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**Current status of the adjuvant therapy in uterine sarcoma: A literature review**

Rizzo A *et al*. Adjuvant therapy in uterine sarcoma

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**Abstract**

Uterine sarcomas (US) are rare mesenchymal tumours accounting approximately for 3%–7% of all uterine cancers. Histologically, US are classified into mesenchymal tumours or mixed epithelial and mesenchymal tumours. The group of mesenchymal tumours includes uterine leiomyosarcoma (uLMS, 65% of cases), endometrial stromal sarcoma (ESS, 21%) – traditionally divided into low grade (LG-ESS) and high grade–undifferentiated uterine sarcoma (5%) and other rare subtypes such as alveolar or embryonal rhabdomyosarcoma. Despite the fact that several drugs demonstrated clinical activity in advanced or metastatic settings, the role of postoperative therapy in US remains controversial. In this review, we have summarised the current state of the art, including the chief trials on adjuvant treatment modalities in US, especially focusing on uLMS, LG-ESS and other rare histotypes.

**Key words:** Uterine sarcoma; Uterine leiomyosarcoma; Endometrial stromal sarcoma; Adenosarcoma; Adjuvant therapy; Chemotherapy; Radiotherapy

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**Core tip:** Uterine sarcomas (US) comprise a group of rare mesenchymal tumours with differing tumour biology, natural history and response to treatment. Clinical trials have shown no definite survival benefit of postoperative treatment (neither chemotherapy, nor radiation, nor hormone blockade) although its use seems reasonable in selected cases. This review aims to summarise the current state of knowledge about adjuvant therapy in US.

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**INTRODUCTION**

Uterine sarcomas (US) are rare malignancies that account for approximately 1% of female genital tract malignancies and 3% to 7% of all uterine tumours[1,2]. The median age of diagnosis appears to be about 56 years and the annual incidence rate is 0.36/100000 woman-years[3,4].

Histologically, US are classified into mesenchymal tumours or mixed epithelial and mesenchymal tumours. The group of mesenchymal tumours includes uterine leiomyosarcoma (uLMS, 65% of cases), endometrial stromal sarcoma (ESS, 21%) – traditionally divided into low grade (LG-ESS) and high grade (HG-ESS) – undifferentiated uterine sarcoma (UUS, 5%) and other rare subtypes such as alveolar or embryonal rhabdomyosarcoma[5,6]. Mixed epithelial and mesenchymal tumours include adenosarcoma (UAS) and carcinosarcoma[5,6]. UASs are considered biphasic tumours with a combination of a malignant mesenchymal component and benign epithelial elements; the presence of myometrial invasion and sarcomatous overgrowth represent the most significant prognostic factors responsible for an increased risk of relapse[7,8]. Carcinosarcomas, or malignant mixed Mullerian tumours, are aggressive malignancies previously considered sarcomas but currently recognised as tumours composed of metaplastic transformation of epithelial cells, and therefore we did not include them in this review[6].

Despite a frequent presentation as localised resectable disease, the risk of recurrence of uLMS ranges between 50% and 70%, with a 5-year overall survival rate of less than 50% in early stages and less than 15% in advanced stages[9,10]. The high rates of distant failure point towards the option of an adjuvant systemic therapy although no additional treatment (neither chemotherapy, nor radiation, nor hormone blockade) is proven to reduce the risk of relapse or to improve progression-free survival (PFS) and overall survival (OS)[11,12].

LG-ESS are considered indolent tumours, often associated with a favourable prognosis[13]. Nevertheless, about one-third of patients develop recurrences, requiring a long-term follow-up and supporting the rationale for a postoperative treatment[14,15].

HG-ESS, according to the updated edition of the WHO classification system, represents a distinct category both from LG-ESS and UUS[16]; although, the term ESS still often primarily refers to a low-grade disease[17]. Consequently, the evolving histological characterisation of US makes it difficult to compare clinical trials conducted in different periods, taking into account that cases of previously considered undifferentiated endometrial sarcomas or high-grade UUS might be included within the class of HG-ESS. LG-ESS and HG-ESS should require separate statistical analyses to derive robust inferences and to avoid this frequent bias.

There is a lack of enough data on adjuvant treatment in rare, high-grade malignancies including HG-ESS, UUS and UAS although the high risk of recurrence characterising these diseases might justify, in selected cases, the choice of a postoperative treatment[18].

