Uterine Sarcoma: 14 years experience in KCCC

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Abstract

Aim of the Work

To asses the profile, pattern of failure and survival for patients with uterine sarcoma seen in KCCC.

Material and Methods

A total of 23 records for patients with uterine sarcoma attending KCCC between July 1993 to May 2007 were available for review. The medical records were assessed for the profile of the disease, histological types, types of treatment, pattern of failure and survival. All cases were proven histologically. The majority of cases 15/23 (65.2%) were endometrial stromal sarcoma, 4/23 (17.4%) had leiomyosarcoma and 4/23 (17.4%) had carcinosarcoma. Twenty two out of 23 patients (95.6%) had surgery and 8/22 (36.4%) were given adjuvant post-operative pelvic radiotherapy. Three patients were treated with palliative intent by radiation. Five patients received palliative chemotherapy.

Results

The mean age of all patients was 53.17±11.06 (range 34-80 years). The majority of patients 15/23 (65.2%) had stage I disease. High tumor grade was seen in 12/23 (52.2%) of patients. The pattern of failure was local in only 2 patients, systemic in 4 patients and both local and systemic in 5 patients. The overall DFS-5 years was 59.6%.The 5 y-DFS for patients treated by surgery & RT was 87.5% compared to 36.4% for those treated by surgery alone. Patients with early disease (stage I) had a 5 year DFS of 74% compared to 33.3% for those with advanced disease (stages III&IV). Patients with high grade tumors had a 5 year- DFS of 27% versus 100% for those with low grade tumors.

Conclusion

Stage and grade are important predictors of survival. Post-operative adjuvant pelvic irradiation is associated with improved 5-years DFS.

Key Words

Uterine sarcoma, Surgery, Radiotherapy, Chemotherapy, Pattern of failure, Survival.

Introduction

Uterine sarcomas are rare tumors representing less than 1% of gynecologic malignancies and 2%- 5% of all uterine malignancies. The only documented etiologic factor in 10% to 25% of these malignancies is prior pelvic radiation, often administered for benign uterine bleeding 5 to 25 years earlier [(1)].

The most common histologic types of uterine sarcomas are carcinosarcoma known also as mixed mesodermal sarcomas (50%), leiomyosarcoma (30%), and endometrial stromal sarcoma (ESS) (15%)[(2)]. Medically operable patients with the pre-operative diagnosis of uterine sarcoma are candidates for surgery. Surgery is standard in the form of hysterectomy, bilateral salpingo-oophorectomy (BSO), and pelvic and periaortic selective lymphadenectomy. Cytologic washings are obtained routinely from the pelvis and abdomen. Thorough examination of the diaphragm, omentum, and upper abdomen are also performed [(3)].

Although there is no firm evidence that adjuvant chemotherapy or radiation therapy is beneficial for patients with uterine sarcoma, many physicians have considered the use of

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adjuvant chemotherapy or radiation therapy in an attempt to reduce the incidence of local and or systemic relapse [4].

Larson et al [5] in a large non-randomized study demonstrated improved survival and lower local failure rate in patients with stage I-II mixed mullerian tumors following postoperative external and intracavitary radiation therapy.

The prognosis for women with various histological types of uterine sarcoma depends primarily on the extent of disease at the time of diagnosis. For women with carcinosarcomas, significant predictors of metastatic disease after initial surgery include tumor location in the uterus, lympho-vascular space invasion and high tumor grade (grades II&III). These factors, along with adnexal spread, lymph node metastases, tumor size, peritoneal cytologic findings, and depth of myometrial invasion correlate with progression-free interval.On the other hand, the presence or absence of stromal heterologous elements, the types of such elements, the grade of the stromal components, and the mitotic activity of the stromal components bear no relationship to the presence or absence of metastases at surgical exploration. The recurrence rate was 44% for homologous tumors and 63% for heterologous tumors. The type of heterologous elements had no effect on the progression-free interval [6].

As for patients with leiomyosarcomas, some investigators considered the tumor size to be the most important prognostic factor. Evans et al [7] demonstrated that patients with tumors greater than 5.0 cm in maximum diameter have a poor prognosis. However, in a Gynecologic Oncology Group study, the mitotic index was reported as the only factor significantly related to progression-free interval.

Leiomyosarcomas matched for other known prognostic factors may be more aggressive than their carcinosarcoma counterparts [8]. The 5-year survival rate for women with stage I disease is approximately 50% versus 0%- 20% for the higher stages.

