Gynaecological sarcomas
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Purpose of review
To review gynaecological sarcomas, their management and future perspectives.

Recent findings
Soft tissue sarcomas are a group of tumours consisting of a wide variety of subtypes. The most common subtypes encountered in the female tract are uterine leiomyosarcomas and endometrial stromal sarcomas. Other subtypes do occur but at a much lower frequency. Mixed Müllerian tumours were previously considered to be a subtype of sarcoma, but recent evidence has revealed that they should in fact be regarded as carcinomas. Given the different approaches for different subtypes of sarcomas, their rarity and the complexity of treatment, the management of patients with gynaecological sarcomas should be delivered by multidisciplinary teams experienced in the treatment of these entities.

Summary
Gynaecological sarcomas are rare tumours and are treated differently from gynaecological carcinomas. Hopefully, improved insight into the pathogenesis of gynaecological sarcomas will yield novel therapies in the near future.

Keywords
gynaecological sarcomas, patient management, subtypes

Introduction
Soft tissue sarcomas (STSs) account for less than 1% of all the malignant tumours occurring in the female tract. Nevertheless, attention needs to be given to these tumours given the important differences in their management compared with more common gynaecological malignancies.

STSs are defined as the malignant tumours that develop from mesenchymal tissue such as connective tissue, muscle, fat and endothelium. Tumours from neuroectodermal origin including primitive neuroectodermal tumours/Ewing’s sarcoma are also regarded as sarcomas. In total, STSs encompass more than 40 different subtypes, and STSs are currently divided into three major groups on the basis of major differences in their sensitivity to systemic treatment and resulting distinct differences in treatment approaches. The first group is formed by the small blue round cell tumours including Ewing- or primitive neuroectodermal tumour-like tumours, desmoplastic small blue round cell tumours, and embryonal rhabdomyosarcomas. These tumours exhibit major sensitivity to chemotherapy, and as a consequence cytotoxic agents play a central role in the treatment of both localized and metastatic disease. The second group consists of the gastrointestinal stromal tumours (GISTs), which, in contrast to other STS subtypes, are characterized by activating mutations in the gene encoding the c-kit receptor. Following the introduction of drugs such as imatinib, which inhibits c-kit signal transduction, the treatment of GIST largely differs from that of other STS subtypes. The third and largest group contains all other STS subtypes and is commonly referred to as non-GIST STSs. It is a very heterogeneous group of tumours differing in terms of histological grade, clinical behavior and probably also sensitivity to systemic treatment. Despite these differences, the subtypes within this group are currently still treated in a similar way.

The review focuses on gynaecological sarcomas, with an emphasis on the different subtypes and their management, and a look at possible future perspectives.

Gynaecological sarcoma subtypes
Many different STS subtypes occur in the gynaecological tract, particularly in the uterus. (Table 1) By far the two most common subtypes belong to the non-GIST STS group, i.e. uterine leiomyosarcoma and endometrial stromal sarcomas. Uterine leiomyosarcomas occur more frequently than endometrial stromal sarcomas with an incidence of 0.64 and 0.19 per 100 000 women,
GIST, gastrointestinal stromal tumour; STS, soft tissue sarcoma.

Activity against mixed Müllerian tumours such as paclitaxel, cisplatin or carboplatin are considered inactive against sarcomas. Thus, mixed Müllerian tumours should not be included in studies of uterine sarcomas [3].

Non-GIST STSs other than these two subtypes do occur, but at a much lower frequency. Small blue round cell tumours, such as embryonal rhabdomyosarcomas, are very uncommonly in the female tract. GISTs can very rarely be found in the female tract presenting as a vulvovaginal/rectovaginal septal mass [2]. They resemble leiomyosarcomas on histopathological examination, but are managed completely differently. Physicians, therefore, must be aware of this possible area of confusion.

A much more common tumour type, which until recently has been considered as a STS subtype, is the group of mixed Müllerian tumours, also known as carcinomas. This tumour type exhibits both epithelial and mesenchymal differentiation. Recent molecular techniques, however, have revealed that mixed Müllerian tumours should in fact be regarded as metaplastic carcinomas and that the sarcomatous parts in these tumours arise through dedifferentiation. In addition, the clinical behavior of mixed Müllerian tumours resembles carcinomas more than sarcomas in terms of dissemination pattern and sensitivity to cytotoxic agents. Mixed Müllerian tumours predominantly show lymphatic spread, in contrast to sarcomas that mostly disseminate through the blood stream. Furthermore, agents showing antitumour activity against mixed Müllerian tumours such as paclitaxel, cisplatin or carboplatin are considered inactive against sarcomas. Thus, mixed Müllerian tumours should not be considered a subtype of sarcomas and, therefore, they should not be included in studies of uterine sarcomas [3].

