Clinical Characteristics, Surgical Management and Adjuvant Therapy of Patients with Uterine Leiomyosarcoma: 27 Years of Experience

Klinische Charakteristika, operatives Management und adjuvante Therapie von Patientinnen mit uterinen Leiomyosarkomen: Erfahrungen der letzten 27 Jahre

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Schlüsselwörter
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- leiomyosarcoma
- uterine neoplasms
- lymphadenectomy
- adjuvant therapy

Abstract

Purpose: To review a single-center experience over a 27-year period in the management of uterine leiomyosarcoma (LMS) for insight into surgical practice, adjuvant therapy and clinical outcome.

Material and Methods: This was a retrospective study of women with histologically proven uterine LMS who were treated at the Department of Obstetrics and Gynecology, University of Tuebingen, Germany, between 1983 and 2010. Inpatient and ambulatory records were reviewed; follow-up and survival data were ascertained.

Results: The study sample comprised 32 patients with uterine LMS. Primary surgical treatment consisted of total abdominal hysterectomy in 28 patients (88%) and laparoscopic total hysterectomy in 4 patients (12%). Lymph nodes were dissected and evaluated in 17 women (53%); positive lymph nodes were present in 1 patient (6%). A total of 17 patients (53%) received adjuvant therapy. Median follow-up for disease-free survival (DFS) was 35.6 months and median DFS was 27.0 months for all patients. The median follow-up for overall survival (OS) was 51.3 months and the median OS was 28.0 months for our study group. The 5-year survival rate was 30%. There was no significant difference in DFS ($p = 0.76$) and OS ($p = 0.51$) between patients who received adjuvant therapy and those who did not.

Conclusion: Uterine LMS are rare and aggressive uterine neoplasms with high recurrence rates and metastatic potential. Surgery consisting of total hysterectomy with or without bilateral salpingo-oophorectomy is the most important treatment-element in patients with uterine LMS. Lymphadenectomy should be reserved for patients with clinically suspicious nodes.

Zusammenfassung

Einleitung: Im Folgenden wird die Erfahrung eines Zentrums von 27 Jahren bezüglich des Managements von uterinen Leiomyosarkomen (LMS) mit besonderem Fokus auf operative Techniken, adjuvante Therapie und klinisches Outcome dargestellt.

Material und Methoden: Dies ist eine retrospektive Studie von Frauen mit einem histologischen Nachweis eines uterinen LMS, die in der Universitätsfrauenklinik Tübingen zwischen den Jahren 1983 und 2010 therapiert wurden. Sowohl der stationäre Aufenthalt als auch die ambulante Betreuung wurden analysiert, die Überlebensdaten wurden exploriert.

Ergebnisse: Die Studienpopulation beinhaltete 32 Patientinnen mit uterinen LMS. Die operative Primärtherapie beinhaltete entweder eine totale abdominale Hysterektomie bei 28 Patientinnen (88%), oder eine totale laparoskopische Hysterektomie bei 4 Patientinnen (12%). Lymphonodektomien wurden bei 17 Patientinnen (53%) durchgeführt, eine Nodalpositivität ergab sich bei einer Patientin (6%). In Summe erhielten 17 Frauen (53%) eine adjuvante Therapie. Der mittlere Nachbeobachtungzeitraum für Disease free Survival (DFS) betrug 35.6 Monate, das DFS an sich betrug 27,0 Monate für alle Patientinnen. Der mittlere Nachbeobachtungszeitraum für Overall Survival (OS) betrug 51,3 Monate bei einem mittleren OS von 28,0 Monaten. Das 5-Jahres-Überleben betrug 30%. Beim Vergleich zwischen den Patientinnen, die eine adjuvante Therapie erhielten und denen ohne diese Therapie fanden sich keine signifikanten Unterschiede im DFS ($p = 0,76$) und im OS ($p = 0,51$).

