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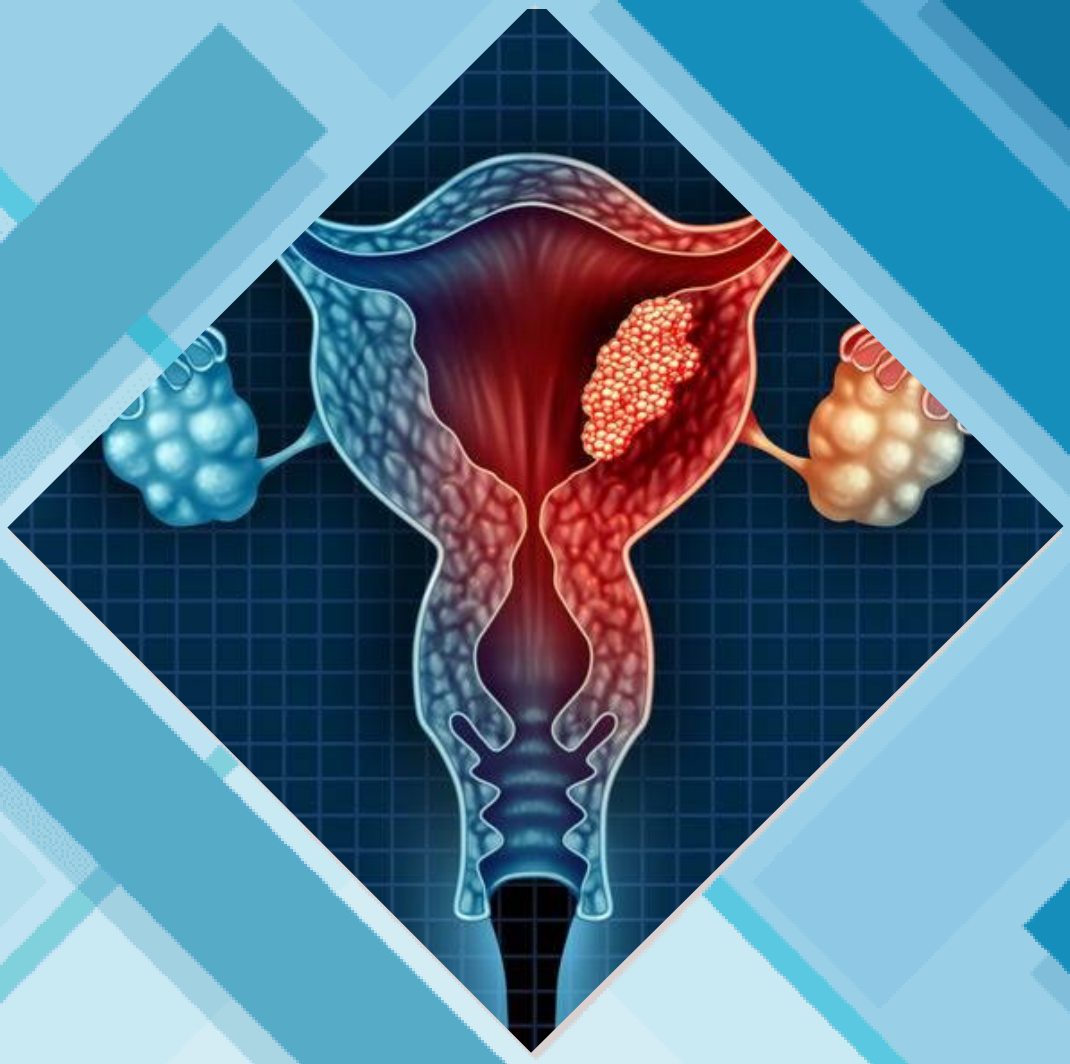

Uterine Carcinoma

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بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ)

[المجادلة: ١١]

