Uterine Sarcoma: Prognostic Factors and Treatment Evaluation

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ABSTRACT: **Background:** Uterine sarcoma constitutes a highly malignant group of uterine tumors. It accounts for 2–6% of uterine malignancies and its incidence is 1.7 in 100,000 women. The three most common variants of uterine sarcoma are endometrial stromal sarcoma, leiomyosarcoma and carcinosarcoma. Based on relatively small case series, the literature provides little information on the risk factors, the natural course of the disease and the preferred treatment.

Objectives: To evaluate uterine sarcoma patients treated in a tertiary referral center in Israel over a 20 year period (1980–2005).

Methods: We conducted a retrospective review of the charts of 40 uterine sarcoma patients, including their tumor characteristics, stage at diagnosis, treatment modalities, follow-up and survival.

Results: The patients' mean age was 53 years (range 32–76); 30% of the patients had carcinosarcoma, 55% had leiomyosarcoma and 15% had ESS. Half of the patients presented with stage I disease, 23% stage II, 10% stage III and 15% stage IV. Thirty-nine patients were treated with surgery. Adjuvant radiotherapy was administered to 39% of the patients, adjuvant chemotherapy to 21% and combined radiotherapy and chemotherapy to 9%. The mean follow-up period was 44 months, at which time disease had recurred in 44% of the patients. The disease stage was correlated with the 5-year survival rate, which was 73.1% for stages I-II and 22.2% for stages III- IV.

Conclusions: In accordance with other larger studies our data show that the only prognostic factor that was significantly correlated with prognosis was the stage of the disease at diagnosis. Despite advances in diagnosis and treatment, survival has not improved over the last 25 years.

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KEY WORDS: uterine sarcoma, tumor characteristics, prognostic factors, treatment evaluation, overall survival

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Uterine sarcoma is a rare disease, accounting for 2–6% of uterine malignancies and an annual incidence of 1.7 per 100,000 women [1,2]. Despite intensive treatment, local recurrence and distant metastasis are common. Overall survival is poor: 5-year survival rates of 50–70% for patients in stage I and 0–20% for the remaining stages [2,3].

Uterine sarcoma is comprised of three main pathological subgroups: carcinosarcoma (formerly known as MMMT, malignant mixed Müllerian tumor) (50%), leiomyosarcoma (30%) and endometrial stromal sarcoma (15%). Every group has its own risk factors, presenting symptoms, treatment response and prognosis [3]. The strongest prognostic factor for all the sarcomas is the stage at diagnosis [1-3]. Recently, a new International Federation of Gynecology and Obstetrics classification and staging system was specifically designed for uterine sarcomas in an attempt to reflect their differing biological behavior [4]. Briefly, two new classifications have been developed: a) staging for leiomyosarcoma and b) staging for ESS and adenosarcomas [3]. The staging for carcinosarcoma has remained as for endometrial carcinoma.

Total abdominal hysterectomy with bilateral salpingo-oophorectomy, and debulking of the tumor if present outside the uterus, is the standard initial treatment. The benefit of adjunctive chemotherapy and radiotherapy is in question [3-8]. Some patients may respond to hormonal treatment [9].

Given its low incidence, current data on uterine sarcoma are based on small retrospective series of patients, and there are as yet no standard treatment guidelines. We present here our accumulated experience of 25 years of treating women with uterine sarcoma at the Hadassah-Hebrew University Medical Center.

PATIENTS AND METHODS

The study included all 40 patients who were treated in the Hadassah-Hebrew University Medical Center for uterine sarcoma during the years 1980–2005. Patients' medical records were reviewed, and information regarding patients' medical history, tumor characteristics, treatment modalities and

ESS = endometrial stromal sarcoma

follow-up was recorded. Survival information was obtained from the National Cancer Registry. Stage of disease was determined using the FIGO staging classification: Stage I – sarcoma confined to the uterine corpus, stage II – sarcoma confined to corpus and cervix, stage III – sarcoma confined to the pelvis, and stage IV – extrapelvic sarcoma. Institutional Review Board approval was obtained for this retrospective study.