Materials and Methods

The available medical records of 23 patients with uterine sarcomas seen in KCCC between July 1993& May 2007 were retrospectively reviewed. Eleven patients (47.8%) were pre-menopausal and 12 (52.2%) were post-menopausal. Endometrial biopsy was the basis of diagnosis in 14 patients. Histological verification was available for all patients. The histological types are demonstrated in Table 1. The majority of cases 15/23 (65.2%) were endometrial stromal sarcoma, 4/23 (17.4%) had leiomyosarcomas & 4/23 (17.4%) had carcinosarcomas (mixed müllerian tumors).

Histological types	N	%
Endometrial stromal sarcoma	15	65.2%
Leiomyosarcoma	4	17.4%
Carcinosarcoma	4	17.4%
Total	23	100.0%

Table 1: Histological types of uterine sarcomas.

Endometrial stromal tumors were classified into low grade, previously known as endolymphatic stromal myosis with modest degree of mitotic activity(less than 10/10 HPF) and high grade known as endometrial stromal sarcomas with 10 or more mitoses/10 HPF. Tumor grading is presented in Table 2. Grading was available for 18/23 patients (78.3%), the majority of them 12/18 (66.7%) had high grade tumors.

Tumor Grade (n=18)	N.	%
High	12	66.7%
Low	6	33.3%
Total	18	100.0%

Table 2: Tumor grade for patients with uterine sarcoma.

Patients were staged (Table 3) retrospectively according to the FIGO staging system 1988 for endometrial cancer. The majority 68.2% of patients had stage I. This was also observed for the different histological subtypes as 9/14 (64.3%) in endometrial stromal sarcoma, 2/4 (50%) in leiomyosarcoma and 4/4 (100%) in carcinosarcoma had stage I disease too.

Stage n=22	N	%
I	15	68.2
II	0	0
III	6	27.3
IV	1	4.5
Total	22	100.0

Table 3: Staging of patients with uterine sarcoma (FIGO staging system 1988).

Primary Treatment

Twenty two patients underwent surgery. Surgery was in the form of total abdominal hysterectomy and bilateral salpingo-oophrectomy in 14 patients, subtotal hysterectomy and bilateral salpingo-oophrectomy in 3 patients. In one patient hysterectomy was done through laparoscopy without salpingo-oophrectomy then after 2 months she underwent BSO. In another patient TAH without BSO was performed. Another patient had subtotal hysterectomy without BSO. In one patient TAH+BSO+ pelvic LN dissection was done and in another patient TAH+ left SO only. Only in one patient surgery was aborted after exploration due to uterine fixation and pelvic and para-aortic lymphadenopathy.

Eight patients had adjuvant RT (Five patients with external beam irradiation (EBRT) and 3 patients with both EBRT plus vault application. No patients received vault application only. EBRT was given to whole pelvis by megavoltage linear accelerators through CT assisted planning for a dose of 46 GY/23 f, 2 GY per fraction. Vault application was given by low dose rate brachytherapy aiming at 40 GY equivalent at 0.5 cm depth from vaginal mucosa using a selectron afterloading machine.

None of the patients in the current study received adjuvant chemotherapy.

Salvage treatment

Exploration for recurrent disease was done for three patients either for adhesiolysis and by-pass surgery for recurrent intestinal obstruction in one patient, retroperitoneal LN dissection followed by RT in another patient and exploration only for a third one. Two out of the three patients who had exploration had palliative RT.

Five patients in the current study received palliative chemotherapy. Chemotherapy was mainly Ifosfamide based. One patient was given one course of a combination of Ifosfamide +ADR+ Cisplatin, then Cisplatin was withhold for another course due to poor tolerance. In another patient, Gemcitabine+Docetaxel were given for 2 courses but due to reaction to Docetaxel, it was changed to Ifosfamide+ADR for 6 cycles. In a third patient, 6 cycles of Ifosfamide+ADR were given. A fourth patient received 6 cycles of CYVADIC chemotherapy. Another patient received first line Ifosfamide+ADR for 8 cycles then after progression she received second line of chemotherapy with Taxol+Gemcitabine but due to poor tolerance, only one cycle was possible.

Statistical Analysis

Disease free- survival was calculated from the date of histological diagnosis to first local or distant recurrence. The DFS was analyzed using the Kaplan-Meier method. P-values <0.05 were considered to be statistically significant.

Results

The mean age of all patients was 53.17±11.06 with a range of 34-80 years. Six patients (26.1%) were above 60 years. No patient had a past history of previous malignancy and no patient received previous pelvic irradiation.

