9 Uterine Sarcomas

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Chapter Outline

Chapter Overview

Uterine sarcomas are very rare neoplasms, comprising 1% of all gynecologic malignancies. However, these sarcomas are some of the most aggressive tumors of the gynecologic tract. Sarcoma patients have an overall survival rate of less than 50%, even when the disease is diagnosed at an early stage. There is no designated staging system for uterine sarcomas, and most clinicians use the International Federation of Gynecology and Obstetrics staging system for endometrial cancer. Although surgical resection is the mainstay of treatment, multidisciplinary teams, including radiation oncology, gynecologic oncology, and sarcoma specialists, are important. The benefit of surgical lymph node staging is unclear, especially in the setting of uterine leiomyosarcoma. Adjuvant radiation therapy has historically been of little survival value, but palliatively, it can offer improved quality of life and pain control. Chemotherapy does not appear to be effective when given adjuvantly but can produce limited response rates of approximately 17% to 40% when given for recurrences. Because of the rarity of these tumors, literature on them is scarce, and reports often cover a broad range of histologic subtypes of sarcoma.

Introduction

This chapter reviews the presentation, evaluation, and treatment of women with sarcomas of the uterus.

Uterine sarcomas comprise only 1% of all gynecologic malignancies and fewer than 5% of all cancers of the uterus. However, sarcomas are some of the most aggressive tumors of the gynecologic tract. Because of the low incidence of uterine sarcomas and the fact that they lack a preinvasive stage, there is no established practice for screening for these tumors.

Because of the rare nature of uterine sarcomas and their often aggressive clinical course, the literature on them is scarce. Clinical-trial reports and literature reviews often include a broad range of histologic subtypes of sarcoma, which limits interpretation and application of the results. At M. D. Anderson Cancer Center, we have tried to tailor our approach to patients with uterine sarcomas by histologic subtype. We do not rely heavily on reported response rates from protocols that have included multiple subtypes. We believe strongly that patients with uterine sarcomas should be referred to major academic centers with options for participation in clinical trials.

Staging

The staging of uterine sarcomas is based on the International Federation of Gynecology and Obstetrics staging system for uterine corpus cancer (see the chapter "Treatment of Endometrial Cancer").

Uterine Malignant Mixed Müllerian Tumors

Epidemiology and Tumor Features

Uterine malignant mixed müllerian tumors (MMMTs) are an uncommon but extremely aggressive subtype of uterine malignancy. These tumors usually present in women over the age of 50 years and peak in incidence during the seventh and eighth decades. MMMTs are more common in African American than in Caucasian patients.

MMMTs of the uterus contain both malignant epithelial and malignant sarcomatous components. Although MMMTs have historically been grouped with all other uterine sarcomas, at M. D. Anderson we believe that MMMTs are actually mixed tumors consisting of both carcinomatous and sarcomatous elements (Figure 9–1). While some authors have suggested renaming these tumors "sarcomatoid carcinomas," we prefer to retain the term "MMMT" to emphasize the mixed components.

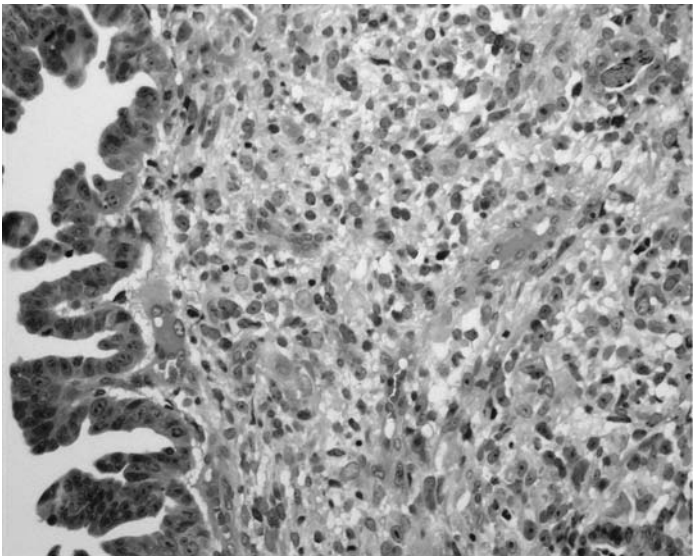

Figure 9–1. Malignant mixed müllerian tumor (MMMT). This MMMT is composed of high-grade serous carcinoma (on the left) and high-grade unclassified sarcoma.

MMMTs are more likely than endometrial stromal sarcomas (ESSs) or leiomyosarcomas (LMSs) to present with postmenopausal bleeding, and the presence of malignancy can usually be determined preoperatively with an endometrial biopsy. Abnormal bleeding usually occurs as a result of the origin of MMMTs in the endometrium rather than in the myometrium. Patients typically present with a bulky polypoid mass extending into and even through the endocervical canal. In contrast with LMS, uterine MMMT quickly metastasizes to pelvic and para-aortic lymph nodes.

The carcinomatous component of uterine MMMTs may be papillary serous, endometrioid, clear cell, squamous, or undifferentiated. The mesenchymal components may be "homologous"—similar to tissues normally present in the uterus, such as smooth muscle or uterine stromal tissue—or "heterologous," resembling tissue foreign to the uterus, such as striated muscle or cartilage. Often the sarcomatous component is consistent with fibrosarcoma, ESS, or rhabdomyosarcoma. The epithelial component, müllerian in origin, has the greatest influence on survival. Typically, recurrences of MMMTs are composed of carcinoma of endometrioid or papillary serous subtype. However, recurrences and distant metastases composed of sarcoma or mixed carcinoma and sarcoma also occur.

The recurrence rate for stage I and II MMMTs is 50%. Distant metastases account for 50% to 80% of all recurrences. The most common sites of metastasis are the lung and omentum. Features associated with poor prognosis include adnexal spread, lymph node metastasis, and high grade of tumor. Unfortunately, the 5-year survival rate for patients with MMMTs is less than 20%.

