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Review Article

# Uterine sarcoma Part I—Uterine leiomyosarcoma: The Topic Advisory Group systematic review

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ABSTRACT

Uterine sarcomas account for 3–7% of all uterine cancers. Because of their rarity, unknown etiology, and highly divergent genetic aberration, there is a lack of consensus on risk factors for occurrence and predictive poor outcomes as well as optimal therapeutic choices. Tumor types according to the World Health Organization classification include leiomyosarcoma, endometrial stroma sarcoma, and undifferentiated sarcoma. Staging is done using the 2014 Federation International Gynecology and Obstetrics and 2010 American Joint Committee on Cancer tumor, lymph node, and metastases systems. Tumor grade can be classified based on the French Federation of Cancer Centers Sarcoma Group system or the Broder's system that incorporates tumor differentiation, mitotic count, and tumor necrosis. This review is a series

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uterine sarcoma
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of articles discussing uterine sarcoma, and this is Part I, which focuses on one of the subtypes of uterine sarcomas—uterine leiomyosarcoma. The clinical characteristics, diagnosis, outcome, and recent advances are summarized in this article.



## Overview of uterine sarcomas

Uterine sarcomas are rare tumors, accounting for 3–7% of uterine malignancies and less than 1% of all malignancies from female genital organs [1–5]. Because of their rarity, unknown etiology, and highly divergent genetic aberration, there is a lack of consensus on risk factors for their occurrence and predictive poor outcomes as well as optimal therapeutic choices. The diversity of uterine sarcoma can be classified according to the World Health Organization (WHO) classification, which includes the most common uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine sarcoma [3,4]. Based on the WHO classification of soft-tissue sarcomas [4], other rare malignant mesenchymal tumors include adenosarcoma, rhabdomyosarcoma, perivascular epithelioid cell tumor, malignant type (PEComa), angiosarcoma, neurogenic sarcoma, osteosarcoma, chondrosarcoma, liposarcoma, primitive neuroectodermal tumor, myxofibrosarcoma, alveolar soft-tissue sarcoma, and epithelioid sarcoma.

Carcinosarcomas [malignant mixed mesodermal tumors or malignant mixed müllerian tumors (MMMTs)] are no longer considered as sarcoma due to their different spreading pattern. Carcinosarcomas spread as a dedifferentiated or metaplastic form of endometrial cancer (EC) [6,7], in which the mesenchymal part retains epithelial features (i.e., "conversion theory," which is supported by various molecular studies reporting similar chromosomal aberrations, cytogenetic aspects, concordant loss of heterozygosity, identical *p*53 and *K-ras* mutations, and matching X-inactivation patterns in both histological components of the majority of MMMT cases) [8]. However, because MMMT behaves more aggressively than the usual type of EC, even for Type II EC [9,10], it is still included in most retrospective studies of uterine sarcomas, and in the separate section of "mixed epithelial and mesenchymal tumors" of the 2014 WHO classification [4,11]. Besides MMMT, there are also some arguments for including ESSs because of the significant difference in their tumor behaviors. ESS is divided into (1) ESS, low-grade; (2) ESS, high grade; and (3) undifferentiated uterine sarcoma (UUS) [1,11].

Two staging systems are used for uterine sarcomas, including the 2014 Federation International Gynecology and Obstetrics (FIGO) and 2010 American Joint Committee on Cancer tumor, lymph node, and metastases systems (Table 1). The FIGO staging is more frequently applied in clinical practice. Tumor grade can be classified based on the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system or the Broder's system that incorporates tumor differentiation, mitotic count, and tumor necrosis (Grade 1, mild cytologic atypia; Grade 2, more nuclear irregularity; Grade 3, between Grades 2 and 4; and Grade 4, presence of bizarre cells) [11]. Evaluation of cytologic atypia is often subjective, but Oliva et al [11] provided the key components, which can help in such investigations (Table 2). Because MMMT might be better classified as mixed epithelial and mesenchymal tumors, we excluded the category of MMMT, and only focused on pure uterine sarcoma, mainly on uLMS and ESS. The series of documents attempted to provide updated information for this unusual uterine pathology, and we present by the order of clinical characteristics, diagnosis, pathology, treatment, and future perspectives.

## Clinical characteristics and diagnosis

The median onset of uterine sarcomas is 50–70 years depending on the histological subtypes, but most women are of postmenopausal age. Identified risk factors, although uncertain, include previous pelvic irradiation and prior treatment with tamoxifen [12]. Clinical characteristics of uterine sarcoma vary greatly, and are also different by the histological subtypes [13]. Most symptoms and/or signs are nonspecific, including abdominal pain, enlarged abdominal circumference, enlarged uterine size, abnormal vaginal bleeding, and rapid uterine growth in perimenopausal or postmenopausal women with low estrogen levels. However, one study argued the relationship between rapid uterine growth and normal control, because there was no statistically significant difference in the diagnosed sarcoma between rapid uterine growth and normal control (0.27% vs. 0.23%) [14]. In addition, the absence of specific symptoms or signs made the diagnosis of many patients either incidental (when examining the resected specimen after myomectomy or hysterectomy) or by the appearance of accompanied

**Table 1**
2014 FIGO and 2010 American Joint Committee on Cancer TNM system for staging uterine sarcomas (leiomyosarcoma and endometrial stromal sarcoma).

