Uterine Sarcoma

Introduction

- Sarcomas are a rare form of uterine cancer that can arise from the endometrial lining of the uterus or the myometrium.
- Compared to the more common endometrial carcinomas, uterine sarcomas behave more aggressively and are associated with a poorer prognosis.
- This topic review will cover the uterine sarcomas that arise in adults (ie, leiomyosarcomas, carcinosarcomas, and endometrial stromal sarcomas).

Epidemiology

- 40 to 60 years of age
- < 4 percent of uterine malignancies
- Incidence: 17 per million women annually
- In US: two- to three-fold higher incidence of carcinosarcomas and leiomyosarcomas (but not endometrial stromal sarcomas) among African-American compared to Caucasian women

Risk factors

- Lack of large epidemiologic studies
- Parity and time of menarche and menopause: inconclusive
- History of pelvic irradiation: 5 to 10 percent
- Long-term use of tamoxifen in women with breast cancer increases the risk of uterine sarcomas (MMT)

Classification

- Gynecologic Oncology Group (GOG)
  - Mixed homologous mullerian sarcoma
  - Mixed heterologous mullerian sarcoma
  - Leiomyosarcoma
  - Endometrial stromal sarcoma (ESS)
  - Undifferentiated sarcomas (high-grade ESS)

MMMT

- Malignant mixed mullerian tumors (carcinosarcomas)
- Most common type of uterine sarcoma
  - One series they represented 43 percent (51/119) of all cases
- Both epithelial (carcinoma) and sarcomatous elements must be present
- Both components arise from a common progenitor cell

MMMT

- The carcinomatous component is usually a high-grade adenocarcinoma.
  - Endometrioid
  - Serous
  - Clear cell
  - Squamous: less commonly
  - Undifferentiated: less commonly

MMMT

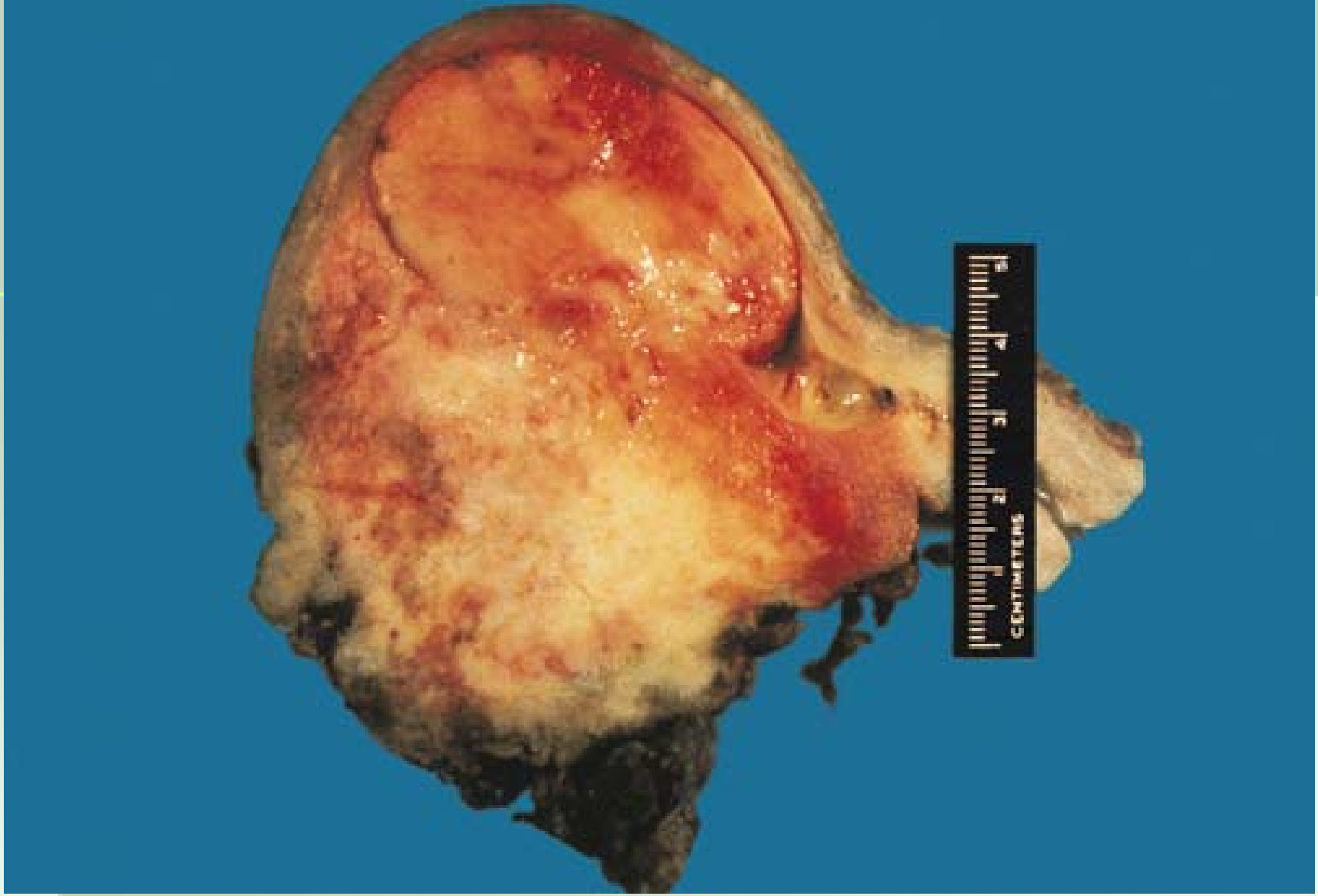
- Sarcomatous components in a mixed homologous mullerian sarcoma may resemble
  - Leiomyosarcoma
  - Fibrosarcoma
  - Malignant fibrous histiocytoma
  - Undifferentiated sarcoma
- Sarcomatous component of a mixed heterologous mullerian sarcoma (mixed mesodermal sarcoma)
  - Rhabdomyosarcoma
  - Chondrosarcoma
  - Osteosarcoma
  - Liposarcoma

