Original Article

Outcome and prognostic factors in 110 consecutive patients with primary uterine leiomyosarcoma: A Rare Cancer Network study

Alessandra Franzetti Pellanda[1,2*], Berardino De Bari[1,3*], Elisabeth Deniaud-Alexandre[4,5], Marco Krengli[6], Paul Van Houtte[7], Antonella Richetti[8,9], Salvador Villà[10], Hadassah Goldberg[11], Ewa Szutowicz-Zielińska[12], Michel Bolla[13], Heidi Rutten[14], Marc Van Eijkeren[15], Philip Poortmans[14,16], Guido Henke[17], Yavuz Anacak[18], Steve Chan[19], Christine Landmann[20†], Carine Kirkove[21], Luciano Scandolaro[22], Jacques Bernier[23,24], René-Olivier Mirimanoff[1], Mahmut Ozsahin[1**]**

[1]Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland; [2]Clinica Luganese Moncucco, 6903 Lugano, Switzerland; [3]Centre Hospitalier Régional Universitaire "Jean Minjoz", INSERM, UMR1098, 25030 Besançon, France; [4]Hôpital Tenon, 75970 Paris, France; [5]Centre Hospitalier Départemental, 85925 Vendee, France; [6]Università degli Studi del Piemonte Orientale e Ospedale Maggiore della Carità, 28100 Novara, Italy; [7]Institut Jules Bordet, 1000 Brussels, Belgium; [8]Ospedale di Circolo, 21100 Varese, Italy; [9]Istituto Oncologico della Svizzera Italiana, EOC, 6500 Bellinzona, Switzerland; [10]Catalan Institute of Oncology, Universitat Autònoma de Barcelona, 08916 Barcelona 08916, Spain; [11]Rambam Medical Center, 31096 Haifa, Israel; [12]Medical University, 80210 Gdansk, Poland; [13]Hôpital Michallon, BP217, 38043, Grenoble cedex 09, France; [14]Radboud University Medical Center, 6525 Nijmegen, The Netherlands; [15]Ghent University Hospital, 9000 Gent, Belgium; [16]Institute Verbeeten, 90120 Tilburg, The Netherlands; [17]Kantonsspital St. Gallen, 9007, St. Gallen, Switzerland; [18]Karadeniz Technical University, 61080 Trabzon, Turkey; [19]Nottingham University Hospital, NHS trust, NG5 1PB Nottingham, United Kingdom; [20]Kantonsspital Basel, 4031 Basel, Switzerland; [21]UCL St. Luc, 1200 Brussels, Belgium; [22]Presidio Ospedaliero Sant'Anna, 22100 Como, Italy; [23]Ospedale San Giovanni, 6500 Bellinzona, Switzerland; [24]Clinique de Genolier, Genolier, 1272 Switzerland

*These authors equally contributed as a first author.

**These authors equally contributed as a senior author.

†Deceased.

Correspondence to: Prof. Mahmut Ozsahin, MD, PhD. Department of Radiation Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Switzerland. Email: mahmut.ozsahin@chuv.ch.

Abstract

Objective: Primary uterine leiomyosarcomas (ULMS) are rare, and the optimal treatment is controversial. We aimed to assess the outcome and prognostic factors in a multicenter population of women treated for primary ULMS.

Methods: We retrospectively collected data of 110 women treated in 19 institutions of the Rare Cancer Network (RCN). Inclusion criteria consisted of a pathology report confirming the diagnosis of ULMS, aged 18–80 years, complete International Federation of Gynecology and Obstetrics (FIGO) stage information, complete information on treatment, and a minimum follow-up of 6 months. Local control (LC) and locoregional control (LRC), overall survival (OS) and disease-free survival (DFS) rates were computed using the Kaplan-Meier method. Univariate analysis was implemented using the log rank test, and multivariate analysis using the Cox model.

Results: All patients underwent surgery. Seventy-five patients (68%) received adjuvant radiotherapy (RT), including brachytherapy in 18 (16%). Seventeen patients (15%) received adjuvant chemotherapy. Median follow-up was 58 (range, 6–240) months. Five-year OS and DFS rates were 50% and 34%, and LC and LRC rates were 88% and 72%, respectively. On multivariate analysis, independent favorable prognostic factors were younger age, FIGO stage I, small tumor size, previous uterine disease, and no vascular invasion for OS and DFS. FIGO stage was the only favorable factor influencing LRC. Adjuvant local or systemic treatments did not improve the outcomes. Eight patients treated with RT presented a grade 3 acute toxicity, and only one patient with grade 3 late toxicity.

