Endometrial Cancer Treatment (PDQ®)–Health Professional Version

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General Information About Endometrial Cancer

Cancer of the endometrium is the most common gynecologic malignancy in the United States and accounts for 7% of all cancers in women. Most cases are diagnosed at an early stage and are amenable to treatment with surgery alone.[1] However, patients with pathological features predictive of a high rate of relapse and patients with extrauterine spread at diagnosis have a high rate of relapse despite adjuvant therapy. The most common cause of death in patients with endometrial cancer is cardiovascular disease because of related metabolic risk factors.[2]

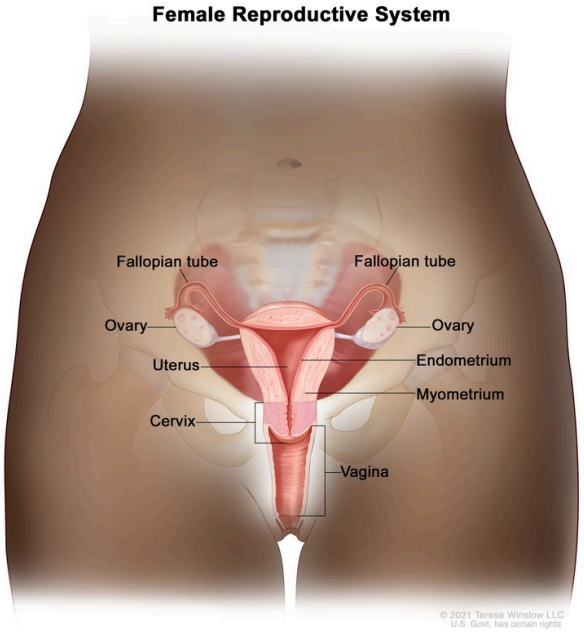
Incidence and Mortality

Estimated new cases and deaths from cancer of the uterine corpus, which includes the endometrium, in the United States in 2025:[1]

- New cases: 69,120.
- Deaths: 13,860.

Anatomy

The endometrium is the inner lining of the uterus and has both functional and basal layers. The functional layer is hormonally sensitive and is shed in a cyclical pattern during menstruation in reproductive-age women. Both estrogen and progesterone are necessary to maintain a normal endometrial lining. However, factors that lead to an excess of estrogen, including obesity and anovulation, lead to an increase in the deposition of the endometrial lining. These changes may lead to endometrial hyperplasia and, in some cases, endometrial cancer. Whatever the cause, a thickened lining will lead to sloughing of the endometrial tissue through the endometrial canal and into the vagina. As a result, heavy menstrual bleeding or bleeding after menopause are often the initial signs of endometrial cancer. This symptom tends to happen early in the disease course, allowing for identification of the disease at an early stage for most women.



Anatomy of the female reproductive system.

Risk Factors

Increasing age is the most important risk factor for most cancers. Other risk factors for endometrial cancer include the following:

- Hormone therapy.[3-6]
  - Postmenopausal estrogen therapy.[7-14]
- Selective estrogen receptor modifiers.[15-17]
  - Tamoxifen therapy.
- Obesity.[18,19]
- Metabolic syndrome.[20]
- Diabetes.[21,22]
- Reproductive factors.
  - Nulliparity.[23]
  - Early menarche or late menopause.[24]
  - Polycystic ovary syndrome.[25]
- Family history/genetic predisposition.
  - Mother, sister, or daughter with uterine cancer.[26]
  - Certain genetic syndromes, such as Lynch syndrome.[27-30]
- Endometrial hyperplasia.[31]

For more information, see Endometrial Cancer Prevention.

Prolonged, unopposed estrogen exposure has been associated with an increased risk of endometrial cancer.[9,32] However, combined estrogen and progesterone therapy prevents this increased risk.[33,34]

Tamoxifen, which is used to treat and prevent breast cancer (NSABP-B-14), is associated with an increased risk of endometrial cancer related to the estrogenic effect of tamoxifen on the endometrium.[15,35] It is important that patients who are receiving tamoxifen and experiencing abnormal uterine bleeding have follow-up examinations and biopsy of the endometrial lining. The U.S. Food and Drug Administration released a black box warning that includes data about the increase in uterine malignancies associated with tamoxifen use. For more information about risk factors for Lynch syndrome–associated endometrial cancer, see the Lynch Syndrome section in Genetics of Breast and Gynecologic Cancers.

Clinical Features

Irregular vaginal bleeding is the most common presenting sign of endometrial cancer. It generally occurs early in the disease process and is the reason why most patients are diagnosed with highly curable stage I endometrial cancer.

Diagnostic Evaluation

The following procedures may be used to detect endometrial cancer:

- Transvaginal ultrasonography.
- Endometrial biopsy.
- Pelvic examination.
- Dilatation and curettage.
- Hysteroscopy.

To definitively diagnose endometrial cancer, a procedure that directly samples the endometrial tissue is necessary.

The Pap smear is not a reliable screening procedure for the detection of endometrial cancer, even though a retrospective study found a strong correlation between positive cervical cytology and high-risk endometrial disease (i.e., high-grade tumor and deep myometrial invasion).[36] A prospective study found a statistically significant association between malignant cytology and increased risk of nodal disease.[37]

Prognostic Factors

Prognostic factors for endometrial cancer include:

- Tumor stage and grade (including extrauterine nodal spread).
- Hormone receptor status.

Tumor stage and grade (including extrauterine nodal spread)

Table 1 highlights the risk of nodal metastasis based on findings at the time of staging surgery:[38]

Table 1. Risk of Nodal Metastasis in Clinical Stage I Endometrial Cancer

Prognostic Group	Patient Characteristics	Risk of Nodal Involvement
A	Grade 1 tumors involving only endometrium	<5%
	No evidence of intraperitoneal spread	
B	Grade 2–3 tumors	5%–9% pelvic nodes
	Invasion of <50% of myometrium	
	No intraperitoneal spread	4% para-aortic nodes
C	Deep muscle invasion	20%–60% pelvic nodes
	High-grade tumors	10%–30% para-aortic nodes
	Intraperitoneal spread	

A Gynecologic Oncology Group study related surgical-pathological parameters and postoperative treatment to recurrence-free interval and recurrence site. Grade 3 histology and deep myometrial invasion in patients without extrauterine spread were the greatest determinants of recurrence. In this study, the presence of the following factors greatly increased the frequency of recurrence:[39,40]

- Positive pelvic nodes.
- Adnexal metastasis.
- Positive peritoneal cytology.
- Capillary space involvement.
- Involvement of the isthmus or cervix.
- Positive para-aortic nodes (includes all grades and depth of invasion). Of the cases with aortic node metastases, 98% were in patients with positive pelvic nodes, intra-abdominal metastases, or tumor invasion of the outer 33% of the myometrium.

