Gynecologic Oncology 131 (2013) 629–633

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Does adjuvant chemotherapy improve survival for women with early-stage uterine leiomyosarcoma?☆

Stephanie Ricci [a], Robert L. Giuntoli II [a], Eric Eisenhauer [b], Micael A. Lopez [c], Lauren Krill [a], Edward J. Tanner III [a], Paola A. Gehrig [d], Laura J. Havrilesky [c], Angeles Alvarez Secord [c], Kimberly Levinson [a], Heidi Frasure [e], Paul Celano [f], Amanda Nickles Fader [a,*]

[a] Johns Hopkins Hospital, Baltimore, MD, USA
[b] Ohio State University Medical Center, Columbus, OH, USA
[c] Duke University Medical Center, Durham, NC, USA
[d] University of North Carolina, Chapel Hill, NC, USA
[e] University Hospitals, Case Western Reserve, Cleveland, OH, USA
[f] Greater Baltimore Medical Center, Baltimore, MD, USA

HIGHLIGHTS

- Leiomyosarcoma is an aggressive disease with a poor prognosis.
- High rates of distant failure argue for adjuvant systemic therapy.
- Extra-pelvic recurrences were significantly higher in the radiation subgroup.
- Recurrences were more successfully treated in the adjuvant chemotherapy group.
- Adjuvant chemotherapy was independently associated with overall survival.
- Pelvic radiation improves local pelvic control but does not improve survival.

ARTICLE INFO

Article history:
Received 31 July 2013
Accepted 30 August 2013
Available online 7 September 2013

Keywords:
Uterine leiomyosarcoma
Adjuvant therapy
Chemotherapy

ABSTRACT

Objectives. To examine whether adjuvant therapy after primary surgery for treatment of early-stage uterine leiomyosarcoma (LMS) improves recurrence and survival rates.

Methods. A multisite, retrospective study of women diagnosed with stage I–II high grade LMS from 1990–2010 was performed. All patients (pts) underwent primary surgery followed by observation (OBS), radiotherapy (RT), or chemotherapy (CT) postoperatively.

Results. One hundred eight patients were identified with long-term follow-up; 94 pts (87.0%) had stage I and 14 (13.0%) had stage II disease. The mean patient age was 55.4 years and mean BMI was 28.0. Thirty-four (31.5%) patients underwent OBS, 35 (32.4%) received RT, and 39 (36.1%) received chemotherapy. After a median follow-up of 41.8 months, a recurrence was diagnosed in 70.8%. Recurrence was evident in 25/34 (73.5%) OBS, 23/35 (65.7%) RT, and 28/39 (71.8%) of CT cohorts and was not different based on treatment ($p = 0.413$). However, extra-pelvic recurrences were significantly higher in the RT (95.2%) than in the OBS (60%) or CT (64.3%) cohorts ($p = 0.012$). Additionally, recurrences were more likely to be successfully treated or palliated in those who initially received CT ($p = 0.031$). On multivariate analysis, stage ($p < 0.001$) and chemotherapy ($p = 0.045$) were associated with overall survival.

Conclusions. Women with early-stage, high grade uterine LMS experience high recurrence rates and poor survival outcomes, irrespective of adjuvant therapy. These rates are higher than previously reported in the literature. Although women treated with CT had similar recurrence rates as those treated with OBS or RT, treatment with adjuvant chemotherapy may decrease the risk of extra-pelvic recurrence and improve survival.

Introduction

Uterine leiomyosarcoma is a rare malignancy that arises most commonly in the smooth muscle of the uterus. It accounts for approximately 2.0% of all uterine malignancies [1]. Compared with the more common

☆ This work was presented at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer in Los Angeles, California, March 8–12, 2013. There was no funding provided for this work.

* Corresponding author at: 600 N. Wolfe St, Phipps 287, Baltimore, MD 21287, USA. Fax: +1 443 849 2946.
E-mail address: afader1@jhmi.edu (A.N. Fader).

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.08.037

endometrioid endometrial carcinomas, uterine sarcomas behave more aggressively and are associated with a poorer prognosis. Uterine leiomyosarcoma is often detected at the time of hysterectomy and most women present with apparent early-stage, resectable disease. However, approximately 40% will have extra-uterine disease spread at the time of surgery [1]. Recurrence rates range from 53 to 71% for all stages and are often extra-pelvic, multisite and lethal [2–7]. Recurrence and prognosis are ultimately dependent upon the mitotic activity, or grade, of the tumor and the stage at presentation.

The high rate of distant failure, even in the setting of early-stage disease, provides the rationale for consideration of adjuvant systemic therapy [2]. However, the role of adjuvant therapy in completely resected, uterine-limited leiomyosarcoma is unclear. Radiation therapy appears to improve local control for women with stage I disease, however, it has failed to improve overall survival due to high rates of distant metastasis [7,8]. 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 ($p = 0.004$) but no effect on survival with radiotherapy [8]. Although this study suggested that primary radiation may have limited utility in this setting, it was not powered to detect differences in survival in women with leiomyosarcoma, given that all uterine sarcoma types and even those diagnosed with carcinosarcoma were allowed on the trial.