Conclusions: In this large population of primary ULMS patients, we found good results in terms of LC and LRC. Nevertheless, OS remains poor, mainly due to the occurrence of distant metastases. An early diagnosis seemed to improve the prognosis of the patients. Adjuvant local or systemic treatments, or more aggressive surgical

procedures such as the Wertheim procedure, did not seem to impact the outcome.

Keywords: Uterine leiomyosarcoma; prognostic factors; radiotherapy; overall survival; local control

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Introduction

Uterine sarcomas are rare, and account for approximately 2%–6% of all malignant uterine tumors (1). Histologic classification of these neoplasms is based on the differentiation and/or growth pattern of the neoplastic cells and their presumed cell of origin. Primary uterine leiomyosarcoma (ULMS) is a rare type of cancer with a definite pathological identity amongst the different categories of uterine sarcoma. ULMS arises from the myometrial muscle, has a peak incidence occurring at the age of 50, and accounts for 30% of all uterine sarcoma (1). Looking at the prognostic factors, some investigators found the tumor size to be the most important prognostic factor, for patients with a tumor diameter larger than 5 cm presenting a poorer prognosis (2). However, a Gynecologic Oncology Group (GOG) study did not confirm these data, as in this study; only the mitotic index was the factor significantly related to progression-free interval (3). In a study by Oláh *et al.* (4), ULMS, matched for other known prognostic factors, presented a more aggressive behavior when compared to their carcinosarcoma counterparts. In most studies, the number of ULMS was low: in the study by the GOG, only 59 patients with ULMS were collected over a period of 9 years (3). Evans *et al.* (2) collected only 37 ULMS patients amongst all the patients who received a diagnosis of any type of uterine smooth muscle neoplasm diagnosed before 1977 at the University of Texas, M. D. Anderson Hospital. In the study by Oláh *et al.* (4), the data were obtained from the West Midlands Regional Cancer Registry, serving a catchment area of 2.6 million women. A total of 367 patients with a diagnosis of uterine sarcoma were identified, and included both ULMS and mixed mesodermal tumors (MMT). In a recent study by Davidson *et al.* (5), a total of 137 patients with ULMS were identified amongst a population of 294 patients diagnosed with uterine sarcoma in Norway from 1970 to 2000.

Due to its rare incidence, it is difficult to collect a sufficiently high number of patients to derive strong conclusions about the prognostic factors and the outcomes of patients affected by ULMS. The majority of recently published series dealing with uterine sarcoma not only report on small numbers of patients, but often do mix different subgroups such as carcinosarcomas, ULMS, and sarcomas arising in the endometrial stroma (5-9). One of the largest populations of ULMS patients from a single institution was published by Giuntoli *et al.* (10), in 2003; the authors have reported data on 208 patients collected at the Mayo Clinic over a period of 30 years.

The aim of the Rare Cancer Network (RCN, www.rarecancer.net), a multi-institutional international group, is to conduct retrospective studies in collecting data on rare forms of cancers (11). In this regard, the RCN launched a study aiming at identifying the outcomes and numerous potential prognostic factors in a population of patients affected by ULMS, most of them treated with surgery and adjuvant radiotherapy (RT). In this article, the results enrolling 110 patients from 19 RCN institutions are reported.

Materials and methods

Patient selection

One hundred and twenty-six consecutive patients treated between 1980 and 2000 in 19 member institutions of the RCN were collected in this retrospective study. All investigators obtained their own Institutional Review Board (IRB) approval for patient's data collection.

Inclusion criteria consisted of a pathology report confirming the diagnosis of ULMS, patient aged 18–80 years, International Federation of Gynecology and Obstetrics (FIGO) staging assessment, complete information on treatment, and a minimum follow-up period of 6 months. All pathological reports and the staging assessments were centrally reviewed. Among the 126 cases received, 110 matched these criteria and were included in the analysis: there were 23 patients from France (2 centers), 20 from Italy (3 centers), 18 from Belgium (3 centers), 11 from the Netherlands (2 centers), 10 from Switzerland (4

centers), 8 from Spain (1 center), 7 from Israel (1 center), 7 from Poland (1 center), 3 from United Kingdom (1 center), and 3 from Turkey (1 center). The exclusion criteria for 16 women consisted of uterine sarcoma other than ULMS (n=4), or incomplete information on staging and treatment (n=12).

Staging procedures

Initial staging was performed by local and systemic investigations. Concerning local investigations, all patients received a full pelvic examination. Pelvic ultrasound was performed in 50 patients (45%), pelvic computed tomography (CT)-scan in 26 (24%), hysteroscopy in 8 (7%), laparotomy in 3 (3%), and pelvic magnetic resonance imaging (MRI) in 2 (2%). For the remaining patients, no further data were available about local investigation procedures. Systemic investigations were performed by abdominal ultrasound in 21 patients (19%), thoracic CT-scan and/or chest X-ray in 91 (83%), urography in 2 (2%), and rectoscopy in 2 (2%). For the remaining patients, no further data were available about systemic investigation procedures.

