RESEARCH COMMUNICATION

Uterine Sarcoma: Clinicopathological Characteristics, Treatment and Outcome in Iran

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Abstract

Objective: Uterine sarcomas are rare and heterogeneous tumors with histopathological diversity characterized by rapid clinical progression and a poor prognosis. The aim of this study was to investigate clinical and histopathological characteristics together with treatment and outcome of Iranian patients with uterine sarcomas. Materials and methods: Records of 57 patients with histologically verified uterine sarcoma treated at the Vali-e-Asr Hospital were reviewed (1999-2004). Results:The lesions were 19 leomyosarcoma (LMSs), 17 malignant mixed Mullerian tumors (MMMT), 16 endometrial stromal sarcomas (ESSs), 3 unspecified sarcomas, 2 rabdomyosarcomas. Median age at diagnosis was 50 (17-81) years. Clinical stages (based on FIGO) were 30 with stage I disease, 9 with stage II, 12 with stage III and 6 with stage IV. Only one patientdid not undergo surgery and most cases with LMS and ESS were treated with simple total hysterectomy (STH). Forty patients (out of 57) received adjuvant radiotherapy. The median follow-up period was 19 (2-96) months and median disease free period was 16 (1-86) months. The overall survival rates after 1, 2, and 5 years were 71%, 58% and 52%, respectively. Survival was related to histological type of ESS (p=0.0018), grade I (p=0.0032) and early stage (p=0.045) significantly, but was not linked to postoperative irradiation. However, local recurrence rate was significantly improved after adjuvant radiotherapy. Twenty-one patients had relapse, 16 in the pelvic and 5 in extrapelvic sites. Conclusion: Based on the findings in this series, prognosis is dependent on histopathological subtype, grade and tumor stage. Adjuvant radiotherapy decreases local recurrence rate, but without significant impact on survival.

Key Words: Uterine sarcoma - Iranian patients - survival - chemotherapy - radiotherapy

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Introduction

Uterine sarcomas are rare and heterogeneous tumors, accounting for fewer than 4 percent of uterine malignancies and occurring in 17 per million women annually (Platz and Benda, 2000). They include leiomyosarcomas (LMSs), which can arise from the myometrium, and endometrial stromal sarcomas (ESS) as well as malignant mixed Mullerian tumors (MMMT), which can arise from the endometrium(Giuntoli et al., 2003; Kokawa et al., 2006).

LMS and MMMT comprise approximately 40%, ESS 15% and other sarcomas 5% of all uterine sarcomas (Livi et al., 2004). It has been reported that racial differences in the incidence of uterine sarcomas exist (Brooks et al., 2004). Several investigations demonstrated that the occurrence of LMS and MMMT is higher in blacks than in whites (Livi L et al., 2003; Saga et al.,2004). Uterine sarcomas occur primarily in women 40 to 60 years of age (Dinh et al.,2004; Kelly and Craighead,2005). Histories of pelvic radiation also were seen as a risk factor, noted in 5 to 10 percent of patients (Meredith et al.,1986).

Abnormal uterine bleeding, abdominal or pelvic mass and pain were the most common symptoms of patients with uterine sarcomas (Bell,et al.,1994). Compared to the more common types of endometrial cancer, women with uterine sarcomas have a poor prognosis due to the aggressive nature of this tumor (Meredith et al.,1986; Bell,et al.,1994; Dinh et al., 2004; Kelly and Craighead, 2005). The most frequent prognostic factors include tumor stage, histological subtype, grade, lymphovascular invasion and menopausal status (Major et al.,1993; Nola et al.,1996; Iwasa et al.,1998). Standard treatment for early-stage patients is hysterectomy and surgical staging. About half of these patients develop recurrent disease within 5 years of initial therapy (Iwasa et al.,1998).

Postoperative radiation seems to improve local disease control of the patients with a resectable stage, but it has

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not had a significant impact on overall survival (OAS) (Sutton et al.,2000; Giuntoli et al.,2003). Adjuvant chemotherapy using single agents including ifosfamide and doxorubicin has been undertaken(Curtin et al.,2001; Omura et al.,1998; Sutton et al.,1996; Sutton et al.,2000). Combination regimens have not proven to be more effective than therapy with the single agent ifosfamide(Fujita ET AL.,2004).

