

## **EVERYONE'S GUIDE FOR CANCER THERAPY**

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### **Uterus: Uterine Sarcomas**

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Uterine sarcomas are very rare. They are responsible for only 1 to 5 percent of all malignancies of the uterus (see "*Uterus: Endometrial Carcinoma*" for the much more common cancer of the uterus) and account for less than 1 percent of all gynecologic malignancies (see "*Cervix*").

Uterine sarcomas are treated like other uterine cancers; however, the rate of cure is less-50-70 percent for early-stage disease and less than 10 percent for advanced sarcomas.

Symptoms are similar to those of endometrial carcinoma, but some women are first diagnosed as having a common benign uterine tumor called a fibroid. After this rapidly growing, presumably benign fibroid is surgically removed, the pathologist finds that it is a cancerous tumor.

**Types** There are two general categories of tumors, pure and mixed. Those pure tumors arising from the smooth muscle of the uterine wall or from a benign fibroid are known as leiomyosarcomas and are considered benign if there are less than 5 dividing cells (mitoses) on microscopic examination and malignant if there are more than 10 dividing cells. If there are

between 5 to 10 dividing cells, they are considered a low-grade malignancy. Other histologic criteria, such as the degree of cellular nuclear atypia are also factored into a diagnosis of benign versus malignant.

Another 15 percent of uterine sarcomas arise from the supporting (stromal) cells that surround the glands within the lining of the uterus (the endometrium) and are known as pure endometrial stromal sarcomas. They are classified according to grade, from the less virulent low-grade tumors to the extremely virulent high-grade tumors.

The most common type of uterine sarcomas-half of all cases-arise from both the endometrial glands *and* the supporting stromal cells of the endometrium. These are known as mixed mesodermal sarcomas, and are further subdivided into homologous and heterologous tumors. The homologous variety-also known as carcinosarcomas-contain malignant cells transformed from cells normally found in the uterus. The heterologous type contains cellular elements not normally found in the uterus, including malignant bone, fat, cartilage and striated muscle.

Heterologous mixed mesodermal tumors are the most common type of uterine sarcoma and account for 1 to 3 percent of all uterine cancers. Homologous tumors are much less common.

**How It Spreads** Uterine sarcomas can grow locally to involve the tissue surrounding the uterus and cervix, to the rectum and bladder, to the groin, pelvic and aortic lymph nodes, to the surfaces of the abdominal cavity and distantly to the liver, lung, and brain.

Leiomyosarcomas spread by direct local extension, abdominal implantation or via the bloodstream. The lung is the most common site of metastases, followed by the liver, brain and bone.

Low-grade stromal sarcomas are usually slow growing and tend to remain confined to the uterus in about 70 percent of cases. Spread beyond the uterus occurs via the lymph system or via the bloodstream. High-grade stromal sarcomas spread in similar way, but they behave much more aggressively and are often advanced at the time of diagnosis.

**What Causes It** The exact cause is unknown. Like the more common endometrial carcinoma, heterologous mixed mesodermal tumors appear to be associated with diabetes, hypertension and obesity. There is also a significant association with previous pelvic radiation (10 to 30 percent of cases). The average time interval between pelvic radiation and development of the sarcoma is 15 to 20 years.

Unlike other uterine sarcomas, leiomyosarcomas have no association with previous pelvic radiation.

### **RISK FACTORS**

Heterologous mixed mesodermal tumors can occur in any age group, including infants, but they most commonly occur in postmenopausal women with a median age of 65. Homologous mixed mesodermal tumors can also occur in all age groups, but the median age is 57 years. The average age for leiomyosarcomas at diagnosis is 53.

Low-grade stromal sarcomas occur much more frequently in premenopausal women, with 70 percent occurring in women under 50. High-grade stromal sarcomas most commonly occur in postmenopausal women.

*At Significantly Higher Risk*

- Previous pelvic radiation.

**SCREENING**

Uterine sarcoma can occasionally be detected by a routine Pap smear, but screening for all uterine tumors is not as satisfactory as that for cervical cancer because of the inaccessibility of the uterine cavity. There is no screening program routinely used for women without symptoms.

Although not as yet used for routine screening, sonography can occasionally detect uterine malignancies. The endometrial cavity is usually thicker than normal from sarcomas arising from the endometrium.

**COMMON SIGNS AND SYMPTOMS**

With heterologous mixed mesodermal tumors, postmenopausal bleeding is the most common symptom. Abnormal uterine bleeding is also the first symptom of pure endometrial stromal sarcomas.

