Guideline Resource Unit
guru@ahs.ca

UTERINE SARCOMA

Effective Date: June, 2023

Cancer Care Alberta

Background

Uterine sarcomas are rare and represent approximately 3.2% (1.9% leiomyosarcomas; 1.3% endometrial stromal sarcomas) of all invasive uterine cancers.[1] The annual incidence rate is less than two per 100,000 women.[1, 2] The median age at which uterine sarcoma is diagnosed is 56 years (range: 19-85 years).

WHO classification of uterine sarcoma is based upon the differentiation/growth pattern of the neoplastic cells and their presumed cell of origin (See Appendix B).[3] This classification recognizes the most common histologies as leiomyosarcoma (LMS), low-grade endometrial stromal sarcoma (LG-ESS), undifferentiated uterine sarcomas, and other rare (heterologous) types such as rhabdomyosarcoma. There are also other low to intermediate malignant potential uterine mesenchymal tumour types such as PEComa (perivascular epithelioid cell neoplasm), UTROST (uterine tumour resembling ovarian sex cord tumours) and inflammatory myofibroblastic tumours that may behave in clinically malignant manners.

Recently, with the aid of molecular techniques, such as Next Generation Sequencing (NGS)-based genetic analyses, new entities such as high-grade ESS, characterized by YWHAE:NUTM2A/B or BCOR genetic abnormalities and SMARCA4 deficient uterine sarcomas (SDUS) associated with SMARCA4 mutation have been identified.[3, 4]

The discovery and characterization of new fusion driven sarcomas will ultimately lead to a decrease in the category of undifferentiated sarcomas and allow more accurate diagnosis of uterine sarcomas. Fusion driven sarcomas almost always show wild type p53 immunohistochemistry staining and can show significant morphologic overlap between tumour types. Morphologically, BCOR-altered high-grade ESS can resemble other myxoid stromal neoplasms such as myxoid leiomyosarcoma and inflammatory myofibroblastic tumour. [5] Smooth muscle tumour variants now include leiomyoma with fumarate hydratase (FH) deficiency which are most frequently a sporadic mutation. A small proportion are associated with germline FH mutations as part of hereditary leiomyomatosis and renal carcinoma (HLRCC) syndrome.

Uterine leiomyosarcomas are aggressive tumours with high rates of recurrence.[3, 6] They originate from the myometrium or myometrial vessels. A small proportion arises from pre-existing leiomyomas. In 60% of cases, disease is limited to the uterus. The incidence of sarcoma in leiomyomas and rapidly growing tumours is 0.23% and 0.27%, respectively.[7] Patients typically present with non-specific abdominal/pelvic symptoms due to the growing size of the tumour, with the mass identified initially by abdominal/pelvic ultrasound. In these settings, growing uterine mass with a query of uterine fibroid in postmenopausal patients should trigger the suspicion for uterine sarcoma. Prognostic factors include tumour size >5 cm. The most common mode of spread is hematogenous, with lymphatic spread being rare. Recurrences of up to 70% are reported in stage I and II disease with the site of recurrence being distal, most commonly the lungs or the upper abdomen.[6, 8-10] Survival rates are dependent on the stage of disease at diagnosis.[6, 11] The five-year survival rate is 50-55% for stage I and 8-12% for stage II-IV. Overall, the five-year survival rate, for all stages, ranges from about 30% to 50%.[3, 6, 9]

Local recurrences are salvageable with surgery. Isolated pulmonary metastasis can also be resected, with overall survival of 45% and 35% at five and ten years respectively.[12]

Endometrial stromal sarcomas are the second most common type of malignant uterine mesenchymal tumours after leiomyosarcomas and are composed of cells that may resemble endometrial stromal cells in proliferative endometrium.[3] Based on the WHO classification, endometrial stromal lesions are categorized into:

- Endometrial stromal nodule (ESN)
- Low-grade endometrial stromal sarcoma (LG-ESS)
- High-grade endometrial stromal sarcoma (HG-ESS)
- Undifferentiated uterine sarcoma (UUS)

ESN is a benign neoplasm characterized by limited myometrial extension. 70% contain JAZF1 fusions.

LG-ESS morphologically resemble the stroma of proliferative phase endometrium. Two thirds harbor JAZF1 fusions. In a retrospective analysis of 21 cases of LG-ESS recommended quantification of both, ER and PR receptors as it may have implications on response to the treatment. In one of the largest studies by Davidson et al reported that ER and PR expression was 53% and 67% in patients with uterine sarcoma.[13] A universal scoring method for ER and PR expression has not been agreed on. The most frequently used scoring systems assign points to the intensity and distribution of positive cells and either multiply or add the points to obtain a final score. To date, there is no correlation between ER/PR expression and prognosis or defined positive and negative scores predictive of treatment response. Recurrence rates are 20-60% at 10 years follow up, with recurrences usually being local. Late recurrences can occur in the lungs and abdomen. Lymph node involvement is rare. Recent studies suggest that less than 10% die of their disease Removal of the ovaries at the time of surgery is essential due to the high rate of hormone receptor expression[14-16]. The overall 5-year survival rate for Stage I/II ESS is >90 % with 60% survival if advanced.[3, 6, 17]

