Medically Inoperable Endometrial Cancer

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Case Presentation

**HPI:** 73-year-old woman presented to ED after falling in the shower. She reported vaginal bleeding for the last 4 months with passage of large blood clots. She had not seen a physician in many years.

**Gynecologic History:** menopause age 50, G1P1, used OCPs for 1 year, no hormone therapy replacement

**PMHx:** Obesity (BMI 40), HTN, venous stasis of bilateral lower extremities causing lymphedema

**Surgical Hx:** non-contributory

**Medications:** Norvasc, Colace, Ferrous sulfate

**Social History:** non-smoker
Case Presentation

• Transvaginal Ultrasound
  – Uterus measuring 9.4 x 5.5 x 6.7cm for a total volume of 181mL. Endometrial stripe thickness is ill defined with echogenicity extending into myometrium. Intramural fibroid in left lower uterine segment measuring 3.2 x 2.6cm

• Endometrial Biopsy (EMB)
  – Benign endocervical polyp with extensive squamous metaplasia.

• Dilation and Curettage (D&C) with hysteroscopy
  – Pathology: fragments of endometrioid adenocarcinoma, FIGO grade 3. Additional fragments of endometrium with hyperplasia and endometrial intraepithelial neoplasia

• Cervical biopsies
  – Negative for malignancy

• Patient was deemed medically inoperable due to her morbid obesity
Case Presentation

- **MRI Pelvis**
  - Central uterine neoplasm measuring 6.5 x 6 x 3.5 cm with deep myometrial invasion to within 5 mm of the uterine serosal surface without extrauterine invasion
  - No pelvic metastatic disease identified
- **CT Chest**
  - No intrathoracic disease
Epidemiology

• Endometrial carcinoma is the most common gynecologic cancer in the United States
• It is estimated that there will be 66,570 new cases of endometrial cancer in 2021
• According to SEER data, ~3.1% of women will be diagnosed with uterine cancer at some point in their life
Medically Inoperable Patients

• Standard upfront treatment for endometrial adenocarcinoma is a TAH-BSO; however, some patients are unable to undergo surgery due to:
  – Medical comorbidities
    • Cardiovascular disease
    • Pulmonary disease
    • Venothromboembolic disease
    • Cerebrovascular accidents
    • Hemophilia
  – Morbid obesity
  – Performance status is a key factor in determining suitability for anesthesia
Work-up Pearls for Medically Inoperable Patients

• TVUS to evaluate endometrial thickness
• EMB or D&C if EMB is non-diagnostic
  – Pathology
    • Grade and histology are important factors
• MRI to assess the depth of myometrial invasion
  – Contrast-enhanced and T2 weighted MRI have been shown to have negative predictive values greater than 85% for identifying deep myometrial involvement
• CT Chest/Abdomen/Pelvis or PET-CT to assess nodal or distant disease
Staging for Medically Inoperable

• Clinical staging relies on pelvic examination
  – Sounding the uterus: assess size of cavity
  – Rectal/bimanual exams: evaluate parametria and adjacent organs

Clinical staging system for endometrial cancer

• Stage I—confined to the uterus
  – IA—Uterine cavity sounds to <8 cm
  – IB—Uterine cavity sounds to >8 cm
• Stage II—Involves the corpus and cervix
• Stage III—Parametrium, adnexa, or vagina but confined to true pelvis
• Stage IV
  – A—Involving local structures (rectum/bladder)
  – B—Metastatic
Medical Management

• When using hormonal therapy, imaging should show no evidence of cervical invasion, pelvic or aortic lymphadenopathy, or involvement of the ovaries

• Oral progestin
  – Ushijima et al. cites regression in 55% of patients with presumed early-stage disease.
  – Can be associated with recurrence rates of 25% or higher

• Levonorgestrel-releasing IUD
  – Used in precancerous and Grade 1 endometrial adenocarcinoma
  – Can be used in combination with oral progestin in morbidly obese patients as a bridge until sufficient weight loss for safe surgery is achieved
Management with Radiotherapy

• Stage I, Grade 1 or 2 endometrial cancer with minimal myometrial invasion
  – Brachytherapy alone
    • GTV = gross disease and endometrial lining (delineated on MRI)
      – EQD$_2$ of 80-90 Gy
    • CTV = whole uterus extending out to uterine serosa
      – D$_{90}$ EQD$_2$ of 48-62.5 Gy

<table>
<thead>
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<th>HDR total dose (Gy)</th>
<th>HDR dose fractionation</th>
<th>EQD$_2$ (Gy)</th>
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<td>36.5</td>
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<td>34</td>
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<td>40–50</td>
<td>5 Gy × 9–10</td>
<td>50–62.5</td>
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Management with Radiotherapy

- Stage I endometrial cancer with deep myometrial invasion (>50% of myometrial depth)
  - EBRT 45-50 Gy (uterus + nodal areas at risk) + Brachytherapy
  - GTV = gross residual disease after EBRT + endometrial lining
    - EQD$_2$ 80-90 Gy
  - CTV = whole uterus to serosal surface, including cervix and upper 1-2 cm of vagina
    - EQD$_2$ 65-75 Gy

