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Endometrial Cancer Therapeutic Discussion Deck
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Disease Overview
Endometrial Cancer
Epidemiology
Endometrial Cancer is the Most Common Gynecologic Malignancy in the United States

Among gynecologic malignancies, uterine corpus cancers are the most frequently diagnosed\(^1\)

- Endometrial cancers make up > 90% of all uterine corpus cancers\(^2\)

Estimated New Gynecologic Cancer Cases in United States for 2021\(^1,3-5\)

- 12,940 deaths from uterine cancer are predicted to occur in the United States in 2021\(^1\)
- This represents 2.1% of all cancer deaths in the United States in 2020\(^1\)

Epidemiology

Incidence of New Endometrial Cancer Cases has Been Rising

- Between 2009 – 2018 incidence of new endometrial cancer cases increased an average of 0.5% each year\(^1\)
- Death rates have also been rising an average of 1.9% each year between 2009-2018\(^1,2\)

Age-adjusted Rates of Uterine New Cases and Deaths\(^1\)

<table>
<thead>
<tr>
<th>Year</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology
While Overall Survival is High, Prognosis for Distant Disease is Poor

**Uterine Cancer Mortality in the US**

<table>
<thead>
<tr>
<th>4.9</th>
<th>12,940</th>
</tr>
</thead>
<tbody>
<tr>
<td>deaths per 100,000 women per year[^a]</td>
<td>2021 estimated total deaths</td>
</tr>
</tbody>
</table>

**Overall estimated 5-year survival in the US**

81.1%

for all patients with uterine cancer based on data from SEER 18, 2011–2017

**5-y Relative Survival Rate: Only 17.3% for Cases With Distant Disease at Diagnosis[^b]**

<table>
<thead>
<tr>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>94.9%</td>
<td>69.3%</td>
<td>17.8%</td>
</tr>
<tr>
<td>67.0%</td>
<td>20.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Estimated 5-year survival</td>
<td>Percentage of diagnosed cases by stage</td>
<td></td>
</tr>
</tbody>
</table>

[^a]: Age-adjusted data from 2014–2018.
[^b]: Based on data from SEER 18, 2011–2017, All Races, Female by SEER Summary Stage 2000.
Anatomy & Pathogenesis

Uterine Malignancies

- Uterine malignancies can be divided into two categories
  - Uterine corpus (body) malignancies
    - Endometrial carcinoma: arise from the epithelial cells of the endometrium
    - Uterine sarcoma: arise from the muscle and connective tissue of the myometrium
  - Cervical malignancies

Endometrial Cancer Classification

Endometrial Cancer is Typically Classified into Two Pathogenic Types With Certain Clinical, Metabolic, and Endocrine Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Type I (Endometrioid)</th>
<th>Type II (Non-endometrioid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>60-70%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>~ 60</td>
<td>~ 70</td>
</tr>
<tr>
<td>Onset of menopause (age)</td>
<td>After 50</td>
<td>Before 50</td>
</tr>
<tr>
<td>Background endometrium</td>
<td>Hyperplasia</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Estrogen associated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Associated obesity, hyperlipidemia, and diabetes mellitus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>Low (grades 1-2)</td>
<td>High (grade 3)</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Lymph nodes, ovaries</td>
<td>Peritoneum</td>
</tr>
<tr>
<td>Sensitivity to progestogens</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favorable</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Outcome (5-year survival)</td>
<td>86%</td>
<td>59%</td>
</tr>
</tbody>
</table>

**Risk Factors**

Risk Factors Vary by Endometrial Cancer Type

- The greatest risk factor for type I endometrial cancer is long-term exposure to endogenous or exogenous estrogen without adequate opposition by a progestin\(^1,2\)
- Risk factors for type I endometrial cancer include
  - Genetics (Lynch syndrome, Cowden syndrome, MSI)\(^3,4\)
  - Family history of endometrial, ovarian, breast or colon cancer\(^4\)
- Type II endometrial cancer is not estrogen-dependent, and as such has a different risk factor profile\(^2\)

---

**Notes**

MSI = microsatellite instability

Risk and Protective Factors

Many Risk Factors for Type I Endometrial Cancer Are Related to Unopposed Estrogen Exposure

**Risk Factors**

1. Obesity*¹ (Including central obesity)
2. Early Menarche*¹ and/or Late Menopause*¹
3. Estrogen Secreting Tumors*¹
4. Chronic Anovulation*¹ and/or Nulliparity*¹
5. Lynch or other hereditary genetic syndromes²
6. Unopposed Estrogen Therapy*¹,²
7. Tamoxifen*¹

**Protective Factors**

1. Pregnancy²
2. Oral contraceptives or intrauterine devices²
3. Physical activity²

**Risk factors related to:**
- Metabolic & Endocrine
- Medication Use
- Genetics & Family History

---

*Endogenous estrogen source; † Exogenous estrogen source.
Many Risk Factors for Type II Endometrial Cancer are not Estrogen-dependent

