INTRODUCTION

Endometrial stromal tumors are a subset of uterine mesenchymal neoplasms that account for less than 10 percent of uterine sarcomas and approximately 1 percent of all uterine malignant neoplasms [1]. The World Health Organization (WHO) classifies endometrial stromal neoplasms and related tumors into five categories: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), undifferentiated uterine sarcoma (UUS), and uterine tumor resembling ovarian sex cord tumor (UTROSCT) (table 1) [2]. Another type of uterine sarcoma, uterine adenosarcoma, is a rare mixed epithelial-nonepithelial neoplasm that accounts for 5 to 9 percent of all uterine sarcomas [3].

ESN is a benign neoplasm that is cured with simple hysterectomy; thus, much of the discussion below will focus on invasive endometrial stromal neoplasms: LG-ESS, HG-ESS, and UUS. UTROSCT, no longer considered a true endometrial stromal neoplasm, and uterine adenosarcoma are also reviewed here because the diagnosis and treatment approach for these malignancies is generally the same as for endometrial
stromal neoplasms.

An overview on the classification, clinical manifestations, diagnosis, and treatment of uterine sarcomas in general, including leiomyosarcoma, is covered separately. (See "Uterine sarcoma: Classification, clinical manifestations, and diagnosis").

**TERMINOLOGY**

The 2014 World Health Organization (WHO) classification system recognizes the following tumor types under the category "endometrial stromal and related tumors" (table 1):

- Endometrial stromal nodule (ESN)
- Low-grade endometrial stromal sarcoma (LG-ESS)
- High-grade endometrial stromal sarcoma (HG-ESS)
- Undifferentiated uterine sarcoma (UUS)
- Uterine tumor resembling ovarian sex cord tumor (UTROSCT)

The terminology and classification system for endometrial stromal sarcoma (ESS) and related tumors has been changed several times. An understanding of the shifts in nomenclature is essential to be able to interpret prior studies in relation to the new designations.

Endometrial stromal neoplasms were historically characterized as either low-grade or high-grade neoplasms, and this classification is used in the older literature [4].

In the 2003 WHO classification system, terminology was changed as follows:

- Tumors previously referred to as low-grade endometrial stromal sarcomas were referred to simply as endometrial stromal sarcomas.
- Tumors previously referred to as high-grade endometrial stromal neoplasms were referred to as: undifferentiated endometrial sarcomas or high-grade undifferentiated uterine sarcomas. This reflected the composition of high-grade tumors as pleomorphic, anaplastic cells with little or no evidence of endometrial stromal differentiation [5,6].
However, a subset of ESS with greater mitotic activity and nuclear atypia not meeting the undifferentiated, pleomorphic characteristics defined as undifferentiated endometrial sarcoma has been described. These have been referred to in the literature by various terms including "histologically high-grade ESS," "ESS with high-grade histologic features," and "undifferentiated endometrial sarcoma with nuclear uniformity."

The 2014 WHO classification system addressed this by including two separate categories: HG-ESS and UUS. Of note, the term undifferentiated endometrial sarcoma is no longer favored in this system.

The 2014 system also introduced UTROSCT as a distinct histologic entity. Previous terminology described tumors with these elements as two categories: group I composed of ESN or LG-ESS with sex cord-like elements and group II consisting entirely of sex cord-like elements without stromal components [7]. The term UTROSCT is now reserved for group II tumors, while group I tumors are classified under LG-ESS.

The evolving categorization of these neoplasms makes it challenging to interpret studies performed at different times, especially as some neoplasms previously considered undifferentiated endometrial or high-grade undifferentiated uterine sarcomas may now be categorized as HG-ESS. Similarly, previous reports of UTROSCT may contain cases currently recognized as LG-ESS. In this topic, the pathologic, molecular, genetic characteristics, and treatment recommendations are based on the 2014 WHO classification system [8]. When studies performed using previous classification systems are described, the terminology used in the study will be used; an explanation of how the tumors correspond to current categories will be provided, when possible.

ENDOMETRIAL STROMAL NEOPLASMS

Histopathology — Endometrial stromal sarcomas (ESS) and related neoplasms are classified by circumscription/invasion into surrounding myometrium and the degree of differentiation. However, heterogeneous morphologic features (eg, fibrous, myxoid, epithelioid, rhabdoid, and smooth-muscle differentiation) can complicate their characterization [9]. Therefore, immunohistochemistry and the presence of molecular
alterations are sometimes used in an effort to classify these neoplasms more precisely.

Contemporary studies have identified subsets of endometrial stromal neoplasms with overlapping molecular and genetic profiles and intermediate prognosis, which stresses the difficulty that can be encountered when trying to distinguish these entities through conventional means. Immunostains are frequently required to differentiate endometrial stromal neoplasms from smooth-muscle neoplasms; intraoperative diagnosis using frozen sections is uncommon. (See 'Molecular characteristics' below.)

**ESN** — Endometrial stromal nodule (ESN) is the least common type of the endometrial stromal neoplasms [10]. The histologic features of ESN are identical to low-grade endometrial stromal sarcoma (LG-ESS), but ESN has a circumscribed, noninfiltrating border without evidence of myometrial or vascular invasion. Approximately two-thirds are found as isolated lesions within the myometrium with no apparent connection to the endometrium. They may be confused grossly and histologically with a leiomyoma [11]. (See 'LG-ESS' below.)

**LG-ESS** — Low-grade endometrial stromal sarcomas (LG-ESS) are low-grade sarcomas with metastatic potential. Like ESN, they are composed of uniform cells that mimic proliferative endometrial stroma. However, they have myometrial and/or vascular invasion, which are distinguishing characteristics [11]. LG-ESS often form distinctive finger-like projections that invade the myometrium, veins, and lymphatics. Histologically, they are characterized by densely uniform stromal cells with minimal cellular pleomorphism, mild nuclear atypia, and variable mitotic figures (picture 1). Of note, an isolated finding of frequent mitotic figures does not confer an adverse prognosis in an otherwise typical LG-ESS.

