Results of postoperative radiotherapy in the treatment of uterine sarcomas: a retrospective analysis of 46 patients

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Summary

Purpose: The aim of this study was to evaluate treatment outcome, survival data and prognostic factors in patients with uterine sarcoma treated by postoperative radiotherapy. *Materials and Methods:* The records of 46 patients treated between 1993 and 2003 were reviewed. Median age was 55 (range 31-75). There were 21 mixed mullerian tumors, 12 leiomyosarcomas, 11 endometrial stromal sarcomas and two adenosarcomas. According to FIGO classification 65.2% were Stage I, 17.4% Stage II, 13% Stage III and 4.3% Stage IV. All patients received external radiotherapy with 1.8 Gy daily fractions up to 50.4-64 Gy (median 50.4 Gy). Intracavitary brachytherapy was applied to 39 patients. Twelve patients received adjuvant chemotherapy. *Results:* Median follow-up time was 48 months (6-144 months). Seventeen patients (37%) developed distant metastases and one patient had local failure. Five-year overall, disease-free and local recurrence-free survival rates were 57.8%, 60.5% and 97.8%, respectively. Univariate analysis demonstrated that stage ($p = 0.011$), histologic subtype ($p = 0.010$), tumor size ($p = 0.044$), positive peritoneal cytology ($p = 0.006$) and the use of chemotherapy ($p = 0.005$) had a significant effect on overall survival. Prognostic factors influencing disease-free survival were stage ($p = 0.009$), positive peritoneal cytology ($p = 0.000$) and the use of chemotherapy ($p = 0.002$). The only prognostic factor affecting local control was stage ($p = 0.000$). *Conclusion:* Postoperative radiotherapy seems to be an effective adjuvant treatment providing high local control rates in uterine sarcomas. However its efficacy should be clarified by randomized trials. The important prognostic factors influencing the treatment results were stage, histologic subtype, tumor size and positive peritoneal cytology.

Key words: Uterine sarcoma; Radiotherapy; Prognostic factors.

Introduction

Uterine sarcomas are rare tumors which comprise 3% to 7% of all malignancies of the uterus [1]. They carry a poor prognosis with a 2-year overall survival rate of less than 50% even at an early stage [1-3]. Due to the rarity of these tumors and the different characteristics and prognosis of the various histological subtypes optimum treatment strategy has not yet been defined. The recommended primary treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. The role of adjuvant treatment after surgery is controversial and the overall prognosis remains poor. The impact of radiotherapy on local recurrence has been demonstrated by some authors [4-13] whereas others have demonstrated no benefit from adjuvant radiotherapy [14-16]. The role of adjuvant chemotherapy is also controversial [2, 6, 17-19].

Several prognostic factors influencing survival have been proposed. Most notably tumor stage, grade, and histologic subgroup are predictive of outcome [1, 2, 4, 5, 14, 20]. Lymph node involvement, depth of myometrial invasion, lymphovascular invasion, peritoneal cytologic findings, mitotic count, age and menopausal status are the other proposed factors [4, 7, 20-22].

In the present study 46 cases of uterine sarcoma who received adjuvant radiotherapy were evaluated retrospectively regarding treatment outcome, survival and prognostic factors.

Materials and Methods

The records of 46 patients with histologically verified uterine sarcoma who were treated by postoperative radiotherapy at the Radiation Oncology Department of Ege University Hospital between January 1993 and December 2003 were reviewed retrospectively.

Total abdominal hysterectomy and bilateral salpingo-oopherectomy (TAH-BSO) were performed in 41 patients. Wertheim's radical hysterectomy with pelvic lymphadenectomy (Type III hysterectomy) was performed in three and a subtotal hysterectomy only in one patient. The adnexa were conserved in one young patient (31 years old). Patients were staged using the FIGO staging system for endometrial cancer. Complete blood count, liver and kidney function tests, chest X-ray and abdominopelvic computed tomography (CT) were performed in all patients before radiotherapy.

