TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 841-846
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doi:10.3906/sag-1603-135

Impact of adjuvant treatment on oncologic outcomes in patients with stage I leiomyosarcoma of the uterus

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Received: 19.03.2016 • **Accepted/Published Online:** 18.11.2016 • **Final Version:** 12.06.2017

Background/aim: This study aimed to evaluate the role of adjuvant therapy for stage I uterine leiomyosarcoma (LMS).

Materials and methods: Clinicopathological data of cases of stage I uterine LMS from 1998 to 2015 were retrieved from the computerized database of Hacettepe University Hospital. The Kaplan–Meier method was used to estimate survival and progression-free survival, and survival differences were analyzed by log-rank test. Cox regression analysis was performed to account for the potential influence of confounding factors.

Results: We evaluated the outcomes of 35 patients with histologically proven stage I LMS. The median age at diagnosis was 50 years. All patients underwent surgical treatment and 20 patients (57.1%) received adjuvant therapy. Twelve of these patients (34.3%) received adjuvant chemotherapy, 3 (8.6%) received adjuvant pelvic irradiation, and 5 (14.2%) received adjuvant chemotherapy with pelvic irradiation. The median follow-up duration was 34 months (range: 3–231 months). Twenty-three (65.7%) patients had a recurrence during follow-up. Adjuvant therapy did not significantly improve median progression-free survival or median overall survival. Cox regression analysis did not demonstrate any significant impact of the factors studied, including age, menopausal status, tumor size, mitotic count, staging surgery, or adjuvant therapy.

Conclusion: Adjuvant therapy for surgically treated stage I uterine LMS did not improve oncologic outcomes.

Key words: Leiomyosarcoma, uterus, adjuvant, therapy

1. Introduction

Leiomyosarcoma (LMS) of the uterus is a rare tumor that accounts for approximately 1% of all uterine malignant neoplasms and arises from the smooth muscle cells of the uterus. This malignancy is a highly aggressive tumor compared with other uterine cancers and it is associated with a significant risk of recurrence and death, even in early stages (1,2).

The main treatment for LMS is surgical excision including total abdominal hysterectomy with or without bilateral salpingo-oophorectomy (2,3). However, debulking of any tumor outside the uterus should be a goal of the surgery since the most important prognostic factor is residual disease following primary surgery (1,4).

LMS is staged by the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system and stage I LMS is defined as a tumor confined to the corpus of the uterus (5). Although LMS is usually diagnosed at an early stage, its prognosis is very poor. Most patients will develop recurrence after primary treatment even if the disease is confined to the uterus. Five-year disease-specific survival for patients with stage I and II disease is 51% and 25%, respectively. For all stages of patients with LMS of the uterus, 5-year disease specific survival is only 32% (1,6).

The current recommendations for adjuvant treatment in uterine LMS remain controversial. After surgery, adjuvant treatment with pelvic radiotherapy and/or chemotherapy may be considered (7,8). However, it is not clear whether any adjuvant therapy options offer a survival benefit. Furthermore, results are conflicting regarding the adjuvant treatment especially for patients with stage I uterine LMS. Therefore, the aim of this study was to evaluate the role of adjuvant treatment in patients with stage I LMS of the uterus.

2. Materials and methods

This retrospective study included patients with histologically proven stage I uterine LMS. Clinicopathological and outcome data of patients with FIGO stage I uterine LMS from 1998 to 2015 were retrieved from the computerized

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database of Hacettepe University Hospital. The clinical and pathological characteristics including age, menopausal status, operative procedure, tumor size, mitotic count, stage, adjuvant treatment, and survival were determined and compared. All patients were staged according to the 2009 FIGO staging system. Uterine LMS was pathologically diagnosed by the presence of coagulative tumor cell necrosis, cytologic atypia, and 10 or more mitoses per 10 high-power fields.

Data recording and statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Basic characteristics were compared by using the Mann–Whitney U test or chi-square test as appropriate. Overall survival (OS) was calculated from time of diagnosis until death or time of last follow-up. Progression-free survival (PFS) was calculated from time of diagnosis until the diagnosis of disease recurrence. The Kaplan–Meier method was used to estimate OS and PFS, and survival differences were analyzed by log-rank test. Cox regression analysis was performed to account for the potential influence of confounding factors. Differences were considered statistically significant at $P < 0.05$.

As this study represents a retrospective database review, local ethics committee permission was not sought.

3. Results

Outcomes of 35 patients with histologically proven stage I LMS were evaluated. The median age at diagnosis was 50 years (range: 22–66). Twenty (57.1%) patients were postmenopausal and 15 (42.9%) were premenopausal. Demographic, clinical, and pathological characteristics of the study patients are presented in Table 1.