The diagnosis of LG-ESS may be complicated by variant morphologic features such as fibrous or myxoid changes and glandular, smooth-muscle, or sex cord-like differentiation [9]. In neoplasms with focal smooth-muscle differentiation, the neoplasm is categorized as LG-ESS if the smooth-muscle component involves <30 percent of the total volume. Neoplasms composed of a larger smooth-muscle component are designated as mixed endometrial stromal and smooth-muscle neoplasms [11].

**HG-ESS** — High-grade endometrial stromal sarcoma (HG-ESS) is a term in the 2014 World Health Organization classification system that refers to a group of
malignant neoplasms with endometrial stroma differentiation that exhibit high-grade nuclear atypia, sometimes associated with a low-grade spindle cell component [11].

The infiltrative pattern and vasculature are similar to LG-ESS, but typically there is a more destructive growth pattern with extensive myometrial invasion, necrosis, and lymphovascular invasion. Mitotic activity is generally >10 per 10 high-powered fields.

HG-ESS is associated with more frequent recurrences and higher mortality than LG-ESS. Overall, prognosis with HG-ESS is worse than with LG-ESS but better than with undifferentiated uterine sarcoma [12].

**UUS** — Undifferentiated uterine sarcoma (UUS) is characterized by marked cytologic atypia, nuclear pleomorphism, high mitotic activity, and extensive invasion. UUS lack any features of normal endometrial stromal differentiation and often exhibit hemorrhage and necrosis. In addition, similar to HG-ESS, UUS do not have the finger-like invasive projections characteristic of LG-ESS, but rather show destructive myometrial invasion.

**Molecular characteristics**

**ESN and LG-ESS** — The following molecular features are characteristic of low-grade endometrial stromal sarcoma (LG-ESS), and are also found in endometrial stromal nodules (ESN):

- The majority are immunoreactive for the estrogen receptors (ER) and progesterone receptors (PR).

- They are typically strongly positive for CD10 (an endopeptidase, a type of cell surface protein), positive for smooth muscle actin, and are negative h-caldesmon and histone deacetylase 8 (HDAC8).

- Many contain characteristic gene translocations, such as the t(7;17) translocation, resulting in the expression of a fusion protein composed of two zinc finger genes (JAZF1 and JJAZ1).

While these characteristics help to distinguish LG-ESS from other uterine sarcomas, neoplasms that contain variant morphologic features (eg, highly cellular leiomyoma) can
lead to difficulties in diagnosis. Therefore, evaluation should be based on a panel of molecular characteristics as outlined above.

**Chromosomal rearrangements** — Cytogenetic analyses have identified several recurrent nonrandom chromosomal translocations in LG-ESS and ESN, with the most frequent ones involving chromosome arms, including 6p, 7p, and 17q.

The most common translocation involves the short arm of chromosome 7 and the long arm of chromosome 17 [t(7;17)]. This results in the fusion of two zinc finger genes, JAZF1 and JJAZ1 (also referred to as SUZ12), and the production of the JAZF1/JJAZ1 (or JAZF1/SUZ12) gene fusion protein. This is characteristic of LG-ESS (present in up to 50 percent) and has not been found in other uterine sarcomas or smooth-muscle neoplasms [13,14]. In addition, there were no histologic features that correlated with the presence of this gene fusion protein. The JAZF1/JJAZ1 gene fusion has been shown to disrupt transcriptional repression of the polycomb repressive complex 2 (PRC2) [15]. This may lead to activation of genes normally repressed by PRC2 and in cell models has resulted in increased cellular proliferation, which may explain oncogenic activity of the fusion protein in LG-ESS [15].

Other gene fusion proteins associated with LG-ESS include the t(6;7), t(6;10), and t(1;6) rearrangements, which result in the production of the JAZF1/PHF1, EPC1/PHF1, and MEAF6/PHF1 fusion proteins, respectively [16,17]. The function of these fusion proteins has not yet been determined.

**HG-ESS** — High-grade endometrial stromal sarcomas (HG-ESS) are frequently CD10, ER, and PR negative, but exhibit strong diffuse cycle D1 positivity [11]. Expression of the BCOR (BCL6 corepressor) protein is consistently positive in HG-ESS [18]. In an older study, HG-ESS were more likely to exhibit high c-kit expression, which was associated with poorer prognosis [19-21].

Rearrangements involving t(10;17) are frequently identified in these tumors and result in a 14-3-3 fusion to FAM22 (known as YWHAE-FAM22 or YWHAE-NUTM2), leading to aberrant localization of 14-3-3 in the nucleus and possible oncogenic transformation [12,22]. ZC3H7B-BCOR gene fusions have been identified in HG-ESS showing morphologic characteristics of myxoid leiomyosarcoma [23].
Next-generation sequencing assays with the capability to identify fusion transcripts may assist in the differentiation of the individual ESS subtypes [24].

**UUS** — CD10, ER, and PR staining can be variable in undifferentiated uterine sarcoma (UUS) [11]. Cyclin D1 can also be diffusely positive. In cyclin D1-positive cases, CD10 is also typically positive, which can help differentiate from HG-ESS (which are typically cyclin D1 positive but CD10 negative). Tumors may be positive for smooth muscle actin, desmin, epithelial membrane antigen, or keratin. UUS frequently show complex chromosomal abnormalities.

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**CLINICAL PRESENTATION**

Uterine sarcomas may present with abnormal uterine bleeding, pelvic pressure symptoms (eg, pressure, urinary frequency, constipation), enlarged uterus, or abdominal distension. The amount of bleeding varies and may be accompanied by a foul-smelling vaginal discharge. Typically, patients with endometrial stromal neoplasm or uterine adenosarcoma are postmenopausal and present with postmenopausal bleeding.

Sarcomas may also be asymptomatic and may be detected incidentally as a uterine mass on pelvic examination or imaging. Frequently, a benign leiomyoma is suspected.

It is not possible to reliably distinguish between a leiomyoma and uterine sarcoma based on symptoms. The clinical presentation of uterine sarcoma is discussed in detail separately. (See "[Uterine sarcoma: Classification, clinical manifestations, and diagnosis](https://www.uptodate.com/contents/classification-and-treat...Title=1-18&usage_type=default&display_rank=1#H4150926217)"., section on 'Clinical presentation'.)

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**EVALUATION**

Endometrial stromal neoplasms are typically discovered during the evaluation of abnormal uterine bleeding or uterine mass. Since sarcomas are rare, typically another condition is suspected initially (eg, benign leiomyoma or endometrial carcinoma).

