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The effect of adjuvant treatment modalities on survival outcomes in cytoreductive surgery performed patients with advanced stage uterine sarcomas

Sitoredüktif cerrahi yapılan ileri evre uterin sarkomlu hastalarda adjuvan tedavi modalitelerinin sağkalım sonuçları üzerine etkisi

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Summary

Aim*: To analyse the effect of adjuvant treatment modalities on survival outcomes in cytoreductive surgery (CRS) performed on patients diagnosed with advanced stage uterine sarcomas.*

Materials and Methods*: Between the years of 1/1994–1/2009; among (n=122) patients with uterine sarcoma that were diagnosed and treated at our center, n=26 (21%) who had advanced (FIGO stage III and IV) disease were the subject of this retrospective study. The stage of the disease, tumor histology, presence of lymphadenectomy, optimality of cytoreductive surgery, adjuvant radiotherapy (RT) and chemotherapy (CT) applications, disease-free survival (DFS) and overall survival (OVS) rates were the main outcome measures. Data were presented by performing descriptive analyses, Kaplan-Meier and the log-rank test.*

Results*: Histologically, cases consist of 9 (34.6%) leiomyosarcoma;3 (11.4%) endometrial stromal sarcoma and 14 (54%) carsinosarcoma. Systematic lymphadenectomy was performed in the forms only bilateral pelvic (n = 9); bilateral pelvic + para-aortic (n=17). Optimal cytoreduction was achieved in 23 (88%) of 26 patients. Only CT (n = 10) and CT + RT (n=16) were applied as adjuvant treatments. The mean survival of patient groups on which (CRS+ adjuvant CT)–(CRS+adjuvant CT+RT) were performed was determined as [12.6–42.3] months (p< 0.05) in terms of DFS and, [21.8–52.8] months (p<0.01) in terms of OVS, respectively.*

Conclusion*: Due to the low quantity of patients, different tumor types and different CT regimens, data of the treatment modalities from this particular patient setting are inconclusive, especially in terms of effectiveness of adjuvant CT alone following CRS. But there is evidence for the combination of adjuvant CT and RT following CRS provides significantly higher DFS and OVS rates.*

Key Words: *Uterine sarcomas, advanced stage, cytoreductive surgery, adjuvant chemotherapy, adjuvant radiotherapy.*

Özet

Amaç: Sitoredüktif cerrahi (SRC) yapılan ileri evre uterin sarkomlu hastalarda adjuvan tedavi modalitelerinin sağkalım sonuçları üzerine etkisini analiz etmektir.

Gereç ve Yöntem:1/1994-1/2009 yılları arasında; merkezimizde teşhis ve tedavi edilen (n=122) uterin sarkom tanılı hastadan, n=26 (%21)'i ileri (FIGO evre III ve IV) hastalığa sahipti ve bu retrospektif çalışmanın olgularıydı. Hastalığın evresi, tümör histolojisi, lenfadenektomi varlığı, sitoredüktif cerrahinin optimalitesi, adjuvan kemoterapi (KT) ve radyoterapi (RT) uygulamaları, hastalıksız ve genel sağkalım oranları ana ölçüm parametreleriydi. Veriler tanımlayıcı analizler, Kaplan-Meier and log-rank test yapılarak sunuldu.

Bulgular: Histolojik olarak vakalar; 9 (%34.6) leiomyosarkom, 3 (%11.4) endometriyal stromal sarkomdan ve 14 (%54) karsinosarkomdan oluşmaktaydı. Sistematik lenfadenektomi, sadece bilateral pelvik (n=9); bilateral pelvik + paraaortik (n=17) hastaya uygulandı. Optimal sitoredüksiyon, (23/26) %88 hastada elde edildi. Adjuvan tedavi olarak sadece KT (n=10) ve RT+KT (n=16) hastaya uygulandı. (SRC+adjuvan KT)-(SRC+adjuvan KT+RT) uygulanan hasta gruplarının ortalama sağkalım süreleri sırasıyla; hastalıksız sağkalım açısından [12.6–42.3] ay (p<0.05) ve ortalama sağkalım açısından [21.8–52.8] ay (p<0.01) olarak saptandı.