According to our clinical protocol, patients with one or more adverse prognostic factors such as high histologic grade, deep myometrial invasion, mitotic count above 10 per 10 high-power fields, and suboptimal surgery were offered adjuvant radiotherapy. External RT was delivered by a 6-25 MV linear accelerator (Philips SL 25) through individually shaped pelvic portals including the tumor bed and regional lymph nodes using an AP/PA or a four-field technique (AP/PA and opposed laterals) with 1.8 Gy daily fractions up to 50.4-64 Gy (median 50.4 Gy). In one patient the paraaortic field was added because of

Revised manuscript accepted for publication July 9, 2007

enlarged paraaortic nodes detected in abdominopelvic CT. Intracavitary vaginal vault irradiation with ovoids was applied to 39 patients via the microSelectron high-dose rate remote afterloader Ir-192. One fraction of 9.25 Gy or two fractions of 6.5 Gy were given to a depth of 5-7 mm from the vaginal surface. Mainly adriamycin-based chemotherapy was administered to 12 patients in an adjuvant setting.

The patients were followed by physical and radiological examinations (chest X-ray, abdominopelvic ultrasound or CT every other 6 months) with 3-month intervals for the first two years, 6-month intervals for the second two years and annually thereafter.

Overall survival was defined as the time from diagnosis to death or to last follow-up. Local recurrence-free survival was defined as the time from diagnosis to first clinical or radiological evidence of local recurrence. Survival analysis was performed using the Kaplan-Meier method. Potential prognostic factors such as age, menopausal status, FIGO stage, histologic subtype, grade, tumor size, mitotic count, peritoneal cytology, lymphovascular invasion, total tumor dose and the use of chemotherapy were analyzed to assess their impact on local control, disease-free and overall survival. Univariate analysis using the Log-rank test and multivariate analysis using the Cox regression model were performed to assess the significance of prognostic factors.

Results

The median age of the patients was 55 years (range: 31-75) which differed according to histology: 58 years for mixed mullerian tumors (MMT), 56 years for leiomyosarcomas (LMS), 44 years for endometrial stromal sarcomas (ESS) and 59 years for adenosarcomas (AS). Sixty-five percent of the patients were postmenopausal. The majority of the patients were multiparous (84.8%) and the median number of parity was three (range: 0-8). The most common presenting symptom at diagnosis was bleeding (82.6%) followed by pelvic or abdominal pain (10.9%) and vaginal discharge (6.5%). One patient had previous colon cancer.

Histologically MMT accounted for 45.6%, LMS 26.1%, ESS 23.9%, and AS 4.3%. According to the FIGO classification 30 (65.2%) patients were classified as Stage I, eight (17.4%) as Stage II, six (13.0%) as Stage III, and two (4.3%) as Stage IV. The median uterine size was 6.5 cm. In most of the patients (58.7%) tumor size was greater than 5 cm. The grade was not clearly specified in 18 patients (39%); most of the identified ones were high grade (67.9%). Mitotic count was not identified in 30 patients (65.2%); among the remaining 16 patients two had less than ten mitoses, seven had 10-19 mitoses and seven had more than 20 mitoses per 10 high-power fields. Lymph-node sampling or pelvic lymphadenectomy was performed in 15 patients (32.6%); nine with MMT and six with LMS. Among these one patient with MMT had lymph node metastasis. Lymphovascular invasion was documented in ten patients (21.7%), necrosis in 11 (23.9%) and positive peritoneal cytology in three patients (6.5%). Patient and tumor characteristics are indicated in Table 1. Table 2 outlines identified tumor characteristics according to stage.

Table 1. — *Patient characteristics*.

	No. of patients	%
Age		
Median 55 (range 31-75)		
Menopausal status		
Premenopausal	16	34.8
Postmenopausal	30	65.2
FIGO stage		
Stage I	30	65.2
Stage II	8	17.4
Stage III	6	13.0
Stage IV (IVa)	2	4.3
Histologic subtype		
MMT	21	45.6
LMS	12	26.1
ESS	11	23.9
AS	2	4.3
Histologic grade		
1	6	13.0
2	3	6.5
3	19	41.3
Not specified	18	39.2
Tumor size		
≤ 5 cm	16	34.8
> 5 cm	27	58.7
Not specified	3	6.5
Necrosis		
(+)	11	23.9
(–)	35	76.1
Mitotic count		
< 10	2	4.3
10-19	7	15.2
≥ 20	7	15.2
Not specified	30	65.2
Lymphovascular invasion		
(+)	10	21.7
(–)	36	78.3
Peritoneal cytology		
(+)	3	6.5
(–)	43	93.5

Table 2. — *Tumor characteristics by stage*.