The patient is evaluated with history, pelvic examination, endometrial sampling, and
imaging. However, these examinations are generally not effective to differentiate between a benign uterine mass and uterine sarcoma. Endometrial sampling may identify endometrial carcinoma or hyperplasia, but has a low sensitivity for uterine sarcoma [25]. There are no tumor markers for uterine sarcomas.

The evaluation for suspected uterine sarcoma is discussed in detail separately. Information specific to endometrial stromal tumors is reviewed below. (See "Differentiating uterine leiomyomas (fibroids) from uterine sarcomas", section on 'Endometrial sampling' and "Uterine sarcoma: Classification, clinical manifestations, and diagnosis", section on 'Diagnostic evaluation'.)

**Role of imaging** — Endometrial stromal tumors have a nonspecific appearance on ultrasound, typically characterized as a heterogeneous hypoechoic endometrial mass, which can show extensive myometrial involvement [26]. On magnetic resonance imaging (MRI), these neoplasms appear as large masses with or without evidence of myometrial invasion [26].

The characteristic pattern of low-grade endometrial stromal sarcoma (LG-ESS) consists of worm-like projections in the vessels or along ligaments, which are best visualized on MRI with diffuse weighted imaging [27]. In imaging studies, imaging characteristics do not appear to differ between tumors identified as endometrial stromal sarcoma (ESS; corresponding to LG-ESS) and undifferentiated endometrial sarcoma (UES), a group that likely corresponded to both high-grade endometrial stromal sarcoma (HG-ESS) and undifferentiated uterine sarcoma (UUS) [28].

Positron emission tomography (PET) with computed tomography (CT) is a promising imaging technique to distinguish between benign and malignant endometrial masses. However, it has only been studied in a few small retrospective trials, and there appears to be significant variability in fluorodeoxyglucose (FDG) mean standard uptake values (SUVs) between benign and malignant neoplasms [28].

The approach to differentiating a uterine sarcoma from a benign leiomyoma on pelvic imaging is discussed in detail separately. (See "Differentiating uterine leiomyomas (fibroids) from uterine sarcomas", section on 'Imaging'.)
DIAGNOSIS

Endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS) are histologic diagnoses based upon pathologic evaluation. Typically, the diagnosis is made based upon the pathology evaluation of the uterine tissue following hysterectomy or planned myomectomy for presumed benign leiomyomas.

Rarely, the diagnosis is made with endometrial sampling. The pathologic diagnosis of endometrial stromal neoplasms generally requires the evaluation of vasculature and borders for infiltration and invasion; thus, superficial endometrial biopsies are typically not sufficient to distinguish between benign and malignant neoplasms.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of endometrial stromal neoplasm is similar to the differential diagnosis for uterine fibroids, endometrial carcinoma, and other uterine sarcomas. All of these entities may present with a uterine mass, abnormal uterine bleeding, and pelvic pain. In general, distinguishing between these diagnoses requires surgical exploration and pathologic analysis of the hysterectomy specimen. (See "Uterine sarcoma: Classification, clinical manifestations, and diagnosis", section on 'Differential diagnosis'.)

STAGING AND SURGICAL TREATMENT

For women with low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), or undifferentiated uterine sarcoma (UUS), disease stage is determined using the 2017 Tumor, Node, Metastasis (TNM) staging system of the combined American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), which is consistent with the International Federation of Gynecology and Obstetrics (FIGO) staging system (table 2). Given that endometrial stromal nodule (ESN) is a benign entity, it does not require staging. However, it is important to note that because the histologic features of ESN are identical to LG-ESS,
the diagnosis of ESN cannot be made based solely on a biopsy.

**Diagnosis based on biopsy** — For patients with a diagnosis of LG-ESS, HG-ESS, or UUS made by biopsy, we recommend imaging of the chest, abdomen, and pelvis to rule out distant metastases. The imaging results are useful to select appropriate patients for surgical staging and cytoreduction, if needed due to extrauterine disease. Extrauterine disease, most commonly in the ovary, has been found at initial diagnosis in up to 32 percent of women with LG-ESS [12,29-31]. Because of the change in nomenclature, it is difficult to report the rate of extrauterine disease in each of the high-grade categories (HG-ESS and UUS), since previous studies were based on prior classification systems. However, a small study of HG-ESS showed extrauterine disease in 10 out of 12 patients [12]. This is in line with other studies that showed high rates of extrauterine disease at diagnosis in "high-grade uterine sarcoma" (HGUS) or "high-grade endometrial stromal sarcoma" where cases of both HG-ESS and UUS were likely included [29,30].

**Disease confined to the uterus** — Patients with suspected LG-ESS, HG-ESS, or UUS confined to the uterus should undergo staging surgery, including a total extrafascial hysterectomy with or without bilateral salpingo-oophorectomy (BSO) [32] (see 'Fertility preservation' below). Whether systematic lymphadenectomy is needed is unclear. Lymph node metastases are uncommon in high-grade uterine sarcomas. (See 'Role of lymphadenectomy' below.)

In patients undergoing hysterectomy for a presumed uterine sarcoma, morcellation should not be attempted. In one study, neoplasm morcellation in women with LG-ESS was associated with a lower five-year disease-free survival (DFS) compared with those who did not have a morcellation (55 versus 84 percent, respectively; odds ratio [OR] 4.03, 95% CI 1.06-15.3) [33]. However, no significant impact on overall survival (OS) was reported.

**Extrauterine disease present** — There are very few studies addressing the question of the role of surgery in patients with extrauterine disease.

- In a 2007 retrospective study, the role of surgery was evaluated in 105 women, of whom 72 and 31 had "low-grade" and "high-grade" ESS, respectively [30]. Of note, this study was performed prior to the 2014 classification system and the high-grade
ESS group likely included both HG-ESS and UUS. Among women with HG-ESS, optimal cytoreduction to <2 cm of residual disease resulted in a significantly longer median OS (52 versus 2 months). However, the impact of surgery in women with LG-ESS was not clear; 82 percent were alive at 78 months regardless of surgery.

