

Clinical management for uterine sarcomas

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Malignant pure mesenchymal uterine tumours encompass endometrial stromal sarcoma (ESS), uterine leiomyosarcoma (ULMS) and undifferentiated sarcomas. ESS refers to low-grade ESS and is distinctive from undifferentiated uterine sarcomas. For both entities, there are no pathognomonic features on any imaging technique. In early stage disease and both for ESS and ULMS, hysterectomy with bilateral salpingo-oophorectomy but without lymphadenectomy is the standard surgical treatment. The clinical benefit of chemotherapy is limited and this underscores the importance of targeted therapy. ESS and ULMS are driven by different pathways resulting in a different clinical behaviour. ESS is typically a hormone sensitive tumour with an indolent growth. ULMS is notorious for its aggressive growth and poor outcome. Individualisation of treatment is mandatory since randomised trials are nearly non-existing. The progesterone and oestrogen receptor are clinically important targets for most primarily advanced or recurrent ESS and a subset of recurrent ULMS.

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Introduction

Mesenchymal tumours, other than uterine fibroids, are uncommon since sarcomas of the uterus comprise only 3% of uterine malignancies.¹ Uterine sarcomas encompass leiomyosarcoma (ULMS), carcinosarcoma and endometrial stromal sarcoma (ESS) according to traditional classification systems. The focus in this contribution will be on the most common pure mesenchymal tumours: ULMS and ESS. ESS was formerly classified as low-grade ESS. Tumours that used to be termed high-grade ESS are currently called poorly differentiated or undifferentiated uterine sarcoma. Although there is no universal staging system for uterine sarcomas, the FIGO surgical staging system for endometrial

cancer is used.

No imaging modality can offer a reliable preoperative diagnosis. Computed tomography (CT) is unable to differentiate between different types of uterine pathology. Ultrasonography and magnetic resonance imaging (MRI) offer a much more detailed analysis of pathology. However, while several features at ultrasonography and MRI may raise suspicion of a uterine sarcoma, there are no pathognomonic features on any imaging technique. Hysterectomy is advocated when imaging modalities cannot exclude a malignancy.

The purpose of this manuscript is to present the current standard treatment of ULMS and ESS. Only few series are reported and results from

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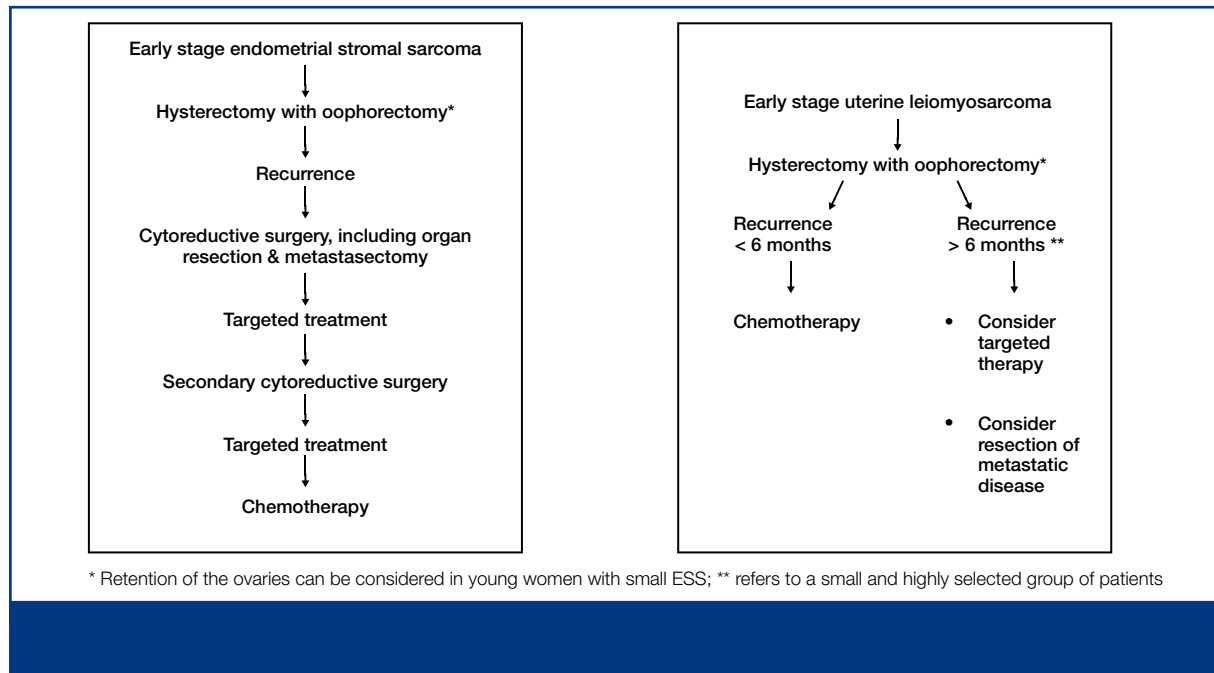


