Early Stage Endometrial Cancer

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Case: Intro

• HPI:
  – 56 y.o. female, G0P0, with 4 yr hx of irregular menses, thought to be perimenopausal
  – Bleeding accompanied by worsening abdominal pain, led to transvaginal US
  – Pelvic US showed enlarged uterus, large polypoid mass in endometrial cavity, 25.4 mm endometrial stripe (normal < 5 mm)
  – CT A/P showed nodular enhancing masses in endometrium, suspicious for cancer
  – Bx showed high-grade adenocarcinoma
Epidemiology

- Uterine cancer: most common GYN malignancy
  - Cases per year: 65,620
  - Deaths per year: 12,590
- 5 year Relative Survival: 81.2%
- Median Age at Diagnosis: 63

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2020</th>
<th>Estimated Deaths 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>276,480</td>
<td>42,170</td>
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<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>228,820</td>
<td>135,720</td>
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<tr>
<td>3. Prostate Cancer</td>
<td>191,930</td>
<td>33,330</td>
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<tr>
<td>4. Colorectal Cancer</td>
<td>147,950</td>
<td>53,200</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>100,350</td>
<td>6,850</td>
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<tr>
<td>6. Bladder Cancer</td>
<td>81,400</td>
<td>17,980</td>
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<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>77,240</td>
<td>19,940</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>73,750</td>
<td>14,830</td>
</tr>
<tr>
<td>9. Uterine Cancer</td>
<td>65,620</td>
<td>12,590</td>
</tr>
<tr>
<td>10. Leukemia</td>
<td>60,530</td>
<td>23,100</td>
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</table>

Uterine cancer represents 3.6% of all new cancer cases in the U.S.
Risk Factors

• Phenotypic
  – Continuous unopposed estrogen stimulation
  – Obesity
  – Tamoxifen
  – Cirrhosis
  – Nulliparity
  – Diabetes

• Genotypic (3%)
  – Lynch Syndrome (HNPCC) – most commonly from germline mutations of MMR proteins (MLH1, MSH2, MSH6, or PMS2)
Classification

• Type I
  – Endometrioid
  – Associated with obesity, increased estrogen exposure
  – Better prognosis (overall survival of 85% at 5 years)

• Type II
  – Non-endometrioid
  – Considered high grade
  – Serous, clear cell, grade 3 endometrioid histologies
  – Associated with TP53 mutation
  – Worse prognosis (overall survival of 55% at 5 years)
Workup & Evaluation

• Common presenting symptoms: Postmenopausal vaginal bleeding, menorrhagia, metrorrhagia, abdominal pain, abdominal distension

• History and Physical
  – Physical exam should include inspection of external genitalia, vagina, cervix + pelvic exam, and rectal exam

• Labs: CBC (can consider LFT, renal function, chemistry profile)

• Imaging: Can consider Vaginal Ultrasound, CT c/a/p, Pelvic MRI, and PET

• Biopsy: Endometrial sampling (D&C if EMBx is negative)
Case: Imaging

Pre-op CT of the pelvis: nodular enhancing masses centered in the endometrium with suspected myometrial invasion at > 50% in thickness on the right, concerning for invasive endometrial carcinoma.
Anatomy
## Current Staging as of 2009

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the uterus</td>
</tr>
<tr>
<td>IA</td>
<td>&lt;50% invasion of the myometrium</td>
</tr>
<tr>
<td>IB</td>
<td>≥50% invasion of the myometrium</td>
</tr>
<tr>
<td>II</td>
<td>Tumor invades the cervical stroma but does not extend beyond the uterus</td>
</tr>
<tr>
<td>III</td>
<td>Local or regional spread of tumor</td>
</tr>
<tr>
<td>IIIA</td>
<td>Serosal or adnexal invasion</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal or parametrial involvement</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastasis to pelvic or paraaortic lymph nodes</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Pelvic lymph node involvement</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Paraaortic lymph node involvement (with or without pelvic nodes)</td>
</tr>
<tr>
<td>IV</td>
<td>Extension to the pelvic wall, lower one-third of the vagina, or hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td>IVA</td>
<td>Invasion of bladder or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases, including abdominal, or involvement of inguinal lymph nodes</td>
</tr>
</tbody>
</table>

