Uterine sarcoma: a report of 57 cases over a 16-year period analysis

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Summary

Uterine sarcomas comprese approximately 4-9% of all uterine malignant tumors with a poor prognosis. We report 57 cases of sarcoma originating in the uterus treated from 1990 to 2006 at the Department of Obstetrics and Gynecology of Democritus University of Thrace, Greece and the Department of Obstetrics and Gynecology of Aschaffenburg Hospital, Germany. The median age of occurrence was 49 years with the commonest symptom being abnormal uterine bleeding. Forty-nine patients underwent a total hysterectomy and bilateral salpingo-oophorectomy whereas 17 cases underwent radical lymphadenectomy. During the last follow-up (December 2006), six patients were alive and well with no evidence of disease, 23 patients had died of undercurrent disease, and 28 were alive with recurrence of disease. These rare cancers can be aggressive, and account for a greatly disproportionate number of deaths from uterine cancers. Treatment for this rare disease should be performed according to international protocols in order to have the most updated information.

Key words: Uterine sarcoma; Surgical; Postoperative treatment; Follow-up.

Introduction

Cancer of the uterine corpus accounts for about 6% of cancers in women [1]. Uterine sarcomas are extremely rare and comprise approximately 4-9% of all invasive uterine cancers and account for less than 3% of all female genital tract malignancies [2,3]. In various studies the average incidence of the three main histological sarcoma-subgroups, respectively, were reported as 41,7%-50% for leiomyosarcoma (LMS), 30% for mixed müllerian tumors (MMT), 7-15% for endometrial stromal sarcoma (ESS) and about 5% for others [4-6]. The last group includes liposarcoma, rhabdosarcoma and fibrosarcoma. LMS, which comprises only 1% of gynecologic malignancies, has a notoriously poor prognosis [7]. In contrast to MMT, which contains both epithelial and mesenchymal elements, LMS occurs almost always as a pure homologous tumor. Rarely, heterologous leiomyosarcomas such as rhabdomyosarcoma, osteogenic sarcoma, and chondrosarcoma of the uterus have been described [8]. Endometrial stromal sarcomas are rare uterine malignancies accounting for less than 1% of all uterine cancers [9]. ESS is characterized by cells that resemble those of the endometrial stroma during the proliferative phase of the menstrual cycle and have traditionally been classified as either low-grade or high-grade. Low-grade ESS is generally a slow growing malignancy with an indolent clinical course, but with a tendency for late recurrences. Pure uterine sarcomas of the homologous type arise from native elements, as in endometrial stromal sarcoma and leiomyosarcoma. A mixed müllerian tumor has histologic features of carcinoma and sarcoma. MMT with an incidence of 1.5% of all malignant diseases of the uterus is a rarity among the malignancies of the female genital tract [10]. Primary locations of MMT may be the endometrium, the cervix and the ovary. Development of endometrial hyperplasia, endometriosis, endometrial polyps and endometrial adenocarcinomas has been described [11]. All sarcomas carry a poor prognosis with an overall survival of less than 50% at two years, even when presenting at an early stage [12].

Approximately 33% of patients seen are already in advanced stages of disease [5], and distant metastases are frequent. The rarity of these tumors as well as their pathologic diversity, has made it difficult to define optimal management. This study analyzes retrospectively the treatment results of adjuvant radiotherapy and chemotherapy after the initial surgical investigation.

Materials and Methods

This is a retrospective study of women during the time period 1/9/90-31/12/06, who were treated at the Department of Obstetrics and Gynecology of Democritus University Alexandroupolis, Greece and the Department of Obstetrics and Gynecology of Aschaffenburg Hospital, Germany. Data were extracted by chart review that included patient information. The following variables were included: age, menopausal status, family history of cancer, histological subtype, tumor stage, tumor grade, operative procedure, adjuvant radiotherapy, adjuvant chemotherapy, disease-free survival, site of recurrence and current disease status. A pathologist at each institution reviewed the histopathology at the time of surgery. We received the final histological diagnosis a few days postoperatively. All patients in both institutions had primary sur-

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gical management. The main indication for surgery was uterine myoma. Other indications for surgery were history of abnormal bleeding and recurrent abdominal pain despite conservative treatment. Patients with any abnormality such as bleeding or atypical smears were evaluated histologically. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the gold standard for the surgical procedure of uterine sarcoma in cases of tumor limited to the uterine corpus. The surgical procedures were removal of as much tumor as possible in cases with pelvic and/or abdominal spread. Omentectomy was performed and any suspiciously enlarged lymph node was biopsied when malignancy was recognized pre- or intraoperatively. The records of 57 patients treated postoperatively were examined retrospectively.