	Stage I	Stage II	Stage III	Stage IVa
Histologic subtype				
MMT	10	8	3	–
LMS	10	–	–	2
ESS	8	–	3	–
AS	2	–	–	–
Grade				
1	4	–	2	–
2	3	–	–	–
3	12	4	3	–
Tumor size				
≤ 5 cm	10	4	2	–
> 5 cm	18	3	4	2
Mitotic count				
< 10	1	–	–	1
10-19	5	1	1	–
≥ 20	7	–	–	–
Necrosis				
(+)	8	–	2	1
(–)	22	8	4	1
Lymphovascular invasion				
(+)	4	2	3	1
(–)	26	6	3	1
Distant metastasis				
(+)	12	1	3	1
(–)	18	7	3	1

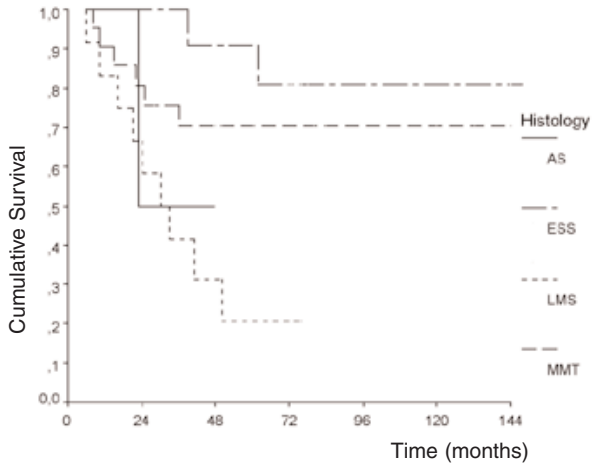

Figure 1. — Univariate analysis of overall survival by histology (p = 0.010). AS: adenosarcoma; ESS: endometrial stromal sarcoma; LMS: leiomyosarcoma; MMT: mixed mullerian tumor.

Median follow-up was 49 months (range 6-148 months). Seventeen patients (37%) had developed distant metastases mainly in multiple sites (41.2%). Locoregional recurrence was detected in one patient both inside and outside the radiation field six months after radiotherapy. This patient had a Stage IVa tumor with rectal involvement and died four months after the detection of recurrence.

During follow-up 16 patients (34.8%) had died of cancer, and two patients had died of intercurrent disease. Five-year overall, disease-free and local recurrence-free survival rates were 57.8%, 60.5% and 97.8%, respectively. Univariate analysis for overall survival demonstrated statistical significance for stage (p = 0.011), histologic subtype (p = 0.010), tumor size (p = 0.044), positive peritoneal cytology (p = 0.006) and the use of chemotherapy (p = 0.005). With respect to histology LMS predicted the worst prognosis followed by AS, MMT and ESS with an overall survival rate at 5 years of 20.8%, 50%, 70.2% and 80.8%, respectively (Figure 1). In multivariate analysis tumor size (p = 0.019) and positive peritoneal cytology (p = 0.026) affected overall survival. According to univariate analysis prognostic factors influencing disease-free survival were stage (p = 0.009), positive peritoneal cytology (p = 0.000) and the use of chemotherapy (p = 0.002). The only prognostic factor affecting local control was stage (p = 0.000) (Table 3).

Table 3. — *Prognostic factors for overall, disease-free and local progression-free survival*.

