New treatment options for endometrial cancers

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Faculty Disclosure

• Nothing to disclose.
Patients with advanced or recurrent endometrial cancer have a poor prognosis and limited treatment options are available once for platinum/taxane refractory endometrial cancer.

- Novel treatment options are needed for this poor prognosis group of patients.
Objectives and Expected Outcome

- Discuss emerging treatment options for endometrial cancers
  - Attendees will understand the appropriate use of immune checkpoint inhibitors and other emerging treatments in the treatment of endometrial cancer

- Describe the role of biomarkers when selecting targeted therapies for endometrial cancers
  - Attendees will understand the use of biomarkers in treatment selection for endometrial cancers
Endometrial Cancer

- Accounts for nearly 50% of new gynecologic cancers in the US
- 4th most common cancer in women in US
- 6th most common cause of cancer death in women in US
- 2017 estimates:
  - 61,380 new cases
  - 10,920 deaths

Endometrial Cancer

- Average age of onset is 60 years
  - 75-85% occur in women 50 years and older
  - Rare in women younger than 30, reported in patients as young as 15

- Most common in Caucasian women
  - African American women have a 40% lower risk of developing disease, but 54% greater risk of dying from disease
    - effect is not explained by imbalances in psychosocial, clinicopathologic, and treatment factors
    - Black women have a higher incidence of high-risk (grade 3 and nonendometrioid) tumors
Most women are diagnosed with disease confined to the uterus

- 73% are stage I
- 10% are stage II

Endometrial cancer is one of the “good cancers”... when diagnosed at an early stage

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Five-year overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>90.3</td>
</tr>
<tr>
<td>IB</td>
<td>80.8</td>
</tr>
<tr>
<td>II</td>
<td>80.5</td>
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<tr>
<td>IIIA</td>
<td>68.5</td>
</tr>
<tr>
<td>IIIB</td>
<td>53.1</td>
</tr>
<tr>
<td>IIIIC1</td>
<td>58.3</td>
</tr>
<tr>
<td>IIIIC2</td>
<td>51.2</td>
</tr>
<tr>
<td>IVA</td>
<td>22.0</td>
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<tr>
<td>IVB</td>
<td>21.1</td>
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# Two types of endometrial cancer

<table>
<thead>
<tr>
<th></th>
<th>TYPE 1 (70-80%)</th>
<th>TYPE 2 (10-20)</th>
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</thead>
<tbody>
<tr>
<td><strong>Molecular alterations</strong></td>
<td>Microsatellite instability and mutations in PTEN (80%), PIK3CA, K-ras, β-catenin</td>
<td>P53 mutations (90%), HER2/neu amplification and overexpression</td>
</tr>
<tr>
<td><strong>Hormone sensitivity</strong></td>
<td>Yes – related to obesity, estrogen excess</td>
<td>No - arises from endometrial atrophy</td>
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<tr>
<td><strong>Precursor lesion</strong></td>
<td>Hyperplasia</td>
<td>No</td>
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<tr>
<td><strong>Histologic grade</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Histologic subtype</strong></td>
<td>Endometrioid</td>
<td>Serous, clear cell</td>
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<td><strong>Behavior</strong></td>
<td>Favorable</td>
<td>Aggressive</td>
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<tr>
<td><strong>5-year survival</strong></td>
<td>85%</td>
<td>43%</td>
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• Mutations in mismatch repair genes
• Most HNPCC gynecologic cancers associated with MSH2 mutations
• Tumors frequently exhibit microsatellite instability (MSI)
• Risk of **Endometrial Cancer** is up to 71%
• Risk of **Colorectal Cancer** is 40-60%
• Risk of **Ovarian Cancer** is 9-12%
• Increased risk of stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin cancers
Cowden syndrome - PTEN hamartoma tumor syndrome

- Rare autosomal dominant syndrome that occurs from a mutation in **PTEN tumor suppressor gene**
- Characterized by benign and cancerous tumors of the breast, thyroid, endometrium, colorectal, kidney, and skin (melanoma)
- Lifetime risk of **endometrial cancer is 13 to 28%**
- No established guidelines for endometrial screening
Molecular prognostic features

• The Cancer Genome Atlas (TCGA), 2013
  • genomic, transcriptomic, and proteomic analyses
  • over 370 endometrial cancers
  • four molecular subtypes based on tumor cell genomic architecture with distinct prognostic outcomes

• Clinically applicable molecular classification system
  • can be performed on standard formalin-fixed, paraffin-embedded material and serve as a surrogate for diagnosis of the four TCGA molecular subtypes
Four molecular subtypes (TCGA and pragmatic molecular classification subtype nomenclature)

- Ultramutated/DNA polymerase epsilon (POLE) mutated group (POLEmut)
- Hypermutated/microsatellite unstable group (MMRd)
- Copy number low group (NSMP)
- Copy number high (serous-like) group (p53abn)
Relationship between type 1/2 endometrial carcinoma, histomorphologic classification, and molecular classification