**Presentation and diagnosis**

Presenting signs and symptoms of gynaecological sarcomas are nonspecific such as vaginal bleeding or a gradually increasing mass causing pain. Occasionally, leiomyosarcomas are found in resected uterine leiomyomas occurring in an estimated 0.5% of women undergoing a hysterectomy for leiomyomas. Approximately 50% of the cases with leiomyosarcoma present with stage I disease, i.e. disease confined to the uterus, and following local extension (stage II and III), gynaecological sarcomas disseminate via hematogenous spread (stage IV), preferentially to the lungs.

As with all tumours, the exact diagnosis of gynaecological sarcomas is based upon histology. The histopathological diagnosis and exact subtyping is difficult, and therefore this should take place in specialized centres. Immunohistochemistry can contribute to the final pathological diagnosis, e.g. using CD10 for endometrial stromal sarcoma [4] and CD117 to discriminate GISTs. In the future, gene expression profiling by microarray analyses can be anticipated to play a role in diagnosis as well. Using microarray analyses, the vast majority of genes expressed in uterine leiomyosarcoma are similar to those found in their nonuterine counterpart [5].

In addition to the histological classification, histological grade is important. Several grading systems are available.

In contrast to non-gynaecological STSs, which are usually categorized as low, intermediate or high grade, gynaecological sarcomas are frequently classified as low or high grade. Low-grade tumours are mainly at risk of local recurrence. Low-grade tumours may dedifferentiate into high-grade tumours if they are present for a long period of time. High-grade tumours pose a risk of not only local, but also distant recurrence, often shortly after primary treatment. A prognostic model for uterine leiomyosarcoma is the Borders four-level system, which uses cytologic atypia, necrosis and the mitotic index. Borders grade 1 tumours correspond to low-grade disease bearing a better prognosis than Borders 2, 3 or 4 sarcomas that are regarded as high-grade tumours [6]. In endometrial stromal sarcomas the mitotic index has emerged as an independent negative prognostic factor, and can be used to distinguish between low- and high-grade disease [7].

**Treatment**

Gynaecological sarcomas should be treated as sarcomas and not as carcinomas (Table 2). A crucial aspect in the management of these patients is a multidisciplinary approach that includes pathologists, radiologists, surgeons, gynaecologists, radiotherapists and medical oncologists. In view of their rarity, the management of these tumours should be undertaken by physicians experienced in these malignancies.

Small blue round cell sarcomas and GISTs of the female tract are very rare, and their management differs completely from that of non-GIST gynaecological sarcomas. The management of these tumours is beyond the scope of this review.

**Treatment of localized disease**

Surgical resection forms the mainstay of treatment for localized disease. Patients with uterine sarcomas require a hysterectomy at least; frequently, ovaries and lymph nodes are also removed, as is common for carcinomas of the uterus. In women without evident extra-uterine disease, however, involvement of regional lymph nodes or
ovaries is uncommon [6] and standard oophorectomy or lymph node resection is not justified. Many patients initially presenting with stage I leiomyosarcoma relapse and the 5-year survival rate is approximately 50%. Recurrence rates for stage II and III disease are higher. Risk factors for recurrence, both local and distant, include stage, tumour size, mitotic count and grade [6,7]. Given the high local relapse rate, adjuvant radiotherapy is commonly applied after surgery. Indeed, retrospective studies and preliminary results of a randomized study, only published in abstract form, suggest that adjuvant radiotherapy reduces local recurrence rates; however, it fails to improve overall survival in uterine sarcomas [8]. It should be noted that the interpretation of these studies is severely hindered by the inclusion of patients with mixed Müllerian tumours – a tumour type showing greater radiosensitivity than true uterine sarcomas.

