Hormonal therapy in gynecological sarcomas


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Gynecological sarcomas are rare, constituting 3–5% of uterine malignancies. Endometrial stromal sarcomas and some uterine leiomyosarcomas are characterized by estrogen receptor (ER) and progesterone receptor (PgR) expression with variable impact on their clinical behavior and potential response to systemic therapies. A variety of hormonal treatments have been tested, since they act as targeted treatment against ER and PgR and have a tolerable side effect profile, which allows them to be administered for prolonged periods. Their role has been studied more extensively in endometrial stromal sarcomas, as the majority of cases are ER/PgR positive, while recently, an emerging role for hormonal manipulation has been described in ER/PgR-positive uterine leiomyosarcomas. Owing to the rarity and heterogeneous nature of uterine sarcomas, current treatment recommendations are based on small retrospective studies and case reports. This review comprises a critical appraisal of the existing data regarding hormonal manipulation in uterine sarcomas and attempts to make recommendations for endocrine treatments in specific settings, as well as suggest targets/medications for future research.

Keywords: aromatase inhibitors • bilateral oophorectomy • endometrial stromal sarcoma • GnRH analogues • hormonal treatment • progestins • uterine leiomyosarcoma

Hormonal therapy in gynecological sarcomas

Endometrial sarcomas are rare, constituting only 1% of female genital malignancies and approximately 3–5% of uterine malignancies [1,2]. They encompass uterine leiomyosarcoma (ULMS), which is the most common histologic subtype, endometrial stromal sarcoma (ESS), and undifferentiated endometrial sarcoma. Carcinosarcoma is now being considered an aggressive, metaplastic form of endometrial carcinoma, and thus is no longer included in pure mesenchymal tumors of the uterus [2]. Owing to their rarity, most of the published data grouped them together, although there is a significant difference in molecular biology, histopathology and clinical behavior, and hence in their clinical management.

ULMS, accounting for 1–2% of all uterine malignancies [2], has an aggressive natural history, even at early stages, with recurrence rates of 50–70% (mostly to lungs) and a 5-year overall survival (OS) of less than 50%, which is expected to be even lower in advanced stages (5-year OS <15%) [2]. On the other hand, the less common ESS, accounting for less than 10% of all uterine sarcomas [2], exhibits a more indolent behavior, with a 5-year disease-specific survival (DSS) of approximately 90% for stages I–II and 50% for advanced stages III–IV [3]. However, even in early stages an almost 50% recurrence rate has been documented [4]. Although ULMS and ESS are considered to have different oncogenic mechanisms implicated in their development [2], they share some common characteristics, presumably due to their common organ of origin, the uterus. To a variable degree both subtypes are able to express hormone receptors (i.e., estrogen [ER] and progesterone [PgR] receptors). Understandably, hormonal treatments have been used as part of their systemic treatment, as other systemic modalities have limited impact on OS and disease-free survival (DFS) [5]. Hormonal therapies have been used in the adjuvant and the recurrent/metastatic setting, but the rationale is generally empirical [4], being extrapolated from data from hormone-sensitive breast cancer [6] and the less common endometrial [7] and ovarian cancers [8]. Indeed, there are no prospective randomized controlled studies of hormonal therapy in uterine sarcoma, mostly due to their rarity and aggressive nature, nor specific cell lines or animal models to test in vitro or in vivo [4]. However, in the era of targeted therapies and as our understanding of their molecular pathophysiology has evolved, endocrine treatment of uterine sarcomas has begun to be more actively explored, in view
also of the fact that they can be easily administered (mostly oral agents) and are well tolerated with minimal side effects and high rate of compliance.

Undifferentiated endometrial sarcoma (previously known as high-grade ESS) has been documented to have different pathologic and clinical features from ESS [3]; they rarely, if ever, express ER and PgR, hence endocrine treatments are generally not recommended [9].

Uterine adenosarcoma is a mixed tumor, composed of epithelial and sarcomatous elements, whose management depends mainly on the degree of differentiation of the sarcomatous component. In more than half of cases the sarcomatous component is low grade [10] and according to one study, the ER/PgR expression is positive in 90% of cases [11]. For these reasons, it has been suggested to be managed similarly to ESS [12]. On the other hand, in poorly differentiated sarcomatous component, adenosarcoma resembles undifferentiated endometrial sarcoma, and hence should be managed accordingly [13].

Surgical treatments
Bilateral salpingoophorectomy
The mainstay of treatment in operable stages of ESS and ULMS is total abdominal hysterectomy (TAH) [3,14–16]. Bilateral salpingoophorectomy (BSO) in premenopausal women is indicated as therapeutic maneuver in order to remove macroscopic and/or microscopic disease in the adnexal areas [4,16]. However, the role of BSO as a hormonal manipulation is still debatable in both subtypes, with only retrospective studies published [12], which produced conflicting conclusions.

More specifically, two large SEER database analyses of women with ESS, which studied patients between 1988 and 2003 (n = 408) [3] and between 1988 and 2005 (n = 384) [17], respectively, concluded that ovarian-sparing surgery in premenopausal women (<50 years) with early stage ESS (stage I–II) did not adversely impact OS. The authors noted that the SEER data could not distinguish those women that may had already undergone any type of ovarian surgery, a fact that may have influenced the outcome of the studies [3]. These findings were similar to the ones previously published by smaller retrospective studies (i.e., lack of any effect of BSO on progression-free survival [PFS] and OS of patients with ESS) [14,18,19]. It is notable that in one of the studies, which observed that BSO – a surgical hormonal manipulation – had no impact on PFS, it was nevertheless concluded that the use of adjuvant hormonal treatments was beneficial to all patients, even to those that were diagnosed with early stage disease [14].

