Zdravljenje maternič nih sarkomov v Univerzitetnem kliničnem centru Maribor v obdobju 1996–2011

Treatment of uterine sarcomas at the Maribor University Clinical Centre between 1996 and 2011

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Izvleček

Namen: *Maternični sarkomi so redki maligni tumorji s slabšo prognozo od endometrijskih karcinomov. Pričujoča retrospektivna študija predstavlja pregled kliničnih in histoloških značilnosti, zdravljenja in izida zdravljenja pri bolnicah, ki smo jih zaradi maternič nih sarkomov zdravili v naši ustanovi v 16–letnem obdobju.*

Metode: *V obdobju 1996–2011 smo v Univerzitetnem kliničnem centru Maribor zdravili 22 bolnic s sarkomom maternice (srednja starost 60,5 let). Podatke smo zbrali retrospektivno iz bolnišničnih in ambulantnih popisov ter iz Registra raka za Slovenijo. Vse tumorje smo klasificirali v skladu z novo FIGO klasifikacijo maternič nih sarkomov.*

Rezultati: *Večina bolnic je pred diagnozo navajala pomenopavzne krvavitve. Najpogostejši histološki podtip je bil leiomiosarkom (50 %), sledila sta*

Abstract

Purpose: *Uterine sarcomas are rare malignant tumours with a worse prognosis than endometrial carcinomas. This retrospective study was performed to determine the clinical and histologic characteristics, treatment, and outcomes in uterine sarcoma patients treated at our hospital over a 16–year period.*

Methods: *Twenty–two patients (median age, 60.5 years) with uterine sarcomas were treated at our facility between 1996 and 2011. Information was collected from hospital and follow–up records and from the Cancer Registry of Slovenia. All tumours were classified according to the new FIGO classification for uterine sarcomas.*

Results: *The majority of the patients presented with postmenopausal bleeding. The most common histologic subtype was leiomyosarcoma*

mu karcinosarkom (40,9 %) in endometrijski stromalni sarkom (9,1 %). Vse bolnice smo primarno zdravili kirurško, od tega 21 z laparotomijo in eno laparoskopsko. 8 bolnic je prejemalo pooperativno radioterapijo, 4 so prejemale pooperativno kemoterapijo. Progres bolezni smo ugotovili pri 8 izmed 17 bolnic, za katere smo imeli zadostne podatke. 5–letno celokupno preživetje je bilo 44 %.

Zaključek: *Celokupno preživetje bolnic, zdravljenih zaradi sarkoma maternice, je v naši raziskavi relativno dobro. Zaradi majhnega števila bolnic in njihove heterogenosti bi bile za zanesljivo analizo dejavnikov, ki vplivajo na preživetje bolnic z maternicnim sarkomom, potrebne večje multicentrične raziskave.*

(50%), followed by carcinosarcoma (40.9%), and endometrial stromal sarcoma (9.1%). All of the patients were initially treated surgically, 21 by laparotomy and 1 laparoscopically. Eight patients were treated with post–operative radiotherapy and 4 patients received post–operative chemotherapy. Disease progression was observed in 8 of 17 patients who had sufficient follow–up information for this analysis. The 5–year overall survival was 44%.

Conclusion: *The overall survival of patients treated for uterine sarcomas in our study was comparatively good. Due to the small number and heterogeneity of the patients, larger multi–centre trials are needed for a reliable analysis of factors influencing patient survival.*