All patients had regular follow-up visits until the end of the study and were evaluated with a mean follow-up of 48 months. During the first year the patients were followed up at three-month intervals, and then at six-month intervals. Pelvic examination, abdominal and vaginal ultrasonography, and serum CA125 determination were performed at each check-up, and in case of any suspicion of recurrence or metastasis, magnetic resonance imaging (MRI) was carried out. The clinical course of the disease was recorded from the patients' notes by three independent clinical physicians. Follow-up for all surviving patients ranged a minimum of three months postoperatively to a maximum of 13 years with a median follow-up observation time of three years (SD 3.714). All examined study parameters (pre- and intraoperative) were retrospectively analyzed and correlated with recurrence and survival-rate.

Results

A total of 57 women with uterine sarcomas (Group A = 8 from Alexandroupolis hospital and Group B = 49 from Aschaffenburg hospital) were identified during the period from 1/9/1990 to 31/12/2006. The characteristics of the 57 subjects are presented in Table 1. The mean age was 51.14 ± SD 11.682 years (range 30-81 years). The mean parity of the women was 1.73 ± SD 1.027 (range 0-4). None of the women was receiving hormone replacement therapy (HRT) nor had had any gynecological malignancy in the past. Although no prior malignancies had occurred in our patients and none had a family history of gynecological cancer, endometriosis was surgically documented in two cases. Five patients had severe medical conditions such as heart, pulmonary or renal disease. Two cases had had a cerebral insult nine years before and diabetes mellitus for 20 years. In the study-patients, LSM cases accounted for 33 (57.89%), MMT cases for 17 (29.82%), ESS for six (10.53%) and other sarcomas and angiosarcoma one case (1.75%).

Table 1. — *Patient characteristics and presenting symptoms*.

Patient characteristics			
Age	Mean ± SD, Range	51.14 ± 11.68	(30-81)
Parity	Mean ± SD, Range	1.73 ± 1.02	(0-4)
Mass	Mean ± SD, Range	51.45 ± 30.27	(17-115)

Presenting symptoms	Frequency	
Abnormal vaginal bleeding	80.7%	(46/57)
Pelvic mass	14.03%	(8/57)
Abdominal pain	5.26%	(3/57)

Table 2. — *Correlation of tumor histology to tumor stage and grade*.

Histological type	Stage I	Stage II	Stage III	Grade 1	Grade 2	Grade 3
LMS	32 (96.96%)	1 (3.03%)	0	30 (90.9%)	3 (9.1%)	0
MMT	14 (82.35%)	2 (11.76%	1 (5.88%)	14 (82.3%)	2 (11.76%)	1 (5.88%)
ESS	4 (66.6%)	1 (16.6%)	1 (16.6%)	6 (100.0%)	0	0
Other	4 (100.0%)	0	0	1 (100%)	0	0
Total	51	4	2	51	5	1

The most common presenting symptom was abnormal vaginal bleeding, occurring in 46 patients (80.7%). Other features such as a vaginal ultrasound of a pelvic mass and recurrent abdominal pain were observed in eight (14.03%) and three (5.26%) patients, respectively (Table 1). The masses were located in the uterine wall (n = 5) and three presented as a polypoid mass penetrating the endometrial cavity from the myometrium. In all patients myomas were detected preoperatively at clinical and vaginal ultrasound examination. By mass we refer to the largest length of the tumor involved. The mean mass length was 51.45 ± 30.27 range (17-115). Most of the uterine myomas showed several calcifications at ultrasound and were always associated with sarcoma. Especially concerning vaginal bleeding, hypermenorrhea occurred in 33 cases (33/46, 57.89%), metrorrhagia in nine cases (9/46, 19.56%) and spotting in the last four (4/46, 8.69%). Fractional curettage was performed in all patients (46) with abnormal uterine bleeding. Histological diagnosis was made through fractional curettage in 15 patients (32.7%). In the other 31 (67.3%) sarcomas were diagnosed by hysterectomy.

