JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

Characterizing the efficacy and trends of adjuvant therapy versus observation in women with early stage (uterine confined) leiomyosarcoma: a National Cancer Database study

Anthony B. Costales [ID],[1] Milena Radeva [ID],[2] Stephanie Ricci [ID] [1]

[1]Division of Gynecologic Oncology, Ob/Gyn and Women's Health Institute, Cleveland Clinic, Cleveland, OH, USA
[2]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA

🔓 **OPEN ACCESS**

Correspondence to
Anthony B. Costales
Division of Gynecologic Oncology, Ob/Gyn and Women's Health Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk A81, Cleveland, OH 44195, USA.
E-mail: costales@bcm.edu

ORCID iDs
Anthony B. Costales [ID]
https://orcid.org/0000-0003-4326-9782
Milena Radeva [ID]
https://orcid.org/0000-0002-8057-4244
Stephanie Ricci [ID]
https://orcid.org/0000-0001-5856-9265

ABSTRACT

Objective: The utility of adjuvant therapy for women with uterine confined leiomyosarcoma remains uncertain. We sought to identify trends, analyze efficacy, and assess survival impact of adjuvant therapy in this patients.
Methods: We performed an observational cohort study of 1030 women with early stage leiomyosarcoma from the 2008–2014 National Cancer Database. Multi-nominal logistic regression was used to identify trends in receipt of adjuvant treatment. Demographic and clinical characteristics were compared. Kaplan-Meier curves were used to estimate survival.
Results: There were 547 who (53.1%) received observation, 79 (7.7%) received radiation alone, 340 (33.0%) received chemotherapy alone, and 64 (6.2%) received chemoradiation. Patients were more likely to be observed if tumor size was <5 cm (hazard ratio [HR]=0.97; 95% confidence interval [CI]=0.95–0.99; p=0.017) and less likely to be observed if lymphovascular space invasion (LVSI) was present (HR=0.60; 95% CI=0.41–0.89; p=0.010). Patients were more likely to receive chemotherapy if they were younger (HR=0.78; 95% CI=0.65–0.94; p=0.010) and if they had LVSI (HR=1.47; 95% CI=1.01–2.16; p=0.040). There was an independent association between older age, tumor size >5 cm, and LVSI with worsened survival, with the strongest predictor of mortality being the presence of LVSI. With a median survival of 61.9 months, there was no difference in estimated overall survival at 1 and 3 years based on receipt of adjuvant treatment as compared to observation (p=0.500).
Conclusion: Although women with uterine confined leiomyosarcoma experience high recurrence rates and poor survival outcomes, adjuvant treatment does not appear to confer a survival benefit.

Keywords: Leiomyosarcoma; Uterus; Chemotherapy

INTRODUCTION

Leiomyosarcoma (LMS), a rare gynecologic malignancy, accounts for 1% of all uterine malignancies, with 5,058 newly diagnosed cases estimated for the year 2018 [1]. However,

JOURNAL OF
GYNECOLOGIC
ONCOLOGY

it contributes to a significant proportion of uterine cancer deaths [2]. Surgery is considered the mainstay of treatment with the majority being uterine-confined, early-stage disease. Recurrence rates range from 53 to 71% and are often extra-pelvic, multi-site, and lethal [3-8]. Recurrence and prognosis are ultimately dependent upon the tumor size, mitotic activity or grade of the tumor, and the stage at presentation [9].

The high rate of distant failure, even in the setting of early-stage disease, provides the rationale for consideration of adjuvant systemic therapy [3]. However, the role of adjuvant therapy in completely resected, uterine-limited LMS is unclear. Radiation therapy appears to improve local control for women with stage I disease, however it has failed to improve overall survival (OS) due to high rates of distant metastasis [7,10]. Specifically, a randomized study from the European Organization for Research and Treatment of Cancer (EORTC) of adjuvant pelvic radiotherapy versus observation after surgery in patients with stage I–II uterine sarcoma demonstrated a reduction in local relapse, but no effect on survival with radiotherapy [10].

In early stage LMS, there has only been 1 randomized study comparing adjuvant chemotherapy to observation that failed to show a significant improvement in progression free or OS [11]. Additionally, there has only been 1 phase II study which demonstrated similar 2- and 3- year progression free survival rates [12]. A Gynecologic Oncology Group phase III trial comparing adjuvant chemotherapy versus observation for uterine-limited LMS showed no improvement in observed OS and recurrence free survival in patients treated with chemotherapy, although this study was closed early secondary to low accrual of just 38 patients [13]. A multi-center study of 140 patients with stage I and II LMS, in which 44% were observed, showed no improvement in disease free survival or OS at 5 years [14].

Despite the absence of data from randomized controlled trials, post-operative chemotherapy is commonly considered for women with stage I- IV uterine LMS. A multi-site retrospective study comparing adjuvant therapy in early stage LMS found similar recurrence rates for women treated with chemotherapy and observation. However, they noted that patients treated with adjuvant chemotherapy had a decreased risk of extra-pelvic recurrence and improved OS [15].