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Sonuç: Hasta sayısının azlığı, farklı tümör tipleri ve KT rejimleri nedeniyle bu özel hasta grubundan gelen tedavi verileri, özellikle SRC'yi takiben sadece adjuvan KT'nin etkinliği açısından bir sonuca ulaşmamıştır. Fakat SRC'yi takiben adjuvan KT+RT kombinasyonunun anlamlı derecede yüksek hastalıksız ve genel sağkalım oranları sağladığına dair kanıt bulunmaktadır.

Anahtar Sözcükler: Uterin sarkomlar, ileri evre, sitoredüktif cerrahi, adjuvan kemoterapi, adjuvan radyoterapi.

Introduction

Uterine sarcomas are rare forms of gynecologic cancers with an incidence of 1.7/100.000 and are generally seen in the postmenopausal period (1). Uterine sarcoma definition includes carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, adenosarcoma and undifferentiated endometrial sarcoma which originate from mesenchimal uterine tissues like endometrial stroma, uterine muscle and supporting tissues (2). They have a worse prognosis than all other uterine malignancies. Also they have aggressive behavior with poor overall survival rates of approximately 30% (3,4) and a great tendency toward local recurrence and distant spread (5).

Cytoreductive surgery (CRS) is the primary treatment for all patients with uterine sarcomas and survival prolongs with the optimality of CRS. The most important prognostic factor is the extent of the tumor at the time of treatment (6-8). Although the use of adjuvant therapies such as chemotherapy (CT), radiotherapy (RT), chemoradiotherapy (CRT), hormonotherapy and molecularly targeted therapy is still controversial and no advantage has been shown by one over the other, these treatment modalities have been used to provide better survival (2,7). Standardized treatment for any histologic type has not yet been established especially for advanced stages.

The aim of the present retrospective study was to analyse the effect of adjuvant RT and CT on survival outcomes in twenty-six patients on which CRS was performed with advanced stage uterine sarcomas and also broaden the knowledge of these rare tumors.

Materials and Methods

During a 15-year period; among 122 patients with uterine sarcoma who were diagnosed and treated at our center, n = 26 (21%) had advanced (FIGO stage III and IV) disease and were the subject of this retrospective study. Patient age at diagnosis, presenting symptoms, tumor size, presence of lymphadenectomy, optimality of cytoreductive surgery, adjuvant RT and CT applications, date and site of all recurrences, therapy for recurrent or metastatic disease, and disease-free and overall survival status at last follow-up were the main outcome measures. Data regarding demographic and disease-related characteristics were obtained from patients' files.

Patients were assigned stage III for disease which was confined to the pelvis and/or retroperitoneal nodes, and stage IV for distant spread. Histologic analysis was performed on paraffin-embedded and formalin-fixed tissues. We retrieved FIGO stage III-IV of three subtypes of histology: leiomyosarcoma (LMS), carcinosarcoma (CS), endometrial stromal sarcoma (ESS). Uterine sarcomas were classified according to 2003 World Health Organization (WHO) classification and the 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria for endometrial carcinoma was used to assign stages for uterine sarcomas in spite of the different biologic behavior of both tumor categories (9). The optimality was defined according to the Gynecologic Oncology Group (GOG) definition in which optimal cytoreduction has been defined as <1cm of maximal residual tumor size. The follow-up period was defined as the time interval between the date of surgery and either the date of death or the latest date of confirmed survival.

Statistical analysis was performed by using SPSS 16 (Chicago, IL, USA). Descriptive statistics, Kaplan-Meier and log-rank test were used and a p value of less than 0.05 was considered to be statistically significant.

Results

Clinico-pathologic characteristics and performed treatment modalities of 26 patients with advanced stage uterine sarcomas are described and presented in Table 1 and 2, respectively. Nine of 26 patients had LMS, three had ESS and fourteen had CS. The median follow-up was 32.4 [range: 6-85] months. The mean age of patients at the time of diagnosis was 57.2 [range: 34-76] years. All the advanced stage sarcomas arose in the uterine corpus. Eighteen patients were postmenopausal (69%) and eight were premenopausal (31%).