- Similarly, in a retrospective study evaluating patients with undifferentiated endometrial sarcoma (UES), which likely included patients that would be included in either HG-ESS and UUS under the current classification, patients with residual measurable disease following initial surgery had a significantly lower one-year OS compared with those without measurable disease (36 versus 80 percent, respectively) [29].

For patients with disease outside of the uterus, the decision to proceed with surgery must be individualized and based on the specific clinical scenario. In the absence of high-quality data, we offer surgical staging and cytoreduction of disease to patients without extra-abdominal metastatic disease, provided that the surgeon (preferably a gynecologic oncologist) believes that the disease is resectable. Otherwise, patients who are not surgical candidates (including those with extra-abdominal metastatic disease) should be offered medical treatment.

**Diagnosis posthysterectomy** — For patients in whom a diagnosis of LG-ESS, HG-ESS, or UUS was made following hysterectomy for a presumed benign condition, we perform baseline imaging. This includes chest imaging, usually by computed tomography (CT), in addition to a CT of the abdomen and pelvis. (See 'Evaluation' above.)

We do not perform a second surgery solely for staging purposes. Instead, we follow the general recommendations for surgical evaluation of uterine leiomyosarcoma diagnosed posthysterectomy. (See "Treatment and prognosis of uterine leiomyosarcoma", section on 'Postoperative diagnosis'.)

For patients with imaging evidence of extrauterine disease, we offer cytoreduction if the disease is deemed to be resectable. (See 'Extrauterine disease present' above.)

**Role of lymphadenectomy** — The benefit of routine lymphadenectomy is controversial [30,34-36]. We perform a lymphadenectomy only in patients with preoperative evidence
of enlarged lymph nodes (based on imaging) or intraoperative findings of lymphadenopathy, in patients without extrauterine disease.

A case series reported a 5 percent risk (range, 0 to 16 percent) of nodal involvement in patients with early-stage LG-ESS [37]. While nodal metastases have been associated with poorer prognosis, routine lymphadenectomy does not appear to improve outcomes [1].

**Fertility preservation** — Hysterectomy and BSO should be performed in women with a presumed or suspected diagnosis of uterine sarcoma, particularly in those with LG-ESS.

However, ovary and uterus-sparing procedures may be reasonable in premenopausal patients who desire fertility preservation. While some studies suggest that OS is not adversely affected by ovarian preservation [1,31,38], other single-institution studies suggest that ovarian preservation results in an increased recurrence rate [39-41].

These studies have primarily focused on LG-ESS and were based on relatively small series. In one series of patients with LG-ESS, ovary-sparing procedures were associated with a higher risk of relapse at five years compared with those who underwent BSO (87 versus 27.4 percent, respectively) [42]. An evaluation of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database evaluated 1482 women with uterine sarcoma, of whom 520 (35.1 percent) were diagnosed with LG-ESS [43]. In this study there was no difference in OS or cancer-specific survival in the LG-ESS cohort. Other studies show similar lack of impact on OS, likely because of responses to secondary treatment approaches. However, we believe ovarian preservation should only be offered as an option for those patients with LG-ESS who strongly desire preservation of ovarian function. A meta-analysis of 17 studies reports a significantly increased recurrence rate with ovarian preservation versus BSO (OR 2.70, 95% CI 1.39-5.28) with no difference in death rate (OR 0.80, 95% CI 0.18-3.47) [44].

Similarly, patients who underwent a myomectomy (n = 19) rather than hysterectomy (n = 134) also experienced a higher rate of relapse (79 versus 25 percent, respectively) [42]. There was no impact on survival. However, similar to ovarian conservation, myomectomy should only be offered as an option for those patients with LG-ESS who
strongly desire fertility. For such patients, hysterectomy and BSO should be performed once fertility is no longer an issue.

For women diagnosed with uterine sarcoma following a hysterectomy for what was preoperatively felt to be a presumed benign condition, a repeat surgical procedure to remove the ovaries is controversial. In our practice, we perform a BSO based on an individualized consideration of the patient’s diagnosis and the risks and benefits of a second surgery.

ADJUVANT THERAPY

Adjuvant therapy is not indicated for women following hysterectomy for endometrial stromal nodules (ESN). For women with either a low-grade or high-grade endometrial stromal sarcoma (LG-ESS or HG-ESS) or undifferentiated uterine sarcoma (UUS), there is no consensus regarding the role of adjuvant therapy. Our approach is described below.

LG-ESS

Stage I — For women with stage I disease, we prefer surveillance rather than adjuvant treatment. However, some experts prefer to administer adjuvant endocrine therapy. In the absence of prospective data, either approach is reasonable and supported by the National Comprehensive Cancer Network (NCCN) guidelines. There is no role for adjuvant radiation therapy (RT) for these patients. (See 'Is there a role for adjuvant RT?' below and 'Surveillance and follow-up' below.)

The recommendation for surveillance comes from the relatively good prognosis following surgery alone for patients with surgically defined stage I LG-ESS compared with more advanced-stage disease. (See 'Prognosis' below.)

Stage II to IV disease — There are limited data on the role of adjuvant therapy for advanced LG-ESS. Given their increased risk of recurrence, we offer these patients adjuvant therapy rather than observation. In the absence of prospective data and given the high likelihood of estrogen receptor (ER) and progesterone receptor (PR) expression for these neoplasms, we administer endocrine therapy, which is consistent
with the NCCN guidelines [45]. RT may be administered (in addition to endocrine therapy) to reduce the risk of a locoregional recurrence. (See 'Molecular characteristics' above and 'Is there a role for adjuvant RT?' below.)

**Endocrine therapy** — For patients with advanced disease, we often administer endocrine therapy. The data to support administration of adjuvant endocrine therapy for stage II to IV LG-ESS are limited to retrospective studies [39,46-48] and our understanding of the pathophysiology from hormonal manipulation in other hormonally sensitive malignancies (eg, breast or prostate cancer).

- In one report of 22 patients with LG-ESS, 4 of 13 patients (31 percent) treated with adjuvant [megestrol acetate](https://www.uptodate.com/contents/medication-classification-and-treatment) (160 mg daily) relapsed compared with six of nine (67 percent) who did not receive treatment [47].