| FIGO | TNM | Definition |
|---|---|---|
| I[a] | | Tumor limited to uterus |
| IA | T1aN0M0 | <5 cm |
| IB | T1bN0M0 | >5 cm |
| II | | Tumor extends beyond the uterus but limited within the pelvic cavity |
| IIA | T2aN0M0 | Adnexal involvement |
| IIB | T2bN0M0 | Involvement of other pelvic tissues |
| III | | Tumor invades abdominal tissues (not just protruding into the abdominal cavity) |
| IIIA | T3aN0M0 | 1 site |
| IIIB | T3bN0M0 | >1 site |
| IIIC | T3bN1M0 | Pelvic and/or para-aortic lymph node metastases |
| IV | | |
| IVA | T4NxM0 | Tumor invades bladder and/or rectum |
| IVB | T4NxM1 | Distant metastasis |

FIGO = Federation International Gynecology and Obstetrics; TNM = tumor, lymph node, and metastases staging system.
[a] I is not applied for adenosarcoma ($x = 0$ or 1).

**Table 2**
Key factors for evaluation of cytologic atypia.

*The following three key factors should be kept in mind:*
1. Evaluate atypia at medium power magnification (10×)
2. Compare cytologic features of tumor with surrounding myometrium if possible
3. Look for background nuclear atypia not atypia of bizarre type that often is confined to groups of cells in an otherwise banal-appearing leiomyoma

*Cytologic atypia includes more than one of the following features:*
1. High nuclear size (high nuclear to cytoplasmic ratio)
2. Irregular nuclear membranes
3. Nuclear pleomorphism
4. Hyperchromatism
5. Prominent nucleoli or more than one nucleoli

symptoms or signs after the disease has already disseminated to an advanced stage [15–18].

## Part I: Uterine leiomyosarcoma

### *Diagnosis*

Once tumors are suspected, the two key tools for diagnosis are radiology and histopathology. Initial assessment of uterine masses is likely to be clinical and using ultrasound and possibly magnetic resonance imaging (MRI). Ultrasound, especially transvaginal ultrasound and colored Doppler ultrasound, is always considered as the first-line assessment because of its cost effectiveness and reliability [19]. One study showed that higher sarcoma index, based on three independent risk factors—increased neutrophil-to-lymphocyte ratio (>2.1), large tumor size (>8.0 cm), and lower body mass index (body mass index ≤20)—was associated with an increased risk of uterine sarcoma (0, 13.6%; 1, 21.7%; 2, 62.5%; and 3, 100%) [20]. However, because the study included only a limited number of study population and had a retrospective nature, its reproducibility is highly questioned. The Morphological Uterus Sonographic Assessment group provided the consensus statement about the terms and definitions to aim in order to facilitate consistent reporting of myometrial lesions (a structured report) when using ultrasonography in both daily clinical practice and for research purpose (describing the sonographic appearance of the myometrium and myometrial lesions and harmonizing nomenclature for future research) [21]. However, this consensus also found that although uLMS often presents as purely myometrial lesions and is typically a single, large tumor, its ultrasound features might not be easily distinguished from those of ordinary myomas or it may appear as an irregularly vascularized mass, with a regular or irregular outline, often with irregular anechoic areas due to necrosis [21], suggesting that at present, it is not possible to accurately discriminate between benign and malignant mesenchymal tumors based on any ultrasound parameters [22].

### *Magnetic resonance imaging*

MRI is reported to have a better resolution to distinguish the components of soft tissues. Therefore, MRI might be an appropriate tool for the diagnosis of uLMS. One study from Taiwan showed that contrast-enhanced MRI (CE-MRI) yielded a significantly superior diagnostic accuracy and a significantly higher specificity than diffusion-weighted MRI (DW-MRI). Besides, CE-MRI also had a comparably high sensitivity as DW-MRI in the differentiation between uLMS, smooth muscle tumors of uncertain malignant potential, and uterine fibroids, suggesting that CE-MRI can provide accurate information and is preferable to DW-MRI; however, a combination of DW-MRI and apparent diffusion coefficient value of less than $1.08 \times 10^{-3}$ $mm^2/s$ can achieve a diagnostic accuracy comparable with CE-MRI [23]. Although another early report has agreed on the aforementioned findings, they found that apparent diffusion coefficient values for cellular leiomyomas overlapped [24]. Therefore, Arleo et al [25] commented that there are no definitive imaging findings that reliably differentiate ordinary leiomyomas from leiomyoma variants (of course, LMS is included), although certain MRI features indicate the different types of myoma degeneration [25]. Finally, the use of positron emission tomography/computed tomography (PET/CT) to differentiate between ordinary leiomyomas, leiomyoma variants, and LMS remains limited [26,27], because ordinary leiomyomas can uptake $^{18}$F-fluorodeoxyglucose in PET/CT [27,28].

### *Hysteroscopy and dilatation and curettage*

With regard to uterine carcinoma, hysteroscopy, curettage, and/or sampling do not always provide useful information about the disease [4]. Findings in patients with uterine carcinoma may often be false negative, which results in uncertain diagnosis even when these patients have abnormal uterine bleeding or postmenopausal bleeding requiring histological diagnosis [29]. For those symptomatic women, especially after menopause, the polyp, adenomyosis, leiomyomas, malignancy, hyperplasia–coagulopathy, ovulation dysfunction, endometrial disorders, iatrogenic causes and not-yet-classified entities (PALM-COEIN) system should be applied to minimize the risk of missing diagnosis [29].