Follow-up

The median follow-up was calculated adopting the method described by Schemper *et al.* (12). Follow-up methods consisted of last clinical visit when available, or telephone call to either the patient or her general practitioner. Death certificates were obtained for deceased patients.

Statistical analysis

Means were compared by Student's *t*-test, and 95% confidence intervals (95% CI) were calculated from standard errors. Proportions were compared using the Chi-square test for values greater than 5, and Fisher's exact test for those less than or equal to 5. Kaplan-Meier product-limit estimates were used to evaluate the overall survival (OS), disease-free survival (DFS), local control (LC), locoregional control (LRC), and distant metastases-free survival (13). Time to any event was measured from the date of surgery. The events were all causes of death for OS, relapse or all causes of death for DFS, and local or locoregional relapse for LC and LRC, respectively. For distant metastases-free survival, the events included distant metastasis or all causes of death. Patients without any of the above-mentioned events were censored at their last follow-up. No patient was lost to follow-up (minimum follow-up period of 6 months). Information pertaining to the cause of death was always obtained from the clinical records and/or death certificates. No autopsies were carried out. Differences between groups were assessed using the log rank test. $P<0.05$ was considered statistically significant. Multivariate analysis was carried out using the Cox stepwise regression analysis to determine the independent contribution of each prognostic factor (14). Prognostic factors with a P-value less than 0.20 in univariate analysis were included in multivariate analysis. *Table 1* summarizes

Table 1 Factors explored in univariate analysis

Endpoints	Variables
OS, DFS, LRC	Adjuvant RT (yes *vs.* no)
	Adjuvant RT (EBRT *vs.* EBRT+BRT)
	FIGO stage (I *vs.* others)
	FIGO stage (I *vs.* II *vs.* III *vs.* IV)
	Type of surgery (TAH±BSO *vs.* Wertheim)
	Grading (grade 1 *vs.* other)
	Grading (grade 1 *vs.* 2 *vs.* 3 *vs.* unknown)
	Number of mitoses/field (<5 *vs.* 5–9 *vs.* ≥10 *vs.* unknown)
	Vascular invasion (yes *vs.* no)
	Necrosis in the surgical specimen (yes *vs.* no or unknown)
	Median age (<54 years old *vs.* ≥54 years old)
	PUD (yes *vs.* no)
	Delivery (yes *vs.* no)
	Previous cancer (yes *vs.* no)
	Previous surgery on the uterus for any reason (yes *vs.* no)
	Adjuvant chemotherapy (yes *vs.* no)
	Tumor size (≤8 cm *vs.* >8 cm)
	Tumor size (known *vs.* unknown)
	Pregnancy (yes *vs.* no)
	Family history for ULMS (yes *vs.* no)
	Hormonal treatment (yes *vs.* no)
	Symptoms at diagnosis (yes *vs.* no)
	Site of the tumor (body *vs.* others)
	Acute toxicity (yes *vs.* no)
	Late toxicity (yes *vs.* no)

OS, overall survival; DFS, disease-free survival; LRC, locoregional control; RT, radiotherapy; EBRT, external beam radiotherapy; BRT, brachytherapy; FIGO, International Federation of Gynecology and Obstetrics; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PUD, previous uterine disease; ULMS, uterine leiomyosarcoma.

the prognostic factors that have been studied in the univariate and multivariate analyses.

Results

Tables 2 and *3* summarize the data of the 110 patients enrolled in this analysis in terms of baseline characteristics (*Table 2*) and treatment (*Table 3*). Details on both full history and physical examination were available for 90 patients (82%). Twenty-three patients had no symptoms reported, and the diagnosis was made during a routine gynecological examination, while 87 patients presented at least one symptom. Median age was 54 (range, 19–77) years. Five patients presented a previous oncological history, including 3 breast cancer, 1 melanoma and 1 osteosarcoma, all of whom treated with curative intent. Fourteen women had a past medical history of benign uterine disease, twelve of them having undergone uterine surgery. Seventy-three women (66%) presented a previous history of pregnancy. In only 11 patients (10%), a previous hormonal treatment was reported. All patients underwent surgery as initial treatment. Seventy-five patients received adjuvant RT with different technologies (Linac, Co-60, Betatron, Neutron), 18 of whom had a combination of external-beam radiotherapy (EBRT) and brachytherapy (BRT). Five women underwent a focal treatment with palliative intent at the time of locoregional recurrence or distant metastasis. No data on the planned RT were available for the patients treated with a palliative intent.