When the only evidence of extrauterine spread is positive peritoneal cytology, the influence on outcome is unclear. The value of therapy directed at this cytological finding is not well founded,[41-46] and some data are contradictory.[47] Although the collection of cytology specimens is still suggested,

a positive result does not upstage the cancer. Other extrauterine disease must be present before additional postoperative therapy is considered.

Involvement of the capillary-lymphatic space on histopathological examination correlates with extrauterine and nodal spread of tumor.[48]

Hormone receptor status

When possible, progesterone and estrogen receptor statuses, assessed either by biochemical or immunohistochemical methods, are included in the evaluation of patients with stage I and stage II cancer.[49-51]

One report found progesterone receptor levels to be the single most important prognostic indicator of 3-year survival in clinical stages I and II disease. Patients with progesterone receptor levels of 100 or greater had a 3-year disease-free survival rate of 93%, compared with 36% for those with a level below 100. After adjusting for progesterone receptor levels, only cervical involvement and peritoneal cytology were significant prognostic variables.[52]

Other reports confirm the importance of hormone receptor status as an independent prognostic factor.[53] Additionally, immunohistochemical staining of paraffin-embedded tissue for both estrogen and progesterone receptors has been shown to correlate with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) grade and survival.[49-51]

Other prognostic factors

Other factors predictive of poor prognosis include:[51,54,55]

- A high S-phase fraction.
- Aneuploidy.
- *PTEN* loss-of-function variant.
- *PIK3CA* variant.
- *TP53* variant.
- Oncogene expression (e.g., overexpression of the *HER2/neu* oncogene has been associated with a poor overall prognosis).

A general review of prognostic factors has been published.[56]

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Cellular Classification of Endometrial Cancer

Endometrial cancers are classified as one of the following two types:

- Type 1 may arise from complex atypical hyperplasia and is pathogenetically linked to unopposed estrogenic stimulation.
- Type 2 develops from atrophic endometrium and is not linked to hormonally driven pathogenesis.

The most common type of endometrial cancer is endometrioid adenocarcinoma.

Frequency of endometrial cancer cell types is as follows:

1. Endometrioid (75%) comprises malignant glandular epithelial elements; an admixture of squamous metaplasia is not uncommon.
    a. Ciliated adenocarcinoma.
    b. Secretory adenocarcinoma.
    c. Papillary and villoglandular adenocarcinomas are histologically similar to those noted in the ovary and the fallopian tube. The prognosis is worse for these tumors.[1]
    d. Adenocarcinoma with squamous differentiation.
        - Adenoacanthoma.
        - Adenosquamous cells contain malignant glandular and squamous epithelial elements.[2]
2. Mixed, defined as two carcinomatous cell types, with the smaller component making up at least 10% of the total (10%).
3. Uterine papillary serous (<10%).
4. Clear cell (4%) is histologically similar to those noted in the ovary and the fallopian tube. The prognosis for clear cell tumors is worse.[1]
5. Carcinosarcoma (3%), also known as malignant mixed mesodermal tumor, has both carcinomatous and sarcomatous elements. This tumor was historically categorized as a subtype of uterine sarcomas; however, recent evidence points to its origin as an adenocarcinoma that has undergone differentiation into the sarcomatous elements.
6. Mucinous (1%).
7. Squamous cell (<1%).
8. Undifferentiated (<1%).

Molecular Subgroups

PTEN variants are more common in type 1 endometrial cancers; *TP53* and *HER2/neu* overexpression are more common in type 2 endometrial cancers, although some overlap exists.

The Cancer Genome Atlas's full genetic display of hundreds of endometrial cancers identified four subtypes to further characterize endometrial cancers:[3]

- *POLE* ultramutated. This subtype has clinical significance, and adjuvant therapies are avoided.
- Microsatellite instability hypermutated.
- Copy number low.
- Copy number high.

These categories can be used to stratify patients into low- and high-risk prognostic categories. A modification of The Cancer Genome Atlas methods into more accessible tests was also successful in discriminating cancers into relevant prognostic categories. However, a combination of previously known risk factors with the genetic data was the most effective at determining prognostic categories.[4]

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Stage Information for Endometrial Cancer

The pattern of endometrial cancer spread is partially dependent on the degree of cellular differentiation. Well-differentiated tumors tend to limit their spread to the surface of the endometrium; myometrial invasion is less common. Myometrial invasion occurs much more frequently in patients with poorly differentiated tumors and is frequently a harbinger of lymph node involvement and distant metastases.[1,2]

Metastatic spread occurs in a characteristic pattern. Regional spread to the pelvic and para-aortic nodes is common. Distant metastasis most commonly involves the following sites:

- Lungs.
- Inguinal and supraclavicular nodes.
- Liver.
- Bones.

- Brain.
- Vagina.

FIGO Staging

The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and the American Joint Committee on Cancer (AJCC) have both designated staging systems for endometrial cancer. The FIGO system is the most commonly used staging system for endometrial cancer.[3-5] The 2023 FIGO staging update has not been widely adopted because it incorporates molecular-based results, and some physicians do not have access to those data for their patients. Additionally, given the significant changes in the 2023 FIGO staging system, especially in the definition of early stage disease, more outcome data are needed so it might be more prudent to use the 2021 system in a clinical setting while discussing prognosis and treatment with patients. Therefore, both the 2023 and the 2021 FIGO staging systems are presented in this section.

