

EVERYONE'S GUIDE FOR CANCER THERAPY
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4th Edition 2001

Uterus: Endometrial Carcinoma

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Endometrial cancer-carcinoma of the lining of the uterus-is the most common gynecologic malignancy and accounts for about 13 percent of all malignancies occurring in women. There are about 34,000 cases of endometrial cancer diagnosed in the United States each year, but encouragingly, there has been a significant decrease in the number of women who develop endometrial cancer each year since 1975.

Similarly, the death rate from endometrial cancer has steadily declined from 1950 to 1985, falling more than 60 percent. Since this cancer is usually diagnosed at an early stage, the cure rate is high, with a five-year survival of 85 percent.

Types All endometrial carcinomas arise from the glands of the lining of the uterus. Adenocarcinoma accounts for 75 percent of all endometrial carcinoma. Endometrial adenocarcinomas that contain benign or malignant squamous cells are known as adenocanthomas and adenosquamous carcinomas respectively and account for 30 percent of endometrial cancers.

The remaining types of endometrial carcinoma have a poorer prognosis. Three percent have a clear cell carcinoma, and about 1 percent has a papillary carcinoma.

Uterine sarcoma is another kind of uterine malignancy. (*See "Uterus: Uterine Sarcomas"*).

How It Spreads From where it arises in the lining of the uterus, endometrial carcinoma eventually invades the wall of the uterus and may involve the cervix. With time, it can grow through the wall of the uterus into the surrounding tissues (the parametrium), the bladder and the rectum.

It can also spread by the lymphatic system to the vagina, fallopian tubes, ovaries, the pelvic and aortic lymph nodes and to the lymph nodes in the groin and above the collarbone (supraclavicular). Like ovarian carcinoma, endometrial cancer can also spread throughout the abdominal cavity and occasionally through the bloodstream to the lung, liver and brain. How rapidly it spreads depends on the grade (histologic virulence) of the cancer.

Endometrial cancer is often associated with a primary carcinoma of the ovary. (*See "Ovarian Germ Cell Cancer"*).

What Causes It Unknown.

RISK FACTORS

The use of birth control pills and postmenopausal hormone replacement therapy with estrogen and progesterone, decrease the risk of developing endometrial cancer by half.

At Significantly Higher Risk

- Obesity greater than 50 pounds (23 kg) over ideal body weight (10 times as likely).
- Postmenopausal women.
- Menopause after age 52 (2.4 times as likely).
- Lack of children (twice as likely).
- Women with hypertension (twice as likely).
- Diabetics (2.8 times).
- Women who do not ovulate, those with polycystic ovaries (Stein-Leventhal syndrome).
- Estrogen replacement therapy without supplemental progesterone (seven times as likely).
- History of pelvic radiation therapy (eight times).

SCREENING

Screening for endometrial carcinoma is not as satisfactory as screening for cancer of the cervix because of the inaccessibility of the uterine cavity. Pap smears detect only a small percentage of endometrial cancers.

There have been studies of other screening methods that can be performed in the doctor's office, with several showing the benefit of using endometrial biopsies to screen high-risk women who have no symptoms. This procedure is associated with some discomfort, however, and may not be cost-effective in the absence of risk factors. A uterine sonogram (ultrasound) maybe suggestive of uterine cancer if the lining of the uterus cavity demonstrates increased thickness. Routine annual screening for women without symptoms is not recommended by the American College of Obstetricians and Gynecologists.

COMMON SIGNS AND SYMPTOMS

In 90 percent of cases, there is abnormal uterine bleeding, ranging from insignificant staining to a hemorrhage. There may also be pain in the pelvis, back or legs, bladder or rectal symptoms, weight loss and general weakness. Five percent of women will have no symptoms.

DIAGNOSIS

Physical Examination

- On a gynecologic examination, the external genitalia are usually normal. The cervix may be involved with cancer (Stage II), and the vagina may also be involved (Stage III).
- Occasionally the uterus will be enlarged or softened and masses may be detected in the pelvis (a rectal examination is an important aspect of the pelvic examination).
- Enlarged lymph nodes in the neck and groin.
- Enlarged liver, abdominal mass or excessive abdominal fluid (ascites).

Blood and Other Tests

- Complete blood count.
- Serum liver and kidney tests.
- Serum CA-125 is produced by a small percentage of women with endometrial carcinoma, usually advanced, which can be useful in follow up to detect recurrences.

Imaging

- A uterine sonogram with thickened endometrial cavity may be suggestive of a uterine cancer.
- CT scan of the abdomen and MRI scan of the pelvis may be useful for determining the extent of the cancer in the pelvis, the presence of ovarian disease and the presence of

involved pelvic and aortic lymph nodes and liver metastases. It is usually performed for advanced cancer.

- Chest x-ray.