### *Pathology*

Among mesenchymal tumors of the uterus, smooth muscle neoplasms are most common; however, they are a common source of diagnostic problems, because leiomyoma variants display a wide spectrum of gross and morphologic appearances often causing a concern for malignancy [19]. In addition, criteria for diagnosis of malignant smooth muscle tumors are significantly different in soft tissues from those in the uterus [30]. The main reason is that hormonal milieu might influence the morphology of the uterus. For example, progestins are associated with increased mitotic activity, infarction, and other morphologic changes, resulting in the incorrect diagnosis [30].

On sectioning of uLMS, a fleshy, variegated cut surface with common hemorrhage and/or necrosis can be noted. By contrast, if a smooth muscle tumor grossly has the typical white, firm, and whorl cut surface, it is often benign [30]. With regard to microscopic features, uLMS usually displays marked nuclear atypia, high mitotic rate, and tumor cell necrosis. Mitotic index is an important factor in establishing the diagnosis of uLMS; however, cutoff values of 10 mitoses/10 high-power fields, ≥4 mitoses/10 high-power fields, and ≥2 mitoses/10 high-power fields are used for spindle, epithelioid, and myxoid uLMS, respectively [11]. Parra-Herran and colleagues [31] performed a clinicopathologic analysis of 30 cases of myxoid uLMS, and concluded that myxoid uLMS is an aggressive neoplasm characterized by infiltrative tumor borders (96%) and variability of other features [mitotic count (≥2 mitoses/10 high-power fields), atypia (2+/3+ nuclear atypia means two times the size and three times the size of the nuclei of adjuvant nonneoplastic myometrium), and necrosis].

The Broder's system is one of the frequently used grading systems applied to uLMS, and it divides uLMS into the following four categories: Grade 1, mild cytologic atypia; Grade 2, more nuclear irregularity; Grade 3, between Grades 2 and 4; and Grade 4, presence of bizarre cells [30]. The FNCLCC system divides soft-tissue sarcomas into three based on tumor cell necrosis, mitoses, and degree of differentiation [4].

Evaluation of necrosis of smooth muscle tumors indicated that three types of necrosis could be encountered: (1) ulceration with underlying necrosis if submucosal; (2) infarct-type necrosis in benign and malignant neoplasms; and (3) tumor cell necrosis, which is specific for uLMS and defined by an abrupt transition from necrotic to nonnecrotic areas without interposed granulation tissue [30]. The infarct-type necrosis should be evaluated in conjunction with nuclear atypia and mitoses, because of its overlapping appearance in both benign and malignant neoplasms [30]. It should be emphasized that criteria for malignancy are hard to define with certainty in epithelioid and myxoid smooth muscle tumors; additionally, *p16*, *p53*, *Ki-67*, and other cell-cycle regulatory markers are often not helpful in differentiating between benign and malignant smooth muscle tumors, as overlap in their expression is common

[30]. Finally, in terms of pathological view, patients with adverse outcome have tumors with two or more of the following features: tumor size of 5 cm or more, infiltration, high-grade cytologic features, mitotic rate of 1/50 or more high-power fields, necrosis, or lymphovascular invasion [30].

### *Treatment*

The gold standard of management for uLMS is surgery, and patients with suspected or confirmed uLMS should have their uterus removed *en bloc*, with maximal effort to avoid intraoperative rupture, morcellation, or spillage of tumor into the peritoneal cavity [32]. The indication for adnexa is optional, depending on the patient's menopausal status, because the ovaries can be preserved in young women with tumors limited to the uterus, similar to the management of early stage EC [9]. Nevertheless, most diagnoses of uLMS are made *a posteriori* after surgery for supposed benign uterine pathology, and procedures resulting in potential tumor spillage (e.g., morcellation in endobags) might be associated with a high risk of worsening the prognosis if uLMS is the postoperative pathological diagnosis [33]. The incidence of retroperitoneal lymph node metastases is low for uLMS; therefore, it is not recommended to use pelvic and para-aortic lymph node dissection in routine practice, even for patients who had been found to have lymph node involvement, because hematogenous and widespread dissemination of tumor is usually already present. However, lymphadenectomy can be performed as part of a cytoreductive effort, because surgical tumor cytoreduction should be attempted in symptomatic patients with extensive advanced tumors [4]. Cytoreduction should aim to achieve macroscopically complete resection in one specimen *bloc* and minimize microscopically positive margins [33]. This is best achieved by resecting the tumor *en bloc* with adherent structures, even if not overtly infiltrated [33], because patients with no residual disease after surgical resection have an improved survival rate compared with those who undergo a suboptimal surgical resection [33]. Pulmonary metastasectomy, preferring wedge resection, showed a relatively promising result with 5- and 10-year survival rates of 46.8% and 34.3%, respectively, although the overall 3-year disease-free survival rate was only 27.8% [34], which is very similar to the management of pulmonary metastases from ECs [35].