- In a second study involving 31 women with LG-ESS, those who received medroxyprogesterone (250 mg daily) had a lower recurrence rate compared with those who did not (14 versus 29 percent), although five-year overall survival rates were unchanged (86 versus 83 percent) [39].

- The role of other endocrine agents is limited to use for metastatic disease and is discussed below. (See 'Recurrent and metastatic ESS' below.)

There are no formal recommendations on duration of adjuvant endocrine therapy. We and others prefer to treat for five years of hormonal therapy [49]. However, some experts treat patients with different durations based on stage; women with stage I disease may be offered treatment for two years, while those with stage II to IV disease are treated indefinitely [47]. (See "Adjuvant endocrine therapy for non-metastatic, hormone receptor-positive breast cancer".)

**Is there a role for adjuvant RT?** — Radiation therapy (RT) is a reasonable option for patients who wish to reduce their risk of a local recurrence, although whether it improves survival is not clear. While one study suggests there is an improvement in the rate of local control [41], other studies do not [1,50,51].

Given the indolent nature of LG-ESS, the propensity for long-term survival (without adjuvant treatment), and the potential complications of RT (including fibrosis, stricture,
fistula, and second malignancies), the role of RT should be individualized, taking into account the risks and benefits of treatment.

**HG-ESS and UUS** — While both high-grade endometrial stromal sarcoma (HG-ESS) and undifferentiated uterine sarcoma (UUS) have a high risk of recurrence, it is not clear whether any form of adjuvant therapy after complete resection of disease improves survival compared with observation. Consistent with NCCN guidelines, we offer systemic therapy to patients with ≥ stage II disease. For women with stage I disease, observation is favored although systemic adjuvant therapy may also be considered. External beam RT can be considered for those with stage II and III disease [45]. Given that patients with HG-ESS and UUS have an overall poor prognosis, participation in clinical trials should be encouraged. In the absence of high-quality data, choice of chemotherapy regimen is individualized based on a risk/benefit assessment and consideration of maintaining options for subsequent therapy. (See 'Chemotherapy agents' below and "Treatment and prognosis of uterine leiomyosarcoma", section on 'Adjuvant treatment'.)

**SURVEILLANCE AND FOLLOW-UP**

We follow patients with endometrial stromal sarcoma with physical examination every three months for the first two years and then every 6 to 12 months. We also obtain computed tomography scans of the chest, abdomen, and pelvis every 6 to 12 months (or as clinically indicated) for the first five years in accordance with the National Comprehensive Cancer Network (NCCN) guidelines [52]. Although late recurrences may occur in patients with low-grade endometrial stromal sarcoma (LG-ESS), we do not favor long-term surveillance with CT scans given the increased radiation exposure risk [53,54].

**PROGNOSIS**

The changing classification of endometrial stromal tumors makes comparisons of prognosis challenging, especially for the high-grade variants. However, it is clear that the prognosis for women with low-grade endometrial stromal sarcoma (LG-ESS) is
significantly better than it is for women with either high-grade endometrial stromal sarcoma (HG-ESS) or undifferentiated uterine sarcoma (UUS), regardless of stage.

In a Surveillance, Epidemiology, and End Results (SEER) analysis of endometrial stromal sarcoma separated by grade (1 to 3), where grade 1 and 2 most likely represent currently defined LG-ESS and grade 3 likely is a mix of HG-ESS and UUS, the five-year disease-free survival by grade was: 91.4 percent (grade 1), 95.4 percent (grade 2), and 42.1 percent (grade 3), respectively [1]. Late recurrences have been identified in low-grade disease in up to 60 percent [3].

In a small study that initially identified the YWHAE-FAM22 translocation characteristic of HG-ESS, of the 10 patients for whom longitudinal clinical information was available, only one patient showed no evidence of disease with <4 years of follow-up, seven were living with recurrent disease (1- to 10-year follow-up), and two had died of disease within two years [12]. This was compared with 17 patients with LG-ESS harboring characteristic JAZF1 rearrangements: 13 patients (76 percent) showed no evidence of disease (1 to 34 years of follow-up, average 10 years), two were alive with disease, and two had died of disease (one within one month and the other nine years of initial diagnosis) [3,55].

In a study of women with undifferentiated endometrial sarcoma (UES), which likely had a mix of HG-ESS and UUS, the overall survival (OS) was poor, regardless of stage. Of 19 patients, the median progression-free survival (PFS) and OS were 7 and 12 months, respectively [29]. Women with stage I disease had a relatively better prognosis compared with those presenting with more advanced disease, although with median PFS and OS of only 15 and 27 months, respectively, they are far worse than for women with LG-ESS.

**RECURRENT AND METASTATIC ESS**

The standard approach to treatment of recurrent and metastatic low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS) is discussed below. However, we believe the best option for treatment in patients with recurrent or metastatic disease is participation
in a properly designed clinical trial.

**LG-ESS** — LG-ESS recurs most commonly in the abdomen/pelvis (40 to 50 percent), followed by the lung (approximately 25 percent) [56,57]. However, spine and hematologic recurrences have also been described [56,58-60]. Late recurrences are common even with early-stage disease [3]. Treatment for metastatic disease depends on whether and what type of adjuvant therapy was administered.

**No prior treatment** — For women who are treatment naïve, endocrine therapy is the primary treatment for recurrent and metastatic LG-ESS. Although there are only low-quality data available, they support activity of these agents in LG-ESS. As an example, one retrospective study included 47 patients with recurrent LG-ESS, 30 of whom were treated with endocrine therapy either as single-agent therapy (n = 22) or in combination with other treatment [56]. Five patients (17 percent) had a complete response, three (10 percent) had a partial response, and 53 percent had stable disease for a clinical benefit rate of 80 percent. The median time to neoplasm progression was 24 months. In a second study of 13 patients with metastatic LG-ESS, initial treatment with endocrine therapy resulted in an objective response rate of 46.2 percent (zero complete responses, six partial responses), median progression-free survival of 4 years, and a five-year progression-free rate of 30.8 percent [61].

Although the data to support their use are limited, widely used endocrine agents include the following:

- **Medroxyprogesterone acetate** and **megestrol acetate** are the most commonly used progestins and have been associated with durable responses [62,63].

- Aromatase inhibitors [64].