Figure 1. Treatment strategy for early stage endometrial stromal sarcoma and uterine leiomyosarcoma.

level 1 evidence studies are non-existing. Knowledge of tumour biology forms the basis to delineate targeted treatment modalities. This contribution is a summary of a recently published review.²

Uterine leiomyosarcoma (ULMS)

Most ULMSs are sufficiently differentiated, at least focally, to permit recognition of their smooth muscle nature. They are obviously malignant on microscopic examination. The diagnostic strategy should include a search for the mitotic index, presence of atypia and coagulative tumour cell necrosis.³ ULMSs needs to be distinguished from mitotically active or atypical leiomyomas and uterine smooth muscle neoplasms with low malignant potential. Coagulative tumour cell necrosis is decisive and should be distinguished from hyaline and ulcerative necrosis.³

Current treatment of ULMS

Adnexal or lymphatic spread is only present in approximately 3% of early stage ULMS.^{4,5} Lymph node involvement is more frequent in advanced stage disease. In a series of 1,396 patients, adnexectomy and lymphadenectomy failed to be independent prognostic factors on survival.⁶ The ovaries are however frequently removed because of the age,

small chance of ovarian metastasis and the potential for a low-grade hormone sensitive ULMS. A simple hysterectomy with oophorectomy but without lymphadenectomy is therefore standard treatment for early stage ULMS (Figure 1). In premenopausal women, a simple hysterectomy may be considered.⁷ There is no proven benefit for any adjuvant treatment. Only two randomized trials explored the benefit of adjuvant treatment.^{8,9} The value of adjuvant doxorubicin was already investigated almost 20 years ago. Randomising 156 women with resected stage I-II sarcoma including various histologies (ULMS, carcinosarcoma and ESS) and non-random use of adjuvant pelvic radiation, survival rates were comparable for doxorubicin or control group.⁸ This single randomized trial on adjuvant chemotherapy contained only 48 ULMS. Recurrences occurred in 11/25 (44%) and 14/23 (61%) cases in the doxorubicin and control arm, respectively. Although this study is considered negative, the results are in fact inconclusive. Reed *et al.* randomized 103 ULMS to either observation or pelvic radiation, 51 Gy in 28 fractions over 5 weeks. There was no benefit for patients with ULMS receiving adjuvant radiotherapy.⁹ In advanced stage or recurrent disease treatment is palliative only.⁷ Quality of life should be considered

Table 1. Single agent and combination chemotherapy activity in uterine leiomyosarcomas as reported in the literature.²

Series	Drug	Schedule	Response	RR n (%)
Omura (1983)	Doxorubicin	60 mg/m ² , 3w		7/28 (25)
Sutton (1992)	Ifosfamide	1.5 mg/m ² , 5d	6 PR	6/35 (17)
Sutton (1999)	Paclitaxel	175 mg/m ² , 3w	3 CR	3/33 (9)
Gallup (2003)	Paclitaxel	175 mg/m ² , 3w	4 CR	4/48 (8)
Look (2004)	Gemcitabine	1000 mg/m ² , 1-8-15	1 CR, 8 PR	9/42 (20)
Anderson (2005)	Temozolomide	50-75 mg/m ² , 6-8w	1CR	1/13 (8)
Sutton (2005)	Liposomal doxorubicin	50 mg/m ² , 4w	1 CR, 4 PR	5/35 (16)
Amant (2009)	ET-743	1.5 mg/m ² , 3w	5 PR	5/11 (45)
Hensley (2002) 'single institution'	Gemcitabine Docetaxel	900 mg/m ² , d1&8 100 mg/m ² , d8	3 CR, 15 PR	18/34 (53)
Hensley (2008) 'collaborative study'	Gemcitabine Docetaxel	900 mg/m ² , d1&8 100 mg/m ² , d8	3 CR, 10 PR	13/48 (27)