## Adjuvant radiotherapy or systemic therapy for uterine-confined diseases and completely resected advanced-stage diseases

### *Radiotherapy*

The role of adjuvant radiation therapy (RT) for patients with uLMS is highly controversial and it is often not generally indicated after complete resection of Stage I/II uLMS because the European Organization for Research and Treatment of Cancer trial 55,874 (a randomized study, level of evidence II) failed to show any benefit of postoperative adjuvant RT (50.4 Gy) to treat Stage I and Stage II uLMS [35]. Postoperative RT did not improve local (20% with RT vs. 24% without RT) or distant progression rates and did not have any impact on survival [36]. The aforementioned concept is also supported by results from the Surveillance, Epidemiology, and End Results database [37]. Among 1088 women with uLMS (22% of patients with adjuvant RT and 78% without), adjuvant RT had no effect on survival for Stage I/II (early stage), with a hazard ratio (HR) of 1.1 and 95% confidence interval (CI) of 0.9–1.4 [37]. However, one retrospective study from the United States showed the 5-year locoregional failure-free survival rate to be 87% for 2206 women with nonmetastatic uterine sarcoma, including uLMS, suggesting that adjuvant RT is associated with improved outcome compared with surgery alone (HR = 0.4, $p < 0.001$) [38].

Recent retrospective studies from Asia showed the relatively conflicted data. One study from China [39] showed that patients with uLMS undergoing postoperative adjuvant RT might have a better 5-year locoregional failure-free survival rate and a 5-year overall survival (OS) rate than those who did not receive postoperative adjuvant RT (78.7% vs. 44.0%, $p = 0.037$; 71.8% vs. 40.2%, $p = 0.018$, respectively), but another study from South Korea [40] showed that postoperative adjuvant RT might not reduce pelvic failure in patients with noncarcinosarcoma type of the uterus (12.5% vs. 9.9%, $p = 0.886$). Because of conflicted data from the available studies, the Gynecologic Cancer InterGroup (GCIG) consensus commented that patients with uLMS after complete resection of uterus-limited diseases might not have survival benefits when they were managed by adjuvant RT [41].

### *Chemotherapy*

Similar to adjuvant RT, the benefits of CT for patients who had complete resection for uterus-limited disease are also controversial [41]. The first-line reasonable regimens include doxorubicin (19% of response rate), doxorubicin plus ifosfamide (17% of response rate for ifosfamide alone, and 30% of response rate for combination), gemcitabine (20% of response rate), and gemcitabine plus docetaxel (36% of response rate), and the second-line therapy includes pazopanib, trabectedin, dacarbazine, or temozolomide or fixed dose-rate gemcitabine plus docetaxel after doxorubicin-treated failure (27% of response rate) [41,42].

Roque and colleagues [43] evaluated 128 women with uLMS and the data showed that among 128 women, 56 (44%) with adjuvant CT, 41 (32%) with adjuvant RT, and 31 (24%) with observation, there was no difference in progression-free survival (PFS) or OS between the gemcitabine–docetaxel and other treatment groups, although the limitations of their study were that 80% of patients belonging to early stage disease were treated with RT and the mitotic count was uniformly 10 or greater in the gemcitabine–docetaxel group, suggesting the need for novel therapies to treat uLMS. A multicentric retrospective study was conducted to evaluate the role of adjuvant treatment for 140 women with Stage I/II uLMS after surgery [62 patients with observation, 14 patients with RT, 52 patients with CT (54 patients based on doxorubicin and ifosfamide combination), and 12 patients with concurrent chemoradiotherapy], and the results showed that adjuvant CT was not associated with a significant survival benefit (68.7% in the CT + RT group vs. 65.6% in the observation group, $p = 0.521$) [44]. Therefore, the authors concluded that adjuvant CT should not be considered as a standard of care for patients with Stage I/II uLMS without confirmation of the randomized clinical studies [44]. By contrast, another multicentric study that enrolled 108 patients with Stage I/II uLMS (94 in Stage I, and 14 in Stage II) showed that adjuvant CT may decrease the risk of extrapelvic recurrence and improve survival, although the authors found that women treated with CT had similar recurred rates as those treated with observation or RT [45]. The other important finding in a study by Ricci et al [45] was that after initial CT treatment, recurrences were more likely to be successfully treated or palliated ($p = 0.031$).

Omura et al [46] conducted a small prospective randomized trial to investigate the effect of doxorubicin (60 mg/m$^2$ every 3 weeks in eight courses) on uterine sarcoma (including uLMS); in their study, no significant advantage was noted for OS and PFS between the two groups, although a trend emerged in favor of CT, particular for uLMS (Table 3) [46]. Hensley et al [42] investigated the efficacy of four cycles of the combination of gemcitabine and docetaxel in patients with completely resected uLMS and found that the 2-year PFS rate

**Table 3**
The response rates of currently popular regimens in the management of patients with uterus-limited leiomyosarcoma or advanced-stage uterine leiomyomas undergoing complete resection of the tumor.