FIGO stages I to IV are further subdivided by the histological grade (G) of the tumor, for example, stage IB G2. Carcinosarcomas, which had previously been designated as sarcomas, are now considered poorly differentiated adenocarcinomas; as such, they are included in this system.[5]

2023 FIGO staging for endometrial cancer

Table 2. 2023 FIGO Definitions for Stage I Cancer of the Endometrium[a,b,c]

Stage	Description
I	Confined to the uterine corpus and ovary.[d]
IA	Disease limited to the endometrium OR nonaggressive histological type, i.e., low-grade endometrioid, with invasion of less than half of myometrium with no or focal LVSI OR good prognosis disease.
IA1	Nonaggressive histological type limited to an endometrial polyp OR confined to the endometrium.
IA2	Nonaggressive histological types involving less than half of the myometrium with no or focal LVSI.
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary.[d]
IB	Nonaggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI.[e]

Stage	Description
IC	Aggressive histological types[f] limited to a polyp or confined to the endometrium.

Stage	Description

T = primary tumor; N = regional lymph node; M = distant metastasis; p = pathological; AJCC = American Joint Committee on Cancer; ESGO-ESTRO-ESP = European Society of Gynaecological Oncology, European Society for Radiotherapy and Oncology, European Society of Pathology; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; ITC = isolated tumor cell; LVSI = lymphovascular space involvement; MMRd = mismatch repair deficiency; NSMP = no specific molecular profile; *POLEmut* = pathogenic *POLE* mutation; p53abn = *TP53* abnormal; SLN = sentinel lymph node; WHO = World Health Organization.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[3]

[b]Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histological type and LVSI must be recorded. If available and feasible, molecular classification testing (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions (see Table 6).

[c]In early endometrial cancer, the standard surgery is a total hysterectomy with bilateral salpingo-oophorectomy via a minimally invasive laparoscopic approach. Staging procedures include infracolic omentectomy in specific histological subtypes, such as serous and undifferentiated endometrial carcinoma, as well as carcinosarcoma, due to the high risk of microscopic omental metastases. Lymph node staging should be performed in patients with intermediate-high/high-risk disease. SLN biopsy is an adequate alternative to systematic lymphadenectomy for staging proposes. SLN biopsy can also be considered in patients with low-/low-intermediate-risk disease to rule out occult lymph node metastases and to identify disease truly confined to the uterus. Thus, the ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma, which is endorsed by FIGO. In assumed early endometrial cancer, an SLN biopsy in an adequate alternative to systematic lymphadenectomy in high-intermediate and high-risk cases for the purpose of lymph node staging and can also be considered in low–/intermediate-risk disease to rule out occult lymph node metastases. An SLN biopsy should be done in association with thorough (ultrastaging) staging as it will increase the detection of low-volume disease in lymph nodes.

[d]Low-grade endometrioid carcinomas involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

[e]LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.

[f]Grade and histological type are as follows: (1) Serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high grade by definition. For endometrioid carcinomas, grade is based on the proportion of solid areas: low grade = grade 1 (≤5%) and grade 2 (6%–50%); and high grade = grade 3 (>50%). Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one. The presence of unusual nuclear atypia in an architecturally low-grade tumor should prompt the evaluation of *TP53* and consideration of serous carcinoma. Adenocarcinomas with squamous differentiation are graded according to the microscopic features of the glandular component; (2) Nonaggressive histological types are composed of low-grade (grade 1 and 2) endometrioid carcinomas. Aggressive histological types are composed of high-grade endometrioid carcinomas (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type

Stage	Description
carcinomas, and carcinosarcomas; and (3) It should be noted that high-grade endometrioid carcinomas (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making. Without molecular classification, high-grade endometrioid carcinomas cannot appropriately be allocated to a risk group, and thus, molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade endometrioid carcinomas were grouped together with the aggressive histological types in the actual FIGO classification. [g]Micrometastases are considered to be metastatic involvement (pN1 [mi]). The prognostic significance of ITCs is unclear. The presence of ITCs should be documented and is regarded as pN0(I+). According to the AJCC 8th edition staging, macrometastases are >2 mm in size, micrometastases are >0.2–2 mm and/or >200 cells, and ITCs are ≤0.2 mm and ≤200 cells. These definitions are based on staging established by FIGO and the 8th edition of the AJCC Cancer Staging Manual.	

Table 3. 2023 FIGO Definitions for Stage II Cancer of the Endometrium[a,b,c]

Stage	Description
II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion.
IIA	Invasion of the cervical stroma of nonaggressive histological types.
IIB	Substantial LVSI[e] of nonaggressive histological types.
IIC	Aggressive histological types[f] with any myometrial involvement.

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; LVSI = lymphovascular space involvement.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[3]

For the explanations for footnotes [b-f], see Table 2.

Table 4. 2023 FIGO Definitions for Stage III Cancer of the Endometrium[a,b,c]

Stage		Description
III		Local and/or regional spread of the tumor of any histological subtype.
IIIA		Invasion of uterine serosa, adnexa, or both by direct extension or metastasis.
	IIIA1	Spread to ovary or fallopian tube[d] (except when meeting stage IA3 criteria).
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa.
IIIB		Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum.
	IIIB1	Metastasis or direct spread to the vagina and/or the parametria.
	IIIB2	Metastasis to the pelvic peritoneum.
IIIC		Metastasis to the pelvic or para-aortic lymph nodes or both.[g]
	IIIC1	Metastasis to the pelvic lymph nodes.
	IIIC1i	Micrometastasis.
	IIIC1ii	Macrometastasis.
	IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes.
	IIIC2i	Micrometastasis.
	IIIC2ii	Macrometastasis.

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[3]

For the explanations for footnotes [b-d] and [g], see Table 2.

Table 5. 2023 FIGO Definitions for Stage IV Cancer of the Endometrium[a,b,c]

Stage	Description
IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis.
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa.
IVB	Abdominal peritoneal metastasis beyond the pelvis.
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone.

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[3]

For the explanations for footnotes [b-c], see Table 2.

Table 6. 2023 FIGO Definitions for Endometrial Cancer Stage With Molecular Classification[a,b]

Stage Designation	Molecular Findings in Patients With Early Endometrial Cancer (Stages I and II After Surgical Staging)
$IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type.
$IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type.

