Operative and Conservative Treatment of Uterine Sarcomas

Operative und konservative Behandlung uteriner Sarkome

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Abstract

Uterine sarcomas are rare, aggressive mesenchymal tumours with a relatively poor prognosis. The term comprises various histological subtypes, such as leiomyosarcoma, endometrial stromal sarcomas as well as undifferentiated uterine sarcomas, which require different operative and systemic/radiation therapy strategies accordingly. The evidence on operative, adjuvant and palliative treatment currently available is presented here.

Zusammenfassung

Uterussarkome sind seltene, aggressive mesenchymale Tumoren mit relativ schlechter Prognose. Sie umfassen diverse histologische Subtypen, etwa Leiomyosarkome, endometriale Stromasarkome sowie undifferenzierte uterine Sarkome, die entsprechend unterschiedliche operative und system- bzw. strahlentherapeutische Strategien erfordern. Die gegenwärtig verfügbare Evidenz zur operativen, adjuvanten und palliativen Therapie wird dargestellt.

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Introduction

Uterine sarcomas are rare, particularly aggressive mesenchymal tumours that make up approx. 3% of all uterine malignancies [1]; its incidence is around 0.5–3.3 per 100 000 women per year [2]. Various histological subtypes are included under the term uterine sarcomas; the most frequent is leiomyosarcoma (LMS), followed by endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS) and pure heterologous sarcomas. Mixed epithelial and mesenchymal tumours include adenosarcomas and carcinosarcomas (mixed Mullerian tumours); as the latter have an epithelial origin, they are not included under sarcomas.

This article focuses on uterine tumours of mesenchymal origin, i.e. LMS, ESS and UUS.

Leiomyosarcoma (LMS) of the Uterus

LMS makes up approx. 1% of all uterine malignomas, with its incidence standing at 0.1–0.3 per 100 000 women per year [3,4]. Apart from a rapidly growing tumour in the pelvis, patients are typically asymptomatic and the diagnosis generally presents itself intraoperatively or postoperatively.

Upon initial diagnosis, the LMS is limited to the uterus in the majority of cases and the cure rate – between 20 and 60% in total – ultimately depends on the tumour stage and the kind of primary operation [5]. Other prognostic factors were discussed, but without a conclusive result so far [6]. Due to the relatively high rate of recurrence and the frequent distant metastasis, a comprehensive radiological staging with a CT or MRI of the thorax, abdomen and pelvis is necessary [7].

Operative treatment

Surgical tumour removal is currently the central component of treatment for the LMS, and total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO), if necessary, is generally the method of choice. Leaving the adnexa does not lead to a deterioration in the prognosis, meaning that this can be left in pre-menopausal women if they do not appear remarkable intraoperatively. Due to the low prevalence of lymph node metastases (3% in early stages), the extensive removal of pelvic and paraaortal lymph nodes is generally not indicated [6]. Lymph node involvement increases in later stages, however. As the LMS is frequently first diagnosed during or

Table 1 Adjuvant chemotherapy in the event of leiomyosarcoma.

	Entity	Stage	Design	Schedule	PFS	OS
Omura 1985	Uterine sarcomas	I, II	II (n = 156)	Adriamycin 60 mg/m² q 21 vs. observation	No significant difference	73 months vs. 55 months; p = n. s.
Harter 2011	Uterine/ovarian sarcomas	I–IV and recurrence	II (n = 40)	Pegylated lip. doxorubicin 40 mg/m² + carboplatin AUC 6 q28	8.6 months	29.5 months
Pautier 2012	Uterine sarcomas	I, II	II (n = 81)	Doxorubicin 50 mg/m² d1, ifosfamide 3 g/m²/d d1–2 + cisplatin 75 mg/m² d3, q21 → RT vs. RT	3 year PFS: 51 vs. 40%; p = 0.0048	3-year survival rate: 81 vs. 69%; p = 0.41
Hensley 2009	Uterine leio-myosarcomas	I–IV (18 Patients stage I/II)	II (n = 25)	4 × gemcitabine 900 mg/m² d1 and 8 + docetaxel 75 mg/m² d8	Stage I/II: 2 year PFS: 59%	Stage I/II: not reported
Hensley 2013	Uterine leio-myosarcomas	I, II	II (n = 47)	4 × gemcitabine 900 mg/m² d1 and 8 + docetaxel 75 mg/m² d8 → 4 × doxorubicin 60 mg/m² q21	2 year PFS: 78%	Not reported