MMMT

- The most common pattern is a mixed homologous carcinosarcoma consisting
  - Serous papillary carcinoma
  - Endometrial stromal sarcoma

MMMT

- Aggressive
- They tend to form bulky polypoid masses that often fill the uterine cavity and extend into or through the endocervical canal.
- It is not uncommon to see obvious myometrial invasion, and intraabdominal as well as retroperitoneal nodal metastases.
- The behavior of carcinosarcomas usually reflects the carcinomatous component, which predominates within metastatic sites.
  - Usually a papillary serous carcinoma → the clinical course mimics epithelial ovarian cancer.



- Tumor is massive, filling the endometrial cavity, extending down into the endocervical canal and invading into and through the myometrium.
- The variegated "fish-flesh" cut surface is characteristic.

Leiomyosarcoma & Mitotically active leiomyomas

- Leiomyosarcomas account for one-third of uterine sarcomas
- Gross appearance:
  - Large (>10 cm)
  - Yellow or tan solitary mass
  - Soft, fleshy cut surfaces
  - Areas of hemorrhage and necrosis

Leiomyosarcoma & Mitotically active leiomyomas

- Benign leiomyomas (fibroids) and leiomyosarcomas are independent entities.
- Leiomyosarcomas are much less common and not hormonally driven.
- Leiomyomas only rarely (0.23 percent of cases in one large series) degenerate into leiomyosarcomas

Leiomyosarcoma & Mitotically active leiomyomas

- Microscopically, most leiomyosarcomas are with
  - Hypercellularity
  - Coagulative tumor cell necrosis
  - Abundant mitoses (10 to 20 per 10 high power fields[HPF]),
  - Atypical mitoses
  - Cytologic atypia
  - Infiltrative borders
- Diagnostic problems arise in smooth muscle tumors
  - Less cellular
  - Less atypical
  - Less mitotically active

Leiomyosarcoma & Mitotically active leiomyomas

- Many authors believe that mitotic activity is the single most reliable indicator of malignant potential
- A large retrospective study from Stanford suggested the use of three main criteria:
  - Frequent mitotic figures
  - Significant nuclear atypia
  - Presence of coagulative necrosis
- > 10 mitosis /10HPF, with or without atypia

Leiomyosarcoma & Mitotically active leiomyomas

- Others classify leiomyomas with increased mitotic activity (ie, >5 mitoses per 10 HPF) but no marked cytologic atypia as "mitotically active benign leiomyomas" only when they arise in women under the age of 35 or with pregnancy
  - Typically small
  - Well-circumscribed
  - Almost always behave in a benign fashion
- Leiomyomas are more likely to have a high mitotic count if they are excised during
  - Secretory phase of the menstrual cycle
  - Pregnancy
  - Receiving exogenous progestins