- Gonadotropin-releasing hormone analogs [65,66].

There have been several reports of selective estrogen receptor modulator (SERM; eg, tamoxifen or toremifene)-associated LG-ESS, thus SERMs should not be administered to women with LG-ESS because there is a concern they may increase the risk of recurrence [67-69]. This has been attributed to their agonist activity on endometrial stromal cells [46,49].
Previously treated — Patients who progress after initial hormone therapy may still achieve benefit from second-line hormone therapy. In 10 patients with LG-ESS who had received prior hormone therapy, all achieved stable disease >6 months with second-line endocrine therapy [61]. Patients who no longer respond to endocrine therapy are candidates for cytotoxic chemotherapy. The approach to these patients is similar to those patients with metastatic or recurrent leiomyosarcoma; available treatment combinations include gemcitabine plus docetaxel and doxorubicin-based regimens.

For patients who progress despite combination chemotherapy, there are few data to support the use of subsequent treatments. However, for women who maintain a good performance status and those who desire further treatment, who are willing to accept the increased risk of treatment-related toxicity, and understand that the survival benefits of treatment are unknown, single-agent cytotoxic chemotherapy is reasonable. Options for treatment in the second or later-line setting mirror those for metastatic leiomyosarcoma.

Is there a role for surgery? — Surgical resection is a reasonable option for women with recurrent LG-ESS, particularly for select women with solitary metastases (particularly involving the lung). Several reports suggest that long-term survival for women with ESS is possible following surgical resection [70-73]. Ideal candidates are those who relapse following a long progression-free interval >12 to 18 months and have a solitary recurrence amenable to complete resection.

HG-ESS and UUS — Chemotherapy is the treatment of choice for patients with recurrent or metastatic HG-ESS and UUS. As with patients with metastatic LG-ESS, only selected patients who present with a solitary metastasis should be considered for metastasectomy.

Chemotherapy agents — Few data are available to guide chemotherapeutic choices, but drugs with activity in undifferentiated soft tissue sarcoma, specifically gemcitabine plus docetaxel, ifosfamide, and doxorubicin, have shown some efficacy [29,74]. A retrospective analysis of seven patients with YWHAE-rearranged HG-ESS suggest improved response with anthracycline-based chemotherapy [75]. Otherwise, the approach to these patients is similar to those patients with metastatic or recurrent leiomyosarcoma and undifferentiated soft tissue sarcoma. Participation in clinical trials
UTROSCT

The clinical presentation, evaluation, and differential diagnosis of uterine tumor resembling ovarian sex cord tumors (UTROSCT) are similar to that of endometrial stromal neoplasms and are described above. Information specific to UTROSCT is presented here. (See 'Endometrial stromal neoplasms' above.)

Histopathology — UTROSCT are uterine neoplasms that resemble ovarian sex cord tumors without recognizable endometrial stroma. UTROSCT are histologic diagnoses based upon pathologic evaluation.

The cell of origin for UTROSCT is, as yet, undefined. UTROSCT are typically described as having features resembling ovarian sex cord tumors along with positive staining with at least two markers that are commonly positive in ovarian sex cord-stromal tumors (inhibin, calretinin, CD56, melan-A, cluster of differentiation 99 [CD99], forkhead box L2 [FOXL2], or steroidogenic factor-1 [SF-1]).

UTROSCT is included in the 2014 World Health Organization (WHO) classification system with endometrial stromal sarcoma (ESS) and related tumors because the original description of UTROSCT described two types: group I included endometrial stromal nodule (ESN) or low-graded endometrial stromal sarcoma with sex cord-like elements and group II included tumors with sex cord-like elements without stromal components [7]. The term UTROSCT is now reserved for group II tumors, while group I tumors are classified under LG-ESS.

Molecular characteristics — Unlike low-grade endometrial stromal sarcoma (LG-ESS), which can exhibit sex cord-like features, UTROSCT do not exhibit any recognizable endometrial stroma and are not associated with the JAZF1-SUZ12 fusion characteristic of LG-ESS, indicating these two entities have distinct pathogeneses [76,77]. In addition, UTROSCT do not have PHF1 gene rearrangements associated with ESS with sex cord-like elements or mutations characteristic of ovarian sex cord/stromal tumors (such as FOXL2 or DICER1 mutations as seen in ovarian granulosa cell tumors and Sertoli-Leydig cell tumors, respectively) [78-80]. Other gene
Fusions have been reported for UTROSCT with a series of four identifying NCOA2 and NCOA3 fusions and one report of CREB1-CTNNB1 fusion [81,82].

**Imaging** — Imaging can be used to facilitate staging prior to surgery or when the diagnosis was made following hysterectomy for a presumed benign condition. Few data are available about the appearance of UTROSCT on imaging. On magnetic resonance imaging (MRI), some UTROSCT may have a sponge-like appearance more typical of ovarian granulosa cell tumors [83]. However, they may also have imaging characteristics similar to uterine leiomyomas [84]. There are no reported studies of positron emission tomography (PET) imaging for UTROSCT.

**Staging** — There are no formal recommendations on staging UTROSCT; however, it is reasonable to surgically stage disease according to the 2017 American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Tumor, Node, Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) surgical staging systems for uterine sarcomas (table 2).

**Treatment** — No universal treatment protocol for UTROSCT has been established. Traditionally, UTROSCT is treated with hysterectomy with or without bilateral salpingo-oophorectomy. However, case reports of ovary and uterus-sparing procedures for UTROSCT have been published [85,86]. Although frequently associated with low-malignant potential, recurrence and malignant metastases do occur [76]. In addition, hysteroscopic approaches may lead to incomplete excision [87]. Thus, ovary- and uterus-sparing procedures should only be undertaken in patients after careful consideration of the risks and with close monitoring.

The role of adjuvant radiation, chemotherapy, or endocrine therapy for the treatment of UTROSCT is unclear. We generally do not recommend adjuvant therapy as UTROSCT are typically considered to be of uncertain or low-malignant potential [88,89]. While late recurrences and metastases have been reported [76], it is not clear whether any form of adjuvant therapy after complete resection of disease improves survival compared with observation. Although late recurrences may occur in patients with UTROSCT, we do not favor long-term surveillance with computed tomography scans given the increased radiation exposure risk [].