Zusammenfassung: Uterine LMS sind seltene und aggressive uterine Neoplasien mit einem hohen

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Rezidiv- und Metastasierungsrisiko. Die operative Therapie beinhaltet als wichtigstes Element die totale Hysterektomie mit oder ohne beidseitige Adnexektomie. Eine Lymphonodektomie sollte den Fällen mit klinisch auffälligen Lymphknoten vorbehalten sein.

Introduction

Uterine leiomyosarcomas (LMS) are rare uterine neoplasms, which account for 1% of all uterine malignancies and approximately one third of all uterine sarcomas [1]. Uterine LMS carry a poor prognosis with five-year survival rates ranging between 4 and 75% for all stages of disease, and five-year recurrence rates ranging between 45 and 73% [2–4]. The histologic diagnosis of uterine LMS relies on the presence of mitotic activity, necrosis and atypia. Nevertheless, in some cases, in the absence of cytogenetic and molecular characterization, leiomyoma variants (uterine lesions with a benign clinical course or having low malignant potential) are misdiagnosed as uterine LMS [5,6].

Symptoms of uterine LMS are commonly reported as abdominal pain, the presence of a pelvic mass and abnormal bleeding [7]. The absence of pathognomonic features on imaging techniques like ultrasonography, CT and MRI makes a reliable preoperative diagnosis of uterine LMS difficult [8,9]. Thus, the diagnosis of LMS is often unexpected and discovered incidentally following surgery for uterine leiomyomas [10,11].

Surgery is the most important element in the therapy of uterine LMS; total hysterectomy with or without bilateral salpingo-oophorectomy (BSO) represent the initial standard management for LMS [12]. Furthermore, primary surgery, complete cytoreduction and secondary cytoreductive surgery can help to achieve favorable prognoses in patients with uterine LMS [3,13,14].

However, the role of adjuvant therapy after surgery for LMS continues to be undefined [4,15]. Two randomized controlled trials, both including only a total of 151 patients with uterine LMS, have addressed the potential benefit of adjuvant therapy [16,17]. Neither the administration of adjuvant chemotherapy with doxorubicin nor adjuvant radiation therapy did improve survival of patients with LMS [16,17].

Due to the rareness of the disease and lack of prospective RCTs, guidelines of therapeutic management for uterine LMS have low levels of evidence. Hence, there is a continued need for review of past and current practice. The present study reviews the experience over a 27-year period of the Department of Obstetrics and Gynecology, University of Tuebingen, Germany, in the management of uterine LMS for insight into surgical practice, adjuvant therapy and clinical outcome.

Material and Methods

This was a retrospective study conducted at the Department of Obstetrics and Gynecology, University of Tuebingen. Using institutional databases from the clinical cancer registry of the Comprehensive Cancer Centre Tuebingen, we identified all women who were included in the registry with uterine LMS as final diagnosis between January 1st, 1983 and January 31st, 2010.

Diagnoses of the identified uterine LMS cases were manually compared with the pathology reports; the sources agreed in 32 out of 33 (97%) of cases. Only histologically confirmed cases were analyzed. One case was excluded because histology revealed a diagnosis of benign metastasizing leiomyoma. Thus, the study group comprised 32 patients with a diagnosis of uterine LMS.

A retrospective medical record review of both inpatient and ambulatory records (Department of Obstetrics and Gynecology, University of Tuebingen) was performed to ascertain sociodemographic and anthropometric variables, as well as to confirm intraoperative and pathologic findings. Furthermore, adjuvant therapy data were recorded. The clinical cancer registry of the Comprehensive Cancer Centre Tuebingen provided follow-up and survival data. Time to disease recurrence and death or last contact was calculated. Premenopausal status was defined as occurrence of at least one menstrual period within 12 months before surgery. Adjuvant treatment was performed in selected patients at the discretion of the tumor board. We assessed the disease stage retrospectively for every patient using the new 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, used specifically for uterine sarcomas [18]. We grouped the study sample in patients with “disease limited to the uterus” (FIGO stages IA and IB) and patients with “extrauterine disease” (FIGO stages IIA – IVB) to analyze the influence of disease stage on survival.