Surgical Treatment

The M. D. Anderson approach to clinical evaluation and treatment of patients with uterine MMMTs is outlined in Figure 9–2. At our institution, we believe that surgical treatment of MMMTs should consist of exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, aspiration of abdominal fluid for cytologic evaluation, pelvic and para-aortic lymph node dissection, and tumor debulking at the time of presentation. Clinical staging of uterine MMMTs is unreliable; tumors are often upstaged after thorough surgical staging. Direct serosal invasion and intraperitoneal metastasis are common. As many as 15% to 40% of tumors with disease clinically confined to the uterus have retroperitoneal lymph node involvement. The risk of nodal spread is proportional to the depth of invasion. As with endometrial cancer, more accurate surgical staging of MMMTs may allow physicians to better assess the value of or need for postoperative radiation therapy or chemotherapy. We always attempt surgical debulking in patients with uterine MMMTs. Patients with minimal residual disease may have

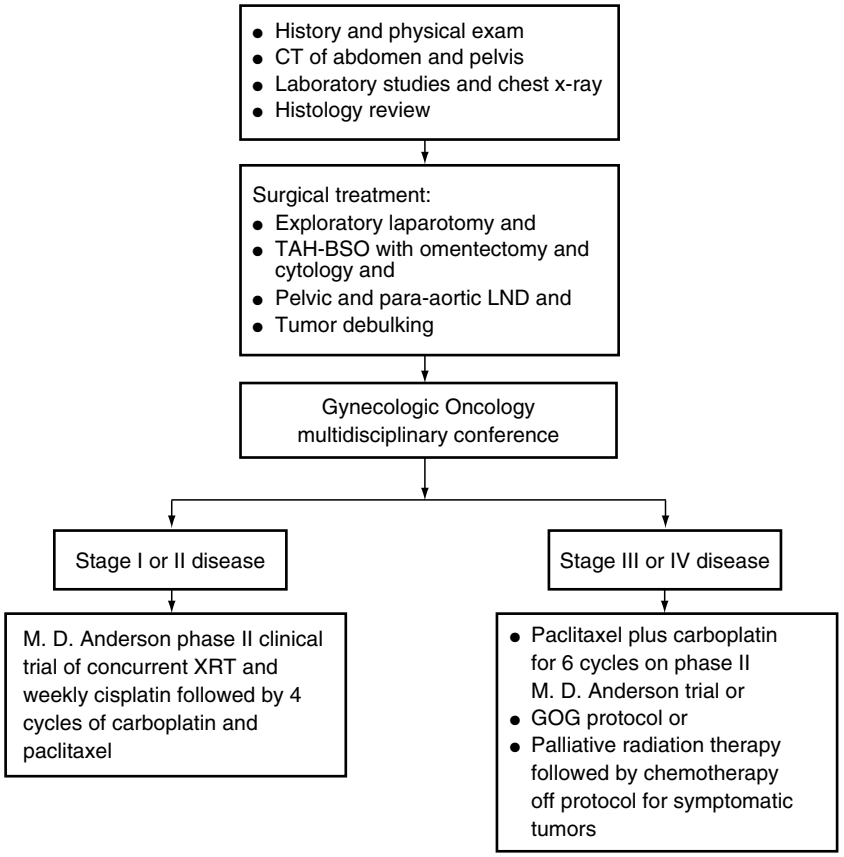

Figure 9–2. Algorithm for clinical evaluation and treatment of patients with malignant mixed müllerian tumors of the uterus. CT, computed tomography; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; LND, lymph node dissection; XRT, radiation therapy; GOG, Gynecologic Oncology Group.

longer survival than those left with gross residual disease after surgical debulking.

Pathologic Evaluation

Important features of MMMTs that should be evaluated by the pathologist include the depth of myometrial invasion and the presence or absence of extrauterine extension and lymphatic or vascular invasion. At M. D. Anderson, pathologists also estimate the percentages of the primary tumor composed of carcinomatous and sarcomatous components and classify the histologic subtypes present in each component (if they are differentiated enough to classify). Pathologists also state whether recurrences

and metastases are composed of carcinoma, sarcoma, or mixed carcinoma and sarcoma.

Radiation Therapy

The role of radiation therapy in the treatment of MMMTs is controversial. Historically, treatment for uterine MMMTs has included adjuvant pelvic radiation therapy with or without brachytherapy. Unfortunately, because of the rarity of the tumor, no well-controlled, randomized treatment studies have been performed, and most published reports are based on small nonrandomized trials. The most disappointing confounder has been the historical pattern of grouping all uterine sarcoma subtypes together to increase study subject numbers. Furthermore, many participants in these studies had incompletely staged disease and had previously received various types of radiation therapy or chemotherapy. The best conclusion that can be drawn from these reports is that radiation therapy may improve locoregional control. In a retrospective study done at M. D. Anderson (Callister et al, 2004), patients treated with pelvic radiation therapy had a lower rate of pelvic recurrence than patients treated with surgery alone (28% vs 48%, $P = .0002$), but the overall 5-year survival rates (36% vs 27%, $P = .10$) and distant metastasis rates (57% vs 54%, $P = .96$) were not significantly different. However, patients treated with pelvic radiation therapy had a longer mean time to any distant relapse (17.3 vs 7.0 months, $P = .001$) than patients treated with surgery alone.

