

Uterine Sarcoma: Analysis of Treatment Failure and Survival

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ABSTRACT

During the period from January 1985 to June 1999, 75 patients with uterine sarcoma were accrued in the National Cancer Institute, Cairo University. Surgery was the initial therapy for all patients. Of the 75 patients, 34 received postoperative irradiation and/or chemotherapy. Twenty-two (32%) survived 2 years, while 3 patients (4.3%) survived 5 years. The overall recurrence rate was similar in patients who received adjuvant treatment (94%) and in those who did not (97%). There was no difference in local pelvic recurrence between patients who received adjuvant therapy and those who did not (21.4% Vs. 25%); however the median time to pelvic recurrence was longer, 11 months (range 2-21 months) for the irradiated group versus 6 months (range 2-11 months) for the non irradiated group. There was neither a difference in the incidence of distant relapse (38.2% vs. 34.4%), nor a difference in the median time to relapse, 7 months for both (range 2-17) between patients who received adjuvant therapy and those who did not. Local and distant relapses were observed in 27% of patients who received adjuvant therapy versus 32% in the no adjuvant therapy group, with a median time to relapse of 3 months (1-10 months) for both groups. Most of the failures occurred in the pelvis, followed by lung and abdomen. Relapsing patients did not benefit of either local radiotherapy or chemotherapy. In conclusion, uterine sarcomas have an aggressive clinical behavior, with a propensity to recur both locally and at remote sites. Surgery in the form of total abdominal hysterectomy (TAH) plus bilateral salpingo-oophorectomy remains the treatment of choice. The role of pelvic lymphadenectomy and aortic lymph node sampling may be beneficial especially in early stage disease, although its role in improving survival has not yet been demonstrated. There is no definite evidence that adjuvant pelvic irradiation or systemic chemotherapy improves survival. The policy of adjuvant therapy following surgery for uterine sarcoma needs further evaluation.

Key Words: Uterine sarcoma - Survival - Pattern of failure.

INTRODUCTION

Sarcomas of the uterine body are rare tumours which account for less than 3% of all female genital tract malignancies. It also repre-

sents 3-7% of malignant tumours of the uterine corpus [25]. They carry a poor prognosis, with an overall survival < 50% at two years, even when they present at an early stage, as they have a high propensity to relapse both locally and distally [12,20,32].

Histologically, they are heterogeneous and are classified into three main groups: leiomyosarcoma (LMS), mixed mesodermal tumours (MMT) and endometrial stromal sarcomas (ESS). The rarity of these tumours and their pathologic diversity have made sarcomas of the uterus difficult to study in large numbers. In addition, the adaptation of the International Federation of Gynecology and Obstetrics (FIGO) staging system of endometrial carcinoma for the uterine sarcoma seemed impractical [35]. Although uterine sarcomas that arise in the endometrium (ESS & MMS) can be staged surgically according to the FIGO classification for endometrial carcinoma, it is inapplicable for a sarcoma that arise from the myometrium (LMS), since stage I & II cannot be divided into substages.

Lewis et al. [18] have consequently modified the FIGO classification for uterine carcinoma and accommodated it for uterine sarcomas by omitting the substages as follows: Stage I: tumour confined to the uterine body; Stage II: tumour confined to the uterine body and cervix; Stage III: tumour spread outside the uterus, but confined to the true pelvis and stage IV: tumour spread outside the true pelvis.

The optimal management has been a challenge and a subject of debate that has not yet been established [8]. The treatment of uterine sarcoma has traditionally been modeled after

that for endometrial carcinoma with primary surgery in the form of total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) being the mainstay of treatment [31,35]. Since most of the patients treated for uterine sarcomas die of distant metastases, the value of postoperative adjuvant pelvic irradiation has been questioned [14,35]. Some authors [8,23,31,35] have claimed that there was no definite evidence that pelvic radiotherapy is beneficial even in preventing pelvic recurrence, whereas others [9] have suggested that postoperative adjuvant pelvic radiotherapy might be effective in preventing pelvic recurrence and consequently, distant failure.