YHWAE fusion HG-ESS are frequently CD10, ER and PR negative. BCOR-altered HG-ESS are CD10 positive and have variable ER and PR expression. In addition, both types usually express BCOR, pan-TRK and are Cyclin D1 positive. They have a destructive growth pattern. The mitotic rate is not reliable in distinguishing low grade from high grade ESS. They can show expansile, permeative, or infiltrative myometrial invasion and often have necrosis. HG-ESS have a five-year overall survival of about 50%. Recurrences are common in the first two-three years and optimal lymph node debulking is essential in their management. Genetic testing is recommended for initial diagnosis of HG-ESS, and for any recurrent LG-ESS if the genetic status was not initially established. In contrast to HG-ESS which harbors the above-mentioned genetic alterations, undifferentiated uterine sarcoma (UUS) lacks diagnostic genetic fusion and is typically p53-mutated. It is important to note that UUS is a diagnosis of exclusion after entities such as leiomyosarcoma and sarcoma-predominant carcinosarcoma have been excluded pathologically. UUS when strictly defined is clinically aggressive with a five-year overall survival of about 25%.

Adenosarcomas have a benign epithelial component with a malignant mesenchymal component. Metastases occur in less than 20% of cases and are usually local. Cases with sarcomatous overgrowth are associated with a worse prognosis. Rare cases show malignant transformation of the epithelial component, and these cases should not be classified as carcinosarcomas.[18]

Uterine tumours resembling ovarian sex cord tumours (UTROSCT) have characteristic genetic abnormalities (gene fusions involving ESR1 or GREB1).[3] They were classified as a distinct entity by the WHO in 2014.[5] A subset UTROSCT can behave in a malignant manner based on the findings of more aggressive histologic features. Uterine inflammatory myofibroblastic tumours (IMT) is also characterized by genetic fusion, typically involving ALK and such genetic fusion can be targeted by kinase inhibitor (targeted therapy). Diagnostically, uterine IMT, particularly those that display more aggressive histologic features can be mistaken for leiomyosarcoma or STUMP (smooth muscle tumour of uncertain malignant potential), and it is important to evaluate for the possibility of uterine IMT by ALK immunohistochemistry or NGS genetic fusion analysis given its known response to targeted therapy.

The purpose of this guideline is to recommend options for the management of uterine sarcoma, based on the best evidence available.

Guideline Questions

- What is the optimal surgical staging for leiomyosarcoma?
- What is the role of adjuvant chemotherapy and/or radiotherapy for leiomyosarcoma?
- For leiomyosarcoma, is there a role for hormonal adjuvant therapy?
- What treatment options exist for metastatic or recurrent leiomyosarcoma?
- What are the best management options for adenosarcoma?
- What is the optimal surgical staging for endometrial stromal sarcoma and undifferentiated endometrial sarcoma?
- What is the role of adjuvant chemotherapy and/or radiotherapy for endometrial stromal sarcoma and undifferentiated endometrial sarcoma?
- For endometrial stromal sarcoma and undifferentiated endometrial sarcoma, is there a role for hormonal adjuvant therapy?
- What treatment options exist for metastatic or recurrent endometrial stromal sarcoma and undifferentiated endometrial sarcoma?

Search Strategy

Entries to Medline and EMBASE and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: leiomyosarcoma or adenosarcoma uterine or endometrial stromal sarcoma AND bilateral salpingo oophorectomy or total abdominal hysterectomy or lymphadenectomy or surgery or surgical resection or chemotherapy or radiotherapy or megestrol acetate or medroxyprogesterone or progestin. Among the relevant studies returned by the search, those that did not report response rates or survival rates were further excluded.

Articles were limited to clinical trials, retrospective reviews, and systematic reviews. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations. Existing guidelines considered for this review include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2023),[19] the BC Cancer Agency (BCCA) guidelines (2018),[20] the National Cancer Institute guidelines (2022),[21] and the Tom Baker Cancer Centre guidelines (2008).[22] An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence-based perspective was used to draft proposals. Where evidence was weak, recommendations were based on group consensus.

Target Population

The following recommendations apply to adult cancer patients with uterine sarcoma.

Recommendations

There was limited high level evidence (e.g., meta-analyses, systematic reviews, or randomized controlled trials) on gynecologic sarcomas available to inform these guidelines. Recommendations were based largely on data from phase II trials, retrospective reviews, case studies, and in some circumstances non-gynecologic sarcomas, as well as expert opinion.

I. Principles of Staging

Staging investigations may include (in most cases for LMS and undifferentiated endometrial sarcoma):

- preoperative CT of the abdomen and pelvis to rule out extrauterine disease
- preoperative CT of the chest to rule out lung metastases

An expert pathology review should be performed by a pathologist with experience in gynecologic and/or sarcoma pathology.

II. Treatment

Leiomyosarcoma Options:[19, 20]

Stage I (tumour limited to uterus) *(Level of Evidence: I Strength of Recommendation: A):*

- Total hysterectomy with bilateral salpingo-oophorectomy (BSO).
- Ovarian preservation may be considered in young women on a case-by-case basis.
- There is no high-level evidence to support the use of post-operative adjuvant radiotherapy or adjuvant chemotherapy.

Stage II (tumour extends to the pelvis)[3, 19] *(Level of Evidence: III Strength of Recommendation: C):*

No standard therapy has been established; options include:

- Neoadjuvant radiotherapy, followed by resection of gross tumour if debulking is achievable.
- Neoadjuvant chemotherapy +/- radiotherapy, followed by resection of gross tumour if debulking is achievable.
- Resection of gross tumour if debulking achievable; consider adjuvant chemotherapy +/- radiotherapy.