Stage Designation	Molecular Findings in Patients With Early Endometrial Cancer (Stages I and II After Surgical Staging)

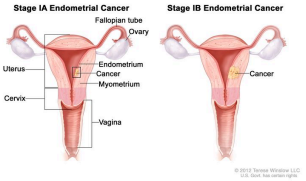
FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; LVSI = lymphovascular space involvement; MMRd = mismatch repair deficiency; MSI = microsatellite instability; NSMP = no specific molecular profile; *POLEmut* = pathogenic *POLE* mutation; p53abn = *TP53* abnormal.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[3]

[b]When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages. A pathogenic *POLE* mutation (*POLEmut*) is associated with a good prognosis. MMRd or MSI and NSMP are associated with an intermediate prognosis. Abnormal *TP53* (p53abn) is associated with a poor prognosis. When the molecular classification is known the staging is modified as follows: (1) FIGO Stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLEmut* or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of "m" for molecular classification, and a subscript is added to denote *POLEmut* or p53abn status, as shown in the table. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals MMRd or NSMP, it should be recorded as Stage Im_{MMRd} or Stage Im_{NSMP} and Stage IIm_{MMRd} or Stage IIm_{NSMP}; (2) FIGO Stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as Stage IIIm or Stage IVm with the appropriate subscript for the purpose of data collection. For example, when molecular classification reveals p53abn, it should be recorded as Stage $IIIm_{p53abn}$ or Stage IVm_{p53abn}.

2021 FIGO staging for endometrial cancer

Table 7. 2021 FIGO Definitions for Stage I Cancer of the Endometrium[a]

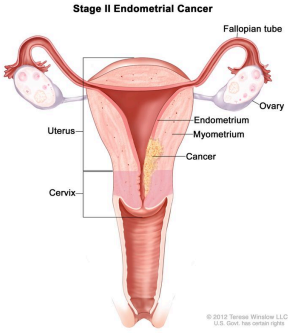
Stage	Description	Illustration
I[b]	Tumor confined to the corpus uteri.	
IA[b]	No or less than half myometrial invasion.	
IB[b]	Invasion equal to or more than half of the myometrium.	

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[4]

[b]G1, G2, or G3 (G = grade).

Table 8. 2021 FIGO Definitions for Stage II Cancer of the Endometrium[a]

Stage	Description	Illustration
II[b]	Tumor invades cervical stroma but does not extend beyond the uterus.[c]	

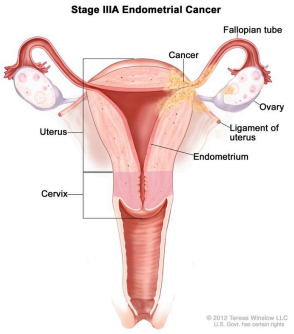
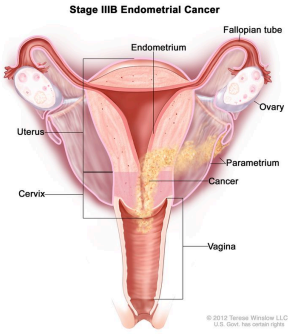
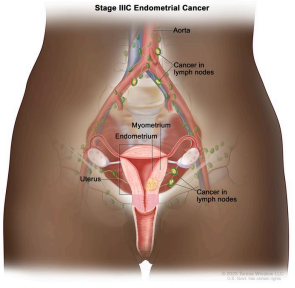
FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[4]

[b]G1, G2, or G3 (G = grade).

[c]Endocervical glandular involvement is considered stage I; it is no longer considered stage II.

Table 9. 2021 FIGO Definitions for Stage III Cancer of the Endometrium[a]

Stage	Description	Illustration
III[b]	Local and/or regional spread of the tumor.	
IIIA[b]	Tumor invades the serosa of the corpus uteri and/or adnexae.[c]	
IIIB[b]	Vaginal and/or parametrial involvement.[c]	
IIIC[b]	Metastases to pelvic and/or para-aortic lymph nodes.[c]	
IIIC1[b]	Positive pelvic nodes.	
IIIC2[b]	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes.	

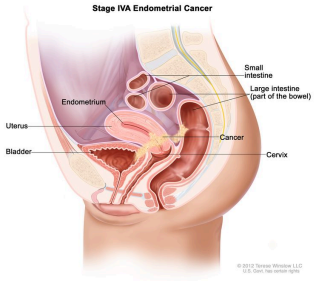
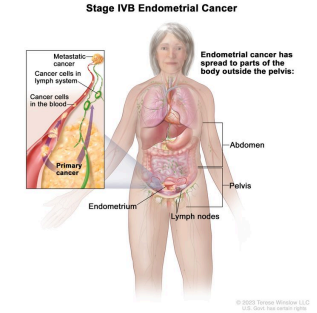
FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[4]

[b]G1, G2, or G3 (G = grade).

[c]Positive cytology has to be reported separately without changing the stage.

Table 10. 2021 FIGO Definitions for Stage IV Cancer of the Endometrium[a]

Stage	Description	Illustration
IV[b]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases.	
IVA[b]	Tumor invasion of bladder and/or bowel mucosa.	
IVB[b]	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes.	

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[4]

[b]G1, G2, or G3 (G = grade).

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Treatment Option Overview for Endometrial Cancer

The degree of tumor differentiation has an important effect on the natural history of this disease and on treatment selection.

Patients with endometrial cancer who have localized disease are usually cured. Best results are obtained with one of two standard treatments:

- Hysterectomy with bilateral salpingo-oophorectomy.
- Hysterectomy with bilateral salpingo-oophorectomy and adjuvant radiation therapy (when deep invasion of the myometrial muscle [more than 50% of the myometrium] or grade 3 tumor with myometrial invasion is present).

Patients with regional and distant metastases are rarely cured, although they are occasionally responsive to standard hormone therapy.

Progestational agents have been evaluated as adjuvant therapy in several randomized trials. A meta-analysis by the Cochrane group confirms no clinical benefit to adjuvant progestogens in clinical stage I disease.[1][Level of evidence A1]

The treatment options for each stage of endometrial cancer are presented in Table 11.

Table 11. Treatment Options for Endometrial Cancer

Stage (FIGO Staging Definitions)		Treatment Options
Stage I and stage II endometrial cancer	Grades 1 and 2	Surgery with or without lymph node sampling
		Postoperative vaginal brachytherapy
		Radiation therapy alone
	Grade 3 (includes serous, clear cell, and carcinosarcoma)	Surgery

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

Stage (FIGO Staging Definitions)		Treatment Options
		Postoperative chemotherapy with or without radiation therapy
Stage III, stage IV, and recurrent endometrial cancer	Operable disease	Surgery followed by chemotherapy or radiation therapy
	Inoperable disease	Chemotherapy and radiation therapy
	Inoperable disease in which the patient is not a candidate for radiation therapy	Hormone therapy
		Biological therapy
	Advanced or recurrent disease	Immunotherapy
		Clinical trials

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

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Treatment of Stage I and Stage II Endometrial Cancer

Treatment Options for Stage I and Stage II Endometrial Cancer

Treatment of stage I and stage II endometrial cancer depends on the grade and histological type.