Utilizing the National Cancer Database (NCDB), we analyzed sociodemographic, disease, and treatment characteristics of a large cohort of women with uterine LMS. We sought to review the survival impact of adjuvant chemotherapy and expand on a previously published NCDB study, which briefly looked at this early stage cohort, identify trends in the adjuvant treatment of these women in the absence of prospective randomized data, identify prognostic factors with regards to mortality, and interrogate the survival impact of adjuvant therapy in women with early stage uterine confined LMS [9].

MATERIALS AND METHODS

We performed an observational cohort study of women with early stage uterine LMS from 2008–2014 employing the NCDB. The primary objective of this study was to determine the survival impact based on treatment group, defined as the time from diagnosis to death. Secondary objectives included trends in the use of adjuvant therapy amongst various sociodemographic and prognostic factors, as well as the effect of these factors on mortality.

Inclusion criteria for early-stage disease was restricted to International Classification of Disease for Oncology codes LMS not otherwise specified, epithelioid LMS, and myxoid LMS, American Joint Committee on Cancer (AJCC) stages I and II, underwent primary definitive surgery performed, did not have positive lymph nodes reported, and all margins were grossly and microscopically negative (i.e. no residual disease). Adjuvant treatment represented the first planned course of cancer-directed therapy used following primary surgery, excluding treatments for recurrence. Specific chemotherapy regimens, besides single-agent or multi-agent regimens, could not be discerned given the constraints of using the NCDB. Patients were considered to have received adjuvant chemoradiation if they had received both radiotherapy and chemotherapy within 6 months after primary surgery. Survival time was measured from the date of diagnosis until death, censoring, or last follow-up, as verified by the NCDB vital status determination.

The variables were analyzed via the definitions provided by the NCDB Participant Use Data File (PUF) data dictionary. As the International Federation of Gynecology and Obstetrics staging was not available in NCDB data until 2010, AJCC tumor, node, metastasis staging was available for all diagnosis years in the PUF and the 6th and 7th editions were used to identify our cohort. Years of diagnosis were divided into 2008–2011 and 2012–2014. We categorized race into 3 groups (white, African-American, and other), ethnicity into 3 groups (non-Hispanic, Hispanic, and unknown), and median income quartiles was identified for patients between the years of 2008-2012 and were divided into 4 groups (<$38,000, $38,000–$47,999, $48,000–$62,999, and >$63000). Insurance status was categorized into 6 groups as follows: uninsured, private, Medicaid, Medicare, other government, and unknown. Data regarding hospital type and location were analyzed.

With regard to tumor or procedural characteristics, we evaluated tumor size, lymphovascular space invasion (LVSI), and performance of bilateral salpingo-oophorectomy (BSO) or lymphadenectomy at the time of primary surgery. With regards to lymph node dissection, this was restricted by whether a patient had any lymph nodes examined, none examined, or unknown at the time of primary surgery. Identification of the performance of a BSO was determined by employing the procedural codes included in the Facility Oncology Registry Data Standards definitions for corpus uteri.

The 4 treatment groups were compared by demographic and clinical characteristics. Categorical factors were summarized using frequencies and percentages, while continuous variables were summarized by using means and standard deviations. To evaluate categorical factors, Pearson χ^2 and Fisher Exact tests were used, and analysis of variance and Kruskal-Wallis tests were used for continuous factors. The association of a set of pre-identified factors: age, race, period of diagnosis, income, facility type, insurance, Charlson-Deyo score, tumor size, lymph node dissection, and stage, with the primary and treatment modalities was analyzed using multinomial logistic regression. Cox proportional hazards analysis was used to evaluate the effect of demographic and clinical factors on mortality. The Kaplan-Meier method was used to estimate survival between groups and was calculated at 1 and 3 years. There was insufficient data to calculate survival at 5 years. Comparisons of adjuvant therapy groups were made using hazard ratios and 95% confidence intervals (CIs). All tests were 2-tailed and performed at a significance level of 0.05. Analysis was performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 1,030 patients with early-stage uterine LMS were identified. **Table 1** summarizes the demographic and clinical characteristics of the study population. The median age at diagnosis was 55 years (range, 44–66), and the majority of patients were white (73.9%) or African-American (20.2%). Stage I disease accounted for 90.8% of the cohort.

Table 1. Demographic and clinical characteristics of the study population-National Cancer Database: 2008–2014