Staging is demonstrated in Table 3. Nine patients with endometrial stromal sarcoma had stage I disease while 2/4 patients with leiomyosarcoma had stage I disease and all the 4 patients with MMMT had stage I disease.

The Pattern of Failure

At follow up, 11/23 patients (47.8%) failed after primary treatment. The pattern of failure is demonstrated in Table 4. Systemic failure was the commonest pattern of failure and it occurred either alone (4/11) or in association with loco-regional failure (5/11). Local recurrence only was observed in 2/11 patients. Lung was the commonest site for distant metastases being seen in six patients. In one patient there was associated mediastinal LN & abdomino-pelvic masses.

Pattern of Failure (n=11)	Number of Pts
Local	2 18.2%
Loco/Regional and Systemic	5 45.4%
Systemic	4 36.4%

Table 4: Pattern of Failure after treatment

Role of Adjuvant Post-operative Radiotherapy

Out of the 8 patients who received adjuvant RT, no patient had local failure and only one patient developed both regional and systemic failure. The local control rate was 100% for those patients treated by surgery and adjuvant post-operative radiotherapy while it was 63.6% for those treated by surgery alone. For patients treated by surgery alone, 4/14 had local failure along with other patterns of failure (no isolated local failure) and 3/14 patients developed isolated systemic failure. The 5 year DFS was 87.5% for patients treated by surgery plus post-operative radiotherapy as compared to 36.4% for those treated with surgery alone.

Role of Salvage Chemotherapy

Only five patients were treated by chemotherapy mainly with a palliative intent. The response is demonstrated in Table 5. Generally, patients tolerated chemotherapy poorly and response was not encouraging.

The overall DFS at 1 y & 5 y were 67% & 59.6% respectively (Fig. 1)

The DFS at 1 y and 5 y were 80% & 70% for pre-menopausal women compared to

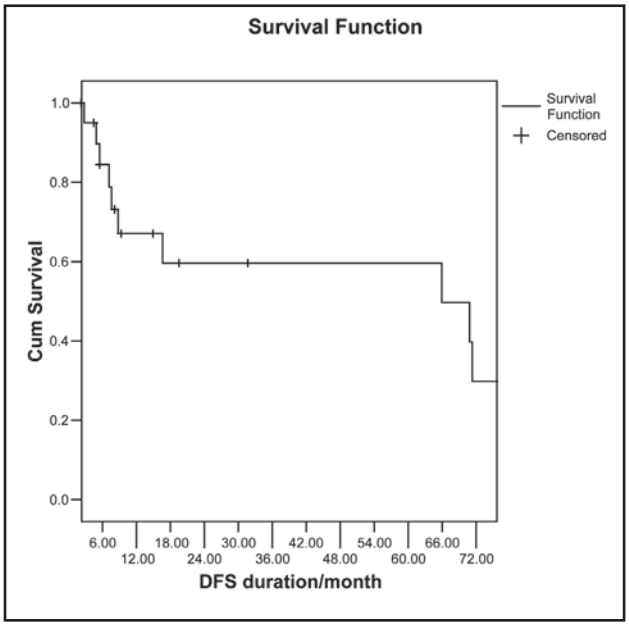

Fig. 1: Disease free survival in all patients.

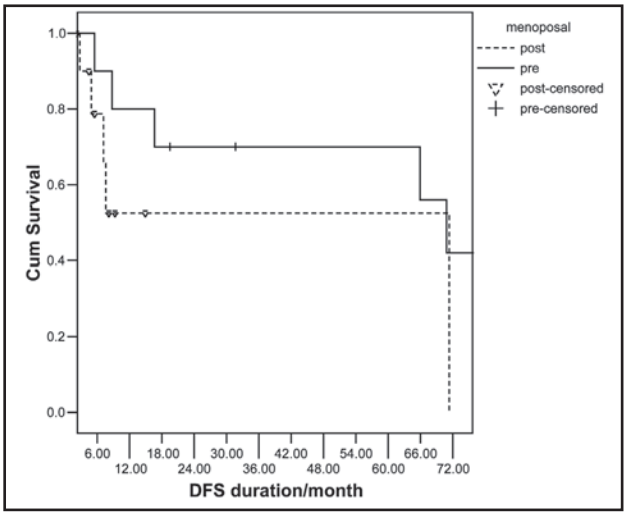

Fig. 2: Disease-free survival according to menopausal status.