Forty-nine patients underwent total abdominal hysterectomy and salpingo-oophorectomy, and in 17 cases with advanced disease pelvic lymphadenectomy and omentectomy were performed. In five of them paraortal lymph node sampling was carried out. In these 17 radically operated (FIGO Stage I/II) patients, three patients with ESS (FIGO Stage II) and two with MMT (FIGO Stage I) had lymph node metastases. One patient with MMT (FIGO Stage III) had lymph node and ovarian metastases in both ovaries and another case with ESS (FIGO Stage III) had omental metastases. In four women (30-36 years) the surgical procedure was only total hysterectomy without salpingo-oophorectomy. The remaining four cases with FIGO Stage III were treated with subtotal hysterectomy, salpingo-oophorectomy and biopsy of the pelvic tumor mass. According to FIGO classification, Stage I, II, and III tumors were identified in 51, four, and two patients, respectively. The classification of uterine sarcomas, histological type, tumor stage and histological grade are shown in Table 2. Thirty-five patients (61.40%) were postmenopausal. No statistically significant correlation was found concerning menopausal status nor any of the patients' characteristics (histological type, stage, grade of sarcomas (Table 3). The frequency of tumor histological type concerning menopause is shown in Table 4. Adjuvant treatment with radiotherapy was administrated in 52 cases. Chemotherapy was used with consistency for adjuvant therapy in 36 patients. No

Table 3. — *Relationship of histological type, stage, grade and treatment to menopause - A) Premenopausal 22 (38.5); B) Postmenopausal 35 (61.40%).*

Histological type	A		B		Total cases: A + B
LMS	13	34.21%	25	65.78%	38
MMT	6	50.0%	6	50.0%	12
ESS	3	50.0%	3	50%	6
Others	0		1	100%	1
Stage					
I	19	38.0%	31	62.0%	50
II	2	40.0%	3	60.0%	5
III	1	50.0%	1	50.0%	2
Grade					
1	21	41.17%	30	58.82%	51
2	1	20.0%	4	80.0%	5
3	0		1	100.0%	1
Postoperative Treament					
No treatment	1	20.0%	4	80.0%	5
Radiotherapy	6	37.5%	10	62.5%	16
Chemotherapy + Radiotherapy	15	41.66%	21	58.33%	36

Table 4. — *Frequency of histological type to menopause. A: Premenopausal 22: 38.5%; B: Postmenopausal 35: 61.40%.*

Histological type	A		B	
LMS	13	59.1%	25	71.43%
MMT	6	27.27%	6	17.15%
ESS	3	13.63%	3	8.57%
Other	0	0.0%	1	2.85%
Total	22		35	

additional treatment was recommended in three patients because they had other severe diseases. Two patients with Stage I sarcoma refused treatment. After three and five years, recurrence rates of 54.54% and 70.96%, respectively, were recorded for patients who had received postoperative radiation, no adjuvant treatment and adjuvant chemotherapy (Tables 5 and 6). The results of correlation between tumor recurrence and the following parameters: tumor-stage, grade, histological type, treatment and CA125 values in sera are presented in Tables 5 and 6. Serum samples were analyzed for CA125 and the results were correlated to the course of the primary disease. The values of CA125 correlated positively in observed patients (total 31) with recurrence of the disease especially in histological subtype MMT (6/9 = 66.6%). From eight study patients sera were not available at the exact follow-up time but rather two months later. At the time of final analysis, 40.35% of patients (23/57) had died due to progressive sarcoma disease; 49.12% (28/57) were alive with disease recurrence and 10.52% (6/57) were alive without evidence of disease. At the same time 64.28% of the patients had an isolated local recurrence (18/28) and 35.71% (10/28) pelvic recurrence with distant metastases. Three patients recurred after seven months. In a total of 15, recurrence was limited to the pelvis. Metastatic disease was detected in ten patients; four had pulmonary metastases, four in the abdomen, one in the brain and one in the spine, respectively. Recurrent disease in

Table 5. — *Recurrence rate at 3 years by histological type, stage and grade. A) Recurrence negative 5 (45.46), B) Recurrence positive 6 (54.54%).*

Histological type	A		B		Total cases: A + B
LMS	5	83.33%	1	16.66%	6
MMT	0	0.0%	4	100.0%	4
ESS	0	0.0%	1	50%	1
Stage					
I	5	54.45%	4	45.45%	9
II	0	0.0%	1	100.0%	1
III	0	0.0%	1	100.0%	1
Grade					
1	4	50.0%	4	50.0%	8
2	1	50.0%	1	50.0%	2
3	0	0.0%	1	100.0%	1
Treament					
No treatment	0	0.0%	2	100.0%	2
Radiotherapy	3	60.0%	2	40.0%	5
Chemotherapy + Radiotherapy	2	50.0%	2	50.0%	4
CA125 value					
< 30 Uml	4	66.6%	2	33.3%	6
> 30 Uml	1	20.0%	4	80.0%	5

Table 6. — *Recurrence rate at 5 years by histological type, stage, grade and correlation to treatment and CA125 values. A) Recurrence negative 9 (29.04%); B) Recurrence positive 22 (70.96%).*