The Gynecologic Oncology Group has evaluated its experience with pelvic radiation therapy for uterine sarcoma in a retrospective study. In this study (Omura et al, 1985), patients with stage I or II uterine sarcomas were randomly assigned to receive doxorubicin or no chemotherapy after surgery. The use of adjuvant pelvic radiation therapy was not mandated but was left to the discretion of the individual investigator, and the study was not stratified on the basis of use of radiation therapy. In a subset analysis, the authors demonstrated a reduction in pelvic recurrences in patients who received pelvic radiation therapy compared to patients who did not; however, patients who underwent radiation therapy had a higher rate of distant metastasis, and there was no significant difference in the 2-year survival rate between the 2 groups.

Several single-institution studies show that pelvic radiation therapy improves local control, and the results of 2 collaborative trials will be available soon. The European Organization for Research and Treatment of Cancer trial 55874 is an important randomized trial directly addressing the benefit of adjuvant pelvic irradiation. In this study, patients with early-stage uterine sarcomas were randomized to receive either surgery alone or surgery followed by adjuvant radiation therapy. Another study that may help address the question of the importance of radiation therapy is Gynecologic Oncology Group trial 150, which is a phase III randomized study of whole-abdominal radiation therapy versus combination

chemotherapy in optimally debulked stage I, II, III, or IV carcinosarcoma of the uterus. This trial has just finished accruing patients, and results are pending.

At M. D. Anderson, patients with stage I or II uterine MMMTs are offered pelvic radiation therapy to improve local control but are clearly told that it may not improve survival. The pelvis is treated adjuvantly with a 4-field technique to a total dose of 45 to 50 Gy. Presently, we are conducting a phase II trial evaluating adjuvant pelvic radiation therapy concurrent with weekly cisplatin followed by 4 courses of carboplatin and paclitaxel in patients with stage I, II, or IIIA uterine MMMTs. In patients with extensive pelvic disease who are poor candidates for surgery, palliative radiation therapy followed by chemotherapy off protocol is also considered.

Chemotherapy

Over the past 2 decades, standard adjuvant treatment of uterine MMMTs at M. D. Anderson has shifted from primarily locoregional radiation therapy to chemotherapy. Unfortunately, chemotherapy has shown only minimal evidence of improved survival. There is no definitive proof for any survival benefit of adjuvant chemotherapy in uterine sarcomas.

Historically, we have treated recurrent MMMTs with platinum-based therapy (cisplatin or carboplatin) in combination with ifosfamide, although other chemotherapeutic agents have also been used. Cisplatin and ifosfamide are the most widely studied systemic agents in the treatment of recurrent uterine MMMTs, with reported response rates of 18% to 44% for single-agent cisplatin and 39% for single-agent ifosfamide. Trials of combination therapy reveal higher response rates for cisplatin plus ifosfamide than for ifosfamide alone (57% vs 39%) but no significant improvement in survival for cisplatin plus ifosfamide over ifosfamide alone in patients with advanced, recurrent, or persistent disease.

Experience with paclitaxel in uterine MMMTs is limited. However, at M. D. Anderson, we recently completed a study of single-agent paclitaxel in uterine papillary serous carcinoma, 1 of the many subtypes of the carcinomatous component of uterine MMMTs. In this study, the overall response rate was 77%. Because of the significant influence of the carcinomatous component on survival, the use of paclitaxel in combination with carboplatin for advanced uterine MMMTs has become standard at our institution.

As mentioned in the preceding section, we are conducting a phase II trial of adjuvant pelvic radiation therapy concurrent with weekly cisplatin followed by 4 courses of carboplatin and paclitaxel in patients with uterine MMMTs. This trial is based on the evidence that postoperative radiation therapy may improve local control in patients with uterine MMMTs; the previously documented response rate of 18% to 44% for single-agent cisplatin in patients with uterine MMMTs; and moderate response rates

with paclitaxel for uterine papillary serous carcinoma and ovarian MMMTs. The adjuvant radiation therapy with cisplatin as a radiosensitizer is designed to maintain local control, while the 4 additional courses of systemic therapy are designed to minimize any risk of distant recurrence. We believe that our new regimen may have better activity than the previous regimen of cisplatin and ifosfamide because of the addition of paclitaxel. In addition, eliminating ifosfamide and substituting carboplatin for cisplatin should improve tolerability and reduce the incidence and severity of neurotoxicity, nephrotoxicity, and gastrointestinal toxicity in these often elderly patients. This regimen will also allow patients with uterine MMMTs to be treated as outpatients, thus reducing the overall cost of treatment and potentially improving patients' quality of life.

Only patients with stage I, II, or IIIA uterine MMMTs with no gross residual disease after surgical treatment are eligible for this protocol. Treatment of patients with no gross residual disease can be justified by the poor outcomes observed in patients with small-volume extrauterine disease: recurrence rates of 40% to 60% have been observed in patients with disease that is apparently limited to the uterus. Patients will be evaluated for adverse reactions and progression-free survival.

Hormonal Therapy

Approximately 30% of uterine MMMTs express estrogen or progesterone receptors. At M. D. Anderson, we consider hormonal therapy for recurrent disease in patients with estrogen- or progesterone-receptor-positive tumors heavily pretreated with chemotherapy.

Treatment Summary

Ultimately, the ideal treatment for uterine MMMTs may be combined radiation therapy and chemotherapy or molecular targeted therapy after optimal surgical debulking. However, the best treatment has yet to be determined. Because current therapies are associated with poor response rates and high recurrence rates, it is critical to search for additional treatment options. Because of the rarity of uterine MMMTs, we believe patients with these tumors should be referred to major cancer treatment centers, where larger and more informative trials can be conducted to help answer these questions more efficiently and effectively.

Leiomyosarcoma

Epidemiology and Tumor Features

Uterine LMS accounts for approximately 1% of all uterine malignancies but 40% of all uterine sarcomas. The average patient age at diagnosis of LMS is 53 years. Unfortunately, because of the tumor's stromal rather than

endometrial origin, LMS is not often diagnosed preoperatively. Although some patients complain of pain or bleeding and undergo endometrial biopsy because of these symptoms, most women with LMS lack symptoms, although some present with a rapidly enlarging pelvic mass and thus do not undergo biopsy before surgery. Even with an endometrial biopsy, LMS is diagnosed preoperatively in only 15% of cases.