Uterine sarcomas exhibit two features that increase the need for systemic therapy: a significantly high incidence of local recurrence even in early stages and a high propensity to disseminate [4]. The validity of adjuvant chemotherapy in uterine sarcomas has remained uncertain and has yet to be demonstrated [2,3,8,9,19,36].

The current study was undertaken to assess the impact of multimodality approaches in the treatment of patients with uterine sarcomas as regards treatment failure and survival.

MATERIAL AND METHODS

This study includes 75 patients with histologically proven uterine sarcoma who have been treated at NCI, Cairo University, between January, 1985 and June, 1999. Twenty three patients were studied prospectively, while 52 patients were studied retrospectively.

Surgery was performed for all patients. Patients were staged according to the modified FIGO staging system for endometrial carcinoma [18]. In the prospective group of patients, postoperative adjuvant pelvic irradiation was given for patients with stages I & II uterine sarcomas, while concomitant chemo-radiotherapy was given for patients with stages III & IV. The rationale of adjuvant therapy was to evaluate the impact of multimodal therapy on treatment results. In the retrospective group of patients, adjuvant therapy was given according to the surgeon decision.

Those who received postoperative adjuvant pelvic irradiation have been planned to receive a total dose of 50 Gy delivered through either two parallel opposed antero-posterior fields or

four fields (box technique). The radiation volume for the former group extended from L4-5 interspace superiorly and inferiorly to encompass the upper half of the vagina. Laterally, the field stopped 1.5-2 cm beyond the border of the bony pelvis. The anterior border of the lateral field used for the latter group was placed at the pubic symphysis while the posterior border was placed at S2-3 interspace. Shaping of the field was performed in most of the cases. Patients received a midline dose of 180-200 cGy per fraction, 5 fractions a week by 6-MV linear accelerator. None received brachytherapy.

A variety of chemotherapeutic regimens have been used in the adjuvant setting or as palliative therapy. Doxorubicin 60 mg/m² every 3w was the main drug used in the adjuvant setting. Cisplatin in a dose of 60 mg/m² every 3w, was given in the chemo-radiation setting. Ifosfamide was given as 1.5 gm/m²/D1-5 every 3w mainly for patients with advanced or recurrent disease.

The median follow up was 22 months with a range of 2-180 months. Statistical analysis of the data was carried out with the X² test. Survival curves were drawn using the Kaplan-Meier method.

RESULTS

The median age at presentation was 45 years (range 15-80 years). Using the modified FIGO staging system, 20 patients (27%) had stage I disease, 17 patients (23%) stage II, 14 patients (19%) stage III and 14 patients (19%) stage IV. The staging of 10 patients (13%) could not be estimated from the files.

The histopathological classification revealed; 37 patients (49%) had LMS; 25 patients (33%) MMT; 10 patients (13%) ESS and three patients (4%) had rare types of uterine sarcomas (liposarcoma, rhabdomyosarcoma and sarcoma botryoides).

Fifty-four patients (72%) had a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), while 13 patients (17.3%) underwent Wertheim's operation with selective paraaortic lymph node sampling. Four patients (5%) had subtotal hysterectomy. Anterior pelvic exenteration was performed in one patient (1.3%) who had bladder invasion. Three patients (4%) were explored and proved to have

irresectable disease where only biopsies were taken. Table (1) summarizes the patients characteristics.

Six patients (8%) died due to surgical or general complications within a month after surgery. Table (2) summarizes the causes of postoperative mortality observed in six patients.

The survival time ranged from 1-156 months with a median survival time of 12 months. The 2-year overall survival rate was 31.9%, while at 5 years it was only 4%, Fig. (1).

In 27 patients (36%), there was microscopic residual disease after initial surgery as evidenced by positive resection margin. Fig. (2) shows that patients who proved to have negative resection margin had a significantly higher overall survival rate ($p = 0.02$).

Following initial surgery, a total of 21 patients (28%) received postoperative pelvic irradiation, 8 patients (10.6%) received adjuvant chemotherapy and 5 patients (6.7%) received a combination of both.