INTRODUCTION

Uterine sarcomas are malignant tumours of mesenchymal origin that carry a worse prognosis than more common epithelial uterine carcinomas, and have an overall 5–year survival from 17.5%–54.7% (1). Uterine sarcomas have been traditionally divided into three major subtypes: carcinosarcoma, also known as malignant mixed Mullerian tumor (MMMT); leiomyosarcoma; and endometrial stromal sarcoma (2). Carcinosarcomas and leiomyosarcomas each represent approximately 40% of uterine sarcomas and endometrial stromal sarcomas represent approximately 15% of all uterine sarcomas (3). Previously staged like endometrial carcinomas, a new classification and staging of uterine sarcomas was introduced in 2008, reflecting the different characteristics of the tumour (4). As uterine sarcomas represent only 4%–9% of all uterine malignancies, randomized studies analyzing prognostic factors or treatment outcomes are scarce (5). The conventional initial treatment for uterine sarcomas is surgical, consisting of total abdominal hysterectomy, bilateral salpingo–oophorectomy, and metastasectomy in the case of tumour spread outside the uterus (6). The benefits of adjuvant or primary radiotherapy and chemotherapy are controversial (7–9). Hormonal therapy can also be useful in some patients (10, 11).

The present retrospective study summarizes our experience with uterine sarcomas between 1996 and 2011.

MATERIAL AND METHODS

We retrospectively analyzed information on 22 patients with the diagnosis of uterine sarcoma treated at the Maribor University Clinical Centre between January 1996 and December 2011. Patient hospital records, surgical and histology reports, and records on post–operative treatment and follow–up visits were evaluated. Information on disease progression was obtained from records of follow–up visits and the hospital's electronic patient information system. Information on date and cause of death was additionally obtained from the Cancer Registry of Slovenia. The median time of follow–up was 19.5 months (range, 4–168 months).

According to the histologic diagnosis, the patients were divided into those with leiomyosarcomas, carcinosarcomas (MMMTs), and endometrial stromal sarcomas. The 2008 International Federation of Gynaecology and Obstetrics (FIGO) staging system for uterine sarcomas was used for all patients and applied retrospectively for patients treated before

2008. Stage I represents disease confined to the uterus. Stage II indicates that the cancer has spread outside the uterus, but not outside the pelvis. Stage III signifies disease that has invaded various abdominal tissues or spread to the pelvic and/or para–aortic lymph nodes. Stage IV is defined as spread to the rectum, bladder, or distant locations. Tumour differentiation was specified as low (G1), moderate (G2), or high grade (G3).

Data on disease progression were not available for 5 patients who were lost to follow–up. Information on date and cause of death was available for all patients from the Cancer Registry of Slovenia, therefore the overall survival (the period between the date of diagnosis and the date of death for any reason) was calculated for all patients using the Kaplan–Meier method.

Statistical analysis was performed using SPSS Statistics 17.0 (IBM, Armonk, NY, USA).

RESULTS

The median age of the patients was 60.5 years (range, 34–87 years). Of the patients, 77.3% were postmenopausal at the time of diagnosis. The most common presenting symptom was postmenopausal bleeding, which was present in 65% of the patients. Figure 1 shows the prevalence of other presenting symptoms. Patient distribution according to histologic subtype of sarcoma, FIGO 2008 stage, and tumour differentiation is shown in Table 1.

In 9 patients (40.9%) the diagnosis was made with cervical dilatation and curettage, 7 (31.8%) were diagnosed post–operatively after hysterectomy, 3 patients (13.6%) were diagnosed with hysteroscopy, 1 (4.5%) was diagnosed after laparoscopic myomectomy, 1 patient was diagnosed after pelvic exenteration with resection of the bladder and rectum, and 1 patient was diagnosed after ablation of a struc-