Prognostic factor	No. of patients	5-year overall survival (%)	5-year disease-free survival (%)	5-year local progression-free survival (%)
Age				
≤ 55	23	68.4	68.1	100
> 55	23	48.5	40.7	95.6
		(p = 0.081)	(p = 0.088)	(p = 0.317)
Menopausal status				
Premanopausal	16	73.8	72.7	100
Postmenopausal	30	49.5	47	96.6
		(p = 0.074)	(p = 0.071)	(p = 0.465)
Stage				
I	30	57.5	55.5	100
II	8	87.5	87.5	100
III	6	31.5	41.6	100
IV	2	0	0	50
		(p = 0.011)	(p = 0.009)	(p = 0.000)
Histologic subtype				
MMT	21	70.2	76.2	100
LMS	12	20.8	23.8	91.6
ESS	11	80.8	72.7	100
AS	2	50	50	100
		(p = 0.010)	(p = 0.061)	(p = 0.418)
Grade				
1	6	83.3	83.3	NA
2	3	66.6	66.6	
3	19	62.3	55.6	
		(p = 0.519)	(p = 0.456)	
Mitotic count				
< 10	2	50	50	NA
10-19	7	57.1	57.1	
> 20	7	67.1	71.4	
		(p = 0.873)	(p = 0.919)	
Tumor size				
≥ 5 cm	16	78.8	72.2	100
> 5 cm	27	43.5	49.9	96.3
		(p = 0.044)	(p = 0.145)	(p = 0.441)
Lymphovascular invasion				
(+)	10	60	60	100
(–)	36	57	60	97.2
		(p = 0.940)	(p = 0.875)	(p = 0.598)
Peritoneal cytology				
(+)	3	0	0	100
(–)	43	62.1	64.9	97.6
		(p = 0.006)	(p = 0.000)	(p = 0.791)
Chemotherapy				
(+)	12	33.3	33.3	91.7
(–)	34	73.6	80.5	100
		(p = 0.005)	(p = 0.002)	(p = 0.113)

NA: Not available.

Discussion

Uterine sarcomas are rare and highly malignant tumors of the female genital tract. Optimal management consists of complete surgical removal. The role of adjuvant radiotherapy is controversial as different conclusions have been reached by different series [2, 4-16], and the results with chemotherapy have been disappointing [2, 6, 12, 16-19].

In a Gynecologic Oncology Group study to determine the role of adjuvant radiotherapy in patients with Stage I and II uterine sarcoma, 60 patients out of 157 received radiotherapy. Although no difference was observed in the survival rates, local control rates increased from 23% to 54% (except for LMS) in those who received radiotherapy (p = 0.028) [6]. Preliminary results of the only randomized trial of adjuvant pelvic radiation for all histologic types of uterine sarcomas showed significantly lower pelvic relapse rate in the radiotherapy arm (12% vs 21%; p = 0.004) without a difference in overall or disease-free survival and in this EORTC-GCG study radiotherapy appeared to be more beneficial for MMT [13]. The only statistically significant improvement in

Table 4. — *Comparison of the results of various retrospective trials on uterine sarcoma and prognostic factors*.

Author	No. of patients	Treatment	Median follow-up (months)	5-year OS (%)	5-year LC (%)	5-year DFS (%)	Prognostic factors
Livi *et al*. [4]	141	Only surgery 36 pts RT 74 pts. (37 with BRT) CT 20 pts	36	27.7	–	–	Stage, Histologic subtype, Grade, Age, *RT is favored*
Kelly *et al*. [5]	87	Surgery 82 pts RT 16 pts CT 25 pts	–	48	–	–	Stage, Histologic subtype, CT (adverse factor) *RT is favored*
Chauveinc *et al*. [7]	73	Surgery 73 pts RT 37 pts CT 24 pts	96	45	LF 25.7%	–	Stage, Histologic subtype, Grade, Menopausal status *RT is favored*
Knocke *et al*. [10]	72	Surgery 72 pts RT 72 pts (55 with BRT)	92	52.3	77.9	58.5	Stage, Age *RT is favored*
Ferrer *et al*. [11]	103	Surgery 103 pts RT 79 pts (24 with BRT) CT 33 pts	49	56	57.4	48.7	Stage, Histologic subtype, Grade, Age *RT is favored*
Major *et al*. [21]	360	Surgery 360 pts RT 132 pts	–	–	LF 56%	–	Histologic subtype, Grade, Myometrial invasion, LVSI, Peritoneal cytology, Adnexal involvement, Lymph node involvement, Tumor size, Mitotic index *RT is favored*
Yamada *et al*. [33]	62	Surgery 62 pts RT 20 pts CT 20 pts	22	74 (early stage)	LF 55%	–	Myometrial invasion, LVSI, Peritoneal cytology, Adnexal involvement, Serosal involvement, Lymph node involvement, *RT is favored*
Ege University	46	Surgery 46 pts RT 46 pts (39 with BRT) CT 12 pts	49	57.8	97.8	60.5	Stage, Histologic subtype, Tumor size, Peritoneal cytology, CT (adverse factor)