For patients with recurrent UTROSCT, there are limited data to guide management. In
our practice, we offer repeat surgical resection if technically feasible. For patients for whom surgery is not an option, we offer radiation therapy for localized disease and systemic therapy for metastatic disease.

There are no formal systemic treatment recommendations for UTROSCT. Response to neoadjuvant carboplatin and paclitaxel has been reported [90]. Early reports of response to endocrine therapy have been presented [91]; however, these cases may now be considered ESS with sex cord-like differentiation rather than group II UTROSCT. In group II tumors, endocrine therapy with high-dose progestin and aromatase inhibitors appears to be ineffective [92].

**Prognosis** — UTROSCT have traditionally been considered to be of uncertain or low-malignant potential [88,89]. However, in the largest series (34 consultation cases) with long-term follow-up (at least 6 months, mean 39 months), 8 (23 percent) developed extrauterine metastases [76]. The presence of necrosis and significant mitotic activity (≥2 mitoses per high-powered fields) was significantly associated with malignant behavior [76]. Recurrence was identified between 11 and 129 months after initial diagnosis [76]. Bias due to consultation/referral practices may have influenced the high number of malignant cases in this series. The series, however, does show that UTROSCT are not a uniformly benign histology.

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**ADENOSARCOMA**

A variant of uterine sarcoma comprising non-neoplastic glandular epithelium associated with sarcoma is termed adenosarcoma. The clinical presentation, evaluation, and differential diagnosis of uterine adenosarcoma are similar to that of endometrial stromal neoplasms and are described above. Information specific to uterine adenosarcoma is presented here. (See ‘Endometrial stromal neoplasms’ above.)

**Histopathology** — Adenosarcoma of the uterus is a rare mixed neoplasm in which a benign/non-neoplastic epithelial component is mixed with a malignant stromal (ie, sarcomatous) element (picture 2A-B) [93]. These are typically considered low-grade neoplasms. These neoplasms present as solid, typically edematous polypoid masses usually arising from the fundus and generally have low malignant potential and a good
The majority of adenosarcomas are diagnosed at stage I (60 percent in a large series [95]) with an overall survival (OS) of >80 percent [96].

On histopathology, adenosarcoma comprises bland endometrial glands (the "adeno" portion) adjacent to a typically variable cellular stroma with mitosis and increased cellularity around the epithelium (the "sarcoma" portion). It is a difficult diagnosis to make, and it is critical for an experienced gynecologic pathologist to review the pathology. The majority of adenosarcomas present in the endometrium, but they may also arise from the myometrium, cervix, or extraterine müllerian tissues [97].

While adenosarcomas typically have a low malignant potential, a subgroup exhibits sarcomatous overgrowth, defined as the sarcomatous component constituting more than 25 percent of the neoplasm [98-100]. In our experience, any degree of stromal overgrowth or high-grade component may be associated with an increased risk of recurrence. This occurs in 8 to 54 percent of uterine adenosarcomas and 30 percent of ovarian adenosarcomas [96]. Adenosarcomas with sarcomatous overgrowth are associated with higher rates of recurrence and significantly poorer prognosis [101]. Other poor prognostic features include advanced age at diagnosis, myometrial invasion, and lymphovascular invasion.

**Molecular characteristics** — Adenosarcoma typically stains positive for CD10 and may also express Wilms' tumor protein (WT-1), estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), smooth muscle actin (SMA), cytokeratin, and desmin [102,103]. Next-generation sequencing has also identified amplification of the E3 ubiquitin protein ligase (MDM2) and cyclin-dependent kinase 4 (CDK4) in 28 percent of cases and alterations in the phosphatidylinositol-4,5-bisphosphate 3-kinase pathway (referred to as the PIK3CA/AKT/PTEN pathway) in 72 percent [102]. Adenosarcomas with sarcomatous overgrowth were more likely to exhibit MYBL1 amplification and mutations in ATRX. TP53 mutations are not common in adenosarcoma but may be more common in the subset with sarcomatous overgrowth.

**Imaging** — Imaging can be used to facilitate staging prior to surgery or when the diagnosis was made following hysterectomy for a presumed benign condition. Few data are available about the appearance of adenosarcomas on imaging. They typically appear as large polypoid masses with multiseptated cystic appearance and
heterogeneous solid components exhibiting low signal intensity on T2-weighted magnetic resonance imaging (MRI) images \[104\]. Their appearance can mimic gestational trophoblastic disease \[96\]. Sonographic features of adenosarcoma may include expansion of endometrial cavity associated with a thickened heterogeneous and cystic echogenic complex mass \[104\]. There are no reported studies of positron emission tomography (PET) imaging for adenosarcomas.

**Staging** — Uterine adenosarcomas are surgically staged according to the 2017 American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Tumor, Node, Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) surgical staging systems for uterine sarcomas (table 2).

**Treatment** — Surgical treatment of uterine adenosarcoma usually parallels the surgical management of endometrial stromal sarcoma. The role of fertility preservation and ovarian conservation in adenosarcoma is uncertain due to limited information. A Surveillance, Epidemiology, and End Results (SEER) study evaluating uterine sarcomas had a cohort of 162 patients with adenosarcoma \[43\]. There was no difference in OS or cancer-specific survival based on oophorectomy status. Polypectomy or local resection of disease has also been reported as a treatment approach in the literature; of seven cases, two women developed recurrent disease, with one having successful relapse therapy, and the other was lost to follow-up \[101\].

The role of adjuvant radiation, chemotherapy, or endocrine therapy for the treatment of adenosarcoma is unclear. We generally follow the treatment recommendations for low-grade endometrial stromal sarcoma (LG-ESS). However, the increased recurrence rate of adenosarcomas with sarcomatous overgrowth (44 compared with 14 percent without overgrowth in a Gynecologic Oncology Group study of 31 patients) raises the question regarding the role of adjuvant therapy for these patients \[100\].

For patients with recurrent uterine adenosarcoma, secondary cytoreduction seems to be rational for patients who are surgical candidates and have disease that is amenable to surgical resection \[101\]. In our practice, we offer repeat surgical resection if technically feasible. For patients in whom surgery is not an option, we offer radiation therapy.
For patients with metastatic adenosarcoma without sarcomatous overgrowth, we often administer endocrine therapy similar to metastatic LG-ESS, although few data on response to hormone therapy are available [105].