Risk Factors

1. Older Age
2. Parity
3. History of Breast Cancer
4. African American Race

References:
### Genetics of Endometrial Cancer

Common Genetic Alterations According to Pathogenic Endometrial Cancer Type

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Pathogenic Type</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type I</td>
<td>Type II</td>
<td></td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>52-78%</td>
<td>1-11%</td>
<td></td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>36-52%</td>
<td>24-42%</td>
<td></td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>28-40%</td>
<td>0-2%</td>
<td></td>
</tr>
<tr>
<td>ARID1A mutation</td>
<td>25-48%</td>
<td>6-11%</td>
<td></td>
</tr>
<tr>
<td>PIK3R1 mutation</td>
<td>21-43%</td>
<td>0-12%</td>
<td></td>
</tr>
<tr>
<td>CTNNB1 mutation</td>
<td>23-24%</td>
<td>0-3%</td>
<td></td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>15-43%</td>
<td>2-8%</td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>9-12%</td>
<td>60-91%</td>
<td></td>
</tr>
<tr>
<td>PPP2R1A mutation</td>
<td>5-7%</td>
<td>15-43%</td>
<td></td>
</tr>
<tr>
<td>HER2 amplification</td>
<td>0%</td>
<td>27-44%</td>
<td></td>
</tr>
</tbody>
</table>

- Most endometrial cancers (~95%) are caused by sporadic (somatic) mutations

A family history of Lynch syndrome, which accounts for ~5% of all endometrial carcinomas, increases the risk of endometrial cancer\(^1\)

- Caused by germline mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2\(^1\)
- MMR pathway maintains genomic integrity by correcting base substitution mismatches and insertion-deletion mismatches resulting from DNA replication errors\(^2\)
- MMR mutations cause alterations within microsatellite regions, resulting in MSI; this may affect genetic expression, resulting in aberrant cell growth or cell death\(^2\)

Acquired (non-germline) microsatellite instability (MSI) accounts for ~25% of MSI cases\(^1,3\)

- Caused by hypermethylation of the MLH1 promoter and epigenetic silencing of MLH1\(^3\)

The immune microenvironment in MSI-H endometrial tumors exhibits elevated CD8 and granzyme B-cells, which may allow these patients to respond favorably to immunotherapy\(^4\)
Histopathology of Endometrial Cancer

Histology

Common Histologic Subtypes For Endometrial Tumors

- **Endometrioid Carcinoma** (most common)
  - Differentiation: Well differentiated (usually low-grade), Type I
  - Characteristics: Proliferation of back-to-back endometrial glands without intervening stroma
  - Some tumors may have squamous differentiation

- **Papillary Serous Adenocarcinoma**
  - Differentiation: Less differentiated (high-grade), Type II
  - Characteristics: Complex papillary architecture, psammoma bodies in ~ 60%, and marked nuclear atypia

- **Clear Cell Carcinoma**
  - Differentiation: Less differentiated (high-grade), Type II
  - Characteristics: Tubulocystic, papillary, or solid patterns, psammoma bodies in ~ 10%, cells may be clear because of glycogen presence

- Less common histologic subtypes include squamous cell, transitional cell, glassy cell and undifferentiated carcinoma

Histopathology of Endometrial Cancer

Common Histologic Subtypes

Endometrioid adenocarcinoma (low-grade)*

Papillary serous adenocarcinoma

Clear cell carcinoma

*Although less common (15-20%), high-grade endometrioid carcinomas have an aggressive disease course and unfavorable prognosis, similar to type II tumors.1,2

Endometrial Carcinoma is Graded According to the Degree of Cellular Differentiation

Grading Developed by the International Federation of Gynecology and Obstetrics (FIGO)

Grade 1 (G1)
- Characteristics
  - Cells well differentiated
  - ≤ 5% non-squamous or non-morular solid growth pattern

Grade 2 (G2)
- Characteristics
  - Cells are moderately differentiated
  - 6 – 50% non-squamous or non-morular solid growth pattern

Grade 3 (G3)
- Characteristics
  - Cells are poorly differentiated
  - > 50% non-squamous or non-morular solid growth pattern

Histopathology of Endometrial Cancer

Molecular subgroups include:
- POLE ultramutated
- MSI hypermutated
- Copy-number low, MSS
- Copy-number high, serous-like

Histopathology of Endometrial Cancer
Most Endometrial Tumors Can Be Classified into One of Four Molecular Subgroups

MSI = microsatellite instability; MSS = microsatellite stable; POLE = polymerase epsilon.

Histopathology of Endometrial Cancer

Molecular Subgroups Correlate Closely With Disease Progression\textsuperscript{1,2}

\textbf{PFS According to Molecular Subgroup}\textsuperscript{2}

- Given the correlation with disease prognosis, the trend in the endometrial cancer field is shifting to a combination of molecular classification and histology\textsuperscript{3}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig.png}
\caption{Progression-free survival according to molecular subgroup.}
\end{figure}


\textit{MSI} = microsatellite instability; \textit{MSS} = microsatellite stable; \textit{PFS} = progression-free survival; \textit{POLE} = polymerase epsilon.