In the current Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging system, stage II describes tumor that invades the cervical stroma; this is equivalent to the prior stage IIB. Almost all randomized trials for early-stage cancer excluded stage IIB patients. As a result, there is a paucity of quality data on which to base clinical decisions for patients with stage II endometrial cancer.

Low-risk histology:

Grades 1 and 2 tumors are considered low-risk unless they have serous or clear cell histologies.

Treatment options for patients with low-risk histological subtypes of stage I endometrial cancer include:

1. Surgery: Hysterectomy with bilateral salpingo-oophorectomy and possible lymph node dissection.
2. Postoperative vaginal brachytherapy.
3. Radiation therapy alone.

Most patients do well with surgery alone. However, patients with stage I disease who have high-risk histologies are at a greater risk of recurrence and are eligible for adjuvant therapy.

High-risk histology:

Grade 3 tumors of any histology and any serous tumors, clear cell tumors, or carcinosarcomas are considered high-risk.

Treatment options for patients with stage I or stage II endometrial cancer who have high-risk histologies include:

1. Surgery: Hysterectomy with bilateral salpingo-oophorectomy, with pelvic and para-aortic lymph node dissection.
2. Postoperative chemotherapy with or without radiation therapy.

Patients with serous or clear cell histologies have higher rates of recurrence than do patients with other stage I or stage II endometrioid carcinomas. Management guidelines are based on the outcomes reported in institutional case series that used a regimen of adjuvant carboplatin plus paclitaxel, and occasionally, radiation therapy for patients with this histological subtype.[1-9]

Carcinosarcomas have been evaluated in clinical trials both separately and with other sarcomas because of their prior designation in this group. In a nonrandomized Gynecologic Oncology Group (GOG) study of patients with stage I or II carcinosarcomas, patients who underwent pelvic radiation therapy had a significant reduction in recurrences within the radiation treatment field but no improvement in survival.[10] One nonrandomized study that predominantly included patients with carcinosarcomas appeared to show benefit for adjuvant therapy with cisplatin and doxorubicin.[11]

Surgery

If the uterine cervix is involved, patients may consider one or more of the following options:

- Standard hysterectomy with bilateral salpingo-oophorectomy, followed by adjuvant radiation therapy.
- Radical hysterectomy.
- Pelvic and para-aortic lymph node dissection.

Single-institution reviews suggest that radical hysterectomy is more beneficial than standard hysterectomy in cases of cervical involvement of the tumor.[12-14]

Surgery with or without lymph node sampling

Table 12 highlights the risk of nodal metastasis based on findings at the time of staging surgery:[15]

Table 12. Risk of Nodal Metastasis in Clinical Stage I Endometrial Cancer

Prognostic Group	Patient Characteristics	Risk of Nodal Involvement
A	Grade 1 tumors involving only endometrium	<5%
	No evidence of intraperitoneal spread	
B	Grade 2–3 tumors	5%–9% pelvic nodes
	Invasion of <50% of myometrium	
	No intraperitoneal spread	4% para-aortic nodes
C	Deep muscle invasion	20%–60% pelvic nodes
	High-grade tumors	10%–30% para-aortic nodes
	Intraperitoneal spread	

For patients in Group A, lymph node dissection has limited utility. Conversely, full pelvic and para-aortic lymph node dissection is important for patients in Group C, given the likelihood of positive findings. The difficulty lies in determining how to manage patients in Group B.

There are several accepted surgical approaches for patients with presumed stage I endometrial cancer, with intermediate risk for lymphatic spread.

Both retrospective and prospective data support stratifying patients with presumed stage I endometrial cancer into two groups based on the following characteristics:

- Low risk: Well-differentiated or moderately differentiated tumor and/or depth of myometrial invasion is less than 50% and/or tumor is smaller than 2 cm.
- High risk: Poorly differentiated tumor and/or depth of myometrial invasion is 50% or more and/or tumor is 2 cm or larger.

Evidence (lymph node dissection):

1. In two studies, patients with low-risk cancer had a sufficiently low risk of lymph node metastasis such that lymph node sampling could be omitted. For patients meeting high-risk criteria, a full

pelvic and para-aortic lymph node dissection was suggested, given patterns of lymphatic spread.[16,17]

2. An alternative strategy is the use of sentinel lymph node dissection in patients with presumed stage I endometrial cancer.[18] Although this strategy has been widely adopted at various academic centers, a prospective multicenter trial to determine the false-negative rate for this protocol is lacking. For cases in which isolated tumor cells are identified using the sentinel lymph node approach, it is unclear whether treatment is necessary.
3. In patients with high-risk histology (serous, clear cell, carcinosarcoma, or undifferentiated tumors), hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection is the standard approach.
4. Laparotomy has been the standard surgical approach. However, laparoscopy is now favored because of the improvement in patients' postoperative recovery without significant impact on outcomes.

Evidence (treatment or surgical staging using laparoscopy vs. laparotomy):

1. For patients with early-stage endometrial cancer, several randomized trials have compared total laparoscopic hysterectomy (TLH) with the standard open procedure, total abdominal hysterectomy (TAH). Feasibility of the laparoscopic approach has been confirmed, but this approach is associated with a longer operative time.[15,19,20] TLH has an improved [15,19] or similar [20] adverse event profile and a shorter hospital stay [15,19,20] than does TAH.
    - TLH is associated with less pain and a quicker resumption of daily activities,[20,21] although one study found that most of the gains in quality of life favoring laparoscopy at the 6-week postsurgical period were no longer significant at 6 months.[20,21]
2. A GOG trial (GOG-LAP2) randomly assigned 2,616 patients with clinical stages I to IIA disease in a 2:1 ratio to comprehensive surgical staging via laparoscopy or laparotomy.[22][Level of evidence A1]

    Time to recurrence was the primary end point, with noninferiority defined as a difference in recurrence rate of less than 5.3% between the two groups at 3 years.

    a. The recurrence rate at 3 years was 10.24% for patients in the laparotomy arm and 11.39% for patients in the laparoscopy arm, with an estimated difference between groups of 1.14% (90% lower bound, -1.278; 95% upper bound, 3.996).
        - Although this difference was lower than the prespecified limit, the statistical requirements for noninferiority were not met because of fewer-than-expected recurrences in both groups.

    b. The 5-year overall survival (OS) rate was 89.8% in both groups.
3. A Cochrane review of the use of laparoscopic staging included four randomized controlled trials that reported OS and progression-free survival (PFS). Ninety percent of the patients were from the GOG-LAP2 trial.[23][Level of evidence A1]
    - Overall, laparoscopy and laparotomy were associated with similar OS and PFS rates.