| Regimens | Patients (*n*) | Outcome | Authors/published y/reference |
|---|---|---|---|
| Doxo vs. Obs | 48 | RR: 11 (44%) vs. 14 (61%) | Omura et al/1985 [46] |
| Gem + Doc | 15 | 2-y PFS 59% (median PFS of 39 mo) | Hensley et al/2009 [42] |
| Gem + Doc followed by Doxo | 46 | 2-y PFS 78% (67–91%)<br>3-y PFS 57% (44–74%) | Hensley et al/2013 [47] |
| Doxo + Ifos + Cis + RT vs. RT alone | 53 | 3-y PFS 55% (40–70%) vs. 41% (27–57%)<br>3-y OS 81% (66–91%) vs. 69% (52–82%)<br>5-y OS 72% (53–85%) vs. 55% (37–72%) | Pautier et al/2013 [48] |

Data are presented as *n* (%) or 95% confidence interval.
Cis = cisplatin; CR = complete response rate was presented as percentage (*n*, %); Doc = docetaxel; Doxo = doxorubicin and/or Adriamycin; Gem = gemcitabine; Ifos = ifosfamide; Obs = observation; OS = overall survival; PFS = progression-free survival; PR = partial response rate was presented as percentage (*n*, %); RR = recurrence rate; RT = radiotherapy.

of patients in Stages I and II was 59%, and the median PFS was 39 months (Table 3). A 3-year Phase II trial (SARC 005) evaluated 46 patients with uLMS who received treatment with four cycles of gemcitabine (900 mg/m$^2$ on Day 1 and Day 8) plus docetaxel (75 mg/m$^2$ on Day 8 with a 21-day interval) followed by doxorubicin. Their data showed that the median time to recurrence was 27.4 months, and the 2-year PFS and 3-year PFS were 78% and 57%, respectively (Table 3), suggesting the need for a prospective randomized trial of adjuvant CT versus observation to determine whether adjuvant CT can improve survival in women with uterus-limited uLMS [47].

A French randomized study enrolling 53 patients with uLMS showed that the combination of four cycles of multiagent CT therapy (a 28-day interval), including doxorubicin, ifosfamide, cisplatin, and RT (45 Gy in 5 weeks), might provide a better 3- or 5-year disease-free survival than RT alone (51% vs. 40% or 51% vs. 29%; Table 3) [48]. In fact, the primary end point of this French study was met with the improvement in the 3-year PFS [48]. Although these results of adjuvant CT seemed to be promising, the multiagent CT and the combination of CT and RT were associated with statistically significantly increased toxicity, including two deaths in a French randomized study, and therefore the GCIG consensus did not recommend adjuvant CT as a standard treatment for uterus-limited uLMS patients [41]. Furthermore, the key components against the routine use of adjuvant CT are the heterogeneity of the tumor types and their stages and the very small sample size and no OS benefit [41]. However, the GCIG consensus agreed that for patients with locally advanced completely resected uLMS, postoperative surveillance and/or therapy could be individualized.

### *Adjuvant radiotherapy or systemic therapy for advanced diseases and recurrent diseases*

The value of adjuvant CT might be important for advanced or recurrent uLMS [49]. By contrast, RT might only play a minor role in such cases. At present, doxorubicin-based CT, especially doxorubicin as a single agent, remains the best choice as a first-line treatment for uLMS that is not amenable to curative-intent surgery [50], because the results of gemcitabine-based chemotherapy are conflicting (5% of complete response rate and 20–30% of partial response rate) [49]. A summary of current therapeutic agents in uLMS treatment showed that the response rates of these studies seemed to be relatively disappointing with complete response rate less than 10% (4.8% and 6.3%, respectively) [51,52] and partial response rate in less than one third of patients [51–63] (Table 4).

For single-agent liposomal doxorubicin regimen, patients received liposomal doxorubicin (50 mg/m$^2$) intravenously over 1 hour and courses were repeated every 4 weeks [55]. For single-agent paclitaxel regimen, patients received paclitaxel (175 mg/m$^2$) intravenously over 3 hours—135 mg/m$^2$ paclitaxel for patients with prior pelvic RT—and courses were repeated every 3 weeks [56,57], but the dose of paclitaxel can be reduced by 110 mg/m$^2$ [57]. For single-agent gemcitabine regimen, intravenous gemcitabine was administered over 30 minutes at a dose of 1000 mg/m$^2$ on Days 1, 8, and 15, with cycles repeated every 28 days [58]. For single-agent ifosfamide regimen, patients received ifosfamide (1.5 g/m$^2$) daily intravenously for 5 days with mesna (2-mercaptoethane sodium sulfonate), and the dosage of ifosfamide could be reduced to 1.2 g/m$^2$ for those who had received prior RT [59]. For single-agent etoposide regimen, patients received an oral form of 50 mg/m$^2$/d (30–40 mg/m$^2$/d for those with prior RT) as a single dose for 21 days, every 28 days [60]. Trabectedin (1.5 mg/m$^2$) was administered intravenously over 24 hours every 3 weeks [63].