Leiomyosarcoma & Mitotically active leiomyomas

- In contrast, the clinical behavior of leiomyomas with increased mitotic activity but no marked cytologic atypia is less certain in older women
- Smooth muscle tumor of uncertain malignant potential
- Treated with a simple hysterectomy
- Better prognosis than leiomyosarcoma

Leiomyosarcoma & Mitotically active leiomyomas

- The designation atypical (also called pleomorphic, sympathic, or bizarre) leiomyoma
  - Presence of giant cells
  - Diffuse moderate to severe atypia
  - Mitotic count less than 10 mitoses per 10 HPF
  - Without coagulative necrosis
- High cure rate with surgery alone

Classification of problematic uterine smooth muscle tumors based on patho features

Group	Mitotic Index (MI) (per 10 HPF)	Atypia	Coagulation necrosis	Designation
I	20 >MI ≥5	None or mild	None	Leiomyoma with increased MI
II A	MI ≥10	Diffuse, moderate or severe	None	Leiomyosarcoma
II B	<10	Diffuse, moderate or severe	None	Atypical leiomyoma with low risk percent or recurrence
III	All subsets	Diffuse, moderate to severe	Present	Leiomyosarcoma
IV A	≥10 F	Insignificant	Present	Leiomyosarcoma
IV B	≤10	Insignificant	Present	Smooth muscle tumors of low malignant potential limited experience
V	All subsets	Focal or multifocal, moderate to severe	None	

MI: mitotic index; HPF: high-power field.

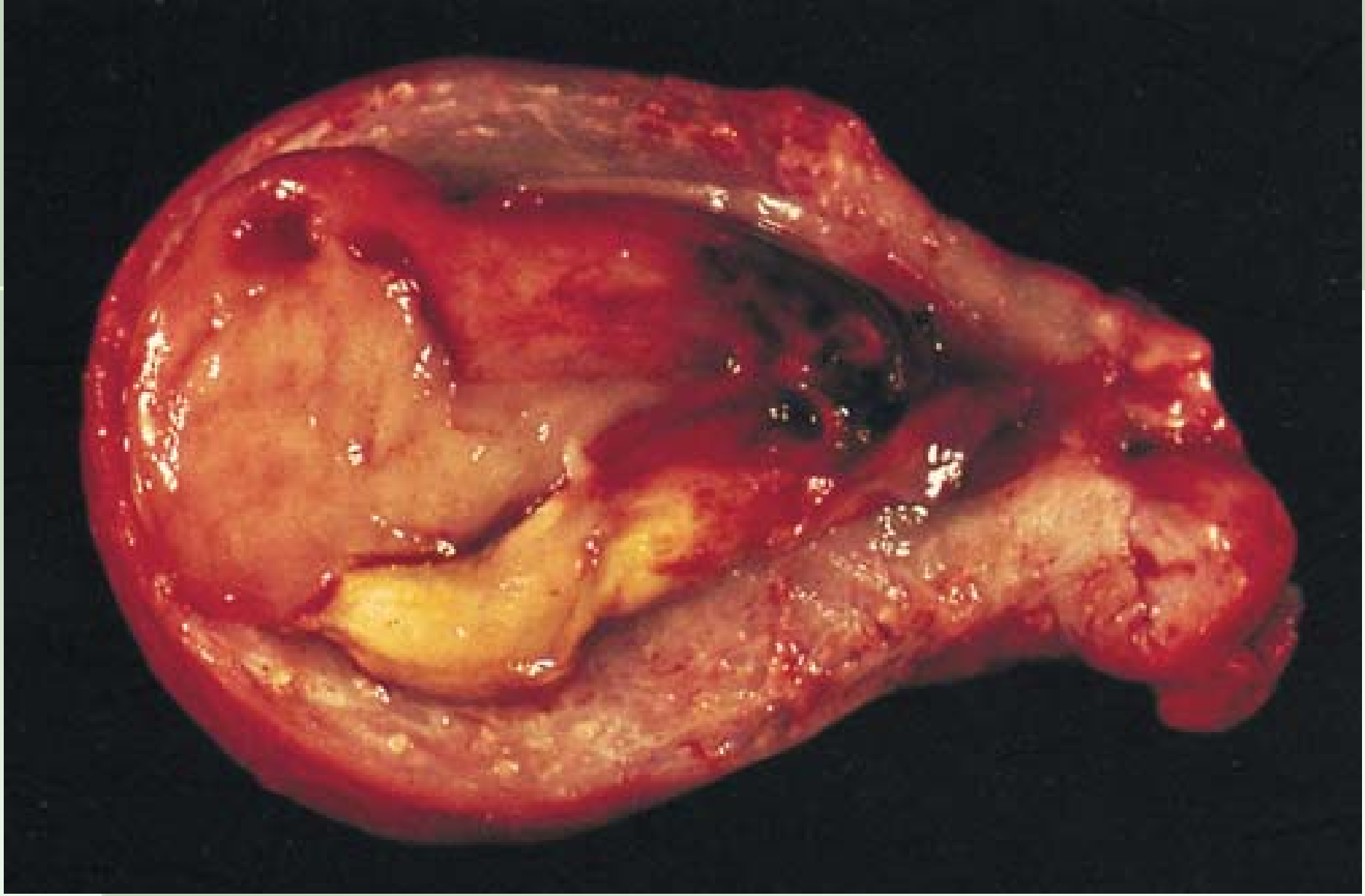
Data from Bell, SW et al. Am J Surg Pathol 1994; 18:535.