Data was coded and entered into an Excel spreadsheet version 2007 (Microsoft, Redmond, Washington DC, USA). Statistical analysis was carried out using JMP for Windows version 8.0 (SAS Institute Cary, NC, USA) and Prism 5 (GraphPad Software, La Jolla, CA, USA). Means, standard deviations (SD) and medians are reported for continuous variables and frequency counts and percentages for categorical variables. Survival curves were generated using the Kaplan-Meier method and compared using the long-rank test. Calculation of disease free survival (DFS): 7 patients were lost to follow-up, 11 patients were censored having no disease recurrence at last follow-up and 14 patients had disease recurrence. Calculation of overall survival: 5 patients were lost to follow-up, 12 patients were censored being alive at last follow-up and 15 patients died of uterine LMS. p-values < 0.05 were considered statistically significant in all statistical analyses.

Results

The study sample comprised 32 patients with uterine LMS that underwent treatment at our institution. Between January, 1st 1983 and December, 31st 1999 a total of 12 cases were identified, between January, 1st 2000 and January, 31st 2010 we identified 20 women that underwent treatment for uterine LMS. The median follow-up for survivors was 87.5 months. Patient characteristics are summarized in **Table 1**. The mean age was 56.0 years (range 34–81). At the time of primary surgical treatment, 69% of the patients were postmenopausal. A pelvic mass was the most common presenting symptom and was reported by 44% of the patients; abdominal pain was reported by 38% of the patients, abnormal bleeding was reported by 34% of the patients and 13% of the patients reported both abdominal pain and abnormal bleeding as presenting symptoms (**Table 1**).

Tumor markers were evaluated in 22 women and were elevated in 10 women (45%). CA 125 was elevated in 9 patients, CEA in 3

Table 1 Characteristics of 32 patients with leiomyosarcoma of the uterus.

Characteristics	Value
	Mean
Age at diagnosis (range), years	56,0 (34–81)
Size uterine lesion (± SD), cm	10,2 (± 4,2)
Uterine/composite compound weight (± SD), g	766,2 (± 623,3)
Preoperative symptoms*	**No. (%)**
Pelvic mass	14 (44)
Abdominal pain	12 (38)
Abnormal bleeding	11 (34)
Abdominal pain and abnormal bleeding	4 (13)
FIGO Stage	
I	23 (72)
II	3 (9)
III	2 (6)
IV	4 (13)
Grade	
I	6 (19)
II	8 (25)
III	18 (56)
Mitosis < 10/10 HPF	14 out of 27 (52)
Mitosis ≥ 10/10 HPF	13 out of 27 (48)
Bilateral Salpingo-oophorectomy	27 (84)
Lymphadenectomy	
Pelvic	17 (53)
Para-aortic	5 (16)
Adjuvant chemotherapy	8 (25)
Adjuvant radiation therapy	5 (14)
Combined adjuvant therapy	4 (13)

* The sum of numbers for each variable exceeds the total number of patients because some patients had multiple conditions that apply.

patients and CA 15-3 in 1 patient (data not shown). The mean size of the uterine lesions was 10.2 ± 4.2 cm (SD; range 4–40 cm) (**Table 1**).

There were 23 patients (72%) with FIGO stage I, 3 patients (9%) with stage II, 2 patients (6%) with stage III and 4 patients (13%) with stage IV disease. Distribution by grade revealed 6 patients (19%) with grade 1 disease, 8 patients (25%) with grade 2 disease and 18 patients (56%) with grade 3 disease. The median mitotic count of all patients was 9 (range 5/10 high-power fields [HPF] – 50/10 HPF). Fourteen women had a low mitotic count (< 10/10 HPF), whereas 13 women had a higher mitotic count (≥ 10/10 HPF) (**Table 1**).