Endometrial cancer is the most common gynecologic cancer in the United States\(^1\)

Endometrial cancer is classified into 2 pathogenic types based on clinical, metabolic, and endocrine characteristics\(^2\)

Risk factors for Type I endometrial cancer include metabolic and endocrine factors, certain medication use, and genetics\(^3,4\)

Risk factors for Type II endometrial cancer include older age, parity, breast cancer history, and African American race\(^5-10\)

Frequency of genetic alterations varies to pathogenic type (I vs. II) although up to 40% of Type I tumors have microsatellite instability\(^2\)
Clinical Features & Diagnosis
Clinical Features & Diagnosis

Screening for Endometrial Cancer

- There is currently no available recommended guidelines for screening or routine screening tests to identify endometrial cancer in the general population\(^1\).
- The American Cancer Society recommends the following screening criteria based on risk for development of EC.\(^2\)
  - High risk patients (identified primarily as Lynch syndrome-associated mutations) should receive annual screening with an endometrial biopsy starting at the age of 35\(^2\).
  - Intermediate risk patients (identified primarily as obesity, PCOS with oligomenorrhea) should receive symptom assessments but do not require annual routine biopsy after age 35\(^2\).
  - Average risk patients (general population) should receive education on symptoms but there are no recommended disease screening in this population\(^2\).
- Women should be informed about risks and symptoms at the onset of menopause (especially unexpected bleeding and spotting) and to report these to their physicians\(^3\).

EC, endometrial cancer; PCOS, polycystic ovary syndrome

Abnormal uterine bleeding is the most common symptom (75-90% of women)\textsuperscript{1,2}, with bleeding pattern varying according to patient age.

**Signs & Symptoms**

Most Patients with Endometrial Cancer Present with Abnormal Vaginal Bleeding

- Abnormal uterine bleeding is the most common symptom (75-90% of women)\textsuperscript{1,2}, with bleeding pattern varying according to patient age.

**< 45 Years Old\textsuperscript{3}**
- Any abnormal bleeding that is persistent in the setting of:
  - Unopposed estrogen exposure
  - Failed medical management of bleeding
  - High-risk women (e.g. Lynch syndrome)

**45 Years Old – Menopause\textsuperscript{3}**
- Any abnormal bleeding including:
  - Intermenstrual
  - Frequent (< 24 days between episodes)
  - Heavy* (Total volume > 80 mL)
  - Prolonged bleeding (> 8 days)

**Postmenopausal Women\textsuperscript{1}**
- ANY bleeding, including spotting or staining

- The probability of endometrial cancer in women presenting with abnormal uterine bleeding is usually low (5 – 10%), but chances increase with age and risk factors\textsuperscript{4}

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\textsuperscript{3} Excessive menstrual blood loss which interferes with a woman’s physical, social, emotional, and/or material quality of life.
Initial Work-Up and Evaluation

General Overview

Components of Initial Work-Up and Evaluation

- History and Physical
- Pelvic examination
- Complete blood counts (CBC)
- Expert pathology review with additional endometrial biopsy (using D&C) as clinically indicated
  - D&C usually performed under general or regional anesthesia
  - Low-pressure devices (e.g., Pipelle, Endocell) are less invasive sampling method alternative due to their small diameter (<2.4 mm) and flexible design
  - Pathologic assessment should include universal testing of endometrial tumors for MMR gene mutations
- Imaging
  - Chest x-ray (non-fertility sparing)
  - Pelvic MRI (fertility-sparing; preferred)
  - TVUS (fertility-sparing)
- Consider genetic evaluation
- Consider liver and renal function tests, chemistry profile

---

*aInitial preoperative evaluation for known or suspected malignancy

*bPreoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation/morcellation should be avoided.

*cSee Principles of Pathology for Endometrial Carcinoma (ENDO-A)

*dSee Principles of Imaging for Endometrial Carcinoma (ENDO-B)

*All recommendations are category 2A unless otherwise indicated

D&C = dilation and curettage; MMR = mismatch repair; MRI = magnetic resonance image; TVUS = transvaginal ultrasound
Clinical Features & Diagnosis

Additional Work-Up and Evaluation

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend additional work-up¹,*
  - For suspected or gross cervical involvement of endometrioid histologyᵃ
    - Cervical biopsy or pelvic MRI (if not previously done)ⁱ
  - For suspected extrauterine disease of endometrioid histology
    - Serum CA-125 levels (optional)
    - Imaging (if clinically indicated and not previously done)ⁱ
  - For disease of serous, clear cell, or undifferentiated/dedifferentiated carcinoma or for carcinosarcoma⁵ histologies
    - Serum CA-125 levels (optional)
    - Imagingⁱ

ᵃSee UN-1 for classification of uterine neoplasms
ⁱSee Principles of Imaging (ENDO-B)
⁵Also known as malignant mixed mesodermal tumor or malignant Müllerian tumor
*All recommendations are category 2A unless otherwise indicated

CA-125 = cancer antigen 125; MRI = magnetic resonance imaging.

