Gynecologic Oncology 133 (2014) 531–536

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Adjuvant chemotherapy in stage I–II uterine leiomyosarcoma: A multicentric retrospective study of 140 patients

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HIGHLIGHTS

- This is a retrospective analysis on adjuvant treatments of early stage uterine leiomyosarcoma.
- Adjuvant chemotherapy does not improve disease-free and overall survival compared to observation.
- Mitotic index and age resulted to be the most significant prognostic factors.

ARTICLE INFO

Article history:
Received 14 January 2014
Accepted 1 March 2014
Available online 11 March 2014

Keywords:
Uterine leiomyosarcoma
Adjuvant therapy
Chemotherapy
Prognostic factors

ABSTRACT

Objective. About 50–60% of patients with stage I–II uterine leiomyosarcoma (ULMS), primarily treated with surgery, relapse and die from progressive disease. In this retrospective study we describe the impact of adjuvant chemotherapy in this subset of patients.

Methods. 140 women treated from 1976 to 2011 were included in the study. Univariate and multivariate analysis were used to test the association of clinical features and adjuvant treatments with overall survival (OS) and disease-free survival (DFS).

Results. 62 women did not receive any further treatment after hysterectomy, 14 had radiotherapy (RT), 52 chemotherapy and 12 chemo-radiotherapy. Chemotherapy based on doxorubicin and ifosfamide combination was used in 54 cases. After a median follow-up of 63 months, 87 women (62%) have relapsed, and 62 (44%) have died. The vast majority of patients who relapsed had distant recurrences (72%).
The 5 year median DFS and OS were 43% and 64% respectively. After 5 years of follow up 68.7% of women treated with chemotherapy (±RT) vs 65.6% of patients only observed were alive ($p = 0.521$). In the univariate analysis no factors had a statistical impact on DFS, while number of mitosis (>20 × 10HPF), age (>60 years) and adjuvant radiotherapy were found as negative prognostic factors for OS. In the multivariate analysis only mitosis and age remained significant for OS.

Conclusion. Adjuvant chemotherapy was not associated with a significant survival benefit and should not be considered as standard of care for patients with stage I–II ULMS until randomized clinical studies will give further information.

Introduction

Uterine leiomyosarcoma (ULMS) is a rare uterine malignancy, with an annual incidence of 0.64 per 100,000 women, accounting for 1.5–3% of all uterine malignancies and approximately for 40% of all uterine sarcomas [1–4]. ULMS present high malignant potential with 5-year overall survival rates ranging between 10% and 73% [5,6]. Clinically important prognostic factors include age, tumor size, mitotic count and stage [7–10].

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http://dx.doi.org/10.1016/j.ygyno.2014.03.001
0090-8258/

The therapy of choice in high grade stage I–II LMS is surgery [11]. Although apparently limited to the uterus, ULMSs relapse in 45%–80% of cases [8,12,13] with lungs, abdominal cavity and liver being the most common site of recurrence.

The role of adjuvant treatment for LMS limited to the uterus remains undefined.

Current staging systems fail to identify patients at higher risk for relapse and death, and thus it is complicated to select patients who could potentially benefit from adjuvant therapies [14]. The role of adjuvant radiotherapy has been investigated by the EORTC trial that demonstrated that external beam radiotherapy was not associated with improved survival for the subgroup of patients with ULMS [15].

Studies on adjuvant chemotherapy have shown controversial results in uterine sarcomas [16,17]; Omura and colleagues did not show any difference in progression-free interval or survival in patients with stage I or II uterine sarcomas, when randomly assigned to adjuvant chemotherapy with doxorubicin for six courses or no further treatment [18]. However, there is no available randomized clinical trial comparing chemotherapy with no immediate treatment specific for LMS confined to the uterus.

The aim of our study is to retrospectively analyze the outcome of stage I–II ULMS, treated with surgery at three centers, and followed by adjuvant treatment (chemotherapy and/or radiotherapy) or observation only.

Materials and methods

All patients with histologically proven ULMS, FIGO stages I and II, treated from January 1976 to December 2011, at the Departments of Gynaecologic Oncology of the European Institute of Oncology (Milan), the Department of Obstetrics and Gynecology of San Gerardo Hospital, Monza, University of Milan-Bicocca and the Department of Clinical and Experimental Medicine, University of Pisa, were included in this analysis.