The most presenting symptom was postmenopausal bleeding (27%). The other symptoms are presented in Table-1. Four patients had a history of previously pelvic radiation therapy. Six patients had systemic disease and none of the patients had received tamoxifen therapy. Six (23.1%) of the patients were found to have stage IIIA disease, three (11.5%) had stage IIIB, eleven (42.4%) had stage IIIC, four (15.4%) had stage IVA and two (7.6%) had stage IVB disease at diagnosis. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with peritoneal cytology and infracolic omentectomy were performed on all patients. A

lymphadenectomy was performed as part of the surgical staging (only bilateral pelvic n=9; bilateral pelvic + para-aortic n=17). Overall the incidence of lymph node metastases was [pelvic n=16 (61.5%); para-aortic n=9 (53%)]. Optimal cytoreduction was achieved in 23 (88%) of 26 patients.

Table-1. Clinicopathologic characteristics of patients with advance uterine sarcomas.

Age (year)*	57.2 [34-76]
Menopausal status**	
Premenopausal	8 (31%)
Postmenopausal	18 (69%)
Preoperative diagnosis**	
Yes	14 (54%)
No	12 (46%)
Tumor size (cm)*	8.7 [3-15]
Types of sarcoma (n, %)	
Leiomyosarcoma (LMS)	9 (34.6%)
Endometrial stromal sarcoma (ESS)	3 (11.5%)
Carsinosarcoma (CS)	14 (53.8%)
Lymph node metastases**	
Pelvic	16/26 (61.5%)
Para-aortic	9/17 (53%)
FIGO stage**	
IIIA	6 (23%)
IIIB	3 (11.5%)
IIIC	11 (42.3%)
IVA	4 (15.3%)
IVB	2 (7.6%)
Adjuvant treatment**	
CT	10 (38.5%)
CT + RT	16 (61.5%)
Recurrence localization**	
Local (Pelvic)	13 (50%)
Distant	10 (38.4%)
Rectosigmoid	2 (7.7%)
Surrenal gland	1 (3.8%)
Lung	2 (7.7%)
Mediastinum	1 (3.8%)
Retroperitoneum	2 (7.7%)
Femur	1 (3.8%)
Cerebrum and cerebellum	1 (3.8%)
Presenting symptoms**	
Postmenpausal bleeding	7 (27%)
Menorrhagia	5 (19%)
Myoma uteri	2 (7.7%)
Pelvic mass	5 (19%)
Pelvic pain	2 (7.7%)
Myoma uteri + Menorrhagia	5 (19%)
Prior pelvic radiotherapy**	
Yes	4 (15%)
No	22 (85%)

Values are expressed as *: median with range; **: n (%)

Only CT (n = 10) and both RT+CT (n = 16) were applied to patients as adjuvant treatments. Adjuvant chemotherapy regimens were administered to 26 patients and these regimens are described in Table-2. In total, 23 relapses were noted (88%). The majority of recurrences were within the first two years and localized in the pelvis (56%). Colonic, surrenal gland, lung, mediastinal, retroperitoneal, femur, cerebral and cerebellar localizations were the locations of extrapelvic recurrences (Table-2). The treatment modalities at recurrent settings were surgery with hemicolectomy + colostomy (n=1); RT (n=12) and RT + CT (n=10).

Table-2. Performed treatment modalities for patients with advanced stage uterine sarcomas.

Treatment modality	**n, %**
Surgery	
Total abdominal hysterectomy	
Tip 1	19 (73%)
Tip 2	7 (27%)
Lymphadenectomy	
Only bilateral pelvic	9 (34.6%)
Bilateral pelvic + para-aortic	17 (65.4%)
Optimal cytoreduction	
Yes	23 (88.4%)
No	3 (11.6%)
Radiation	
Pelvic radiation	16 (61.5%)
Brachytherapy	5 (19.2%)
Whole abdominal	14 (53.8%)
Chemotherapy regimens	
Ifosphamide + doxorubicin	9 (34.7%)
Vincristine + actinomycin-D + cyclophosphamide	7 (27%)
Cyclophosphamide + cisplatin + doxorubicin	3 (11.5%)
Cyclophosphamide + doxorubicin	4 (15.3%)
Ifosphamide + etoposide	3 (11.5%)

After adjuvant treatments, optimally cytoreduced patients had longer mean overall survival rates than suboptimally cytoreduced patients (52.4 vs. 21.3 months, ($p< 0.01$), (Figure-1). The mean survival of the patients performed (CRS + adjuvant CT) – (CRS + adjuvant CT+RT) was determined to be [12.6–42.3] months ($p < 0.05$) in terms of DFS and, [21.8–52.8] months ($p<0.01$) in terms of OVS, respectively. (Figure-2, Figure-3).