All patients underwent surgical treatment and 20 patients (57.1%) received postoperative adjuvant therapy (Table 2). The surgical procedure consisted of total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) in 14 (40%) patients, surgical staging with lymphadenectomy and omentectomy in addition to TAH and BSO in 9 (25.7%) patients, and TAH alone in 2 (5.7%) patients. Ten patients were referred after having TAH+BSO or TAH at other centers. Of these, 9 patients underwent lymphadenectomy and omentectomy, while 1 patient underwent BSO, lymphadenectomy, and omentectomy. Of patients who received adjuvant treatment, 12 (34.3%) received chemotherapy (ifosfamide ± adriamycin or docetaxel + gemcitabine), 3 (8.6%) received pelvic irradiation, and 5 (14.2%) received chemotherapy with pelvic irradiation. The median follow-up duration was 34 months (range: 3-231 months). Twenty-three (65.7%) patients experience a recurrence during follow-up (Table 3). The median PFS and median OS were similar between

Table 1. Basic demographic and histopathological characteristics of patients.

	Adjuvant therapy (n = 20)		
Characteristic	No (n = 15)	Yes (n = 20)	P
Age at diagnosis, years	51.1 ± 14.5	47.6 ± 10.1	NS*
Maximal tumor size (cm)	8.5 ± 5.7	9.1 ± 3.4	NS*
Mitotic count (per 10 HPFs)	14.6 ± 5.9	20.7 ± 10.7	NS*
Median follow-up, months (range)	36 (3–113)	31 (6–231)	NS*
Stage			NS#
IA	3 (20.0%)	2 (10.0%)	
IB	12 (80.0%)	18 (90.0%)	
Menopausal status			NS#
Premenopausal	6 (40.0%)	9 (45.0%)	
Postmenopausal	9 (60.0%)	11 (55.0%)	

Data are given as mean ± SD or n (%).
HPF, High-power field; NS, nonsignificant.
*Mann–Whitney U test, #chi-square test.

Table 2. Primary surgical procedures and adjuvant treatments.

	Number	Percent
Type of surgery		
TAH	2	5.7
TAH + BSO	14	40.0
TAH + BSO + LND + omentectomy	9	25.7
LND + omentectomy*	9	25.7
BSO + LND + omentectomy#	1	2.9
Adjuvant therapy		
No adjuvant therapy	15	42.9
Chemotherapy	12	34.3
Radiotherapy	3	8.5
Chemotherapy and radiotherapy	5	14.3

TAH, Total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LND, lymph node dissection.
*Patients who were referred after having TAH + BSO at other centers.
#Patients who were referred after having TAH at other centers.

Table 3. Recurrence rates and patterns according to adjuvant treatment status.

	No adjuvant therapy (n = 15)	Adjuvant therapy (n = 20)	P
Recurrence			NS*
Yes	8 (53.3%)	15 (75.0%)	
No	7 (46.7%)	5 (25.0%)	
Sites of recurrence			NS*
Pelvis	4 (50.0%)	9 (60.0%)	
Lung	3 (37.5%)	5 (33.3%)	
Pelvis and lung	0	1 (6.7%)	
Subcutaneous nodules	1 (12.5%)	0	

Data are given as n (%).

patients who received adjuvant treatment compared with those who did not receive adjuvant therapy (Figures 1 and 2). Cox regression analysis did not demonstrate any significant impact of the factors studied on median PFS and OS. These factors included age, menopausal status, tumor size, mitotic count, staging surgery, and adjuvant therapy.

4. Discussion

Patients with uterine LMS have a high risk of recurrence and mortality, regardless of the stage of the disease. Recurrence rates vary between 53% and 71% (9,10). Abeler et al. found that patients with early stage (stage I) uterine LMS had an overall 5-year survival of 51% (11). However, in the literature, there is limited information