The combination of gemcitabine and docetaxel was prescribed as follows: gemcitabine (675–900 mg/m$^2$) on Days 1 and 8 over 90 minutes, gemcitabine with docetaxel (60–100 mg/m$^2$) on Day 8 of a 21-day cycle with granulocyte growth factor, based on previous RT status [51,53]. For adding bevacizumab in the combination of gemcitabine and docetaxel, bevacizumab (15 mg/kg) was intravenously administered over 90 minutes after gemcitabine administration on Day 1 [53]. The combination of ifosfamide and doxorubicin involved administration of ifosfamide (5.0 g/m$^2$/24 h) and mesna (6.0 g/m$^2$/36 h) by continuous intravenous infusion preceded by intravenous administration of doxorubicin (50 mg/m$^2$) over 15 minutes of a 21-day cycle if counts allowed [54]. For a combination regimen of mitomycin, doxorubicin, and cisplatin, patients received mitomycin (8 mg/m$^2$) and doxorubicin (40 mg/m$^2$) intravenously, followed immediately by cisplatin (60 mg/m$^2$) in 1 L of 0.45% saline plus mannitol (25 g) [61]. For combination regimen of dacarbazine, mitomycin, doxorubicin, and cisplatin regimen, the patients were treated with sargramostim 250 μg/m$^2$ subcutaneously over 12 hours for 4 days (days −6 through −3), followed by a 2-day rest (days −2 and −1) [62]. Then, chemotherapy on day 0 consisting of dacarbazine of 750 mg/m$^2$ intravenously over 2 hours, mitomycin 6 mg/m$^2$ intravenously, doxorubicin 40 mg/m$^2$ intravenously and cisplatin 60 mg/m$^2$ intravenously over 2 hours was prescribed [62]. Finally, sargramostim 250 μg/m$^2$ was administered subcutaneously at 12-hour interval on days 1 through 14 [62]. Patients were retreated at 4-week intervals [62]. Administration of the combination of doxorubicin and trabectedin was as follows: 60 mg/m$^2$ doxorubicin by a 10–15-minute central venous infusion on Day 1, followed by a 3-hour central venous infusion of 1.1 mg/m$^2$ trabectedin on Day 1, then a subcutaneous administration of pegfilgrastim (6 mg) on Day 2. The treatment was given every 3 weeks for a maximum of six cycles [64]. The regimens and dosages are summarized in Table 5.

Gupta et al [65] proposed a clinical practice guideline, and suggested that doxorubicin has been considered the standard of

**Table 4**
Summary of trials to investigating the role of adjuvant therapy for patients with advanced and recurrent uterine leiomyosarcomas.

| Regimens/trials | Patients (n) | Outcome | Authors/published y |
|---|---|---|---|
| Gem + Doc/Phase 2/first line | 42 | PFS 4.4 mo (15, 35.5%) | Hensley et al/2008 [51] |
| Gem + Doc/Phase 2/second line | 51 | PFS 6.7 mo (13, 27%) | Hensley et al/2008 [52] |
| Gem + Doc vs. Gem + Doc + bevacizumab/Phase 3/first line | 54 vs. 53 | PFS 6.2 mo vs. 4.2 mo (17, 31.5%)<br>OS 26.9 mo vs. 23.3 mo (19, 35.8%) | Hensley et al/2015 [53] |
| Ifos + Doxo/Phase 2/first line | 33 | (10, 30%) | Sutton et al/1996 [54] |
| Liposomal Doxo/Phase 2/first line | 35 | (5, 14.3%) | Sutton et al/2005 [55] |
| Paclitaxel/Phase 2/first line | 34 | (3, 9.1%) | Sutton et al/1999 [56] |
| Paclitaxel/Phase 2/second line | 53 | (4, 8.4) | Gallup et al/2003 [57] |
| Gem/Phase 2/second line | 48 | (9, 20.5%) | Look et al/2004 [58] |
| Ifos/Phase 2/first line | 35 | (6, 17.2%) | Sutton et al/1992 [59] |
| Oral etoposide/Phase 2/first–second line | 36 | (2, 6.95) | Rose et al/1998 [60] |
| Mitomycin + Doxo + Cis/Phase 2/first line | 41 | (8, 23%) | Edmonson et al/2002 [61] |
| Dacarbazine + mitomycin + Doxo + Cis/Phase 2/first line | 18 | (5, 27.8%) | Long et al/2005 [62] |
| Trabectedin/Phase 2/first line | 20 | (2, 10%) | Monk et al/2012 [63] |
| Trabectedin + Doxo/Phase 2/first line | 47 | (47, 87.2%) | Pautier et al/2015 [64] |
| Trabectedin vs. dacarbazine/Phase 3/second line | 134 vs. 78 | PFS 4.0 mo vs. 1.5 mo | Demetri et al/2016 [67] |

Data are presented as *n* (%) or 95% confidence interval.
Cis = cisplatin; CR = complete response rate was presented as percentage (*n*, %); Doc = docetaxel; Doxo = doxorubicin and/or Adriamycin; Gem = gemcitabine; Ifos = ifosfamide; Obs = observation; OS = overall survival; PFS = progression-free survival; PR = partial response rate was presented as percentage (*n*, %); RR = recurrence rate; RT = radiotherapy.