Most women with a leiomyosarcoma will have abnormal uterine bleeding, pressure or pain in the abdomen or pelvis, abnormal vaginal discharge or uterine fibroids, but many will have no symptoms.

## **DIAGNOSIS**

### ***Physical Examination***

- A careful pelvic examination.
- Examination of the lymph nodes in the groin and above the collarbone.
- Examination of the abdomen to detect an enlarged liver, abdominal masses and excess fluid (ascites).

### ***Blood and Other Tests***

- Serum liver and kidney function tests.

### ***Imaging***

- Chest x-ray.
- Pelvic and abdominal CT scans to detect pelvic extension of tumor, pelvic and aortic lymph nodes and liver metastases.
- Pelvic MRI (on occasion).

### ***Endoscopy and Biopsy***

- Cystoscopy and sigmoidoscopy (occasionally).

- The definitive diagnosis is made by a pathologist evaluating either an office endometrial biopsy, tissue removed during a D&C (dilation and curettage) or the tissue specimen after the uterus and cervix are removed (hysterectomy). Although stromal and mixed mesodermal tumors are diagnosed from an endometrial biopsy or D&C, most leiomyosarcomas are diagnosed after a hysterectomy for what is thought to be benign uterine fibroids. A preoperative diagnosis of leiomyosarcomas is uncommon.

## **STAGING**

The International Federation of Gynecology and Obstetrics (FIGO) staging classification for uterine sarcoma is the same as that for endometrial carcinoma. Uterine sarcomas are surgically staged.

## **TREATMENT OVERVIEW**

Surgery is the primary treatment and can lead to a cure if the tumor is confined to the uterus. Radiation and chemotherapy may also be used after surgery for some stages.

**Surgery** Whenever possible, the uterus and cervix are removed (hysterectomy) along with the fallopian tubes and ovaries on both sides. The pelvic and aortic lymph nodes are removed and fluid from the pelvis and abdomen is taken for analysis (peritoneal cytologic washings). Sarcomas thought to be confined to the uterus can also be treated laparoscopically in selected cases (see "*Uterus: Endometrial Carcinoma*").

**Radiation** External beam radiation therapy is often given to the pelvis after surgery to decrease local recurrence in early-stage disease. This does not appear to improve survival, however. Side effects of radiation can include diarrhea, nausea and vomiting, bleeding from the bladder or rectum, vaginal scarring, intestinal obstruction, or leaks (fistulas) in the urinary or intestinal tracts.

**Chemotherapy** Although there is no definite proof of increased survival with adjuvant chemotherapy (treatment even if there is no obvious evidence of residual disease), many gynecologic oncologists and medical oncologists recommend its use even for early stages of disease. Metastatic sarcomas that have spread to distant organs are generally treated with chemotherapy.

## **TREATMENT BY CELL TYPE**

### **MIXED MESODERMAL SARCOMAS**

The prognosis depends mainly on the stage of the cancer. There does not seem to be any difference in survival between homologous and heterologous mixed mesodermal tumors.

**Standard Treatment** Hysterectomy, removal of tubes and ovaries on both sides, washings to check for malignant cells in the abdominal cavity and removal of the pelvic and aortic lymph nodes on both sides.

After surgery, many women are treated with radiation therapy five days a week for five weeks to the entire pelvis, including the upper vagina.

Chemotherapy may be used as an adjuvant therapy, although there is no documented proof of its benefit.

### **Investigational**

- Adriamycin + ifosfamide + DTIC.
- A clinical trial now being done by the Gynecologic Oncology Group is comparing ifosfamide and cisplatin versus ifosfamide without cisplatin for the treatment of mixed mesodermal tumors. Thirty-five percent of women respond to intravenous ifosfamide alone.
- Adriamycin in combination with DTIC or Cytosin has been shown to be more effective than Adriamycin alone for advanced disease.
- Vincristine and Cytosin have also been used in combination with actinomycin-D or Adriamycin, with or without DTIC, with some effectiveness.
- Mitoxantrone, a drug similar to Adriamycin, with ifosfamide is being studied.

## **LEIOMYOSARCOMA**

Good prognostic factors for this tumor type include the presence of a small tumor, a tumor arising from a benign uterine fibroid (5 to 10 percent of all cases), a low number of dividing cells and being premenopausal.

**Standard Treatment** Abdominal hysterectomy, removal of the tubes and ovaries, washings to check for malignant cells in the abdominal cavity and removal of the pelvic and aortic lymph nodes.

Any additional treatment for women with early-stage disease and borderline tumors has not been shown to be beneficial.