¹Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms V.1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed [January 24, 2021]. To view the most recent and complete version of the guideline, go online to NCCN.org.
Clinical Features & Diagnosis

Genetic Testing

NCCN Guidelines®¹, *Principles of Molecular Analysis

- NCCN Guidelines recommend universal testing of endometrial tumors for defects in the MMR pathway (e.g. MLH1, MSH2, MSH6)
  - Testing may be performed on the initial presurgical biopsy or D&C material or the final hysterectomy specimen
  - MLH1 loss should be further evaluated for promoter methylation to assess for an epigenetic process rather than a germline mutation
- Genetic counseling should be offered to the following patients:
  - Patients with all other MMR abnormalities
  - Patients without MMR defects but who have a significant family history of endometrial and/or colorectal cancer
- NCCN Guidelines also support the use of ancillary studies to complement morphological assessment of histologic tumor type:
  - POLE mutations
  - MMR/MSI
  - Aberrant p53 expression

SGO Clinical Practice Statement²
Screening for Lynch Syndrome in EC

- All women diagnosed with endometrial cancer should undergo clinical screening
  - Review of personal and family history
  - And/or molecular screening for Lynch syndrome
- Two main strategies for assessing Lynch syndrome
  - Germline testing recommended for women at an increased risk for Lynch syndrome defined by clinical criteria, but women who do not have a suggestive family history may not be identified by clinical criteria
  - Universal molecular tumor testing for either all endometrial cancers or cancers diagnosed at < 60 years old regardless of personal or family history
- IHC for MLH1, MSH2, MSH6, and PMS2 expression is recommended as it is the most cost-effective and widely available
- Tumors that show loss of MLH1 on IHC should undergo further testing for MLH1 hypermethylation

*All recommendations are category 2A unless otherwise indicated

EC = Endometrial Cancer; MMR = Mismatch Repair; dMMR = Mismatch Repair Deficient; MSI = microsatellite instability; POLE = DNA polymerase epsilon.

Clinical Features & Evaluation

Surgical Staging

- Endometrial cancer is staged by examining tissue removed during surgery\(^1\)
- Most widely adopted staging systems\(^1\)
  - International Federation of Gynaecology and Obstetrics (FIGO) stage\(^2\)

**Surgical Staging**

**FIGO Staging**

- **Stage IA Endometrial Cancer**: Tumor confined to endometrium (Left) only or < 50% myometrial invasion (Right)
- **Stage IB Endometrial Cancer**: ≥ 50% myometrial invasion

*Most common sites include inguinal lymph nodes, peritoneum (intraperitoneal), lung, bone, and liver*

Surgical Staging Continued

FIGO Staging

- Stage IIIA: Serosa and/or adnexae invasion
- Stage IIIB: Vaginal or parametrial involvement
- Stage IIIC: Regional pelvic or para-aortic retroperitoneal lymph node metastasis

Surgical Staging Continued

FIGO Staging

- Stage IVA: Bladder and/or bowel mucosa metastasis
- Stage IVB: Distant metastasis

*Most common sites include inguinal lymph nodes, peritoneum (intraperitoneal), lung, bone, and liver

Survival, Stage at Diagnosis and Recurrence

Majority of Endometrial Cancers Are Diagnosed at an Early Stage When Prognosis is More Favorable


Stage at Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proportion of Endometrial Cancer by Stage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>67</td>
</tr>
<tr>
<td>Regional</td>
<td>20</td>
</tr>
<tr>
<td>Distant</td>
<td>9</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
</tbody>
</table>

5-Year Survival by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proportion of Patients Survived (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>95</td>
</tr>
<tr>
<td>Regional</td>
<td>69.4</td>
</tr>
<tr>
<td>Distant</td>
<td>17.3</td>
</tr>
<tr>
<td>Unstaged</td>
<td>53.2</td>
</tr>
</tbody>
</table>
Survival, Stage at Diagnosis and Recurrence

10 – 15% of Women With Endometrial Cancer Will Recur After First-line Treatment

Recurrence Rate by Stage at Diagnosis3

- 10-15% of women diagnosed with endometrial cancer (all stages) will have a recurrence1,2
  - ~ 75% of recurrences are symptomatic1
  - Most recurrences occur within the first 3 years after treatment1
- Recurrence rates increases with more advanced stage at diagnosis3
- Other factors associated with increased risk of recurrence include age, tumor histopathology, progesterone receptor expression, and obesity3

Characteristics of Endometrial Cancer

Summary


<table>
<thead>
<tr>
<th>Stage</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Confined to the uterus</td>
</tr>
<tr>
<td>Stage II</td>
<td>Cervical invasion but not extended beyond uterus</td>
</tr>
<tr>
<td>Stage III</td>
<td>Regional spread beyond the uterus</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Stage IA (<50% myometrium)
Stage IB (≥ 50% myometrium)
Stage IIIA (Serosa)
Stage IIIB (Vagina)
Stage IIIC (Pelvic or lymph nodes)
Stage IVA (Bladder and/or rectal mucosa)
Stage IVB (Distal to upper abdomen, groin nodes, etc.)