Uterine LMS presents as a solitary, poorly demarcated myometrial mass. This sarcoma arises from myometrial smooth muscle and smooth muscle from the myometrial vessels. Histologically, LMS usually consists of highly cellular, spindle-shaped smooth muscle cells with hyperchromatic nuclei and many mitoses (Figure 9–3). The nuclei are characterized by moderate to marked atypia, and mitotic counts of more than 10 mitoses per 10 high-power fields are common. Coagulative necrosis also may be present.

Smooth muscle tumors of uncertain malignant potential (STUMP) have atypical features that are not fully diagnostic of LMS. These tumors may have (1) more than 20 mitoses per 10 high-power fields and no necrosis or atypia, (2) fewer than 10 mitoses per 10 high-power fields and diffuse significant nuclear atypia but no coagulative necrosis, or (3) fewer than 10 mitoses per 10 high-power fields with coagulative necrosis but no atypia. These tumors are generally associated with a low risk of recurrence.

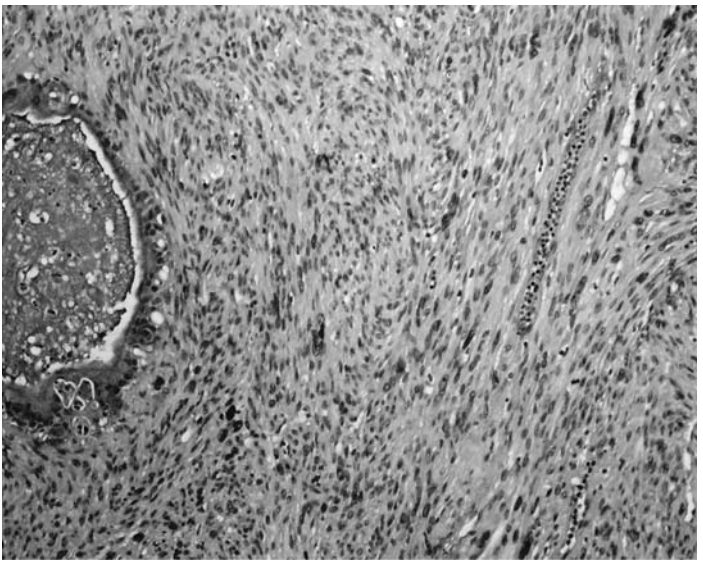

Figure 9–3. Leiomyosarcoma. This tumor involving the endocervix is characterized by fascicles of spindle cells with moderate to marked nuclear atypia and mitotic figures.

Another distinct subtype of LMS, myxoid LMS, is characterized by malignant behavior even when the mitotic count is fewer than 2 mitoses per 10 high-power fields. Histologically, myxoid LMS has an intercellular myxoid substance and infiltrates the myometrium. Myxoid LMS may be highly aggressive despite a low mitotic count and only mild to moderate nuclear atypia.

Sixty percent of women with LMS present with disease clinically limited to the uterus. Cure rates for these patients range from 20% to 60%, with rates depending on the success of primary resection. Recurrent disease is not curable unless it is resectable. Favorable prognostic features include premenopausal status, low mitotic count, pushing margins, hyalinization, absence of necrosis, origin in a uterine leiomyoma, and small tumor size. The recurrence rate is approximately 70% for stage I and II disease, and the site of recurrence is often distant. Recurrence risk is higher with higher stage or higher mitotic count. Unlike the case with uterine MMMTs, in patients with uterine LMS, pelvic and para-aortic lymph nodes are not typically involved at primary surgical evaluation.

Surgical Treatment

The M. D. Anderson approach to clinical evaluation and treatment of patients with uterine LMS is outlined in Figure 9–4. If the diagnosis is made or suspected preoperatively, we ordinarily recommend computed tomography or magnetic resonance imaging of the abdomen and pelvis prior to surgical exploration to evaluate for extrauterine spread. In addition, chest radiography and possibly chest computed tomography should be considered to rule out distant metastasis. The staging of uterine LMS has been adopted from a modified International Federation of Gynecology and Obstetrics system for uterine corpus cancer, and therefore surgery is required for staging (see the chapter "Treatment of Endometrial Cancer").

At M. D. Anderson, we consider total abdominal hysterectomy and bilateral salpingo-oophorectomy to be the minimum standard surgical treatment for uterine LMS. For patients with extrauterine disease detected at surgery, there are no clear guidelines regarding surgical debulking. After metastasis is proven by computed tomography–guided biopsy, patients are discussed in a multidisciplinary conference. Random biopsies of retroperitoneal lymph nodes rarely reveal metastatic spread; thus, we do not typically include lymph node sampling in our surgical treatment plan.

If the diagnosis of LMS is made after a myomectomy, we recommend a completion hysterectomy and surgical staging. We aim for optimal surgical cytoreduction because the literature suggests a survival benefit in patients with minimal residual disease.