Leiomyosarcoma & Mitotically active leiomyomas

- Myxoid leiomyosarcomas
  - Do not fit well into the Stanford scheme and are classified separately
  - Dense myxoid appearance may obscure the smooth muscle etiology of this tumor
  - Extent of nuclear pleomorphism
  - True number of mitotic figures
  - Apparently bland features
  - Behave in a highly malignant manner
  - Considered high-grade leiomyosarcomas

Endometrial stromal sarcoma

- Pure endometrial stromal tumors
  - Benign (endometrial stromal nodules)
  - Malignant (endometrial stromal sarcomas, ESS)
- Composed of cells that are identical to those found in the stromal component of the endometrium
- Arise within the endometrium and infiltrate the myometrium
- Historically, there were two subtypes:
  - Low grade
  - High grade



- Low-grade endometrial stromal sarcoma
- This soft, fleshy tumor grows predominantly as a polypoid lesion in the endometrial cavity but also invades the myometrium of the fundus

Endometrial stromal sarcoma

- Low-grade ESS (ESS)
  - Comprised of cells resembling proliferative endometrial stromal cells that have infiltrated the myometrium
  - As worm-like plugs of tumor within the vascular or lymphatic channels
  - Cytologic atypia: mild to moderate
  - Mitoses: less than 10 (but usually 0 to 3) per 10 HPF
  - Slow-growing, Infrequently metastasize or recur after resection
- High-grade ESS (undifferentiated uterine sarcomas)
  - Cellular atypia: moderate to marked
  - With prominent chromatin clumps and nucleoli
  - Mitoses: 10 mitoses per 10 HPF
  - Cytologic atypia may be so extreme as to make it difficult to recognize the tumor's origin from endometrial stroma
  - Classified as undifferentiated uterine sarcomas
  - Enlarge and metastasize quickly → often fatal

Adenosarcoma

- Rare mixed tumor
- Benign epithelial component is mixed with a malignant stromal element
- Solid polypoid masses
- Arising from the fundus
- Low malignant potential
- Good prognosis
- Variant: adenosarcoma with sarcomatous overgrowth → worse prognosis, similar to carcinosarcoma

Clinical manifestations

- Vaginal bleeding: the most common
  - Amount: from spotting to menorrhagia
- Pain
- Foul smelling vaginal discharge
- On pelvic examination:
  - Enlarged uterus
  - Tumor may protrude through the cervical os (carcinosarcomas)

Clinical manifestations

- Risk of sarcoma: rapidly growing (not substantiated)
  - 1332 women for hysterectomy or myomectomy of presumed uterine leiomyomas
  - Incidence of uterine sarcomas: 0.23 percent
  - 341 women with a rapidly growing uterus by clinical or ultrasound examination (one diagnosed uterine sarcoma, 0.27 percent)
  - Most women with a rapidly enlarging uterus or uterine mass do not have a sarcoma

Clinical manifestations

- Considered in postmenopausal women with presumed uterine leiomyomas producing symptoms sufficiently bothersome to consider hysterectomy
- In this group the incidence of sarcoma is higher but still small (1 to 2 percent)