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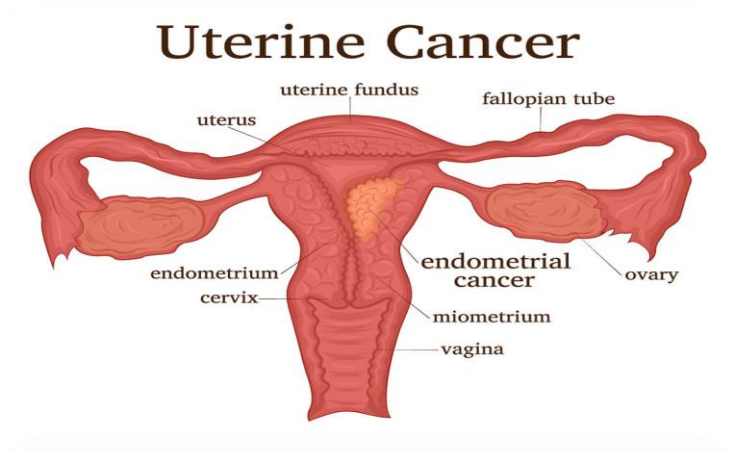
Abstract

Uterine carcinosarcomas (malignant mixed Mullerian tumors) have been traditionally regarded as a subtype of uterine sarcoma. Adjuvant oncological treatments have often been similar to those directed against high-grade uterine sarcomas such as leiomyosarcoma and undifferentiated uterine sarcoma. However, there is now convincing evidence that most uterine carcinosarcomas are monoclonal neoplasms and are in reality metaplastic carcinomas. Although aggressive, the behavior of uterine carcinosarcoma is more akin to that of high-grade endometrioid type endometrial adenocarcinoma and aggressive morphological subtypes of uterine carcinoma. The sarcomatous component is derived from the carcinomatous element which is the driving force. Although the designation carcinosarcoma is likely to remain, adjuvant treatments should probably be similar to those directed against aggressive high grade endometrial carcinomas. Prospective studies should be performed to ascertain whether such adjuvant therapies are more effective than traditional sarcoma based therapies in the treatment of these aggressive neoplasms.
[1,10]

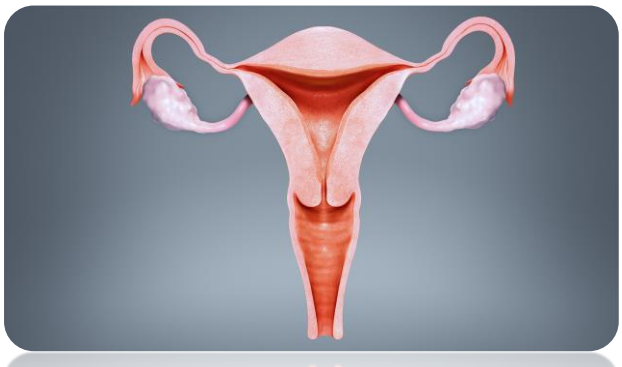
Introduction

Uterine cancer is the fourth most frequent cancer in women, with an estimated 34,000 cases and 6000 deaths in the United States in 1996.1 It is the most curable of the 10 most com- mon cancers in women and the most frequent and curable of the gynecologic cancers. Ninety-seven per- cent of all cancers of the uterus arise from the glands of the endometrium and are known as endometrial carcinomas. The remaining 3 percent of uterine can- cers are sarcomas, which are not discussed here. Nu- merous changes in the pathological description of endometrial cancer, identification of prognostic vari- ables, staging, and treatment have occurred in the past 15 years. This article will review the current understanding of the epidemiology, diagnosis, prog- nostic factors, and initial treatment of endometrial carcinoma.[2]



Definition of the uterus

The uterus is an organ in the female reproductive system. It is also called the womb. It is a hollow organ and holds the fetus during pregnancy. The uterus has a shape similar to that of an upside-down pear and has thick walls.

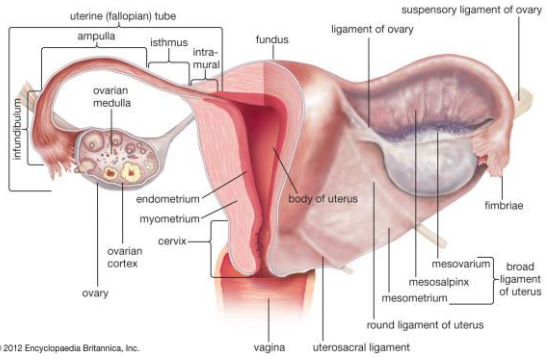


It is situated in the middle of the pelvis, behind the bladder and above the rectum. The uterus is held in position by muscles, ligaments and fibrous tissue.