Future analyses may determine whether there are subgroups of patients for whom there is a clinically significant decrement when laparoscopic staging is used.[22][Level of evidence B1]

Postoperative vaginal brachytherapy

Adjuvant radiation therapy reduces the incidence of local and regional recurrence. However, improved survival rates have not been confirmed, and radiation therapy increased toxicity.[24-28] Vaginal cuff brachytherapy is associated with less radiation-related morbidity than is external-beam radiation therapy (EBRT) and has been shown to be equivalent to EBRT in the short term for patients with stage I disease.[29] However, long-term follow up of a randomized trial comparing EBRT plus vaginal brachytherapy (VBT) to VBT alone found decreased OS and increased toxicity in the EBRT plus VBT arm.[30]

Evidence (VBT):

1. Results of two randomized trials that used adjuvant radiation therapy in patients with stage I disease did not show improved survival but did show reduced locoregional recurrence (3%–4% in the radiation therapy group vs. 12%–14% in the control group after median follow-up of 5–6 years; $P < .001$), with an increase in side effects.[27,31,32][Level of evidence B1]
2. Results of a study by the Danish Endometrial Cancer Group suggest that the absence of radiation therapy does not improve the survival of patients with stage I intermediate-risk disease (grades 1 and 2 with >50% myometrial invasion or grade 3 with <50% myometrial invasion).[33]
3. The PORTEC-2 trial (NCT00411138) randomly assigned patients with stage I endometrial cancer who did not undergo lymph node dissection to undergo VBT or EBRT, with prevention of vaginal recurrence as the primary outcome.[29,34][Level of evidence A1]
    - At 5 years, there was no difference in the rates of vaginal recurrence, locoregional recurrence, PFS, or OS (84.8% [95% confidence interval (CI), 79.3%–90.3%] for VBT vs. 79.6% [95% CI, 71.2%–88.0%] for EBRT; $P = .57$).
    - The VBT group had significantly fewer gastrointestinal toxic effects and improved quality of life, making VBT the preferred option for adjuvant treatment of patients with stage I disease.
4. The Norwegian Radium Hospital trial included 568 patients with clinical stage I endometrial cancer between 1968 and 1974 (before FIGO surgical staging was initiated).[30][Level of evidence A1] After hysterectomy and bilateral salpingo-oophorectomy, patients were randomly assigned to receive either EBRT and VBT or VBT alone.
    - An updated report presenting over 20 years of follow-up data showed no difference in OS between the treatment groups. Median OS was 20.5 years in the EBRT/VBT group and 20.48 years in the VBT-alone group ($P = .186$). In all women, there was an increased risk of secondary cancers after EBRT (hazard ratio [HR], 1.42; 95% CI, 1.01–2.0).
    - A post hoc subset analysis of women younger than 60 years at the time of trial registration showed increased mortality in the EBRT/VBT arm (HR, 1.36; 95% CI, 1.06–1.76). Further, the risk of secondary cancers doubled in this group (HR, 2.02; 95% CI, 1.3–3.15).

Postoperative radiation therapy

If the cervix is not clinically involved, but extension to the cervix is noted on postoperative pathology, radiation therapy is considered.[22][Level of evidence A1]

Radiation therapy alone

Patients who have medical contraindications to surgery may be treated with radiation therapy alone, but cure rates may be lower than those attained with surgery.[35-37]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Stage III, Stage IV, and Recurrent Endometrial Cancer

Treatment Options for Stage III, Stage IV, and Recurrent Endometrial Cancer

Treatment options for patients with stage III, stage IV, and recurrent endometrial cancer include:

1. Surgery followed by chemotherapy or radiation therapy.
2. Chemotherapy and radiation therapy.
3. Hormone therapy.
4. Biological therapy.
5. Immunotherapy.
6. Clinical trials.

Treatment of patients with stage IV endometrial cancer is dictated by the site of metastatic disease and symptoms related to disease sites.

Surgery followed by chemotherapy or radiation therapy

In general, patients with stage III or stage IV endometrial cancer are treated with surgery, followed by chemotherapy, radiation therapy, or both. Observational studies support maximal cytoreductive surgery for patients with stage IV disease, although these conclusions need to be interpreted with care because of the small number of cases and likely selection bias.[1,2]

For many years, radiation therapy was the standard adjuvant treatment for patients with endometrial cancer. However, several randomized trials have confirmed improved survival when adjuvant chemotherapy is used instead of radiation therapy.

Doxorubicin was historically the most active anticancer agent used, with useful but temporary responses obtained in as many as 33% of patients with recurrent disease. Paclitaxel, when combined with platinum chemotherapy or when used as a single agent, also has significant anticancer activity.[3]

Evidence (surgery followed by chemotherapy or radiation therapy):

1. Several randomized trials by the Gynecologic Oncology Group (GOG) have used doxorubicin because of its known antitumor activity.[4]
    - Adding cisplatin to doxorubicin increased response rates and progression-free survival (PFS) when compared with doxorubicin alone. However, adding cisplatin did not affect overall survival (OS).
2. A three-drug regimen of doxorubicin, cisplatin, and paclitaxel with granulocyte-colony stimulating factor (G-CSF) was significantly superior to cisplatin and doxorubicin, as shown by the following results:[5,6][Level of evidence B3]
    - Response rate was 57% with the three-drug regimen, compared with 34% with the cisplatin and doxorubicin regimen.
    - PFS was 8.3 months with the three-drug regimen, compared with 5.3 months with the cisplatin and doxorubicin regimen.