STATISTICAL ANALYSIS

The data were analyzed using SPSS v. 15 (SPSS, Chicago, USA), a general database management system. The endpoints were overall survival, 5-year survival, and recurrence rate. Survival curves were calculated by the Kaplan-Meier estimator. The statistical significance of each variable was first tested by the log rank test (univariate analysis). A Cox regression model (for multivariate analysis) was then applied.

RESULTS

Patients' clinical characteristics are presented in Table 1. Mean age was 53 years (range 32–76). Twelve patients (30%) had carcinosarcoma, 22 (55%) had leiomyosarcoma and 6 (15%) had ESS. Uterine sarcomas were more prevalent in women of Ashkenazi* origin (50–70%) than in those of Sephardic descent (20–25%). As described in the literature, disease incidence was distributed in a distinctive pattern according to patient age. The peak incidence of leiomyosarcoma was at age 40–55, while the incidence of carcinosarcoma and ESS increased steadily with age.

Eight of ten patients with a personal or familial history of cancer had carcinosarcoma. Four of the study patients had had breast cancer and all four were treated with tamoxifen. Familial history was mostly of breast cancer (including one in a male sibling), uterine adenocarcinoma and gastrointestinal malignancies.

FIGO = International Federation of Gynecology and Obstetrics
*Ashkenazi refers to people of European descent, and Sephardic to people of Middle Eastern and North African descent

Table 1. Patients' characteristics

	ESS	LMS	CS	Total
No. of patients	6 (15%)	22 (55%)	12 (30%)	40
Mean age (yrs)	52.5	46.7	64.8	53
Ethnic origin				
Ashkenazi	3 (60%)	10 (53%)	8 (67%)	11
Sephardic	1 (20%)	4 (21%)	3 (25%)	8
Arab	1 (20%)	5 (26%)	1 (8%)	7
Hormone replacement therapy	0	1	2	3
Family history of cancer	1	1	8	10
History of breast cancer and tamoxifen therapy	1	1	2	4

Table 2. Presenting symptoms by histological subtypes

Presenting symptom	ESS	Leiomyosarcoma	Carcinosarcoma
Postmenopausal bleeding	3 (50%)	1 (5%)	8 (73%)
Abnormal uterine bleeding	2 (33%)	12 (55%)	1 (9%)
Mass effect	1 (17%)	8 (35%)	1 (9%)
Other		1 (5%)	1 (9%)

The main presenting symptoms were abnormal uterine bleeding, postmenopausal bleeding and abdominal mass (including abdominal pain or discomfort, urinary symptoms and infertility) [Table 2]. Time from symptoms to diagnosis was shorter in cases of abnormal bleeding, especially in cases of postmenopausal bleeding, but it was not statistically significant and there was no correlation with survival. Half of the patients presented with stage I disease, 23% stage II, 10% stage III and 15% stage IV. Diagnosis of uterine sarcoma in our center increased by 300% between the periods 1980–1985 and 2001–2005, with a remarkable increase in diagnosis of carcinosarcoma in the later period.

TREATMENT [Table 3]

- **Surgery**

Of the 40 patients 39 (98%) were treated initially with surgery. Thirty-four of the patients (85%) had TAH-BSO, 2 had subtotal hysterectomy, one patient had total abdominal hysterectomy, one patient had TAH and unilateral salpingo-oophorectomy, one patient had a debulking operation and one patient did not undergo surgery. Four of the patients underwent surgery in other hospitals before being admitted to our facility. In 11 cases

TAH-BSO = total abdominal hysterectomy with bilateral salpingo-oophorectomy

Table 3. Initial treatment by stage

		I	II	III	IV	Total
Initial treatment	Surgery	9	4	1	2	16
	Surgery+chemotherapy	1	0	2	4	7
	Surgery+radiotherapy	10	2	1	0	13
	Surgery+chemotherapy+ radiotherapy	0	3	0	0	3
Leiomyosarcoma	Surgery	8	2	1	2	13
	Surgery+chemotherapy	1	0	0	4*	5
	Surgery+radiotherapy	3	1	0	0	4
	Surgery+chemotherapy+ radiotherapy	0	0	0	0	0
Carcinosarcoma	Surgery	0	1	0	0	1
	Surgery+chemotherapy	0	0	1	0	1
	Surgery+radiotherapy	5	1	1	0	7
	Surgery+chemotherapy+ radiotherapy	0	3	0	0	3
ESS	Surgery	1	1	0	0	2
	Surgery+chemotherapy	0	0	1	0	1
	Surgery+radiotherapy	2	0	0	0	2
	Surgery+chemotherapy+ radiotherapy	0	0	0	0	0