Stage III (tumour invades abdominal tissues)[19, 21] *(Level of Evidence: III Strength of Recommendation: C):*

No standard therapy has been established; options include:

- Neoadjuvant radiotherapy, followed by resection of gross tumour if debulking is achievable.
- Neoadjuvant chemotherapy +/- radiotherapy, followed by resection of gross tumour if debulking is achievable.
- Resection of gross tumour if debulking achievable; consider adjuvant chemotherapy +/- radiotherapy.

Stage IVA (tumour invades bladder and/or rectum)[3, 19, 21] *(Level of Evidence: II Strength of Recommendation: B):*

- Neoadjuvant radiotherapy, followed by resection of gross tumour if debulking is achievable.
- Neoadjuvant chemotherapy +/- radiotherapy, followed by resection of gross tumour if debulking is achievable.
- Palliative chemotherapy may be used in patients for whom surgery is not an option.
- Palliative radiotherapy may be used for specific symptom control (e.g. bleeding, pain).

Stage IVB (distant metastasis)[3, 19, 21] *(Level of Evidence: III Strength of Recommendation: C):*

- In select patients with limited metastatic disease, neoadjuvant radiotherapy or neoadjuvant chemotherapy, followed by debulking surgery can be considered. For isolated lung metastases, consider referral to a thoracic surgeon for resection.
- Palliative chemotherapy may be used in patients for whom surgery is not an option.
- Palliative radiotherapy may be used for specific symptom control (e.g. bleeding, pain).

Palliative Chemotherapy Options[3] *(Level of Evidence: III Strength of Recommendation: C):*

- There is no standard chemotherapy regimen.
- Agents that have been used include: doxorubicin, ifosfamide, gemcitabine, docetaxel, trabectedin (not available in Canada), dacarbazine, and cisplatin.
- Combination chemotherapy should be used only in fit patients.

Adjuvant Chemotherapy Options[23] *(Level of Evidence: I Strength of Recommendation: A):*

***Docetaxel + Gemcitabine*:**

- Days 1,8: Gemcitabine 900mg/m2 IV at a rate of 10mg/m2 /minute, followed by:
- Day 8: Docetaxel 75-100mg/m2 IV over 60 minutes. Repeat cycle every 3 weeks for 4-6 cycles. OR Days 1,8: Gemcitabine 675mg/m2 (if prior pelvic radiation) IV at a rate of 10mg/m2 /minute, followed by:
- Day 8: Docetaxel 75mg/m2 IV over 60 minutes. Repeat cycle every 3 weeks for 6 cycles.
- Doxorubicin Day 1: Doxorubicin 60-75mg/m2 IV push. Repeat cycle every 3 weeks for 6 cycles.

Combination chemotherapy regimens:[24]

Day 1-4	Doxorubicin 60mg/m2 + Dacarbazine 750mg/m2 as a continuous IV infusion over 96 hours. Repeat cycle every 3 weeks for 6 cycles. Maximum Doxorubicin 360 mg/m2.
Day 1-3	Doxorubicin 25mg/m2 IV push + Ifosfamide 2500 mg/m2 IV continuous infusion over 24 hours daily. Repeat cycle every 3 weeks for 6 cycles.

Recurrent disease:[19]

- Surgery for localized disease.
- Chemotherapy followed by CT scan to determine disease response.
- Palliative radiotherapy for specific symptom indication (e.g., bleeding, pain).
- Where possible, patients should be considered for enrolment in a clinical trial.

Adenosarcoma Options:[19]

- Total hysterectomy with bilateral salpingo-oophorectomy (BSO).
- Resection of gross tumour in advanced cases, if debulking is achievable.

Adjuvant treatment is not typically required.

Where possible, patients should be considered for enrolment in a clinical trial.

LG-ESS Options:[19]

- Total hysterectomy with bilateral salpingo-oophorectomy (BSO).
- Resection of gross tumour in advanced cases, if debulking is achievable.
- Post-operative hormonal therapy (typically letrozole) in patients with advanced or metastatic disease.

Where possible, patients should be considered for enrolment in a clinical trial.

HG-ESS and Undifferentiated Endometrial Sarcoma Options[19] *(Level of Evidence: II Strength of Recommendation: B):*

Stage I (tumour limited to uterus):

- Total hysterectomy with bilateral salpingo-oophorectomy (BSO).
- Selective biopsy of pelvic +/- para-aortic lymph nodes

Stage II (tumour extends to the pelvis):

- Total hysterectomy with BSO.
- Resection of gross tumour if debulking is achievable.

Stage III (tumour invades abdominal tissues):

- Total hysterectomy with BSO.
- Resection of gross tumour if debulking is achievable.

Stage IVA (tumour invades bladder and/or rectum):

- Resection of gross tumour if debulking is achievable.
- Neoadjuvant chemotherapy can be considered, followed by debulking surgery.
- Palliative radiotherapy, if surgery is not an option.
- Palliative chemotherapy, if surgery is not an option.

Stage IVB (distant metastasis) [19]***:***

- Neoadjuvant chemotherapy, followed by debulking surgery; refer patient to a thoracic surgeon for resection of isolated lung metastases.
- Palliative chemotherapy and/or radiotherapy if surgery is not an option.
- Palliative radiotherapy may be used for specific symptom control (e.g. bleeding, pain).
- Palliative chemotherapy may be used in patients who have unresectable disease.