**Table 5**
Current use of chemotherapy regimen.

| Regimen | Dosage | Interval |
|---|---|---|
| Trabectedin | Trabectedin >24 h (1.5 mg/m$^2$, Day 1) | A 21-d interval |
| Doxorubicin | Doxorubicin 60 min (50–75 mg/m$^2$, Day 1) | A 21-d interval |
| Liposomal doxorubicin | Liposomal doxorubicin 60 min (50 mg/m$^2$, Day 1) | A 28-d interval |
| Ifosfamide | Ifosfamide 24 h (1.2–1.5 g/m$^2$, Day 1–Day 5) with mesna | A 28-d interval |
| Paclitaxel | Paclitaxel >3 h (175 mg/m$^2$ or 110–135 mg/m$^2$, Day 1) | A 21-d interval |
| Etoposide | Oral etoposide (50 mg/m$^2$, Day 1–Day 21) | A 28-d interval |
| Doxorubicin and trabectedin | Doxorubicin 15 min (60 mg/m$^2$, Day 1)<br>Trabectedin >24 h (1.1 mg/m$^2$, Day 1) | A 21-d interval |
| Ifosfamide and doxorubicin | Doxorubicin 15 min (50 mg/m$^2$, Day 1)<br>Ifosfamide 24 h (5.0 gm/m$^2$, Day 1 and mesna, 6.0 g/m$^2$/36 h) | A 21-d interval |
| Gemcitabine and docetaxel | Gemcitabine 90 min (675–900 mg/m$^2$, Day 1–Day 8)<br>Docetaxel 60 min (60–100 mg/m$^2$, Day 8) | A 21-d interval |
| Doxorubicin, ifosfamide, and cisplatin | Doxorubicin 60 min (50 mg/m$^2$, Day 1)<br>Ifosfamide 24 h (3 g/m$^2$, Day 1–Day 2)<br>Cisplatin >2 h (75 mg/m$^2$, Day 3) | A 28-d interval |
| Mitomycin, doxorubicin, and cisplatin | Mitomycin 30 min (8 mg/m$^2$, Day 1)<br>Doxorubicin 30 min (40 mg/m$^2$, Day 1)<br>Cisplatin >2 h (60 mg/m$^2$, Day 1) | A 28-d interval |
| Dacarbazine, mitomycin, doxorubicin, and cisplatin | Dacarbazine >2 h (750 mg/m$^2$, Day 1)<br>Mitomycin 30 min (6 mg/m$^2$, Day 1)<br>Doxorubicin 30 min (40 mg/m$^2$, Day 1)<br>Cisplatin >2 h (60 mg/m$^2$, Day 1) | A 28-d interval |

care for more than 30 years for women with uLMS, although evidence supported the alternative choices of the other agent (gemcitabine), which might be valuable in the future clinical trials [50]. A recent ongoing trial (a prospective randomized controlled Phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas), although not yet fully published, showed a similar outcome between doxorubicin (75 mg/m$^2$ every 3 weeks) and gemcitabine (650 mg/m$^2$ on Days 1 and 8 every 3 weeks) and docetaxel (75 mg/m$^2$ every 3 weeks), but the tolerance of doxorubicin appeared better [50].

Trabectedin (YONDELIS) is a tetrahydroisoquinoline alkaloid, originally isolated from the marine tunicate *Ecteinascidia turbinata* and works based on interaction with the minor groove of the DNA double helix, which triggers a cascade of events that interfere with several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in $G_2$–M cell-cycle arrest and ultimately apoptosis [66]. Monk et al [63] reported the results from a Phase II study (Gynecologic Oncology Group: GOG 87M) and confirmed the modest activity of trabectedin as the first-line therapy in advanced, persistent, or recurrent uLMS [63]. In addition, no unusual toxicities were found, and more than half of the patients had more than 6 months of PFS and did not have treatment-ending toxicity for more than 10 cycles [63], suggesting that PFS rather than overall response rate would have been a better metric to assess the activity of this drug in uLMS patients [63,66].

The value of trabectedin, especially combined with other antineoplastic agents as first-line therapy, seemed to be further supported by a Phase II nonrandomized, multicenter trial (LMS-02) by the French Sarcoma Group [64]. Among a total of 47 patients with uLMS who were treated with trabectedin and doxorubicin, 28 women (59.6%, 95% CI 44.3–73.6) achieved a partial response and 13 women (27.7%, 95% CI 15.6–42.6) had stable disease; 41 women (87.2%, 95% CI 74.3–95.2) achieved disease control [64]. The data of the LMS-02 study support the notion that the combination of doxorubicin and trabectedin is an active first-line regimen for advanced uLMS that provides clinically meaningful benefits to patients with uLMS, and the therapeutic benefits possibly result from

synergistic activity of the combination [64]. However, the study also showed that the rate of progression seems to increase after 6 months, which raises the question of whether treatment should be continued with trabectedin alone [64]. A Phase III randomized multicenter clinical trial was conducted to compare the effects of trabectedin with dacarbazine in patients with advanced liposarcoma or LMS after prior therapy with an anthracycline and at least one additional systemic regimen; in this study, 212 patients were uLMS cases [67]. Among the patients with uLMS, 134 patients received trabectedin treatment and 78 received dacarbazine therapy. The results showed HR of 0.58 (95% CI 0.41–0.81) for PFS in the trabectedin group compared with the dacarbazine group, which significantly favored the survival benefits of trabectedin treatment [67]. Of most importance, there are two advantages of using the trabectedin treatment: (1) the therapeutic benefit of continued disease control can be maintained by extended trabectedin dosing beyond six cycles, which has been reported in a recent study as well [68]; (2) the safety and tolerability of trabectedin were consistent with extensive prior experience and reports [69]. All these findings suggested that trabectedin might be a promising drug in the management of this highly lethal disease—uLMS.