Only pathologically confirmed high-grade ULMS, according to the Stanford criteria – including coagulative tumor cell necrosis, more than 5 mitoses per 10 HPF, and significant cytological atypia) [19] – were included. All slides were reviewed by a dedicated experienced pathologist at each center. Demographic and clinical data were collected from patient charts and medical notes.

All patients were staged according to the 1998 International Federation of Gynaecology and Obstetrics (FIGO) staging system for endometrial cancer, or modified FIGO staging system, specifically selecting patients with disease confined to the uterus.

The standard surgical procedure consisted of peritoneal cytology, total abdominal hysterectomy, with or without bilateral salpingo-oophorectomy. Lymphadenectomy, omentectomy and peritoneal biopsies were performed optionally. Patients were proposed to receive chemotherapy, radiotherapy or observation only, according to clinician's decision. The antineoplastic agents and schedule have been chosen by physicians according to the historical period, performance status and age of the patients. The technique for radiotherapy was either a three or a four-field pelvic brick or box technique with parallel opposed pair radiation fields.

After the surgical treatment and optional adjuvant treatments, all patients were followed with gynecologic visit every 3 months during the first two years, then every 6 months. Chest X-ray and pelvic and abdominal ultrasound examination and/or chest-abdominal and pelvic CT scan were performed annually. The consultation of clinical data was authorized by the institutional review board of the three institutions.

Statistical analysis

Absolute and percentage frequencies were used to describe patients' population. Survival curves were built using the Kaplan–Meier method in which Disease-Free Survival (DFS) was defined as the time from diagnosis to the earliest occurrence of relapse or death from any cause, while overall survival (OS) was defined as the time from diagnosis to death from tumor progression or death from any cause. Student's *t*-test, Kruskal Wallis sum rank test and rank test for equality of survivor function were used to analyze the differences between treatment groups of patients. Univariate logistic regression model was used to estimate the odds ratios and the p-values for association between outcomes (death and relapse) and clinical and histopathological parameters.

Stata software 9.0 (Stata Corporation, College Station, Texas, USA) was used for performing statistical analysis and a p-value <0.05 was deemed as statistical significance.

Results

A total of 140 patients were included in this study. The mean age was 51.3 ± 9.6 (range 20.6–74.1). Patient characteristics are described in Table 1.

The vast majority of women had tumor stage I, tumor size larger than 5 cm. Half of the women had tumors with more than 20 mitosis $\times$ 10HPF.

All patients received total hysterectomy, in five cases following previous myomectomy, for suspicious benign disease. Nine patients received pelvic lymphadenectomy and one patient omentectomy. Bilateral salpingo-oophorectomy was performed in 131 patients (93.5%).

The median dose of radiotherapy in 26 patients was 50.4 Gy (range 45–50.4). The radiation dose was delivered daily, with 1.80 Gy per fraction. No patients received brachytherapy on the vaginal vault.

Chemotherapy consisted of a combination of doxorubicin and ifosfamide in 54 cases (Ifosfamide 2 g/m^2/day, days 1–5 and Mesna 2 g/m^2/day, in association with doxorubicin 25 mg/m^2/day, days 1–3 every 21 days, with G-CSF support), gemcitabine and docetaxel in 4 cases (gemcitabine 900 mg/m^2 on days 1 and 8, followed by docetaxel 75 mg/m^2 on day 8); one woman received single agent chemotherapy with doxorubicin, two women were treated with doxorubicin and dacarbazine and two with a combination of platinum, epirubicin and ifosfamide. In one case the chemotherapy regimen was not recorded. The median number of cycles was 4 (range 2–6).

After a median follow up of 63 months, 87 patients have relapsed and 62 have died of progressive disease. The overall median DFS at 3 and 5 years are 49% and 43% respectively and the median OS at 3 and 5 years are 70% and 64% respectively.

Table 2 reports the sites of recurrence according to the primary treatment after surgery. Almost 72% of patients who relapsed had distant with or without concomitant locoregional recurrences. Adjuvant

Table 1
Clinical and histopathological characteristics.

	Overall population (n = 140)	Percentage frequencies
Patients median age (range)	51	21–74
Stage		
• I	125	(89.3%)
• II	15	(10.7%)
Tumor size		
• <5 cm	10	(7.1%)
• >5 cm	68	(48.6%)
• Missing data	62	(44.3%)
No. of mitosis		
• <20	63	(45.0%)
• >20	62	(44.3%)
• Missing data	15	(10.8%)
Post surgical treatment		
• Observation	62	(44.3%)
• EBRT	14	(10.0%)
• Chemo	52	(37.1%)
• Chemo-EBRT	12	(8.6%)