Factor	Total (n=1,030)	Obs (n=547)	RT (n=79)	CT (n=340)	CT + RT (n=64)	p-value
AJCC analytic stage group						<0.001[†]
Stage I	935 (90.8)	523 (95.6)	67 (84.8)	294 (86.5)	51 (79.7)	
Stage II	95 (9.2)	24 (4.4)	12 (15.2)	46 (13.5)	13 (20.3)	
Histology						0.420[†]
8,890 (LMS NOS)	929 (90.2)	489 (89.4)	69 (87.3)	315 (92.6)	56 (87.5)	
8,891 (epithelioid LMS)	56 (5.4)	31 (5.7)	4 (5.1)	16 (4.7)	5 (7.8)	
8,896 (myxoid LMS)	45 (4.4)	27 (4.9)	6 (7.6)	9 (2.6)	3 (4.7)	
Demographic and clinical characteristics						
Age at diagnosis (yr)	55.4±11.4	56.5±12.3	58.1±11.0	53.7±9.9	52.3±9.0	<0.001[*]
Race						0.980[†]
White	756 (73.9)	404 (74.3)	57 (72.2)	251 (74.5)	44 (69.8)	
African-American	207 (20.2)	108 (19.9)	18 (22.8)	67 (19.9)	14 (22.2)	
Other	60 (5.9)	32 (5.9)	4 (5.1)	19 (5.6)	5 (7.9)	
Ethnicity						0.730[†]
Non-Hispanic	915 (88.8)	487 (89.0)	66 (83.5)	306 (90.0)	56 (87.5)	
Hispanic	89 (8.6)	45 (8.2)	10 (12.7)	27 (7.9)	7 (10.9)	
Unknown	26 (2.5)	15 (2.7)	3 (3.8)	7 (2.1)	1 (1.6)	
Period of diagnosis						0.100[†]
2008–2011	603 (58.5)	308 (56.3)	54 (68.4)	198 (58.2)	43 (67.2)	
2012–2014	427 (41.5)	239 (43.7)	25 (31.6)	142 (41.8)	21 (32.8)	
Median income quartiles 2008–2012						0.420[†]
<$38,000	199 (19.4)	99 (18.2)	17 (21.5)	69 (20.3)	14 (21.9)	
$38,000–$47,999	216 (21.1)	114 (21.0)	14 (17.7)	78 (22.9)	10 (15.6)	
$48,000–$62,999	243 (23.7)	122 (22.5)	26 (32.9)	80 (23.5)	15 (23.4)	
$63,000+	368 (35.9)	208 (38.3)	22 (27.8)	113 (33.2)	25 (39.1)	
Facility type						0.710[†]
Community cancer program	54 (5.6)	29 (5.7)	6 (7.7)	15 (4.7)	4 (6.9)	
Comprehensive cancer program	396 (41.1)	211 (41.3)	31 (39.7)	129 (40.8)	25 (43.1)	
Academic/research program	400 (41.5)	221 (43.2)	30 (38.5)	129 (40.8)	20 (34.5)	
Integrated network cancer program	113 (11.7)	50 (9.8)	11 (14.1)	43 (13.6)	9 (15.5)	
Facility location						0.030[†]
East	387 (40.2)	207 (40.5)	36 (46.2)	118 (37.3)	26 (44.8)	
Central	390 (40.5)	189 (37.0)	32 (41.0)	149 (47.2)	20 (34.5)	
West	186 (19.3)	115 (22.5)	10 (12.8)	49 (15.5)	12 (20.7)	
Primary payor						0.002[†]
Not insured	72 (7.0)	34 (6.2)	8 (10.1)	23 (6.8)	7 (10.9)	
Private insurance	623 (60.5)	316 (57.8)	36 (45.6)	228 (67.1)	43 (67.2)	
Medicaid	87 (8.4)	42 (7.7)	8 (10.1)	33 (9.7)	4 (6.3)	
Medicare	226 (21.9)	144 (26.3)	23 (29.1)	51 (15.0)	8 (12.5)	
Other government	6 (0.58)	2 (0.37)	2 (2.5)	2 (0.59)	0 (0.0)	
Insurance status unknown	16 (1.6)	9 (1.6)	2 (2.5)	3 (0.88)	2 (3.1)	
Charlson-Deyo score						0.560[†]
0	841 (81.7)	440 (80.4)	64 (81.0)	286 (84.1)	51 (79.7)	
1	154 (15.0)	84 (15.4)	14 (17.7)	46 (13.5)	10 (15.6)	
2	35 (3.4)	23 (4.2)	1 (1.3)	8 (2.4)	3 (4.7)	
Tumor size						0.001[†]
≤5 cm	190 (18.5)	125 (22.9)	8 (10.1)	49 (14.5)	8 (12.7)	
>5 cm	758 (73.8)	371 (67.9)	66 (83.5)	269 (79.4)	52 (82.5)	
Unknown, size not stated	79 (7.7)	50 (9.2)	5 (6.3)	21 (6.2)	3 (4.8)	
Tumor size (cm)	9.73±6.40	9.07±5.69	10.6±4.45	10.57±7.75	9.59±5.51	0.007[*]

(continued to the next page)

Table 1. (Continued) Demographic and clinical characteristics of the study population-National Cancer Database: 2008–2014

Factor	Total (n=1,030)	Obs (n=547)	RT (n=79)	CT (n=340)	CT + RT (n=64)	p-value
Lymph node evaluation						0.350
Performed	395 (38.3)	196 (35.8)	33 (41.8)	142 (41.8)	24 (37.5)	
Not performed	632 (61.4)	348 (63.6)	46 (58.2)	198 (58.2)	40 (62.5)	
BSO (ovarian removal)						0.640[†]
Performed	810 (78.6)	436 (79.7)	66 (83.5)	261 (76.8)	47 (73.4)	
Not performed	122 (11.8)	65 (11.9)	6 (7.6)	42 (12.4)	9 (14.1)	
Unknown	98 (9.5)	46 (8.4)	7 (8.9)	37 (10.9)	8 (12.5)	
Lymphovascular space invasion						0.004[†]
Present	174 (16.9)	70 (12.8)	16 (20.3)	72 (21.2)	16 (25.0)	
Not present	591 (57.4)	327 (59.8)	38 (48.1)	195 (57.4)	31 (48.4)	
Unknown	265 (25.7)	150 (27.4)	25 (31.6)	73 (21.5)	17 (26.6)	