Type 1

Endometrioid endometrial carcinoma
Grade 1 to 2

Type 2

Clear cell carcinoma
Serous endometrial carcinoma

NSMP
MMRd
POLEmut
NSMP clear cell carcinoma
p53abn

Legend:
- >50%
- 10 to 50%
- <10%
Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular classification figure
• Stage I: confined to uterus
  • IA: inner ½
  • IB: outer ½
• Stage II: cervical stromal involvement
• Stage III: extra-uterine spread
  • IIIA: serosal/adnexal involvement
  • IIIB: vaginal/parametrial involvement
  • IIIC1: pelvic nodal involvement
  • IIIC2: aortic nodal involvement
• Stage IV: regional, distant metastases
  • IVA: bowel or bladder mucosa
  • IVB: distant metastases
Surgical staging

- Total hysterectomy, bilateral salpingo-oophorectomy +/- pelvic and aortic lymphadenectomy
  - Serous cancers - omentectomy, peritoneal biopsies and washings
- Surgical approach may vary
  - Minimally invasive preferred
When is lymph node sampling necessary?

• Balance between morbidity and utility
  • Lymphadenectomy is low risk, but not risk free
• Intraoperative triage identifies a subgroup of patients at very low risk of lymph node involvement

• Mayo Clinic intraoperative triage
  • Endometrioid of any grade without myometrial involvement (MI)
  • Grade 1 or 2 with <50% MI
  • Primary tumor <2cm

• University of Kentucky intraoperative triage
SLND following lymphatic mapping has become a standard option for the management of the retroperitoneal lymph nodes in endometrial cancer

Meta-analysis of nine prospective studies
- 429 patients with high-grade endometrial carcinoma:
  - SLND correctly identified 80 of the 87 patients with positive lymph nodes
  - pooled sensitivity: 92 percent (95% CI 84-96 percent)
  - False-negative rate was 8 percent, which is similar to that observed in low-grade endometrial cancer

The NCCN and the SGO both support the role of sentinel lymphadenectomy in the management of women with EC
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection

Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region

Peritoneal & serosal evaluation & washings

Retroperitoneal evaluation

- Excision of all mapped SLN with ultrastaging
- Any suspicious nodes must be removed regardless of mapping

- If there is no mapping on a hemi-pelvis, a side-specific LND is performed
- Para-aortic LND-- done at attending discretion
Primary treatment

• Surgery
• Radiation
  • Medically inoperable
  • 15% survival decrement per stage
  • Most die of other causes
• Hormonal therapy
  • May consider for young women who desire future fertility
  • Only appropriate in grade 1 cancers without evidence of myometrial invasion
    • MRI most sensitive to detect myometrial invasion
    • CT to rule out metastatic disease
  • Tumor must be hormone receptor positive
  • Megace 80-100 mg BID
  • Resample with D&C in 3 months – if persistent disease at 6-9 months, consider hysterectomy
Adjuvant treatment after primary surgery

- **Low-risk** endometrial cancer
  - Grade 1, confined to the endometrium
  - Risk of recurrence is very low following surgical treatment alone

- **Intermediate-risk** endometrial cancer
  - Confined to uterus, invades the myometrium or occult cervical stromal invasion
  - Adverse prognostic factors define low and high-intermediate-risk patients
    - deep myometrial invasion
    - grade 2 or 3 differentiation
    - presence of lymphovascular invasion within the cancer

- **High-risk** endometrial cancer
  - Stage III or higher, regardless of histology or grade, or serous or clear cell carcinoma, regardless of stage
  - High risk of relapse and death
Defining a high-intermediate risk (HIR) group

HIGH-INTERMEDIATE RISK
Age ≥70 with one risk factor
Age ≥50 with two risk factors
Age ≥18 with three risk factors

Risk Factors:
• Grade 2 or 3 tumor
• (+) lymphovascular space invasion
• Deep myometrial invasion

• Approximately one-third of the patients fall into HIR group
• HIR group represents 2/3 of recurrences and 2/3 of all cancer related deaths in GOG #99
• Cumulative incidence of recurrence for HIR group is 26%
• Radiation therapy reduces the risk of local recurrence, but does not improve overall survival (GOG 99)
  • Pelvic radiation resulted in a reduction in local recurrence
    • 2 versus 9%, HR 0.42, CI 0.21 – 0.83
    • No statistically significant reduction in risk of death
      • HR 0.73, 90% CI 0.43-1.26
  • Radiation therapy can be administered as vaginal brachytherapy, pelvic RT, or intensity-modulated RT
• Superiority of VCB/C compared with pelvic RT was not demonstrated. Acute toxicity was greater with VCB/C; late toxicity was similar. Pelvic RT alone remains an effective, well-tolerated, and appropriate adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.
Carboplatin and paclitaxel is the standard-of-care

- GOG 209 compared carboplatin plus paclitaxel with TAP
  - 1300 women with chemotherapy-naïve advanced endometrial cancer, including women with stage III disease
  - carboplatin and paclitaxel results in an equivalent overall response rate, similar PFS, and is also less toxic
  - median progression-free survival of 13 months and overall survival of 37 months
A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. (Matei et al. 2017)

