Uterine sarcomas – an evaluation of treatment results and prognostic factors

Kazimierz Karolewski, Bogdan Gliński, Jerzy Jakubowicz, Pawel Blecharz, Janusz Ryś, Tomasz Bieda, Krzysztof Urbański

Centre of Oncology, M.Sklodowska-Curie Memorial Institute, Cracow Department, Cracow, Poland

Submitted: 13 Febrauary 2008
Accepted: 8 June 2008

Arch Med Sci 2009; 5, 2: 215-221

Corresponding author
Pawel Blecharz, MD
Centre of Oncology
M.Sklodowska-Curie
Memorial Institute
Cracow Department
Cracow, Poland
E-mail: pawel.blecharz@interia.pl

Abstract

Introduction: The objective of this study was to evaluate the efficacy of surgery plus adjuvant radiotherapy in 98 uterine sarcoma (US) patients and to analyse reasons for treatment failure and the prognostic factors in those patients.
Material and methods: Between 1980 and 2000, 98 patients with uterine sarcoma were treated with surgery followed by postoperative radiotherapy. This group consisted of 70 patients with leiomyosarcoma (LMS) and 28 patients with endometrial stromal sarcoma (ESS).
Results: Five-year survival rate with no evidence of disease (NED) was 49% for 98 US patients. In the ESS subgroup, 5 year survival rate with NED was 75% and in the LMS subgroup only 38.6%. Analysis of the outcomes based on stage of disease revealed that in the early stage group (FIGO stages I and II) 60.8% of US patients survived for 5 years with NED, whereas in locally advanced stages (stages III, IVA) only 12.5% survived for 5 years with NED. In the LMS subgroup the dominant reason for treatment failure was distant metastases, while in the ESS subgroup, there were locoregional recurrences.
Conclusions: Combined surgery plus radiotherapy was a relatively effective therapy only in the treatment of early stage US (stages I and II). Independent prognostic factors in this group of patients were stage and microscopic type of sarcoma. The basic reason for failure of combined treatment in the group of LMS patients was the spread of malignancy, while in ESS patients it was regional recurrence.

Key words: uterine sarcomas, treatment, surgery, radiotherapy, prognostic factors.

Introduction

Uterine sarcomas (US) are rare tumours, making up 2 to 7% of all uterine malignancies [1, 2]. The choice of treatment in patients with uterine sarcoma is total abdominal hysterectomy (TAH) or bilateral salpingo-oophorectomy (BSO) with or without lymph node sampling [1-3]. The role of postoperative radiotherapy is the subject of controversy, and few clinical trials have been carried out as yet to conclusively define its role [1, 3, 4]. The majority of reports point out that postoperative radiotherapy improves curability but does not positively affect survival [4] and some authors say that it not only reduces the number of failures in treatment but also improves overall survival rates [1, 5]. Anthracycline-based chemotherapy plays rather a palliative role in the management of US [6, 7], as does adjuvant hormone therapy [8, 9].

Numerous controversies are raised by the issue of prognostic factors in US patients and the literature mentions many of them, including US microscopic type, degree of differentiation, mitotic index, p53 and Ki67 protein expression, patient age, hormonal status, tumour size and location, stage of disease, depth of endometrial infiltration, regional lymph node status, and other factors [3, 5, 10]. In multivariate analyses presented by various authors only some of them repeatedly show independent prognostic effects. The objective of this retrospective study is to assess the efficacy of combined treatment of patients with US (surgery plus radiotherapy) and to analyze the prognostic factors in this group of patients.

Material and methods

Between 1980 and 2000, 128 patients with uterine sarcomas were treated at the Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Krakow Branch. In this analysis group, 11 (8.6%) patients had advanced US with numerous distant metastases, qualifying solely for palliative treatment. In 2 (1.5%) patients, surgery alone was performed, as both patients died shortly after the operation due to non-gynaecological causes. In 17 (13.3%) patients, postoperative chemotherapy with CYVADIC (cyclophosphamide, vincristine, doxorubicin and dacarbazine) was applied. The subject of further analysis is a group of 98 (76.6%) patients managed with the combined treatment of surgery followed by radiotherapy.