Systemic chemotherapy was delivered to 22 patients: 17 received it after RT with curative intent, whereas 5 patients who presented with a metastatic disease at diagnosis underwent chemotherapy before a palliative RT. The majority of patients received a combination of 2 or 3 drugs amongst the following: doxorubicine, epirubicine, ifosphamide, vincristine, or etoposide. One patient received two cycles of paclitaxel as a single drug.

Survival

After a median follow-up period of 58 (range, 6–240) months, the 5-year OS (*Figure 1A*) and DFS (*Figure 1B*) were 50% (95% CI: 49%–61%) and 34% (95% CI: 24%–44%), respectively.

Patterns of failure

Local and locoregional failure

Four patients presented a local relapse, 16 patients a

Table 2 Baseline characteristics of patients enrolled in the study (N=110)

Variables	n	%
Age (year) [median (range)]	54	19–77
Symptoms at diagnosis*		
No symptoms	23	21
Metrorrhagia	65	59
Abdominal pain	32	29
Dysuria	9	8
Constipation	3	3
Hematuria and rectal bleeding	1	1
FIGO stage**		
Stage I	80	73
Stage II	10	9
Stage III	9	8
Stage IVA	7	6
Stage IVB	4	4
Pathological nodal status		
pN0	82	75
pN+	3	3
pNx	25	23
Grading***		
Grade 1	16	15
Grade 2	9	8
Grade 3	24	22
Not available	61	55
Localization in the uterus		
Corpus	89	81
Isthmus cervix	8	7
Fundus	9	8
Not available	4	4
Gynecological history		
PUD		
Yes	14	13
No	96	87
Pregnancy		
Yes	73	66
No	37	34
Previous hormonal therapy		
Yes	11	10
No	87	79
Not available	12	11

FIGO, International Federation of Gynecology and Obstetrics; PUD, previous uterine disease; *, Some of the patients presented more than one of the reported symptoms; **, Almost always postoperative staging, except for IVB patients; ***, Evaluated on the surgical specimen report, or on the biopsy.

Table 3 Treatment details (N=110)

Variables	n	%
Surgery		
Surgical technique		
TAH+BSO	82	75
Simple abdominal hysterectomy (TAH)	10	9
Wertheim surgery	17	15
Vaginal hysterectomy	1	1
Lymphadenectomy		
Yes	85	77
No	25	23
RT		
No RT	35	32
EBRT	57	52
EBRT+BRT	18	16
Irradiation equipment		
Linear accelerator	68	91 (of irradiated patients)
Cobalt	4	5 (of irradiated patients)
Neutron	2	3 (of irradiated patients)
Betatron	1	1 (of irradiated patients)
Volumes		
Whole pelvic irradiation	74	99 (of irradiated patients)
Whole pelvic and abdominal irradiation	1	1 (of irradiated patients)
Delivered dose (Gy) [median (range)]	48.6	40.0–66.6
Fraction No. [median (range)]	25	20–40
Energy (MV) [median (range)]	16	1–45
Chemotherapy		
No chemotherapy	88	80
Systemic chemotherapy before RT	5	5
Adjuvant chemotherapy after RT	17	15
Cycle No. [median (range)]	4	2–6

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RT, radiotherapy; EBRT, external beam RT; BRT, brachytherapy.

regional nodal relapse, and 6 patients a local and regional nodal failure. The 5-year LC (*Figure 1C*) and LRC (*Figure 1D*) were 88% (95% CI: 81%–95%) and 72% (95% CI: 62%–82%), respectively.

Systemic relapse

Altogether, 55 patients presented a systemic relapse. The 5-year distant metastases-free survival was 42% (95% CI: 31%–53%). The sites of failure were lung (n=43), liver (n=17), bone (n=15), brain (n=8), and the retroperitoneal lymph nodes (n=7). Of the 55 patients who had a systemic relapse, 9 (16%) had previously received adjuvant chemotherapy, whereas for the 55 patients without distant metastasis, 13 (24%) were given adjuvant chemotherapy. The risk of systemic relapse was not statistically different between the groups of locally relapsing and not relapsing patients (P=0.340).