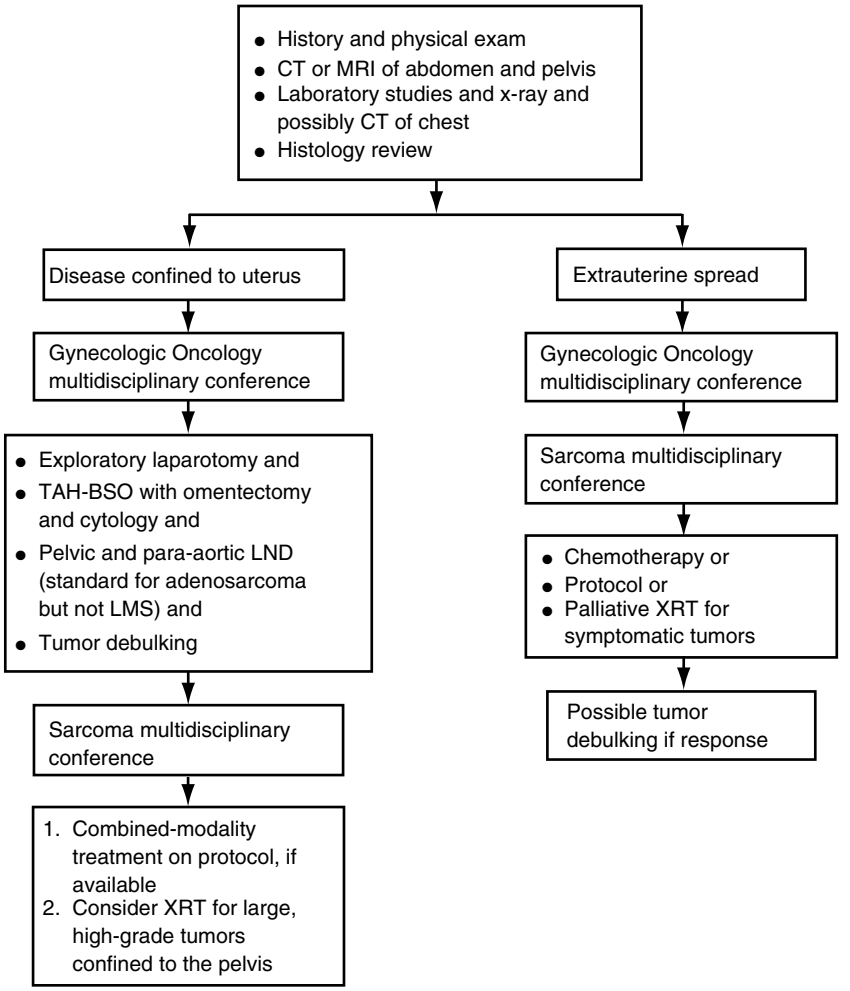

Figure 9–4. Algorithm for clinical evaluation and treatment of patients with leiomyosarcoma or adenosarcoma of the uterus. CT, computed tomography; MRI, magnetic resonance imaging; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; XRT, radiation therapy; LND, lymph node dissection; LMS, leiomyosarcoma.

Pathologic Evaluation

Important features that should be included in the gross and microscopic evaluation of uterine LMS are tumor size, presence or absence of coagulative tumor cell necrosis, degree of nuclear atypia, highest mitotic count per 10 high-power fields, presence or absence of vascular invasion, and status of the surgical margins. The 3 main criteria used to determine treatment and prognosis are necrosis, nuclear atypia, and mitotic count.

In tumors that lack necrosis and nuclear atypia, classification is as follows: 5 to 20 mitoses per 10 high-power fields, mitotically active leiomyoma; more than 20 mitoses per 10 high-power fields, STUMP.

In tumors that lack coagulative necrosis but have diffuse moderate to severe nuclear atypia, classification is as follows: fewer than 2 mitoses per 10 high-power fields, atypical leiomyoma; 2 to 10 mitoses per 10 high-power fields, STUMP; more than 10 mitoses per 10 high-power fields, uterine LMS.

In tumors with coagulative necrosis but without significant nuclear atypia, classification is as follows: fewer than 10 mitoses per 10 high-power fields, STUMP; at least 10 mitoses per 10 high-power fields, LMS.

Tumors with coagulative necrosis and significant nuclear atypia, regardless of mitotic count, are classified as LMS.

The prognostic significance of tumor grade in patients with uterine LMS is controversial. Past studies of the significance of grade have used various criteria for the diagnosis of LMS, have used different grading systems, and have come to different conclusions. Currently, we do not grade uterine LMS.

Radiation Therapy

Pelvic radiation therapy has historically been used for adjuvant treatment of uterine LMS. Adjuvant irradiation is considered for patients with a high risk of recurrence due to a high mitotic count or advanced stage. However, although radiation therapy has been shown to reduce the pelvic relapse rate by 50%, studies have not demonstrated a significant survival benefit with this approach. In patients with LMS, in contrast to patients with other uterine sarcomas, the dominant pattern of recurrence is outside the pelvis and abdominal cavity. At least two thirds of patients with uterine LMS have some component of distant disease at first recurrence. Thus, although the rate of recurrence in the pelvis is not insubstantial, little is potentially gained by delivering pelvic radiation therapy as a postoperative adjuvant treatment.

We reserve pelvic radiation therapy for patients with the highest risk of pelvic recurrence, such as patients with close surgical margins. Because lymph node metastasis is uncommon, when radiation therapy is necessary, irradiation of the operative bed (usually the lower pelvis) is usually sufficient for local control.

Chemotherapy

A randomized Gynecologic Oncology Group phase III trial evaluating adjuvant doxorubicin compared with no treatment in patients with stage I or II uterine sarcoma failed to find any significant survival advantage with chemotherapy (Omura et al, 1985). There are no established potentially curative therapies for unresectable LMS. First-line treatment for LMS is usually doxorubicin and/or ifosfamide. Single-agent ifosfamide

has a response rate of 17% (Sutton et al, 1992). Doxorubicin has been associated with a response rate of 10% to 19% alone or in combination with ifosfamide (Hannigan et al, 1983; Berchuck et al, 1988). Although a response rate as high as 30% for the combination has been reported, it does not appear to offer a survival advantage (Sutton et al, 1996a). Median survival remains approximately 11 months. High-dose chemotherapy with doxorubicin and ifosfamide is associated with a 25% response rate in recurrent and advanced LMS. Gemcitabine is associated with a response rate of 20%, docetaxel has a response rate of approximately 15%, and liposomal doxorubicin has a response rate of 16% (Sutton et al, 2005). Other regimens include vincristine, doxorubicin, and cyclophosphamide; platinum, doxorubicin, and cyclophosphamide; paclitaxel and carboplatin; and dacarbazine. These regimens have shown no additional benefit and increased toxicity compared with doxorubicin alone. Regardless of the agent, 80% of patients with uterine LMS who are treated with chemotherapy eventually have progression of disease.

