ARRO Case: Early-stage Endometrial Cancer

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Case Presentation

• 70 y/o African American female presenting with an episode of post-menopausal vaginal bleeding.
Relevant Past Medical History

• PMH:
  – Hypertension
  – History of sarcoidosis (in remission)
  – Glaucoma
  – Osteoarthritis
  – Obesity – BMI 35

• GYN:
  – G5P1041
  – Last Pap smear: 6/22/2012 negative
  – Hormonal contraceptives: none.
  – HRT use: minimal - premarin for 2 months

• Social:
  – Married, monogamous
  – Never smoker
  – Occasional wine drinker

• Family:
  – Two brothers with prostate cancer
Physical Exam

• Pelvic:
  – External genitalia is normal including normal vulva, vagina and urethra. Perineum and anal area without erythema or lesions.
  
  – Speculum exam reveals normal appearing cervix and vagina without erythema, inflammation or lesions.
  
  – Bimanual exam reveals palpably normal uterus and cervix without lesions or nodularity. No masses appreciated.
Pelvic ultrasound: “The endometrial stripe is thickened. The endometrial stripe measures 16.6 mm. Heterogeneous.”
Differential Diagnosis by Imaging Findings

• Endometrial carcinoma
  – Risk of carcinoma is ~7% if the endometrium is >5 mm and 0.07% if the endometrium is <5 mm

• Hyperplasia

• Polyp

• Endometritis

Pathology

• Endometrial biopsy:
  – Endometrioid adenocarcinoma, FIGO grade 2

Epidemiology

• In 2017, >61K new cases estimate, >10k deaths

• Most (67%) diagnosed at early stage due to post-menopausal bleeding

• 4th most common in females (lung, breast, colorectal); ~6% of cancers in women.

• In USA: 1st MC GYN cancer; 2nd MC GYN cancer death (ovarian is #1). Worldwide MC GYN Ca is cervical.

• Median age at diagnosis: 62

• 5- and 10-year survival rate 82% and 79%

Clinical Presentation

- Postmenopausal uterine bleeding
- Perimenopausal heavy or prolonged bleeding
- Pelvic pressure
- Low back pain
- Vaginal discharge
- Bowel or bladder symptoms
- + pap smear
Risk Factors

- Endogenous and exogenous estrogens
  - Obesity
  - Early age at menarche
  - Nulliparity
  - Late on-set of menopause
  - Older age
  - Tamoxifen
  - HNPCC
Work Up

• H&P (including bimanual pelvic exam)

• Ultrasound to measure endometrial stripe then Endometrial biopsy or fractional D&C &/or hysteroscopy

• CT C/A/P

• Role for MRI to investigate depth of invasion pre-operatively and PET-CT for lymph node evaluation, however not standard at our institution
Staging

• 2009 FIGO staging for carcinoma of the endometrium:
  – stage 0: carcinoma in situ
  – stage I: limited to the body of the uterus
    • Ia: no or less than half (≤ 50%) myometrial invasion
    • Ib: invasion equal to or more than half (≥ 50%) of the myometrium
  – stage II: cervical stromal involvement (endocervical glandular involvement only is stage I)
  – stage III: local or regional spread of the tumour
    • IIIa: tumour invades the serosa of the body of the uterus and/or adnexa
    • IIIb: vaginal or parametrial involvement
    • IIIc: pelvic or para-aortic lymphadenopathy
      – IIIc1: positive pelvic nodes
      – IIIc2: positive para-aortic nodes with or without pelvic nodes
  – stage IV: involvement of rectum and or bladder mucosa and or distant metastasis
    • IVa: bladder or rectal mucosal involvement
    • IVb: distant metastases, malignant ascites, peritoneal involvement
Prognostic Factors

- Age
- Grade
- Depth of invasion
- LVSI
- Non-endometrioid histology
- Lymph node evaluation
- Race
- Comorbidities
Pathology

- **Epithelial Carcinomas** - Arise within the epithelium of the uterine lining - 90% of uterine neoplasms
  - *Endometrial Adenocarcinoma / Endometrioid* (90% of epithelial carcinomas)
  - *Papillary Serous Carcinoma*
    - (< 10% of epithelial carcinomas) – account for ~40% of endometrial cancer deaths) - Associated with more aggressive disease and worse outcomes
  - *Clear Cell Carcinoma*
    - (< 5% of epithelial carcinomas) . Associated with older women; Seen in ovarian, cervical and vaginal cancers. Very aggressive, especially if mixed with PSC.
  - *Mucinous Carcinoma*
    - Tend to be well-differentiated; 50% clinical course is similar to endometrioid adenocarcinoma.
  - *Mixed cell tumors* - > 5% but < 50% non-endometrioid histology
  - *Squamous Cell Carcinoma*
  - *Carcinosarcoma* – contain both epithelial and stromal components

- **Mesenchymal Carcinomas** - (outside scope of this presentation) – <10%
  - Include leimoyosarcoma, stromal sarcoma, rhabdomyosarcoma, adenosarcoma

- **Grading**
  - *Grade 1* – Less than 5 percent solid growth patterns
  - *Grade 2* – 6 to 50 percent solid growth patterns
  - *Grade 3* – Greater than 50 percent solid growth