For metastatic adenosarcomas with sarcomatous overgrowth, we manage patients in the same fashion as UUS. Responses to chemotherapy, including liposomal doxorubicin, trabectedin, anthracyclines, and ifosfamide, have been reported [106-108]. However, there is no consensus available on which chemotherapy to use.

**Prognosis** — The majority of women with adenosarcoma present with early-stage disease and have a favorable outcome. In a study of the SEER database, five-year survival for patients with stage I to II disease was 63 to 84 percent, 48 percent for stage III, and 15 percent for stage IV [95]. However, the SEER database does not capture sarcomatous overgrowth. Patients whose tumors exhibit sarcomatous overgrowth may present with more advanced disease (29 versus 7 percent without overgrowth), are more likely to develop a recurrence (44 versus 14 percent without overgrowth), and are more likely to die of the disease (31 versus 7 percent without overgrowth) [100].

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**SUMMARY AND RECOMMENDATIONS**

- Endometrial stromal neoplasms are a subset of uterine mesenchymal neoplasms that account for less than 10 percent of uterine sarcomas and approximately 1 percent of all uterine malignant neoplasms. (See 'Endometrial stromal neoplasms' above.)

- The World Health Organization (WHO) classifies endometrial stromal neoplasms and related tumors into five categories: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), undifferentiated uterine sarcoma (UUS), and uterine tumor resembling ovarian sex cord tumor (UTROSCT) (table 1). (See 'Histopathology' above.)

  - ESN is a benign endometrial stromal neoplasm that resembles proliferative endometrium. It is a well-circumscribed neoplasm that exhibits a noninfiltrating expansile border and lacks myometrial or vascular invasion. A simple
hysterectomy is curative.

- **LG-ESS** is a low-grade sarcoma that mimics proliferative endometrial stroma, exhibits characteristic myometrial and vascular invasion, and has metastatic potential. Cytologic atypia, nuclear pleomorphism, and neoplasm cell necrosis are rarely seen.

- **HG-ESS** is a stromal tumor with high-grade nuclear atypia that exhibits some features of LG-ESS but has a more destructive growth pattern and higher mitotic activity.

- **UUS** is a high-grade sarcoma characterized by marked cytologic atypia and evidence of brisk mitotic activity and lacks any features of normal endometrial stromal differentiation.

- **UTROSCT** is comprised of two tumor types: group I composed of ESN or LG-ESS with sex cord-like elements and group II consisting entirely of sex cord-like elements without stromal components. The term UTROSCT is now reserved for group II tumors, while group I tumors are classified under LG-ESS.

- Endometrial stromal neoplasms, UTROSCT, and uterine adenosarcoma are histologic diagnoses based upon pathologic evaluation. Typically, the diagnosis is made based upon the pathology evaluation of the uterus following hysterectomy, but in some cases, the diagnosis is made with endometrial sampling. (See 'Diagnosis' above and 'Recurrent and metastatic ESS' above and 'Adenosarcoma' above.)

- Endometrial stromal neoplasms and adenosarcoma are staged according to the 2017 Tumor, Node, Metastasis (TNM) staging system of the combined American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), which is consistent with the International Federation of Gynecology and Obstetrics (FIGO) staging system (table 2). Staging includes total hysterectomy with bilateral salpingo-oophorectomy. For patients with evidence of extrauterine disease, surgical staging and cytoreduction are performed only if there is no extra-abdominal disease and the intra-abdominal metastases are resectable. Other
patients are treated with medical therapy. (See 'Staging and surgical treatment' above.)

- Our approach to adjuvant medical treatment is based on stage and histologic subtype of endometrial sarcoma:

  - For patients with surgical stage I LG-ESS, we suggest observation rather than adjuvant endocrine therapy (Grade 2C). However, some experts prefer to administer endocrine therapy. (See 'Stage I' above.)

  - For women with surgical stage II to IV LG-ESS, we suggest adjuvant endocrine therapy rather than chemotherapy (Grade 2C) (see 'Stage II to IV disease' above). Radiation may be considered.

  - For women with HG-ESS or UUS who have undergone surgery, we suggest chemotherapy rather than endocrine therapy, regardless of stage (Grade 2C). We extrapolate the treatment of these patients from the approach to patients with leiomyosarcoma. (See "Treatment and prognosis of uterine leiomyosarcoma", section on 'Chemotherapy'.)

  - LG-ESS generally has an indolent course, with overall survival rates of 65 to 76 percent at 10 years. By contrast, patients with HG-ESS and UUS frequently succumb to their disease within a few years of diagnosis, regardless of stage. (See 'Prognosis' above.)

  - For patients with recurrent LG-ESS, we suggest endocrine therapy if they are treatment naïve or received clinical benefit from the last endocrine therapy and other endocrine therapy options are still available (Grade 2C). (See 'No prior treatment' above.)

  - For patients with recurrent or metastatic LG-ESS who no longer respond to endocrine therapy, and those patients with advanced, recurrent, or metastatic HG-ESS or UUS, we offer chemotherapy. However, we believe the best option for these patients is participation in a properly designed clinical trial. (See 'Previously treated' above and 'UUS' above.)

  - UTROSCT are rare neoplasms arising in the uterus that exhibit features
resembling ovarian sex cord tumors along with positive staining with at least two markers, which are commonly positive in ovarian sex cord-stromal tumors, without recognizable endometrial stroma. UTROSCT are generally of low-malignant potential; however, malignant cases have been reported. Information on treatment approaches is limited. (See 'UTROSCT' above.)

- Uterine adenosarcoma is a rare mixed neoplasm in which a benign epithelial component (endometrial glands; the "adeno" portion) is mixed with a typically low-grade sarcoma element (the "sarcoma" portion). The majority of adenosarcomas are diagnosed at stage I. For patients with adenosarcoma without sarcomatous overgrowth, our approach is the same as for LG-ESS. For patients with recurrent or metastatic adenosarcoma with sarcomatous overgrowth, we offer chemotherapy. However, we believe the best option for these patients is participation in a properly designed clinical trial. (See 'Adenosarcoma' above.)

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