
- 60-90% regression rate
- Hysterectomy if
  - Disease progression on therapy
  - Fertility no longer desired
  - Acceptable surgical risk
Endometrial Carcinoma

Grade

• Architectural Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated or non endometrioid tumor</td>
</tr>
</tbody>
</table>

- 1 Well differentiated: <5% solid tumor
- 2 Moderately differentiated: >5-50% solid tumor
- 3 Poorly differentiated or non endometrioid tumor: >50% solid tumor

• Nuclear Grade
  • Nuclear atypia may raise architectural grade by 1
Endometrial Carcinoma Evaluation

- History
  - Comorbidities (Obesity, DM, HTN, HL, OSA)
  - Prior surgery
  - Hormonal therapies
  - Personal history of other malignancies
  - Family history of other malignancies
Endometrial Carcinoma Evaluation

- Exam
  - Uterine size
  - Local organ spread
  - Regional and distant adenopathy
Endometrial Carcinoma Evaluation

- Imaging
  - CXR
  - ?pelvic U/S

- High grade and non endometrioid carcinoma- CT imaging of utility
Surgical Staging

- Peritoneal visual assessment, inc upper abdomen
- Washings, not included in staging by FIGO
- Biopsy of visible abnormalities or adenopathy
- Pelvic lymph node dissection
  - Can be omitted for stage IA grade 1 tumors.
- Periaortic lymph node sampling- High grade tumors
Sentinel Lymph Node Biopsy

- Cervical injection (ICG now typically)
- Bilateral sentinel node dissection
- If no sentinel node- then side specific pelvic lymphadenectomy
- Not recommended outside of trial setting currently
Sentinel Lymph Node Biopsy

- Typically paired with pathologic ultra-staging of sentinel nodes
- Limited long term outcome data
- Less lymphedema

- Advocated in lower risk population that may be able to avoid lymph node assessment at all
Carcinoma of the endometrium - FIGO 2009

Stage I  
IA  Tumour confined to the corpus uteri  
IB  Invasion equal to or more than half of the myometrium

Stage II  
Tumour invades cervical stroma, but does not extend beyond the uterus

Stage III  
IIIA  Tumour invades the serosa of the corpus uteri and/or adnexae  
IIIB  Vaginal and/or parametrial involvement  
IIIC  Metastases to pelvic and/or para-aortic lymph nodes  
IIIC1  Positive pelvic nodes  
IIIC2  Positive para-aortic lymph nodes with or without positive pelvic lymph nodes

Stage IV  
IVA  Tumour invasion of bladder and/or bowel mucosa  
IVB  Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes
CHANGES TO STAGE I

- old IA and IB is now IA (FIGO figures show no difference in outcome; pathological difficulties)
- old IC is now IB
- endocervical glandular involvement alone will still be stage I
CHANGES TO STAGE II

- single category of stage II (cervical stromal involvement)
CHANGES TO STAGE III

- IIIA - uterine serosal or adnexal involvement
- IIIB - vaginal and/or parametrial involvement
- IIIC - pelvic and/or para-aortic nodes (IIIC1 - pelvic nodes; IIIC2 - para-aortic nodes)
CHANGES TO STAGE IV

• none
PERITONEAL WASHINGS

- to be performed and reported separately ie not part of staging system
- Considered in treatment planning
Endometrial carcinoma - Hormonal therapy

- As for EIN
- Not a suitable surgical candidate
- Desires fertility preservation

- Endometrial sampling q 3-6 monthly if result would alter treatment
- Typically lifelong as underlying risk factors remain
Fertility Preservation

- Not standard of care
- Grade 1 tumor
- Limited to endometrium on MRI or U/S
- Pregnancy not otherwise contraindicated
- Hysterectomy once fertility no longer desired
Post op treatment

- Observation
- Brachytherapy
- External beam radiation
- Chemotherapy
- Hormonal therapy
- Palliation only
<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>No adverse risk factors</td>
<td>Observation</td>
<td>Observation or Vaginal Brachytherapy</td>
</tr>
<tr>
<td></td>
<td>+ Adverse risk factors</td>
<td>Observation or Vaginal Brachytherapy</td>
<td>Observation or Vaginal Brachytherapy And/or EBRT</td>
</tr>
<tr>
<td>IB</td>
<td>No adverse risk factors</td>
<td>Observation or Vaginal Brachytherapy</td>
<td>Observation or Vaginal Brachytherapy</td>
</tr>
<tr>
<td></td>
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Stage II

- External beam radiation +/- brachytherapy
Stage III/IV

- Chemotherapy
- Possible addition of radiation for pelvic control
Tumor testing for germline mutation

- On those <50yo or family history suspicious for Lynch Syndrome.

- IHC for mismatch repair protein expression (MLH1, MSH2, MSH6, PMS2)
  - Normally expressed
  - Abnormal if not expressed.

- Abnormal methylation of MLH1 promoter can mimic MMR mutation - but is sporadic, not germline
MSI

- High MSI (microsatellite Instability)
- Infers impaired mismatch repair protein function
- IHC more commonly performed
Lynch Syndrome

- If Abnormal MMR IHC or MSI-high results
- Proceed with germline testing.

- Also if MMR or MSI testing is negative, but family or personal history remains suspicious, can offer genetic counselling and Lynch panel or multipanel testing.