Palliative chemotherapy options:

- There is no standard chemotherapy regimen.
- Agents that have been used include: doxorubicin, ifosfamide, gemcitabine, docetaxel, dacarbazine, and cisplatin.
- Combination chemotherapy should be used only in fit patients.

Recurrent disease**:**

- Surgery for localized disease.
- Chemotherapy followed by CT scan to determine disease response.
- Palliative radiotherapy for specific symptom indication (e.g., bleeding, pain).
- Palliative chemotherapy may be used in patients who have unresectable disease.

Where possible, patients should be considered for enrolment in a clinical trial.

III. Hormone Therapy

For patients whose tumours express estrogen and/or progesterone receptors, consider a trial of hormone therapy (e.g. palliative setting): GnRH analogs (i.e., leuprolide, zoladex), aromatase inhibitors (i.e., anastrozole, letrozole) and progestins (i.e., medroxyprogesterone acetate, megestrol acetate). A universal scoring method for ER and PR expression has not been agreed on. The most frequently used scoring systems assign points to the intensity and distribution of positive cells and either multiply or add the points to obtain a final score. To date, there is no correlation between ER/PR expression and prognosis or defined positive and negative scores predictive of treatment response.

IV. Follow Up[19]

- Regular chest x-ray is recommended; other imaging investigations should be performed, only as clinically indicated.
- Follow-up visits should typically occur every 3-6 months during years 1 and 2 and then annually for years 3 through 5.
- Follow-up visits can also be planned according to risk stratification (i.e., tumour grade, size, and site): intermediate/high-risk patients could be seen every 3-4 months for the first 2-3 years and

annually thereafter. Low-risk patients could be seen every 4-6 months for the first 3-5 years and annually thereafter.

Discussion

LMS

National guidance on treatment options for uterine leiomyosarcoma includes surgery, adjuvant radiotherapy and/or chemotherapy, and hormone therapy, depending on the stage of disease. [19] However, the role of adjuvant radiotherapy and/or chemotherapy is controversial, as there is no high-level evidence to support its use in these patients. Regarding surgery, total hysterectomy with bilateral salpingo oophorectomy is the preferred option; [19, 25] however, retrospective studies and case studies on surgical treatment for leiomyosarcoma support ovarian preservation in select cases of stage I disease. [21, 22, 25] Retrospective data among patients with uterine sarcoma (36% of which had leiomyosarcoma) showed no additional benefit of lymphadenectomy in terms of overall (OR=1.57; p=0.207) or disease-free (OR=0.93; p=0.812) survival.[26]

Most of the available data on adjuvant therapy for leiomyosarcoma is from phase II studies and retrospective studies. No randomized controlled trials have compared adjuvant chemotherapy with adjuvant radiotherapy or adjuvant therapy with observation. Four retrospective studies with small numbers of patients have shown mixed results. [27-30] The largest retrospective study to date (87 patients) comparing these treatments showed that five-year survival was significantly higher among patients who had received radiotherapy (70% versus 35%), but that there were no differences after 90 months of follow-up; pelvic recurrences were significantly lower in the radiotherapy group (18% versus 49%; P=.02). [31] Radiotherapy may improve local control but has not been shown to improve survival.

Chemotherapy may be considered for control of hematogenous spread but has shown limited success in extending overall survival.

Among completely resected stage I-IV high grade patients, Hensley, et al. (2009) demonstrated a progression-free survival rate of 45% at two years with a median progression-free survival of 13 months, with the use of gemcitabine (900 mg/m^2 over 90 min days 1 and 8) plus docetaxel (75 mg/m^2 day 8) every three weeks for four cycles. [32] Relatively promising results using this regimen were also observed among patients with advanced and unresectable disease with no prior cytotoxic therapy (median progression-free and overall survival of 4.4 months and 16+ months, respectively) [33] and among patients with advanced or recurrent and unresectable disease who had progressed after one prior cytotoxic therapy, mostly doxorubicin-based (median progression-free survival of 5.6+ months). [34] A phase II study among patients with metastatic soft tissue sarcoma (32% of whom had leiomyosarcoma, both uterine and otherwise), demonstrated that combination therapy with gemcitabine and docetaxel, though more toxic, achieved better progression-free survival (median 6.2 vs. 3.0 months) and overall survival (median 17.9 vs. 11.5 months) than gemcitabine monotherapy.

However, it should be noted that among patients with leiomyosarcoma (n=38, both uterine and otherwise), one of nine (11.1%) progressed on gemcitabine alone, whereas eight of 29 (27.5%) progressed on gemcitabine plus docetaxel. [35] Combination therapy is far more toxic than gemcitabine alone [36] and the most common toxicities associated with gemcitabine and docetaxel were thrombocytopenia (14.5-39.4%), neutropenia (17-20.8%), and anemia (24-25%). The French trial, which stratified LMS and uterine LMS, failed to show any PFS and OS benefit of the combination in both subgroups. [33,35]

A randomized controlled phase 3 trial study comparing single-agent doxorubicin versus doxorubicin and ifosfamide chemotherapy published in 2014, showed an advantage for the combination for progression-free survival but not overall survival. Combination therapy was associated with significantly more Grade 3 and 4 adverse events including leucopenia, febrile neutropenia, anemia and thrombocytopenia. [37]

Other agents that have been used include dacarbazine, docetaxel, epirubicin, gemcitabine, liposomal doxorubicin, and paclitaxel. [19, 38, 39]