Data are shown as mean±standard deviation or number (%). Data not available for all subjects. Missing values: tumor size (cat) = 3, tumor size (when available) = 84, race = 7, facility type = 68, facility location = 68.
BSO, bilateral salpingoophorectomy; CT, chemotherapy; CT + RT, chemoradiation; LMS, leiomyosarcoma; NOS, not otherwise specified; Obs, observation; RT, radiation therapy.
*Analysis of variance; †Pearson's χ^2 test.

BSO was performed in 78.6% of the patients and a lymph node evaluation was performed in 38.3% of patients. LVSI was present in just 16.9% of the surgical specimens. Observation was the most common post-operative management occurring in 547 patients (53.1%) followed by adjuvant chemotherapy in 340 patients (33.1%), radiotherapy in 79 patients (7.7%), and combination chemoradiation in 64 (6.2%). There were no significant differences between the adjuvant treatment groups with respect to race, ethnicity, median income quartiles, or Charlson-Deyo score. Radiation was prescribed less after 2011 (9.0% vs. 5.6, p=0.002). With regards to the use of adjuvant treatment based on receipt of a BSO, there were no significant differences between the treatment groups. However, patients with LVSI were more likely to have received adjuvant treatment rather than observation as compared to those without LVSI (59.8% vs. 44.7%, respectively; p=0.004), with the greatest difference being between the patients receiving adjuvant chemotherapy (41.4% vs. 33.0%, respectively; p=0.040).

In the patients who received adjuvant radiation, the majority of patients received external beam radiotherapy (EBRT) (83.9%), while only 32.5% of these patients received both EBRT and brachytherapy. Only 14.7% of patients received brachytherapy alone.

Multi-variable analyses of factors associated with adjuvant treatment modalities are shown in **Table 2**. Patients were more likely to be observed if their tumor size was <5 cm (p=0.017) and less likely to be observed if LVSI was present (p=0.010). Patients were more likely to receive chemotherapy if they were younger (p=0.010), and if they had LVSI (p=0.040), with a trend toward increased chemotherapy use in larger tumor sizes (p=0.051). A later period of diagnosis (2012-2014) (p=0.002) indicated less use of radiotherapy, while having private insurance indicated increase use of adjuvant radiation (p=0.039).

The median OS for the entire cohort was 62 months. Stratified by adjuvant treatment modality, the receipt of any adjuvant therapy had no effect on mortality as compared to observation (**Fig. 1**). The 3-year OS for observation was 73.7% (95% CI=0.66–1.98), chemotherapy was 71.3% (0.68–2.08), and radiation was 68.2% (0.81–2.97).

After adjusting for age, race, period of diagnosis, income, facility type, insurance provider, co-morbidity index score, tumor size, lymph node evaluation, performance of BSO, LVSI status, treatment modality, and stage, there was no association between treatment modality and survival (**Table 3**). There was an independent association between older age, tumor size

Table 2. Logistic regression models of factors associated with adjuvant treatment modalities-National Cancer Database: 2008–2014