following an operation for another indication (e.g. apparent leiomyoma), the method of laparoscopic uterus extraction via morcellation presents a potentially serious risk of an iatrogenic stage progression. This approach, e.g. in the context of a laparoscopically assisted supracervical hysterectomy, increases the risk of a dissemination of the tumour cells, which leads to a significant deterioration in overall and recurrence-free survival time (5-year survival rate: 73 → 46%!). Patients for whom such an intervention is planned due to a suspected diagnosis of a leiomyoma should be fully and openly informed. [7].

Adjuvant treatment

Due to the LMS's high level of aggression with a correspondingly high risk of local and/or distant recurrence even following the complete surgical removal of the primary tumour, additional non-surgical treatment approaches are also of significant interest. As radiation therapy has not proven to be effective in an investigation of stage I and II patients [8], current investigations concentrate on an optimisation of systemic therapy.

A certain standard regime with a proven efficacy is not (yet) currently available, but there are hints that chemotherapy (primarily doxorubicin ± ifosfamide) following complete surgical resection could increase overall progression-free survival time [9]; in a small randomised study, a combination of ifosfamide, doxorubicin and cisplatin with subsequent radiation therapy displayed a significant advantage in progression-free survival in comparison with radiation alone (3-year PFS 51 vs. 40%), but cannot be recommended for daily clinical use due to its toxicity [10].

In a single arm phase II study conducted by Hensley et al. [11], 47 patients received four cycles of gemcitabine in combination with docetaxel followed by four further cycles of doxorubicin following an operation upon the initial diagnosis of a uterine LMS. The progression-free 2 year and 3 year survival rates stood at 78% and 57% respectively. This schema is currently being carried out in a randomised study vs. the observation for patients with an initial diagnosis of an FIGO I LMS (GOG 277 protocol) (**Table 1**).

Treatment for recurrent LMS

Due to the relative rarity of LMS, there exist only a few systematic studies that investigated the treatment and prognosis of the recurrent form alone in comparison with other subtypes of uterine carcinoma or extra-pelvic forms of sarcoma, and it is currently unclear whether surgical tumour reduction can improve the prognosis in these cases. As with other issues regarding the treatment and management of the recurrent LMS, this must be decided on an individual basis.

In a randomised phase II study of patients with different soft tissue sarcomas [12], gemcitabine was compared with gemcitabine/docetaxel. The combination presented a significant advantage over monotherapy with gemcitabine with regard to progression-free survival (PFS) (6.2 vs. 3.0 months, p = 0.02) and overall survival (OS) (17.9 vs. 11.5 months, p = 0.03). However, the toxicity was significantly higher in the combination arm, and over 40% of patients terminated the treatment before its scheduled end due to poor tolerance. A further phase II study [13] comprised patients with advanced or recurrent liposarcoma or leiomyosarcoma, in which treatment with anthracycline and ifosfamide remained unsuccessful. Two different application schema of trabectedin monotherapy were compared in this study: a 24-hour intravenous infusion of 1.5 mg/m² every three weeks and a weekly infusion of 0.58 mg/m² over three hours. Here, the 24-hour infusion displayed a better clinical effect with a median PFS of 3.3 vs. 2.2 months (HR: 0.755; 95% CI: 0.574–0.992; p = 0.0418) and a median OS of 13.9 vs. 11.8 months (HR: 0.843; 95% CI: 0.653–1.090; p = 0.1920).