Treatment of Recurrent Disease

In contrast to uterine MMMTs, which tend to recur intra-abdominally, LMS frequently recurs outside the abdomen. There are no clear treatment guidelines for patients with recurrent LMS. Surgical treatment can be considered, especially in patients with a solitary liver or lung metastasis. Five-year survival rates can be as high as 33% to 55% in such patients. Levenback et al (1992) published a review of 45 patients who underwent resection of pulmonary metastases of uterine sarcoma (LMS in 84%; MMMT or ESS in 16%). Five- and 10-year survival rates after hysterectomy were 65% and 50%, respectively, with a mean follow-up time of 25 months. Patients with unilateral and small-volume metastases had a better prognosis than those with bilateral metastases. The only factor identified as a contraindication to resection of pulmonary metastases was extrathoracic tumor. We also consider surgical treatment for local recurrences if resection is feasible.

Endometrial Stromal Sarcoma

Epidemiology and Tumor Features

ESSs represent fewer than 5% of all uterine sarcomas. Historically, ESSs have been referred to as endolymphatic stromal myosis. These tumors are most commonly seen in premenopausal women, but age at presentation may range from 20 to 80 years. Patients typically present with bleeding and pain.

ESS may arise from uterine stroma, adenomyosis, or possibly endometriosis. ESS resembles cells from the endometrial stroma during the proliferative phase of the menstrual cycle. Histologically, ESS is

composed of sheets of uniform cells with darkly staining small round or ovoid nuclei. Vascular invasion is common. Historically, ESS has been classified as low grade or high grade. Low-grade ESS is characterized by fewer than 10 mitoses per 10 high-power fields and lack of significant atypia and often expresses estrogen and progesterone receptors. We no longer include high-grade ESS in the category of ESS; rather, we now group high-grade ESS together with high-grade or undifferentiated uterine sarcomas. This is important because the low-grade and high-grade variants have vastly different prognostic factors and therapeutic options. Throughout the remainder of this section, "ESS" will refer to low-grade ESS.

As with uterine LMS, it is rare to make the diagnosis of uterine ESS preoperatively because of the tumor's stromal rather than endometrial origin. However, the finding on endometrial biopsy of hyperplastic stroma with few glands may suggest the presence of ESS. Grossly, ESS resembles pale yellow rubbery growths extending through the myometrium into lymphatic and venous channels (Figure 9–5). On evaluation of a hysterectomy specimen, close attention should be given to vessels in the broad ligament and adnexa.

Although low-grade ESSs tend to be less aggressive than other uterine sarcomas, one third have spread beyond the uterus at the time of diagnosis. As many as 30% to 50% of patients have recurrence, although recurrence may be delayed as long as 36 months to 10 years. Recurrences are

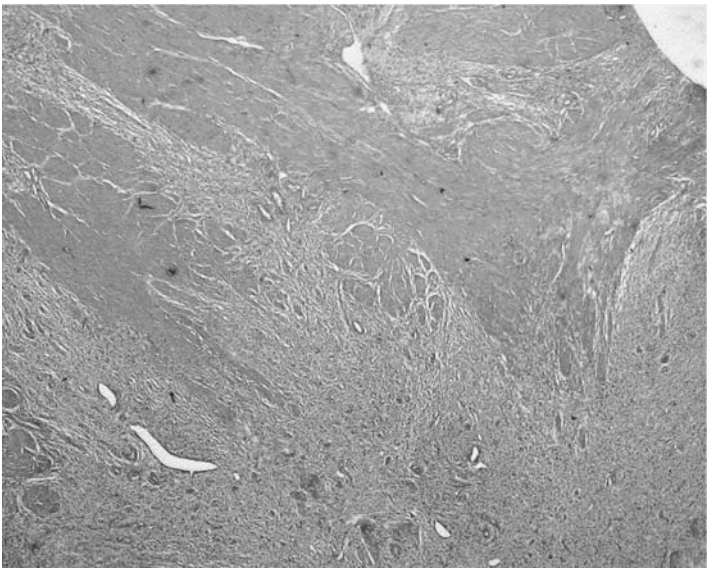

Figure 9–5. Endometrial stromal sarcoma. This sarcoma is characterized by tissue resembling proliferative endometrial stroma, diffusely invading the myometrium.

usually local, but late recurrences may involve the lung and abdomen. Stage at presentation is the best predictor of recurrence risk. Tumors are frequently estrogen receptor and progesterone receptor positive.

Surgical Treatment

The M. D. Anderson approach to clinical evaluation and treatment of patients with uterine ESS is outlined in Figure 9–6. Surgical treatment of ESS typically includes an exploratory laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy, omental biopsy, and aspiration of abdominal fluid for cytologic evaluation. There is little need for lymph node sampling. If tumor is palpable in the parametrium, a more extensive procedure, such as a radical hysterectomy, should be performed. Nodal involvement by low-grade ESS is rare. Bilateral oophorectomy is essential because of the high rate of expression of estrogen and progesterone receptors in ESS.

All recurrences should be evaluated for resectability. Occasionally with long-term remissions, surgery can be considered for recurrences. Prognosis, if excision is successful, is good; the 5-year survival rate is up to 90%.