Primary surgical treatment consisted of total abdominal hysterectomy in 28 patients (88%) and laparoscopic total hysterectomy in 4 patients (12%). Six women (19%) underwent surgery for presumed symptomatic leiomyoma recurrence. BSO was performed in 84% of the patients (27/32), 8 out of 10 premenopausal patients underwent BSO. Lymph nodes were evaluated in 17 women (53%), 12 women underwent pelvic lymphadenectomy and 5 women underwent pelvic and para-aortic lymphadenectomy (**Table 1**). Positive pelvic lymph nodes were present in 1 patient (6%) with extrauterine disease; there were no reported positive para-aortic lymph nodes.

A total of 17 patients (53%) received adjuvant therapy (**Table 1**). Among those, 5 patients received adjuvant radiation therapy. Adjuvant chemotherapy was administered to 8 patients and 4 patients received combined adjuvant radiation therapy and chemotherapy (**Table 1**). Chemotherapy consisted of doxorubicin in 2 patients (one patient also received radiation therapy), doxorubicin and ifosfamide in 3 patients, non-pegylated liposomal doxorubicin and carboplatin in 2 patients and epirubicin and ifosfamide in 1 patient. The administered chemotherapy regimen was unknown in 4 patients.

Table 2 Sites of local and distant recurrence in 32 patients with uterine leiomyosarcoma.

Site	No. of cases (%)
Vagina	2 (6)
Pelvis	3 (9)
Lung	8 (28)
Bone	3 (9)
Brain	1 (3)
Lung and pelvis	2 (6)

There were a total of 19 (59%) disease recurrences in our study group. Five women had pelvic recurrence, 12 women had distant recurrence and 2 patients had both pelvic and distant recurrence (**Table 2**). The sites of distant recurrence included lungs (10 patients), bone (3 patients), and brain (1 patient) (**Table 2**).

DFS and OS of patients with LMS are shown in **Figs. 1** and **2**. Median follow-up for DFS was 35.6 months and median DFS was 27.0 months for all patients (**Fig. 1**). By log-rank test DFS was not significantly related to menopausal status ($p = 0.52$), mitosis rate ($p = 0.27$) and age (< 50 years vs. ≥ 50 years; $p = 0.83$).

The median follow-up for OS was 51.3 months and the median OS was 28.0 months for our study group (**Fig. 2**). The 5-year survival rate was 30% (**Fig. 2**). OS was not significantly related to menopausal status ($p = 0.40$), mitosis rate ($p = 0.69$) and age (< 50 years vs. ≥ 50 years; $p = 0.86$). There was no significant difference in DFS ($p = 0.76$) and OS ($p = 0.51$) between patients who did or did not receive adjuvant therapy. Furthermore, the clinical stage of uterine LMS, "disease limited to uterus" (FIGO stage I, OS54.0 months) vs. "extrauterine disease" (FIGO stages II–IV, OS17.0 months), also was not statistically significant in determining survival (data not shown).

Discussion

Uterine LMS are a rare and aggressive subtype of uterine malignancies. Due to the rareness of the disease high-level evidence guidelines of therapeutic management are nonexistent. Hence, there is a need for individual centers to report data of surgical management, adjuvant treatment and clinical outcome in patients with this disease. The present study reviewed the experience over a 27-year period in our department in the management of uterine LMS.

Menopausal status and patient age at diagnosis have been identified in several studies as independent prognostic factors for survival in women with uterine LMS [19–21]. Postmenopausal patients with uterine LMS have been described to have a poor prognosis compared to premenopausal patients with LMS [22,23]. Our results, however, are in accordance with the results of Barter et al. and Mayerhofer et al. indicating that menopausal status has no prognostic significance on survival in patients with LMS [7, 24]. Additionally, younger women with uterine LMS have been reported to have better outcomes [3,4,19,25,26]. Conversely, in our series of patients age (< 50 years vs. ≥ 50 years) did not have any significant effect on survival, in concordance with previous published data [23,24].