The lower end of the uterus is called the cervix and it opens into the vagina. The upper end is called the fundus and is connected to the fallopian tubes. Between the fundus and the cervix is the corpus, which is the main body of the uterus and the isthmus, which is where the walls of the uterus begin to narrow toward the cervix. The uterus is made up of three layers of tissue. The Perimetrium is the layer that lines the outer part of the uterus. The Myometrium is the middle layer of the uterus which consists of smooth muscle while the innermost layer is known as the endometrium.[10]

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.

Functions of the Uterus

The uterus performs multiple functions but the major role of the uterus is to hold the fetus and nourish it till the time of delivery. The uterus accepts the fertilized ovum from the fallopian tubes. The fertilized ovum gets implanted into the endometrium, and the nourishment is derived from the blood vessels which form exclusively for this very cause. The fertilized ovum grows into an embryo, and then develops into a fetus, and grows and develops till childbirth.[1]

It consists of various types of cells that produce and release several types of hormones, including some below:

The uterus is also a secondary sex organ for females. It is required for uterine orgasm to occur. Blood flow is directed to the pelvis, ovaries as well as external genitalia such as the vagina, labia and the clitoris by the blood vessels and nerves of the uterus. The uterus plays a major role in sexual response.

The uterus also provides support to the bladder, bowel and pelvic bones. It separates the bladder and the bowels in females.[2]

Conditions of the Uterus

The most common disorders related to the uterus are:

- **Endometriosis** is a condition in which the lining of the uterus, which is called the endometrium, grows in the outside of the uterus, in the fallopian tubes, ovaries, or along the pelvis.
- **Uterine fibroids** are growths on the walls of the uterus, which are not cancerous. These fibroids may not cause any symptoms but could lead to fertility issues.
- **Uterine prolapse** occurs when part of the uterus slips into the vagina. Surgery, childbirth, menopause, or extreme physical activity are some of the causes of uterine prolapse.
- **Pelvic inflammatory disease** is an infection in the reproductive organs of the females. If this disease is not treated, it could lead to an ectopic pregnancy.
- **Cancer** can occur in any part of the uterus but it is most common in the endometrium.[10]

PATHOLOGY

Endometrial cancer is usually preceded by endometrial hyperplasia. Endometrial carcinoma is commonly classified into 2 types.

Type I tumors are more common, are usually estrogen-responsive, and are usually diagnosed in younger, obese, or perimenopausal women. These tumors are usually low-grade. Endometrioid adenocarcinoma is the most common histology. These tumors may show microsatellite instability and have mutations in *PTEN*, *PIK3CA*, *KRAS*, and *CTNNBI*.

Type II tumors are usually high-grade (eg, serous or clear cell histology). They tend to occur in older women. About 10 to 30% have *p53* mutations. Up to 10% of endometrial carcinomas are type II.

Endometrioid adenocarcinomas account for about 75 to 80% of endometrial cancers.

Uterine papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas are considered more aggressive, high-risk histologies and are thus associated with a higher incidence of extrauterine disease at presentation. Carcinosarcomas have been reclassified as high-risk malignant epithelial tumors.[17]

Endometrial cancer may spread as follows:

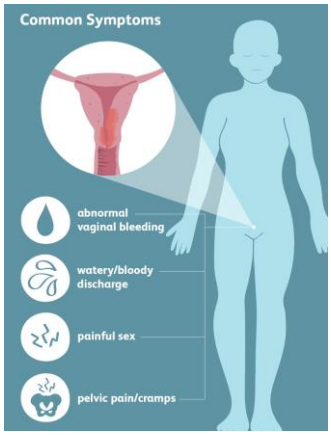
- From the surface of the uterine cavity to the cervical canal
- Through the myometrium to the serosa and into the peritoneal cavity
- Via the lumen of the fallopian tube to the ovary, broad ligament, and peritoneal surfaces
- Via the bloodstream, leading to distant metastases
- Via the lymphatics

The higher (more undifferentiated) the grade of the tumor, the greater the likelihood of deep myometrial invasion, pelvic or para-aortic lymph node metastases, or extrauterine spread.[14]