Endoscopy and Biopsy

- The definitive diagnosis is made on an endometrial biopsy, which involves a small scraping of the uterus and is usually performed in the doctor's office. A dilation and curettage (D&C) is required for some women-those who have biopsy-proven endometrial hyperplasia (see below), those who have an insufficient specimen on an office biopsy or who can't have an endometrial biopsy done in the office because of a small cervical opening or discomfort.

STAGING

Cancer of the uterus is surgically staged. Between 70 and 80 percent of all endometrial cancers are Stage I. In 1988, the International Federation of Gynecologists and Obstetricians (FIGO) staging was revised to include the grade of the cancer (degree of virulence) determined on microscopic examination. The cancers are divided into three grades, with Grade 1 (well-differentiated) having the best prognosis and Grade 3 (poorly-differentiated) having the poorest.

ENDOMETRIAL CANCER PRECURSORS

Endometrial hyperplasia, an overgrowth of the lining of the uterus, is a precursor to the development of cancer. This disorder tends to progress from a simple, benign hyperplasia confined to the lining of the uterus, to more severe atypical forms of hyperplasia and eventually

to an invasive malignancy. The risk factors for endometrial hyperplasia are similar to those of endometrial carcinoma.

Abnormal uterine bleeding is usually the first symptom. The diagnosis is made by evaluating the lining of the uterus by biopsy or dilation and curettage (D&C).

Treatment depends on the degree of hyperplasia, the presence of nuclear atypia, the age of the woman and her reproductive desires. Total abdominal hysterectomy and removal of both tubes and both ovaries is recommended for postmenopausal women and women who have completed childbearing. Women who want to keep their reproductive organs can be treated with a number of different oral progestational hormones for several months. The cure rate depends on the degree of hyperplasia and the sensitivity of the endometrium to the progestational therapy.

TREATMENT OVERVIEW

Treatment of endometrial carcinoma is based primarily on the stage and grade of the cancer.

The standard therapy is an abdominal hysterectomy with removal of both fallopian tubes and ovaries, removal of pelvic and aortic lymph nodes and washings from the abdominal cavity to look for malignant cells.

Many gynecologic oncologists also recommend obtaining a specimen from the cancer for analysis of its estrogen and progesterone receptor content in women with advanced stage disease.

The receptor content has prognostic value and may be useful in the selection of hormone therapy for recurrent or metastatic cancer.

Surgery Most gynecologic oncologists recommend a midline abdominal incision to gain access to the upper abdomen. However, laparoscopic surgery (minimal invasive surgery) including a hysterectomy, removal of both tubes and ovaries, removal of the pelvic and para-aortic lymph nodes can be performed in non-obese women, allowing a quicker release from the hospital, a quicker recovery, and where applicable, an earlier return to work. Complications of surgery include infection, bleeding and injury to the bladder, rectum or ureter causing a leak (rare). There may also be blood clots in the legs, occasionally dislodging and traveling to the lungs (pulmonary embolism).

Radiation In the past, women who have Stages Ib, Ic, or IIa uterine cancer were often treated two to six weeks after surgery with radiation to the entire pelvis and upper vagina. External beam radiation was given daily, five days a week for four to five weeks. Although pelvic external beam radiation therapy will decrease the frequency of recurrences in the pelvis and vagina, it does not statistically improve the five-year survival rate and as a result is recommended less often today.

Intracavitary radiation (radioactive material temporarily placed directly into or near the tumor) is used in certain cases, as well. The radioactive material is of different types and left in place for different amount of time depending on a number of factors, including size and location of the tumor, the type of radiation i.e. low-dose rate or high-dose rate (*see Radiation Therapy chapter*).

Side effects of radiation can include diarrhea, nausea and vomiting, bleeding from the bladder or rectum, vaginal scarring, intestinal obstruction, or leaks (fistulas) from the urinary or intestinal tract.

Chemotherapy Treatment with chemotherapy after surgery is used for later stages of the disease and recurrent cancer.

TREATMENT BY STAGE

ENDOMETRIAL HYPERPLASIA

Total abdominal hysterectomy and removal of both tubes and both ovaries is the treatment of choice when fertility is no longer an issue or when progestational hormone therapy is contraindicated. For those women who desire more children or preservation of the uterus, a D&C, therapy with oral progestational agents, induction of ovulation and avoidance of postmenopausal estrogen therapy without progesterone is frequently effective. Careful follow-up with an endometrial biopsy or a D&C is necessary.

STAGE IA

The tumor is limited to the endometrium.

Standard Treatment Standard therapy is removal of the uterus, both tubes and ovaries, the pelvic and aortic lymph nodes. Unfortunately, the precise grade and depth of uterine wall invasion cannot be definitely determined at the time of surgery in women thought to be stage I prior to surgery. As a result, the pelvic lymph nodes and aortic lymph nodes should be removed

in all patients with Grade 2 or 3 cancer, and sometimes with Grade 1. Postoperative radiation therapy is not required.