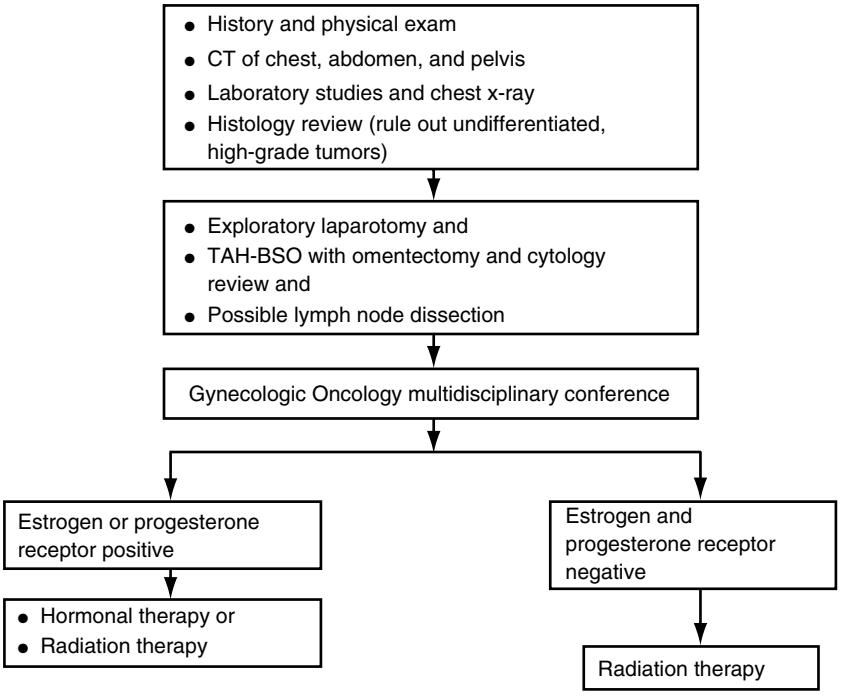

Figure 9–6. Algorithm for clinical evaluation and treatment of patients with endometrial stromal sarcomas. CT, computed tomography; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Radiation Therapy

The combination of adjuvant radiation therapy and high-dose progesterone has shown some benefit in patients with ESS. Although many institutions recommend this combination for early-stage disease, at M. D. Anderson we recommend hormonal therapy alone for early-stage disease, and we reserve the combination of hormonal therapy and radiation therapy for recurrent or high-grade ESS. Adjuvant radiation therapy clearly reduces the incidence of pelvic recurrence.

Chemotherapy

Doxorubicin, ifosfamide, paclitaxel, and carboplatin have been associated with minimal response rates in patients with ESS. However, in patients with estrogen or progesterone receptor expression, hormonal therapy is the first choice for systemic therapy. Interpretation of ESS treatment response rates in the literature is made difficult by the fact that many of the earlier studies may have failed to differentiate between low-grade and high-grade ESS.

Hormonal Therapy

At M. D. Anderson, the first-choice adjuvant therapy for low-grade ESS has historically been leuprolide, depot formulation, or medroxyprogesterone acetate. Unfortunately, the dose and route of administration are not standardized. Large tumors and tumors with lymph-vascular space invasion or parametrial extension are associated with a high risk of recurrence, and patients with such tumors often receive postoperative treatment. We usually consider medroxyprogesterone acetate, 100 mg per day indefinitely or until disease progression, versus radiation therapy. Options include 1 month, 2 months, or for life. However, often patients cannot tolerate extended hormonal therapy because of side effects. In such situations, the question remains how long to continue the drug. Recently, we have considered, on the basis of case reports, the use of aromatase inhibitors for adjuvant therapy and treatment of recurrent endometrial stromal tumors (Leunen et al, 2004). We also try to enroll these patients in clinical trials of adjuvant hormonal therapy. Many innovative hormonal therapies are being explored at M. D. Anderson, including selective progesterone receptor modulators (mifepristone) and newer selective estrogen receptor modulators. Because we believe that lack of response to hormonal therapy is due to the absence of estrogen or progesterone receptors and that sequential or combination therapy may increase response rates, we are planning combination studies in vitro and in vivo.

The presence of estrogen and progesterone receptors has been shown to correlate directly with survival and response to hormonal therapy and inversely with tumor grade. Fifty to 60% of primary endometrial

cancers and the majority of low-grade ESSs are both estrogen and progesterone receptor positive. Progesterones in the primary treatment of well-differentiated and recurrent endometrial cancers have been associated with response rates of 18% to 25% and stable disease rates of 20% to 50%. Progesterones in the treatment of low-grade ESS have been associated with response rates ranging from 33% to 45%.

The role of mifepristone, an antiprogesterone, in the treatment of endometrial cancer is currently being explored in a clinical trial at M. D. Anderson. Mifepristone acts on the endometrium and blocks the action of progesterone at the cellular level by binding the progesterone receptor. The affinity of mifepristone for the progesterone receptor is 5-fold greater than that of endogenous progesterone. As a result, mifepristone can produce a progesterone-like effect in the absence of progesterone. In our clinical trial, we are administering mifepristone to patients with progesterone-receptor-positive advanced or recurrent endometrial cancer or low-grade ESS.

Undifferentiated Sarcomas

Epidemiology and Tumor Features

Undifferentiated uterine sarcomas are high-grade epithelioid or spindle cell sarcomas that cannot be classified into 1 of the standard categories. These tumors usually present with abdominal or pelvic pain in postmenopausal women and represent less than 5% of all uterine sarcomas. Necrosis is a common finding. Recurrence often occurs within 2 years. The stage at diagnosis is the most significant predictor of prognosis.

Surgical Treatment

The treatment of choice for undifferentiated uterine sarcomas is surgery. Lymph node dissection is indicated after total abdominal hysterectomy and bilateral salpingo-oophorectomy to determine risk of recurrence. Extended surgical exploration is important to determine the appropriate type and extent of therapy.