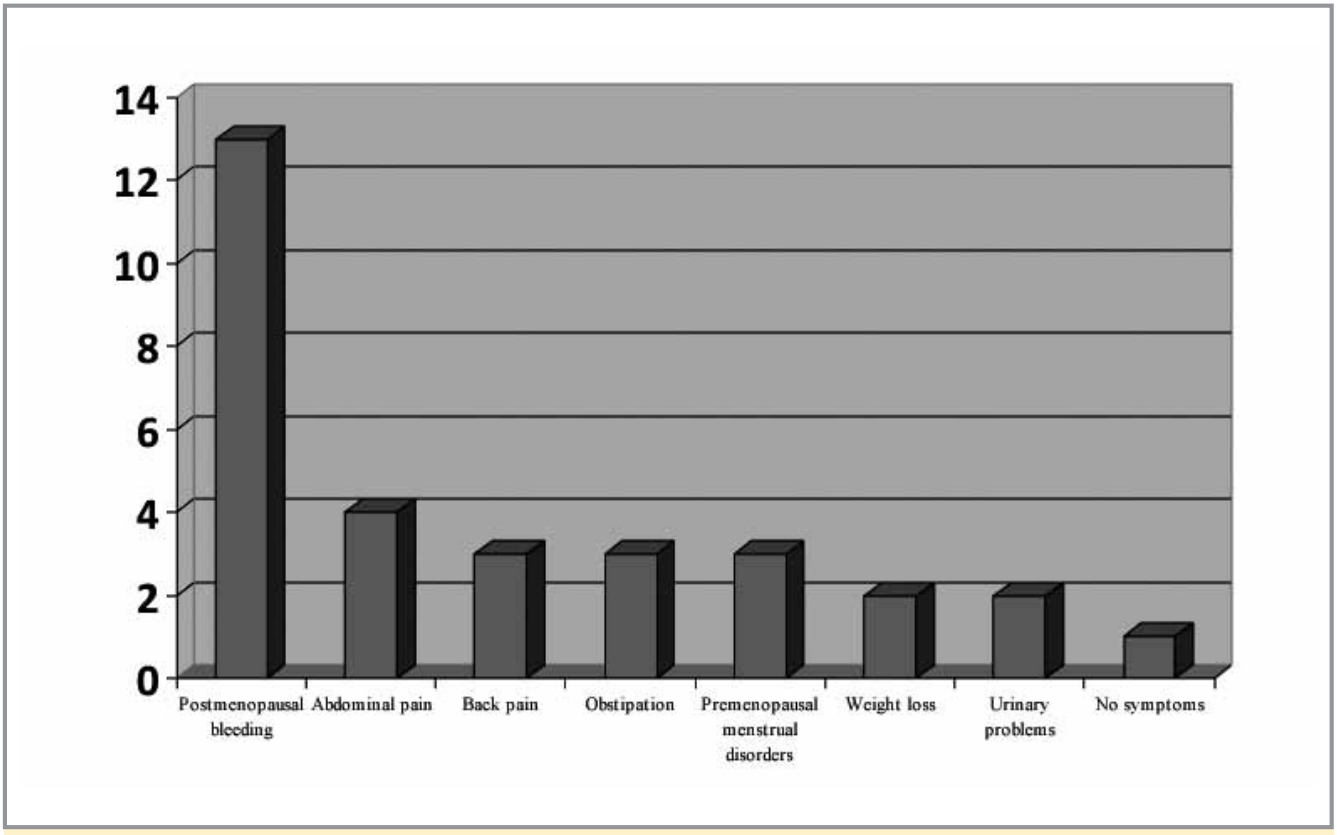

Figure 1. *The prevalence of different presenting symptoms. One patient could name more than one presenting symptom. The data for 2 patients were unavailable. N = 20.*

Table 1: *Patient distribution according to histologic subtype of sarcoma, stage, and differentiation.*

	Leiomyosarcoma	Carcinosarcoma	Endometrial stromal sarcoma	Total
No. of patients (%)	11 (50.0)	9 (40.9)	2 (9.1)	22
Median age (yrs)	59	67	58.5	60.5
FIGO stage – N (%)				
I	5 (45.5)	6 (66.7)	0	11 (50.0)
II	2 (18.2)	1 (11.1)	0	3 (13.6)
III	1 (9.1)	1 (11.1)	1 (50.0)	3 (13.6)
IV	3 (27.3)	1 (11.1)	1 (50.0)	5 (22.7)
Differentiation – N (%)				
G1	2 (18.2)	1 (11.1)	0	3 (13.6)
G2	2 (18.2)	3 (33.3)	0	5 (22.7)
G3	7 (63.6)	3 (33.3)	1 (50.0)	11 (50.0)
Unknown	0	2 (22.2)	1 (50.0)	3 (13.6)

ture protruding from the cervical canal. Nineteen (86.4%) patients underwent pre–operative chest imaging and lung metastases were noted in 1 patient. Seventeen (77.3%) patients had a pre–operative abdominal ultrasound examination, and liver metastases were demonstrated in 1 patient.