Five-Year Survival 95 percent.

Investigational

- The most significant study in progress is whether postoperative pelvic radiation therapy improves survival in women with intermediate or high-grade cancers.
- Laparoscopic surgery.

STAGE IB

The tumor invades the uterine wall, but through less than half of its thickness.

Standard Treatment The abdominal removal of the uterus, both tubes and ovaries, removal of the pelvic and para-aortic lymph nodes, and abdominal washings is all that is required.

Five-Year Survival Up to 85 percent.

Investigational

- The most significant study in progress is whether postoperative pelvic radiation therapy improves survival.
- Laparoscopic surgery.

STAGE IC

The tumor invades the uterine wall by more than half of its thickness.

Standard Treatment Surgery is the same as Stage IB. Some gynecologic oncologists recommend whole pelvis radiation after surgery to decrease the frequency of recurrent disease in the vagina and pelvis. Although it does not statistically improve the five-year survival rate, it is effective in decreasing the incidence of local recurrences in the field of radiation.

Five-Year Survival Up to 75 percent.

STAGE IIA

The glands that line the cervix are involved.

Standard Treatment This stage is generally treated like Stage IB.

Five-Year Survival Up to 70 percent.

Investigational See Stage Ib.

STAGE IIB

The tumor cells invade the cervix.

Standard Treatment Before surgery, whole-pelvis external beam radiation therapy is given five days a week, over five weeks. After a two-week break, this is followed by a 2-3 day application

of radioactive cesium to the upper vagina, cervix and uterus or by high-dose rate brachytherapy (*see Radiation Therapy*). Six weeks later, an abdominal hysterectomy is performed, along with removal of both tubes and ovaries, pelvic and aortic lymph node dissection and cytological assessment of the abdominal cavity.

Alternative therapy for younger, women in good medical condition is a radical abdominal hysterectomy, removal of the tubes and ovaries, removal of all the pelvic and aortic lymph nodes and surgical staging.

Five-Year Survival Up to 60 percent.

Investigational

- Studies are looking at the role of adjuvant chemotherapy with Adriamycin, mitoxantrone, cisplatin, Cytosan, carboplatin, Taxol, ifosfamide, Doxil, Topotecan, or progestational hormones in various regimens and doses.
- High-dose rate brachytherapy (*see Radiation Therapy*).

STAGE IIIA

This stage is defined by involvement of the uterine surface and/or the tubes and ovaries and/or the presence of malignant cells in the abdominal fluid (positive peritoneal washings).

Standard Treatment After surgery, the type of additional treatment is controversial and should be considered investigational as there is not enough information about the risk of recurrence,

prognosis, and benefit of therapy. The chance of malignant cells being present within the abdominal cavity (Stage IIIa) increases with higher grades of cancer and with deeper invasion of the tumor into the uterine wall.

There is much controversy over the significance of malignant cells floating in the abdominal cavity. Many gynecologic oncologists recommend treatment with radiation therapy to the entire abdomen, intra-abdominal radioactive substances such as chromic phosphate, progestational hormone therapy, or intravenous or intraperitoneal combination chemotherapy.

Five-Year Survival Up to 60 percent.

Investigational

- Postoperative pelvic radiation.
- Pelvic and whole-abdomen radiation.
- Intravenous combination chemotherapy with Taxol, cisplatin or carboplatin and Adriamycin, Doxil, or Topotecan in various doses and schedules.
- Intra-abdominal chemotherapy (cisplatin or carboplatin).
- Occasionally high-dose progestational hormones.
- Intra-abdominal radiation (radioactive phosphorus).

STAGE IIIB

Vaginal metastases.

Standard Treatment This stage is generally treated by abdominal hysterectomy, removal of the tubes and ovaries on both sides, thorough staging and, occasionally, surgical excision of the metastases.

These cases are then usually treated with external beam radiation therapy to the pelvis and vagina, five days a week for four to five weeks. This is followed by either a temporary cesium insertion or the placing of radioactive iridium directly into the cancer (interstitial implant). Sometimes radiation therapy precedes surgery.

Endometrial cancer that extends locally outside the uterus is usually treated with radiation therapy-five weeks of external radiation therapy to the pelvis followed by two temporary cesium insertions two weeks apart or by a radioactive interstitial implant (low-dose rate or high-dose rate *see Radiation Therapy*)-followed by surgery, if possible.

Five-Year Survival Up to 40 percent.

Investigational See Stage IIb.

STAGE IIIC

Metastases to the pelvic and/or aortic lymph nodes.