OS: Overall survival; LC: Local control; DFS: Disease-free survival; RT: Radiotherapy; BRT: Brachytherapy; CT: Chemotherapy; LVSI: Lymphovascular space involvement; pts: Patients.

survival from adjuvant radiotherapy was reported in surveillance, epidemiology, and end results data which included 2,677 cases treated between 1989 and 1999. The survival rate of women with Stage II disease who received adjuvant radiotherapy was 55% compared with 31% for those women who did not ($p < 0.01$) and the survival rate of women with Stage III-IV disease was 33% with adjuvant radiotherapy compared with 25% without radiotherapy [23]. Given the importance of preventing local recurrence adjuvant pelvic radiotherapy is recommended by many clinicians [4, 5, 7, 10, 11, 21, 24]. Higher doses delivered to tumor volume are radiobiologically expected to give better local disease control. Livi noted that the best results were obtained after postoperative external radiotherapy plus brachytherapy with a total dose higher than 50 Gy ($p = 0.001$) and the reduction in local recurrence seemed to be influenced by brachytherapy dose to the vaginal vault [4]. Larson *et al*. in a study of 147 patients with MMT reported a better local control rate for patients treated with adjuvant combined brachytherapy and external beam therapy compared with patients treated with each modality alone [9]. In another series improvement both in local control and overall survival was reported in 84 patients with Stage I disease treated with a combination of pelvic external beam radiotherapy followed by intracavitary brachytherapy [24]. In Knocke *et al*.*'s* study 72 patients were given postoperative external radiotherapy and brachytherapy. The five-year local control rate was 77.9% and overall survival was 52.3% [10]. In our study 39 patients were treated with a combination of external radiotherapy and intracavitary brachytherapy. Our local control rate of 97.8% was excellent when compared with data from the literature regarding local control by surgery alone [21, 25-27].

Several prognostic factors have been identified that have a profound influence on outcome [1, 4, 5, 10, 14, 16,

20, 24, 28]. Prognosis has been reported to vary inversely with the initial stage at presentation and according to the literature approximately 50-75% of all patients present with clinical Stage I disease [1, 4, 5, 10, 11, 29]. The corresponding rate was 65.2% in the present series. As in all published data, stage was the main prognostic factor in this series for overall, disease-free and local-recurrence free survival. However our overall and disease-free survival of Stage II patients were better than that of Stage I patients (Table 3). Twelve patients out of 30 with Stage I disease (40%) had developed distant metastases and ten patients had died due to distant metastases, whereas the distant metastases rate of Stage II patients was 12.5% (1/8). Also there were more high-grade tumors, tumors > 5 cm, and mitotic count ≥ 20 in Stage I patients than in Stage II patients (Table 2).

Histologic grade is also a powerful parameter for predicting outcome [2, 4, 7, 11, 21, 28]; however it was not a prognostic factor in the current study which could be attributed to patients with unspecified grade. These patients were referred to our university hospital from other hospitals and their histologic material was unable to be retrieved for review.