## Prior Staging from 1989

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Tumour limited to endometrium</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion to &lt;1/2 myometrium</td>
</tr>
<tr>
<td>IC</td>
<td>Invasion to &gt;1/2 myometrium</td>
</tr>
<tr>
<td>IIA</td>
<td>Endocervical glandular involvement only</td>
</tr>
<tr>
<td>IIB</td>
<td>Cervical stromal invasion</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumour invades serosa and/or adnexa and/or positive peritoneal cytology</td>
</tr>
<tr>
<td>IIIB</td>
<td>Metastases to pelvic and/or paraaortic lymph nodes</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumour invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases including intra-abdominal and/or inguinal lymph nodes</td>
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</tbody>
</table>
Surgical Management

• TAH/BSO for apparent stage I disease
• Radical Hysterectomy for gross cervical invasion/uncertainty of endocervical vs endometrial
• Omental and peritoneal biopsies for high-risk disease
• Variable recs for surgical LN evaluation
  – SLNB slowly becoming standard of care
Surgical Management

Types of hysterectomy

- Supracervical
- Total
- Radical

- Right parametrium
- Left parametrium
Case: Path Findings

- Patient underwent robot assisted TAH/BSO/SLNB
- Path: endometrioid carcinoma, 6 cm in greatest dimension, FIGO grade 3, 72% myometrial invasion, LVSI -, no cervical stromal involvement, margins negative, 0/3 LN
- Final stage: FIGO stage IB (pT1bN0M0) endometrioid adenocarcinoma

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Adjuvant Treatment Recs

- Stage IA, grade I or II, endometrioid histology, no LVSI = consider observation
- Stage IA, grade III or stage IB, grade I-II = consider vaginal cuff brachytherapy
- **Stage IB, grade III = pelvic EBRT**
- Stage II = pelvic EBRT + vaginal cuff brachy boost
- Stage III-IV = definitive or adjuvant chemoRT, chemo alone, or RT alone +/- brachy
High-Intermediate Risk

High-Intermediate Risk are stage I endometrial cancer patients who require adjuvant treatment

Common risk factors include:

- **GOG99 HIR**: age $\geq 70$ with 1 risk factor, $\geq 50$ with 2 risk factors, or any age with 3 risk factors. **Factors are grade 2-3, LVI, or IC**
- **PORTEC-1**: HIR group requires 2/3 factors: **age >60, invasion >50%, and/or grade 3**
- **PORTEC-2**: HIR: **age >60 and IC grade 1-2, or IB grade 3. Stage II A any age, (grade 3 and >1/2 invasion excluded)**
- **GOG249**: HIR defined as: age $\geq 70 + 1$ risk factor, age $\geq 50 + 2$ risk factors, age $\geq 18 + 3$ factors. Risk factors: **grade 2 or 3, LVSI, >50% myometrium**
Support for Adjuvant Recommendations

- Stage IA, grade I or II, endometrioid histology, no LVSI = consider observation
  - PORTEC-1: 715 pts, stage I (excluded stage IC with grade 3 and stage IB with grade 1), randomized to 46 Gy WPRT vs observation
    - 5 yr LRR 4% for WPRT vs 14% for obs
    - 5 yr LRR for HIR Group 4% for WPRT vs 23% for obs
    - 10 yr OS of 66% for WPRT vs 73% for obs (p=0.09)
  - HIR Group requires 2 of following 3: age >60, invasion > 50%, or grade 3
  - Observation after surgery reasonable for low risk patients
  - Confirmed by GOG99
Support for Adjuvant Recommendations