PR: partial remission; CR: complete remission; N: number of patients

at every stage. ULMS with transperitoneal spread is more difficult to resect when compared to ovarian cancer. This is mainly explained by a more infiltrative growth. As a result, cytoreductive surgery without residual tumour is less likely to be achieved. Systemic treatment is the best option when the aim is to prolong life. Single agent treatment has the least toxicity and is favoured. Response rates of single agent and combination chemotherapy are summarised in *Table 1*. Combinations that are not mentioned are too toxic or showed less activity. Doxorubicin still shows the best balance between activity and toxicity and is a first line option with a response rate of 25%. Gemcitabine is active in combination with docetaxel¹⁰ but has also activity as a single agent drug.¹¹ A prospective randomized phase II study has shown that gemcitabine-docetaxel is superior to gemcitabine alone for soft tissue sarcoma in terms of response rate, progression-free survival and overall survival.¹² However, response rates were low (16% and 8%) and more toxicity was noted in the combination arm. Most patients received prior cytotoxic therapy in this series. In a previously unexposed series of ULMS, post resection gemcitabine-docetaxel yielded a 2-year progression free survival of 39 months.¹³ This combination deserves to be further investigated in ULMS. Trabectedin (formerly known as ecteinascidin-743 or ET-743) is a novel tetrahydroisoquinoline isolated from a marine tunicate is a promising drug but the reported activity refers to a pooled analysis with low numbers.

ULMS showing a disease-free interval exceeding 6 months or more deserve a different approach.¹⁴ Disease free interval is an indicator of tumour biology and these ULMS might have a less aggressive growth pattern. This subset of ULMS is more likely to express hormonal receptors that allow targeted treatment (see below). Hormonal treatment or surgery may first be considered instead of chemotherapy. Resection of a solitary metastasis may improve the outcome.¹⁴ Since most ULMS portend an aggressive growth, resection of isolated metastases will benefit only a highly selected group.

Targeted treatment in ULMS

Targets to the ER and PR successfully have been used in the subset of ULMS with indolent growth. Case reports show responses to medroxyprogesteroneacetate, aromatase inhibitor or mifepristone (an antiprogesterone also designated RU-486) (*Table 2*). Aromatase inhibitors block the conversion of androgens to oestrogens in peripheral fat tissue. The antiprogesterone activity of mifepristone (RU-486) results from a competitive interaction with progesterone at the PR. Ideally, the receptor status is determined in the recurrent tumour. The results from a running clinical phase II trial (NCT00414076), comparing the use of letrozole vs. expectative management in ULMS are eagerly awaited. The efficacy of mifepristone (RU-486) and ICI 182,780 (a pure oestrogen antagonist

also called fulvestrant) deserves further study. Clinically applicable approaches to counteract the effects of PTEN loss in ULMS include PI3K, AKT and mTOR inhibitors.

Endometrial stromal sarcoma (ESS)

Endometrial stromal neoplasms are exclusively composed of cells resembling the endometrial stroma in its proliferative phase. The stromal nodule is the benign variant; it has well circumscribed borders and is rare. Endometrial stromal sarcoma (ESS) represents the entity with infiltrating borders and behaves like a low-grade sarcoma, with the potential for recurrence and metastasis.¹⁵ Microscopic findings that unequivocally correspond to ESS include a uniform population of endometrial stromal-type cells invading the myometrium and myometrial vessels. Historically, ESSs were subdivided into low-grade and high-grade tumours. However, high-grade tumours lack the typical growth pattern and vascularity of low-grade ESS and show destructive myometrial invasion rather than the lymphatic permeation of a low-grade ESS. Moreover, they demonstrate marked cellular pleomorphism and brisk mitotic activity. As a result, ESS is now considered best restricted to malignancies that were formally referred to as low-grade ESS. In this chapter we only discuss the ESS according to the new definition (i.e. former low-grade ESS).

Endometrial sarcomas without recognisable evidence of a definite endometrial stromal phenotype, designated as poorly differentiated endometrial sarcomas, are almost invariably high grade,¹⁶ and termed poorly differentiated or undifferentiated uterine sarcoma. These high grade tumours show similarity with ULMS when the clinical presentation, imaging studies, treatment modalities and prognosis are considered.

Current treatment of ESS

Preoperative imaging is mandatory since ESS tends to spread to the lungs and peritoneum.¹⁵ Most ESSs (65-86%) will present with disease limited to the uterus (stage I-II disease).^{15,17} Hysterectomy is the cornerstone of the treatment in early stage disease (Figure 1). The peritoneal cavity should be explored simultaneously.