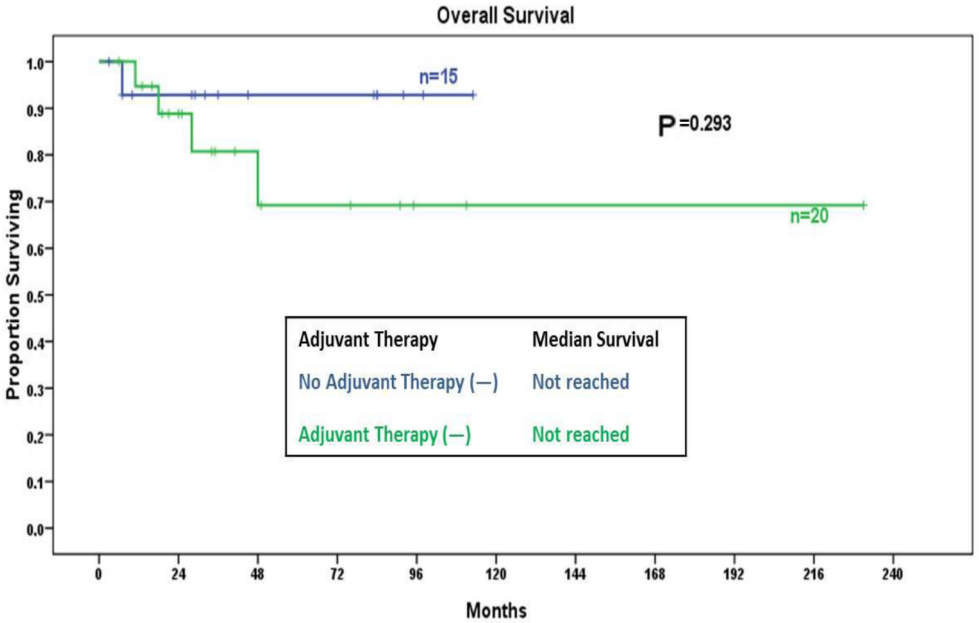

Figure 1. Progression-free survival of patients with stage I uterine LMS.

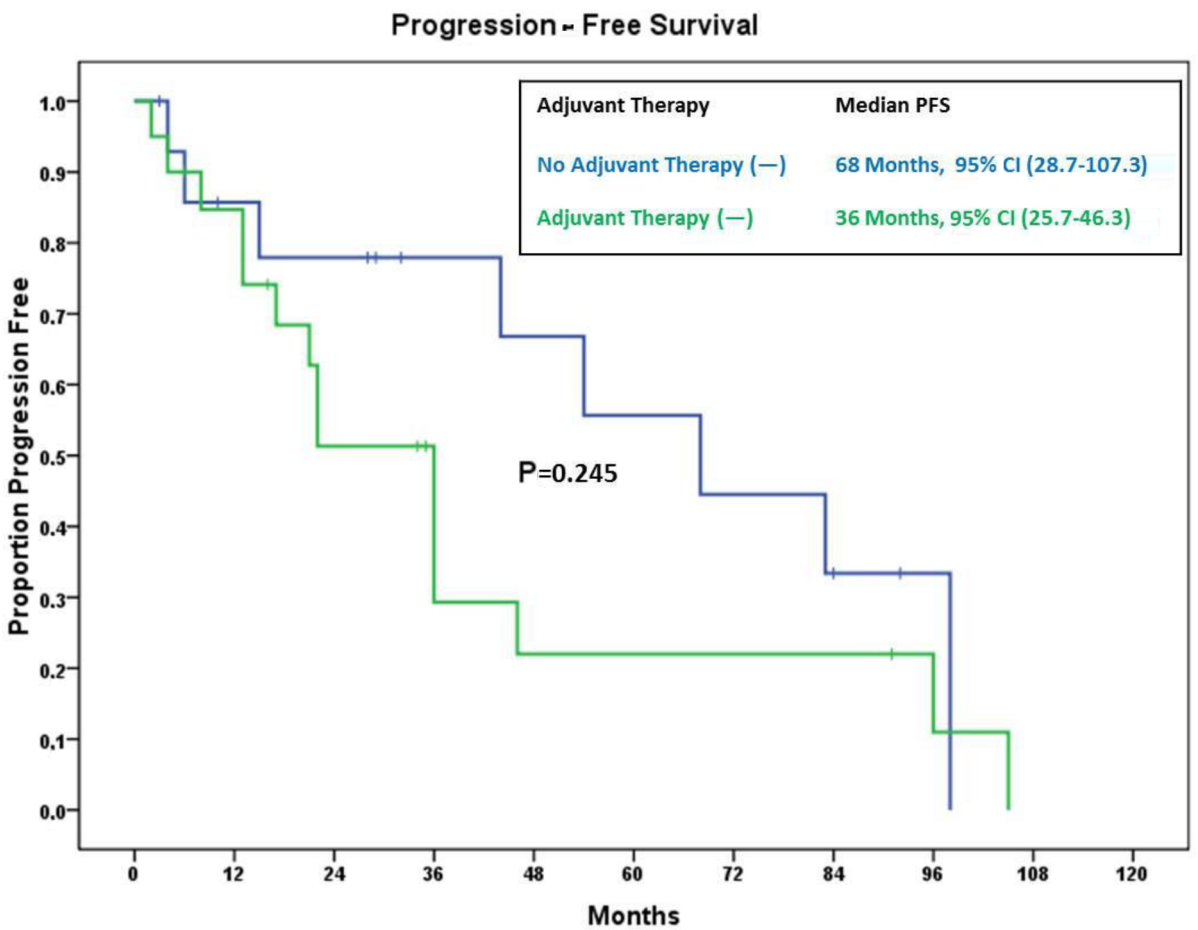

Figure 2. Overall survival of patients with stage I uterine LMS.

on the role of postoperative adjuvant treatment despite these high recurrence and mortality rates. Chemotherapy and/or pelvic radiotherapy may be considered following the surgery for uterine LMS. While adjuvant pelvic radiotherapy may be used to reduce the risk of local recurrences, systemic recurrences and metastatic disease may be prevented with chemotherapy. However, the effectiveness of any form of adjuvant treatment on survival has not been consistently shown (1,12).