Because of the low incidence of this malignancy and its pathologic diversity, there is no consensus on the optimum management, with considerable variation in type of surgery and choice of adjuvant treatment offered. The purpose of this study was to correlate clinical outcome with histological subtype and clinical parameters, with analysis of the role of adjuvant radiotherapy in the management of these patients.

Patients and Methods

Fifty-seven consecutive patients (median age 50 years, range 17-81 years) with the histologically verified uterine sarcoma were treated at the Vali-E-Asr Hospital (1999-2004) have been evaluated. The time of diagnosis was considered as the date of the primary surgical procedure. Time to recurrence, death or last contact was considered. Study's inclusion criteria required the pathologic diagnosis of uterine sarcoma at the time of surgery. The histologic subtype was divided into LMS, ESS, and MMMT. By use of modified 1988 FIGO criteria for endometrial adenocarcinoma, the stage was retrospectively assigned on the basis of surgical and pathologic findings. Patients were assigned stage I for disease confined to the corpus, stage II for disease confined to the corpus and cervix, stage III for disease confined to the pelvis or retroperitoneal nodes, and stage IV for distant spreading.

In the case of incomplete surgical staging, the stage was assigned on the basis of available pathologic findings with unevaluated areas considered negative. A questionnaire was then used to gather data and was transferred into the statistical package (SPSS, version 13) to evaluate the results.

Statistical analysis

Descriptive analysis is presented for median age, clinical stage, grade, adjuvant therapy and surgical procedure for each histologic subtype. The Fisher exact test was used to compare the disease-free interval and overall follow-up period between LMS, EES, and MMMT. Survival curves were generated using the Kaplan–Meier method. A univariate analysis of potential prognosis and predictive factors for all sarcomas related to histology, clinical stage, grade, age at diagnosis, surgical procedure and adjuvant treatment was performed using the log-rank test to determine statistical significance. Cox's proportional hazards regression model was employed for the multivariate analysis.

Results

Patient characteristics

From 57 uterine sarcomas, 19 cases had LMS, 16 had ESS, 17 had CS, 3 had unspecified and 2 had rhabdomyosarcoma. The case characteristics are given in Table 1.

Women with ESS were more likely to present with stage I disease compared with women with LMS and MMMT. The incidence of stage III disease for MMMT was higher than that for ESS and LMS.

Analysis of treatment was divided into three groups: surgical alone, adjuvant chemotherapy after surgery, and adjuvant radiation therapy after surgery. The surgical procedure was divided into simple hysterectomy (STH), extended hysterectomy (EH), and radical hysterectomy (RH). Most of the cases with LMS and ESS were treated with STH. In patients with MMMT; SHT, EH, and RH were performed in 7 out of 17 (41.1%), 4 out of 17 (15.7%), and 6 out of 17 (35.2%) cases, respectively. Lymph node dissection was performed in 5 out of 19 (26.3%) of LMS and 1 out of 16 (6.25%) of ESS, and the incidence increased in patients with MMMT (11 out of 17 women, 64.7%).

Over than half of LMS (68.4%) patients underwent adjuvant chemotherapy at the time of initial treatment.

Table 1. Characteristics of the Uterine Sarcoma Cases

Characteristic	Histological subtypes															
	LMS				MMT				ESS							
Stage	I		II		III		IV		I		II		III		IV	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Primary treatment																														
Surgery	9	47.4	3	15.7	4	21.5	2	10.5	7	41.1	4	23.5	5	29.4	1	5.8	12	75.0	3	18.7					1	6.2				
No surgery							1	5.3							1	5.9														
Adjuvant chemotherapy	6	31.5	2	10.5	2	10.5	3	15.8	5	29.4	4	23.5	4	23.5	1	5.9	3	18.7	1	6.2	1	6.2								
Adjuvant radiotherapy	3	15.8			1	5.3							1	5.8			8	50.0	2	12.5										
Lymph node dissection																														
Not done	7	36.8	2	10.5	2	10.5	3	15.8	3	17.6	1	5.9	2	11.8			10	62.5	2	12.5	2	12.5	1	6.2						
Done	2	10.5	1	5.3	2	10.5			4	23.5	3	17.6	4	23.5					1	6.2			1	1.6						
Chemotherapy																														
With cisplatin	6	31.5	2	10.5	2	10.5	1	5.3	6	35.3	3	17.6	4	23.5	1	5.9			1	6.2	1	6.2	1	6.2						
Without cisplatin	1	5.3	1	5.3																										
Relapse																														
Pelvic	2	16.6	1	8.3	2	16.6	1	8.3	1	12.5	1	12.5	1	12.5	1	12.5	1	33.3	1	33.3					1	33.3				
Extrapelvic	2	16.6			6	50.0	3	25.0	1	12.5	1	12.5	4	50.0	1	12.5	1	33.3												