pelvic or para-aortic lymph nodes were dissected. In two cases the surgical procedure included omentectomy.

In 11 cases pelvic or para-aortic lymph nodes were dissected but none showed any malignancy. In two patients the surgical procedure included omentectomy, in one of whom (with carcinosarcoma) it led to upstaging of the disease.

- **Adjuvant radiotherapy**

Sixteen patients (47%) were treated with adjunctive radiotherapy. Ten patients had carcinosarcoma (62%). Fifteen patients were treated with external beam radiation, with a mean dose of 46 GY (37.8– 50.4 GY) in several daily fractions. Seven patients were treated additionally with intracavitary vaginal brachytherapy, mean dose 25.5 GY (10–36 GY). One patient was treated with brachytherapy without external beam radiation. Radiation therapy, external or local, conferred no benefit in rate of recurrence or patient survival.

- **Chemotherapy**

Ten patients (29%) were treated with adjunctive chemotherapy. The treatment protocol changed considerably during the 25 years of the study. In the last several years a protocol was established combining ifosphamide and adriamycin (IFOS+ADR). Patients with all histological subtypes were treated with chemotherapy, mostly in stages III- IV.

There was no correlation between chemotherapy and improved prognosis. On the contrary: patients treated with chemotherapy survived for a shorter time than patients in matching stages, although the difference in survival was not statistically significant.

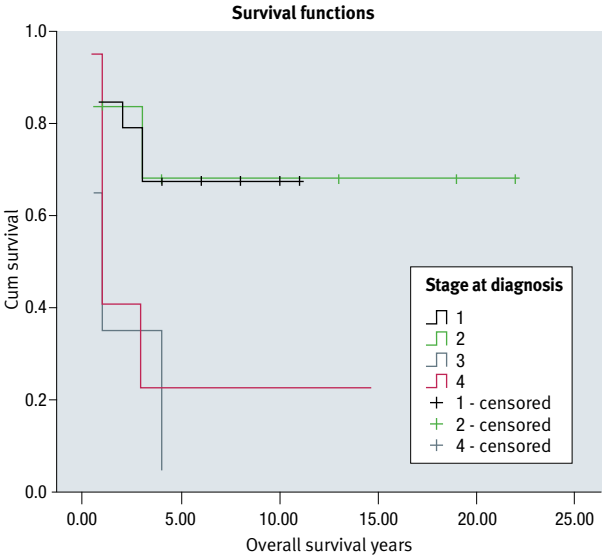
Patients treated with chemotherapy or radiotherapy alone did not experience more side effects than patients who underwent surgery alone, but patients who received combined chemoradiation (three patients) experienced side effects that included thrombocytopenia and radiation colitis.

FOLLOW-UP

The patients were generally treated at Hadassah-Hebrew University Medical Center in either the Gynecology Clinic or the Oncology Clinic. Follow-up examinations were usually performed every 3 months during the first 2 years, every 4 months during the third year, every 6 months until the fifth year, and annually thereafter. Follow-up visits included a physical examination. Chest X-ray or abdominal and pelvic computed tomography was performed as indicated by clinical symptoms to rule out recurrent or metastatic disease. Six patients were lost to follow-up immediately after surgery and were therefore not included in this analysis.

The mean follow-up was 44 months. The actuarial 5-year survival rate was 60% overall, 80% for patients with ESS, 50% for patients with leiomyosarcoma and 66.7% for carcinosarcoma patients.