On the other hand, three subsequent, relatively large retrospective studies showed convincingly decreased recurrence rates in premenopausal patients with stage I–II ESS who had undergone BSO with their primary TAH [20–22]; in the multivariate analysis, TAH without BSO was found to be one of the main independent factors for disease recurrence [22].

These discrepancies should be interpreted cautiously since all studies were retrospective, most of them including a small number of subjects, which had been recruited over a long period of time, during which the management may have changed, with a variable impact on the OS. One could debate that such a long period of observation is necessary in view of the known indolent natural history of ESS. It should also be commented that none of the studies examined BSO as an independent prognostic factor of OS in a cohort including only ER/PgR-positive ESS patients. Such type of trials would have been able to show the impact of BSO as hormonal manipulation more clearly, since the high frequency of ER and PgR expression has been long established in ESS [23]. Therefore, one could speculate that the results of the studies may just reflect the long clinical course of ESS, in which BSO in early stages may not have such a profound impact on OS. While ovarian-sparing surgery may cause a decrease in the PFS, it may not detrimentally affect OS, as typically ESS may respond to serial hormonal therapy and surgical debulking [14]. Another speculation could be that ovarian-sparing surgery may have some positive effect due to the continuous endogenous production of progesterone by the ovaries, which may be beneficial in an environment of sustained estrogen production [18].

Data for premenopausal women with ULMS seem more straightforward, since no study showed an adverse effect of ovarian-sparing surgery on the outcome of patients, unless there was evidence of macroscopic involvement of the ovaries [15,16,24]. The subset analysis of women <50 years old (n = 341) with stage I or II disease, which was performed within the context of the largest retrospective study of women with ULMS (a SEER database analysis of 1396 patients between 1988 and 2003), showed no difference in 5-year DSS between those women who did not undergo BSO and those women who did [16], a conclusion that was consistent with the findings of previous smaller studies [15,24]. There are two critical points that have to be mentioned regarding these data:

- There were no available data regarding the number of women who had previously undergone unilateral or BSO, although it was estimated that this number would be low [16].
- There were no data about the hormonal status of the patients.

It has been recognized that there are different subtypes of ULMS with different biological [25] and clinical behavior [26]. Particularly, ER and PgR expression has been associated with sensitivity to estrogens and better PFS [27] and OS [28]; hence as in ESS, ovarian preservation in ULMS may have a variable impact on PFS and OS, depending on the hormonal status of the disease, making ER/PgR expression an important factor to be taken into account in the decision making for BSO.

Since this question remains open and until prospective studies produce more solid data, the decision for BSO would be better made after detailed discussion with the patient, balancing the benefits (reduction of risk recurrence and improved OS) and the occurrence of estrogen deprivation symptoms. In the premenopausal setting, patients may wish to retain their fertility (albeit using surrogacy) and be seriously concerned about the impact of irreversible castration on their quality of life, knowing the likelihood of vasomotor symptoms and increased risk for osteoporosis, cardiovascular and cerebrovascular events. According to a prospective observational study that evaluated the role of
ovarian preservation for benign diseases, women aged <55 years who had undergone BSO had an estimated 8.5% increase in the risk of all-cause mortality [29]. The patients who wish to retain their ovaries are strongly advised to be followed-up more closely both clinically and with appropriate imaging at regular intervals.

**Pharmacological treatments**

The few epidemiologic studies that have been performed in order to identify risk factors for the development of uterine sarcomas indicated the significant role of hormone receptors in their pathophysiology and consequently the role of unopposed estrogens (hyperestrogenism) in their etiology [30]. Under physiological conditions, mesenchymal uterine cell proliferation and differentiation is regulated in part by hormones that function by binding to their receptors (i.e., ER and PgR) [4]. As has been noted in other hormone-driven types of cancers, settings that can predispose to high levels of circulating estrogen, such as obesity (BMI >27) [30], use of exogenous estrogens, in the form of hormone replacement therapy [6,18,30,31] or ovulation-stimulating drugs [4], endometriosis [32,33], pregnancy [34] and polycystic ovarian syndrome [4], have been recognized as predisposing factors for the development of uterine sarcomas.

Gynecological sarcomas exhibit a variable rate of ER and PgR expression. The majority of ESS expresses ER that ranges between 40 and 100% [18,20,31] and PgR 60–100% [18,20,31]. On the other hand, ULMS expresses both receptors to a lesser degree (i.e., 25–60% of cases are ER positive [28,35–38] and 35–60% are PgR positive) [28,35–38]. The main subtype of ER that uterine sarcoma cells express is ER-α, which can stimulate proliferation of the tumor cells [18,39], while there is almost negative expression of the ER-β subtype, which induces apoptosis [38].

Hormone receptors seem to have significant prognostic value; both ER and PgR expression in ESS and ULMS has been positively correlated with DSS and OS in most of the studies [28,38–40], although not fully confirmed by others [35,38]. In uterine-body confined ULMS, both ER and PgR expression has been associated with an improved PFS, and PgR expression with an improved OS, although the latter did not reach statistical significance probably due to sample size [38].