A systematic review from Ontario examined systemic therapies for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma as first- or second-line therapy and found that gemcitabine plus docetaxel studies reported longer median overall survival times (14.7-17.9 months vs. 12.1 months) and higher objective response rates (27-53% vs. 25%) than studies of doxorubicin alone. Single agent gemcitabine was similar to doxorubicin alone, in terms of tumour response rate (21% vs. 25%, respectively). The review concluded that doxorubicin, gemcitabine, and gemcitabine plus docetaxel are treatment options in this setting. [40]

The GeDDiS trial was a randomized phase III trial which compared combination gemcitabine with docetaxel versus doxorubicin in the first line setting on untreated advanced unresectable or metastatic soft tissue sarcomas. Progression free survival at 24 weeks was similar, as were Grade 3 and 4 adverse events – neutropenia, febrile neutropenia, fever and fatigue. However, combination therapy was associated with significantly more dose delays, lower dose intensity, lower quality of life scores and worse compliance. Hence, it was concluded that single agent doxorubicin was a better option. [41]

Sunitinib (50 mg/d oral for four weeks, with two weeks rest) [42] and trabectedin (1.5 mg/m^2 IV every three weeks) [43] have been evaluated as single agent therapies in patients who failed chemotherapy; the median progression-free survival times were 1.5 months for sunitinib and 3.3 months for trabectedin. Of note, uterine leiomyosarcoma comprised only 22% of the study population in the trabectedin study.

Recently, there has been significant interest in the use of combination of doxorubicin with dacarbazine. An analysis by the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group retrospectively evaluated doxorubicin plus dacarbazine, doxorubicin plus ifosfamide and doxorubicin alone as first-line treatments for advanced/metastatic

leiomyosarcoma. This was the largest retrospective analysis of first-line treatment of advanced LMS[23, 44]. Three hundred three patients from 18 EORTC-STBSG sites were identified. One hundred seventeen (39%) received doxorubicin plus dacarbazine, 71 (23%) received doxorubicin plus ifosfamide, and 115 (38%) received doxorubicin. In the 2:1:2 propensity score-matched population (205 patients), the estimated median PFS was 9.2 months (95% confidence interval [CI], 5.2-9.7 months), 8.2 months (95% CI, 5.2-10.1 months), and 4.8 months (95% CI, 2.3-6.0 months) with ORRs of 30.9%, 19.5%, and 25.6% for doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin alone, respectively. PFS was significantly longer with doxorubicin plus dacarbazine versus doxorubicin (hazard ratio [HR], 0.72; 95% CI, 0.52-0.99). Doxorubicin plus dacarbazine was associated with longer OS (median, 36.8 months; 95% CI, 27.9-47.2 months) in comparison with both doxorubicin plus ifosfamide (median, 21.9 months; 95% CI, 16.7-33.4 months; HR, 0.65; 95% CI, 0.40-1.06) and doxorubicin (median, 30.3 months; 95% CI, 21.0-36.3 months; HR, 0.66; 95% CI, 0.43-0.99). Adjusted analyses retained an effect for PFS but not for OS. [44]

Results from the recently published LMS-04 trial demonstrated that the combination of doxorubicin and trabectedin prolonged the primary endpoint of progression-free survival (PFS) compared with doxorubicin alone. Furthermore, median OS was 30.5 months with doxorubicin plus trabectedin compared with 24.1 months for doxorubicin alone (HR 0.74; 95% CI 0.49–1.12). Longer-term OS analyses of the LMS-04 trial are awaited. [23]. Trabectedin was approved by Health Canada in 2016. However, at present there is no access to this drug in Alberta.

The Phase III ANNOUNCE placebo-controlled trial of Olaratumab in combination with doxorubicin in advanced soft tissue sarcomas failed to show an improvement in survival in comparison to doxorubicin alone. [45]

ESS

Literature on the treatment of endometrial stromal sarcoma (ESS) and adenosarcoma is limited to case studies and a couple of retrospective studies. Most patients have been treated with hysterectomy and bilateral salpingo oophorectomy, plus or minus adjuvant chemotherapy or adjuvant radiotherapy, or hysterectomy and unilateral salpingo oophorectomy with adjuvant therapy. [3, 46, 47]

Regardless of treatment, the outcomes are favorable for patients with this type of uterine sarcoma, as patients are typically found to be alive and disease free well beyond three years. [3, 46-48]

Salvage therapy for metastatic or recurrent ESS has consisted of neoadjuvant chemotherapy followed by secondary cytoreduction [49, 50] in three cases reported in the literature. One case of recurrent, low-grade disease with lung metastasis that was treated with goserelin for two years followed by anastrozole for ten years has remained disease-free. [51] Overall, however, data is limited in this group of patients and treatment will likely require an individualized approach.

Undifferentiated Sarcomas

These sarcomas are a diagnosis of exclusion. Most of them are misdiagnosed high grade ESS. The presence of BCOR expression in >50% of cells may help in categorizing these tumours as high-grade ESS[52].

These tumours are extremely rare with a poor prognosis. For early-stage disease consideration can be given to a hysterectomy with bilateral salpingo-oophorectomy and adjuvant radiotherapy and/or chemotherapy. Presentation, however, is usually in the advance setting and treatment may have to be for palliative control of disease. SEER data from 2012-2018 suggests a 5-year relative survival rate of 71% for localized disease and 18% if advanced[53].