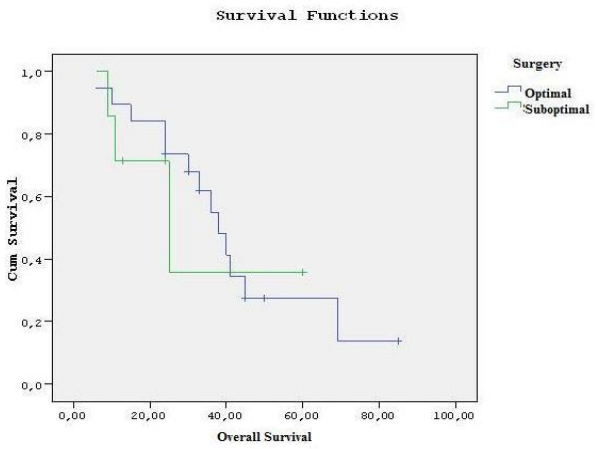

Figure-1. Overall survival curves regarding to optimality of cytoreductive surgery.

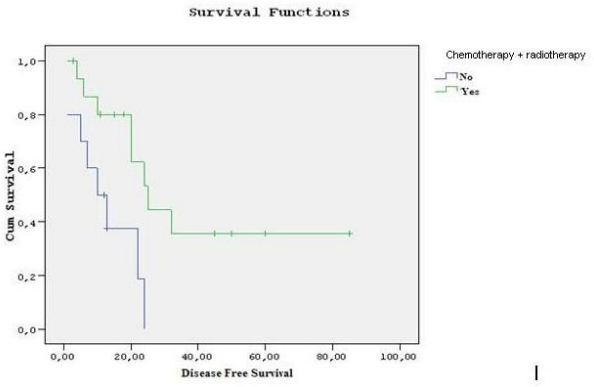

Figure-2. Disease free survival curves regarding to adjuvant chemotherapy + radiotherapy.

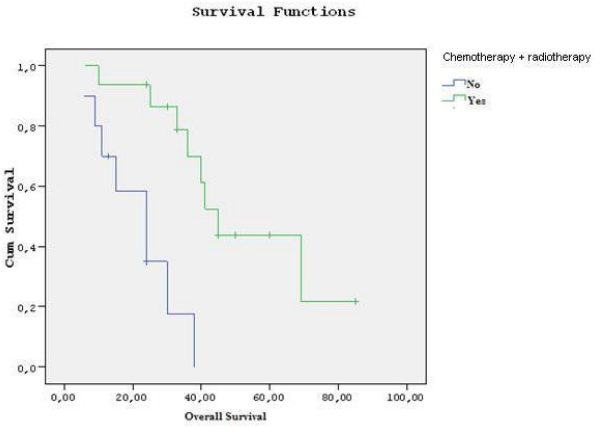

Figure-3. Overall survival curves regarding to adjuvant chemotherapy+radiotherapy.

Discussion

Despite appropriate primary therapy, uterine sarcomas have an aggressive behavior with a poor disease free and overall survival prognosis. Standardized treatment for any histologic type has not been established yet due to rarity and heterogeneity of these tumors. Appropriate treatment includes total abdominal hysterectomy with bilateral salpingo-oophorectomy, removal of pelvic and para-aortic lymph nodes, omentectomy, peritoneal cytology and maximal tumor reductive surgery in advanced stage uterine sarcomas (7,8,10).

As with other gynecologic malignancies, initial optimal cytoreductive surgery plays an important role in uterine sarcomas. Adjuvant treatment modalities such as CT, RT and CT+RT have been implemented for the treatment but significant benefit to survival has not been shown (2,6). The role of adjuvant radiotherapy and chemotherapy is uncertain but some studies have demonstrated the advantage of radiotherapy for disease specific survival in early-stage tumors as well as local control in advanced-stage tumors (6,7,10). The lack of efficacious adjuvant treatments in advanced stage disease are associated with recurrence, poor overall and disease free survival rates. Taxanes and cisplatin-based chemotherapy (7) as well as ifosfamide plus doxorubicin (11) along with whole pelvic irradiation, gemcitabine plus docetaxel (12,13) and aromatase inhibitors (14) may lead to increased survival in patients with metastatic sarcomas. Patients may also receive adjuvant radiation or hormonal treatment with progestational agents especially for endometrial stromal sarcomas (15). In a study performed in Turkey, Aksoy et al. (11) stated that ifosfamide and doxorubicin regimen has moderate anti-tumor activity (46%) with acceptable toxicity in patients with advanced stage uterine sarcomas. In their series, the median progression-free survival time of 42 patients was eight months (range, 4-35) and the results were satisfactory especially in patients with leiomyosarcoma histology. In our series, we could not draw any conclusion regarding adjuvant chemotherapy in advanced stage uterine sarcomas due to administered non-homojen CT regimens.