Standard Treatment After surgery, women with positive pelvic and negative aortic lymph nodes receive external beam pelvic radiation therapy. If the para-aortic lymph nodes are involved, radiation therapy to the aortic region is given, as well.

Many gynecologic oncologists also recommend adjuvant chemotherapy such as cisplatin or carboplatin or Taxol + Adriamycin for women with positive pelvic and/or aortic node metastases.

Five-Year Survival Up to 60 percent.

Investigational Pelvic and para-aortic radiation versus chemotherapy (various drugs and doses).

STAGE IVA

The tumor invades the bladder or rectum.

Standard Treatment Treatment of cancer involving the bladder or rectum is usually by external radiation therapy to the pelvis followed by two insertions of radioactive cesium or interstitial radiation with iridium inserted directly into the tumor.

Another alternative is whole-pelvis radiation therapy followed by the surgical removal of the uterus, vagina, bladder and/or rectum (pelvic exenteration) is another acceptable therapy.

Five-Year Survival Up to 10 percent.

Investigational

- Studies are looking at the role of adjuvant chemotherapy with Adriamycin, mitoxantrone, cisplatin, Cytosan, carboplatin, ifosfamide, Taxol, Topotecan, Doxil or progestational hormones in various doses and regimens.

STAGE IVB

Distant metastases, intra-abdominal spread or disease in the lymph nodes of the groin.

Standard Treatment Treatment is based on the location of the distant metastasis, with the most common sites being the lungs or liver. Therapy is rarely curative, but may be palliative.

There is a 20-to 30 percent response rate to progestational hormones. If the metastatic cancer or the initial uterine tumor is sensitive to progestational hormones, as shown by the number of progesterone receptors it contains, then the response rate to hormone therapy will be significantly higher. The most commonly used progestational agent is Megace. Similarly, if the tumor contains many estrogen receptors, then anti-estrogen therapy with tamoxifen may be effective with a response rate of 20 to 30 percent. Sometimes the two hormones are used together.

Chemotherapy with carboplatin or cisplatin or Taxol + Adriamycin every three to four weeks has been shown to be effective in some patients, with response rates in the range of 30-40 percent.

Chemotherapy is frequently given alone to those women whose tumors are estrogen and progesterone receptor negative. Women with very small intra-abdominal metastases can be treated with intra-abdominal chemotherapy (cisplatin or carboplatin).

Occasionally, palliative radiation therapy may be given to a localized distant metastasis.

Five-Year Survival Up to 5 percent.

Investigational

- Chemotherapeutic drugs given in various doses and combinations are being studied. These include cisplatin, carboplatin, Taxol, Adriamycin, mitoxantrone, Cytosan, ifosfamide, 5-fluorouracil, methotrexate, Topotecan, Doxil with or without progestational hormones or antiestrogenic drugs.

TREATMENT FOLLOW-UP

Most gynecologic oncologists recommend a general physical and pelvic examination including a Pap smear every three months for the first two years, then every six months for another three years.

- The serum CA-125 level can be monitored if it was elevated before therapy.
- X-ray studies are done whenever specific signs and symptoms warrant.

RECURRENT CANCER

Approximately 70 percent of recurrences take place within three years of the initial therapy. Symptoms of recurrent cancer may include vaginal bleeding or discharge, pain in the pelvis, abdomen, back or legs, leg swelling (edema), weight loss and chronic cough.

Local recurrences-those on the pelvic wall, in the vagina and the tissue surrounding the cervix and uterus (parametrium)-are the most common sites in women who have not received pelvic radiation; distant metastases to the lung, liver or abdominal cavity may also occur.

Radiation therapy, if not given previously, may cure those women with a vaginal or parametrial recurrence. In women who have a localized vaginal recurrence involving the bladder or rectum, the removal of the bladder and/or rectum and vagina (pelvic exenteration) can be curative in up to 40 to 50 percent of cases.

Unfortunately, most women with recurrent endometrial cancer outside the pelvis cannot be cured. But symptoms may be relieved with progestational therapy, anti-estrogen therapy or chemotherapy as noted above.

ESTROGEN REPLACEMENT THERAPY

In the past, estrogen replacement therapy has been given to women with a low risk of recurrent cancer. Its safety, however, is unproven and as a result, the Gynecologic

Oncology Group is conducting a study looking at its safety. It will be several years until the final answer is known. Until then, its use should be carefully considered.

THE MOST IMPORTANT QUESTIONS YOU CAN ASK

- What qualifications do you have for treating uterine cancer? Will a specialist in gynecologic oncology be involved in my case?
- Can my surgery be performed using minimally invasive surgical techniques (laparoscopy)?
- Why do I need radiation therapy?
- Is chemotherapy of any benefit?
- What symptoms of recurrent cancer should I be looking for after treatment?
- Can I use estrogen replacement therapy?