In a Gynecologic Oncology Group (GOG) study, 156 patients with stage I (disease limited to corpus) or stage II (disease limited to the corpus and cervix) uterine sarcomas were evaluated in a randomized study. Patients receiving adjuvant chemotherapy consisting of doxorubicin were compared with those not receiving adjuvant therapy. Pelvic irradiation was optional before randomization. Although women who received doxorubicin had a lower recurrence rate, this was not statistically significant. There was no difference in PFS or OS (13). On the other hand, Hensley et al. designed a prospective study and evaluated 23 patients with completely resected stage I–IV uterine LMS. All patients were treated with adjuvant gemcitabine and docetaxel. Of these 23 patients, 18 were at stage I or II. Among these 18 patients, 2-year PFS was found to be 59% and median PFS was 39 months. The authors concluded that adjuvant treatment with gemcitabine plus docetaxel for uterine LMS yielded higher PFS rates than historical rates (14). Another important study for adjuvant treatment with chemotherapy in patients with uterus-limited LMS was published by Hensley et al. In this study, 47 patients with uterus-limited LMS received 4 cycles of gemcitabine plus docetaxel followed by doxorubicin. The median time to recurrence was 27 months, the 2-year PFS rate was 78%, and the 3-year PFS rate was 57% (15). Similarly, Piver et al. showed a low recurrence rate in patients with stage I LMS who were treated with adjuvant chemotherapy (16). Park et al. evaluated prognostic factors and treatment outcomes of patients with uterine sarcoma. The study group consisted of 127 patients. Of these, 46 patients had LMS of the uterus. An adjuvant chemotherapeutic regimen containing ifosfamide was the preferred regimen for LMS. They found that in early stage disease, adjuvant therapy and any adjuvant treatment modality did not significantly influence PFS or OS (17). Hsieh et al. also found no significant survival benefit in patients with uterine LMS who received postoperative adjuvant therapy (18). Conversely, Durnali et al. designed a retrospective study including 93 patients with uterine sarcoma. Of the 93 patients, 54 (58%) had LMS. The patients with LMS were mostly stage I (48.1%). Of the 54 patients with LMS, 41 (76%) patients received adjuvant therapy. Adjuvant therapy was chemotherapy in 20 patients, radiotherapy in 9, and sequential chemotherapy plus radiotherapy in 12. They also performed subgroup analyses for the LMS cohort and found that adjuvant sequential chemotherapy plus radiotherapy showed a significantly positive effect on OS (19).

Reed et al. published a phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of stage I and II uterine sarcomas. The study group consisted of 103 patients with LMS, 91 carcinosarcomas, and 28 endometrial stromal sarcomas. Patients were randomized to either observation or pelvic radiation. There was no difference in either overall or disease-free survival in patients with LMS. Furthermore, while adjuvant pelvic radiotherapy provided increased local control in carcinosarcoma, a similar benefit was not observed in LMS. In fact, there was a trend for reduced OS rates in adjuvant pelvic radiation group, although this did not reach statistical significance (20). In contrast to this study, Chauveinc et al. and Salazar et al. found improved local control with adjuvant pelvic radiotherapy without any benefit for overall survival (21,22). Likewise, Giuntoli et al. published a retrospective review of 208 patients with uterine LMS. Of these 208 patients, 130 were at stage 1, 34 received adjuvant chemotherapy, and 36 received adjuvant radiotherapy. They found that adjuvant pelvic radiotherapy significantly reduced the risk of pelvic local recurrence, but adjuvant chemotherapy did not improve clinical outcome and adjuvant treatment did not significantly improve OS (2).

In light of these findings, we retrospectively evaluated the outcomes of 35 patients with surgically approached, histologically proven stage I LMS. In the current study, we found that adjuvant therapy for surgically treated, uterus-confined disease did not improve PFS or OS. However, our study has the inherent limitations of a retrospective study design. In addition, the small number of patients and many different treatment regimens in our series are other limiting factors. Therefore, it would be wiser to wait for the results of ongoing trials on the role of adjuvant therapy in early stage uterine LMS before drawing definitive conclusions.

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