More MMMT Patients received adjuvant chemotherapy (82.3%). ESS Patients (62.5%) received more adjuvant radiotherapy compared to LMS (15.7%) and MMMT (5.8%) patients.

Chemotherapy was performed on 21 patients with cisplatin + doxorubicin + cyclophosphamide regimen and on 11 patients with cyclophosphamide + doxorubicin + Taxol. Thirty-two of 57 patients (56.1%) received adjuvant chemotherapy with cisplatin alone or in combination, whereas 2 out of 57 women (3.5%) underwent adjuvant chemotherapy without cisplatin. Adjuvant external beam radiotherapy (EBRT) to the whole pelvis was prescribed for 10 patients, with a dose range of 36 Gy in 20 fractions over 4 weeks to 60 Gy in 33 fractions over 6–12 weeks. Adjuvant EBRT plus intracavitary ovoid treatment was prescribed for 4 patients: 2 received 45 Gy in 25 fractions EBRT plus 8 Gy (at 0.5 cm) in two insertions using high-dose rate brachytherapy, and the other two received 45–50 Gy in 25–30 fractions EBRT plus different intracavitary techniques with doses ranging from 5.5 to 25 Gy as a single insertion.

Also relapse was occurred in 21 patients, in 16 seen in the pelvis and in 5 in extra pelvic sites.

Univariate analysis

The median follow-up period for all sarcomas was 19 (2-96) months and median disease free period was 16 (1-86) months. The 1-year overall survival rate of the 57 patients was 71%, the 2-year overall survival rate was 58% and the 5-year overall survival rate was 52%. The overall survival curve is shown in Figure 1 and histologic-dependent overall survival rates can be seen in Figure 2, with the significant difference between ESS and those with MMMT or LMS (P = 0.0018).

There was a striking difference between patients survival with stage I, II, III, and IV (P =0.045). The 5-year overall survival rate of patients with ESS was 82% as compared with only 41% for patients with MMMT and 47% for patients with LMS (P = 0.0018). 5 years local recurrence rate was 25%.

Univariate analysis demonstrated that advanced stage and MMMT histologic subgroup had a significantly adverse effect on survival. Advanced stage, certain histologic subgroups, and failure to use radiation adversely predicted for local recurrence using univariate analysis. Curves and log-rank tests were generated to evaluate the influence of individual variables on OAS (Fig 1). Early stages (I and II), and grade 1 were all associated with significantly improved OAS rates.

However, lymph node dissection, adjuvant chemotherapy, and adjuvant radiation did not seem to affect the outcome (data not shown). Patients treated with radiotherapy after surgery had better situation in case of local recurrence (Fig 3).

Multivariate analysis

The influence of specific factors on survival as determined by univariate analysis may have resulted from selection bias rather than from the variable itself. Therefore, multivariate analysis was performed to account for the potential influence of confounding factors. A Cox proportional hazards model was employed. The following variables were considered: early clinical stage (stage I and II), grade, histological type and adjuvant treatment at the initial treatment (adjuvant chemotherapy and adjuvant radiotherapy). The factors found to have an independent influence on cause-specific survival were histological type, early stage, and grade (P< 0.05). All the three factors