In all patients the classical laparotomy and hysterectomy with bilateral adnexectomy (TAH and BSO) was performed. The FIGO classification for cancer staging was used to assess tumour advancements [11]. Adjuvant radiotherapy involving brachy- and teletherapy was started 3-4 weeks after surgical treatment. For intravaginal brachytherapy (Selectron LDR/MDR) applicators employing the after-loading technique were used (until 1990, radium, and since 1991, caesium). The latter involved 2 applications, a 20 Gy surface dose each, with 7-day interval periods. For radium applicators, there was a single application with a surface dose of 50 Gy. The postoperative teletherapy was performed with Cobalt 60 gamma photons (32 patients) or X-photons with 6-10 MeV energy obtained from linear accelerators (66 patients). Four-field technique was used with anterior, posterior and two lateral beams ("box technique"). The total dose was 50.4 Gy given in 24 fractions over 5 weeks. Postoperative radiotherapy was very well tolerated. Ninety six (98%) patients completed their scheduled treatment. In 2 (2%) patients the treatment was discontinued due to deterioration of performance status and intensification of coexisting diseases. Late complications (stages 3 and 4 according to the Chassagne *et al*. classification), were found in 2 (2%) patients in the form of rectovaginal fistula in one patient and intestinal stenosis requiring surgical treatment in the other. The sequelae appeared at months 18 and 23 post-treatment and both patients survived without evidence of disease.

Survival, calculated from the date of surgery, was a median time period of 98 months (66-194 months). Total recurrence-free survival rate was measured by the Kaplan Meier method. The log-rank test by Peto *et al*. was used for assessment of significance. Cox's proportional hazard model analysis was applied to assess the influence of selected factors on survival data.

Results

The patients' age ranged between 36 and 76 years. The medium age was 61 years. From among 70 LMS patients, 31 (44.3%) were aged under 60 years, whereas from among 28 ESS patients, as many as 21 (75%) patients were aged under 60 years. This difference was statistically significant (log-rank test, $p < 0.02$). The mean age of LMS patients (63 years) was significantly higher than that for ESS patients (52 years).

Stage I US was diagnosed in 58 (59.2%) patients, stage II in 16 (16.3%) and stages III or IVA in 24 (24.5%) patients. In 5 patients (4 stage III and 1 stage IVA), metastatic regional lymph nodes were found. No statistically significant differences in grade were observed between the group of patients with LMS and those with ESS.

Leiomyosarcoma (LMS) was found in 70 (71.4%), and endometrial stromal sarcoma (ESS) in 28 (28.6%) patients. From among 28 ESS patients, low-grade ESS was diagnosed in 25 and high-grade ESS in only 3 patients. No other US microscopic types (e.g. rhabdo-, myo-, lipo-, or fibrosarcoma) were found. Although many authors consider mixed müllerian sarcomas (carcinosarcomas) histologically as belonging to sarcomas [12, 13], those neoplasms were not included in the US group in accordance with the present WHO standpoint [14-16].

Table I presents population, clinical and microscopic characteristics of these patients. Forty nine percent of patients survived five years with no evidence of disease (5-year NED). The treatment results, depending on clinical and histological parameters, are presented in Tables II, III.

Uni- and multivariate analyses did not show statistical significance for such parameters as: age, differentiation, or depth of myometrial infiltration. The factors providing statistically significant differences in patients' survival were: LMS histological type and FIGO stage III and IVA advancement.

As seen in Table III, 22 (52.4%) patients from among 42 stage I LMS patients and 4 (40%) patients

Table I. Characteristics of the analyzed group of patients

Population, microscopic and clinical features	Microscopic type of sarcoma				Total	
	LMS		ESS		No. of pts.	%
	No. of pts.	%	No. of pts.	%		
Age:						
– under 60	31	44.3	21	75.0	52	53.1
– 60 and over	39	55.7	7	25.0	46	46.9
Clinical stage of disease:						
– I	42	60.0	16	57.2	58	59.2
– II	10	14.3	6	21.4	16	16.3
– III	11	15.7	3	10.7	14	14.3
– IVA	7	10.0	3	10.7	10	10.2
Grade:						
– G1	32	45.7	25	89.3	57	58.2
– G2 + G3	38	54.3	3	10.7	41	41.8
Depth of uterine stroma infiltration:						
– up to 1/2 of thickness	42	60.0	18	64.3	60	61.2
– above 1/2 of thickness	28	40.0	10	35.7	38	38.8
Total	**70**	**100.0**	**28**	**100.0**	**98**	**100.0**