Adjuvant therapy did not seem to improve the local control of the disease as shown by the similar rate of local recurrence for those who received and those who did not receive adjuvant therapy, 21.4% Vs. 25%, respectively ($p = 0.25$). However, it was obvious that the median time to pelvic recurrence was longer for those who received postoperative adjuvant pelvic irradiation in comparison to those who did not, 11 months Vs. 6 months, respectively.

The incidence of distant metastases was the same for patients who received adjuvant systemic therapy and those who did not (38% Vs. 34%, respectively). Moreover, the median time to disseminate was 7 months in both groups.

Simultaneous local and distant relapse was evident in 9/34 patients (27%) in the adjuvant therapy group, in comparison to 10/32 patients (32%) in the no adjuvant therapy group. The median time for concomitant failure was 3 months (range 1-10 months).

The lungs were the most common site for distant spread (n=19) followed by the abdomen (n=14), bones (n=4), brain (n=2) and lastly, extra-abdominal lymph nodes (n=1).

Patients proved to have local pelvic recurrence were offered salvage therapy in the form of palliative pelvic irradiation (9/15), chemo-

therapy (single agent adriamycin) (2/15) and attempt at surgical excision plus chemotherapy (combination of adriamycin and dacarbazine) (3/15) and palliative symptomatic treatment (1/15). No significant response could be detected and eventually all died of uncontrollable local recurrence after a median time of 5 months.

Thirty-one patients out of the 48 who developed distant metastases \pm local recurrence were offered various regimens of chemotherapy with minimal or no response, while 4 patients received short courses of palliative irradiation to involved bony sites and 13 patients received no further treatment. All died after a median time of 4 months (1-11 months) after relapse.

Table (1): Patients characteristics.

Age	Median 45 years	
	No.	(%)
<i>Stage:</i>		
I	20	(26.6)
II	17	(22.6)
III	14	(18.6)
IV	14	(18.6)
Unknown	10	(13.6)
<i>Grade:</i>		
1	15	(20)
2	25	(33)
3	35	(47)
<i>Histology:</i>		
LMS	37	(49.4)
MMT	25	(33.3)
ESS	10	(13.3)
Others	3	(4)
<i>Therapy:</i>		
Surgery	32	(43)
Surgery + radiotherapy	21	(28)
Surgery + chemotherapy	8	(11)
Surgery + radio + chemo	5	(7)

LMS : Leiomyosarcoma.

MMT: Mixed mesodermal tumours.

ESS : Endodermal stromal sarcoma.

Table (2): Causes of postoperative mortality.

Cause of death	No. of patients
Myocardial infarction	1
Pelvic sepsis and ARDS	2
Pulmonary embolism	1
Liver cell failure	1
Intestinal fistula	1

ARDS: Adult respiratory distress syndrome.

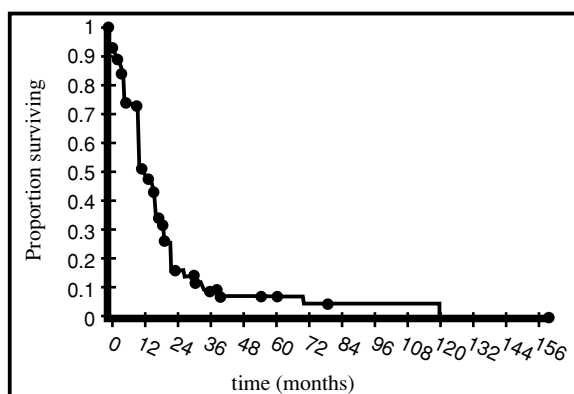


Fig. (1): Overall survival of 75 uterine sarcoma patients.