- UpToDate: https://www.uptodate.com/contents/endometrial-carcinoma-histopathology-and-pathogenesis
# Bokhman subtypes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed Estrogen</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>Racial Predilection</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Growth</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Precursor</td>
<td>Atypical hyperplasia</td>
<td>Endometrial intraepithelial carcinoma</td>
</tr>
<tr>
<td>Histology</td>
<td>Endometrioid</td>
<td>Serous, Clear cell</td>
</tr>
<tr>
<td>Grade</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Depth of Invasion</td>
<td>Superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>Molecular genetic changes</td>
<td>Diploid; Low allelic instability;</td>
<td>Aneuploid; High allelic instability;</td>
</tr>
<tr>
<td>Associated gene mutations</td>
<td>1) K-Ras, 2) MLH1 methyl, 3) PTEN</td>
<td>1) TP53, 2) ERBB2 (HER2)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Favorable</td>
<td>Poor clinical outcomes</td>
</tr>
</tbody>
</table>

Genetic subtypes

- **TCGA** -
  - POLE-mutant (best prognosis)
  - MSI-high
  - Copy number low MSS
  - Copy number high

However, currently does not change management.

Management

• Surgical staging, which includes:
  – Hysterectomy and salpingo-ophorectomy,
  – Lymph node evaluation (controversial - institution/surgeon dependent)
  – Peritoneal cytology

• Adjuvant Treatment, which, dependent on prognostic factors, could include:
  – External beam
  – Brachytherapy
  – Chemotherapy
  – Or combination of the above
Adverse risk factors include: age, LVSI, tumor size, lower uterine segment or surface cervical glandular involvement.

Aside from stage IA, grade 1 without other risk factors (which there is general agreement to observe) there is a high degree of variability in treatment options.
Low risk

• Sorbe et. al 2009 –
  – 645 pts treated wit TH/BSO, pelvic cytology, LN sampling - having no MI or < 50 %, Grade 1-2
  – Randomized to observation or VBT
  – Rate of vaginal recurrences:1.2% in the treatment group versus 3.1% in the control group

• Conclusions – VBT has limited impact on low-risk patients

High-intermediate risk

- **GOG 99 HIR**
  - 3 risk factors:
    - LVSI, outer 1/3 myometr invas, gr2-3
    - Age > 70 with 1 factor
    - Age 50 – 70 with 2 factors
    - Any age with all 3 factors

- **PORTEC-1 HIR**
  - 2 of 3 required
    - Age > 60, gr 3, ≥ 50% myo invasion
    - No IC + grade 3 (= high risk)

- EBRT reduced LR in both studies (but not OS).


EBRT vs Vaginal Brachytherapy

- **PORTEC-2**
  - Patients age >60 with <50% MI G3 or > 50% and G1-2
  - Randomized to VBT or EBRT
  - Vaginal recurrences similar, slightly higher pelvic relapses with VBT
  - QOL improved with VBT (especially GI toxicity)


Other literature

• Other highly relevant studies on this topic:
  – Norwegian study (historical)
  – ASTEC/ EN 5
  – Sorbe IJROBP 2012
  – Japanese GOG 2033
  – High risk: PORTEC-3 and GOG 249
  – PORTEC-4
Back to our patient - Surgery

- Our patient was taken for a Robot-assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and removal of pelvic and para-aortic lymph nodes.

  - Pathology:
    - Pelvic Washings: Negative
    - Uterus, cervix, bilateral ovaries and fallopian tubes, resection:
      - 1. FIGO 2 Endometrioid adenocarcinoma with invasion of greater than one-half of myometrium (3.9/4.0 cm) with lymphovascular involvement
      - 2. Unremarkable cervix and bilateral fallopian tubes
      - 3. Endometriosis, right ovary
      - 4. Unremarkable left ovary
    - C. Right pelvic lymph nodes, resection: Negative for malignancy, four lymph nodes
    - D. Right pelvic lymph nodes, resection: Negative for malignancy, four lymph nodes
    - E. Right para-aortic lymph nodes, resection: Negative for malignancy, one lymph node
    - F. Left para-aortic lymph nodes, resection: Negative for malignancy, one lymph node

- Summary: 70 y/o F with Stage IB, grade 2, endometrioid adenocarcinoma of the uterus with LVSI

- Recommendation: Vaginal cuff brachytherapy
Brachytherapy

- Most patients the postoperative vagina can be treated by a cylinder.

- Use the largest size that fits comfortably in the vagina to avoid air gaps and folds.
  - Cylinder sizes range from 1.5 cm to 4 cm.

- When fitting patient – evaluate vaginal cuff for dehiscence.

- The proximal 3-4 cm (active length) of the vagina should be treated.
Treatment - Brachytherapy

- Treatment ideally 6-8 weeks post-op
- Post placement CT scan:
  - Verify proper placement
  - Vaginal cuff dehiscence
  - Minimize air gaps

Dose/ fx:
- 7 Gy x 3 fx to 0.5 cm depth
- 6 Gy x 5 fx to surface – our preference

- Account for anisotrophy to avoid under dosage at apex


Follow-up

- H/P + pelvic exam 3-6 months x 2-3 years, then then 6 months or annually
- CA-125 if initially elevated
- Imaging as clinically indicated
- Vaginal dilators (or sexually activity) to prevent stenosis