The administration of postoperative chemotherapy has also been extensively examined in patients with localized non-GIST STSs regardless of the site of origin. In a meta-analysis of 14 randomized trials exploring doxorubicin-containing chemotherapy, absolute decreases of 6% [95% confidence interval (CI) 1–10] and 10% (95% CI 5–15) were seen at 10 years in the local recurrence rate and overall recurrence-free survival, respectively, for patients who received adjuvant chemotherapy. This finding, however, was not translated into a statistically significant improvement in overall survival (hazard ratio 0.89; 95% CI 0.76–1.03) [9]. There is one trial in localized uterine sarcoma. This study randomly assigned patients to observation or adjuvant doxorubicin after local treatment. Both approaches were equivalent in terms of local recurrences, progression-free and overall survival [10]. This study can be criticized, however, because of the small numbers of patients in the trial and the fact that patients with mixed Müllerian tumours were included. In view of these results, postsurgery chemotherapy cannot be considered standard of care for patients with a localized gynaecological sarcoma who are at high risk for relapse.

### Treatment of advanced disease

Similar to other STSs, gynaecological sarcomas generally metastasize to the lungs. In the situation where there are a limited number of metastases that are confined to the lungs and do not progress rapidly, durable progression-free survival can be obtained by metastasectomy. This procedure, however, is not feasible for the majority of patients with advanced disease for which palliative systemic treatment is indicated. There are only two agents with consistent antitumour activity against STSs, i.e. doxorubicin and ifosfamide. Although never directly compared, it is generally assumed that both drugs exhibit equivalent antitumour activity yielding response rates of 15–25% and a median overall survival of 10–12 months [11]. Single-arm studies specifically exploring ifosfamide in uterine leiomyosarcomas [12] and in endometrial stromal sarcomas [13] yielded similar outcomes.

Eight randomized trials have been conducted exploring doxorubicin monotherapy to combinations in metastatic non-GIST STSs, irrespective of histological subtype or primary site. In a meta-analysis of these studies from the Cochrane group [14], combination chemotherapy produced slightly higher response rates, but this result was not statistically significant (odds ratio 1.26; 95% CI 0.96–1.67). In addition, the overall survival at 2 years was equivalent between doxorubicin and the tested combinations (odds ratio 0.84; 95% CI 0.67–1.06). Combination chemotherapy is associated with increased toxicity, in particular more bone marrow suppression. In two of these randomized studies not only were patients with uterine sarcomas enrolled, but also those with mixed Müllerian tumours. Doxorubicin as single agent was compared with the combination of doxorubicin and dacarbazine in one trial [15], and to doxorubicin and cyclophosphamide in the other [16]. The outcomes of both studies were consistent with the overall results from the meta-analysis showing no benefit for combination chemotherapy over doxorubicin alone.

Given the major heterogeneity between non-GIST STSs, including different sensitivity to systemic agents, it is increasingly recognized that studies exploring compounds in STS should be stratified or specifically designed for particular histological subtypes and sites. In gynaecological STS subtypes several single-arm phase 2 studies have been carried out. Studies in uterine leiomyosarcomas have explored the efficacy of single agents such as etoposide, gemcitabine, paclitaxel, temozolomide and cisplatin, and combination regimens including hydroxyurea, dacarbazine and etoposide, and the combinations of doxorubicin + ifosfamide and gemcitabine + docetaxel [17]. In particular, the latter combination attracted attention in view of a high response rate of 53% and a median overall survival of 17 months [18]. A randomized study comparing gemcitabine to the
combination of gemcitabine and docetaxel has been performed in patients with advanced STSs, but the number of patients with uterine leiomyosarcomas included in this study is too small to draw firm conclusions [19]. Small studies performed in endometrial stromal sarcomas have focused on hormonal treatment as this entity, especially low-grade disease, frequently expresses estrogen or progesterone receptors [20] and the enzyme aromatase [21]. Tamoxifen exerts agonistic effects on endometrial tissue and patients using estrogen replacement therapy or tamoxifen are at increased risk of developing uterine sarcomas [22]. These observations support the assumption that estrogen may act as a driving factor for endometrial stromal sarcomas. Antitumour activity has been seen after the termination of estrogen replacement treatment or the administration of tamoxifen [23**]. In addition, small series have reported the use of aromatase inhibitors in postmenopausal women and durable progression-free survivals, and even complete responses, have been seen [23**,24].