In the hitherto only double blind randomised placebo-controlled phase III study into treatment of metastatic and recurring soft tissue sarcoma, the application of pazopanib was investigated [14]. In comparison with the placebo, the oral treatment with 800 mg/day extended PFS by a median of 3 months (4.6 vs. 1.6 months; HR: 0.31; 95% CI: 0.24–0.40; p < 0.0001), the difference in the OS was somewhat less pronounced and not statistically significant (12.5 vs. 10.7 months; HR: 0.86; 95% CI: 0.67–1.1; p = 0.25).

In a further phase III study, ridaforolimus was used in maintenance therapy following cytotoxic chemotherapy induction. This displayed a significant advantage over the placebo regarding the primary endpoint (PFS) (17.7 vs. 14.6 weeks; HR: 0.72; p < 0.0001), whereby stomatitis presented as a side effect in the ridaforolimus arm in 52% of patients [15]. The full publication including OS data should enable a definitive evaluation of the potential role of ridaforolimus in the treatment of sarcomas.

Schöffski et al. [16] also showed that recurrent or metastasised LMS responded relatively well to chemotherapy in comparison with other forms of sarcomas. The combination of carboplatin and pegylated liposomal doxorubicin also appears to display a positive effectiveness safety profile in advanced or metastasised (epithelial) mesenchymal gynaecological tumours. In a phase II study of the AGO study group [17], a median PFS of 8.6 months was found in this situation (95% CI: 6.4–10.4 months) and an OS

of 29.5 months, whereby the 1-year survival rate was 77%. Garcia-Del-Muro et al. [18] compared the effectiveness of a combination of dacarbazine and gemcitabine with gemcitabine monotherapy in a population of 113 patients with recurrent soft tissue sarcoma (32 of which had LMS). This study found that the combination regime had a significant advantage with regard to PFS (4.2 vs. 2 months; HR: 0.58; 95% CI: 0.39–0.86; p = 0.005) as well as in terms of OS (16.8 vs. 8.2 months; HR: 0.56; 95% CI: 0.36–0.90; p = 0.014). In a phase II study by Pautier et al., the combination of trabectedin and doxorubicin was investigated. This study evinced a remission rate of 57%, which was significantly higher than the previously established pattern [19].
In Germany, the Pazo Doble study was started, in which gemcitabine in combination with pazopanib was compared against pazopanib alone.

Endometrial Stromal Sarcoma (ESS)

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An ESS is a rare subtype, making up between 6 and 20% of the already rare uterine carcinomas, or 0.2–1% of uterine malignomas, and primarily affects women in their fifties and sixties [2, 22]. The main symptoms of an ESS are abnormal ex utero bleeding (approx. 90%) and a palpable enlargement of the uterus (approx. 70%); pain and dysmenorrhea may be present, but not necessarily. Approximately 30–50% of ESS have already metastasised once the diagnosis has been reached [20]. However, local recurrences or distant metastases can occur up to twenty years following the initial diagnosis [6].
The early common classification of the ESS in low and high grade categories is now obsolete; differentiation must be made between endometrial stromal sarcomas and undifferentiated uterine sarcomas. Although ESS are generally predominately intramyometral, the involvement of the endometrium is frequent, and therefore curettage is often helpful in the preoperative diagnostic workup [21, 22]. In any case, the significance of the evaluation of curettage fragments is limited, meaning that the definitive diagnosis can only be made based on the hysterectomy preparation. Due to the low prevalence, there is only limited significant data on the treatment and outcome, and the existing evidence has predominately been obtained from retrospective case series with a low number of patients.