• Stage IA, grade III or stage IB, grade I-II = consider vaginal cuff brachytherapy
  – PORTEC-2: 427 pts, HIR stage I and stage IIA (excluded grade 3 with greater than 50% invasion), randomized to 46 Gy WPRT vs vaginal cuff brachy 7 Gy x 3 HDR or 30 Gy LDR
    – 5 yr vaginal recurrence 1.6% WPRT vs 1.8% VCB
    – 5 yr pelvic recurrence 0.5% vs 3.8%
    – 5 yr OS 85% WPRT vs 80% VCB (NS)
  – Vaginal cuff brachy had lower rates of grade 1&2 GI toxicity
  – *Vaginal cuff brachy non-inferior to WPRT on this study*
Support for Adjuvant Recommendations

- Stage IB, grade III - Stage II = **pelvic EBRT +/- vaginal cuff brachy boost**
  - GOG249: 601 pts, stage I HIR, stage II (included serous or clear cell histology), randomized to WPRT (+ VCB boost for stage II) vs VCB then 3 cycles carbo/paclitaxel
    - **5 yr OS of 87% for WPRT vs 85% for VCB + CHT (NS)**
    - 5 yr RFS of 76% in both arms
    - Higher pelvic and para-aortic node failures with VCB + CHT (4% vs 9%)
    - **Increased acute toxicity with VCB + CHT**
Case: Treatment Recommendations

• Patient’s High-Intermediate risk factors included grade 3 disease and >50% myometrial invasion (See slide 12)

• Recommended adjuvant radiation to 45 Gy in 25 fx with SIB boost to vaginal CTV to 50 Gy in 25 fx (Boost without cervical stromal involvement is controversial)
Radiation Simulation

- Position: Supine with arms up or on chest
  - CT with IV contrast
  - Full and empty bladder scans
  - Consider:
    - pelvic thermoplastic mask and/or Vac-loc device
    - fiducial markers at vaginal apex
    - rectal balloon
    - Vaginal contrast

**arm down for photo only, not during scan**
Radiation Contouring

• CTV vagina/paravaginal
  – Upper 4.0 cm of vagina or to mid obturator foramen + paravaginal soft tissue lat to vagina

• ITV vagina/paravaginal
  – Merged CTV vagina from full and empty bladder scans, rectal balloon improves immobilization

• CTV lymph nodes
  – 0.7 cm margin around internal (hypogastric/obturator), external and common iliac nodes
  – presacral(1-2 cm anterior to S1-3) always should be included for patients with cervix involvement

• PTV total
  – Additional 0.5-0.7 cm margin from ITV and CTV nodal volume
Contouring: Consensus Guidelines
Case Contours

Green = combined vaginal and LN PTV to 4500 cGy,
Magenta = CTV LN to 4500 cGy, Blue = CTV vaginal/paravaginal to 5000 cGy

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ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY

ARRO
Radiation Technique

- Post-operative RT with IMRT/VMAT
- Prescription
  - 45 Gy in 1.8 Gy/fraction to PTV lymph node
  - SIB boost to 50 Gy in 2 Gy/fraction to PTV vagina
- 50.4 Gy in 1.8 Gy fractions is also an option
Key Dose Constraints

• Per RTOG 0418
  – Small bowel <30% to receive $\geq 40$ Gy
  – Rectum <60% to receive $\geq 30$ Gy, minor deviation 35% to 50 Gy
  – Bladder <35% to receive $\geq 45$ Gy, minor deviation 35% to 50 Gy
  – Femoral heads $\leq 15\%$ to receive $\geq 30$ Gy, minor deviation 20% to 30 Gy
### Key Dose Constraints