The growing body of evidence suggests that ER/PgR expression also has predictive value. As almost all patients with ER/PgR-positive ESS and ULMS have shown response or stability of disease to hormonal treatments [6,18,31,41–43], or have progressed when treated with hormonal replacement therapy (HRT) or tamoxifen [6,18,31]. However, in ER/PgR-positive ULMS the expression of receptors is less intense compared with benign lesions, suggesting that while estrogens may still regulate the proliferation of the tumor cells, this is unlikely to be to the extent observed in normal tissue [36]. Therefore, some patients may respond poorly to hormonal manipulation, even though ER/PgR are expressed in the surgical specimen, emphasizing the functional relationship of ER/PgR expression and response to endocrine treatments [36,40]. Indeed, in ULMS it has been difficult to distinguish whether the favorable outcome of ER-positive ULMS is due to the therapeutic effect of endocrine treatment, or merely the consequence of a more favorable biological behavior [27].

In view of the above, it is suggested that the histological report of every gynecological sarcoma should optimally include the hormone receptor status; the evaluation of immunoreactivity of ER and PgR is suggested to be performed by calculating the percentage of positive cell nuclei and the intensity of staining [4], although in some studies an arbitrary 10% cutoff level has been used [27,28]. Equally important is the re-evaluation of hormone receptors in tumor tissue of the recurrent disease, which may be feasible in uterine sarcomas, as surgical debulking is often part of their management for local or distant recurrence [4]. By this means, more accurate information about the biology of the disease may be available that could better guide further systemic treatment options; in case the recurrence is still strongly ER/PgR positive and low grade, hormonal treatment may be appropriate, while if there is less intense expression of hormone receptors along with a higher mitotic count (grade), then other treatments may be suggested, especially in high-grade ULMS [44].

Hence, depending on the hormonal status, setting (adjuvant or recurrent/metastatic), the volume and pace of the disease (short or prolonged DFS/PFS) endocrine treatment options may include:

- **Withdrawal of all exogenous sources of estrogens and/or**
- **Reduction of endogenous estrogen levels to almost undetectable levels, either by treating predisposing medical conditions or by administering estrogen-lowering or estrogen-antagonistic agents.**

### Withdrawal of HRT & tamoxifen

The negative impact of HRT has been well documented in patients with ESS [6,18,22,31], with higher frequency of recurrence and shorter time to relapse in postmenopausal women receiving HRT [18,22,31], while a case report regarding two patients with ULMS was equivocal [45]. The obvious influence of HRT in the progression of ESS is further depicted by the fact that in three studies all patients that progressed on HRT were strongly ER/PgR positive [6,18,31]; in one of the studies, withdrawal of HRT was considered equivalent to first-line treatment, exhibiting stable disease (SD) in the majority of patients and prolonged DFS (>60 months) in one patient, who underwent surgical removal of lung metastases ‘adjuvant’ setting) [31]. Thus, although no prospective data are available, by taking into consideration the molecular pathophysiology of ESS and by extrapolation from ER-positive ULMS, it is strongly recommended that HRT is not prescribed for alleviation of estrogen deprivation symptoms in postmenopausal patients diagnosed with these subtypes [46].

The same principles apply for the use of tamoxifen in both pre- and post-menopausal patients with uterine sarcomas. Tamoxifen is an integral part of the endocrine management of ER/PgR-positive breast cancer in the early and metastatic setting, as well as in ductal carcinoma in situ [47]. However, as a selective ER modulator, it has an agonist effect on endometrial stromal cells and consequently might stimulate tumor growth [46]. The data from the NSABP treatment trials for breast cancer and from the Breast Cancer Prevention Trial P-1 demonstrated an increase in the incidence of uterine sarcomas in women taking tamoxifen [47].
in accordance with other studies [48,49], although the absolute risk remains small (0.17 cases per 1000 woman-years) [47,50]. Moreover, tamoxifen has been associated with earlier recurrence and disease progression in ESS [6,31]. Therefore, tamoxifen should be withdrawn if a woman develops symptoms indicative of uterine malignancy and is absolutely contraindicated in those women diagnosed with ESS or ER-positive ULMS [46].

GnRH analogues

The pharmacological equivalent of BSO is the GnRH analogues (leuprolide, goserelin and triptorelin); in premenopausal women they suppress the pituitary ovarian axis, thus leading to suppression of ovarian estrogen production to a level comparable to the postmenopausal status [4]. However, it has been suggested that in ESS, GnRH analogues may have an additive action by blocking the intra-tumoral GnRH receptor, expressed in most cases of ESS [51]; this ancillary action may further downregulate mitogenic signal transduction pathways that are implicated in the pathogenesis of ESS [4].

In early stage disease, the published case reports refer only to ESS and emphasize the positive role of the pre-operative (neoadjuvant) use of GnRH analogues. Specifically, administration of leuprolide or triptorelin either as monotherapy [32,33] or in combination with megestrol acetate [52] for a short period of time prior to surgery induced a significant decrease in size of the inoperable tumor, so that it eventually became amenable to complete surgical resection. In one of the cases, when the patient recurred 6 months after her operation, the re-initiation of triptorelin resulted in regression of the recurrence [32].

In the metastatic setting, according to the two main retrospective studies performed in both ESS and ULMS, the main indication for the GnRH analogues was the maximization of the endocrine blockage in premenopausal women, who were also treated with an aromatase inhibitor (AI) [20,27].