Molecular Profiling and Testing

Finally, a recent study by Choi et al suggested that the future management for LMS should include integrated whole-genome, whole-exome, and RNA-Seq results. It would allow for the identification of recurrently mutated genes and deranged pathways. Combining integrated genetic analysis with preclinical validation experiments, suggested that a large subset of uLMS may potentially benefit from existing PARPi/BETi/PIK3CAi-targeted drugs.[54]

Molecular profiling is informative in many mesenchymal malignancies for accurate classification. As more genetic alterations are increasingly being identified in uterine sarcomas/mesenchymal tumours, there can be clinical uncertainty regarding the classification and the behavior of newly described tumour types.

The NCCN guidelines from 2023[55, 56] recommends comprehensive genomic profiling metastatic disease with an assay that is informative for predicting rare pan-tumour targeted therapy opportunities. It should at least NTRK, MSI, and TMB. However, it is to be noted that at present there is no consensus on TMB.

With increasing clinical availability of NGS-based genetic analyses in the province of Alberta, there will be greater utilization of these more comprehensive genetic analyses in the diagnostic work-up of uterine sarcoma/mesenchymal tumours. While these additional analyses may increase the turn-around time of the pathology result, they are essential in most instances and may yield diagnostically as well as therapeutic relevant information.

References

1. National Cancer Institute. SEER Survival Monograph: Cancer of the Corpus Uteri. URL: http://seer.cancer.gov/publications/survival/surv_corpus_uteri.pdf. . April, 2020.

2. Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. *J Natl Cancer Inst*. Mar 1986;76(3):399-402.
3. Memarzadeh S BJS. Uterine sarcoma: Classification, epidemiology, clinical manifestations, and diagnosis. UpToDate; 2023.
4. Zhi W, Zheng X, Jin Y. ZC3H7B-BCOR High-Grade Endometrial Stromal Sarcoma with a Mucoid Grossly Feature: A Case Report and Literature Review. *Int J Womens Health*. 2022;14:1701-1708.
5. Mayr D, Horn LC, Hiller GGR, Höhn AK, Schmoeckel E. [Endometrial and other rare uterine sarcomas : Diagnostic aspects in the context of the 2020 WHO classification]. *Pathologe*. May 2022;43(3):183-195.
6. Arend RC, Toboni MD, Montgomery AM, Burger RA, Olawaiye AB, Monk BJ, et al. Systemic Treatment of Metastatic/Recurrent Uterine Leiomyosarcoma: A Changing Paradigm. *Oncologist*. Dec 2018;23(12):1533-1545.
7. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. *Obstet Gynecol*. Mar 1994;83(3):414-8.
8. Sampath S, Gaffney DK. Role of radiotherapy treatment of uterine sarcoma. *Best Pract Res Clin Obstet Gynaecol*. Dec 2011;25(6):761-72.
9. Gadducci A, Sartori E, Landoni F, Zola P, Maggino T, Cosio S, et al. The prognostic relevance of histological type in uterine sarcomas: a Cooperation Task Force (CTF) multivariate analysis of 249 cases. *Eur J Gynaecol Oncol*. 2002;23(4):295-9.
10. Sagae S, Yamashita K, Ishioka S, Nishioka Y, Terasawa K, Mori M, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. *Oncology*. 2004;67(1):33-9.
11. Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. *Cancer*. Feb 15 1993;71(4 Suppl):1702-9.
12. Levenback C, Rubin SC, McCormack PM, Hoskins WJ, Atkinson EN, Lewis JL. Resection of pulmonary metastases from uterine sarcomas. *Gynecol Oncol*. May 1992;45(2):202-5.
13. Davidson B, Kjæreng ML, Førsund M, Danielsen HE, Kristensen GB, Abeler VM. Progesterone Receptor Expression Is an Independent Prognosticator in FIGO Stage I Uterine Leiomyosarcoma. *Am J Clin Pathol*. Apr 2016;145(4):449-58.
14. Beck TL, Singhal PK, Ehrenberg HM, Rose PG, Lele SB, Krivak TC, et al. Endometrial stromal sarcoma: analysis of recurrence following adjuvant treatment. *Gynecol Oncol*. Apr 2012;125(1):141-4.
15. Kim WY, Lee JW, Choi CH, Kang H, Kim TJ, Kim BG, et al. Low-grade endometrial stromal sarcoma: a single center's experience with 22 cases. *Int J Gynecol Cancer*. 2008;18(5):1084-9.
16. Rauh-Hain JA, del Carmen MG. Endometrial stromal sarcoma: a systematic review. *Obstet Gynecol*. Sep 2013;122(3):676-83.
17. Mbatani N, Olawaiye AB, Prat J. Uterine sarcomas. *Int J Gynaecol Obstet*. Oct 2018;143 Suppl 2:51-58.
18. El Hallani S, Arora R, Lin DI, Måsbäc A, Mateoiu C, McCluggage WG, et al. Mixed Endometrioid Adenocarcinoma and Müllerian Adenosarcoma of the Uterus and Ovary: Clinicopathologic Characterization With Emphasis on its Distinction From Carcinosarcoma. *Am J Surg Pathol*. Mar 01 2021;45(3):374-383.
19. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Uterine Neoplasms, v.1. 2022
20. BC Cancer Agency. Cancer Management Guidelines: Gynecological Sarcomas:Management. URL: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-manual/gynecology/gynecological-sarcomas, 2018.
21. National Cancer Institute. Uterine Sarcoma Treatment. URL:http://www.cancer.gov/cancertopics/pdq/treatment/uterinesarcoma/HealthProfessional/page5. Retrieved: Sep, 2022.
22. Tom Baker Cancer Centre: Management of Gynecological Malignancies (2008). Internal document.
23. Pautier P, Italiano A, Piperno-Neumann S, Chevreau C, Penel N, Firmin N, et al. Doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for metastatic or unresectable leiomyosarcoma (LMS-04): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol*. Aug 2022;23(8):1044-1054.
24. Adkins KE, Solimando DA, Waddell JA. Doxorubicin and Dacarbazine (AD) Regimen for Soft Tissue Sarcomas. *Hosp Pharm*. Mar 2015;50(3):194-8.
25. Juhasz-Böss I, Gabriel L, Bohle RM, Horn LC, Solomayer EF, Breitbach GP. Uterine Leiomyosarcoma. *Oncol Res Treat*. 2018;41(11):680-686.

26. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989-2007. *J Cancer Res Clin Oncol*. Dec 2008;134(12):1277-87.
27. Wu TI, Chang TC, Hsueh S, Hsu KH, Chou HH, Huang HJ, et al. Prognostic factors and impact of adjuvant chemotherapy for uterine leiomyosarcoma. *Gynecol Oncol*. Jan 2006;100(1):166-72.
28. Dinh TA, Oliva EA, Fuller AF, Lee H, Goodman A. The treatment of uterine leiomyosarcoma. Results from a 10-year experience (1990-1999) at the Massachusetts General Hospital. *Gynecol Oncol*. Feb 2004;92(2):648-52.
29. Giuntoli RL, Metzinger DS, DiMarco CS, Cha SS, Sloan JA, Keeney GL, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. *Gynecol Oncol*. Jun 2003;89(3):460-9.
30. Soh LT, Chew SH, Ang L. Uterine leiomyosarcoma--a Singapore experience. *Aust N Z J Obstet Gynaecol*. May 1999;39(2):246-8.
31. Mahdavi A, Monk BJ, Ragazzo J, Hunter MI, Lentz SE, Vasilev SA, et al. Pelvic radiation improves local control after hysterectomy for uterine leiomyosarcoma: a 20-year experience. *Int J Gynecol Cancer*. Aug 2009;19(6):1080-4.
32. Hensley ML, Ishill N, Soslow R, Larkin J, Abu-Rustum N, Sabbatini P, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. *Gynecol Oncol*. Mar 2009;112(3):563-7.
33. Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol*. Jun 2008;109(3):323-8.
34. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol*. Jun 2008;109(3):329-34.
35. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. Jul 01 2007;25(19):2755-63.
36. Gupta AA, Yao X, Verma S, Mackay H, Hopkins L, Group SDSGatGCDS. Systematic chemotherapy for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a systematic review. *Clin Oncol (R Coll Radiol)*. Jun 2013;25(6):346-55.
37. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. Apr 2014;15(4):415-23.
38. Long HJ, Blessing JA, Sorosky J. Phase II trial of dacarbazine, mitomycin, doxorubicin, and cisplatin with sargramostim in uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. Nov 2005;99(2):339-42.
39. Look KY, Sandler A, Blessing JA, Lucci JA, Rose PG, Study GOGG. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. *Gynecol Oncol*. Feb 2004;92(2):644-7.
40. Pautier P, Floquet A, Penel N, Piperno-Neumann S, Isambert N, Rey A, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). *Oncologist*. 2012;17(9):1213-20.
41. Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol*. Oct 2017;18(10):1397-1410.
42. Hensley ML, Sill MW, Scribner DR, Brown J, Debernardo RL, Hartenbach EM, et al. Sunitinib malate in the treatment of recurrent or persistent uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol*. Dec 2009;115(3):460-5.
43. Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. Sep 01 2009;27(25):4188-96.
44. D'Ambrosio L, Touati N, Blay JY, Grignani G, Flippot R, Czarnecka AM, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: A propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Cancer*. Jun 01 2020;126(11):2637-2647.