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<tr>
<th>EBRT (Gy)</th>
<th>HDR total dose (Gy)</th>
<th>HDR dose fractionation</th>
<th>EQD$_2$ (Gy)</th>
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Management with Radiotherapy

• Stage II endometrial cancer (involves cervix)
  – EBRT
    • Consider adding paracervical and pre-sacral LNs
  – Brachytherapy
    • Applicator should include ring or ovoids to deliver dose to cervix
Management with Radiotherapy

- Stage III endometrial cancer
  - EBRT + Brachytherapy
  - SIB with IMRT to treat enlarged lymph nodes
    - Or sequential boost to respect normal tissue tolerances (usually small bowel)
    - 55 Gy in 25 fractions
Medically Inoperable Endometrial Cancer: High-Risk Histologies

- **Histology**
  - Serous carcinoma
  - Clear cell carcinoma
  - Carcinosarcoma
  - Undifferentiated carcinoma

- Consider the addition of systemic therapy
Brachytherapy Applicators

Heyman Capsules

Y-Tandem

Triple Tandem
Brachytherapy Applicators

• There are several techniques available, including single applicator, dual (Y), and triple tandems. Choice of applicator should be specific to patient.

• Single tandem applicators may be less effective, especially for patients with larger uteri.

• Small Dosimetry study by S.B. Johnson et al. of dose planning for 3 patients with inoperable cancer and different uterine shapes, using single, dual, and triple tandems found:
  – Triple tandem applicator improved dose coverage to the uterus regardless of uterine shape for point-based planning and minimized dose to OARs for volumetric planning
  – Regardless of point or volumetric-based normalization, uterine size and shape and proximity of OAR are important considerations for tandem selection
  – Patient with closer OARs received more dose to OARs using single tandem applicator
Dose Specification and Dosimetry

• Volume-based planning preferred over point-based approach
• If MRI is not available or feasible, target-based planning is limited to the CTV (no GTV)
• Best data available for tolerable dose to OARs suggest
  – $D_{2cc}$ Sigmoid and Rectum be limited to 70-75Gy
  – $D_{2cc}$ Bladder to 80-100 Gy
Potential Treatment Side Effects

**Acute complications**
- Procedural
  - Uterine perforation: 13.7% rate of uterine perforation detected with CT
- Fatigue
- Loose stool/diarrhea
- Vaginal irritation/bleeding
- Irritative urinary symptoms

**Late complications**
- Bowel injury
  - Proctitis
  - Sigmoid stricture
  - Bowel obstruction and fistula
- Chronic urinary symptoms
- Pelvic insufficiency fracture
- Chronic diarrhea
- Vaginal stenosis
- Secondary malignancy
Case: Treatment

• Patient diagnosed with Stage I endometrioid adenocarcinoma with deep myometrial invasion

• Treated with combination of EBRT + Brachytherapy
  – EBRT 45 Gy in 25 fractions to the uterus and pelvic lymph nodes with TomoTherapy
  – HDR Brachytherapy with a triple tandem
    • Prescription: 6.5 Gy x 3 fractions
    • HR-CTV $D_{90}$: 77.3 Gy
    • GTV $D_{90}$: 83 Gy
    • Bladder $D_{2cc}$: 64.9 Gy
    • Sigmoid $D_{2cc}$: 65.8 Gy
    • Rectum $D_{2cc}$: 50.4 Gy
Treatment Plan: EBRT
Treatment Plan: Brachytherapy

Triple Tandem
Treatment Plan: Brachytherapy
Treatment Plan: Brachytherapy
Follow-Up

• Relapses most often occur within the first 3 years after treatment with 70% of recurrences being symptomatic.

• Medically inoperable patients are more likely to succumb to their medical comorbidities.

• Recommended Surveillance
  – Pelvic and speculum exams every 3 to 6 months
  – After 5 years of recurrence-free follow-up, may consider returning to annual exams

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Case: Follow-Up

- Patient reported resolution of bleeding, clots, and discharge 1 month following radiation therapy
- She had some intermittent diarrhea and constipation. She reported no pelvic pain.
- Post-treatment PET CT obtained 3 months after treatment
  - Focal mild FDG uptake in central uterus likely related to post-treatment inflammation
- CT Abdomen/Pelvis obtained 3 months before death (for other reasons) showed no residual disease
Management of Recurrent Disease After Definitive Radiation

• Suspected recurrence
  – Obtain imaging and biopsy
  – Review realistic salvage or palliation treatment options with the patient
    • For patients with symptomatic recurrence, the use of palliative radiation may be beneficial for severe bleeding or pain
    • If ER/PR+, hormonal therapy is first-line
    • Uterine artery embolization may be used for treatment of hemorrhage
    • Can consider surgery if medical status has improved
References


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