Anti-estrogen treatments

Progestins & mifepristone

Due to the fact that in uterine sarcomas the PgR seems to be a significant target [12], progestins, which are synthetic derivatives of progesterone, have been used in their treatment. Progestins bind to PgR, which leads to downregulation of the transcription of specific genes, especially of ER, and subsequent reduction of circulating estrogens, events that eventually cause a decrease in endometrial gland and stromal proliferation [53]. Although the main experience is with progestins (i.e., medroxyprogesterone acetate [MPA] and megestrol acetate), mifepristone, a selective PG modulator, has also been used due to the antiprogestational activity it exhibits, resulting from competitive interaction with progesterone at the level of PgR [54].

Most of the case reports referring to the use of progestins in the recurrent or metastatic ESS, as summarized by Amant et al., showed a high response rate (76%) [12], although this has to be considered cautiously due to the known bias of case reports; that is, cases with a positive outcome are published more often compared with cases with a negative outcome [41]. The small retrospective studies in this setting (Table 1) indicate that progestins were the preferred and most frequently used agents as first-line hormonal treatment in ESS, with a relative high response rate and prolonged time to progression (TTP) observed. According to the largest of these, which included 30 patients, treatment with megestrol acetate and mifepristone (notably, few of the patients received AIs) was more effective compared with other modalities used, specifically radiotherapy and chemotherapy, with an overall response rate of 27% (complete response [CR] in 17%, partial response [PR] in 10% of patients) and SD in 53% of the patients; the median TTP was 24 months [20]. These results were in accordance with four other retrospective studies in which progestins were used as first-line treatment in recurrent or metastatic ESS, as summarized in Table 1 [18,31,40,41]. As expected, all patients with ER/PgR-positive ESS who were treated with progestins demonstrated either a response (CR/PR) or stability of their disease [18,40,41]. However, treatment failures have been noted [31,41,43]; it has been hypothesized that this may be related to absence of PgR expression or other mechanisms that contribute to progestin resistance [18,41,43].

In the adjuvant setting (Table 1), progestins have shown reduction in the risk of recurrence in all stages with a median TTP of 132 months, according to the largest series [20]. Moreover, in a study with 22 patients and a median follow-up of 100 months, 31% of patients on adjuvant progestin therapy recurred compared with 67% of patients who did not receive any adjuvant hormonal treatment in all stages [18]. In another study with 31 patients and a median follow-up of 62 months, none of the patients with stage I and 20% with stage III–IV who received adjuvant megestrol recurred compared with 20% of patients with stage I and 75% with stage III–IV who had no adjuvant treatment [14]. In a more recent study, with a median follow-up of 51 months, none of the four patients on adjuvant megestrol recurred [22].

Data are limited to few case reports regarding the management of metastatic ULMS (Table 1) with progestins; all of them refer to low-grade disease, which had durable partial response to MPA [55,56] or mifepristone [57]. Generally progestins showed an acceptable safety profile and high rate of compliance [40,41]; long-term side effects that may occur include thromboembolic events, weight gain (related to a degree of glucocorticoid activity) and alterations in mood, mostly in the form of depression [4], which may eventually lead to early treatment termination.

Aromatase inhibitors

Quite recently AIs have also been introduced in the treatment of uterine sarcomas, especially in ESS patients [4]. Aromatase is the enzyme that mainly provides the circulating estrogens in a postmenopausal environment by converting the adrenal hormone androstenedione to estrone, which is eventually converted to estradiol [42]. The main action of AIs is inhibition of aromatase activity in peripheral adipose tissue [42], by which a profound reduction in circulating estrogen levels is induced [4,18]. Another possible action of AIs in uterine sarcomas may be the direct inhibition of aromatase activity in tumor tissue, which is translated to inhibition of the ability of tumor to synthesize estrogens in situ.
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Review

The first AI to be used in metastatic ESS was aminogluthethimide with hydrocortisone in two patients whose disease was ER/PgR positive (Table 2). Remarkably, one of the patients remained in complete remission for almost 14 years, while the other one had a sustained PR for 3 years, after which due to side effects (diarrhea and asthenia) she was switched to letrozole, a third-generation AI, by which she achieved CR, which was sustained for more than 7 years [6].

AIs had been used as second-line hormonal treatment in recurrent ESS that had become resistant to progestin therapy (Table 2) [31,40,41,43,59]. In one of the case reports, a patient on letrozole achieved partial response for 9 months [59], while in another report, administration of anastrozole to a patient with repeated recurrences while on MPA treatment resulted in significant response, with a PFS of 16 months [43].

Based on the data in metastatic breast cancer [60] that third-generation AIs (the nonsteroidal letrozole and anastrozole and the steroidal exemestane) have shown superiority with regards to efficacy and tolerability over megestrol acetate, AIs have been used empirically as first-line hormonal treatment in ESS. They have shown remarkable efficacy and an acceptable side effect profile in this setting. It has been suggested that AIs exhibit a higher therapeutic index compared with progestins, on the assumption that they produce the same response rate as progestins but with a lower incidence of side effects [41]. Letrozole was the most frequently used AI; an overview of the clinical data on AIs is presented in Table 2. In the three comprehensive, though small retrospective studies, all except two patients showed response to AIs, either complete or partial [31,40,41]. Moreover, all of these patients but one [41] were found to be ER/PgR positive, while those patients that did not respond were found to be ER/PgR negative, indicating a strong relationship between the expression of hormonal receptors and response to AIs [31,40,41].