Pt. No.	Histology	Regimen	No. of Cycles	Response
1	Endometrial Stromal Sarcoma	CYVADIC	6	PR
2	Endometrial Stromal Sarcoma	ADR+Ifosfamide At progression, Taxol+Gemcitabine	8 1	PR Not assesed
3	Endometrial Stromal Sarcoma	ADR+Ifosfamide	6	PR
4	Leiomyoarcoma	ADR+Ifosfamide+Cisplatin ADR+Ifosfamide	1 1	Not assessed* Not assesed
5	Leiomyosarcoma	Gemcitabine+Docetaxel ADR+Ifosfamide	2 6	Not assessed* PR

Table 5: Response to Salvage Chemotherapy.

*Not assessed (when chemotherapy was stopped due to poor tolerance).

52.5% &52.5% for post-menopausal women respectively. The difference was however not statistically significant (p value 0.15).

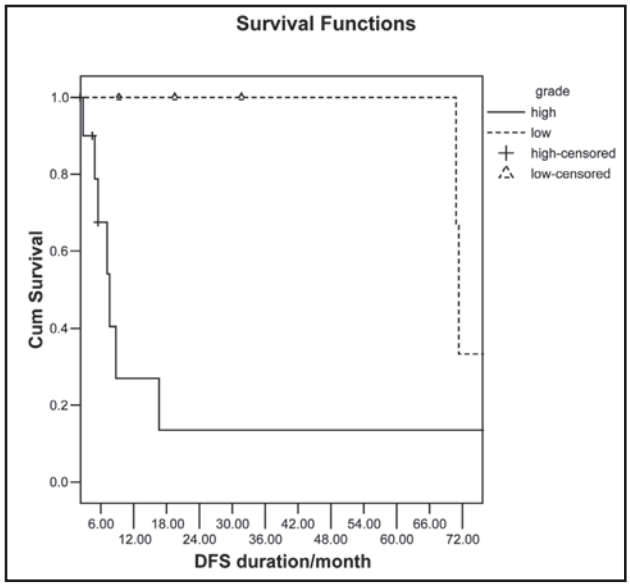

Fig. 3: Disease-free survival for patients with low and high grade tumors.

For patients with high grade tumors, the DFS at 1 year was 27% as compared to 100% for those with low grade tumors, a difference which is statistically significant (p value 0.01).

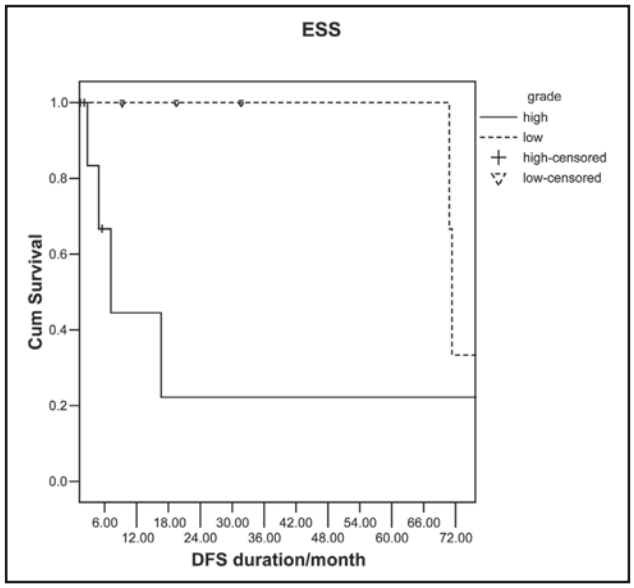

Fig. 4: Disease-free survival according to tumor grade in patients with endometrial stromal sarcoma.

Patients with ESS had a 1 year DFS of 100% for low grade tumors while it was 44.4% in high grade tumors, a difference which is statistically significant (p value 0.03). The DFS at 5 years for the same type of tumor was 100% for low grade tumors while it was 22.2% for high grade tumors.

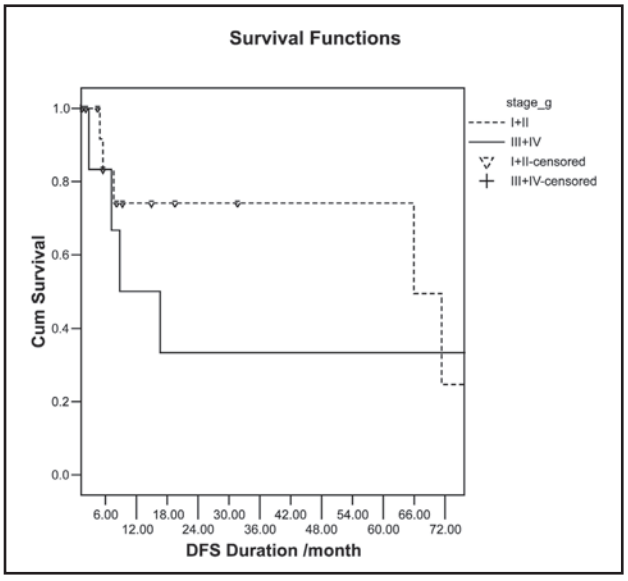

Fig. 5: Disease-free survival for patients with early and advanced stages.