Beyond surgery, the effect of adjuvant treatment modalities such as radiotherapy, chemotherapy and hormonal therapy in US remains poorly understood and its role remains controversial. In this review, we have summarised the current state of knowledge on postoperative therapy in this type of uterine malignancy with many unanswered management questions.

**ADJUVANT RADIOTHERAPY**

***Uterine leiomyosarcoma***

Adjuvant radiotherapy (RT) appears to be of limited clinical value in women with early-stage or advanced-stage resected uLMS, and the retrospective nature of all the available data – except for a phase III randomised trial – makes it difficult to draw conclusion regarding its role in this setting[18].

Several works failed to demonstrate a survival and local control benefit for the addition of adjuvant RT in uLMS[19–22]. The European Organization for the Research and Treatment of Cancer (EORTC) trial 55874 represents the only prospective randomised study investigating the effect of adjuvant RT in 224 completely resected stage I and II US, including 99 patients with uLMS[23]. In this phase, III randomised trial patients were randomly selected to receive 51Gy external beam pelvic radiation or observation. Adjuvant RT showed no improvement in local control and in OS for uLMS compared to observation.

The limited scope of adjuvant RT in uLMS was also confirmed by Wright *et al*[21] in a retrospective study utilising Surveillance, Epidemiology and End Results (SEER) data; in this study, radiation failed to demonstrate survival benefit in early-stage uLMS (HR = 1.1, 95%CI: 0.9-1.4).

The latest version of the National Cancer Comprehensive Network (NCCN)Guidelines suggests the possibility of using postoperative RT in selected cases after a multidisciplinary evaluation; in such cases, pathologic parameters such as cervical, serosal and parametrial involvement should be carefully considered[6].

To summarise, the choice of adjuvant RT in uLMS should be determined on a case-by-case basis, balancing between the risk of relapse, patient performance status and side effects, considering the absence of a proven benefit[24].

***Low-grade endometrial stromal sarcoma***

Due to the rarity of the histotype, no data from randomised controlled clinical trials are available on adjuvant RT in LG-ESS[25]; most data on LG-ESS arise from epidemiologic studies involving results of all US[26,27]. The EORTC trial 55874 included 30 cases of ESS but the small study sample size and the heterogeneous patient population including LG-ESS and HG-ESS did not permit any reliable analysis[23].

Postoperative RT appears to be of limited clinical value in LG-ESS although in several retrospective studies, adjuvant RT has been associated with a better loco-regional control without any impact on survival[28–31]. As RT seems to provide a local control and considering the usually good prognosis of patients with LG-ESS, the benefit of a postoperative treatment should be weighed against its side effects. As in the case of uLMS, the decision of whether to use postoperative RT in LG-ESS should be closely individualised, considering risk factors such as pelvic extension or cervical canal involvement and the possibility of using external beam pelvic radiation alone or combined with brachytherapy[6].

**OTHER HISTOTYPES**

No prospective trials assessing the role of adjuvant RT in HG-ESS, UUS and UAS have been conducted so far.

In a recent observational retrospective cohort analysis, adjuvant RT was associated with an increased survival rate in HG-ESS[32]; in another retrospective study on HG-ESS, postoperative pelvic RT with or without brachytherapy resulted as the only prognostic factor associated with improved PFS and OS but the small number of patients did not allow any definitive conclusions[33]. According to the NCCN guidelines, adjuvant RT might be considered appropriate in HG-ESS according to a category 2A recommendation based on a lower-level evidence[6].

No data on UUS and UAS were included in Reed’s study[23] and several retrospective studies showed no benefit in OS with postoperative RT in resected UAS[7,34,35]. Moreover, the balance between the untested benefit of RT and the well-known pelvic side effects makes this treatment less recommended in the adjuvant setting; current guidelines do not recommend the routine use of adjuvant pelvic radiation in completely resected UUS and UAS[36].

**ADJUVANT CHEMOTHERAPY**

***Uterine Leiomyosarcoma***

Despite the critical need to lower the estimated 50% to 70% risk of recurrence, the role of adjuvant chemotherapy (ChT) for resected uLMS remains controversial[6,9]. Several studies investigating the role of postoperative ChT for resected uLMS had several biases limiting possible interpretations such as patient population heterogeneity, frequent small sample sizes and single-arm design. Studies including patients affected by different histotypes of US might lead to interpretation misunderstandings because a potential benefit might be due to this heterogeneity; an example is the inclusion of low-grade histologies such as LG-ESS characterised by better prognosis compared to uLMS.