Table II. Relation between the treatment results and the population, histological and clinical features

Population, histological and clinical features	No. of treated patients	5-year NED survivals		*P* value
		No. of pts.	%	
Age:				
– under 60	52	25	48.1	NS
– 60 and over	46	23	50.0	
Microscopic type of sarcoma:				
– LMS	70	27	38.6	< 0.01
– ESS	28	21	75.0	
Differentiation grade:				
– G1	57	28	49.1	NS
– G2 + G3	41	20	48.8	
Depth of myometrial infiltration:				
– up to 1/2 of thickness	60	30	50.0	< 0.01
– above 1/2 of thickness	38	18	47.4	
Clinical stage of disease:				
– I	58	37	63.8	
– II	16	8	50.0	NS
– III	14	3	21.4	
– IVA	10	0	0	
Total	98	48	49.0	

from among 10 stage II LMS patients survived 5 years with no evidence of disease. Only one patient with stage III LMS survived for 5 years with no evidence of disease.

In the study group, out of 16 stage I ESS patients, 5-year NED survival was observed in 15 (93.8%) women, and out of 6 stage II patients, in 4 (66.7%). From among 3 patients with high-grade ESS (G2, G3), 1 stage II patient survived for 5 years with no evidence of disease, while the other two, with stage III, died due to sarcoma spread to the lungs. One patient had locoregional recurrence after 4 years and is still alive with stable disease. She was not analyzed as a 5-year NED survivor.

At the time of completion of the study (September 2006), 49 patients had died, including two who died due to concurrent diseases (cerebral haemorrhage, myocardial infarct). The medium time

Table III. Relation between the treatment results, the microscopic type of sarcoma and grade

Grade	Microscopic type of sarcoma						Total		
	LMS			ESS					
	No. of pts. treated	5-year NED survival		No. of pts. treated	5-year NED survival		No. of pts. treated	5-year NED survival	
		No. of pts.	%		No. of pts.	%		No. of pts.	%
I	42	22	52.4	16	15	93.8	58	37	63.8
II	10	4	40.0	6	4	66.7	16	8	50.0
III	11	1	9.1	3	2	66.7	14	3	21.4
IVA	7	0	0	3	0	v	10	0	21.4
Total	70	27	38.6	28	21	75.0	98	48	49.0

Table IV. Causes of failure in combined treatment of patients with uterine sarcoma

Causes of treatment failure	Microscopic type of sarcoma				Total	
	LMS		ESS			
	No. of pts.	%	No. of pts.	%	No. of pts.	%
Loco-regional recurrence	9	21.4	3	50.0	12	25
Loco-regional recurrence + distant metastases	4	9.6	2	30.3	6	12.5
Distant metastases	29	69	1	16.7	30	62.5
Total	42	100.0	6	100.0	48	100.0

to recurrence, starting from the end of treatment, was 13 months. In 43 patients, relapse of the malignant process appeared up to 2 years of follow-up. Sites of recurrences are presented in Table IV.

The most common cause of treatment failure in the analyzed group of patients with US was distant metastases found in 36 (75%) uncured patients. Loco-regional US relapse appeared in 18 (37.5%) patients, and out of this number, in 12 (25%) uncured patients it was the only cause of failure. The metastases locations were: lungs (31 patients), liver (4 patients) and brain (1 patient).

From among 6 uncured ESS patients, locoregional relapse of sarcoma was observed in 5 (93.3%), whereas among 41 LMS patients, this relapse was found only in 12 (29.3%). This difference is statistically significant (log-rank test $p < 0.05$). Thus, the uncured ESS patients died with statistically significantly higher frequency, due to loco-regional relapse of sarcoma, than did the uncured LMS patients in whom the basic cause of treatment failure was generalization of the malignant process.