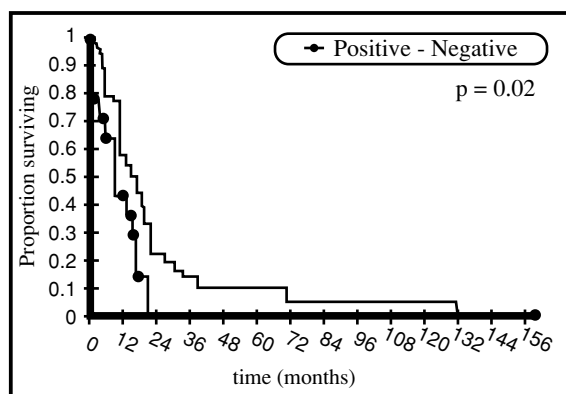


Fig. (2): Overall survival of 75 uterine sarcoma patients according to resection margin.

DISCUSSION

The relative rarity of uterine sarcomas has made assessment of the most effective management difficult. In most of the reported studies to date, including the present report, patients accrued over a prolonged period of time, during which treatment approaches and modalities changed.

Uterine sarcomas are generally considered to be aggressive tumours with propensity for local recurrence and distant metastases even when presenting at an early stage [12,20,32]. Their location within the myometrium allows for early vascular invasion and potential spread to extrapelvic sites [2,32]. Following the diagnosis of uterine sarcoma, the cornerstone of primary management is debulking pelvic surgery by TAH and BSO. Lack of residual disease following initial surgery is a positive prognostic factor on univariate analysis both in the present and other studies [7,20,22,25] but when adjusted for tumour stage and grade, this does not translate to an overall survival benefit. This supports the concept of early and occult metastases.

The need to remove the ovaries in patients with uterine sarcoma is still controversial. Some authors [2,24,38] reported that ovarian tissue preservation did not change the recurrence risk. Conversely, removal of the ovaries during primary surgery is recommended by others [3,17] since these tumours have a propensity for spread to the ovaries. Two reports describing early intra-abdominal metastases emphasized the frequency of tubo-ovarian metastases. Norris et al. [24], found that 10/15 patients with uterine sarcoma have had adnexal metastases.

Also, Show et al. [34], observed that 7/15 patients with early metastases had tubo-ovarian disease. In the current study, adnexal involvement was found in 10/72 patients (14%). Moreover, some authors stressed that BSO was mandatory since these tumours might be stimulated by estrogen [13,37]. Gadducci et al. [11], noted that among stage I low grade uterine sarcoma patients younger than 50 years who underwent TAH, recurrent disease developed in 33.3% of the 21 patients who had BSO and in 23.8% of the 21 patients who were left with one or both ovaries ($p > 0.05$). Therefore, whether BSO is to be systematically included in the primary surgery of low grade uterine sarcoma is still questionable. Conversely, removal of the ovaries should be recommended for high grade uterine sarcomas.

Chen [6] observed that 66% of his patients with clinical stage I uterine sarcoma had nodal metastases, suggesting that lymphatic spread might precede haematogenous spread in early uterine sarcoma. Fleming et al. [10], reported their autopsy experience documenting nodal metastases in 65% of patients with MMS and in 44% of patients with LMS. Also, the frequency of pelvic (40%) and paraaortic (14.5%) nodal involvement in early stage uterine sarcoma reported by other authors [16,31,33] led them to advocate lymphadenectomy as part of the initial surgery. This early nodal spread is at variance with the behaviour of soft tissue sarcoma of the musculoskeletal system, where spread is primarily haematogenous and early lymph node spread rarely occurs ($< 5%$) [28,30]. Meanwhile, the practical value of staging with lymphadenectomy was debatable by some authors [14,19], since

knowledge of nodal status has minimal impact on the clinical management of women with uterine sarcoma.

In the current study, pelvic lymphadenectomy plus paraaortic lymph node sampling were done in 13 patients as a part of Wertheim's operation and was not intended as a standard step. Pelvic and paraaortic lymph nodes were found to be involved in 6 patients (46%). The 2-year survival rate was not different between lymph node positive and lymph node negative patients (median survival 12 months for both groups). However, the number of patients is too small to give a definite conclusion. Since there is neither an effective adjuvant therapy following initial surgery nor active salvage therapy following relapse, we do recommend pelvic lymphadenectomy especially in early stage disease, although its role in prolonging survival has not been demonstrated.