- OS was 15.3 months with the three-drug regimen, compared with 12.3 months with the cisplatin and doxorubicin regimen.
- The 3-drug regimen was associated with grade 3 peripheral neuropathy in 12% of patients and grade 2 peripheral neuropathy in 27% of patients.

Given the toxicity and limited efficacy of these regimens, other treatment options have been widely sought. Several observational studies [7,8] and phase II studies [9-12] suggest clinical activity with the combination of platinum chemotherapy and paclitaxel in patients with endometrial cancer and measurable disease either after primary surgery or at recurrence.

3. The phase III, randomized, open-label, noninferiority GOG-0209 trial (NCT000063999) compared the combination of paclitaxel, doxorubicin, cisplatin (TAP), and G-CSF with carboplatin and paclitaxel (TC) in 1,381 women.[13]
    - The median OS was 37 months for patients in the TC group and 41 months for patients in the TAP group (hazard ratio [HR], 1.002; 90% confidence interval [CI], 0.9–1.12). The median PFS was 13 months for patients in the TC group and 14 months for patients in the TAP group (HR, 1.032; 90% CI, 0.93–1.15).[13]
    - These results led to the use of TC as the standard adjuvant treatment for patients with stages III and IV disease.

4. The use of cisplatin and doxorubicin compared with whole-abdominal radiation therapy was studied in a trial of patients with stage III or IV disease with residual tumors smaller than 2 cm and no parenchymal organ involvement.[14][Level of evidence A1]
    - Results suggest that cisplatin and doxorubicin improved OS, compared with whole-abdominal radiation therapy (5-year survival rate, 55% for cisplatin and doxorubicin vs. 42% for whole-abdominal radiation; adjusted HR, 0.68; 95% CI, 0.52–0.89; P = .02).

5. Several trials support combination chemotherapy for patients with stage III, stage IV, and recurrent carcinosarcoma.
    a. The GOG-108 trial of ifosfamide, with or without cisplatin, as first-line therapy in patients with measurable advanced or recurrent carcinosarcomas demonstrated a higher response rate (54% vs. 34%) and longer PFS in the combination arm (6 months vs. 4 months), but there was no significant improvement in survival (9 months vs. 8 months).[15][Level of evidence A1]
    b. The follow-up GOG-0161 study (NCT00003128) used 3-day ifosfamide regimens (instead of the more-toxic 5-day regimen in the preceding study) for the control and ifosfamide combined with paclitaxel (with G-CSF starting on day 4) for the study arm.[16]
        - The combination regimen produced superior response rates (45% vs. 29%), PFS (8.4 months vs. 5.8 months), and OS (13.5 months vs. 8.4 months). The HR for death also favored the combination regimen (HR, 0.69; 95% CI, 0.49–0.97).[16][Level of evidence A1]
        - In this study, 52% of 179 evaluable patients had recurrent disease, 18% had stage III disease, and 30% had stage IV disease. In addition, there were imbalances between the treatment arms with respect to the sites of disease and the use of prior radiation therapy, and 30 patients were excluded for wrong pathology.

Chemotherapy and radiation therapy

Patients with inoperable disease caused by tumor that extends to the pelvic wall may be treated with a combination of chemotherapy and radiation therapy. The usual approach for radiation therapy is a combination of intracavitary and external-beam radiation therapy (EBRT).[17,18]

For patients with localized recurrences (pelvic and para-aortic lymph nodes) or distant metastases in selected sites, radiation therapy may be an effective palliative therapy. Pelvic radiation therapy may be curative in patients with pure vaginal recurrence when no previous radiation therapy has been used.

Hormone therapy

Progesterone and estrogen hormone receptors are commonly found in endometrial carcinoma tissues. Response to hormone therapy is correlated with the presence and level of hormone receptors and the degree of tumor differentiation.[19] Patients with tumors that are positive for estrogen and progesterone receptors respond best to progestin therapy.

When distant metastases, especially pulmonary metastases, are present, hormonal therapy is indicated. Patients who are not candidates for either surgery or radiation therapy may be treated with progestational agents, the most common hormonal treatment. Progestational agents produce good antitumor responses in 15% to 30% of patients. These responses are associated with significant improvement in survival.[19]

Standard progestational agents include:[19]

- Hydroxyprogesterone.
- Medroxyprogesterone.
- Megestrol.

Evidence (progestin therapy):

1. One study followed 115 patients with advanced endometrial cancer treated with progestins.[20]
    - Responses occurred in 75% of patients (42 of 56) with progesterone receptor–positive tumors.
    - Responses occurred in 7% of patients (4 of 59) without detectable progesterone receptors.

A receptor-poor status may predict a poor response to progestins and a better response to cytotoxic chemotherapy.[21]

Other hormonal agents have shown benefit in treating endometrial cancer. Tamoxifen (20 mg bid) yields a 20% response rate in patients who do not respond to standard progesterone therapy.[22]

Aromatase inhibitors have also been evaluated for the treatment of advanced and recurrent endometrial cancer, although they yield lower response rates than progestational agents.[23]

Biological therapy

Several biological agents have been evaluated for the treatment of endometrial cancer.

1. Mammalian target of rapamycin (mTOR) inhibitors.

   Endometrial cancers often show alterations in the AKT-PI3K pathway, making mTOR inhibitors an attractive choice for clinical study in patients with metastatic or recurrent disease. Phase II studies of single-agent everolimus [24] and ridaforolimus [25,26] have predominantly shown disease stabilization. A phase II study of the combination of everolimus and letrozole showed a 32% response rate.[27][Level of evidence C3]

2. Bevacizumab.

   - Bevacizumab was used as a single agent in a phase II trial. The overall response rate was 13.5%.[28][Level of evidence C3]
   - Bevacizumab combined with temsirolimus has been used.[29]

Immunotherapy

With the published results of The Cancer Genome Atlas, and as more is learned about the molecular drivers of endometrial cancer, the use of immunotherapy has been evaluated for the treatment of advanced and recurrent disease.