With respect to histology LMS tends to have the worst prognosis among the other subtypes [4, 7, 21, 30]. Although adjuvant radiotherapy may reduce the risk of local recurrence in early-stage disease, overall survival tends to be low because of the high rate of pulmonary metastases [21]. Livi *et al*. stated an 18.8% survival rate for LMS at five years [4]. Dinh and associates reported a 65% 2-year survival for 27 patients with uterine LMS although only 19% survived with no evidence of disease and the crude 5-year survival was 42% [20]. In the current study LMS also predicted the worst prognosis with a survival rate of 20.8% at five years. Fifty-eight percent of these patients developed single or multiple organ metastases mainly to the lungs. The patients with ESS had better overall survival (80.8%) like those of some other studies [4, 5, 7, 28, 30-32].

Tumor size greater than 5 cm was an adverse prognostic factor for overall survival. In Major et al's study univariate analysis showed that tumor size was an important prognostic factor for the progression-free interval for MMT [21].

Positive peritoneal cytology was an adverse prognostic factor for overall and disease-free survival in this study. Husseiny *et al*. and Yamada *et al*. also reported similar results [28, 33] and Major *et al*. found that positive peritoneal cytology was significantly related to progression-free survival in early-stage MMT [21]. Other factors including age, menopausal status, mitotic count, lymph node status, depth of myometrial invasion, lymphovascular invasion that have been found as prognostic variables in several studies [2, 4, 5, 10, 11, 20-22, 24, 31] were not statistically significant for prognosis in this study. A comparison of the results of this study with the results of other studies are shown in Table 4.

The role of adjuvant chemotherapy in uterine sarcomas is also controversial [2, 6, 7, 12, 16-19]. It has been suggested that adjuvant chemotherapy may afford a survival benefit by controlling subclinical metastatic disease but this has not been proven yet and the ideal chemotherapeutic agent has yet to be established. Until recently the most active chemotherapy regimen in uterine sarcomas was doxorubicin and ifosfamide yielding a response rate of around 30% in LMS [18]. Lately a phase II study of gemcitabine plus docetaxel exhibited a 53% response rate [34]. Pautier *et al*. published the results of a multidrug regimen combining dacarbazine, cyclophosphamide, or ifosfamide, cisplatin, adriamycin and vindesine [35]. The objective response rate of 54% achieved in their series was high, but the median duration of response was low. Newer agents such as paclitaxel have been tried in combination with some encouraging results [36]. Recently the results of the Gynecologic Oncology Group randomized trial of whole abdominal irradiation versus cisplatin-ifosfamide+mesna in optimally debulked Stage I-IV carcinosarcoma of the uterus were presented at the ASCO 2006 meeting. Adjuvant chemotherapy reduced the recurrence rate and prolonged overall survival; however the authors concluded that due to a high relapse rate and poor overall survival the imperative for new adjuvant therapies remains [37]. In our study the use of chemotherapy was a significant adverse factor for overall and disease-free survival. This finding is likely confounded by the fact that the patients who were given chemotherapy tended to have higher stage and poor prognostic factors.

Researches on uterine sarcomas are being carried out to understand the biology of this malignancy at the molecular level. Recent trials have been investigating COX-2, c-KIT and HER-2/neu expressions in uterine sarcomas hoping to find an association between the expression of these oncogenes and clinicopathologic factors and also to find potential markers for targeted therapies [37-39].

Conclusion

The data presented here are comparable with other published studies [4, 5, 7, 10, 11, 24, 28-31]. Although the prognostic factors proposed in various series differ widely, tumor stage seems to be the most important factor mentioned in each of these studies as well as histologic subtype. These tumors have a poor prognosis and the majority of patients die because of distant metastases. Many authors have suggested that a multimodality approach would be a logical treatment of these aggressive tumors [1, 5, 12, 17, 19, 27, 35]. Therefore radiotherapy should be employed to control local disease and chemotherapy to prevent potential metastases. This is a retrospective study and a control group of patients who were treated with surgery alone is lacking. Although our local control rate was very high favoring radiotherapy the exact value of adjuvant radiotherapy can not be proven and given the small number of patients receiving adjuvant chemotherapy it was not possible to address the value of adjuvant chemotherapy.

The low number of patients in a single institution prevents the development of clinical trials. The optimal adju-

vant therapy hopefully will be elucidated through multicentric randomized trials of radiotherapy, active chemotherapy agents, investigational treatments and molecular studies.

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