Histological type	A		B		Total cases: A + B
LMS	7	36.48%	12	63.15%	19
MMT	2	22.22%	7	77.77%	9
ESS	0	0.0%	3	100.00%	3
Stage					
1	8	27.58%	21	72.41%	29
2	1	50.0%	1	50.0%	2
3	0	0.0%	0	0.0%	0
Grade					
I	9	32.15%	19	67.85%	28
II	0	0.0%	3	100.0%	3
III	0	0.0%	0	0.0%	0
Treatment					
No treatment	0	0.0%	3	100.0%	3
Radiotherapy	7	43.75%	9	56.25%	16
Chemotherapy +Radiotherapy	2	20.0%	10	83.3%	12
CA125 value					
< 30 Uml	6	50.0%	6	50.0%	12
> 30 Uml	3	15.78%	16	84.21%	19

the pelvis was treated by combination chemotherapy and surgery, while in cases of distant metastatic diseases only chemotherapy was used. In one case recurrence in the vulva was treated with external local radiotherapy only. The small number of patients does not permit statistical analysis of individual grades. Overall survival for the 57 patients was 70.17% at three years and 38.7% at five years (Tables 7 and 8). With respect to histology, ESS predicted the worst prognosis, followed by MMT and LMS with a survival rate at five years of 0%, 22.22%, and 52.63%, respectively (Table 8). After treatment no second

Table 7. — *Survival rate at 3 years by histological type, stage, grade and treatment. A) Alive 7 (70.17%); B) Dead 4 (29.82%).*

Histological type	A		B	
LMS	5	83.33%	1	16.66%
MMT	2	50.0%	2	50.0%
ESS	0	0.0%	1	100.00%
Other	0	0.0%	0	0.0%
Stage				
I	7	77.77%	2	22.22%
II	0	0.0%	1	100.0%
III	0	0.0%	1	100.0%
Grade				
1	6	75.0%	2	25.0%
2	1	50.0%	1	50.0%
3	0	0.0%	1	100.0%
Treament				
No treatment	0	0.0%	3	100.0%
Radiotherapy	10	62.5%	6	37.5%
Chemotherapy+ Radiotherapy	2	20.0%	10	83.33%

Table 8. — *Survival rate at 5 years by histological type, stage, grade and treatment A) Alive 12/31 (38.70)%; B) Dead 19/31 (61.29%).*

Histological type	A		B	
LMS	10	52.63%	9	47.36%
MMM	2	22.22%	7	77.77%
ESS	0	0.0%	3	100.0%
Stage				
I	11	37.93%	18	62.06%
II	1	50.0%	1	50.0%
III	0	0.0%	0	0.0%
Grade				
1	12	42.85%	16	57.14%
2	0	0.0%	3	100.0%
3	0	0.0%	0	0.0%
Treament				
No treatment	0	0.0%	3	100.0%
Radiotherapy	10	62.5%	6	37.5%
Chemotherapy + Radiotherapy	2	20.0%	10	83.33%

malignancy has been reported in our series. When we compared postoperative treatment versus no adjuvant treatment, we observed that postoperative treatment (radiotherapy or radiotherapy + chemotherapy) did not improve local recurrence, and it did not give any long-term survival benefit (Tables 7 and 8).

Discussion

Up to 30% of women with leiomyomas will experience abnormal uterine bleeding [13]. The most common pattern is menorrhagia, although other abnormal bleeding patterns may also be seen. The reason why uterine myomas cause abnormal bleeding is essentially unknown, although there are several theories that have been offered as an explanation [14]. Leiomyosarcomas represent neoplasms that arise entirely independently from benign leiomyomas. Further, there is no evidence that women with uterine myomas are at increased risk for this malignant neoplasm. Therefore, labelling leiomyosarcoma as a form of malignant degeneration of leiomyomas is a misnomer. Most leiomyosarcomas occur later in life (the fifth or sixth decade) than benign myomas [15]. Abnormal uterine bleeding and rapid growth of the uterus in a postmenopausal woman are the typical initial features. Abdominal pain and uterinethelargement may occur [15, 16]. As previously noted, these neoplasms are quite uncommon, particularly among women undergoing surgery for presumed leimyomas [17]. Surgery has always been described as the most effective treatment in uterine sarcoma [18, 19]. Taking away all the tumor mass seems to optimize the chance of survival for patients with sarcoma. Removal of the ovaries is recommended in all cases despite tumor stage. Haberal *et al*. reported that retained ovaries had a recurrence rate of 100%, but the recurrence rate was 43% for patients who had oophorectomies at the initial surgery [20, 21].