Total abdominal hysterectomy is the mainstay for the treatment of uterine sarcomas regardless of subtypes. There is no clear consensus about necessity of additional surgical treatments like BSO and lymphadenectomy. While BSO is usually recommended and has been shown therapeutically and prognostically helpful in ESS, in patients with LMS, BSO it did not have any impact on survival (1,16-18). BSO should be a part of surgical management in patients with CS because about 23% of women with CS had occult metastases during surgery (19). Lymphadenectomy is still recommended for CS due to high incidence of lymph node involvement even if in patients in the early clinical stage (20-38%) because it improves surgical staging and provides prognostic information (20). However, it is still unclear whether this procedure improves patient survival in patients with early stage carcinosarcomas (20). On the other hand, Ramondetta et al. (21) suggest that surgical debulking and lymphadenectomy should be considered especially in the early stage and noted that patients with minimal residual disease may have a longer survival than those with gross residual disease after surgical debulking. Contrary to CS, pelvic and/or para-aortic lymphadenectomy is not indicated for LMS and ESS (22). Lymph node dissection should be considered only in women found to have macroscopic lymph node metastasis or extrauterine disease during surgery. In our series, 19 type 1 and seven type 2 hysterectomies were performed. Only bilateral pelvic (n=9) and bilateral pelvic+para-aortic (n=17) lymphadenectomies were performed as part of the surgical staging regardless of sarcoma types. Three patients were suboptimally debulked and had residual tumors >2cm after initial surgery. After adjuvant

treatments, these patients had shorter survival rates than optimally cytoreduced patients as shown in Figure 1 and this data are in concordance with previous literature.

Different radiotherapy response rates were observed in each subtype of uterine sarcoma (22-24). Adjuvant radiation therapy is an effective treatment for patients with ESS due to excellent local control in all stages (23). It was found that radiation therapy predicts an improved overall and disease specific survival in a retrospective analysis of 2461 women with uterine CS (23). Reed et al. (25) demonstrated that patients with LMS did not show the same benefit from radiation as patients with CS. Bokhman et al. (26) have shown that postoperative adjuvant pelvic radiotherapy exerted a positive prognostic effect on patients with ESS and CS, whereas it was not justified in patients with LMS. In present study, we encountered a similar disease free and overall survival benefit in patients treated with surgery plus CT+RT. This result may be explained by the presence of carcinosarcoma in the majority of cases in our series.

Reducing tumor burden plays an active role in increasing effectiveness of chemotherapy in gynecological malignancies (27). Effectiveness of chemotherapy agents especially anthracyclines and ifosfamide have been demonstrated in patients with uterine sarcomas (28-30). There is little evidence in the literature supporting chemotherapy administration except for carcinosarcomas. Makker et al. (31) evaulated 49 women with completely resected stage I-IV CS received in the adjuvant setting by either platinum-based chemotherapy with or without radiation therapy (pelvic or whole abdominal), or radiation therapy alone and showed minimal survival advantage though not statistically significant. We could not compare and give any conclusive results for the effectiveness of chemotheraputic agents in our study due to the administration of many different chemotherapeutics and a limited number of patients.

Conclusion

In the light of these premises, it can be noted that surgery plus adjuvant treatment modalities are still controversial in uterine sarcomas. Due to low patient numbers, different tumor types and CT regimens, and treatment approaches, data from this particular patient setting are inconclusive, especially in terms of effectiveness of CRS followed by only adjuvant CT. However, there is evidence for showing that the combination of adjuvant CT and RT following CRS achieve significant higher disease free and overall survival rates. Moreover, the results of the present study can burden the knowledge and shed some light on future larger sampled trials concerning the adjuvant treatments after cytoreductive surgery for advanced stage uterine sarcomas.

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