Operative treatment

The operative standard approach comprises an exploratory laparotomy, TAH/BSO, omental biopsy and aspiration of peritoneal fluid for the cytological investigation [6]. ESS frequently express oestrogen (ER) and progesterone receptors (PR), meaning that a hormone substitution may be contraindicated following BSO [23]. It is disputed as to whether the BSO in stage I of the ESS influences the PFS or OS, meaning that the theoretically possible improvement in the prognosis is weighed up against the undesired effects of the early surgical menopause [24].
The prevalence of lymph node involvement with ESS reported in the literature varies and amounts to a maximum of 10%, but most report considerably lower rates. While the resection of macroscopically suspect or remarkable lymph nodes is part of standard surgical procedure, systematic pelvic and paraaortal lymph nodectomies are regarded sceptically as routine surgical staging procedure, as the propagation of the ESS is predominately haematogenous [25].

Adjuvant treatment

The evidence for adjuvant treatment methods for ESS is decidedly scarce, and the close-meshed monitoring without specific intervention applies as standard in stages I and II; in further advanced stages, endocrine treatment may be worth considering in the event of ER or PR positive ESS. There are currently no indications of effectiveness for adjuvant radiation therapy for ESS (stages I and II) [10].
There are no studies with regard to chemotherapy that decidedly focus on ESS, and ESS is merely included as a subgroup in larger series, frequently without its own outcome analysis. In principle, the decision regarding the systemic treatment of ESS must be made on an individual basis, and no generally valid recommendations can be made. Should chemotherapy be contemplated, the results for LMS presented above can serve as a guide.
In the case of the receptor-positive forms of advanced/metastasised ESS, endocrine treatment with medroxyprogesterone (MPA) and aromatase inhibitors (AI) appears the most promising. In some cases, endocrine treatment has led to the illness being monitored for a longer duration [26].

Treatment for recurrent ESS

ESS recurrences most frequently occur in the abdominal cavity and pelvis (40–50%), followed by the lung (approx. 25%) [27, 28]. Late recurrences are also frequent following treatment of the primary illness, and so the treatment for the recurrence is of great importance in the context of the management of ESS. The treatment strategy for the ESS recurrence primarily depends on the previous endocrine treatment: should this *not* take place as part of the primary treatment, the administration of MPA and/or AI should be the method of choice in any case in the event of a recurrence.
However, for patients who display a progressive development or a recurrence following antihormonal treatment (in the adjuvant or first-line setting), cytotoxic therapy is the primary treatment considered. Here, especially in the absence of illness-specific evidence, the approach corresponds to that used in the event of recurrent or metastasised LMS, meaning that a gemcitabine/docetaxel and doxorubicin-based schemata is the primary one considered.

Undifferentiated Uterine Sarcoma (UUS)

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This independent entity comprises high-grade epitheloids and spindle cell sarcomas and makes up less than 5% of uterine sarcomas [6]. UUS grow quickly and display aggressive dispersion behaviour with a correspondingly poor prognosis (25–55% 5-year survival rate) [29, 30].

Operative treatment

In the absence of solid illness-specific evidence, TAH/BSO is recommended as the standard approach for a UUS in accordance with the other forms of uterine sarcoma [6]. Similar to the case with ESS, the significance of the systematic lymph nodectomy in the case of USS is not clear, but is disputed due to the primarily haematogenous propagation.

Adjuvant treatment

There is no conclusive clinical data on the adjuvant treatment of UUS. Due to the tumour-biological characteristics of a UUS, cytotoxic chemotherapy may be considered. Analogously to other soft

tissue sarcomas, doxorubicin and/or ifosfamide are primarily discussed.

Treatment for recurrent UUS

No randomised controlled studies exist for the treatment of the recurrent UUS in which UUS is differentiated from other tumour entities. Treatment is based on the same principles as other soft tissue sarcomas.

Summary

To summarise, the treatment of gynaecological sarcomas is complex and each individual entity requires specific treatment. At this stage, it is worth explicitly noting again that the risk factor of morcellation reduces the probability of survival by approx. 40%. Unfortunately, very few studies have been conducted for these entities in the past decade. Study activity into the optimisation of chemotherapeutic approaches as well as targeted treatments is now more active however, which is to be warmly welcomed.

Conflict of Interest

None.

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