Prognostic factors

In univariate analysis (*Table 4*), age <54 years, previous uterine disease (PUD), grade 1 (*vs.* others), FIGO stage (I *vs.* others, and FIGO I *vs.* II *vs.* III *vs.* IV), tumor size

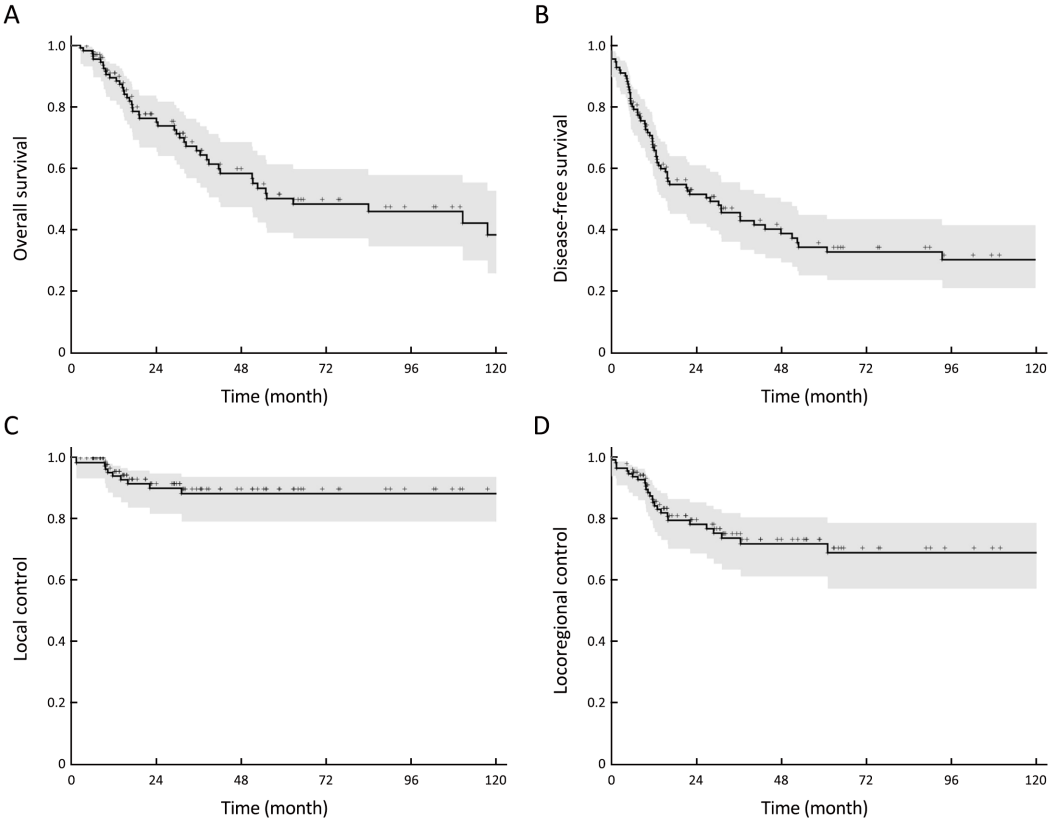

Figure 1 Overall survival (A), disease-free survival (B), local control (C) and locoregional control (D) in 110 patients with uterine leiomyosarcoma (ULMS). Censored patients are shown with the "+" sign, and shaded areas represent 95% confidence intervals.

≤8 cm (*vs.* others) were found to be favorable prognostic factors for OS and DFS (*Figure 2*); while vascular invasion and tumor necrosis were unfavorable prognostic factors only for DFS. FIGO stage I disease was the only favorable prognostic factor for LRC.

Table 5 shows the factors that independently and significantly influenced the considered endpoints in the multivariate analysis. Statistically significant independent favorable prognostic factors were younger age (<54 years), FIGO stage I, tumor size ≤8 cm, PUD, and no vascular invasion for OS and DFS. The FIGO stage was the only favorable independent factor influencing LRC. Adjuvant local or systemic treatments did not improve the outcomes. Noteworthy, none of the analyzed (univariate and multivariate analyses) variables influenced the LC. Interestingly, in univariate analysis, we found a better 5-year LC rate in patients having received also BRT compared to those having received only external pelvic irradiation (67% *vs.* 89%), but this difference was not statistically significant (P=0.060), and was not confirmed in the multivariate analysis. It should be noted that only 16% of patients received also BRT, which could probably explain these results.

RT and LC/LRC

The 5-year LC rate of irradiated patients was 86% (95% CI: 76%–96%) whereas it was 93% in non-irradiated patients (95% CI: 84%–100%) (P=0.400). The LRC was 73% (95% CI: 61%–85%) in irradiated patients and 67% in non-irradiated patients (95% CI: 50%–84%) (P=0.400) (*Table 4*). There was no impact of RT independently from the initial FIGO stage.

Surgical technique and LC/LRC

Surgical technique (*Table 4*) showed no significant impact on 5-year LC or LRC rates. The 5-year LC rate was 87% (95% CI: 78%–96%) with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO; n=82) and 100% (95% CI: 98.7%–100%) with the Wertheim procedure (n=17; P=0.180). The 5-year LRC rate was 70% (95% CI: 59%–81%) with TAH+BSO and 79% (95% CI: 57%–100%) with the Wertheim procedure (P=0.500).