- **QUANTEC**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume segmented</th>
<th>Irradiation type (partial organ unless otherwise stated)</th>
<th>Endpoint</th>
<th>Dose (Gy), or dose/volume parameters</th>
<th>Rate (%)</th>
<th>Notes on dose/volume parameters</th>
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</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>Whole organ</td>
<td>3D-CRT</td>
<td>Grade ≥ 2 late rectal toxicity,</td>
<td>V50 &lt;50%</td>
<td>&lt;15</td>
<td>Prostate cancer treatment</td>
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<td></td>
<td>Grade ≥ 3 late rectal toxicity</td>
<td>&lt;10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Grade ≥ 2 late rectal toxicity,</td>
<td>V60 &lt;35%</td>
<td>&lt;15</td>
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<td>Grade ≥ 2 late rectal toxicity,</td>
<td>V70 &lt;20%</td>
<td>&lt;15</td>
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<td>&lt;10</td>
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<td>Grade ≥ 2 late rectal toxicity,</td>
<td>V75 &lt;15%</td>
<td>&lt;15</td>
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<td>Grade ≥ 3 late rectal toxicity</td>
<td>&lt;10</td>
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<tr>
<td>Bladder</td>
<td>Whole organ</td>
<td>3D-CRT</td>
<td>Grade ≥ 3 late RTOG</td>
<td>Dmax &lt;65</td>
<td>&lt;6</td>
<td>Bladder cancer treatment,</td>
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<td></td>
<td></td>
<td></td>
<td>Variations in bladder size/shape/location during RT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>hamper ability to generate accurate data</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Grade ≥3 late RTOG</td>
<td>V65 ≤50 %</td>
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<td>V70 ≤35 %</td>
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<td>V75 ≤25 %</td>
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<td></td>
<td></td>
<td></td>
<td>V80 ≤15 %</td>
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<tr>
<td>Small bowel</td>
<td>Individual small bowel loops</td>
<td>3D-CRT</td>
<td>Grade ≥ 3 acute toxicity$^5$</td>
<td>V15 &lt;120 cc</td>
<td>&lt;10</td>
<td>Volume based on segmentation of the individual</td>
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<td>loops of bowel, not the entire potential peritoneal</td>
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<td></td>
<td></td>
<td></td>
<td>space</td>
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<tr>
<td></td>
<td>Entire potential space within peritoneal cavity</td>
<td>3D-CRT</td>
<td>Grade ≥ 3 acute toxicity$^5$</td>
<td>V45 &lt;195 cc</td>
<td>&lt;10</td>
<td>Volume based on the entire potential</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>space within the peritoneal cavity</td>
</tr>
</tbody>
</table>
Case: Dose Volume Histogram

- PTV Vagina
- PTV LN
- Bladder
- Rectum
- Large Bowel
- Small Bowel
- Right Femur
- Left Femur
Acute & Late Side Effects

- RTOG 1203 (TIME-C): IMRT vs 3D Conformal
  - IMRT led to decrease in following patient reported events:
    - Diarrhea at 5 weeks (33.7% vs 51.9%, p=.01)
    - Fecal Incontinence at 5 weeks (1.1% vs 9.3%, p=.04)
    - Diarrhea at 1 yr (5.8% vs 15.1%, p=0.4)
    - Antidiarrheal medication at 1 yr (4.6% vs 13%, p=.03)
Treatment Side Effects

• Acute:
  – Diarrhea
  – Abdominal pain
  – Fatigue
  – Dysuria
  – Urinary frequency
  – Myelosuppression

• Late:
  – Vaginal stenosis
  – Vaginal dryness
  – Rare incidences of cystitis, proctitis, sacral insufficiency fractures, bowel obstruction, fistula
Follow-up

• Physical Exam every 3-6 months for 2-3 yrs then every 6 months for 5 years then annually
• Imaging as clinically indicated
• Patient education including sexual health and use of dilator and lubricants
  – Dilator use recommendations vary, consider 1-3 x week for 10 minutes, can be less frequent if sexually active
References


4. NCCN: Clinical Practice Guidelines Uterine Neoplasms


References Cont.


Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com

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