Etiology

- Premenopausal:
  - Polycystic ovarian syndrome (PCOS, Stein-Leventhal syndrome):
    - Increased circulating androgens peripherally converted into estrogen
    - Anovulatory cycles
  - Chronic anovulation: dysregulated estrogen without opposing progesterone secretion → simultaneous proliferation and breakdown
- Peri and postmenopausal:
  - Exogenous estrogen:
    - Estrogen supplementation: systemic therapy to alleviate symptoms of menopause → endometrial proliferation
    - Tamoxifen: hormonal treatment for breast cancer acts as estrogen receptor antagonist in breast but agonist in endometrium
- Any age:
  - Obesity: adipose tissue produces aromatase (enzyme converting circulating androgens to estrogen) → peripheral hyperestrinism
  - Ovarian pathology:
    - Stromal hyperplasia and hyperthecosis: stromal luteinization → hyperandrogenism → hyperestrinism
    - Hormone secreting stromal tumors: granulosa cell tumor, thecoma
  - Inherited cancer syndromes:
    - Hereditary nonpolyposis colon cancer / Lynch syndrome: defect in mismatch repair proteins
    - Cowden syndrome: defect in *PTEN* tumor suppressor gene[1,2,5]

Clinical features :



- Abnormal, dysfunctional or postmenopausal uterine bleeding
- Pelvic pain or mass / compression effect on adjacent structures
- Abdominal bloating
- Dyspareunia, dysuria
- General stigmata of malignancy, i.e. weight and appetite loss, malaise, fatigue
- Rare cases asymptomatic .[8,15] .

Major risk factors for endometrial cancer are:

- Unopposed estrogen
- Age > 50
- Happy ، Obesity
- Diabetes
  [4]

Other risk factors include :

- Tamoxifen use for > 5 yr
- Previous pelvic radiation therapy
- A personal or family history of breast or ovarian cancer
- Family history of hereditary nonpolyposis colorectal cancer or possibly, among 1st-degree relatives, endometrial cancer
- Hypertension

Unopposed estrogen (high circulating levels of estrogen with no or low levels of progesterone) may be associated with obesity, polycystic ovary syndrome, nulliparity, late menopause, estrogen-producing tumors, anovulation (ovulatory dysfunction), and estrogen therapy without progesterone.
[4]

DIAGNOSIS

- Endometrial biopsy
- Surgical staging

The following suggest endometrial cancer:

- Postmenopausal bleeding
- Abnormal bleeding in premenopausal women
- A routine Papanicolaou (Pap) test showing endometrial cells in postmenopausal women
- A routine Pap test showing atypical endometrial cells in any woman[6]

If endometrial cancer is suspected, outpatient endometrial biopsy is done; it is > 90% accurate. Endometrial sampling is also recommended for women with abnormal bleeding, particularly those > 40 yr. If results are inconclusive or suggest cancer (eg, complex hyperplasia with atypia), outpatient fractional D & C with hysteroscopy is done. An alternative is transvaginal ultrasonography; however, a histologic diagnosis is required.

Once endometrial cancer is diagnosed, pretreatment evaluation includes serum electrolytes, kidney and liver function tests, CBC, chest x-ray, and ECG.

Because endometrial cancer sometimes results from an inherited mutation, genetic counseling and/or testing should be considered if patients are < 50 yr or have a significant family history of endometrial cancer and/or HNPCC. [13]

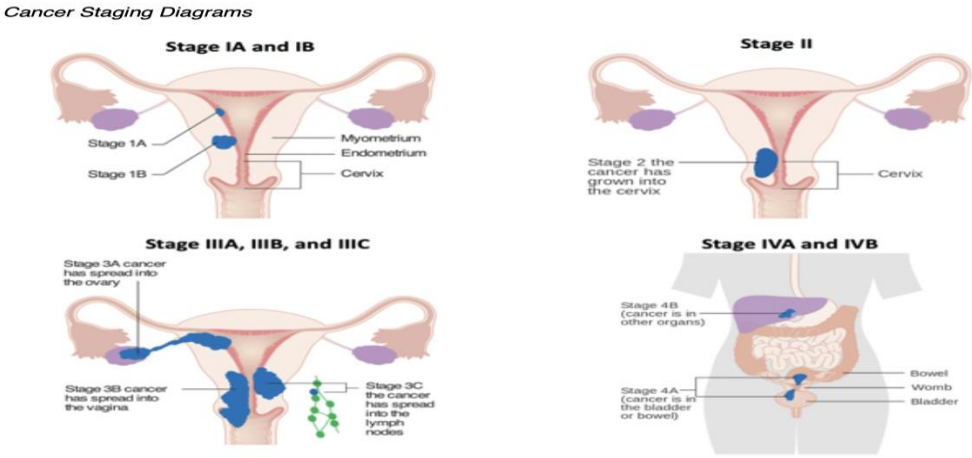
Pelvic and abdominal CT are also done to check for extrauterine or metastatic cancer in patients with any of the following:

- An abdominal mass or hepatomegaly detected during physical examination
- Abnormal liver function test results
- A high-risk histologic subtype of cancer (eg, papillary serous carcinoma, clear cell carcinoma, carcinosarcoma)
  [6]

Staging:

Staging of endometrial cancer is based on histologic differentiation (grade 1 [least aggressive] to 3 [most aggressive]) and extent of spread, including invasion depth, cervical involvement (glandular involvement vs stromal invasion), and extrauterine metastases (see Table: FIGO Staging of Endometrial Carcinoma).[9]

Staging is surgical and includes exploration of the abdomen and pelvis, biopsy or excision of suspicious extrauterine lesions, total abdominal hysterectomy, and, in patients with high-risk features (grade 1 or 2 cancer plus deep myometrial invasion, grade 3 cancer, all cancers with high-risk histology), pelvic and para-aortic lymphadenectomy. Staging can be done via laparotomy, laparoscopy, or robotic-assisted surgery.[11,14]



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

Prognosis

Prognosis is worse with higher-grade tumors, more extensive spread, and older patient age.

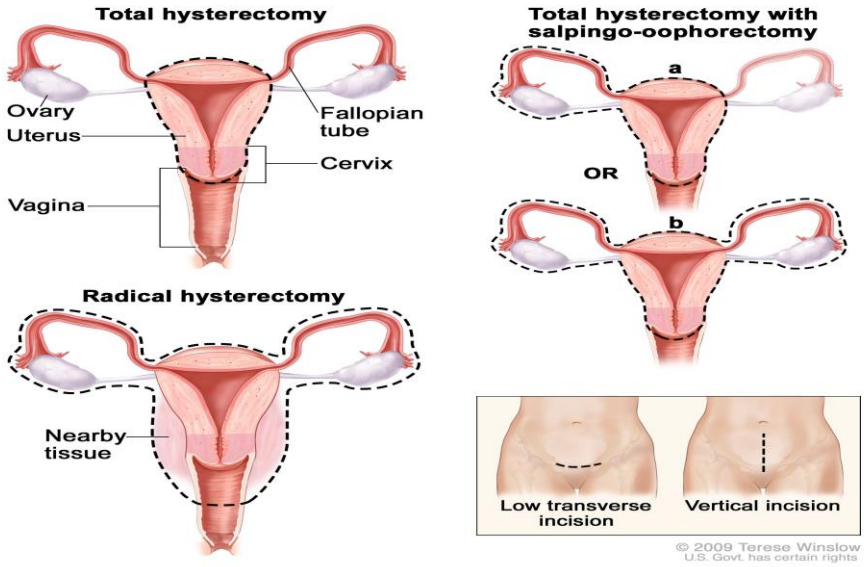
Average 5-yr survival rates are:

- Stage I or II: 70 to 95% .
- Stage III or IV: 10 to 60%

Overall, 63% of patients are cancer-free ≥ 5 yr after treatment.
[1,3]

TREATMENT

- Usually total hysterectomy and bilateral salpingo-oophorectomy
- Pelvic and para-aortic lymphadenectomy for grade 1 or 2 with deep (> 50%) myometrial invasion, for any grade 3, and for all cancers with high-risk histology
- Pelvic radiation therapy with or without chemotherapy for stage II or III
- Multimodal therapy usually recommended for stage IV[6]



In patients with grade 1 or 2 endometrial cancer and < 50% invasion, the probability of lymph node metastasis is < 2%. In these patients, treatment is usually total hysterectomy and bilateral salpingo-oophorectomy via laparotomy, laparoscopy, or robotic-assisted surgery. However, for young women with stage IA or IB endometrioid adenocarcinoma, ovarian preservation is usually safe and recommended to preserve fertility.[7]

If patients have any of the following, pelvic and para-aortic lymphadenectomy is also done:

- Grade 1 or 2 cancer with deep (> 50%) myometrial invasion
- Any grade 3 cancer
- All cancers with high-risk histology (papillary serous carcinoma, clear cell carcinoma, carcinosarcoma)

Whether the extent of para-aortic lymphadenectomy should reach the inferior mesenteric artery vs the renal vessels remains a topic of debate.