Removal of the ovaries in young women is controversial. In our study no significant difference in recurrence rates in patients receiving surgery (3/7 = 2.5%) (salpingo-oophorectomy) versus total hysterectomy alone (2/5 = 40%) was noted. In cases of young women undergoing either removal of the ovaries or premature ovarian failure (in cases of retained ovaries) cryoconservation of the ovarian tissue is recommended to avoid a postmenopausal status.

Cryoconservation of ovarian tissue is currently proposed as an experimental alternative to oocyte and embryo freezing, in the hopes of restoring future fertility in young women before treatment with radiation or chemotherapy [22]. This procedure is a unique opportunity for young patients with malignant diseases to store their gametes before gomadotoxic treatments [23].

Surgical staging using the 1988 FIGO system for endometrial carcinoma was applied retrospectively. Clinical staging was based on clinical examination, fractional curettage and in recent years on MRI. Extirpative surgery is the primary treatment for patients with uterine sarcoma and may be curative in cases where the tumor is confined to the uterus. Unfortunately, the overall prognosis is poor regardless of the stage; the use of adjunctive therapy such as irradiation and chemotherapy in conjunction with hysterectomy does not appear to significantly alter the prognosis. Due to the high incidence of recurrence and poor prognosis of these tumors, they should be studied and managed by a multidisciplinary team composed of surgeons, oncologists, radiotherapists and pathologists. Radio- and chemotherapy are always administrated in the adjuvant setting. In advanced stages of the disease radio- and chemotherapy are the primary treatments. Berchuk *et al*. reported an overall survival of 22% with none of their patients with extrauterine disease (Stages III and IV) surviving more than 20 months [24]. A higher survival probability is often reported for patients with low-grade endometrial stromal sarcoma [25]. In our study, 52 patients (91.22%) received radiotherapy as part of their primary postoperative therapy and 36 patients (63.15%) received additional chemotherapy either after the radio-

therapy or at the time of recurrence. The role of adjuvant radiotherapy in the treatment of uterine sarcoma is still unclear. Some authors have reported no benefit from postoperative irradiation [25-28]. Other studies confirmed the limited role of chemotherapy [29-32]. The benefit of chemotherapy by controlling subclinical distant disease is unproven and not generally accepted or recommended [33]. In our study the recurrence rate of the tumor after radio- or chemotherapy decreased compared to patients with no postoperative treatment (Tables 5 and 6). The length of time from the date of surgery to commencement of irradiation did not seem to affect outcome. We noted no major difference when patients within 30 days of surgery were compared with those of more than 40 postoperative days. Our experience with chemotherapy was very limited. In our patients the chemotherapy response was not determined by histological tumor type, stage or grade. During the chemotherapy diarrhea was only transitory. Survival rates for uterine sarcoma patients have been uniformly poor. Most series report a 5-year survival of 30-48%, which is in agreement with our study (12/31 = 38.7%) [34-37]. Our study emphasized stage and grade as prognostic factors but revealed age as the most important prognostic factor. This has also been confirmed in other studies [38-41]. Piver *et al*. reported an estimated 5-year survival rate of 36% in surgically treated patients with Stage I uterine sarcoma [42]. Gadducci *et al*. obtained a 5-year survival rate of 33% for 23 patients with early-stage uterine sarcoma, the majority of whom were treated with a combination of surgery and pelvic irradiation [43]. The recurrence rate in postmenopausal study women was less than that in premenopausal women ($p = 0.01599$) and is statistically significant. Age is often quoted as an independent prognostic factor. The recurrence rate was positively correlated with decreasing age ($p = 0.0302$). Histopathological classification (ESS) is positively correlated with recurrence rate and survival rate, but is not a statistically significant influencing parameter.

Histological tumor stage and grade lost statistical significance. Postoperative treatment was not significant when evaluated for local recurrence and survival rate. The frequent development of distant metastases is the main reason for the less favorable survival rates observed in uterine sarcoma compared with other uterine malignancies [44]. During the past few years, occasional cases of raised serum CA125 levels have been observed in patients with uterine sarcoma [45]. We confirmed in our series that elevated CA125 levels were related to the extent of the tumor, and high serum CA125 levels were observed in the majority of patients with recurrent or progressive disease of sub-histological type MMT.

Our study is limited by the relative rarity of the sarcomas. Due to the small patient number rigorous statistical analysis was not performed. In the absence of effective systemic treatment, we favor immediate surgery. Prospective multi-institutional studies are necessary to determine the optimal choice of therapy, both for primary disease and metastasis.

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