Effect	Obs	p-value	CT	p-value	RT	p-value	CT + RT	p-value
Age at diagnosis (decades)	1.17 (0.98–1.39)	0.0912	0.78 (0.65–0.94)	0.0100	1.06 (0.82–1.36)	0.6655	0.80 (0.54–1.18)	0.252
Race								
White	Ref.		Ref.		Ref.		Ref.	
African-American	1.27 (0.87–1.85)	0.2111	0.79 (0.54–1.16)	0.2228	1.06 (0.63–1.78)	0.8180	1.09 (0.52–2.32)	0.813
Other/unknown	0.91 (0.49–1.67)	0.7606	1.23 (0.67–2.26)	0.5121	1.00 (0.41–2.40)	0.9925	1.43 (0.47–4.41)	0.529
Period of diagnosis								
2008–2011	Ref		Ref.		Ref.		Ref.	
2012–2014	1.25 (0.94–1.66)	0.1189	0.97 (0.73–1.29)	0.8377	0.51 (0.33–0.78)	0.0018	0.54 (0.29–1.00)	0.050
Income								
<$38,000	Ref.		Ref.		Ref.		Ref.	
$38,000–$47,999	1.17 (0.75–1.84)	0.4934	0.94 (0.60–1.48)	0.7817	0.63 (0.33–1.20)	0.1630	0.57 (0.21–1.51)	0.259
$48,000–$62,999	1.04 (0.66–1.62)	0.8736	0.86 (0.55–1.35)	0.5210	1.11 (0.62–2.01)	0.7195	0.82 (0.33–2.01)	0.659
$63,000+	1.35 (0.88–2.07)	0.1702	0.79 (0.51–1.22)	0.2842	0.92 (0.51–1.65)	0.7851	1.10 (0.48–2.52)	0.828
Facility type								
Community cancer program	Ref.		Ref.		Ref.		Ref.	
Academic/research program	0.99 (0.53–1.84)	0.9800	1.28 (0.67–2.45)	0.4507	0.50 (0.22–1.11)	0.0871	0.55 (0.17–1.83)	0.332
Comprehensive cancer program	0.84 (0.45–1.55)	0.5679	1.44 (0.76–2.75)	0.2652	0.66 (0.30–1.45)	0.3045	0.79 (0.25–2.50)	0.687
Integrated network cancer program	0.68 (0.34–1.38)	0.2890	1.61 (0.78–3.34)	0.2007	0.88 (0.36–2.15)	0.7790	1.12 (0.30–4.14)	0.868
Insurance								
Not insured	Ref.		Ref.		Ref.		Ref.	
Insurance status unknown	1.15 (0.33–4.00)	0.8239	0.78 (0.21–2.92)	0.7103	1.77 (0.45–6.97)	0.4172	2.75 (0.44–16.99)	0.277
Medicaid	0.86 (0.43–1.75)	0.6816	1.22 (0.60–2.46)	0.5844	0.65 (0.26–1.61)	0.3546	0.42 (0.10–1.84)	0.253
Medicare	1.60 (0.82–3.12)	0.1693	0.76 (0.39–1.51)	0.4410	0.49 (0.21–1.17)	0.1080	0.49 (0.13–1.82)	0.288
Other government	0.50 (0.08–3.10)	0.4574	0.83 (0.13–5.12)	0.8417	1.82 (0.27–12.07)	0.5368	0.00 (0.00–I)	0.990
Private insurance	1.11 (0.64–1.93)	0.7134	1.20 (0.69–2.10)	0.5160	0.48 (0.24–0.96)	0.0385	0.66 (0.25–1.76)	0.410
Charlson-Deyo score								
0	Ref.		Ref.		Ref.		Ref.	
1	1.06 (0.72–1.56)	0.7776	1.04 (0.70–1.55)	0.8353	0.94 (0.54–1.63)	0.8273	1.30 (0.60–2.82)	0.512
2+	1.84 (0.82–4.12)	0.1367	0.74 (0.33–1.69)	0.4747	0.58 (0.17–2.02)	0.3910	1.28 (0.28–5.90)	0.749
Tumor size (cm)								
<5	Ref.		Ref.		Ref.		Ref.	
>5	0.97 (0.95–0.99)	0.0167	1.02 (1.00–1.05)	0.0512	1.00 (0.97–1.03)	0.8906	0.97 (0.91–1.02)	0.199
Lymph node evaluation								
Performed	Ref.		Ref.		Ref.		Ref.	
Not performed	1.31 (0.98–1.75)	0.0700	0.78 (0.58–1.05)	0.1026	0.98 (0.65–1.47)	0.9158	1.10 (0.60–2.02)	0.755
BSO								
Not performed	Ref.		Ref.		Ref.		Ref.	
Performed	1.07 (0.66–1.74)	0.78	0.89 (0.55–1.45)	0.64	0.76 (0.39–1.48)	0.42	0.56 (0.24–1.34)	0.190
Unknown	0.91 (0.47–1.76)	0.77	1.14 (0.59–2.21)	0.69	0.75 (0.31–1.83)	0.53	0.73 (0.23–2.32)	0.590
Lymphovascular space invasion								
Not present	Ref.		Ref.		Ref.		Ref.	
Present	0.60 (0.41–0.89)	0.01	1.47 (1.01–2.16)	0.04	1.60 (0.96–2.68)	0.07	1.63 (0.78–3.41)	0.190
Unknown	1.19 (0.84–1.68)	0.33	0.73 (0.51–1.04)	0.08	1.32 (0.82–2.12)	0.26	1.03 (0.50–2.10)	0.940
Stage of disease								
Stage I	Ref.		Ref.		Ref.		Ref.	
Stage II	0.26 (0.15–0.45)	<0.0001	2.62 (1.61–4.27)	0.0001	2.95 (1.71–5.07)	<0.0001	3.58 (1.72–7.45)	<0.001

BSO, bilateral salpingoophorectomy; CT, chemotherapy; CT + RT= chemoradiation; Obs, observation; RT, radiation therapy.