Fewer data, as summarized in Table 3, are available about hormone-positive ULMS, with the first case report being published in 2007, reporting partial response of multiple lung metastases to anastrozole that lasted more than 12 months [61]. A subsequent small retrospective study showed prolonged stability or objective response of disease in all ER-positive patients that received AIs [40].

The most solid data about the role of AIs in ULMS derive from the largest series ever published in 2010 [27]. In this retrospective study, 34 patients were identified who were treated with AIs (74% of whom received letrozole). AIs achieved a low objective response rate (0% CR and 9% PR) but clinical stability in 32% of the patients. Median PFS was 2.9 months. As expected, the patients with low-grade disease had a better 1-year progression-free rate (1-year PFR) compared with those with high-grade disease (60 vs 13%). Objective response and prolonged PFS were more likely to be observed among patients with hormone-positive disease; patients with ER-positive ULMS had a higher PFS compared with those with ER-negative disease, and a 1-year PFR of 26% [27].

AIs have a favorable toxicity profile with the majority of side effects being mild (grade I and II) and attributed to the profound estrogen deprivation they induce [4,27]. Specifically, most of the patients had vasomotor symptoms (hot flushes), fatigue and arthalgias; joint-related toxicities were the main reason for discontinuation of treatment [27]. Moreover, both AIs and GnRH analogues, which is a common combination given to premenopausal women with ESS/ULMS, when administered long term may significantly increase the risk of osteoporosis [4,62].

Table 1. Overview of data on progestins for the treatment of uterine sarcomas, in both recurrent/metastatic setting and adjuvant settings.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Treatment</th>
<th>Clinical response</th>
<th>Response duration (months)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metastatic setting: first line</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chu et al. (2003)</td>
<td>8/10</td>
<td>Meg/progestins NOS</td>
<td>4 CR/3 SD/1 PD</td>
<td>18–180</td>
<td>[18]</td>
</tr>
<tr>
<td>Pink et al. (2006)</td>
<td>3/10</td>
<td>MPA</td>
<td>1 CR/1 SD/1 PD</td>
<td>0/50/9</td>
<td>[31]</td>
</tr>
<tr>
<td>Dahhan et al. (2009)</td>
<td>8/11</td>
<td>Meg</td>
<td>4 CR/3 PR/1 SD</td>
<td>36–252/18–144/26</td>
<td>[41]</td>
</tr>
<tr>
<td>Ioffe et al. (2009)</td>
<td>5/7</td>
<td>Meg 4/Depot MPA (1)</td>
<td>1 PR/3 SD/1 PD</td>
<td>124/6–35/NA</td>
<td>[40]</td>
</tr>
<tr>
<td>Cheng et al. (2011)</td>
<td>30/47</td>
<td>Meg (28/30) mifepristone (3/30)</td>
<td>5 CR/3 PR/16 SD/6 PD</td>
<td>24</td>
<td>[20]</td>
</tr>
<tr>
<td><strong>Adjuvant setting</strong></td>
<td></td>
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<tr>
<td>Katz et al. (1987)</td>
<td>2/9</td>
<td>Meg</td>
<td>2 NED</td>
<td>24–72</td>
<td>[72]</td>
</tr>
<tr>
<td>Chu et al. (2003)</td>
<td>13/24</td>
<td>Meg</td>
<td>9 NED/4 recurred</td>
<td>18–56</td>
<td>[18]</td>
</tr>
<tr>
<td>Malouf et al. (2010)</td>
<td>4/54</td>
<td>Meg</td>
<td>4 NED</td>
<td>NA</td>
<td>[22]</td>
</tr>
<tr>
<td>Cheng et al. (2011)</td>
<td>25/35</td>
<td>NOS</td>
<td>NED</td>
<td>132</td>
<td>[20]</td>
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<tr>
<td><strong>ULMS</strong></td>
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<tr>
<td>Metastatic setting: first line</td>
<td></td>
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</tr>
<tr>
<td>Uchida et al. (1996)</td>
<td>1</td>
<td>MPA</td>
<td>PR</td>
<td>&gt;45</td>
<td>[56]</td>
</tr>
<tr>
<td>Lo et al. (2005)</td>
<td>1</td>
<td>MPA</td>
<td>PR</td>
<td>19</td>
<td>[55]</td>
</tr>
<tr>
<td>Koivistoo-Korander et al. (2007)</td>
<td>1/3</td>
<td>Mifepristone</td>
<td>1 PR/2 PD</td>
<td>&gt;36</td>
<td>[57]</td>
</tr>
</tbody>
</table>

CR: Complete response; ESS: Endometrial stromal sarcoma; Meg: Megestrol; MPA: Medroxyprogesterone acetate; NA: Not applicable; NED: No evidence of disease; NOS: Not otherwise specified; PD: Progression of disease; PR: Partial response; SD: Stable disease; ULMS: Uterine leiomyosarcoma.

[36,58]; intra-tumoral aromatase expression has been demonstrated in approximately 80% of ESS [58] and 60% of ULMS [36].
those patients that were treated with suboptimal doses eventually recurred [18]. Of note, after surgical debulking, all of these patients experienced prolonged stability of their disease when treated with the therapeutic dose of 160 mg of megestrol acetate [18].