Five-year survival rates for uterine LMS range between 4% and 75% for all stages of disease. Kapp et al. interpreted this wide var-

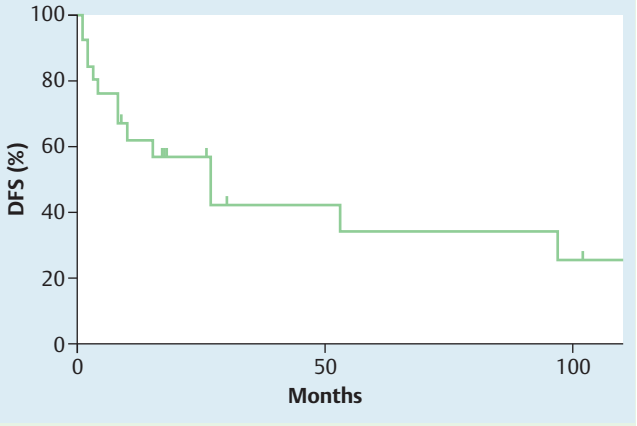

Fig. 1 Kaplan-Meier analysis of disease free survival (DFS) of patients with leiomyosarcoma of the uterus.

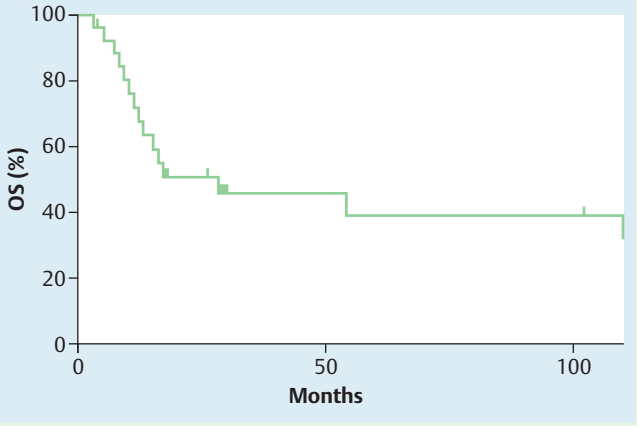

Fig. 2 Kaplan-Meier analysis of overall survival (OS) of patients with leiomyosarcoma of the uterus.

iation as being a result of multiple factors: small sample sizes, failure to use standardized histopathologic criteria, various proportions of low- and high-stage patients and inclusion of patients with various treatment approaches [3]. We observed a five-year OS rate of 30% in accordance with several other studies: Hannigan et al. observed a 5-year OS rate of 29%, Blom et al. reported a five-year OS rate of 33% and Loizzi et al. reported a five-year OS of 32% [23,27,28]. It is clear that early stage disease has an influence on the 5-year overall survival in patients with uterine LMS, since dismal results have been noted in nearly all series for patients with advanced-stage disease [3].

However, in contrast to the majority of studies on uterine LMS, in which tumor stage was strongly correlated with prognosis, we did not observe any correlation between this variable and survival [9,12,29]. We found only one other study that also failed to show a prognostic value of tumor stage in patients with uterine LMS [24]. A possible explanation for this discrepancy to previously published data might be the small sample size of our study.

Another controversial issue regarding prognostic factors in women with uterine LMS is the mitosis rate. We did not observe any correlation between mitosis rate and DFS and OS consistent with several other studies [28,30]. Other studies, on the contrary, found a significant association between mitosis rate and survival at least in subgroups of patients with uterine LMS [7,22,31].

Surgery is the most important treatment-element in patients with uterine LMS; the absence of primary surgery and/or incomplete cytoreduction have been shown to be independent prognostic factors for survival [12]. Many investigators recommend total hysterectomy with bilateral salpingo-oophorectomy (BSO) and lymphadenectomy as the standard treatment for patients with operable uterine LMS [3]. Nonetheless, evidence supporting both BSO and lymphadenectomy for uterine LMS is sparse and controversial.