>5 cm, and LVSI with worsened OS. The strongest predictor of mortality was the presence of LVSI. Medicare insurance status and omission of lymph node dissection was associated with improved survival. There was no patient sub-group for which adjuvant chemotherapy improved mortality as compared to observation (**Table 4**).
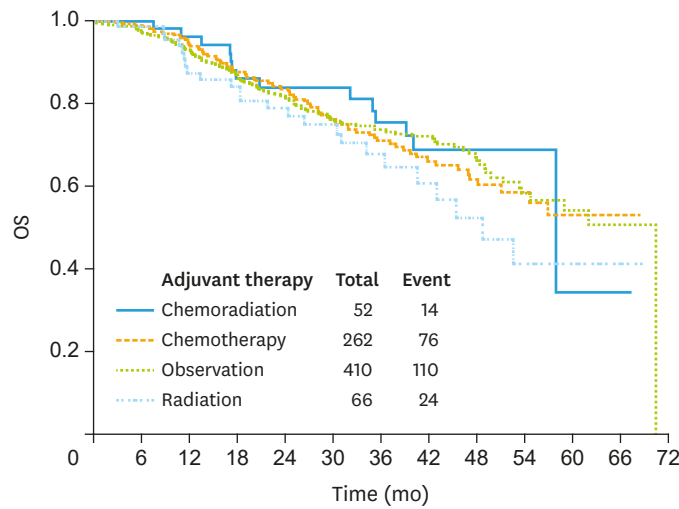
Fig. 1. Kaplan-Meier estimate of OS based on adjuvant therapy.
OS = overall survival.

DISCUSSION

This is the largest outcomes-based study of adjuvant therapy focused on women with early-stage uterine LMS and adds to the literature showing no association between adjuvant therapy and improved survival. The rarity of LMS precludes large institutional cohorts, however the NCDB provides multi-institutional data allowing for the study of a rare disease. Although a previously published NCDB study concerning LMS included early stage patients, our study expanded on this cohort specifically to identify trends in adjuvant therapy and clinico-pathologic factors that may identify a subset of patients for which adjuvant therapy would be beneficial [9]. In addition, this is the first study to demonstrate that LVSI in women with LMS is associated with a poorer prognosis.

Women with LMS have a poor prognosis, with a recurrence rate in early-stage disease of 40%–70% [15]. There have only been 2 randomized trials for early-stage uterine LMS regarding adjuvant therapy. In a prospective randomized trial performed by the EORTC, 99 patients with stage I and II sarcomas, including uterine LMS, were randomized to adjuvant pelvic radiation or observation [10]. They failed to show an improvement in local and distant recurrence rates as well as no improvement in OS. Our series also confirmed this finding, with a concomitant decrease in the use of radiotherapy following this publication. Although not significant, the women in our cohort who received adjuvant radiation alone had the poorest survival outcomes.

The only randomized study to investigate the efficacy of adjuvant chemotherapy by Omura and colleagues randomized stage I and II sarcomas to adjuvant adriamycin or observation [11]. For the 48 patients with LMS, the recurrence rate was 44% in the chemotherapy cohort versus 61% in the observation cohort and had no impact on progression free or OS. Phase II data evaluating gemcitabine and docetaxel showed median 3-year progression free survival rates of 57%–59% in stage I and II patients [12,13]; however, in an informal cross-trial comparison, similar survival outcomes were seen in women who were observed [10]. In a recent retrospective review by Littell et al. [16] evaluating stage I patients receiving adjuvant gemcitabine and docetaxel as compared to observation, they noted a 40% increase in the use

Table 3. Effect of various factors on mortality in patients with early stage leiomyosarcoma-National Cancer Database: 2008–2014

Parameter	HR	95% HR confidence limits		p-value
Age at diagnosis (decades)	1.355	1.121	1.638	0.002
Race				
White	Ref.			
African-American	1.470	0.994	2.174	0.053
Other	1.043	0.558	1.949	0.896
Period of diagnosis				
2008–2011	Ref.			
2012–2014	0.800	0.508	1.259	0.334
Income				
<$38,000	Ref.			
$38,000–$47,999	1.409	0.860	2.308	0.173
$48,000–$62,999	1.239	0.742	2.068	0.412
$63,000+	1.294	0.810	2.067	0.281
Facility type				
Community cancer program	Ref.			
Academic/research program	0.878	0.427	1.805	0.724
Comprehensive cancer program	0.803	0.390	1.654	0.551
Integrated network cancer	0.890	0.396	2.002	0.778
Insurance				
Not insured	Ref.			
Insurance status unknown	0.860	0.294	2.517	0.783
Medicaid	0.664	0.316	1.397	0.281
Medicare	0.496	0.258	0.951	0.035
Other government	1.770	0.483	6.493	0.389
Private insurance	0.701	0.417	1.181	0.182
Charlson-Deyo score				
0	Ref.			
1	0.870	0.574	1.317	0.511
2+	1.309	0.643	2.667	0.458
Tumor size (cm)	1.027	1.009	1.047	0.004
Lymph node evaluation				
Performed	Ref.			
Not performed	0.644	0.480	0.865	0.004
Adjuvant treatment				
Observation	Ref.			
Chemoradiation	0.729	0.402	1.323	0.299
Chemotherapy	0.856	0.600	1.223	0.394
Radiation	0.992	0.593	1.662	0.977
Stage of disease				
Stage I	Ref.			
Stage II	1.631	0.996	2.672	0.052
BSO (ovarian removal)				
Not performed	Ref.			
Performed	0.748	0.476	1.175	0.208
Unknown	0.861	0.459	1.613	0.640
Lymphovascular space invasion				
Not present	Ref.			
Present	1.738	1.176	2.569	0.006
Unknown	1.142	0.806	1.618	0.456

BSO, bilateral salpingoophorectomy; HR, hazard ratio.

of this regimen between 2009 and 2013, but no difference in 2 or 3-year disease free or OS. Our data corroborates that adjuvant treatment in women with early-stage uterine LMS does not confer a survival benefit.