Discussion

The composition of the group in terms of population, clinical and histological factors is similar to the majority of US patient groups treated with surgery followed by radiotherapy presented in the literature [1, 3, 6].

The most common type of sarcoma was LMS, as reported by other authors [1, 11, 13, 15]. The average age of LMS patients was 63 years of age, and was statistically significantly higher than the average age of ESS patients, which is also in agreement with data from the literature [3, 16]. The prognosis of leiomyosarcoma depends chiefly upon the extent of spread. Extrauterine disease is the most potent predictor of survival [17]. For tumours confined to the uterine corpus, some investigators have found that size of neoplasm is an important prognostic factor with the demarcation occurring at 5 cm [17]. A number of histological and immunohistochemical features have been investigated as prognostic factors in uterine LMS. Of these, the most important is mitotic count, accessible to all pathologist [10, 17]. The prognostic significance of Ki67 antigen expression, a widely used immunohistochemical surrogate for counting mitotic figures, is far less clear, as well as p53 overexpression and tumour necrosis [14, 17].

Endometrial stromal sarcomas (ESS) have been traditionally divided into low- and high-grade types based on mitotic count. However, because of the lack of specific differentiation and because they bear no histological resemblance to

endometrial stroma, it has been proposed that they be designated undifferentiated endometrial or uterine sarcoma. In the latest WHO classification [14] the distinction between low grade ESS and undifferentiated endometrial sarcoma is not made on the basis of mitotic count but on features such as nuclear pleomorphism and necrosis. Patients with low-grade stromal sarcomas confined to the uterus present a 5-year survival rate over 90%; however, recurrences are not uncommon, ranging up to 25% in stage I patients. Unfortunately, there are no histopathological parameters to predict which patients with tumour limited to the uterus are at risk of recurrence. For the whole group of low-grade stromal sarcomas the surgical stage is the best predictor of recurrence and survival [16, 17].

Some authors suggest that division between low-grade and high-grade stromal sarcomas (LGSS and HGSS) should be based not only on histological differentiation, but also on analysis of mitotic index, vasculature pattern, nuclear pleomorphism and necrosis [18, 19]. This division is not always clear among some authors [20]. Because of the lack of those data in the material only histological differentiation (G) was studied. In the analyzed group, from among 28 ESS patients, high-grade ESS (G2, G3) was found only in 3 (10.7%), while the remaining 25 (89.3%) patients had low-grade ESS (G1).

The literature presents contrasting views as to the value and significance of differentiation between low-grade and high-grade ESS patients. Some authors underscore significant differences in the clinical course and prognosis of ESS patients, pointing to more aggressive disease and inferior treatment results in the case of high-grade ESS. Other authors, however, question both the diagnostic criteria and prognostic value of differentiation between the two types of ESS [4]. One of our patients with high-grade ESS survived for 5 years with no evidence of disease and the remaining two died in the second year of treatment due to sarcoma spread to the lungs.

The advancement of the malignant process is similar to that reported in the literature. Clinical stage I or II was found in 75.5% of patients, while according to the literature, stage I or II is diagnosed in 59-80% of patients [1, 14, 21, 22].

From among the 98 patients, 49% survived for 5 years with no evidence of disease. The obtained percentage of cure is in agreement with the data from the literature, which reported 5-year disease-free survival rates of 20-57% in US patients. This wide range of 5-year disease-free survival rates probably results from the very diverse population and clinical composition of the presented groups of patients [1, 2, 7, 8, 12, 20]. Among stage I US patients, 63.8% survived with no evidence of disease for 5 years, among stage II patients 50.0%, stage III 21.4%, and stage IVA 0%. These results are in concordance with the data obtained from the literature, where depending on US advancement stage, the respective values are as follows: stage I 50-75% [1, 22], stage II 40-50% [1, 3], stage III 8-16% [1, 3], and stage IVA 0-10% [1].