All patients were initially treated surgically. Seventeen patients (77.3%) underwent total abdominal hysterectomy with bilateral salpingo–oophorectomy. A total abdominal hysterectomy with unilateral salpingo–oophorectomy was performed in 2 patients (9%). Abdominal hysterectomy only was performed in one patient with stage IVB leiomyosarcoma. A patient with stage IA leiomyosarcoma whose diagnosis was established after laparoscopic supracervical hysterectomy underwent laparoscopic resection of the uterine cervix in a secondary procedure. In one patient, the diagnosis of stage IVB endometrial stromal sarcoma was made 6 years after total abdominal hysterectomy for a myomatous uterus. She underwent pelvic exenteration in the Department of Abdominal Surgery of our Clinical Centre. Additional procedures were performed in 9 of the 18 patients treated with total abdominal hysterectomy with bilateral salpingo–oophorectomy, including adhesiolysis in 7 cases, omentectomy in 4 cases, and appendectomy in 3 cases. Pelvic lymphadenectomy was performed in seven patients and para–aortic lymphadenectomy was performed in one patient. Resection of macroscopically visible metastases in the abdominal cavity was performed in three patients. No visible disease remained in the abdominal cavity after the surgery in 19 patients (86.4%), residual tumour < 2 cm in diameter was present in 1 patient (4.5%), and residual tumour > 2 cm remained in 1 patient (4.5%). For one patient we did not have information regarding residual tumour. Peri–operative complications in terms of excessive bleeding were observed in one patient. Post–operative complications were noted in 6 patients (27.3%) and consisted of 5 cases of urinary tract infections, inflammation of the operative wound, and one case of ureterovaginal fistula.

Detailed histologic reports were available for 21 patients. Tumour invasion of the uterine cervix was observed in 2 patients, as was invasion of the ovaries. The fallopian tubes were infiltrated with tumour in one patient. There were 4 patients in whom the disease had spread to different parts of the bowel and 3 patients had histologically–confirmed distant metastases to the retroperitoneum, pouch of Douglas, omentum, and plica vesicouterina. The average

Table 2: Initial treatment combination for different histological subtypes. N = 21.

	Leiomyosarcoma	Carcinosarcoma	Endometrial stromal sarcoma	Total
Surgery	6 (28.6%)	3 (14.3%)	2 (9.5%)	11 (52.4%)
Surgery + radiotherapy	2 (9.5%)	4 (19.0%)	0	6 (28.6%)
Surgery + chemotherapy	1 (4.8%)	1 (4.8%)	0	2 (9,5%)
Surgery + radiotherapy + chemotherapy	1 (4.8%)	1 (4.8%)	0	2 (9.5%)

number of resected lymph nodes in the 7 patients who had undergone lymphadenectomies was 22.1. Lymph node metastases were noted in two patients. Information on post–operative treatment was available for 21 patients and is summarized in Table 2. Of the eight patients who were treated with post–operative radiotherapy at the Ljubljana Institute of Oncology, seven underwent teleradiotherapy and intracavitary radiotherapy was used in one patient. Post–operative chemotherapy was applied in four patients. A patient with stage IIA leiomyosarcoma received three cycles of epidoxorubicin and 1 patient with stage IIIB carcinosarcoma received four cycles of cisplatin and ifosfamide. One patient with stage IVB carcinosarcoma and simultaneous breast cancer received six cycles of paclitaxel and carboplatin; this patient also received letrozole. Detailed information on the chemotherapy of the fourth patient was not available.