Evidence (immunotherapy):

1. Study 309/KEYNOTE-775 (NCT03517449) was a large, international, multicenter, randomized trial that compared the combination of pembrolizumab (200mg intravenously [IV] every 3 weeks for up to 35 cycles) and lenvatinib (20mg orally daily) with physician's choice of chemotherapy. The study enrolled women with advanced or recurrent endometrial cancer who had disease progression after a platinum-based regimen (measurable disease was required). All histologies except carcinosarcoma and sarcoma were permitted. Patients were stratified by mismatch repair (MMR) status. The two primary end points were PFS and OS.[30]

   - After a median follow-up of approximately 12 months in both groups, survivals were statistically longer for patients in the pembrolizumab-lenvatinib group. The benefit persisted despite the patients' MMR statuses. Among all patients, the median PFS was 7.3 months for patients who received pembrolizumab and lenvatinib and 3.8 months for patients who received chemotherapy (HR, 0.56; 95% CI, 0.48–0.66; $P < .001$). The median OS was 18.7 months for patients who received pembrolizumab and lenvatinib and 11.9 months for patients who received chemotherapy (HR, 0.65; 95% CI, 0.55–0.77; $P < .001$). [30][Level of evidence A1]
   - The most frequent serious side effect in the experimental group was hypertension.

2. The double-blind placebo-controlled KEYNOTE-868 study (NCT03914612) included 810 patients with advanced (stage III, stage IVA, or stage IVB) or recurrent endometrial cancer.[31] Patients were randomly assigned to receive six cycles of paclitaxel and carboplatin with either pembrolizumab or placebo. Afterwards, patients received up to 14 cycles of maintenance therapy with pembrolizumab or placebo. Patients were stratified according to MMR statuses (proficient [pMMR; n =588] or deficient [dMMR; n = 222]) to investigate if the checkpoint inhibitor, pembrolizumab, was efficacious in patients with dMMR tumors.

   - After a median follow-up of 12.0 months, the 1-year PFS for patients with dMMR tumors was 74% in the pembrolizumab group and 38% in the placebo group (HR, 0.30; 95% CI,

0.19–0.48; $P < .001$).[31][Level of evidence B1]

- After a median follow-up of 7.9 months, the median PFS for patients with pMMR tumors was 13.1 months in the pembrolizumab group and 8.7 months in the placebo group (HR, 0.54; 95% CI, 0.41–0.71; $P < .001$).[31][Level of evidence B1]
- Regardless of MMR status, pembrolizumab showed significant PFS improvement in patients with advanced or recurrent endometrial cancer.

3. The phase III randomized KEYNOTE-B21 trial (NCT04634877) included 1,095 patients with newly diagnosed high-risk stage I to stage IVA endometrial cancer (including carcinosarcoma) without evidence of disease postsurgery. All patients received either six cycles of chemotherapy with optional EBRT or four cycles of chemotherapy followed by chemoradiation therapy. Vaginal brachytherapy was allowed in both groups. Patients were randomly assigned to receive either adjuvant pembrolizumab or placebo every 3 weeks for six cycles, then every 6 weeks for six cycles. A total of 66% of patients had stage III or stage IVA disease, 26% had dMMR tumors, and 67% were treated with radiation therapy.[32,33]
    - After a median follow-up of 24 months, the 2-year disease-free survival (DFS) rate was 75% in the pembrolizumab group and 76% in the placebo group (HR, 1.02; 95% CI, 0.79–1.32; $P = .57$).[33][Level of evidence B1]
    - In the dMMR cohort, the 2-year DFS rate was 92.4% in the pembrolizumab group and 80.2% in the placebo group (HR, 0.31; 95% CI, 0.14–0.69).
    - No other predetermined subgroup benefitted from adding pembrolizumab.

    This study evaluated giving pembrolizumab to patients with positive lymph nodes after surgery who had no other visible evidence of disease. It also evaluated combining radiation therapy and pembrolizumab. Results were significant because they expanded the population of patients who can receive pembrolizumab.

4. The RUBY trial (NCT03981796) was a large multicenter trial in women with Fédération Internationale de Gynécologie et d'Obstétrique stage III, IV, or recurrent endometrial cancer of all histologies not amenable to curative therapy. Unlike the Study 309/KEYNOTE-775 trial, some patients without measurable disease qualified for inclusion. Women were randomly assigned to receive TC with or without dostarlimab (500 mg IV) every 3 weeks for six cycles followed by maintenance dostarlimab (1,000 mg IV every 6 weeks) for up to 3 years. Patients were stratified by MMR status. The primary end point was PFS.[34]
    - After a median follow-up of approximately 2 years, the dostarlimab group from the overall population had a 36% lower risk of progression or death (HR, 0.64; 95% CI, 0.51–0.80; $P < .001$). The dostarlimab group from the dMMR population had a 72% lower risk of progression or death (HR, 0.28; 95% CI, 0.16–0.50; $P < .001$). Similar benefit was seen in OS (HR, 0.64; 95% CI, 0.46–0.87, $P = .0021$ for the overall population; HR, 0.30; 95% CI, 0.13–0.70 for the dMMR population).[34][Level of evidence B1]

These three studies demonstrate the activity and benefit of immunotherapy in the treatment of patients with advanced stage and recurrent endometrial cancer. These results may also facilitate the incorporation of such treatments into the up-front setting. More data are needed to help discern the role of immunotherapy in patients whose treatment plan would historically include radiation therapy.

Clinical trials

All patients with advanced disease should consider clinical trials that evaluate single-agent or combination therapy for this disease.

Studies of treatment failure patterns have found a high rate of distant metastases in the upper abdomen and in extra-abdominal sites.[35] For this reason, patients with stage III disease may be candidates for innovative clinical trials.

Treatment options under clinical evaluation for stage IV endometrial cancer include the following agents:

1. Paclitaxel and carboplatin with or without metformin in stages III, IV, and recurrent endometrial cancer (GOG-0286B [NCT02065687]).
2. PI3K/mTOR inhibitor in recurrent or persistent endometrial cancer (15-079 [NCT02549989]).
3. Everolimus and letrozole or hormonal therapy in recurrent or persistent endometrial cancer (GOG-3007 [NCT02228681]).
4. Everolimus, letrozole, and metformin in advanced or recurrent endometrial cancer (2012-0543 [NCT01797523]).

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Latest Updates to This Summary (05/14/2025)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

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About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of endometrial cancer. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

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- be discussed at a meeting,
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The lead reviewers for Endometrial Cancer Treatment are:

- Olga T. Filippova, MD (Lenox Hill Hospital)
- Marina Stasenko, MD (New York University Medical Center)

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