Many cytotoxic regimens have been tested in the adjuvant setting with minimal, if any, benefit[24]. Most studies have used ifosfamide, doxorubicin, gemcitabine and docetaxel as single agent or in combination as in the case of advanced or metastatic uLMS[37–39].

 The first study which attempted to evaluate the role of postoperative ChT in completely resected US, randomly selected patients to receive doxorubicin (60 mg/m2 every 3 wk for a total of eight cycles planned) observation[40]. Of the 156 patients included, 48 had uLMS and 25 among them received doxorubicin; the trial indicated no statistically significant difference in OS, PFS and recurrence rates in the two groups, regardless of pelvic radiation. The interpretation of the trial is significantly limited by the non-random use of RT, by the mixed histology population and the lack of protocol-specified imaging for disease status. Although these results were not satisfactory, this trial is considered of major importance because it has set the stage for all the successive studies.

As in the case of doxorubicin, adjuvant ifosfamide has been tested after hysterectomy in US. Kushner *et al*[41] evaluated the role of adjuvant single-agent ifosfamide in 13 patients with completely resected US, 6 of whom had uLMS. Patients were treated with Ifosfamide 1.5 g/m2/d for 3 d repeatedly after every 28 d for a total of three planned cycles. Five of the 6 patients with LMS showed recurrence (83%) and among the four patients with stages I or II, the 2-years PFS was 33%[41]. The small patient population, the lack of a control arm and the heterogeneity of the study group did not permit any reliable findings.

In order to transfer the results obtained in advanced uLMS[42–44], the combination of gemcitabine-docetaxel was tested in the adjuvant setting in a phase 2 trial for women with completely resected stages I–IV uLMS[11]. The aim of this single-arm study was to determine the potential benefit of four cycles of gemcitabine 900 mg/m2 a day on day 1 and day 8 and docetaxel 75 mg/m2 on day 8. On the basis of literature indicating that about the 30% of patients with stages I-IV high grade uLMS are progression-free 2 years after hysterectomy[41,45], the study was designed to determine whether adjuvant treatment of women with completely resected uLMS who received the combination of gemcitabine-docetaxel would result in at least 40% of women remaining progression-free at 2 years. The target enrolment was 39 patients but the study was terminated after 25 patients because of the promising results; in fact, 45% of patients were disease-free at 2 years, supporting a potential benefit of this adjuvant schedule[11].

Similarly, the single-arm SARC 005 study evaluated the combination of gemcitabine and docetaxel followed by doxorubicin in completely resected, high-grade uLMS[46]. Fixed-dose rate gemcitabine and docetaxel (with G-CSF support) were administered every 21 d for a total of 4 cycles; patients negative for recurrence received 4 additional cycles of doxorubicin 60 mg/m2. Forty-seven patients were enrolled, and 46 were evaluated for both PFS and OS at 2 and 3 years; the benefit, similar to the case of the previous study, was considered significant in case of PFS at 2 years of at least 50%. After a median follow-up of 39.8 months, 78% of patients (95%CI: 67%–91%) were progression-free at 2 years and 57% (95%CI: 44%-74%) at 3 years.

These data were considered promising for further investigations even though the two trials presented several limitations. The single-arm nature complicates the possibility of distinguishing between the effect of the treatment and the effect of natural history, and in this specific setting, it is difficult to interpret the response without a frame of reference for comparison. The relatively small number of patients and the single institution study enrolling represent two additional limitations.

The possibility of using a multimodal approach has been explored in a randomised trial providing doxorubicin, ifosfamide and cisplatin followed by pelvic irradiation versus pelvic radiation alone in completely resected US[47]. The schedule was composed as follows: doxorubicin 50 mg/m2 on day 1, ifosfamide 3 mg/m2 on day 1 and day 2, cisplatin 75 mg/m2 on day 3, for a total of 4 cycles. The combined ChT and RT arm showed a prolonged 3-year disease-free survival (DFS) (55% *vs* 41%, *P* = 0.048) but no improvement in OS. Patients randomised to the combined therapy presented severe toxicity in several cases, including 2 cases of death, raising significant concerns regarding the best strategy to follow.