• Although C-RT reduced the rate of local recurrence compared to CT; the combined modality regimen did not increase RFS in optimally debulked, stage III/IVA UC.
Molecular characterization of endometrial tumors is becoming critical in directing treatment for advanced and recurrent disease

- Estrogen receptor (ER) and progesterone receptor (PR) status
- MSI analysis
- Assessment of human epidermal growth factor receptor 2 (HER2) status for uterine serous cancers
- Next-generation sequencing to identify somatic mutations may be useful information for potential enrollment in a clinical trial
Systemic Therapy

### Recurrent or Metastatic Disease\(^a,b\)

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<td>• Cisplatin/doxorubicin(^3)</td>
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<td>• Cisplatin/doxorubicin/paclitaxel(^e,f,3)</td>
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<td>• Carboplatin/paclitaxel/bevacizumab(^e,g,4)</td>
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<td>• Paclitaxel(^5)</td>
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<td>• Albumin-bound paclitaxel(^h)</td>
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<td></td>
<td>• Topotecan</td>
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<td></td>
<td>• Bevacizumab(^b,i,6)</td>
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<td></td>
<td>• Temsirolimus(^7)</td>
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<td></td>
<td>• Docetaxel(^d) (category 2B)</td>
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<tr>
<td></td>
<td>• Ifosfamide (for carcinosarcoma)</td>
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<tr>
<td></td>
<td>• Ifosfamide/paclitaxel (for carcinosarcoma)(^8)</td>
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<td>• Cabozantinib</td>
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Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu.  
Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin

• Median progression-free survival was 8.0 months (control) versus 12.6 months.

Hormone therapy -
Advanced/recurrent endometrial cancer

• Grade 1 or 2 tumors and positive for ER and PR
• No randomized trials have compared chemotherapy with hormonal therapy as first-line treatment
• Hormonal therapy is reserved for women with more limited performance status or for second- or third-line treatment in patient with
  • Single-agent progestins
  • Trials of combination therapies have suggested higher efficacy
  • Sequential administration of megestrol acetate and tamoxifen
    • 27% response rate
    • 53% of the women with response had prolonged response (<20 months)
  • Single-agent aromatase inhibitors fulvestrant, and tamoxifen, lower response rates than combination treatments

Fiorica et al. Gynecol Oncol 2004;92:10-14
Hormone combination therapy

• Combinations of hormone and biologic agents have been shown to be effective in second- or third-line setting
  • Everolimus and letrozole
    • objective response rate of 32%
  • Follow-up study that added metformin
    • objective response rate was 28%
    • PR-positive patients having a 45% response rate
  • Preliminary data from a randomized trial comparing everolimus and letrozole with the older combination of tamoxifen alternating with megestrol acetate
    • Everolimus and letrozole had similar efficacy and a significantly lower risk of blood clots

• Single-agent aromatase inhibitors fulvestrant, and tamoxifen
  • Associated with lower response rates than the combination treatments

Slomovitz et al. Gynecol Oncol 2018;149:2-2. abstract
<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful in Certain Circumstances</th>
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<tbody>
<tr>
<td>Medroxyprogesterone acetate/tamoxifen (alternating)</td>
<td>Everolimus/letrozole (for endometrioid histology)</td>
<td>N/A</td>
</tr>
<tr>
<td>Megestrol acetate/tamoxifen (alternating)</td>
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<tr>
<td>Progestational agents</td>
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<tr>
<td>‣ Medroxyprogesterone acetate</td>
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<tr>
<td>‣ Levonorgestrel intrauterine device (IUD)</td>
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<td>‣ (for select fertility-sparing cases)</td>
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<td>Tamoxifen</td>
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<tr>
<td>Fulvestrant</td>
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Progression after prior chemotherapy

• Given the recognition that recurrent or metastatic endometrial cancer can be treated with immunotherapy, it is important to evaluate the mismatch repair (MMR) status in all patients using the primary tumor or tissue obtained at the time of metastatic disease.

• MMR status is important in assigning the optimal second-line therapy in this population.
For second- and third-line treatment determining MSI status helps guide the choice of targeted therapies.

Pembrolizumab, an immune checkpoint inhibitor, is an effective option for second-line treatment in women with high-MSI endometrial cancer.

KEYNOTE-158 study of single-agent pembrolizumab, 49 patients with high-MSI, recurrent endometrial cancer had an overall response rate of 57%, with 16% of the women having complete responses and 41% having partial responses.
High-grade tumors that are not characterized by high MSI

- multi–tyrosine kinase inhibitor lenvatinib — and pembrolizumab was recently granted accelerated FDA approval
- phase 2 trial
  - objective response rate was almost 40% at 24 months among unselected patients with recurrent endometrial cancer, and among the patients with a response
  - 64.5% had a response that lasted for at least 12 months
  - responses occurred in patients who had tumors without high MSI and in patients with uterine serous cancers
  - side effects of lenvatinib can be clinically significant
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