Figure 1. Overall survival by stage



Of all the characteristics reviewed – including age, year of diagnosis, time from symptoms to treatment, and histological type – the only prognostic factor that reached statistical significance was the stage of the disease at diagnosis: 73.1% for stages I-II and 22.2% for stages III- IV ($P = 0.011$) [Figure 1].

DISCUSSION

Uterine sarcoma is a rare and lethal disease. Data are derived from small series of patients, as in this study, which is based on the experience of a large tertiary care center over a 25-year period, yet the study population comprised only 40 patients.

The age distribution for the different histological subtypes concurs with current data: leiomyosarcoma is more prevalent in relatively young patients aged 40–55, and carcinosarcoma appears at more advanced ages [1,2,10]. African-American origin is known to be a risk factor for sarcoma [1]. In our population sarcomas were more prevalent in women of Ashkenazi origin (50–70%) than in those of Sephardic descent (20–25%). Similar results were reported by Schwartz et al. [10] who conducted an epidemiological study of sarcoma of the uterus in Israel. Previous studies demonstrated a correlation between previous use of tamoxifen and risk for uterine sarcoma, mainly carcinosarcoma [11,12]. In our study four patients had received tamoxifen for breast cancer for prolonged periods, and the sarcoma appeared years after tamoxifen cessation. Eight of the 12 patients with carcinosarcoma (66%) had a first-degree familial history of malignancy, mostly breast cancer but also uterine adenocarcinoma and adenocarcinoma of the colon, compared with only 4.5% in the leiomyosarcoma group and 16% in the ESS patients who had

a family history of cancer. It is possible that carcinosarcoma of the uterus, carcinoma of the breast and adenocarcinoma of the colon originate from the same genetic locus, similar to other familial syndrome mutations like BRCA or HNPCC.

Similar to a previous report from Israel [13], the patients in the current study presented mostly with vaginal bleeding: abnormal bleeding in the younger leiomyosarcoma patients and postmenopausal bleeding in older patients with carcinosarcoma. Postmenopausal bleeding led to more rapid investigation and diagnosis, yet the patients did not have a better prognosis. A possible explanation could be that the disease is so aggressive in nature that early diagnosis does not prevent its dissemination.

Worth mentioning is a group of patients who presented with infertility and underwent conservative myomectomy. Once the pathological examination showed sarcoma the operation had to be expanded to hysterectomy and salpingo-oophorectomy; sometimes the decision was made during the initial operation.

The number of uterine sarcoma patients rose dramatically during our study, particularly the number of carcinosarcoma patients. This seems to be a local effect only, perhaps attributable to the increasing life expectancy and more comprehensive medical care in the elderly population over the years.

As reported previously by Piura and collaborators [15], the majority of patients in our study received adjuvant therapy, almost half of them by adjunctive radiotherapy, a relatively high number compared with other studies [2,3,14]. It was administered mainly to patients with early stages of carcinosarcoma and included external beam radiation and brachytherapy, but it did not correlate with a lower rate of recurrence or better survival. Chemotherapy treatment varied considerably among patients and also changed over time, so it was not possible to draw conclusions about its efficacy. The follow-up period in this study was relatively long, including twice-yearly and later annual examinations. The advantage is early diagnosis of recurrence and prompt treatment. The only prognostic factor that was significantly correlated with prognosis was the stage of the disease at diagnosis, as shown in previous studies [10,13]. Despite advances in diagnosis and treatment, survival has not improved over the last 25 years [10,13,15]. The 5-year survival rate in this study group was slightly better than reported previously [2,12]. Finally, carcinosarcoma was recently reclassified as a dedifferentiated or metaplastic form of endometrial carcinoma. Despite this, and probably because it behaves more aggressively than endometrial carcinoma, carcinosarcoma is still included in most retrospective studies of uterine sarcomas as well as in the 2003 World Health Organization classification [16].

In conclusion, due to the small number of patients and the diversity within the patient group it is not possible to reach statistically significant results. Only large multicenter studies will be able to collect sufficient patient numbers with statistical power necessary for attaining significant results that will help us better understand and treat uterine sarcoma.

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"To give pleasure to a single heart by a single kind act is better than a thousand head-bowings in prayer"

Saadi (c. 1200 AD), Persian poet