Postoperative whole-pelvis external beam radiation therapy for five days a week for five weeks is sometimes given to decrease the local recurrence rate in early-stage disease.

Although postoperative pelvic radiation and/or chemotherapy are often given, they have not been shown conclusively to increase survival. The most commonly used chemotherapeutic drugs include Adriamycin + ifosfamide + DTIC, vincristine + Adriamycin or actinomycin-D + Cytosan + DTIC. Cisplatin has shown not to be of benefit.

Advanced leiomyosarcoma is treated with radiation therapy and/or chemotherapy.

## **Investigational**

- Current studies are looking at postoperative pelvic radiation therapy versus no treatment and chemotherapy in varying doses and schedules.
- For women with advanced disease, Adriamycin in combination with DTIC or Cytosan has been shown to be no more effective than Adriamycin alone.
- Vincristine has been used with actinomycin-D or Adriamycin and Cytosan with or without DTIC with some effectiveness in advanced disease.
- Mitoxantrone, a drug similar to Adriamycin, and ifosfamide are being studied.

## **LOW-GRADE ENDOMETRIAL STROMAL SARCOMA**

**Standard Treatment** The standard treatment for these sarcomas usually includes a hysterectomy, removal of the tubes and ovaries on both sides, pelvic and aortic node dissection and abdominal cytologic washings.

Early-stage disease can also be treated by a radical hysterectomy, removal of the pelvic and aortic lymph nodes, removal of the tubes and ovaries, and abdominal cytologic washings.

Postoperative radiation therapy to the pelvis (4,500 to 5,000 cGy given in divided doses, five days a week for five weeks) is sometimes given to decrease the chance of a pelvic recurrence.

The frequency of recurrence depend primarily the depth of uterine invasion.

Since these tumors frequently contain progesterone and/or estrogen receptors, hormone therapy with progestins or the antiestrogen tamoxifen is sometimes given.

### **Investigational**

- Various types and doses of progestins and antiestrogens are being studied.

### **HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA**

**Standard Treatment** For high grade stromal sarcomas, standard therapy is a hysterectomy, removal of the tubes and ovaries, removal of the pelvic and aortic nodes, and washings from the abdominal cavity to look for malignant cells.

For early-stage cancer, postoperative pelvic radiation therapy (total dose of 4,000 to 5,000 cGy given in divided doses, five days a week for five weeks) is recommended because it decreases the chance of a pelvic recurrence.

Adjuvant chemotherapy is sometimes given, but it should be considered experimental.

### **Investigational**

- Since pelvic and distant recurrences are common and the prognosis of this malignancy is poor, many gynecologic oncologists and medical oncologists recommend adjuvant chemotherapy even though it has not yet been shown to be effective.
- Adriamycin, ifosfamide and DTIC.

- Vincristine and Cytosin in combination with actinomycin-D or Adriamycin with or without DTIC may be somewhat effective.
- Mitoxantrone, a drug similar to Adriamycin, and ifosfamide are being studied.

## **TREATMENT BY STAGE**

### ***STAGE I***

This early tumor is further divided into Stages Ia, Ib and Ic. In Stage Ia, the tumor is limited to the endometrium. In Ib, it invades the wall of the uterus by less than half of its thickness. In Ic, it invades the wall by more than half of the thickness.

**Standard Treatment** Surgery should include a hysterectomy, removal of both fallopian tubes and ovaries, washings from the abdominal cavity to look for malignant cells and removal of the pelvic and aortic lymph nodes.

Postoperative radiation therapy is sometimes given to the entire pelvis (total dose 4,000 to 5,000 cGy, given in divided doses, five days a week for five weeks).

***Five-Year Survival*** 75 percent for Stage Ia, 50 percent for Stages Ib and Ic.

### ***STAGE IIA***

The tumor involves the endocervical glands.

**Standard Treatment** Surgery as for Stage I and sometimes postoperative whole-pelvis radiation therapy.

**Five-Year Survival** 50 percent.

**Investigational** Same as Stage I.

### ***STAGE IIB***

Cervical stromal invasion.

**Standard Treatment** Surgery as for Stage I is standard. An alternative is whole-pelvis external beam radiation therapy (total dose 4,000 to 5,000 cGy given in divided doses five days a week for five weeks), followed two weeks later by the insertion of radioactive cesium into the uterus (intracavitary radiation) for one or two days. This will be followed six weeks later by the hysterectomy, removal of both tubes and ovaries, cytologic washings of the abdominal cavity and removal of the pelvic and aortic lymph nodes.

Equally effective for young women or those in good medical condition is a radical hysterectomy, removal of both tubes and ovaries, removal of the pelvic and aortic lymph nodes and meticulous staging.