2. Histology

- **Type I**
  - Endometrioid cancer; estrogen dependent
  - Typically low grade; favorable prognosis

- **Type II**
  - Includes serous, clear cell, squamous, mucinous, and mixed subtypes
  - Typically high grade; unfavorable prognosis

3. Grade

- **Grade I**
  - Cancer cells are well differentiated

- **Grade II**
  - Cancer cells are moderately differentiated

- **Grade III**
  - Cancer cells are poorly differentiated

Adapted from a diagram by © Cancer Research UK [2002]
Cancer Research UK is independent from GSK.
Treatment of Endometrial Cancer
## Treatment of Endometrial Cancer

### Overview of Endometrial Cancer Treatment

| Surgery<sup>1,2</sup> | Standard of treatment of early-stage endometrial cancer  
|----------------------|----------------------------------------------------------|
|                      |   • Hysterectomy with BSO  
|                      |   • Pelvic and periaortic lymph node dissection  
|                      |   • Sentinel lymph node mapping                          |
| Radiotherapy<sup>2</sup> |   • Vaginal brachytherapy  
|                      |   • External-beam radiation therapy                      |
| Chemotherapy<sup>2,3</sup> |   • Most commonly used regimen:  
|                      |     ○ Carboplatin and paclitaxel                         |
| Hormone therapy<sup>2</sup> |   • Progestational agents (hydroxyprogesterone, medroxyprogesterone, or megestrol<sup>a</sup>)  
|                      |   • Tamoxifen  
|                      |   • Aromatase inhibitors                                 |
| Biologic/targeted therapy<sup>2,4</sup> |   • mTOR Inhibitors  
|                      |   • Bevacizumab  
|                      |   • Pembrolizumab<sup>a</sup>  
|                      |   • Lenvatinib<sup>a</sup>                               |

<sup>a</sup> Megestrol acetate, pembrolizumab and lenvatinib mesylate are the only systemic therapies with FDA approval for the treatment of endometrial cancer.<sup>3</sup>

BSO, bilateral salpingo-oophorectomy; dMMR, deficient mismatch repair; MSI-H, high microsatellite instability; FDA, US Food and Drug Administration; mTOR, mammalian target of rapamycin.
Treatment of Endometrial Cancer

Initial management of endometrial cancer

Initial work-up and evaluation\(^1\-\(^3\)
- Pelvic examination
- Routine blood tests

Clinical examination

Imaging
- Ultrasound examination
- Additional imaging/laboratory testing indicated by clinical assessment or histology

Imaging

Surgery* and FIGO staging\(^1\-\(^3\)
- Total hysterectomy and bilateral salpingo-oophorectomy
- Lymph node dissection
- Debulking for advanced disease

Surgical resection

FIGO staging

Adjuvant therapy\(^1\-\(^3\)

Radiotherapy
- External beam radiotherapy
- Vaginal brachytherapy

Adjuvant therapy after surgery is recommended for women at intermediate and high risk of recurrence. Use of specific therapy options is highly individualized\(^1\-\(^3\)

Chemotherapy
- Carboplatin/paclitaxel

Biopsy and tumor marker testing
- Assess histological type, tumor grade, and depth of myometrial invasion, cervical stromal involvement and lymphovascular space invasion\(^4\-\(^3\)
- Universal testing of endometrial tumors for defects in the MMR pathway\(^4\-\(^3\)
  - IHC is recommended as it is the most cost-effective and widely available\(^5\)
  - Estrogen receptor testing\(^4\,\(^\#\),**

*All recommendations are category 2A unless otherwise indicated

MMR, mismatch repair deficient; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; SGO, Society of Gynecologic Oncology.

\(^1\) Surgery is recommended for medically operable patients and most patients can be managed by surgery alone.\(^3\) \(^2\) US guideline organizations (eg, SGO and NCCN) recommend dMMR screening for all endometrial tumors using IHC to facilitate detection of Lynch syndrome.\(^4\,\(^5\) \(^\#\) ER testing is recommended in settings of stage III, IV, and recurrent disease.\(^1\)

Surgery

Surgery is the Standard Treatment for Endometrial Cancer

- Surgical treatment includes:
  - Hysterectomy with bilateral salpingo-oophorectomy\(^1\)
    - Removal should be en bloc, avoiding IP morcellation or tumor fragmentation\(^2;*\)
  - Consideration of lymph node assessment to complete staging\(^2;*\)
    - Either on all patients with sentinel lymph node sampling, or by selective algorithm to perform lymphadenectomy on patients with risk on lymph node metastasis
  - Therapeutic lymph node removal if suspicious or obviously enlarged\(^2;*\)

\(^*\)All recommendations are category 2A unless otherwise indicated

IP = intraperitoneal

Surgery is the Standard Treatment for Endometrial Cancer (Cont’d.)

– Surgical techniques include laparotomy (open surgery) and laparoscopy/robotic surgery (minimally invasive surgery)\(^1\)
  – Minimally invasive surgery is the preferred approach when technically feasible\(^2,\)*
    – Both techniques show equivalent disease-free and OS in retrospective studies\(^3\)
    – This is recommended as the standard in patients with apparent uterine-confined disease where possible\(^2,\)*
  – A prospective Phase III study is ongoing comparing the clinical benefit of conventional or robotic laparoscopic surgeries in women with gynecological cancers\(^4\)
    – Robotic laparoscopy (RL) was not found superior to conventional laparoscopy (CL) with regard to the incidence of severe perioperative morbidity in patients with gynecologic cancer\(^4\)
    – RL involved a longer operating time than CL\(^4\)
  – Some women will require adjuvant therapy after surgery, to target lymph node disease and prevent recurrence\(^1\)