As seen in Fig. 5, the DFS at 1 year was 74% for patients with early disease stages (I&II) compared to 50% for those with advanced stages (III-IV) though the difference was not statistically significant difference (p value 0.37). As for the DFS at 5 years, patients with stages I&II had a 74% survival compared with 33.3% for those with stages III&IV disease.

Discussion

Uterine sarcomas are uncommon malignancies accounting for approximately 1 in 12 of all uterine cancers yielding an annual incidence of 1.23/100,000 in the female population [8]. Given the uncommon nature of the disease, a number of institutions have reported outcomes of all uterine sarcomas combined. However, because the number of patients in most series is small and the reports are not randomized, it is difficult to make definitive statement about treatment efficacy.

The mean age of all patients in the current study was 53.17±11.06 (range of 34-80 years) is comparable to that reported by Benoit et al [9] who reported median age of 60.5 and a range between 33-91 years.

Denschlag et al [10] reported a tendency of the disease to occur in post-menopausal women (58% of patients were post-menopausal). In our side 52% of patients were post-menopausal.

Leiomyosarcoma was the most common pathological type in Livi et al study [11] accounting

for 51% of his material while in the current study ESS was the commonest type representing 65.2% of the cases reviewed.

Uterine sarcoma has been reported to present at an early stage by several authors. Echt et al [12] reported that 73% of his material had stage I. In the present study stage I was seen in 65.2% of the patients.

In the present review a total of eleven patients failed 11/23 (47.8%). Systemic failure was the commonest pattern of failure seen in 9 patients 9/23 (39.1%) and local recurrence seen in 6 patients 6/23 (26.1%). This is comparable to that reported by Denschlag et al [10] who reported on 94 patients with a failure rate of 60/94 (63.8%). In his material, systemic failure was seen in 38 patients 38/94 (40.4%) and local recurrence seen in 22 patients 22/94 (23.4%).

Radiotherapy has been reported as effective by several authors to add to local control. Echt et al [12] reported local control rate of 100% in patients treated with surgery plus RT as compared to 66.7% for those treated by surgery alone. This is comparable to the local control observed in this study being 100% vs 63.6% respectively for those treated by surgery plus RT vs surgery alone.

In the present study, the 5 year DFS was 87.5% for those patients treated by surgery plus RT as compared to 36.4% for those treated by the surgery alone. Echt et al [12] reported 5 year DFS of 38% vs 18% for patients treated by surgery plus RT and surgery alone respectively. The higher results in the current study may be due to higher number of patients with ESS (65.2%) as compared to 15.2% in the comparable study.

In the current study, the disease free survival at 5 years was 59.6% which is higher than 41% reported by Denschlag et al study [10]. This may be attributed to higher percentage of patients with ESS in the current study (65.2% as compared to 29.8%) in the comparable study. It is also higher than the 36.1% reported by Benoit et al [9] and this is due to higher percentage of patients with stage I disease (65.2% vs 51.4%) and patients with ESS (65.2% vs 16.7%) in the current study. Weitmann et al [13] reported overall survival and disease specific survival of 63.4% and 80.9% at 5 years respectively but he reported only on patients with ESS.

Patients with stages I&II had a 5 y- DFS of 74% vs 33.3% for those with stages III-IV in the current study and this is in agreement with that reported by Echt et al [12] who reported 5 years survival of 50% in stage I, 11% in stage II, 0% in stages III-IV.

Tumor grade has been reported to be among the important prognostic factors for survival. In the present review, the disease free survival of patients with low grade disease was 100% at 5 years while it was 13.5% for high grade tumors in all patients. Livi et al [11] reported poorer prognosis for high grade tumors as compared to intermediate (p 0.02) and low grade (p 0.002) tumors with death rates of 82%, 80% and 60% respectively at the time of analysis.

Conclusion

Post-operative adjuvant RT is effective in reducing the local/loco-regional recurrence in patients with uterine sarcoma and is associated with a tendency for improved DFS. The role of salvage chemotherapy is not defined and further combination chemotherapy needs to be investigated in phase II&III clinical trials.

Stage, grade and adjuvant post-operative radiotherapy are among the prognostic factors & predictors of disease failure.

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