Thus according to the existing published data, in patients who present with advanced stage ESS [14,18] or hormone-positive ULMS with a disease-free interval of more than 6 months [26] the suggested treatment strategy would be cytoreductive surgery, followed by maintenance hormonal treatment, either with an AI or a progestin, on the proposed dosage schedules indefinitely [18].

In the adjuvant setting, data are more uncertain, as there are no prospective studies published to date and the retrospective data are limited [12]; however, it has been proposed that administration of adjuvant hormonal treatment limits the impact of advanced stage [14]. It has been proposed on the basis of two small studies that adjuvant progestin (MPA or megestrol acetate) treatment should be given on a daily basis for at least 2 years [14,18], although in clinical practice oncologists tend to set an arbitrary duration between 2 and 5 years, mostly by extrapolation of data from breast cancer [4]. According to an interesting survey in 2006 [63], adjuvant hormone treatments are increasingly being used in ESS and predominantly in cases with macroscopic residual disease; however, they could also be a potential option for patients without any residual disease after their surgery, in agreement with other studies [14,22]. Hopefully, the outcome of a randomized Phase II study of adjuvant letrozole versus observation after TAH and BSO for early stage ER-positive ULMS will clarify the role of AIs in the treatment of this subtype [101].

**Expert commentary**

Endocrine therapy in ER/PgR-positive gynecological sarcomas has eventually gained the proper role as systemic modality both in the adjuvant/neoadjuvant and recurrent/metastatic setting. Due to their rarity and diversity, most of the studies are retrospective, characterized by small sample size and extend over a long period of time, thus leading to marked heterogeneity in patients’ inclusion criteria and treatment approaches, which inevitably is translated to wide variations in efficacy, safety and survival rates data; one such consequence in the case of ESS could be the observed increased incidence of late recurrence after surgery [20,22] which may not necessarily be related to an aggressive biological behavior [4], rather to the fact that many women were treated inadvertently either with HRT for menopausal symptoms [18,31] or with tamoxifen, which was prescribed either as treatment of a concomitant disease [31] or even as primary hormonal treatment [6,31], both of which are strongly contraindicated. Things are even more complicated by

### Table 2. Overview of data on aromatase inhibitors for the treatment of endometrial stromal sarcomas in both recurrent/metastatic setting and adjuvant settings.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Treatment</th>
<th>Clinical response</th>
<th>Response duration (months)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic setting: first line</strong></td>
<td></td>
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<tr>
<td>Leunen et al. (2004)</td>
<td>1</td>
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<td>PR</td>
<td>36</td>
<td>[42]</td>
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<td>Pink et al. (2006)</td>
<td>5</td>
<td>Letrozole</td>
<td>4 PR/1 PD</td>
<td>3–37/NA</td>
<td>[33]</td>
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<tr>
<td>Ioffe et al. (2009)</td>
<td>3</td>
<td>Letrozole</td>
<td>1 CR/2 PR</td>
<td>88–124/53</td>
<td>[40]</td>
</tr>
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<td>Dahhan et al. (2009)</td>
<td>3</td>
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<td>2 PR/1 PD</td>
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<td>[41]</td>
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<td>Sylvestre et al. (2010)</td>
<td>1</td>
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<td>1 CR</td>
<td>&gt;24</td>
<td>[73]</td>
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<td>1</td>
<td>Letrozole</td>
<td>PR</td>
<td>9</td>
<td>[59]</td>
</tr>
<tr>
<td>Spano et al. (2003)</td>
<td>1</td>
<td>Letrozole</td>
<td>1 CR</td>
<td>84</td>
<td>[6]</td>
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<td>Shoji et al. (2010)</td>
<td>1</td>
<td>Anastrozole</td>
<td>1 PR</td>
<td>16</td>
<td>[43]</td>
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<td></td>
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<td></td>
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<td>Maluf et al. (2010)</td>
<td>6/54</td>
<td>AIs</td>
<td>NED</td>
<td>NA</td>
<td>[22]</td>
</tr>
</tbody>
</table>

AIs: Aromatase inhibitor; CR: Complete response; NA: Not applicable; NED: No evidence of disease; PD: Progression of disease; PR: Partial response.

reason, it is strongly recommended to perform a baseline bone density scan and, depending on the bone status, to suggest the appropriate prophylactic treatment [4,62].

### Dosage & duration of treatment

AIs are administered to patients with gynecological sarcomas at the same dosages that they have been recommended for breast cancer treatment as off-label use, assuming that the active doses for breast cancer will have similar efficacy in ESS and ULMS. There has been no uterine sarcoma-specific trial launched in order to confirm the effectiveness of the dosage, or to test other dosing schedules that may be more efficacious [4], while there is no report in the literature using a different dosage schedule of AI. Significant advantages of AIs, when compared with other hormonal treatments, are their higher therapeutic index [4] and the fact that they can be recommended in ER-positive/PgR-negative disease [4,43], or PgR-resistant disease [18,43].

In the case of progestins, it has been concluded that the most important factor in the treatment of uterine sarcomas is their mechanism of action, rather than the type of progestin used. In the case of megestrol acetate, which is the most commonly used agent, the experience in the recurrent/metastatic setting of ESS and endometrial cancer has led to a recommended dose of 160 mg daily [18], while for MPA the equivalent dose is at least 200 mg [34]. Megestrol acetate should be started at 40 mg orally daily and be increased gradually according to patient’s tolerance, to the recommended total dose of 160 mg or, if needed, to 320 mg daily. It is essential that the patients are not treated with lower doses of progestins, or intermittently, as it has been treated that most of the patients that were treated with suboptimal doses eventually recurred [18]. Of note, after surgical debulking, all of these patients experienced prolonged stability of their disease when treated with the therapeutic dose of 160 mg of megestrol acetate [18].