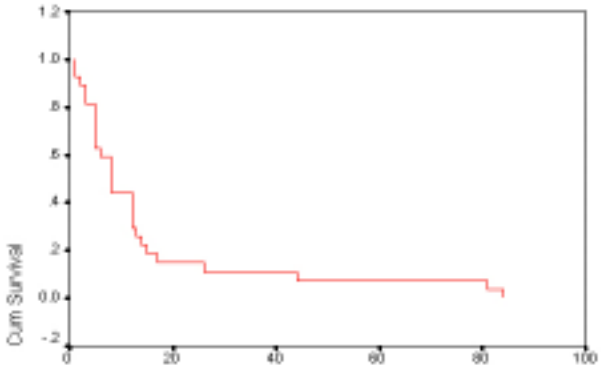

Figure 1. Overall Survival (months) for Patients with Uterine Sarcomas

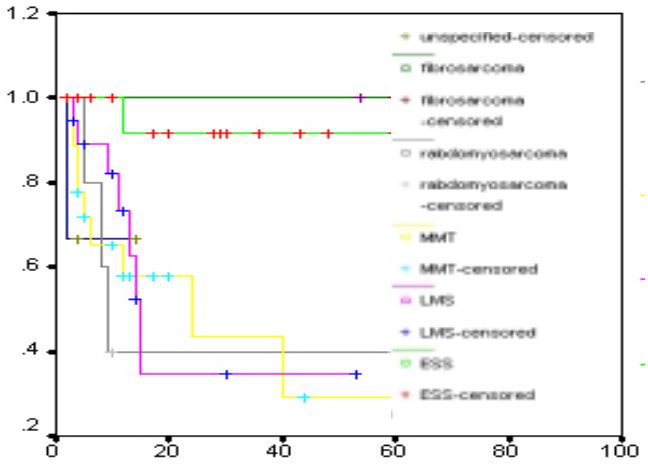

Figure 2. Overall Survival (months) According to Histopathological Type

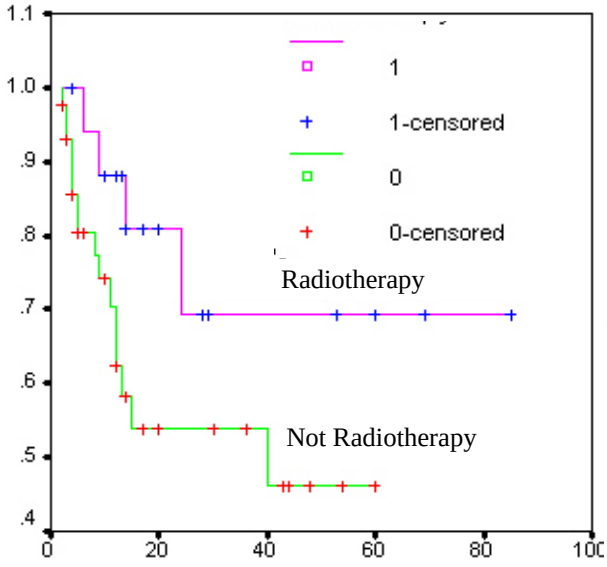

Figure 3. Univariate Analysis of Local Recurrence by Treatment

showed relative risks of less than one, indicating a favorable effect on survival.

Discussion

Uterine sarcoma is a heterogeneous condition, with much debate on how to subdivide these tumors and whether to manage them differently. In this study, the median survival was 2.8 years from initial diagnosis. The overall 1, 2, and 5 years survival rates were 71%, 58% and 52% respectively. Piver et al(1998) reported an estimated 5-year survival rate of 36% in surgically treated patients with stage I uterine sarcoma. Gadducci et al (1989) obtained a 5-year survival rate of 33% for 23 patients with early stage uterine sarcoma, most of who were treated with a combination of surgery and pelvic irradiation. Moskovic et al(1993) reported a median survival of 22 months and a 5-year survival rate of 35%.

The role of radiotherapy is controversial, as different conclusions are noted in small series. In this study, EBRT plus intracavitary irradiation seems to improve local disease-free survival in stage I, but the number of patients was small; radical surgery with clear excision margins may provide adequate treatment. Le et al(2001), Hornback et al(1986) and Gerszten et al (1998) showed a trend in improvement of local disease control, with no statistically significant difference in overall survival in patients treated with adjuvant pelvic radiotherapy. Results of a phase III randomized study comparing adjuvant pelvic radiotherapy with observation in patients with completely respected stage I or II high-grade uterine sarcoma (Pecorelli ,????)