Table 4 Statistical results of univariate analysis

Factors	n	5-year OS (%)	95% CI (%)	P	5-year DFS (%)	95% CI (%)	P	5-year LRC (%)	95% CI (%)	P
Median age (year)										
<54	55	65	51–79	0.001	50	36–64	0.001	79	67–91	0.051
≥54	55	29	38–64		15	3–27		63	47–79	
Grade										
1	16	75	50–100	0.040	56	28–84	0.040	71	46–96	0.800
>1 or unknown	94	46	34–58		30	19–41		72	61–83	
PUD										
Yes	14	73	46–100	0.030	65	37–93	0.008	86	68–100	0.210
No	96	46	34–58		29	19–39		67	56–78	
FIGO stage										
I	80	59	46–72	<0.001	40	28–52	<0.001	77	66–88	0.002
II, III, or IV	30	21	1–41		16	0–33		58	39–77	
FIGO stage										
I	80	59	46–72	<0.001	40	28–52	<0.001	77	66–88	0.001
II	10	25	0–59		38	7–69		70	42–98	
III	9	0			0			23*	0–60	
IV	11	38	1–38		18	0–41		68	37–99	
Tumor size (cm)										
≤8	41	76	60–92	0.004	54	37–71	0.020	80	66–94	0.490
>8	32	42	20–64		19	3–35		67	48–86	
Unknown	37	30	12–48		25	9–41		66	48–84	
Tumor size (cm)										
≤8	41	76	60–92	0.003	54	37–71	0.006	80	66–94	0.240
>8 or unknown	69	35	21–49		22	11–33		67	54–80	
Vascular invasion										
Yes	27	36	14–58	0.190	16	0–32	0.040	76	57–95	0.760
No	83	54	41–67		40	28–52		71	60–82	
Tumor necrosis										
Yes	46	49	32–66	0.310	26	11–41	0.010	74	60–88	0.630
No	64	51	36–66		40	26–54		71	58–84	
Type of surgery										
TAH±BSO	93	49	37–61	0.540	34	23–45	0.880	70	59–81	0.500
Wertheim	17	54	23–85		34	9–59		79	57–100	
Postoperative RT										
Yes	75	46	32–60	0.390	33	21–45	0.810	73	61–85	0.400
No	35	59	39–79		36	19–53		67	50–84	
Adjuvant chemotherapy										
Yes	17	54	22–86	0.870	25	3–47	0.110	66	41–91	0.340
No	93	49	37–61		36	25–47		73	62–84	

OS, overall survival; 95% CI, 95% confidence interval; DFS, disease-free survival; LRC, locoregional control; PUD, previous uterine disease; FIGO, International Federation of Gynecology and Obstetrics; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RT, radiotherapy; *, last follow-up 55 months.