Seventeen patients had sufficient follow–up information for assessment of disease progression. Progression was observed in eight patients (four of nine patients with leiomyosarcomas, two of six patients with carcinosarcomas, and in both patients with endometrial stromal sarcomas). The median time–to–progression in these patients was 9.5 months (range, 4–28 months). The most commonly observed site of progression was the abdominal cavity, followed by the lungs, bone, and soft tissues of the pelvis. In two cases, disease progression was treated with chemotherapy using a combination of ifosfamide and doxorubicin and epidoxorubicin as monotherapy, respectively. Chemotherapy was discontinued in both cases due to inefficacy and adverse reactions.

Overall survival (OS) was calculated for all 22 patients. Twelve patients died during the follow–up period. The median OS was 26 months. The 1–year survival was 60% and the 5–year survival was 44%.

DISCUSSION

Uterine sarcomas arise from mesenchymal and stromal parts of the uterus and are much rarer than tumours of epithelial origin. Uterine sarcomas represent 3%–7% of all malignant uterine tumours (12). As expected, uterine sarcomas were also rare in our institution. We counted 22 cases in 16 years, which is 3.3% of the 661 uterine cancers treated at our institution during this time period. The age range of our patients was wide and presented similar distribution characteristics, as described in other studies (6, 13–15). The same is true for the distribution of different histologic subtypes, with leiomyosarcomas being the most common, followed by carcinosarcomas and a smaller number of endometrial stromal sarcomas.

Symptoms and signs of uterine sarcomas are non–specific and it is impossible to confirm the diagnosis with imaging techniques (16). Ultrasound remains the preferred tool for early detection of female pelvic malignant tumours, but ultrasound does not enable the gynaecologist to reliably differentiate between benign and malignant tumours, let alone between carcinomas and sarcomas. The potential role of PET/CT at present is detection of recurrences, lymph node evaluation, and detection of distant metastases (17). In agreement with most reports in the literature (6, 18), the most common presenting symptom in our study was postmenopausal bleeding, as approximately 80% of all patients were post-

menopausal. The histologic diagnosis was obtained pre–operatively in less than two–thirds of our patients. A pre–operative histologic diagnosis is not always reliable and may underestimate the number of uterine sarcomas by mistaking carcinosarcomas for endometrial adenocarcinomas (18), or overestimate uterine sarcomas by mistaking adenocarcinomas for carcinosarcomas (19).

No clear treatment policy exists worldwide for uterine sarcomas due to the rarity of the disease. The mainstay of treatment is surgery, but very common distant and local recurrence rates seem to require adjuvant therapy. A recent Cochrane review on adjuvant treatment after surgery for carcinosarcomas (20) concluded that adjuvant combination chemotherapy with paclitaxel and ifosfamide are related to a lower risk of disease progression and death than ifosfamide alone in women with stage III or IV uterine sarcomas. Additional radiotherapy to the abdomen is not related to improved survival (20). The role of adjuvant therapy in leiomyosarcomas is even less clear (21).

As stated above, the main treatment for uterine sarcomas remains surgical, with total abdominal hysterectomy and bilateral salpingo–oophorectomy the standard procedure (22). Seventeen of our patients underwent this procedure. Studies differ with respect to the extent of surgery and whether or not there is statistical significance with the outcome. Nassar et al. (18) reported no significant difference in outcomes between cases with total and subtotal hysterectomies, but the number of patients who underwent subtotal hysterectomy was small. Most studies still emphasize the role of cytoreductive surgery, especially for early–stage disease (23, 24). Some authors have mentioned the option of preserving the ovaries in premenopausal women with leiomyosarcomas (22).