This study and others showed that radiotherapy may reduce local recurrence in uterine sarcoma (Le et al., 2001; Hornback et al., 1986; Gerszten et al., 1998). Such a decrease in local recurrence rate in a large number of patients might be expected to translate into a survival advantage, although this has yet to be demonstrated (Le et al., 2001).

In this study, histologically, MMMT predicts the worst prognosis than LMS and ESS. For ESS, the importance of sub-classification into low-grade or high-grade tumors is now well recognized; the former is treated with surgery and hormonal manipulation, whereas the latter is treated with a combination of surgery, chemotherapy and radiotherapy(Giuntoli et al.,2003; Kokawa et al.,2006; L.livi et al.,2004; Brooks et al.,2004; Livi L et al.,2003; Saga et al.,2004; Dinh et al.,2004; Kelly and Craighead, 2005; Knocke et al., 1998). However, we did not notice any statistical difference in cause-specific survival: 66.6% patients with high-grade ESS died of cancer as did 57% with low-grade ESS (P=0.1). This supports the findings of Nordal et al.(1997), Kelly et al.(2005) and Livi et al.(2004) whose patients with ESS had a more favorable prognosis than patients with other histological types (P<0.001). They also reported, in a multivariate analysis, the importance of stage (P<0.001) and age (P<0.001) as prognostic factors in contrast with other reports in the literature. Olah et al.(1992) & Chauveinc et al.(1999) reported that LMS had a poorer prognosis than MMMT when adjusted for other known prognostic factors (Bodner-Adler et al., 2001).

Histological tumor grade was a powerful parameter for predicting outcome in our series on univariate analysis. However, grade of tumors did not effect on local disease-free survival.

The reduction in local recurrence seems to be influenced by brachytherapy dose to the vaginal vault. The localized distribution of dose achieves an accurate boost technique, which can destroy sub-clinical disease with minimal early and late morbidity (Watanabe et al., 1998).

Ferrer et al.(1999) reported 5-year disease-free and overall survival without radiotherapy of 36% and 37%, respectively, compared to 76% and 73% when irradiation was given. Hoffmann et al. (1996) reported an increased disease-free survival for patients treated with adjuvant radiotherapy using doses of 50–60 Gy. The length of time from date of surgery to commencement of irradiation did not seem to affect outcome (P=0.09) in our series. We observed no major difference when patients were treated within 30 days compared with more than 60 days after surgery.

It is known that chemotherapy response is determined by histology. Gershenson et al. (40) reported that cisplatin achieved moderate activity in patients with metastatic MMMT (42% response rate), but was inactive in LMS (18%). Other studies support this observation. It has been suggested that adjuvant chemotherapy may afford a survival benefit by controlling sub-clinical distant disease, but this remains unproven. Newer agents such as paclitaxel have been tried in combination, especially for treatment of metastatic disease, with some encouraging results (Gadduicci and Romanini., 2001). Most recently, gemcitabine plus docetaxel has been shown to be tolerable and highly active in patients with LMS (Hensly et al., 2002).

In this study, acute toxicity from radiotherapy was only transitory. Diarrhea (grade 1-2 RTOG scale) was frequent (40%), but nausea and skin erythema proved minimal; fatigue was also reported. Wang et al. (1998) reported a correlation of increased acute toxicity and diarrhea during irradiation with risk of late rectal injury one patient underwent hemicolectomy for radiation damage 2 years after rapid radiotherapy to a dose of 50 Gy in 20 fractions over 38 days; today, this dose would be given in 25-28 fractions.

In conclusion, the prognosis of uterine sarcomas is dependent on histological subtype, grade, and stage. The histological subtypes of ESS, early stage and low grade of uterine sarcoma are associated with better outcome. In addition, adjuvant radiotherapy decreases local recurrence rate but without significant affect on survival. Local control was significantly improved after adjuvant radiotherapy, with best results at a dose higher than 50 Gy. The emerging concept is that uterine sarcomas can no longer be treated in a homogenous fashion.

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