Previously identified prognostic factors for uterine LMS include age, tumor size, grade, stage, and resection margins [6]. LVSI has been identified as an independent risk factor for nodal

Table 4. Multi-variable analysis of the impact of clinic-pathologic factors on mortality between adjuvant chemotherapy and observation

Subgroup	Adjuvant therapy	HR	95% HR confidence limits		p-value
Race: white	Observation	Ref.			
	Chemotherapy	1.0	0.7	1.4	0.990
Race: black	Observation	Ref.			
	Chemotherapy	1.1	0.5	2.1	0.860
Race: other	Observation	Ref.			
	Chemotherapy	1.6	0.4	5.8	0.470
Charlson-Deyo score: 0	Observation	Ref.			
	Chemotherapy	1.0	0.7	1.4	0.950
Charlson-Deyo score: 1	Observation	Ref.			
	Chemotherapy	1.1	0.5	2.5	0.790
Charlson-Deyo score: 2+	Observation	Ref.			
	Chemotherapy	2.2	0.6	8.0	0.220
Tumor size: <5 cm	Observation	Ref.			
	Chemotherapy	1.0	0.4	2.4	0.940
Tumor size: ≥ 5 cm	Observation	Ref.			
	Chemotherapy	0.8	0.6	1.1	0.230
Lymph node evaluation: not performed	Observation	Ref.			
	Chemotherapy	1.1	0.7	1.7	0.590
Lymph node evaluation: performed	Observation	Ref.			
	Chemotherapy	0.9	0.6	1.4	0.810
BSO (ovarian removal): not performed	Observation	Ref.			
	Chemotherapy	2.1	0.9	4.8	0.080
BSO (ovarian removal): performed	Observation	Ref.			
	Chemotherapy	1.0	0.7	1.4	0.910
LVSI: not present	Observation	Ref.			
	Chemotherapy	0.7	0.5	1.1	0.160
LVSI: present	Observation	Ref.			
	Chemotherapy	1.2	0.7	2.3	0.480

HR, hazard ratio; LVSI, lymphovascular space invasion.

disease and survival outcomes in endometrioid endometrial cancers [17], however, prior to our study, the significance in LMS was unknown. Our study population consisted of early-stage patients with either negative lymph nodes or did not have a lymphadenectomy, thus an assessment of the association between LVSI and nodal disease could not be performed. In node negative patients, LVSI was associated with increased mortality even though these patients were more likely to have received adjuvant chemotherapy. However, this increase use of chemotherapy in patients with LVSI did not translate into improved survival.

Approximately 40%–70% of patients with LMS express estrogen and/or progesterone receptors [18]. Small studies in the use of hormonal blockade have been performed and suggest that this can improve progression free survival, especially in patients with strong estrogen and progesterone receptor expression [19]. As a result, oophorectomy is often performed during surgery for LMS, despite a lack of evidence that it alters survival [7]. Although the mean age at diagnosis in our study was 55 years, our analysis adds to this literature that oophorectomy may be safely omitted for patients with early-stage LMS, especially in pre-menopausal women. However, with recent phase II data suggesting there may be a role for aromatase inhibitors in these early stage patients, counseling regarding oophorectomy for adjuvant treatment planning should be discussed [20].

A review of the literature demonstrates a low incidence of occult lymph node metastasis, with a reported rate between 5%–11% [7-9]. Omitting lymphadenectomy has not been associated with decreased survival [9]. Although difficult to interpret, as none of our patients had nodal disease, omission of lymph node evaluation was associated with improved survival.

Limitations of this study include its retrospective nature and the absence of data regarding specific chemotherapy regimens received during adjuvant treatment. Although we cannot make regimen-specific conclusions, especially adriamycin and the combination of gemcitabine and docetaxel, our data was collected after the only randomized trial with adriamycin and following phase II data, which led to the increased use of gemcitabine and docetaxel [11,12]. With evidence suggesting increased use of the doublet regimen without improvement in disease-free or OS, we feel confident that our results reflect the use of either of these regimens [16]. Coinciding with its retrospective nature, inherent biases include a provider's decision to adjuvantly treat a patient based on tumor size, age, or LVSI status. However, our data showed that among patients with larger tumor sizes (>5 cm), there was no difference in those observed versus treated adjuvantly (49% vs. 51%). This was similarly seen in patients with LVSI.

The poor prognosis of LMS, even in early-stage disease, with high recurrence rates provides a rationale for adjuvant therapy. However, this large retrospective study of women with early-stage uterine LMS indicates that adjuvant treatment, including chemotherapy, does not confer a survival benefit which is concordant with recent publications. In the recently revised National Comprehensive Cancer Network guidelines for management of uterine sarcomas, adjuvant chemotherapy is still listed as an option for the treatment of patients with stage I LMS [21]. In light of our findings, in addition to recent data, patients must be appropriately counseled regarding the lack of evidence to support adjuvant therapy in early stage disease. While an observational treatment strategy may be difficult to accept, administering chemotherapy in the adjuvant setting without evidence for improved survival may preclude the use of therapy to the recurrent setting. The rarity of LMS makes it a difficult disease to study and until we have data regarding newer agents, observation may be the best option for women with early stage disease.