Diagnostic evaluation

- Imaging studies and clinical findings are not specific
- Ultrasound examination, MRI, or CT cannot reliably distinguish between a sarcoma and leiomyoma, endometrial cancer, lymphoma, intravenous leiomyomatosis, or adenomyosis
- Abnormal uterine bleeding or a suspicious uterine lesion → endometrial biopsy prior to surgery

Staging

- Surgical staging

Preoperative evaluation

- Sarcoma: extensive local growth
- Carcinoma: distant spread
  - Intraabdominal
  - Lymphatic
  - Hematogenous
- All uterine sarcomas have the propensity for hematogenous dissemination → early, and most frequently involves lung
- Preoperative thoracic CT scan if the diagnosis is known; postoperative if unknown
- Preoperative CT scan of the abdomen and pelvis → to identify occult extrauterine disease

Surgical staging

- Peritoneal washings for cytology
- Extrafascial total abdominal hysterectomy
- Bilateral salpingo-oophorectomy
- Excision of enlarged lymph nodes
- Biopsy of any suspicious areas
- Extent of surgical staging: controversial, and depend on the tumor type
  - Omentectomy
  - Pelvic and paraaortic lymph node sampling

Surgical staging

- Lymph node involvement
  - Carcinosarcomas: most common
  - Leiomyosarcoma: low risk (3.5 to 11 percent)
  - ESS: few data
- Complete surgical staging is particularly important in carcinosarcomas because these tumors are more likely to be associated with intraabdominal and retroperitoneal metastases than leiomyosarcomas
  - 62 patients with carcinosarcoma confined to the uterus
  - Occult metastases (adnexae, pelvic and paraaortic nodes, omentum): 60 percent

Surgical staging

- Lymph node dissection: unclear
  - Prognostic significance
  - Not therapeutic: similar outcome
  - Some surgeons perform lymph node dissection only in women with clinically suspicious nodes, which typically occur only in the presence of gross extrauterine disease

Surgical staging

- When a uterine sarcoma is diagnosed postoperatively, reexploration for surgical staging is probably unnecessary since the risk of metastasis to lymph nodes and beyond is small
- Ovarian conservation: option for premenopause
  - Two studies: not adversely affect prognosis with stage 1 low grade endometrial stromal sarcoma or leiomyosarcoma
  - These data are too limited
  - Informed consent
  - Close follow-up with serial radiographic imaging

Surgical staging

- In the rare instance where a young woman undergoing myomectomy for leiomyomas is found to have a low-grade leiomyosarcoma, or a smooth muscle tumor of uncertain malignant potential, it may be possible to avoid hysterectomy
  - Informed consent
  - Close follow-up with serial radiographic imaging (preferably with MRI)

FIGO staging

- Same as endometrial carcinomas
  - Stage I: uterine corpus
  - Stage II: cervix
  - Stage III: regional spread to pelvic organs
  - Stage IV: outside of the pelvis
- Stage is the most important prognostic factor for all types of uterine sarcoma

TNM categories	FIGO* stages	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium
T1b	IB	Tumor invades up to or less than one-half of the myometrium
T1c	IC	Tumor invades to more than one-half of the myometrium
T2	II	Tumor invades cervix but does not extend beyond uterus
T2a	IIA	Endocervical glandular involvement only
T2b	IIB	Cervical stromal invasion
T3	III	Local and/or regional spread as specified in T3a, b, and/or N1 and FIGO IIIA, B, and C below
T3a	IIIA	Tumor involves uterine serosa and/or adnexa (direct extension or metastasis) [often termed stage IIIA2] and/or cancer cells in ascites or peritoneal washings [stage IIIA1]
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
N1	IIIC	Metastasis to the pelvic and/or para-aortic lymph nodes
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (Bullous edema is not sufficient to classify a tumor as T4)
M1	IVB	Distant metastasis. (Excluding metastasis to vagina, pelvic serosa, or adnexa. Including metastasis to intra-abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes)

* FIGO: Federation Internationale de Gynecologie et d'Obstetrique.