Thus according to the existing published data, in patients who present with advanced stage ESS [14,18] or hormone-positive ULMS with a disease-free interval of more than 6 months [26] the suggested treatment strategy would be cytoreductive surgery, followed by maintenance hormonal treatment, either with an AI or a progestin, on the proposed dosage schedules indefinitely [18].

In the adjuvant setting, data are more uncertain, as there are no prospective studies published to date and the retrospective data are limited [12]; however, it has been proposed that administration of adjuvant hormonal treatment limits the impact of advanced stage [14]. It has been proposed on the basis of two small studies that adjuvant progestin (MPA or megestrol acetate) treatment should be given on a daily basis for at least 2 years [14,18], although in clinical practice oncologists tend to set an arbitrary duration between 2 and 5 years, mostly by extrapolation of data from breast cancer [4]. According to an interesting survey in 2006 [63], adjuvant hormone treatments are increasingly being used in ESS and predominantly in cases with macroscopic residual disease; however, they could also be a potential option for patients without any residual disease after their surgery, in agreement with other studies [14,22]. Hopefully, the outcome of a randomized Phase II study of adjuvant letrozole versus observation after TAH and BSO for early stage ER-positive ULMS will clarify the role of AIs in the treatment of this subtype [101].

### Expert commentary

Endocrine therapy in ER/PgR-positive gynecological sarcomas has eventually gained the proper role as systemic modality both in the adjuvant/neoadjuvant and recurrent/metastatic setting. Due to their rarity and diversity, most of the studies are retrospective, characterized by small sample size and extend over a long period of time, thus leading to marked heterogeneity in patients’ inclusion criteria and treatment approaches, which inevitably is translated to wide variations in efficacy, safety and survival rates data; one such consequence in the case of ESS could be the observed increased incidence of late recurrence after surgery [20,22] which may not necessarily be related to an aggressive biological behavior [4], rather to the fact that many women were treated inadvertently either with HRT for menopausal symptoms [18,31] or with tamoxifen, which was prescribed either as treatment of a concomitant disease [31] or even as primary hormonal treatment [6,31], both of which are strongly contraindicated. Things are even more complicated by...
Hormonal therapy in gynecological sarcomas

Review

the fact that the International Federation of Gynecology and Obstetrics (FIGO) staging system for uterine sarcomas has recently been revised [64], but it has not yet been fully validated [65,66], which obscures the extrapolation of data from previous studies. In ULMS the situation is further complicated by the lack of standardized histopathologic criteria or a uniform grading system until now [67].

However, even with these limitations, hormonal treatment has been shown to be more effective compared with radiotherapy and chemotherapy, with significant response rates and durable responses in the metastatic setting and almost no evidence of recurrence in the adjuvant setting. Endocrine treatment should be suggested based on the hormone receptor expression of the primary tumor and preferably in the recurrent/metastatic setting on the re-examination of the hormone expression of the recurrent tumor biopsy. The functional relationship of the hormone receptor expression and the response to hormonal treatment has not been fully established, especially in ER-positive ULMS, but in the case of strong expression a course of hormonal therapy should be prescribed.

In ESS, which is low grade by definition and strongly ER/PgR-positive in the vast majority of cases, BSO in premenopausal women is strongly recommended as standard procedure along with TAH, although ovarian sparing can be considered depending on age and extent of myometrial invasion. There are no prospective studies regarding the role of adjuvant hormonal treatment for ESS; however, most of the published empirical data advocate its importance, even in cases of ESS without residual disease after debulking surgery. AIs are currently preferred over progestins as first-line treatment due to the higher therapeutic index, while they are also active as second-line therapy in progestin-resistant disease.

In ULMS the situation requires further elucidation. There is clearly a subset of ULMS with a more indolent clinical behavior; this subset includes mostly ER/PgR-positive and low/intermediate-grade cases and presents with low-volume disease. In these cases a course of hormonal therapy could be administered cautiously, especially in cases with rapidly progressing metastatic disease. Hopefully a Phase II study, which is currently evaluating the efficacy of letrozole in women with advanced ER/PgR-positive ULMS, will elucidate the role of AIs in these cases [102]. In both histologies, GnRH analogues should be an integral part of treatment in premenopausal women, due to the reversible ovarian ablation they induce, in order to maximize endocrine blockage and could be considered in the neoadjuvant setting in order to facilitate complete surgical resection.

Five-year view

During the last decade, there has been a substantial change in the way ESS and ER/PgR-positive ULMS have been treated, with increased acceptance of the hormonal sensitivity of these subtypes. This is better depicted by the fact that the current guidelines (by ESMO NCCN and British Sarcoma Group) consider hormonal treatments as an integral part of the management of ESS and ER positive ULMS [9,68]. AIs are likely to be established as first-line hormonal treatment in ESS due to their superior efficacy and better side effect profile compared with progestins, the agents most commonly used in the past; the same is likely to be seen in the adjuvant setting. The two randomized Phase II studies of the role of letrozole in the adjuvant and metastatic setting in ER-positive ULMS are eagerly awaited, as they will provide prospective data concerning the role of AIs in ULMS [101,102]. Progestins may be used as second-line treatment, provided that PgR is still expressed in the recurrent disease.