Another retrospective study of Littell *et al*[48]compared gemcitabine-docetaxel (33 patients) versus observation (77 patients) in 110 stage I completely resected uLMS and no difference in OS or recurrence was found in the two groups. About half the patients were disease-free at 3 years irrespective of receiving ChT.

The necessity of answering a high-priority research question and the retrospective and/or single-arm nature of previous studies led to design of the GOG-0277 trial[49]. GOG-0277 was a two-arm, international, multicentric, open-label, randomised phase III superiority trial of gemcitabine (gemcitabine 900 mg/m2 on day 1 and day 8) along with docetaxel (75 mg/m2 on day 8) followed by doxorubicin (60 mg/m2 on day 1 of a 21-d cycle for four cycles) versus observation in women with completely resected, uterus-limited, high-grade uLMS. The trial was closed in September 2016, approximately 4 years after being open due to accrual futility, keeping unresolved the dilemma of adjuvant ChT in completely resected uLMS. In this trial, only 38 patients were enrolled at 572 sites. The study was designed before the recent development of new therapeutic options in metastatic uLMS although regimens such as olaratumab-doxorubicin or trabectedin single-agent showed an objective response lower than those of the combination gemcitabine-docetaxel in the metastatic setting[50,51]. It is unclear whether the use of new agents in the adjuvant setting could modify survival outcomes considering recent findings of the phase 3 ANNOUNCE trial which has called into question the proven benefit of olaratumab-doxorubicin in soft tissue sarcomas.

Currently, according to ESMO-EURACAN and NCCN guidelines, observation following completely resected uLMS remains a standard approach although it is worth noting that experts consider the possibility administering adjuvant therapy in selected cases with higher risk of recurrence (*e.g.*, high grade, tumour morcellation, tumour spillage)[6,18,52].

***Low-grade endometrial stromal sarcoma***

There is lack of adequate data in the literature on the use of adjuvant ChT in LG-ESS[53,54]. In a retrospective study by Kim *et al*[55] involving 22 women with completely resected stage I LG-ESS, adjuvant ChT had no effect on the outcome. In this study, 49.1% of the patients received adjuvant ChT and their 10-year recurrence rate was similar to those who had not received the treatment.

Recently, an observational retrospective cohort analysis identified 2414 and 1383 women with LG-ESS and HG-ESS[32]. Four hundred and forty-four patients with HG-ESS (444/1383, 33.4%) and 115 women with LG-ESS (115/2414, 4.8%) received postoperative ChT. Adjuvant ChT was associated with an increased survival in HG-ESS but with no benefit in patients with LG-ESS.

The lack of consensus on the optimal management of LG-ESS is related to the rarity of the disease and to the extensive heterogeneity of previously published series, most of which often included several types of US. Currently, given the good prognosis characterising LG-ESS and the side effects of treatment, adjuvant ChT is not considered clinically meaningful.

**OTHER HISTOTYPES**

In the retrospective study by Seagle *et al*[32], as mentioned previously, the use of adjuvant ChT determined a modest survival benefit for HG-ESS. Recently, a retrospective, single-centre study evaluated prognostic factors in 40 patients affected by HG-ESS[56]; the combination of surgery with RT and ChT appeared to improve PFS in early-stage disease. These findings were confirmed by a retrospective analysis of the French Sarcoma Group in which multivariate analysis of adjuvant chemotherapy in completely resected HG-ESS and UUS was correlated with improved DFS[57]. Presently, with respect to the prospective studies which might validate adjuvant ChT in HG-ESS and UUS, current guidelines consider the use of postoperative ChT appropriate taking into account the high risk of recurrence characterising these diseases[6].

No prospective or randomised controlled trials have evaluated the role of ChT as adjuvant treatment modality in UAS. The lack of data, only supported by case reports or case series, requires a careful clinical and pathological assessment to determine which patients might benefit from the therapy[58,59]. Furthermore, in the case of uLMS, the choice of using adjuvant ChT in UAS might be considered on an individual basis despite the absence of high-quality evidence (*e.g.,* in case of myometrial invasion, high-grade disease or sarcomatous overgrowth)[6].