It must, however, be emphasized that all these studies were not randomized and frequently enrolled small numbers of patients. The exact role of the tested regimens remains to be defined. In summary, doxorubicin monotherapy, or ifosfamide as a valid alternative, should be considered standard of care for patients with advanced disease.

**Future perspectives**

Currently, we are living in the era of targeted treatment. This treatment aims to exert antitumour activity through targeting tumour factor(s) that play an essential role in the pathogenesis of a particular malignancy or drives its growth. GIST is an example of how successful such an approach can be. The treatment of GIST was revolutionized following the discovery that GIST is driven by constitutively activated c-kit and the introduction of imatinib, a tyrosine kinase inhibitor inhibiting the function of c-kit [25]. Hormone receptors present potential targets in endometrial stromal sarcoma and in leiomyosarcomas several factors have similarly been identified, including c-kit [26] and metalloproteinases [27]. Just the presence of a target and the availability of a drug that can inhibit function are not, however, enough to expect antitumour activity. For instance, imatinib is only active against tumours harbouring activated c-kit due to activating mutations in the encoding gene. Until now, such c-kit mutations have not been found in leiomyosarcomas [26] and no responses have been demonstrated in patients with c-kit-positive leiomyosarcomas treated with imatinib [28].

A molecular target must play a pivotal role in pathogenesis or growth control and this holds true for c-kit in GISTs. In most tumours types, however, numerous driving pathways are simultaneously active. Inhibition of only one of these will not result in antitumour activity as long as the activity of the other pathway remains unaffected. Compounds targeting multiple rather than a single driving factor, therefore, are more likely to exert antitumour activity. Studies exploring the efficacy of drugs inhibiting a broad range of different tyrosine kinases and combinations of targeted drugs are ongoing in STSs.

Another promising approach is the application of drugs targeting angiogenesis, as this is thought to be crucial in the pathogenesis of malignancies including STS subtypes. Vascular endothelial growth factor (VEGF) plays an important angiogenesis-promoting role in many malignancies. In some of these, such as renal cell carcinoma, drugs inhibiting VEGF-mediated effects exhibit antitumour activity and such drugs are currently being tested in STSs.

Combining targeted agents and conventional cytotoxic drugs is another promising strategy. VEGF production by STS cell lines has been shown to confer resistance against conventional chemotherapeutic drugs [29]. Drugs inhibiting VEGF-mediated effects, therefore, may sensitize tumour cells to conventional chemotherapy. In addition, inhibition of VEGF has been shown to decrease the interstitial fluid pressure of tumours – a mechanism that may hinder drug penetration into tumours. Intratumoral concentrations of drugs are increased in preclinical models when administered together with compounds inhibiting VEGF activities [30]. This treatment is likely to augment antitumour activity. Trials exploring the combination of VEGF inhibitors and conventional chemotherapeutic agents in humans are well established.

**Conclusions**

Gynaecological sarcomas are rare and are treated by different strategies from more common gynaecological tumours. Patients with such tumours should, therefore, be treated by physicians familiar with the management of these entities and have access to a multidisciplinary approach to management.

Surgical resection forms the cornerstone of treatment for localized non-GIST gynaecological sarcomas. Adjuvant radiotherapy for uterine sarcomas is frequently applied and is likely to reduce local relapses, but has no proven overall survival benefit. There is no place for adjuvant systemic therapy. For patients with advanced disease, palliative chemotherapy with doxorubicin monotherapy should be considered, while ifosfamide is an alternative approach. There is no evidence from randomized studies that other drugs or combinations yield better outcomes.

For the future, attempts must be made to get more insight into the biology of gynaecological sarcomas as this may yield novel targets for treatment. This treatment...
requires close collaboration between basic scientists and clinicians. Clinical trials involving patients with STSs and gynaecological sarcomas should be stratified or specifically designed for certain tumour types given the great heterogeneity in terms of pathogenesis, clinical behaviour and sensitivity to apoptotic triggers such as radiotherapy or chemotherapy. Furthermore, only randomized studies will allow us to draw firm conclusions on the efficacy of novel treatment strategies. Given the rarity of gynaecological sarcomas, progress in the understanding and treatment of these tumours can only be achieved by intense international collaboration, which nowadays can be facilitated by organizations such as the Connective Tissue Oncology Society and the Connective Tissue Cancer Network.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 536).