Eight out of 10 premenopausal patients in our study underwent BSO at primary surgery. Several studies addressed the issue of preservation of ovaries in premenopausal women with uterine LMS and that ovarian preservation did not adversely affect outcome [22,26,32]. Giuntoli et al. unexpectedly found in univariate analysis a significant association between ovarian preservation and improved survival in a series of 208 patients with uterine LMS [4]. However, the presumed correlation of ovarian preservation and improved survival in patients with LMS of the uterus was no longer significant as this specific subgroup of patients was further analyzed in a case-control study [4]. Moreover, a study of 1396 women with uterine LMS revealed no survival difference between women with ovarian preservation and women that underwent BSO [3]. Thus, ovarian preservation in premenopausal women in the absence of hormone-sensitive uterine LMS does not compromise the oncologic outcome.

The role of lymphadenectomy in patients with uterine LMS is likewise unclear, since the literature on lymph node metastases associated with LMS is limited mainly consisting of small, retrospective case series. In agreement with our series demonstrating an incidence of lymph node metastases of 6% (1 of 17 patients), the incidence of lymph node metastases in patients with uterine LMS is described in several other studies as being low, varying between 7 and 9% [3,33,34]. Additionally, involvement of lymph nodes in patients with uterine LMS is mostly associated with advanced stage disease or with macroscopically visible enlargement of the lymph nodes in early stage disease. In a series of 1396 patients, lymphadenectomy failed to be an independent prognostic factor for survival [3]. As a result, lymph node dissection for uterine LMS should be reserved for patients with clinically suspicious nodes [33].

In our series of patients 19 of 32 women with uterine LMS developed disease recurrence. Consistent with other studies, the majority of recurrences involved distant spread outside the pelvis [7,26,35]. Hence, the use of adjuvant therapy to reduce local and distant relapses could be an attractive option in patients with LMS but evidence on the role of adjuvant therapy in uterine LMS is limited [12]. Although the effect of adjuvant therapy cannot be determined reliably in an analysis of a disease with mixed stages and grades, in agreement with previous reports we found no significant difference in DFS and OS between women that received adjuvant therapy and those who did not [4,26,36]. Adjuvant radiation therapy does not appear to have a survival benefit in LMS, although it may reduce local recurrences in women with FIGO stage II–IV disease [21,37]. Regarding adjuvant chemotherapy, only one prospective phase II study and one retrospective study demonstrated benefit on DFS of adjuvant chemotherapy in patients with uterine LMS [38,39]. Thus, women with uterine LMS and higher risk of local recurrence might benefit from adjuvant radiation therapy, but the routine use of adjuvant chemotherapy in uterine LMS is not recommended outside of clinical trials.

Major limitations of this study are its retrospective design and the small number of patients with uterine LMS included. However, the long follow-up augments the assessment of clinical

characteristics. Prospective studies with larger cohorts including new prognostic factors would be important to be able to predict the prognosis of patients with uterine LMS and to gain insight in the pathogenesis of this rare disease in a better way. Additionally, future prospective studies should address the role of adjuvant therapy, patient selection criteria, and optimal adjuvant therapy regimes for uterine LMS.

Conclusions for Practice

Uterine LMS are rare and aggressive uterine neoplasms with high recurrence rates and metastatic potential. Surgery consisting of total hysterectomy with or without BSO is the most important treatment-element in patients with uterine LMS. Lymphadenectomy should be reserved for patients with clinically suspicious nodes. Women with uterine LMS and higher risk of local recurrence might benefit from adjuvant radiation therapy, but the routine use of adjuvant chemotherapy in uterine LMS is not advocated outside of clinical trials.

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Conflict of Interest

None.

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