In addition, if lymph nodes were the first station for micrometastases, its removal might be beneficial. However, the ultimate role of lymphadenectomy remains to be determined in further randomized trials.

The precise role of radiotherapy as an adjuvant treatment of uterine sarcomas remains controversial. Several authors [8,9,23,31,35] showed that it may reduce local pelvic recurrence, but none had demonstrated long term improvement in survival rate. In the current study, postoperative adjuvant pelvic irradiation seemed to delay, but not prevent, local recurrence without any significant impact on survival. The median time to pelvic relapse was 11 months for patients who received adjuvant pelvic irradiation Vs. 6 months for those who did not receive radiotherapy. However, this conclusion is not absolute due to the small number of patients involved in the adjuvant therapy group and the limitations of the retrospective study, the prolonged period of recral of the patients and the wide range of possibly effective prognostic factors. The subsequent lack of durable local control may suggest that the radiotherapy doses delivered were inadequate. This may partly account for the poorer local control of uterine sarcomas compared to peripheral soft tissue sarcomas where higher doses (> 50 Gy) are used in the adjuvant setting.

The delay in local recurrence following adjuvant pelvic irradiation in this study is encour-

aging and a consistent use of a higher dose might result in an improvement of the long term local control of the disease. Such doses might be achieved if an integrated management plan including techniques that reduce the risk of small bowel morbidity at the time of hysterectomy is carried out and/or by adding boost using brachytherapy.

Since no increase in durable local control was seen in the present series, but rather an increase in the time to relapse, an increase in overall survival would only be expected if an effective systemic therapy was also implemented.

The dissemination pattern to lungs, viscera, peritoneum, bones and lymph nodes may suggest that spread occurs concurrently via haematogenous, transcoelomic and lymphatic routes. Postmortem data on 73 cases who died with metastatic uterine sarcomas showed that the most frequent site of metastases was the peritoneal cavity (59%), followed by lungs (52%), then pelvic and paraaortic lymph nodes (40%). No significant association between histological type and metastatic behaviour could be detected [31].

Clearly, the solution to overcome early sub-clinical spread via different routes of spread in uterine sarcomas is an effective systemic therapy. to date, no chemotherapeutic combination has proved to produce a significant durable response. A review of the current literature largely supports this fact. In 1983, Hannigan et al. [15], reported no benefit of a doxorubicin-containing adjuvant regimen. Some nonrandomized small series seemed to show that adjuvant chemotherapy improved the prognosis of patients with early stage uterine sarcoma of different histological types [4,20,39]. Conversely, other studies [1,15] did not show any survival advantage for patients treated with adjuvant chemotherapy. In the GOG randomized trial [25], adjuvant single-agent doxorubicin gave no survival benefit to patients with stages I-II uterine sarcoma. On the other hand, only two randomized studies reported that adjuvant chemotherapy (doxorubicin or CYVADic) for adult soft tissue sarcomas elsewhere improved survival significantly [5,21]. However, several other randomized trials failed to prove such benefit [27,29]. In this series, 8 patients received chemotherapy alone as an adjuvant treatment and an-

other 5 patients received combined adjuvant pelvic irradiation plus systemic chemotherapy. No significant difference in survival could be detected between those who received systemic chemotherapy and those who did not. The median survival was similar in both groups (13 months Vs. 12 months, respectively).

Conclusion:

Uterine sarcomas have an aggressive clinical behavior and dismal survival. The mainstay of treatment is surgery in the form of TAH plus BSO. Pelvic lymphadenectomy may be beneficial especially in early stage disease as it removes early nodal metastases, although its role in improving survival has not been demonstrated.

Adding postoperative adjuvant pelvic irradiation has not been shown to improve local control of the disease or overall survival of patients with uterine sarcomas with the doses used in this study.

The effectiveness of adjuvant systemic chemotherapy should be investigated in multicenter randomized trials, provided that agents selected have already shown activity in patients with metastatic disease.

The treatment of patients with advanced or recurrent disease should be encouraged to enter phase II trials to identify new active drugs for these malignancies.

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