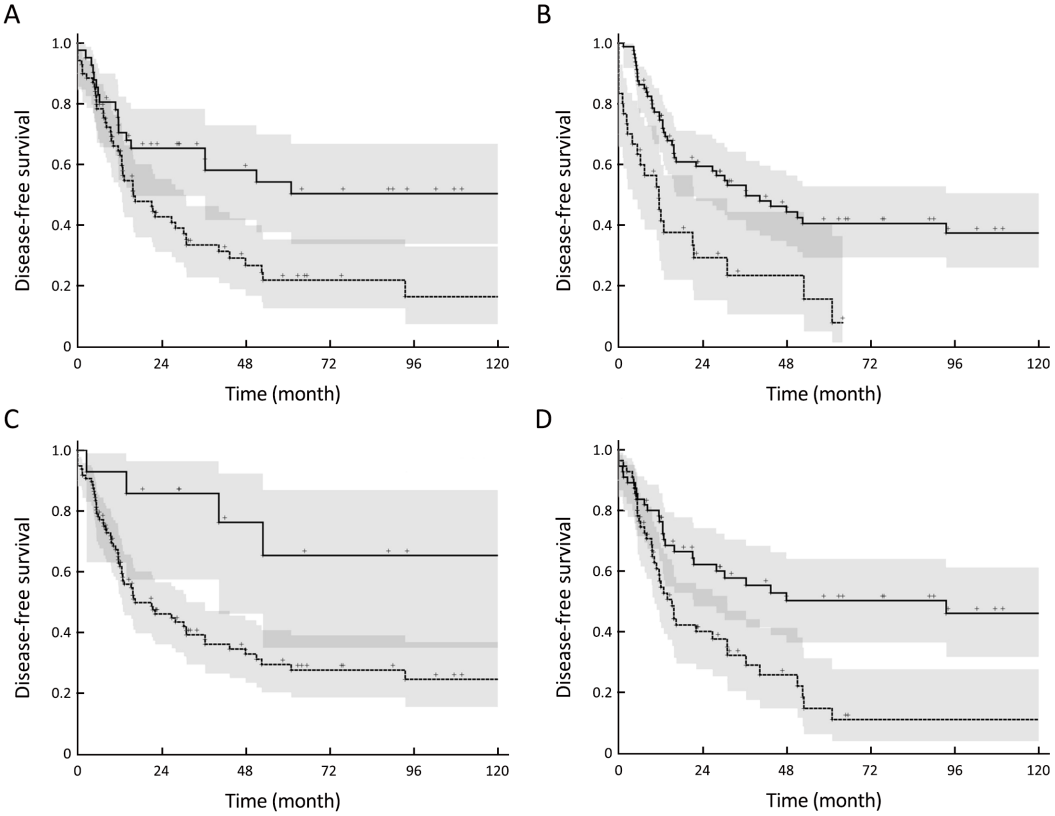

Figure 2 Disease-free survival curves. (A) Tumor size: ≤8 cm (solid line) *vs.* >8 cm or unknown (dashed line); (B) FIGO stage: stage I (solid line) *vs.* II, III, or IV (dashed line); (C) Previous uterine disease (PUD): present (solid line) *vs.* not present (dashed line); (D) Age: <54 (solid line) *vs.* ≥54 (dashed line) years. Censored patients are shown with the "+" sign, and shaded areas represent 95% confidence intervals.

Table 5 Multivariate analysis of factors independently and significantly influencing considered endpoints

Endpoint	Variables	HR (95% CI)	P
OS	Tumor size (≤8 cm *vs*. >8 cm or unknown)	0.29 (0.14–0.62)	<0.001
	FIGO stage (I *vs*. II, III, or IV)	0.31 (0.16–0.62)	0.001
	PUD (yes *vs*. no)	0.29 (0.07–0.80)	0.010
	Age (<54 *vs*. ≥54 years)	0.49 (0.26–0.92)	0.030
	Vascular invasion (yes *vs*. no)	0.45 (0.22–0.96)	0.040
DFS	FIGO stage (I *vs*. II, III, or IV)	0.40 (0.24–0.69)	0.001
	Tumor size (≤8 cm *vs*. >8 cm or unknown)	0.44 (0.25–0.76)	0.003
	PUD (yes *vs*. no)	0.27 (0.08–0.68)	0.003
	Vascular invasion (yes *vs*. no)	0.46 (0.27–0.81)	0.008
	Age (<54 *vs*. ≥54 years)	0.59 (0.35–0.97)	0.040
LRC	FIGO stage (I *vs*. II, III or IV)	0.31 (0.14–0.68)	0.004

OS, overall survival; DFS, disease-free survival; LRC, locoregional control; HR, hazard ratio; 95% CI, 95% confidence interval; FIGO, International Federation of Gynecology and Obstetrics; PUD, previous uterine disease.

Radiation-induced early and late toxicity

Treatment was most often well tolerated. Using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 scoring system (15), grade ≥3 toxicity was moderate, with 8 acute side effects (4 diarrhea, 2

hematological toxicity and 2 abdominal pain), and only 1 case of late complication (vaginal stenosis) was observed.

Discussion

We report one of the largest retrospective series specifically addressing the issue of numerous potential prognostic factors for ULMS. In our experience, the 5-year OS, DFS, LC, and LRC rates were 50%, 34%, 88%, and 72%; respectively. Because of the rarity of this cancer type, it is difficult to obtain large and/or prospective series: we needed the data from 19 European academic institutions to collect 110 cases, over a period of 20 years.

Most of the available studies present the same bias as in our analysis: because of the retrospective nature of the data, the conclusions that could be drawn are of limited value. However, in our series we have obtained complete data for 87% of the patients of the initial population of 126 patients, and for at least 90% of the data of the 110 patients enrolled in this analysis. In particular, treatment data were available for all patients. This makes the results of our analysis rather solid. Compared to other large published series, we decided to focus our analysis only on ULMS, and did not consider other histological subtypes, which are often mixed with ULMS in the other series.