*All recommendations are category 2A unless otherwise indicated
OS = overall survival

Most patients with endometrial cancer have a low risk of recurrence and are managed by surgery alone\(^1\)

Risk groups have been devised based on clinical-pathological prognostic factors to identify patients at risk of recurrence who may benefit from adjuvant therapy\(^1\)

Adjuvant therapy after surgery is recommended for women at intermediate and high risk of recurrence\(^1,2,4\)

### Factors Associated With Worse Prognosis After Surgery

<table>
<thead>
<tr>
<th>Uterine</th>
<th>Extrauterine</th>
</tr>
</thead>
</table>
| • Deep myometrial invasion\(^4\)  
• Higher tumor grade (less differentiated)\(^1\)  
• Tumor size\(^2,4,5\)  
• Negative HR (ER/PR) status\(^3\)  
• HER2 overexpression\(^3\)  
• Lymphovascular space invasion\(^1\) | • Stage ≥ 2\(^1,4\)  
• Unresectable metastases\(^1,4\) |

*All recommendations are category 2A unless otherwise indicated*

ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; HR = hormone receptor; PR = progesterone receptor

Adjuvant Therapy

Risk Categories

- Historically, endometrial cancer was stratified into 3 risk categories (low, intermediate and high) based on tumor stage, grade and depth of myometrial invasion.

- Recently, a new risk stratification was introduced but still based on stage, grade, depth of invasion and clarified LVSI.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Description*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Stage I endometrioid, grade 1-2, &lt; 50% myometrial invasion, LVSI negative</td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Stage I endometrioid, grade 1-2, ≥ 50% myometrial invasion, LVSI negative</td>
</tr>
</tbody>
</table>
| High-intermediate | • Stage I endometrioid, grade 3, < 50% myometrial invasion, regardless of LVSI status  
                       • Stage I endometrioid, grade 1-2, LVSI unequivocally positive, regardless of depth of myometrial invasion |
| High            | • Stage I endometrioid, grade 3, ≥ 50% myometrial invasion regardless of depth of myometrial invasion  
                       • Stage II  
                       • Stage III endometrioid, no residual disease  
                       • Non-endometrioid (serous, clear cell or undifferentiated carcinoma) |
| Advanced        | • Stage III with residual disease  
                       • Stage IVA |
| Metastatic      | • Stage IVB |

*FIGO 2009 staging used; LVSI = Lymphovascular space invasion

Radiotherapy

Radiotherapy is an Essential Component in the Managed of Endometrial Cancer – Localized Control

GOG 258 evaluated cisplatin and tumor volume directed radiotherapy (RT) followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel alone for optimally debulked, advanced endometrial carcinoma

- C-RT reduced the ration of local recurrence compared to CT alone
- The combined modality regimen did not increase RFS in optimally debulked, stage III/IVA UC5

PORTEC-1 trial showed that pelvic EBRT improves locoregional recurrence rates compared to no additional treatment, but has no additional benefit on distant metastasis rates or overall survival

CT = chemotherapy; C-RT = chemoradiation; EBRT = external beam radiation; staging used; LVSI = Lymphovascular space invasion; RFS = Relapsed free survival

Current Treatment of Advanced Endometrial Cancer

NCCN Guidelines

**Locoregional recurrence**
- No Prior RT to site of recurrence
- EBRT\(^g\) ± brachytherapy\(^g\) ± systemic therapy\(^g\)
- or Surgical exploration\(^b\) + resection ± IORT (Category 3 for IORT)
- Disease confined to vagina or paravaginal soft tissue
- EBRT\(^g\) ± brachytherapy\(^g\) ± systemic therapy\(^g\)
- or Pelvic LN
- Para-aortic or common iliac LN
- Locoregional disease\(^2\)
- Upper abdominal peritoneal disease
- Systemic therapy\(^h\) ± EBRT\(^9,0\)

**Isolated metastases**
- Consider resection and/or EBRT\(^g\) or ablative therapy\(^z\)
- Consider systemic therapy\(^h\) (category 2B)
- Not amenable to local treatment or Further recurrence
- Treat as disseminated metastases (see below)

**Disseminated metastases**
- Systemic therapy\(^h\) ± palliative EBRT\(^g\)
- If progression, Best supportive care (see NCCN Guidelines for Palliative Care)

Footnotes:
- \(^a\) See Principles of Radiation Therapy for Uterine Neoplasms
- \(^b\) See Principles of Therapy for Endometrial Carcinoma
- \(^c\) See Principles of Therapy of Imaging
- \(^d\) Consider ablative radiation therapy for 1-5 metastatic lesions if the primary has been controlled (category 2B) (Palma DA, et al. Lancet 2019;393:2051-2058)
- \(^e\) May include patients with isolated common iliac or para-aortic lymph node recurrence
- \(^f\) Consider preoperative EBRT in select patients
- \(^g\) Recommended for small-volume vaginal and/or paravaginal disease
- \(^h\) Consider brachytherapy for locoregional disease with a vaginal component
- \(^i\) Post-resection consolidation EBRT can be considered in patients who were not previously irradiated or who are deemed to have additional tolerance for radiation

All recommendations are category 2A unless otherwise indicated.