Lymphatic involvement by ESS is well established, as evidenced by a prior pathologic designation of endolymphatic stromal myosis. Although nodal involvement increases the stage, lymphadenectomy in all ESS is unlikely to improve the survival.¹⁷⁻¹⁹ A policy of leaving nodes behind in a small series did not result in isolated retroperitoneal recurrences that might hamper the prognosis.¹⁸ In a large population-based analysis including 831 women with all grades ESS, nodal involvement of grade 1 and 2 ESS (probably similar to low-grade ESS) was 6.0% and 8.9%, respectively.¹⁹ However, lymphadenectomy had no demonstrable effect on survival.¹⁹ In another series including 384 ESS, nodal involvement was detected in 7/100 (7%) women undergoing lymphadenectomy.¹⁹ However, also in this large series, no survival benefit was noted for women undergoing lymphadenectomy.¹⁹ This observation may be explained by the high (86 vs. 95% for node positive vs. negative cases in the Shah series, respectively) 5-year survival of node positive ESS.¹⁹ The smaller than expected impact of nodal metastasis is also explained by the tendency of ESS to recur transperitoneally or in the lungs.¹⁵ It appears from these data that systematic lymphadenectomy for ESS is not indicated. When lymph nodes are pathologically enlarged, lymphadenectomy is considered part of a cytoreductive procedure. The controversy on this topic is at least partially fed by the inclusion of both low- and high grade sarcomas in the studies.¹⁷ *Chan et al.* observe a poorer survival in node positive cases. However, the high grade sarcomas count in large part for this outcome. Also, incidences of nodal involvement need to be interpreted with the status of other extra-uterine locations. Lymph node involvement in tumours with other gross extrauterine involvement is unlikely to be prognostic.

Standard treatment for ESS is hysterectomy with bilateral salpingo-oophorectomy. Although surgical castration is a logic intervention for a hormone sensitive disease, the clinical benefit remains unproven. Therefore, in young women this policy deserves a critical analysis. It appears from small^{18,20-22} and large^{17,19} non-randomized series that leaving the ovaries in situ does not worsen the outcome. Management of menopausal symptoms may be challenging in young women. Oestrogen replacement therapy in women with a history of ESS was associated with a poor outcome.²⁰ These data were however based on 5 women only and need

Table 2. Successful targeted treatment in uterine leiomyosarcoma.²

Author	N	Target	Hormone	Clinical response	Response duration
Uchida (1996)	1	Progesterone receptor	medroxyprogesteroneacetate	PR	3 ¾ years
Hardman (2007)	1	Estrogen receptor	anastrazole	PR	1 year
Koivisto-Korander (2007)	1/3\$	Progesterone receptor	mifepristone	PR	3 years
O'Ceirbhaill (2009)	34	Oestrogen receptor	Aromatase inhibitor (74% letrozole)	9% PR	5 months

N: number of patients; PR: partial remission; \$: 1 out of 3 patients

to be confirmed. In young women we advocate a thorough discussion on the risk and benefit of surgical castration. Individualisation of the surgical approach in this group of patients is important. After providing this information, we would accept to treat small ESS (< 2-3 cm) in a woman younger than 35 years of age without surgical castration.

Since ESS express both the ER and PR, adjuvant targeted hormonal treatment can be considered to reduce recurrence rates.^{18,20} Progestins or aromatase inhibitors may be considered. There are no prospective studies investigating adjuvant treatment for ESS. Even retrospective data on clinical benefit are limited. Apart from this, there are no valid data on the duration of treatment and it is unknown whether the menopausal status (e.g. after oophorectomy) affects any treatment induced effect. The benefit of adjuvant medroxyprogesterone acetate 250mg or megestrol acetate 160mg on a daily basis during 2 years has been suggested in two small studies.^{18,20} Side effects of progestins include thrombosis and weight gain (higher circulating oestrogen levels), whereas aromatase inhibitors are associated with osteoporosis and muscle/joint complaints. The history and condition of the patient may help deciding on the treatment of choice, if necessary.

For ESS with primarily transperitoneal spread, cytoreductive surgery is advocated because of the low grade nature of the disease and the efficacy of hormone receptor targeted treatment.²³ Organ resection (splenectomy, partial bowel resection) can be considered, especially if this contributes to the absence of residual tumour.²³ The decision to resect distant metastasis (frequently lung parenchyma) should be taken on an individual

basis. Adjuvant hormonal treatment is advocated until progression.

