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 leiomyosarcoma (LMSs), 17 malignant mixed Mullerian tumors (MMMT), 16 endometrial stromal sarcomas (ESSs), 3 unspecified sarcomas, 2 rhabdomyosarcomas. 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 two patients did 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

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 (ESSs) 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
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, ESS, 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**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Histological subtypes</th>
<th>LMS</th>
<th>MMT</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>9</td>
<td>47.4</td>
<td>3</td>
<td>15.7</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>5.3</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>No surgery</td>
<td>6</td>
<td>31.5</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>13.8</td>
<td>1</td>
<td>5.3</td>
<td>1</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>7</td>
<td>38.8</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Lymph node dissection</td>
<td>10.5</td>
<td>5.3</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Not done</td>
<td>1</td>
<td>5.3</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Done</td>
<td>5</td>
<td>28.6</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1</td>
<td>5.3</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>With cisplatin</td>
<td>2</td>
<td>16.6</td>
<td>1</td>
<td>8.3</td>
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<tr>
<td>Without cisplatin</td>
<td>2</td>
<td>16.6</td>
<td>6</td>
<td>50.0</td>
</tr>
</tbody>
</table>
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
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 et al) is 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.

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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