EBRT, external beam radiation therapy; IORT, intraoperative radiation therapy; LN, lymph nodes

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Current Treatment of Advanced Endometrial Cancer

Treatment of Isolated Metastases

- Surgical resection ± EBRT, EBRT alone, or ablative therapy may be considered¹,*
  - Consider ablative radiation therapy for 1-5 metastatic lesions if the primary has been controlled¹,*
- Systemic therapy may be considered (category 2B)¹,*
  - Hormone therapy is typically used for lower-grade endometrioid histologies, preferable in patients with small tumor volume or an indolent growth pace¹,*
    - Hormonal therapies include megestrol or medroxyprogesterone acetate with alternating tamoxifen, progestational agents alone, aromatase inhibitors, tamoxifen alone, or fulvestrant (category 2B)¹,*
    - No specific hormonal drug or schedule has been found to be superior to others¹,*
  - Chemotherapy¹,*
    - Carboplatin and paclitaxel are increasingly used, with response rates of 40% - 62% and overall survival of 13 – 29 months²-⁴

*All recommendations are category 2A unless otherwise indicated.

EBRT = external beam radiation

Cytotoxic chemotherapy is the mainstay of therapy for metastatic endometrial carcinoma, but response rates are modest and treatment remains palliative\(^1\)

Effective second-line treatment options are extremely limited for patients with recurrent disease\(^2,3\)

### Treatment of Disseminated Metastases

<table>
<thead>
<tr>
<th>Metastases</th>
<th>Treatment(^4,,*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade, asymptomatic, hormone receptor-positive disseminated metastases</td>
<td>Hormone therapy with chemotherapy on progression</td>
</tr>
<tr>
<td>Symptomatic, higher grade, or large volume metastases</td>
<td>Chemotherapy ± palliative EBRT</td>
</tr>
<tr>
<td>Persistent progression of disseminated metastases</td>
<td>Best supportive care or clinical trial</td>
</tr>
</tbody>
</table>

\(^*\)All recommendations are category 2A unless otherwise indicated.

EBRT = external beam radiotherapy

Current Treatment of Advanced Endometrial Cancer

Fertility-Sparing Treatment

- Women < 40 years old represent < 5% of endometrial cancer cases\(^1\)
  - More common in hereditary cases (e.g. Lynch Syndrome),\(^1\) obesity\(^2\) and polycystic ovary syndrome\(^3\)
- Fertility-sparing treatment may be an option, if **ALL** of the following criteria are met.\(^2-4,*\)
  - Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
  - Disease limited to endometrium by MRI (preferred) or TVUS
  - Absence of suspicious or metastatic disease on imaging
  - No contraindications to medical therapy or pregnancy
  - Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma\(^2-4,*\)
- Primary fertility-sparing treatment consists of continuous progestin-based therapy\(^2-4,*\)
- Close follow-up with endometrial sampling every 3-6 months is recommended\(^2-4,*\)

*All recommendations are category 2A unless otherwise indicated.

MRI = magnetic resonance imaging; TVUS = transvaginal ultrasound.

Monitoring After Treatment of Advanced Endometrial Cancer

- Endometrial cancer is most likely to recur within the first 3 years after treatment
  - All patients should receive verbal and written information regarding the symptoms of recurrent EC as most recurrences are symptomatic
  - Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek immediate evaluation

<table>
<thead>
<tr>
<th>Follow-up Schedule and Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Physical exam every 3-6 months for 2-3 years, then every 6 months for up to year 5 then annually</td>
</tr>
<tr>
<td>• CA-125 if initially elevated</td>
</tr>
<tr>
<td>• Imaging as clinically indicated¹</td>
</tr>
<tr>
<td>• Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, smoking cessation, sexual health (including vaginal dilator use and lubricants/moisturizers), nutrition counseling, potential long-term and late effects of treatment²</td>
</tr>
</tbody>
</table>

¹See Principles of Imaging
²See Principles of Gynecologic Survivorship

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# SGO Guidelines

## Treatment of Advanced or Recurrent Endometrial Cancer

<table>
<thead>
<tr>
<th>SGO Recommendations for Advanced or Recurrent Endometrial Cancer¹</th>
<th>Level of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of chemotherapy in the treatment of advanced endometrial cancer improves patient outcomes</td>
<td>A</td>
</tr>
<tr>
<td>Chemotherapy and radiation therapy used in combination may offer superior outcomes compared with single-modality treatment</td>
<td>B</td>
</tr>
<tr>
<td>In women with gross residual disease, chemotherapy with paclitaxel and carboplatin is as effective as other regimens reported in the literature and has less toxicity</td>
<td>B</td>
</tr>
</tbody>
</table>

- Levels of recommendation:
  - A: There is good evidence to support the recommendation
  - B: There is fair evidence to support the recommendation

---

SGO = Society of Gynecologic Oncology.
Treatment of Metastatic or Recurrent Endometrial Cancer

- Initial patient evaluation should include an MRI (for suspected pelvic recurrence) and CT (to assess abdomen and thorax for other metastases)
- Treatment options for recurrent or metastatic disease depend on the extent of disease and prior therapy and are similar to treatment for primary disease*

*All recommendations are category 2A unless otherwise specified

CT = computed tomography; EBRT = external beam radiotherapy; ER = estrogen receptor; IORT = intraoperative radiation therapy; MRI = magnetic resonance imaging; PR = progesterone receptor.