**ADJUVANT HORMONAL THERAPY**

***Uterine leiomyosarcoma***

In uLMS, estrogen receptor (ER) and progesterone receptor (PR) expression has been reported in about 25%–80% of cases and 30%–75% of cases, respectively[60–65]. The possibility of treating patients affected by uLMS with hormonal therapy (HT) was first explored in the metastatic setting with variable activity (stable disease ranging from 32 % to 71% of cases and duration of response ranging from 0.4 and 40.3 mo)[63–65]. The hormonal therapy included aromatase inhibitors (AIs) such as letrozole (2.5 mg daily) or exemestane.

In 2012, Leitao *et al*[62] showed that ER and PR expression might identify cases of uterus-limited LMS associated to a better prognosis. A possible bias in interpreting data from trials about HT might be due to the better outcome which seems to physiologically characterise ER and PR positive uLMS.

Recently, data from a randomised, open-label, phase 2 study of letrozole 2.5 mg daily versus observation in completely resected uLMS was published[66]. Similar to the case of the GOG-0277 trial[49], this trial was prematurely closed due to its low accrual preventing the possibility of drawing definitive conclusions regarding the real benefit of adjuvant hormonal therapy in resected uLMS.

The use of AIs is not routinely recommended as postoperative treatment in resected uLMS. In the recent years, several case reports and case series have suggested a potential benefit in the adjuvant setting provided by AIs but no prospective data are currently available; AIs might represent, according to the latest version of the NCCN Guidelines, an option in cases of hormone-receptor expressing tumours, preferably in case of strongly positive (superior to 90%) disease[6].

***Low-grade endometrial stromal sarcoma***

For ESS, ER expression has been reported in approximately 87% of cases and PR expression in approximately 80%[67]. Although hormonal treatment is not a standard adjuvant therapy for LG-ESS, previous studies indicated that patients with advanced or metastatic LG-ESS might benefit from hormonal therapy including AIs, megestrol acetate or medroxyprogesterone acetate[68,69].

There are no prospective randomised controlled trials conducted for hormonal treatment in LG-ESS in the adjuvant setting. In 2007, Leath *et al*[70] presented data from a retrospective series of 30 cases with completely resected LG-ESS treated with postoperative hormonal therapy (megestrol acetate or medroxyprogesterone). Patients treated with hormonal treatment showed a prolonged, statistically significant (*P* = 0.07), median PFS when compared to the observation cohort (94 mo *vs* 72 mo).

In another retrospective series, 11 out of 114 patients affected by LG-ESS received postoperative treatment with HT[54], and disease-free survival was not different with respect to the type of adjuvant treatment (neither chemotherapy, nor radiation, nor hormone blockade).

According to the ESMO-EURACAN guidelines, although postoperative HT is not a current standard in LG-ESS, it might represent an alternative in this setting and can be considered for ER and/or PR positive disease[18]. The latest edition of of the NCCN guidelines classifies adjuvant HT in LG-ESS in the 2B category defining the intervention “appropriate”[6]. It is worth noting, at the same time, that many authors do not consider the potential benefit provided by adjuvant HT clinically significant considering the good prognosis and the long disease-free intervals characterising LG-ESS in the absence of specific therapy.

***Other histotypes***

HG-ESS are generally composed of cells lacking hormone expression. Nevertheless, some authors suggest considering the possibility of using postoperative HT in sporadic cases of hormone receptor-positive HG-ESS on an individual basis[56].

There is a lack of sufficient data on postoperative hormonal therapy in UUS and UAS; the lack of ER and PR expression in UUS excludes the possibility of using adjuvant hormonal treatment[71]. Furthermore, Amant *et al*[72] reported in 2004 that UAS might express hormone receptor in the epithelial and sarcomatous component; in this retrospective study, the sarcomatous component of UAS expressed the ER and PR in 16/20 (80%) and 12/20 (60%) of cases, respectively. In contrast, the sarcomatous component with sarcomatous overgrowth expressed the ER and PR in 0/8 (0%) and 1/8 (12%), respectively. These findings have been recently confirmed by a retrospective study[73]. Despite these data, the significantly low number of patients does not allow definitive conclusions.

Case reports and case series explore the use of adjuvant HT in UAS although no trials or series of at least 10 patients have been reported in literature[74,75]. Further investigations are required to identify the subset of patients that might obtain a proven benefit from HT in the adjuvant setting. Consequently, adjuvant HT is not a standard in UAS, but its use seems reasonable in selected cases of ER and/or PR expression and in the absence of sarcomatous overgrowth[6](Table 1).