Finally, some investigating tools, including cytoreductive surgery with hyperthermic intraperitoneal CT (CRS-HIPEC), have been reported as the treatment most likely to achieve prolonged survival for peritoneal surface disease from various primaries [70]. For uLMS, the role of CRS-HIPEC needs much evidence to confirm its effectiveness.

## Future perspectives

Recently, somatic variation in LMS using exome sequencing strategy revealed that tumor protein P53, alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) gene, and mediator complex subunit 12 are frequently mutated in LMS, and alternative lengthening of telomeres phenotype was commonly seen in LMS. These findings indicated that ATR inhibitors might be a new possible drug for *ATRX*-deficient tumor, providing a potential novel therapeutic option for LMS [71,72]. However, the benefits of target therapy for uLMS are unclear. For example, a randomized Phase III trial was conducted to determine whether the addition of bevacizumab to gemcitabine–docetaxel increases PFS in uLMS [53]. The results showed that median PFS was 6.2 months for gemcitabine–docetaxel plus placebo versus 4.2 months for gemcitabine–docetaxel plus bevacizumab (HR = 1.12; $p = 0.58$); in addition, median OS was 26.9 months for gemcitabine–docetaxel plus placebo and 23.3 months for gemcitabine–docetaxel plus bevacizumab (HR = 1.07; $p = 0.81$). Both seemed to be similar. In fact, the authors found that a Phase II single-agent study of vascular-targeted agents has mostly yielded negative results; therefore, it is not surprising that antivascular-directed therapy might not play any role in the management of uLMS. The multikinase inhibitors—sunitinib and sorafenib—failed to meet the study's criteria for further investigation of these agents in uLMS [73,74]. Although pazopanib showed the longer median PFS compared with placebo (4.6 months, 95% CI 3.7–4.8 months vs. 1.6 months, 95% CI 0.9–1.8 months) with an HR of 0.31 (95% CI 0.24–0.40; $p < 0.0001$), OS seemed not to reach a statistically significant difference between the two groups (12.5 months, 95% CI 10.6–14.8 months in the pazopanib group vs. 10.7 months, 95% CI 8.7–12.8 months in the placebo), with an HR of 0.86 (95% CI 0.67–1.11; $p = 0.25$) [75].

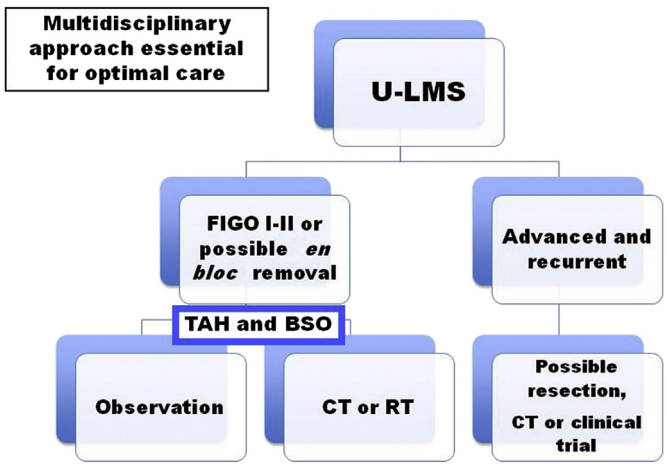


**Figure 1.** A flowchart for the clinical practice in the management of women with a diagnosed uterine leiomyosarcoma. BSO = bilateral salpingo-oophorectomy; CT = chemotherapy; FIGO = Federation International Gynecology and Obstetrics; RT = radiation therapy; TAH = total hysterectomy; U-LMS = uterine leiomyosarcoma.

## Conclusion

The standard treatment for early and far-advanced uLMS is hysterectomy plus bilateral salpingo-oophorectomy and complete cytoreduction of the tumor *en bloc* with adherent structures, even if not overtly infiltrated, respectively. For early stage (uterus-limited) disease, the most important thing is that tumor should be removed in intact and *en bloc* status, although minimally invasive surgery is applied [76,77]. For far-advanced disease, the results of the Taiwan Gynecology Oncology Group 2005 (TGOG-2005) showed that adequate debulking surgery, including dissection of both pelvic and para-aortic lymph nodes, might provide a better chance of survival in FIGO III–IV pure endometrioid-type EC cases [78], which might be also feasible. In fact, residual disease has a negative prognostic impact [79], and metastasectomy should be considered for patients with metastatic uLMS. Adjuvant RT and CT are not administered in routine practice because the survival benefits are doubtful, especially for patients with totally eradicated tumors. Treatment outcomes in uLMS are disappointing, especially in patients with inoperable, locally advanced, recurrent and/or metastatic diseases. Figure 1 presents some useful treatment options when dealing with uLMS patients. Available evidence of chemotherapy for uLMS is shown below. Trabectedin might be one of very promising agents. Other effective regimens include single agent of doxorubicin and gemcitabine, and the combination of therapy, such as gemcitabine plus docetaxel and/or trabectedin-based combination therapy. Besides the waiting for information provided by randomized clinical trials, addition efforts could focus on better defining the molecular etiology of uLMS to provide better care for this highly lethal disease.

## Conflicts of interest

The authors have no conflict of interest relevant to this article.

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