UTERINE SARCOMA

Effective Date: September 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology 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.

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). [3] The most common histologies are leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), adenosarcoma, and others (rare). Carcinosarcomas (also known as MMMT, malignant mixed mullerian tumours) are now classified as high grade or poorly differentiated carcinoma of the endometrium. There has been revised endometrial stromal sarcoma terminology: endometrial stromal sarcoma now replaces the term low-grade ESS and undifferentiated endometrial sarcoma (ES) now replaces the term high-grade ESS. FIGO (Federation Internationale de Gynecologie et d'Obstetrique) staging of sarcomas has been updated in 2010. [4,5] A detailed description of this staging system can be found in the Appendix.

Uterine leiomyosarcomas are aggressive tumours with high rates of recurrence. [6] They originate from the myometrium or myometrial vessels. 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] There is a lack of symptoms with these tumours. Prognostic factors include tumour size >5 cm and a high mitotic index, although they are highly aggressive even with a mitotic count of less than 2 per mm^2. [8] 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. [6,9,10] 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. [9] Overall, the five-year survival rate, for all stages, ranges from about 30% to 50%. [3,6,10] 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 originate in the uterine stroma in adenomyosis or endometriosis. Vascular invasion is common. As stated above, they are classified as ESS and undifferentiated ES. ESS are low grade with <10 mitoses per mm^2 and a lack of atypia. Sixty percent are ER/PR positive. Thirty percent are spread beyond the uterus. Recurrence rates are 30-50% at 10 years follow up, with recurrences usually being local. Late recurrences can occur in the lungs and abdomen. Lymph node involvement is rare. Removal of the ovaries at the time of surgery is essential due to the high rate of receptor expression. [6,13] The overall 5 year survival rate of ESS is about 60%, whereas undifferentiated ES have a five-year overall survival of about 25%. Recurrences in undifferentiated ES are common in the first two years and optimal debulking including lymphadenectomy is essential in their management.

Adenosarcomas have a benign epithelial component with a malignant mesenchymal component. Metastases occur in less than 20% of cases and are usually local.

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?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

Entries to Medline and EMBASE and clinical practice guideline databases (e.g. National Guidelines Clearinghouse, CancerView, etc.) 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.

The original search returned a total of 86 studies, including clinical trials, retrospective studies, and case studies, which were included in the review. The 2013 update of the literature returned a total of 10 new studies which were considered when reviewing the recommendations.

Existing guidelines considered for this review include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2010), [14] the BC Cancer Agency (BCCA) guidelines (2000), [15] the National Cancer Institute guidelines (2008) [16] and the Tom Baker Cancer Centre guidelines (2008). [17] 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 recommendations outlined in this guideline apply to adults over the age of 18 years with uterine sarcoma, including leiomyosarcoma and endometrial stromal sarcoma. This guideline does not cover carcinosarcoma, which should be staged as carcinoma of the endometrium. For recommendations on the management of endometrial carcinosarcoma, please refer to the CancerControl Alberta (Alberta Health Services) guideline, *Endometrial Cancer*. [18]

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 include:

Stage I (tumour limited to uterus):

- 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):
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):
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):

- 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):

- 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

- There is no standard chemotherapy regimen.
- Agents that have been used include: doxorubicin, ifosamide, gemcitabine, docetaxel, trabectidin, 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).

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

Adenosarcoma options include:

- 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.

Endometrial Stromal Sarcoma (formerly low-grade ESS) options include:

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

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

Undifferentiated Endometrial Sarcoma (formerly high-grade ESS) options include:

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):
- 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, ifosamide, 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 tumors 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).

IV. Follow Up

- 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

National guidance on treatment options for uterine leiomyosarcoma includes surgery, adjuvant radiotherapy and/or chemotherapy, and hormone therapy, depending on the stage of disease. [14] 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; [14,19] however, retrospective studies and case studies on surgical treatment for leimyosarcoma support ovarian preservation in select cases of stage I disease. [16-19] Retrospective data among patients with uterine sarcoma (36% of which had leimyosarcoma) 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. [20]

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. [24-27] 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). [28] 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. The most promising results have been seen with single agent doxorubicin and ifosamide and the combination of gemcitabine and docetaxel. 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. [29] 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) [30] 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). [31] 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. [32] Combination therapy

is far more toxic than gemcitabine alone [33] and the most common toxicities associated with gemcitabine and docetaxel were thrombocytopenia (14.5-39.4%), neutropenia (17-20.8%), and anemia (24-25%). In the French trial, which stratified LMS and uterine LMS, failed to showed any PFS and OS benefit of the combination in both subgroups. [30,31] Other agents that have been used include dacarbazine, docetaxel, epirubicin, gemcitabine, liposomal doxorubicin, and paclitaxel. [14,34-41] 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. [42] Sunitinib (50 mg/d oral for four weeks, with two weeks rest) [43] and trabectedin (1.5 mg/m^2 IV every three weeks) [44] 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. At the 2013 ASCO meeting, phase II data was presented which showed that in patients with advanced uterine leiomyosarcoma (N=45), 6 cycles q 3 weeks of doxorubicin (60 mg/m^2) followed by trabactedin (1.1 mg/m^2, 3-h at day 1) and pegfilgrastim (6 mg, day 2) resulted in an overall response rate of 55% (in 33 assessable patients) and a progression-free survival rate (at 12 weeks) of 94.3% (95% CI: 86-100%). [45]

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. [46-58] 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. [46,49,53,54,57]

Most of the evidence on undifferentiated ESS is limited to retrospective studies and case studies. Treatment for undifferentiated or poorly differentiated endometrial stromal sarcoma has typically involved a hysterectomy with or without unilateral or bilateral salpingo oophorectomy. [59-65] Retrospective data has shown no recurrence or survival differences between women who have undergone oophorectomy (26-33%) and those who have had their ovaries preserved (25-42%). [20,61,66] Lymph node dissection has also been shown not to improve survival, versus hysterectomy alone. [20,21] However, optimal cytoreduction (residual ≤2 cm) may improve survival (52 months versus 2 months; P=.007) among patients with high grade ESS and extrauterine disease including stage III/IV disease. [62]

Salvage therapy for metastatic or recurrent ESS has consisted of neoadjuvant chemotherapy followed by secondary cytoreduction [65,67,68] in three cases reported in the literature. A 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. [69] Overall, however, data is limited [70-76] in this group of patients and treatment will likely require an individualized approach.

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

GLOSSARY OF ABBREVIATIONS

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

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX

Staging of uterine sarcoma is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) 2010:

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 Tumor 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.