**CONCLUSION**

Postoperative treatment modalities in US represent a sort of oncologic dilemma, balancing between lack of data, risk of recurrence, side effects and recommendations based on a lower-level evidence. Despite its rarity, achieving novel therapeutic options for US is considered an area of high unmet clinical need. As mentioned previously, studies on US were often affected by limitations such as the retrospective nature, the single-arm design, the population heterogeneity and small sample size. While simultaneously, the rarity of the disease and the poor recruitment in randomised trials raise serious doubts regarding the possibility of answering this question through the tools currently available.

If LG-ESS are considered characterised by a favourable prognosis, the oncologic outcomes of women affected by other USs such as uLMS, UUS and UAS remain poor. In these histotypes, there is the temptation to treat patients instead of starting observation. The retrospective study by Littell *et al*[48] provided useful information on the paradigmatic case of adjuvant ChT in uLMS: the study found an “irrational” and not evidence-based increase in the use of adjuvant gemcitabine-docetaxel ranging from 6.5% of patients between 2006 to 2008 to 46.9% of women between 2009 and 2013, despite unproven benefit.

Similar to several other types of malignancies, in uLMS, agents with high response rates in the advanced disease stage failed to show any benefit in the adjuvant setting. However, considering the fact that any combination or single-agent ever achieved objective responses higher than gemcitabine-docetaxel, future efforts should be directed towards the selection of high-risk patients who might really benefit from adjuvant treatment.

In the era of precision, personalised oncology, one of the fundamental points would be to better define genes and pathways involved in US, providing a novel understanding of the pathophysiological mechanisms underlying the disease. A deeper biological characterisation might be mandatory to understand the molecular biology of US and to better select patients who could benefit more from adjuvant therapy. Progress in the management of US will require collaboration of basic science and clinical oncology to provide effective measures that might soon modify the natural history of this rare, challenging entity.

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**Table 1 Summary of chief trials investigating the role of adjuvant chemotherapy and radiotherapy in uterine sarcomas**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***n* patients** | **Trial population** | **Trial desing** | **% relapse** | **PFS (mo)** | **OS (mo)** | **2-yr** **DFS** | **3-yr DFS** | **3-yr OS** |
| 51 Gy in 28 fractions *vs* observation (Reed *et al*[23], 2008)  | 224 | US, stage I-II (103 uLMS) | Randomised, phase 3 |  | 6.2 *vs* 4.9 (*P* = 0.35) | 8.5 *vs* 6.7 (*P* = 0.92) |  |  |  |
| Doxorubicin 60 mg/m2 (8 cycles) *vs* observation (Omura *et al*[40], 1985)  | 225 | US, stage I-II (48 uLMS) | Randomised, phase 3 | 41% *vs* 53% | NR *vs* 40.2 | 73.7 *vs* 55 (*P* > 0.5) |  |  |  |
| Ifosfamide 1.5 g/m2/d (Kushner *et al*[41], 2000)  | 13 | US, stage I-IV | Single-arm |  | 26 | 41 |  |  |  |
| Gemcitabine 900 mg/m2 d1, d8 + Docetaxel 75 mg/m2 d8 q21d, 4 cycles (Hensley *et al*[11], 2009) | 25 | uLMS, stage I-IV | Single-arm |  | 13 (FU > 49) | NR | All pts 45%Stage I-II 59% |  |  |
| Gemcitabine 900 mg/m2 d1, d8 + Docetaxel 75 mg/m2 d8 q21d 4 cycles followed by doxorubicin 60 mg/m2 q21d 4 cycles (SARC-005) (Hensley *et al*[46], 2013)  | 47 | uLMS, stage I-IIIa | Phase 2 |  | NR (FU > 39) | NR | 78% | 57% |  |
| Doxorubicin 50 mg/m2 d1, ifosfamide 3 g/m2 d1 d2, cisplatin 75 mg/m2 d3 (4 cycles) + G-CSF + RT *vs* RT alone (SARCGYN) (Pautier *et al*[47], 2013) | 81 | US, stage I-III | Randomised, Phase 3 | 38.5% *vs* 62% |  |  |  | 55% *vs* 41% (*P* = 0.048) | 81% *vs* 69% (*P* = 0.92) |

RT: Radiotherapy; US: Uterine sarcomas; DFS: Disease-free survival; PFS: Progression-free survival; OS: Overall survival;uLMS: Uterine leiomyosarcoma.