In the analyzed group, among ESS patients, 5-year NED survival rate was 75%, while the literature reports between 70 and 82% [1, 17, 23]. Among patients with LMS, 5-year NED survival was observed in 38.6% of patients, whereas in the literature this percentage ranges between 15 and 49% [1, 6]. Thus, the results obtained at the Oncology Centre in Krakow are in agreement with the data provided by other authors.

Summing up this part of the study, the combination of surgery followed by postoperative radiotherapy results in cure in around a half of the total number of patients with US based on our own results and the data from the literature. In early-stage cases (stages I and II), 5-year disease-free survival is obtained in over 60% of patients. Surgery combined with postoperative radiotherapy is, however, ineffective in treating US patients with stages III and IVA disease.

As already mentioned in the introduction, the role of postoperative radiotherapy in patients with US remains a subject of controversy [1, 2, 18, 19, 24]. In this study, all patients received combined therapy and there is no control group treated with surgery alone. Therefore it is impossible to provide data that would offer new insights in this debate.

The multivariate analysis of prognostic factors we performed has shown that statistically significant factors affecting the treatment results were: the stage of the disease and the US microscopic type.

In the analyzed group of early-stage US (stages I and II) patients, 5-year NED survival rate was 60.8%, while in advanced disease only 12.5% (including US patients with stage IVA for whom the survival percentage was 0). This dependence is fully confirmed by all reports in the literature [1, 3, 6]. Also the presence of better results in combined treatment of ESS patients, compared to LMS patients (at comparable stages of advancement), is extensively supported by the data from the literature [1, 3, 19]. There are authors who emphasize a particularly poor prognosis in patients with high-grade ESS [24]. In our study group, from among 3 such patients, 1 survived 5 years with no evidence of disease. Some authors stress higher radiosensitivity of ESS [3, 23] although there are also different opinions on this subject [25]. The literature reports a worse prognosis in the group of patients with LMS and that this worse prognosis is connected with early occurrence of distant metastases in this type of sarcoma [3].

Some authors point to the prognostic significance of such factors as age or grade [1, 19]. In our patients,

as well as in the uni- and multivariate analysis, no statistically significant effect of those factors on 5-year NED survival of patients was observed.

The analysis of the literature shows that the studies of other authors describe a number of prognostic factors that we did not analyze. These include: tumour size [24], DNA ploidy [6, 26], mitotic index [26], presence of necrotic foci [27], patients' performance status and p53 protein expression [28].

The basic cause of treatment failure in our study population was distant metastases, found in over 75% of patients not cured from US. In general, the literature points out that the spread of the malignant process to the lungs, liver, brain and bones is most often the reason for failure in patients with uterine sarcoma, particularly in the LMS subgroup [1, 3, 28, 29]. It is slightly different in ESS patients, where loco-regional recurrences are more frequent [20, 29]. This fact was confirmed in our study, in which out of 6 ESS patients not cured from the malignant process, 5 patients (83.3%) developed loco-regional relapses of sarcoma.

In view of the fact that the basic cause of treatment failure in US (in particular in the LMS group) is the spread of the malignant process, further improvement of treatment results is desired in combining surgery or surgery plus radiotherapy with systemic chemotherapy treatment. Attempts in refining treatment have not yielded a breakthrough for patients with US [3, 23, 30-32]. There are items in the literature reporting the effectiveness of hormonal treatment in ESS patients, particularly those with low-grade ESS [24, 33, 34]. These may offer patients and physicians other treatment options.

In conclusion, combined surgical treatment followed with radiotherapy was an effective treatment method in patients with early (FIGO stages I and II) uterine sarcoma, offering a chance of curing over 60% of patients. This combination was ineffective in the group of patients with locally advanced (FIGO stages III and IVA) US, where only single patients with stage III sarcoma were cured. The basic cause of combined treatment failure in LMS patients was the spread of the disease, and in the ESS group, loco-regional relapse of the sarcoma.

Independent prognostic factors in patients treated with surgery followed by postoperative radiotherapy were advancement of disease and its microscopic type.

Acknowledgments

Ethics Committee approval of retrospective medical research is not required by Polish Law. This particular research is not considered to be a medical experiment according to European Union Regulations.

All authors declare that no actual or potential conflicts of interest exist.

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