Stage II or III cancer requires pelvic radiation therapy with or without chemotherapy. Treatment of stage III cancer must be individualized, but surgery is an option; generally, patients who undergo combined surgery and radiation therapy have a better prognosis. Except in patients with bulky parametrial disease, a total abdominal hysterectomy and bilateral salpingo-oophorectomy should be done.[11]

Treatment of stage IV is variable and patient-dependent but typically involves a combination of surgery, radiation therapy, and chemotherapy. Occasionally, hormonal therapy should also be considered.

Tumors respond to hormone therapy with a progestin in 20 to 25% of patients.

Several cytotoxic drugs (particularly carboplatin plus paclitaxel) are effective. They are given mainly to women with metastatic or recurrent cancer. Another option is doxorubicin.[11]

Fertility preservation in endometrial hyperplasia and early endometrial cancer :

Patients with complex endometrial hyperplasia and atypia have up to a 50% risk of having concurrent endometrial cancer. Treatment of endometrial hyperplasia consists of progestins or definitive surgery, depending on the complexity of the lesion and the patient's desire to preserve fertility.

If young patients with grade 1 tumors and no myometrial invasion (documented by MRI) wish to preserve fertility, progestin alone is an option. About 46 to 80% of patients have a complete response within 3 mo of initiation of therapy. After 3 mo, patients should be evaluated via D & C rather than endometrial biopsy.

Alternatively, use of a levonorgestrel-releasing intrauterine device (IUD) is being increasingly used to treat patients with complex atypical hyperplasia or grade 1 endometrial cancer.

Surgery is recommended if conservative treatment is not effective (endometrial cancer is still present after 6 to 9 mo of treatment) or if patients have completed childbearing. Fertility-sparing treatment is contraindicated in patients with high-grade endometrioid adenocarcinomas, uterine papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma.

In young women with stage IA or IB endometrioid adenocarcinoma, ovarian preservation is safe and recommended.[16,17]

General measures

Because obesity and hypertension increase the risk of endometrial cancer and because evidence suggests that certain lifestyle choices may help prevent endometrial cancer, patients should be counseled about the importance of exercise, weight loss, and an adequate diet.[10]

High-risk histologies

Uterine papillary serous carcinoma, clear cell carcinomas, and carcinosarcomas (reclassified as high-risk malignant epithelial tumors) are considered histologically aggressive, high-risk cancers and are thus more likely to have spread outside the uterus at presentation.

Multimodality therapy is typically recommended for these histologically aggressive endometrial tumors. Primary treatment includes abdominal

hysterectomy, bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy, and omental and peritoneal biopsies.

In patients with gross extrauterine disease, cytoreduction should be done to reduce the bulk of the tumor to no gross residual disease.[4]

Adjuvant therapy for papillary serous and clear cell carcinomas depends on the stage:

- Stage IA without myometrial invasion and without residual disease in the hysterectomy specimen: Observation and close follow-up (an acceptable approach)
- Other stage IA and IB or stage II cancers: Usually vaginal brachytherapy followed by systemic chemotherapy with carboplatin and paclitaxel
- More advanced disease: Chemotherapy[12]

Adjuvant therapy for carcinosarcoma also depends on the stage:

- Stage IA without myometrial invasion and without residual disease in the hysterectomy specimen: Observation and close follow-up (an acceptable approach)
- All other stages: Usually systemic chemotherapy with ifosfamide plus paclitaxel . [12,17]

Prevention

To reduce your risk of endometrial cancer, you may wish to:

- **Talk to your doctor about the risks of hormone therapy after menopause.** If you're considering hormone replacement therapy to help control menopause symptoms, talk to your doctor about the risks and benefits. Unless you've undergone a hysterectomy, replacing estrogen alone after menopause may increase your risk of endometrial cancer. Taking a combination of estrogen and progestin can reduce this risk. Hormone therapy carries other risks, so weigh the benefits and risks with your doctor.
- **Consider taking birth control pills.** Using oral contraceptives for at least one year may reduce endometrial cancer risk. The risk reduction

is thought to last for several years after you stop taking oral contraceptives. Oral contraceptives have side effects, though, so discuss the benefits and risks with your doctor.