45. Tap W D WAJ, Papai Z,. ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). J Clin Onco 2019 June;37(18).

46. Stolnicu S, Balachandran K, Aleykutty MA, Loghin A, Preda O, Goez E, et al. Uterine adenosarcomas overgrown by sex-cord-like tumour: report of two cases. *J Clin Pathol*. Oct 2009;62(10):942-4.
47. Ozmen B, Uzum N, Unlu C, Ortac F, Ataoglu O. Surgical conservation of both ovaries in an adolescent with uterine müllerian adenosarcoma: a case report. *J Minim Invasive Gynecol*. 2007;14(3):375-8.
48. Guidozzi F, Smith T, Koller AB, Reinecke L. Management of uterine Müllerian adenosarcoma with extrauterine metastatic deposits. *Gynecol Oncol*. Jun 2000;77(3):464-6.
49. Leiser AL, Hamid AM, Blanchard R. Recurrence of prolactin-producing endometrial stromal sarcoma with sex-cord stromal component treated with progestin and aromatase inhibitor. *Gynecol Oncol*. Aug 2004;94(2):567-71.
50. Ushijima M, Yamakawa Y, Sakabe E, Waki H, Katou K. [A case of recurrent high-grade endometrial stromal sarcoma controlled by a combination of Ifosfamide, adriamycin, and cisplatin]. *Gan To Kagaku Ryoho*. Oct 2010;37(10):2003-5.
51. Alkasi O, Meinhold-Heerlein I, Zaki R, Fasching P, Maass N, Jonat W, et al. Long-term disease-free survival after hormonal therapy of a patient with recurrent low grade endometrial stromal sarcoma: a case report. *Arch Gynecol Obstet*. Jan 2009;279(1):57-60.
52. Cotzia P, Benayed R, Mullaney K, Oliva E, Felix A, Ferreira J, et al. Undifferentiated Uterine Sarcomas Represent Under-Recognized High-grade Endometrial Stromal Sarcomas. *Am J Surg Pathol*. May 2019;43(5):662-669.
53. Allanson ER, Cummings M, Kuchel A, Wastney T, Nicklin J. Undifferentiated uterine sarcoma: a multidisciplinary challenge. *Int J Gynecol Cancer*. Feb 2022;32(2):198-202.
54. Choi J, Manzano A, Dong W, Bellone S, Bonazzoli E, Zammataro L, et al. Integrated mutational landscape analysis of uterine leiomyosarcomas. *Proc Natl Acad Sci U S A*. Apr 13 2021;118(15)
55. Merino DM, McShane LM, Fabrizio D, Funari V, Chen SJ, White JR, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer*. Mar 2020;8(1)
56. McGrail DJ, Pilié PG, Rashid NU, Voorwerk L, Slagter M, Kok M, et al. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. *Ann Oncol*. May 2021;32(5):661-672.

Appendix A: **Federation Internationale de Gynecologie et d'Obstetrique (FIGO) Staging of Uterine Sarcoma** [3]

Leiomyosarcomas

Stage I: Tumour limited to uterus
- IA <5 cm
- IB >5 cm

Stage II: Tumour extends to the pelvis
- IIA Adnexal involvement
- IIB Tumour extends to extrauterine pelvic tissue

Stage III: Tumour invades abdominal tissues (not just protruding into the abdomen).
- IIIA One site
- IIIB More than one site
- IIIC Metastasis to pelvic and/or para-aortic lymph nodes

Stage IV:
- IVA Tumour invades bladder and/or rectum
- IVB Distant metastasis

Endometrial Stromal Sarcomas (ESS) and Adenosarcomas*

Stage I: Tumour limited to uterus
- IA Tumour limited to endometrium/endocervix with no myometrial invasion
- IB Less than or equal to half myometrial invasion
- IC More than half myometrial invasion

Stage II: Tumour extends to the pelvis
- IIA Adnexal involvement
- IIB Tumour extends to extrauterine pelvic tissue

Stage III: Tumour invades abdominal tissues (not just protruding into the abdomen).
- IIIA One site
- IIIB More than one site
- IIIC Metastasis to pelvic and/or para-aortic lymph nodes

Stage IV:
- IVA Tumour invades bladder and/or rectum
- IVB Distant metastasis

Carcinosarcomas
Carcinosarcomas should be staged as carcinomas of the endometrium.

** Note: simultaneous tumours of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumours.*

Appendix B: **WHO Classification of Tumours of Uterine Corpus[3]**

Endometrial epithelial tumours and precursors
Precursors
• Endometrial hyperplasia without atypia
• Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia
Endometrial Carcinomas
▪ Endometrioid carcinoma ▪ Serous carcinoma ▪ Clear cell carcinoma ▪ Undifferentiated carcinoma ▪ Differentiated carcinoma ▪ Mixed carcinoma ▪ Other endometrial carcinomas ▪ Carcinosarcoma
Tumor-like lesion
▪ Endometrial Polyp ▪ Endometrioid metaplasia ▪ Arias-Stella reaction
Mesenchymal Tumors
Smooth muscle tumors
▪ Leiomyoma ▪ Intravenous leiomyomatosis ▪ Smooth muscle tumor of uncertain malignant potential ▪ Metastasizing leiomyoma ▪ Leiomyosarcoma
Endometrial stromal and related tumors
▪ Endometrial stomal nodule ▪ Low-grade endometrial stromal sarcoma ▪ High-grade endometrial stromal sarcoma ▪ Undifferentiated uterine sarcoma
Miscellaneous mesenchymal tumors
▪ Uterine tumor resembling ovarian sex cord tumor ▪ Perivascular epithelioid cell tumor ▪ Inflammatory myofibroblast tumor ▪ Other mesenchymal tumors
Mixed epithelial and mesenchymal tumors
▪ Adenomyoma ▪ Atypical polypoid adenomyoma ▪ Adenosarcoma
Miscellaneous tumors
▪ Central primitive neuroectodermal tumor/CNS embryonal tumor ▪ Germ cell tumors

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Gyne Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Gynecologic Oncology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2013 and updated in 2023.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

BSO: bilateral salpingo oophorectomy, CT: computed tomography, ES: endometrial sarcoma, ESS: endometrial stromal sarcoma, GnRH: gonadotropin releasing hormone, LMS: leiomyosarcoma, USO: unilateral salpingo oophorectomy

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gyne Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Dr. Prafull Ghatage* has nothing to disclose.

Dr. Jeanelle Sabourin reportes Alberta Heath connect care super user.

Dr. Sandra Lee has nothing to disclose.

Dr. Cheng-Han Lee has nothing to disclose.

Ritu Sharma has nothing to disclose.

*** Working group lead**