**Five-Year Survival** 50 percent.

**Investigational** See adjuvant chemotherapy under "Treatment By Cell Type".

### ***STAGE IIIA***

The surface of the uterus and/or the tubes and ovaries are involved and/or there are malignant cells in the abdominal fluid (positive peritoneal washings).

**Standard Treatment** Surgery as for Stage I. Postoperative pelvic radiation therapy with or without whole-abdomen radiation therapy is given. Chemotherapy is also given sometimes.

***Five-Year Survival*** 0 to 20 percent.

**Investigational** See adjuvant chemotherapies under "Treatment By Cell Type."

### ***STAGE IIIB***

There are vaginal metastases.

**Standard Treatment** For women with vaginal metastases, the standard treatment is surgery as for Stage I cancer and postoperative external beam radiation therapy given to the whole pelvis and vagina. This is followed by one vaginal brachytherapy insertion (a radioactive substance is placed against the tumor) for one or two days or interstitial iridium (a radioactive substance placed directly into the tumor) for one or three days.

Women with disease that extends locally outside the uterus are treated with whole-pelvis radiation, one or three intracavitary cesium or interstitial iridium insertions, followed by surgery whenever possible.

***Five-Year Survival*** 0 to 10 percent.

**Investigational** See adjuvant chemotherapies under "Treatment By Cell Type."

- Interstitial radiation therapy with heat (hyperthermia) is being studied.

### ***STAGE IIIC***

Metastases to the pelvic and para-aortic lymph nodes.

**Standard Treatment** Surgery as for Stage I. Postoperative pelvic radiation therapy and radiation to the aortic lymph nodes (if they are involved) is usually given. Chemotherapy is sometimes given, as well.

***Five-Year Survival*** 0 to 10 percent.

**Investigational** See adjuvant chemotherapies under "Treatment By Cell Type."

### ***STAGE IVA***

The tumor invades the bladder or rectum.

**Standard Treatment** Options include external beam radiation therapy to the entire pelvis and intracavitary or interstitial radiation therapy (in one or three insertions). Occasionally, the uterus, vagina, bladder and/or rectum are removed (pelvic exenteration).

**Five-Year Survival** 0 to 5 percent.

### **Investigational**

- Adjuvant chemotherapy.
- Interstitial radiation therapy.

### **STAGE IVB**

There are distant metastases, with spread to organs within the abdomen and/or disease in the groin lymph nodes.

**Standard Treatment** Metastatic sarcomas are usually treated with chemotherapy. Commonly used drugs include Adriamycin or ifosfamide alone and the combinations of Adriamycin + ifosfamide + DTIC; vincristine + actinomycin-D; or Adriamycin + Cytosan + DTIC.

**Five-Year Survival** 0 to 5 percent.

## **Investigational**

- Various doses and combinations of chemotherapy drugs are being evaluated.
- Mitoxantrone, a drug similar to Adriamycin, is being studied.

## **TREATMENT FOLLOW-UP**

A general physical and pelvic examination is performed every three months for the first two years after treatment, then every six months for the next three years.

- A Pap smear is performed at each visit.
- Diagnostic x-ray studies are performed as specific symptoms and signs warrant.

## **RECURRENT CANCER**

Uterine sarcomas most often recur within three years of treatment and occur in the vagina, pelvis, lymph nodes, liver and lungs. Recurrences of leiomyosarcomas are usually distant, with only 5 percent confined to the pelvis. Recurrences of low-grade stromal sarcomas can occur late, sometimes 10 years after initial treatment. Although pelvic recurrences are the most common, it can recur in the abdominal cavity or in the lungs.

Common symptoms of recurrent cancer include vaginal bleeding or discharge, pain in the pelvis, abdomen, back or legs, swelling in the legs or abdomen, chronic cough or weight loss.

**Treatment** There is no standard therapy for recurrent disease.

- Chemotherapy has been used with variable effectiveness but rarely leads to a cure.
- Women with localized disease in the pelvis sometimes benefit from radiation therapy and occasionally by the removal of the pelvic organs (pelvic exenteration).
- Women with low-grade endometrial stromal sarcomas might benefit from progestational hormone or antiestrogen therapy.

### **THE MOST IMPORTANT QUESTIONS YOU CAN ASK**

- What qualifications do you have for treating cancer? Are you a specialist in gynecologic oncology?
- Can my surgery be performed laparoscopically?
- What kind of sarcoma do I have?
- What is the stage?
- What benefit is there to having radiation therapy after surgery?
- Is there any benefit from chemotherapy?