- **Maintain a healthy weight.** Obesity increases the risk of endometrial cancer, so work to achieve and maintain a healthy weight. If you need to lose weight, increase your physical activity and reduce the number of calories you eat each day.[2,3]

Conclusions

Endometrial carcinoma is the commonest female genital tract cancer.

- Routine screening for EC is not recommended. However annual screening is recommended in women at risk for hereditary nonpolyposis colorectal cancer.
- Endometrial carcinoma is a surgically staged disease
- The initial management of endometrial cancer should include total hysterectomy, bilateral salpingo oophorectomy, and pelvic and para-aortic lymphadenectomy.
- Primary radiotherapy or hormonal treatment may be recommmended in special situations.
- Adjuvant radiotherapy and /or chemotherapy are recommended in patients with high risk for recurrence
- Endometrial carcinoma has the best prognosis due to early presentation (PMB).
- Disease stage is the most predictive factor for survival.
- Lymph node metastasis is the most predictive factor for survival in early stage endometrial carcinoma[1,2]

Reference

1-. [Guideline] National Comprehensive Care Network. Uterine Neoplasms. Version 4.2019. NCCN. Available at http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed: September 16, 2019.

2-. [Guideline] National Cancer Institute. Endometrial Cancer Screening–for health professionals (PDQ®). National Cancer Institute. Available at http://www.cancer.gov/cancertopics/pdq/screening/endometrial/HealthProfessional/page1. March 4, 2016; Accessed: September 5, 2016.

3-. [Guideline] Smith RA, Andrews K, Brooks D, DeSantis CE, Fedewa SA, Lortet-Tieulent J, et al. Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2016 Mar-Apr. 66 (2):96-114. [Medline]. [Full Text].

4-. [Guideline] National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal, V1.2016. NCCN. Available at https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. June 23, 2016; Accessed: September 5, 2016.

5-. [Guideline] Committee on Practice Bulletins-Gynecology, Society of Gynecologic Oncology. ACOG Practice Bulletin No. 147: Lynch syndrome. Obstet Gynecol. 2014 Nov. 124 (5):1042-54. [Medline]. [Full Text].

6-. [Guideline] Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016 Jan. 27 (1):16-41. [Medline]. [Full Text].

7. [Guideline] SGO Clinical Practice Endometrial Cancer Working Group, Burke WM, Orr J, Leitao M, Salom E, Gehrig P, et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol. 2014 Aug. 134 (2):385-92. [Medline]. [Full Text].

8. [Guideline] Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct. 24 Suppl 6:vi33-8. [Medline]. [Full Text].

9. Corpus Uteri. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th Ed. New York: Springer-Verlag; 2010. 403-18.

10. [Guideline] Practice Bulletin No. 149: Endometrial cancer. Practice Bulletin No. 149: Endometrial cancer. Obstet Gynecol. 2015 Apr. 125 (4):1006-26. [Medline].

11. [Guideline] SGO Clinical Practice Endometrial Cancer Working Group, Burke WM, Orr J, Leitao M, Salom E, Gehrig P, et al. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol. 2014 Aug. 134 (2):393-402. [Medline]. [Full Text].

12. [Guideline] Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B, et al. The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2014 May-Jun. 4 (3):137-44. [Medline]. [Full Text].

13. [Guideline] Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol. 2011 Jun. 204 (6):466-78. [Medline]. [Full Text].

14. Creasman WT, Kohler MF, Odicino F, Maisonneuve P, Boyle P. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol. 2004 Dec. 95(3):593-6. [Medline].

15. DiSaia PJ, Creasman WT. 7th ed. Clinical Gynecologic Oncology. St. Louis, Mo: Mosby; 2007.

16. Douglas D. Similar outcomes with oral and IUD hormonal therapy for endometrial neoplasms. Medscape Medical Newsfrom WebMD. May 15, 2013. Available at http://www.medscape.com/viewarticle/804217. Accessed: June 3, 2013.

17. Hubbs JL, Saig RM, Abaid LN, Bae-Jump VL, Gehrig PA. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol. 2013 Jun. 121(6):1172-80. [Medline]. 43. Mariani A, Dowdy SC, Keeney GL, et al.