Only one of our sarcoma patients was treated with laparoscopic surgery. Laparoscopic supracervical hysterectomy for presumptive leiomyoma was performed in the asymptomatic patient. Histologic evaluation revealed stage IA leiomyosarcoma. Additional laparoscopic resection of the uterine cervix was performed after the diagnosis. The patient is alive with no signs of the disease 68 months after the diagnosis. In addition, one patient was diagnosed with stage IIIB carcinosarcoma after laparoscopic myomectomy and was then treated with a total abdominal hysterectomy, unilateral salpingo–oophorectomy with salpingectomy on the contralateral side, omentectomy, and adhesiolysis. She underwent post–operative teleradiotherapy and four cycles of post–operative chemotherapy with cisplatin and ifosfamide. Disease progression to the liver, lungs, and abdominal wall was noted 9 months after initial diagnosis. The patient died of the disease 24 months after diagnosis. Although some authors argue that laparoscopic surgery is not inferior to laparotomy in patients with endometrial cancer (25), no large randomised prospective studies comparing laparoscopy and laparotomy exist for uterine sarcoma patients. Tumour morcellation, which more often occurs during laparoscopic surgery, has been shown to decrease disease–free survival and OS in patients with low–stage uterine leiomyosarcoma (26, 27). Cases of early trocar site metastasis after laparoscopic surgery for leiomyosarcoma (28) and early intraperitoneal metastases after laparoscopy in patients with unsuspected endometrial stromal sarcoma (29) have been described. Due to the limited number of cases, we cannot draw statistical conclusions about the superiority of either procedure from our study.

Seven patients in our study underwent pelvic lymphadenectomies and one underwent a para–aortic lymphadenectomy. The average number of resected lymph nodes in these patients was 22.1 and metastatic deposits were found in 2 patients. No consensus has yet been reached on the importance of lymph node resection; it is usually considered important for predicting disease outcome in carcinosarcomas (30), but not essential in other types of uterine sarcomas (31, 32).

Residual tumour remained after surgery in two patients. Despite the usual assumption that complete removal of all visible tumour positively influences the prognosis (33), Moskovic et al. (34) stated that radical surgery does not have such an influence on OS.

Of the patients, 38% received post–operative radiotherapy. While some older studies stated that

post–operative radiotherapy improves OS in early stages of carcinosarcoma and endometrial stromal sarcoma (33, 35), more recent reports have demonstrated that post–operative radiotherapy does not influence OS, but improves local disease control (36–38). Radiotherapy was shown to be an independent prognostic factor of disease–free survival and OS by Nassar et al. (18).

Only 19% of our patients received post–operative chemotherapy. Chemotherapy was comparatively rare in similar studies as well, although it was somewhat more frequent in patients with higher disease stages (6, 13, 18). Although some authors have stated no influence of adjuvant chemotherapy on survival of patients with uterine sarcomas (14, 18), others have declared an increase of recurrence–free survival in those who received adjuvant chemotherapy (7). Systemic chemotherapy was shown to be effective in treatment of recurrent leiomyosarcomas and hormonal therapy has been found useful for recurrences of endometrial stromal sarcomas (31). In our study, none of the patients received hormonal therapy as primary treatment, but one patient received letrozole as treatment for co–existing breast cancer.

Our 1–year OS rate was 60% and the 5–year OS rate was 44%. The 5–year survival rates in similar studies which considered all histologic subtypes of sarcomas were between 36% and 60% (6, 13, 39). OS is clearly influenced by disease stage at the time of diagnosis (1, 6, 13, 18). The OS of the treated patients in our study was good compared to other studies. No relevant conclusion regarding the incidence of progression among different histologic subtypes could be drawn due to the small number of patients. Our study had several limitations. The study was a single–centre retrospective analysis of a rare disease with a small number of subjects. The heterogeneity of the cases further prevented us from drawing reliable conclusions from statistical comparisons and survival analyses. In addition, a major limitation of our study was the systematic loss of any follow–up information for those patients who were referred to other specialists or other cancer centres due to complications of disease or treatment. The only information that could be obtained for these patients was the date and cause of possible death, which was provided by the Cancer Registry of Slovenia. To overcome these limitations, a prospective, multi–centre study with accurate follow–up should be planned.

Due to the rarity of uterine sarcomas, it is important to centralise the care of patients in a university centre, which would be helpful for achieving adequate follow–up and further improving the management of these rare tumours.

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