Grade

- G1: 5 percent or less of a nonsquamous or nonmorular solid growth pattern
- G2: 6 percent to 50 percent of a nonsquamous or nonmorular solid growth pattern
- G3: More than 50 percent of a nonsquamous or nonmorular solid growth pattern

Treatment

Surgery

- Surgical staging
  - Extrafascial abdominal hysterectomy
  - Bilateral salpingo-oophorectomy
  - Peritoneal washings for cytology
  - Pelvic and paraaortic lymph node dissection or sampling: controversial
  - Fertility-preserving surgery
    - Young women
    - Low-grade leiomyosarcoma or
    - Smooth muscle tumor of uncertain malignant potential

Adjuvant RT- stage I & II

- Adjuvant pelvic RT for improved local control in
  - Carcinosarcomas
  - High-grade leiomyosarcomas
  - Undifferentiated uterine sarcomas
- Pelvic RT instead of whole abdominal radiation
- Improvement in survival: unclear

Adjuvant CT- stage I & II

- Not using adjuvant chemotherapy for resected stage I or II uterine sarcoma
- Others disagree, and routinely offer systemic chemotherapy following RT → suggest improved survival

Adjuvant therapy- III & IVa

- Adjuvant systemic therapy rather than RT alone
- RT alone:
  - With pelvic nodal metastases and no evidence of disease in the paraaortic nodes or in the peritoneum
- No consensus as to the choice of adjuvant chemotherapy regimen
- Platinum-based for carcinosarcoma and undifferentiated sarcomas
  - Paclitaxel, doxorubicin and cisplatin (TAP regimen) as used in GOG 177.
- Hormone therapy with megestrol acetate for ESS
  - Start with 40 mg twice daily initially
  - Increasing to 80 mg twice daily if tolerated
  - At least six to 12 months, and continued indefinitely

Adjuvant therapy- III & IVa

- Except ESS, pelvic radiation may be added for better local control
- Pelvic radiotherapy
  - Improved local control
  - Myelotoxicity
  - Involved PA nodes → extended field irradiation

Adjuvant therapy- IVb & recur

- Recurrence
  - Pelvis (most)
  - Lung → pneumothorax
  - Abdomen
  - Bone and brain: uncommon
- Surgery is recommended for
  - Potentially resectable local recurrence
  - Limited metastatic disease, especially involving the lungs
- Unresectable → palliative systemic chemotherapy

Adjuvant therapy- IVb & recur

- Clear differences in the chemotherapy responsiveness of uterine leiomyosarcomas and carcinosarcomas
- Leiomyosarcoma
  - Gemcitabine and docetaxel
  - Doxoubicin +/- ifosfamide
- Non-leiomyosarcoma, especially carcinosarcoma
  - Few carcinosarcomas are true sarcomas
  - Most are very poorly differentiated epithelial tumors with metaplastic changes mimicking sarcomatous tissue
  - Cisplatin-based chemothearpy
  - Paclitaxel, doxorubicin, and cisplatin (TAP), as was used in GOG trial 177.
  - Single agent: doxorubicin, ifosfamide

Adjuvant therapy- IVb & recur

- For endometrial stromal sarcomas
  - Hormone therapy:
    - Less clear than breast and EM carcinoma
    - Lack of prospective studies
  - Initial hormone therapy: progestin
  - Megestrol acetate
  - 40 mg orally twice daily initially, increasing to 160 to 320 mg daily
  - Medroxyprogesterone: lung and peritoneal metastasis
  - Aromatase inhibitors
  - Gonadotropin- releasing hormone analogs
  - Tamoxifen
  - Second-line treatment:
    - Cisplatin +/- paclitaxel/doxorubicin
    - Doxorubicin (usually Doxil)

Prognosis

- Poorer prognosis as compared to other gynecologic malignancies
- Five-year survival rate:
  - Stage I: 50 percent (others: approximately 90 percent)
  - Stage III or IV: 20 to 30 percent

Prognostic factor

- Tumor stage: most important
- Completeness of resection
- Histologic grade: not an independent prognostic factor
  - In most series, prognosis is similar for all histologic types after correcting for disease stage
  - One possible exception is low-grade ESS which may have a better long-term outcome, at least for early stage disease
- Mitotic count
- Vascular and/or lymphatic invasion
- Postmenopausal women
- Steroid receptor expression: unclear
  - Some reports suggest a better long-term prognosis while others do not

Prognostic factor

- Prognostic factors may differ according to histology
- In a Gynecologic Oncology Group (GOG) series of factors that influence progression-free interval in early stage uterine sarcoma
  - Leiomyosarcoma
    - Mitotic index: only independent prognostic factor
  - Carcinosarcoma
    - Tumor size
    - Depth of uterine invasion
    - Lymphatic or vascular involvement
    - Histologic grade and cell type
    - Adnexal extension
    - Lymph node metastases
    - Peritoneal cytologic finding