ESS has an indolent growth with a tendency for late recurrence. Recurrences are common, even in early stage disease. Relapse occurs in 36-56% of early stage disease.^{15,24} The median time to recurrence was 65 and 9 months for stages 1 and 3-4, respectively.¹⁵ The indolent growth makes aggressive and repeated surgery valuable. Secondary and tertiary cytoreductive procedures with or without resection of distant metastases (e.g. lung parenchyma, cardiac) should be considered.^{23,25} Intervals between the surgeries can be extended by targeting the hormone receptors (Figure 1).²⁴

When the hormonal armamentarium is exhausted, in the absence of hormonal receptors or when progression into a high grade malignancy occurs,²⁵ ifosfamide and doxorubicin appear to be active cytotoxic drugs.²⁶

Targeted treatment for ESS

The PR is the most important target for hormonal treatment. Experience is mainly available with progestins (medroxyprogesterone acetate, megestrolacetate, 17-alpha hydroxyprogesterone caproate). At least 25 cases have been reported in 16 studies, with a response rate of 76% (19/25). Aromatase inhibitors reduce oestrogen levels by inhibiting oestrogen synthesis in both tumour tissue and peripheral sites and as a consequence they inhibit the proliferation of the tumour. Letrozole was most frequently used and response rate was induced in 8/9 (88%) cases. Injection of GnRH analogues resulted in partial remission in a single case. The efficacy of mifepristone (RU-486) and ICI 182,780 (fulvestrant) deserves further study.

Key messages for clinical practice

1. Uterine sarcomas are uncommon and randomized studies are hardly available. The evidence is mostly based on retrospective (small) series.
2. Hysterectomy with bilateral salpingo-oophorectomy is the surgical treatment for early stage uterine leiomyosarcoma. For advanced stage and recurrent disease, chemotherapy may prolong life. A subset has an indolent growth rendering surgery and hormone therapy beneficial.
3. Hysterectomy with bilateral salpingo-oophorectomy is the surgical treatment for early stage endometrial stromal sarcoma. For young women, surgical castration can be avoided. Given the low grade tumor, cytoreductive surgery followed by hormonal treatment is advised for advanced stage and recurrent disease.

Other uterine sarcomas

Undifferentiated sarcoma

Undifferentiated uterine sarcoma is a poorly defined group. They do not show evidence of gene-specific fusions, suggesting that these tumours arise by a different pathogenetic mechanism than ESS. Immunohistochemical data are also sparse, including only a few cases per article published.

Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract (GI). Rare cases are identified outside the GI tract and are collectively known as extragastrointestinal stromal tumours (EGISTs). EGISTs that present as gynaecologic masses are rare but may be more common than is currently recognized.²⁷⁻²⁹

Primary activating mutations in the *KIT* or *PDGFRA* genes, which result in constitutive activation of receptor tyrosine kinase activity, are early oncogenic events in majority of adult GISTs. However, a subset of tumors (10-15%) show a wild-type *KIT* and *PDGFRA* genotype. Immunohistochemical staining for *KIT* (CD117) has become integral to the diagnosis of GISTs, nearly 95% of which is positive for this marker. Establishing the diagnosis of *KIT*-negative GIST remains a challenge and is best handled by a reference pathologist with expertise in this area. The use of mutational analysis of the kinase genes *KIT* and *PDGFRA* is the standard of care in such cases.

Imatinib mesylate provides targeted therapy for GIST by inhibiting the *KIT* and *PDGFRA* tyrosine kinases. Clinical benefit is achieved in approximately 85% of patients with unresectable or metastatic disease, with a median progression-free survival of 20 to 24 months. Importantly, the tumour *KIT*/*PDGFRA* kinase genotype has *predictive* significance with regard to the response to imatinib therapy; the presence of a *KIT* juxtamembrane mutation being the single best predictor of response to imatinib. Therefore, mutational analysis before imatinib treatment for unresectable or metastatic disease is strongly recommended.

Conclusion

Uterine sarcomas are uncommon and the diagnosis is preoperatively frequently unknown. As a result, centralisation, large series and randomised trials are problematic. Hysterectomy is the cornerstone of the treatment for early stage ULMS and ESS. There is no proven benefit from any adjuvant treatment (radiotherapy, chemotherapy, hormonal targeted) for both entities. Hormone receptors are the most important targets for primarily advanced or recurrent ESS, as for a subset of recurrent ULMS. Progestins and aromatase inhibitors show the highest clinical activity. The efficacy of new targeted drugs for uterine sarcomas is still explored. Centralisation and intergroup studies are the only appropriate answer to the current lack of evidence.

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