Adjuvant Therapy

Radiation therapy is typically recommended for stage I and II undifferentiated sarcomas. However, concern about distant recurrences has led to consideration of combination treatment.

Adenosarcoma

Epidemiology and Tumor Features

Adenosarcomas consist of a benign epithelial component and a malignant mesenchymal component and make up about 25% of all uterine sarcomas

(Figure 9–7). The mean patient age at presentation is 58 years. Abnormal bleeding, pain, and tissue protruding from the cervical os are common. These tumors tend to form fleshy masses filling the uterine cavity, and deep invasion is rare. The mesenchymal component of adenosarcomas generally resembles ESS or fibrosarcoma. The stromal element is characterized by increased cellularity around the glands; generally, there is little nuclear atypia in the stromal cells, and usually there are at least 2 mitotic figures per 10 high-power fields. Adenosarcomas are typically low-grade malignancies that rarely metastasize, although up to 20% recur locally. Risk of recurrence is greater with greater depth of invasion as well as with pleomorphism or sarcomatous overgrowth.

A variant of the classic adenosarcoma is adenosarcoma with sarcomatous overgrowth, defined as either a sarcomatous component occupying 25% or more of the total tumor volume or the presence of an area of high-grade pure sarcoma. Sarcomatous overgrowth significantly worsens the patient's prognosis. The presence of sarcomatous overgrowth also increases the likelihood of lymphatic spread. Recurrences are much more likely with this variant and with adenosarcomas containing rhabdomyosarcoma or with lymph-vascular space invasion. Recurrences of adenosarcoma may consist of pure sarcoma, and resistance to chemotherapy is common.

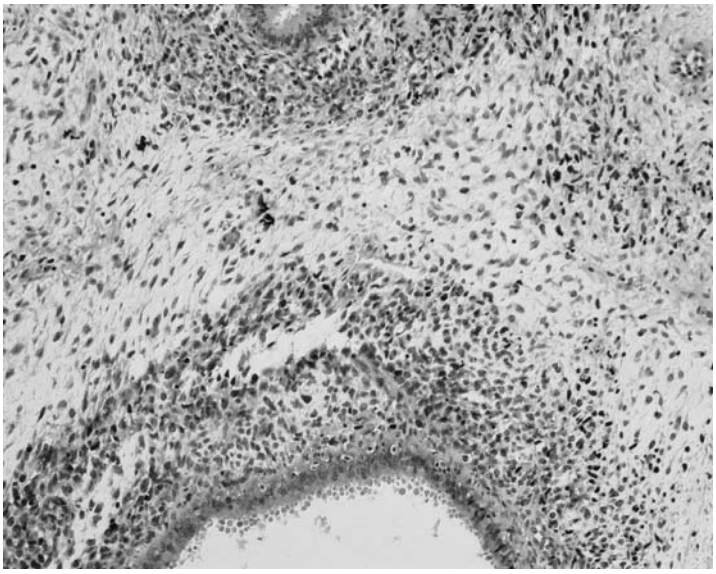

Figure 9–7. Adenosarcoma. Benign glands are surrounded by a cuff of hypercellular stroma. There is mild atypia, and mitotic figures are present.

Surgical Treatment

The M. D. Anderson approach to clinical evaluation and treatment of patients with uterine adenosarcoma is outlined in Figure 9–4. Complete surgical resection is the only treatment that has been successful for patients with adenosarcoma. We support full surgical therapy, including total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, aspiration of abdominal fluid for cytologic evaluation, and lymph node dissection.

Radiation Therapy

Adenosarcoma is rare and is associated with a fairly good prognosis; therefore, it is difficult to assess the role of adjuvant radiation therapy. We use radiation therapy occasionally; the need for radiation therapy is decided on a case-by-case basis.

Chemotherapy

Cisplatin, doxorubicin, ifosfamide, cyclophosphamide, and vincristine have been used to treat uterine adenosarcoma and have produced various response rates. We especially consider adjuvant chemotherapy in cases with sarcomatous overgrowth.

Hormonal Therapy

Because of the low grade of the sarcoma component in most uterine adenosarcomas, hormonal therapy also remains an option.

Summary

Surgical Approach for Uterine Sarcomas

In patients with uterine sarcomas, exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy are recommended, even in patients with metastatic disease, for palliation of symptoms and possibly improved response to therapy. In patients with low-grade ESS, removal of the ovaries is recommended because of the hormonal responsiveness of this tumor. Cytoreductive surgery should be attempted in all patients with uterine sarcomas because of the lack of successful adjuvant and salvage therapies. Except in patients with LMS, extended staging with pelvic and para-aortic lymph node sampling is appropriate to facilitate the evaluation of new therapies.

Radiation Therapy Approach for Uterine Sarcomas

There are no controlled trials showing a survival benefit for adjuvant radiation therapy in patients with uterine sarcomas. The decision to use adjuvant radiation therapy is based on the hypothesis that decreasing the local recur-

rence rate will improve quality of life by reducing the risk of a pelvic recurrence. Thus, a careful discussion of the potential risks and possible benefits of radiation therapy in women with stage I/II sarcoma is required. There is very little evidence to support the use of adjuvant radiation therapy in women with higher-stage disease, but randomized trials currently in progress may provide important information on the use of radiation therapy in the future. At M. D. Anderson, we rely heavily on a multidisciplinary approach to treating uterine sarcomas.

KEY PRACTICE POINTS

- Patients with uterine sarcomas should be referred to large academic centers for participation in clinical trials.
- Multidisciplinary evaluation is important and should include specialists in radiation oncology, gynecologic oncology, and sarcoma.
- Optimal tumor debulking at presentation is ideal.
- Adjuvant radiation therapy improves local control and may delay recurrence but does not improve survival.
- Treatment of patients with extrauterine disease should be discussed in a multidisciplinary setting.

Suggested Readings

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