Despite the absence of data from randomized controlled trials, post operative chemotherapy is commonly considered for women with stage I–IV uterine leiomyosarcoma. Gemcitabine and docetaxel remain the standard-of-care for the treatment of recurrent or metastatic leiomyosarcoma and also show promise in the adjuvant setting [12,16]. Doxorubicin and ifosfamide have also demonstrated activity against this disease [9,15]. However, the utility of chemotherapy for women with primary, early-stage uterine leiomyosarcoma remains uncertain. We endeavored to investigate the impact of chemotherapy compared to other therapies in a large cohort of women with early-stage uterine leiomyosarcoma. Our study objective was to determine whether the addition of adjuvant chemotherapy (with an emphasis on gemcitabine/docetaxel) after primary surgery for treatment of early-stage uterine leiomyosarcoma improves recurrence and survival rates compared to adjuvant radiation or observation after surgery.

Materials and methods

An institutional review board-approved, multisite, retrospective study of women diagnosed with stage I–II high grade uterine leiomyosarcoma from 1990–2010 was performed. Participating academic institutions were all comprehensive cancer centers and included: Greater Baltimore Medical Center, Baltimore, MD; Johns Hopkins Hospital, Baltimore, MD; The Ohio State University Medical Center, Columbus, OH; University of North Carolina at Chapel Hill, Chapel Hill, NC; and Duke University Medical Center, Durham, NC.

Uterine leiomyosarcoma cases were identified from institutional tumor registries and pathology databases. High grade disease was defined by the Stanford criteria [13]. All patients with a known diagnosis of cancer preoperatively had imaging of the chest/abdomen/pelvis with computed tomography prior to surgery and did not have evidence of disease outside of the uterus. Primary surgery which included hysterectomy, bilateral salpingo-oophorectomy +/− lymphadenectomy, followed by 1) observation post operatively (OBS), 2) adjuvant pelvic radiotherapy (RT), or 3) chemotherapy (CT). Radiation regimens included whole pelvic radiation (WPRT: 45.0–54.0 Gy) or a combination of WPRT and brachytherapy. Chemotherapy regimens included gemcitabine/docetaxel, ifosfamide/cisplatin/mesna, doxorubicin/ifosfamide, doxorubicin alone, ifosfamide alone and topotecan alone. Medical records were reviewed for relevant demographic factors such as age at diagnosis, ethnicity, stage, histologic grade, post-operative adjuvant treatment modality, progression-free (PFS) and overall survival outcomes (OS). Given that most cases were diagnosed before 2009, stage was determined according to 1988 FIGO criteria. A minimum of two years follow-up time was required and only high grade uterine leiomyosarcomas were included in the analysis, as reviewed by a gynecologic pathologist at each participating center.

Statistical analysis

Descriptive data for demographics, tumor and treatment characteristics were compared between those patients who were observed after surgery versus those treated with adjuvant radiation or chemotherapy. Statistical tests included chi-square test, Fisher's exact test or one-way ANOVA. One-way ANOVA (or Kruskal–Wallis test for nonparametric variables) was used for continuous clinical variables to compare central tendencies of the variables between groups. For categorical clinical variables and treatment strategies, the Pearson's chi-square test was utilized to compare for equal proportions in each treatment group. An analysis of success of treatment after recurrence, or "salvage/palliation" was also performed. We defined "salvage/palliation" as a partial or complete response for ≥6 months after treatment for recurrence.

PFS and OS curves were estimated using the Kaplan–Meier method and compared via the log-rank test. PFS was calculated from the date of primary surgery to the date of last follow-up, disease progression or death. OS time was calculated from the date of primary surgery to the date of last follow-up visit or death. Data concerning patients without disease progression, or death, at last follow-up were censored. The Cox proportional hazards regression model was employed for multivariate analysis. We controlled for age, stage, adjuvant therapies, nodal involvement and tumor size. All statistical tests were performed using SPSS version 19.0 (Chicago, IL) software; and a two-tailed P value < .05 was considered statistically significant (Fig. 1).

Results

We identified 108 women with stage I or II uterine leiomyosarcoma and long-term follow-up. The clinical and demographic characteristics of the cohort are presented in Table 1. Ninety-four patients (87.0%) had stage I disease and 14 (13.0%) had stage II disease. The mean patient age was 55.4 (SD = 12.5) years and mean BMI was 28.1 (SD = 6.0).

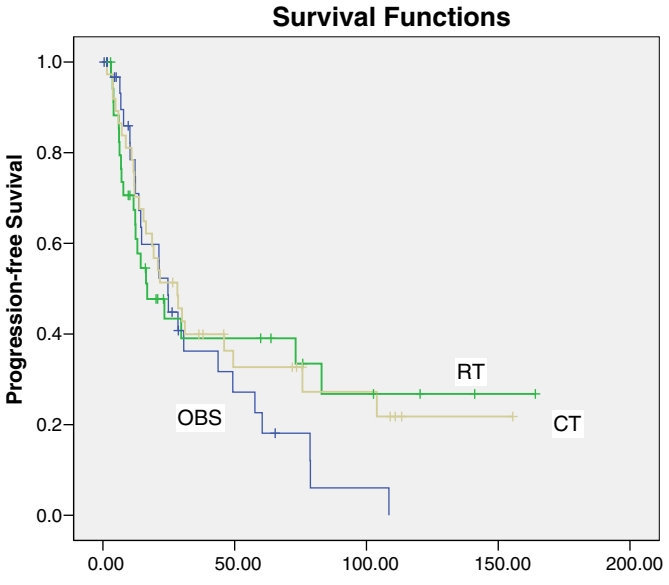

Fig. 1. PFS by adjuvant treatment ($p = 0.586$).