The results in terms of clinical outcomes are comparable to those published by other institutions (16-21) including one very large series using the Surveillance, Epidemiology, and End Results Program (SEER) data (20). Surgery remains the standard initial approach to ULMS (1). The role of adjuvant treatments still remains controversial. A recent SEER-based retrospective analysis on 230 patients treated over a period of 17 years showed that the rate of use of RT and chemotherapy in the treatment of ULMS increased over the investigated period, but the authors could not show any significant survival advantage associated with either mode of adjuvant therapy (22). This study confirmed the available guidelines (1), which consider the role of adjuvant therapies to be controversial (23). Adjuvant RT seemed to be beneficial in some retrospective studies, but it had no impact on OS (10, 24, 27). Data from a retrospective analysis of 3,650 patients with uterine sarcoma (all histological subtypes) using the National Oncology Database showed that amongst the non-metastatic patients receiving definitive surgery (n=2,206) adjuvant RT was associated with an improved outcome compared with surgery alone [hazard ratio (HR)=0.4, P<0.001] (24). A multicenter analysis on 147 patients with ULMS showed a significant 5-year survival advantage for patients who received adjuvant RT (70% *vs.* 35%), but this survival advantage was not sustained as the curves crossed at 90-month follow-up. However, the pelvic recurrence rate was lower in the radiation group (18% *vs.* 49%; P=0.02) (25). Noteworthy, the median follow-up of 24 months limits the long-term value of the latter data. A large retrospective study on 208 patients treated at Mayo Clinic from 1976 through 1999 did not show any impact of RT on OS (10). A study by Livi *et al.* (27) on 141 patients (72 of them affected by ULMS) showed that postoperative RT with a total dose higher than 50 Gy significantly reduced the risk of local recurrence (P=0.001). Interestingly, a recent study on 69 ULMS patients published by Wong *et al.* (28) showed on multivariate analysis that RT independently reduced the risk of local relapse (HR: 0.28; 95% CI: 0.11–0.69, P=0.006) and increased OS (HR: 0.44; 95% CI: 0.23–0.85, P=0.014). One of the potential biases in analyzing the role of adjuvant RT is that most of the patients receiving RT presented a more aggressive disease at diagnosis, thus potentially lessening its impact. Nevertheless, the results of a randomized trial on 224 patients confirmed the data of the retrospective studies (29). This study enrolled patients affected by all uterine sarcoma subtypes, of which 103 patients were treated for a ULMS. All patients were operated on and then were randomized between either observation or pelvic RT (51 Gy in 28 fractions over 5 weeks). The initial analysis showed a reduction in local relapse (14 *vs.* 24, P=0.004), without any effect on either OS or PFS. Noteworthy, the positive impact of adjuvant RT was not confirmed in the subgroup of patients with ULMS (29).

Regarding adjuvant chemotherapy, there is little evidence in the literature supporting its use except for the carcinosarcoma histological subtype. Nevertheless, because of the high risk of systemic relapse, chemotherapy is usually delivered in the postoperative setting (1), despite the negative results of two phase III randomized trials (30,31). In our study, the risk of distant metastases was 55% at 5 years. Nine of the 55 relapsing patients received adjuvant chemotherapy, compared to 13 of the 55 non-relapsing patients. This difference was not statistically significant. Other series reported similar 5-year rates of distant relapses (16-18). Because of the high rate of systemic relapse, more effective systemic treatments represent a major issue in the therapeutic approach to ULMS. The results of our series confirmed that adjuvant RT and/or chemotherapy had no impact on the survival of patients.

In our study, a large number of potential prognostic factors were screened. Finally, on multivariate analysis, tumor size ≤8 cm, FIGO stage I, PUD, younger age (<54 years), and no vascular invasion confirmed their independent impact as significant favorable prognostic factors for OS and DFS. The positive impact of a less advanced FIGO stage on OS has been already shown in many retrospective and prospective studies (9,10,18,20, 22,29,30).

Interestingly, PUD was associated with better OS and DFS on multivariate analysis: to the best of our knowledge, similar results have never been reported before. A potential explanation is that these patients underwent more frequent gynecological clinical controls and, therefore, could have benefited from an early diagnosis. Vascular invasion was associated with a worse prognosis, as reported by others (32-35).

In our series, a younger age (<54 years) was a positive prognostic factor. This result confirms the data of several studies available in the literature (4,17,20,36,37), even if some studies did not (27,38,39). One of the potential explanations could be the different hormonal status of the premenopausal women, as shown by a study by George *et al.* (40). However, more recent reports did not confirm the independent prognostic benefit of the menopausal status when patients' age was taken into account (4). Thus, the reasons of the impact of age still need to be explained, even if, similar to the impact of the PUD reported in our study, it is possible that the more frequent gynecological controls of younger women led to the diagnosis of ULMS at an earlier stage.

Conclusions

This retrospective multicenter RCN study confirmed the poor prognosis of ULMS in spite of a good LC and LRC. An early diagnosis seemed to improve the prognosis of the patients, as an early FIGO stage had a positive impact on OS, DFS, and LRC. In our study, standard adjuvant local or systemic treatments, or more aggressive surgical procedures such as the Wertheim procedure, had no impact on the outcomes of the patients. The poor overall prognosis of this rare and aggressive disease indicates a strong need for newer and better combined approaches.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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