Given the minimal toxicity and high rate of compliance with hormonal treatment, new hormonal options may evolve, similar to the breast cancer model [40]. Fulvestrant, a novel pure anti-estrogen (ER antagonist) that has recently been approved for the treatment of metastatic breast cancer in postmenopausal women, showed no evidence of agonist activity in the endometrium of healthy postmenopausal women [69], implying that it can be suggested for the treatment of uterine sarcomas. Abiraterone acetate, an inhibitor of the steroidal enzyme 17α-hydroxylase/C17,20-lyase, that eventually reduces androgen levels, may also be considered after treatment failure with conventional hormonal options in recurrent uterine sarcomas, since androgen receptor has been observed in approximately 30–40% of ESS [70] and ULMS [37], respectively. Abiraterone acetate has recently been approved in castration-resistant prostate cancer [71]. Although mifepristone did not show encouraging results, other selective PgR modulators, such as asoprisnil, may be worth investigating for the treatment of recurrent ESS/ULMS [4].

### Table 3. Overview of data on aromatase inhibitors for the treatment of uterine leiomyosarcoma in both recurrent/metastatic setting and adjuvant settings.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Treatment</th>
<th>Clinical response</th>
<th>Response duration (months)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic setting: first line</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Hardman et al. (2007)</td>
<td>1</td>
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<td>PR</td>
<td>&gt;12</td>
<td>[61]</td>
</tr>
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<td>Ioffe et al. (2009)</td>
<td>4</td>
<td>Anastrozole (1) Letrozole (3)</td>
<td>3 SD/1 PR</td>
<td>38–50/30</td>
<td>[40]</td>
</tr>
<tr>
<td>O’Cearbhaill et al. (2010)</td>
<td>34</td>
<td>AI (74% letrozole)</td>
<td>9% PR/32% SD</td>
<td>2.9</td>
<td>[27]</td>
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<td>NCT00856050</td>
<td></td>
<td>Letrozole</td>
<td>Ongoing</td>
<td>–</td>
<td>[102]</td>
</tr>
<tr>
<td><strong>Adjuvant setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ioffe et al. (2009)</td>
<td>3</td>
<td>Anastrozole (2) Letrozole (1)</td>
<td>3 NED</td>
<td>18–72</td>
<td>[40]</td>
</tr>
<tr>
<td>O’Cearbhaill et al. (2010)</td>
<td>5</td>
<td>Letrozole (4) Anastrozole (1)</td>
<td>3 NED/2 PD</td>
<td>6.3–11.5</td>
<td>[27]</td>
</tr>
<tr>
<td>NCT00414076</td>
<td>Letrozole vs observation</td>
<td>Ongoing</td>
<td>–</td>
<td>[101]</td>
<td></td>
</tr>
</tbody>
</table>

AI: Aromatase inhibitor; NED: No evidence of disease; PD: Progression of disease; PR: Partial response; SD: Stable disease.
The most important advance in the treatment of hormone-positive gynecological sarcomas is that they will be regarded as chronic diseases, during the clinical course of which the recurrences will be treated with debulking surgery, followed by interval treatment with several lines of endocrine treatment, which hopefully will evolve in the near future. This combination will prolong the clinical course of these diseases.

**Key issues**

- There is evidence that supports the use of hormonal treatments in estrogen/progesterone receptor (ER/PgR)-positive uterine sarcomas. Optimally, the ER/PgR expression should be evaluated in the recurrent tumor specimen to ensure ongoing hormone-sensitive disease.
- Due to their rarity most of the data derive from retrospective studies and extrapolation of prospective clinical trials in other more common endocrine-sensitive types of cancer.
- Bilateral salpingoophorectomy is indicated in premenopausal women with endometrial stromal sarcoma and should be strongly considered in ER-positive uterine leiomyosarcoma, although it can be individualized. These patients should not be treated with hormone replacement therapy for their menopausal symptoms.
- Tamoxifen is contraindicated because it can stimulate tumor growth due to the agonist effect it has on uterine mesenchymal tissues.
- GnRH analogues – pharmacological castration – are indicated in premenopausal women to ensure complete endocrine blockage in combination with a progestin or aromatase inhibitor or in the neoadjuvant setting to render tumors amenable to complete surgical excision.
- Progestins are the hormonal agents that have been used most extensively in the metastatic and adjuvant settings with favorable outcomes and acceptable toxicity profile.
- Aromatase inhibitors are currently the preferred hormonal agents due to their higher therapeutic index as first-line or adjuvant treatment and are active in progestin-resistant disease.
- The dosage of aromatase inhibitors has been arbitrarily extrapolated from the data regarding the treatment of the most common ER/PgR-positive disease, breast cancer. The dosage of progestins must be at least 160 mg of megestrol acetate and at least 200 mg of medroxyprogesterone acetate daily, as suboptimal doses have been related to earlier disease recurrence.
- Hormonal treatment in the metastatic setting should continue until disease progression or unacceptable side effects. The duration of hormonal treatment has been arbitrarily set between 2 and 5 years.
- Gynecological sarcomas should be considered a chronic disease, during which the recurrences should be treated with debulking surgery, amended with interval endocrine treatment.

**References**


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**Websites**