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## Treatment of Metastatic or Recurrent Endometrial Cancer

### Recurrent, Metastatic or High-Risk Disease\(^1,a,b\)

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful in Certain Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic therapies(^a,b)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel (category 1 for carcinosarcoma)</td>
<td>• Carboplatin/docetaxel(^d)</td>
<td>N/A</td>
</tr>
<tr>
<td>• Carboplatin/paclitaxel/trastuzumab(^b) (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)</td>
<td>• Cisplatin/doxorubicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cisplatin/doxorubicin/paclitaxel(^e,f)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Carboplatin/paclitaxel/bevacizumab(^e,g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cisplatin</td>
<td></td>
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<tr>
<td></td>
<td>• Carboplatin</td>
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<tr>
<td></td>
<td>• Doxorubicin</td>
<td></td>
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<tr>
<td></td>
<td>• Liposomal doxorubicin</td>
<td></td>
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<tr>
<td></td>
<td>• Paclitaxel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Albumin-bound paclitaxel(^h)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Topotecan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bevacizumab(^i)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Docetaxel (category 2B)(^d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ifosfamide (for carcinosarcoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ifosfamide/paclitaxel (for carcinosarcoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Carboplatin/Ifosfamide (for carcinosarcoma)</td>
<td></td>
</tr>
<tr>
<td><strong>Biomarker-directed systemic therapy for second-line treatment</strong></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• Lenvatinib/pembrolizumab(^j,k)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pembrolizumab(^l) (for TMB-H or MSI-H/dMMR tumors(^m))</td>
<td></td>
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<tr>
<td></td>
<td>• Nivolumab(^n)</td>
<td></td>
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<tr>
<td></td>
<td>• Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)(^e)</td>
<td></td>
</tr>
<tr>
<td><strong>Hormone therapy(^o)</strong></td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
<td></td>
</tr>
<tr>
<td>• Progestational agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Medroxyprogesterone acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Megestrol acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Levonorgestrel intrauterine device (IUD) (For select fertility-sparing cases)</td>
<td></td>
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<tr>
<td>• Aromatase inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>• Tamoxifen</td>
<td></td>
<td></td>
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<tr>
<td>• Fulvestrant</td>
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</tbody>
</table>

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Footnotes on next page

All recommendations are category 2A unless otherwise indicated.

dMMR, mismatch repair-deficient; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability high; N/A, not applicable; NTRK, neurotrophic tyrosine kinase; TMB-H, tumor mutational burden-high

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Footnotes on next page

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Footnotes

a Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel and docetaxel may cause drug reactions
b Chemotherapy regimens can be used for all carcinoma histologies. Carcinosarcomas are now considered and treated as high-grade carcinomas

* An FDA-approved biosimilar is an appropriate substitute for trastuzumab
* For advanced and recurrent disease only

1 The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity
2 An FDA-approved biosimilar is an appropriate substitute for bevacizumab
3 Albumin-bound paclitaxel is a reasonable substitute for patients with a hypersensitivity to paclitaxel if the skin testing to paclitaxel is negative. If the patient has a positive skin test to paclitaxel then the patient requires desensitization to paclitaxel. Albumin-bound paclitaxel is not a reasonable substitute for paclitaxel if the patient’s skin test is positive

Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy

For advanced or recurrent disease that is not MSI-H or dMMR in patients who are not candidates for curative surgery or radiation and have progressed on prior systemic therapy

* See NCCN Guidelines for Management of Immunotherapy-Related Toxicities

For recurrent endometrial cancer, NCCN recommends MSI-H or dMMR testing if not previously done. Pembrolizumab is indicated for patients with MSI-H or dMMR tumors that have progressed following prior treatment

NCCN recommend TMB-H testing if not previously done. Pembrolizumab is indicated for patients with unresectable or metastatic tumors with TMB-H [≥10 mutations/megabase (mut/Mb)], as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options

For mismatch repair-deficient (dMMR) recurrent, metastatic, or high-risk endometrial carcinoma

Hormonal therapy is typically used for lower-grade endometrioid histologies, preferably in patients with small tumor volume or an indolent growth pace
Treatment of Metastatic or Recurrent Endometrial Cancer

Targeted Therapy

- Results of most targeted agents as monotherapy in phase II studies have shown low response rates\(^1,2\)

- Combination therapies with targeted agents have shown improved outcomes for:
  - Bevacizumab + radiotherapy\(^3,4\)
  - Temsirolimus + bevacizumab\(^5\)
  - Everolimus + letrozole\(^6\)

- Several ongoing trials are evaluating further combinations

- Targeted combination therapies raise tolerability concerns, particularly given that nearly half of patients diagnosed are ≥ 65 years old and are expected to have a high number of comorbidities\(^5,7\)

- Immuno-oncology therapies have recently been approved for MSI-H/dMMR advanced solid tumors and non-MSI-H/dMMR endometrial carcinoma\(^8\)