REFERENCES

1. American Cancer Society. Cancer facts & figures 2018. Atlanta, GA: American Cancer Society; 2018.

2. Gadducci A, Landoni F, Sartori E, Zola P, Maggino T, Lissoni A, et al. Uterine leiomyosarcoma: analysis of treatment failures and survival. Gynecol Oncol 1996;62:25-32.
   PUBMED | CROSSREF

3. Dinh TA, Oliva EA, Fuller AF Jr, Lee H, Goodman A. The treatment of uterine leiomyosarcoma. Results from a 10-year experience (1990–1999) at the Massachusetts General Hospital. Gynecol Oncol 2004;92:648-52.
   PUBMED | CROSSREF

4. Wu TI, Chang TC, Hsueh S, Hsu KH, Chou HH, Huang HJ, et al. Prognostic factors and impact of adjuvant chemotherapy for uterine leiomyosarcoma. Gynecol Oncol 2006;100:166-72.
   PUBMED | CROSSREF

5. Leitao MM Jr, Zivanovic O, Chi DS, Hensley ML, O'Cearbhaill R, Soslow RA, et al. Surgical cytoreduction in patients with metastatic uterine leiomyosarcoma at the time of initial diagnosis. Gynecol Oncol 2012;125:409-13.
   PUBMED | CROSSREF

6. Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer 1993;71:1702-9.
   PUBMED | CROSSREF

7. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer 2008;112:820-30.
   PUBMED | CROSSREF

8. Giuntoli RL 2nd, Metzinger DS, DiMarco CS, Cha SS, Sloan JA, Keeney GL, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89:460-9.
   PUBMED | CROSSREF

9. Seagle BL, Sobecki-Rausch J, Strohl AE, Shilpi A, Grace A, Shahabi S. Prognosis and treatment of uterine leiomyosarcoma: a National Cancer Database study. Gynecol Oncol 2017;145:61-70.
PUBMED | CROSSREF

10. Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group study (protocol 55874). Eur J Cancer 2008;44:808-18.
PUBMED | CROSSREF

11. Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CE, Mangan C, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. J Clin Oncol 1985;3:1240-5.
PUBMED | CROSSREF

12. Hensley ML, Wathen JK, Maki RG, Araujo DM, Sutton G, Priebat DA, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer 2013;119:1555-61.
PUBMED | CROSSREF

13. Hensley ML, Enserro D, Hatcher H, Ottevanger PB, Krarup-Hansen A, Blay JY, et al. Adjuvant gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high-grade leiomyosarcoma: a phase III GOG study. J Clin Oncol 2018;36:5505.

14. Mancari R, Signorelli M, Gadducci A, Carinelli S, De Ponti E, Sesana S, et al. Adjuvant chemotherapy in stage I–II uterine leiomyosarcoma: a multicentric retrospective study of 140 patients. Gynecol Oncol 2014;133:531-6.
PUBMED | CROSSREF

15. Ricci S, Giuntoli RL 2nd, Eisenhauer E, Lopez MA, Krill L, Tanner EJ 3rd, et al. Does adjuvant chemotherapy improve survival for women with early-stage uterine leiomyosarcoma? Gynecol Oncol 2013;131:629-33.
PUBMED | CROSSREF

16. Littell RD, Tucker LY, Raine-Bennett T, Palen TE, Zaritsky E, Neugebauer R, et al. Adjuvant gemcitabine-docetaxel chemotherapy for stage I uterine leiomyosarcoma: trends and survival outcomes. Gynecol Oncol 2017;147:11-7.
PUBMED | CROSSREF

17. Guntupalli SR, Zighelboim I, Kizer NT, Zhang Q, Powell MA, Thaker PH, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol 2012;124:31-5.
PUBMED | CROSSREF

18. Leitao MM Jr, Hensley ML, Barakat RR, Aghajanian C, Gardner GJ, Jewell EL, et al. Immunohistochemical expression of estrogen and progesterone receptors and outcomes in patients with newly diagnosed uterine leiomyosarcoma. Gynecol Oncol 2012;124:558-62.
PUBMED | CROSSREF

19. George S, Feng Y, Manola J, Nucci MR, Butrynski JE, Morgan JA, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. Cancer 2014;120:738-43.
PUBMED | CROSSREF

20. Slomovitz BM, Taub MC, Huang M, Levenback C, Coleman RL. A randomized phase II study of letrozole vs. observation in patients with newly diagnosed uterine leiomyosarcoma (uLMS). Gynecol Oncol Rep 2018;27:1-4.
PUBMED | CROSSREF

21. National Comprehensive Cancer Network. Uterine neoplasms (version 1. 2018) [Internet]. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2018 [cited 2018 Mar 12]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.