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CLINICAL INVESTIGATION **Female Genitalia**

IMPACT OF RADIOTHERAPY ON LOCAL CONTROL AND SURVIVAL IN UTERINE SARCOMAS: A RETROSPECTIVE STUDY FROM THE GRUP ONCOLOGIC CATALÀ-OCCITÀ

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Purpose: In order to provide more information for the clinician and to analyze the impact of radiation therapy on the loco-regional disease-free interval (LRFI), disease-free interval (DFI) and specific overall survival (OS), a multicentric retrospective study of uterine sarcomas has been undertaken using cases reported to the Grup Oncològic Català-Occità (GOCO).

Patients and Methods: One hundred three patients were selected for this study with a median follow-up period of 49 months. Patients were restaged using the FIGO classification for endometrial adenocarcinoma. Radiotherapy was administered postoperatively to the entire pelvis in 52% of cases (54/103) and was combined with brachytherapy in 24 patients. Mean given dose was 48 Gy, with a 95% confidence interval of 45 to 50 Gy. Variables have been tested for homogeneity between hospitals. Univariate and multivariate analyses have also been carried out.

Results: Mean age of the selected patients was 59 years (range 35–84). Stages were distributed as follows: 66 patients (64%) in Stage I; 16 in Stage II (15.5%); 12 in Stage III (11.5%); 9 patients in Stage IVa (9%). Pathological distribution was 41.5% leiomyosarcoma, 39% mixed Mullerian tumours, 16.5% stromal sarcomas, and 2.9% of a miscellaneous group. Overall survival for the entire group was 63.7% and 56% at 2 and 5 years, respectively. Probability of LRFI reached 59.8% at 2 years and 57.4 at 5 years. The DFI at 2 and 5 years were 52.9% and 48.7%, respectively. The LRFI probability was 41% and 36% at 2 and 5 years, respectively, without radiotherapy and reached 76% at 2 and 5 years among those patients treated with radiotherapy. There was also an increase in DFI probability because of the effect of radiotherapy, from 35% to 68.5% and from 33% to 53% at 2 and 5 years, respectively. The overall survival probability for patients treated with radiotherapy was 76% and 73% at 2 and 5 years, respectively and 51% at 2 years and 37% at 5 years without radiotherapy. Multivariate analysis demonstrated that radiotherapy improved LRFI, DFI, and overall survival.

Conclusion: We conclude that postoperative radiotherapy in our series of patients diagnosed with uterine sarcoma has an impact on loco-regional and disease-free progression intervals and survival. **© 1999 Elsevier Science Inc.**

Uterine sarcomas, Radiotherapy, Survival, Loco-regional disease-free interval

INTRODUCTION

Uterine sarcoma is an infrequent tumor, accounting for only 1% to 3 % of female genital tract malignancy, and between 3% and 7% of corpus uteri tumors (1, 2). Classically, it has a poor prognosis that depends on the extent of the disease at diagnosis. The 5-year survival for patients with Stage I disease is between 50% and 75%, and 0% to 20% for the remaining stages (1, 3, 4). Other pathologic factors, such as histology, myometrial or stromal invasion, grade, nodal spread, and mitotic activity have been found as prognostic variables in several studies (5–7).

The small series of patients in reports and poor prognosis associated with these tumors make their clinical management difficult, usually surgery is followed by radiotherapy when poor prognostic factors are present. Although the impact of radiation therapy seems to be established by some authors for local disease control (8–10), and disease-free

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survival (11), few benefits were related in survival (12). In order to provide more information for the clinician, and to analyze the impact of radiation therapy on the loco-regional disease-free interval (LRFI), disease-free interval (DFI), and specific overall survival (OS), a multicentric retrospective study of uterine sarcomas has been undertaken using cases reported to the Grup Oncològic Català-Occità (GOCO).

PATIENTS AND METHODS

One hundred sixty-seven medical charts from patients diagnosed with uterine sarcoma at six different hospitals in the Midi-Pyrénées, Roussillon, and Catalonia areas (included in the GOCO), were reviewed retrospectively from 1979 to 1995. Centers contributed with 11 to 27 patients. We discarded patients with Stage IVb and live patients with a follow-up period of < 24 months without relapse. In the end, 103 patients, with Stages I, II, III, and IVa were selected for this study with a median follow-up period of 49 months (range 24–197). Patients were restaged using the FIGO classification for endometrial adenocarcinoma and all except two patients underwent surgery. Seventy percent of patients had hysterectomy and double anexectomy, 18% underwent Whertheim-Meigs surgery, 7% simple hysterectomy, and the remaining were treated with nonstandard surgical procedures.

Radiotherapy was administered postoperatively to the entire pelvis in 55 cases and was combined with brachytherapy in 24 patients. Cobalt-60 irradiation or 6 to 22 MV fotons from a linear accelerator were employed, using four fields (box-technique) in 70% of treatments. Mean dose was 48 Gy, with a 95% confidence interval of 45 to 50 Gy. Dose per fraction was 180 cGy in 52% of the patients, and 200 cGy in the remaining cases, except for two patients who received 36 Gy at 300 cGy per fraction and 53 Gy at 270 cGy, respectively. No patients received brachytherapy alone without radiotherapy, and it was administered postoperatively with Cesium-137 sources through Fletcher colpostats in the majority of cases and the doses ranged among 15 to 20 Gy referred to 0.5 cm from the mucosa. Thirthy-three patients received chemotherapy and 25 of them (76%) with CYVADIC schedule.

Variables have been tested for homogeneity between hospitals. Chi-square and Kruskal-Wallis tests (13) have been done for this purpose. All significance tests were two-sided, and interval and survival curves were drawn using the Kaplan-Meier method (14). The Mantel-Cox test has been used for statistical comparison of curves (15). Significance of prognostic factors was assessed by the Cox regression model (16). Variables entered in the multivariate analysis were those that were significant in the univariate analysis. LRFI was defined as the time from the end of treatment to the first loco-regional recurrence and DFI also includes the first metastatic site. OS was defined as the time from the end of treatment to death due to the tumor.

RESULTS

Mean age of the selected patients was 59 years (range 35–84), with a mean of 48 years for stromal sarcoma patients and 61 for the remaining pathologies. The difference between these means was significant ($p = 0.003$). Stages were distributed as follows: 66 patients (64%) in Stage I; 16 in Stage II (15.5%); 12 in Stage III (11.5%); and 9 patients in Stage IVa (9%). Pathological distribution was 41.5% leiomyosarcoma, 39% mixed Mullerian tumors, 16.5% stromal sarcomas, and 2.9% of a miscellaneous group. Mullerian tumors and leiomyosarcoma account for more than the 80% of pathologic diagnosis. Tumor size was related in 87 cases, with 20.4% < 5 cm. Grade of differenciation was specified in 65 patients, accounting for 38.5%, 20%, and 41.5% for low, intermediate, and high grade, respectively. Thirteen of the 74 patients had vascular or lymphatic permeation and positive margins were found in 4 patients. Myometrial invasion was observed in 64 patients, in 24 cases it was $< 50\%$, and in 40 cases it was more than 50%. Necrosis was found in 52 tumors and multicentricity was reported in 14 cases. Nodal status was surgically evaluated in 18 cases and only 3 patients were found positive; peritoneal lavage was performed in 20 patients and only 3 were positive.

Age, stage pathology, grade, external radiotherapy, brachytherapy, chemotherapy, and surgery were analyzed for homogeneity between centers. Stages were distributed homogeneously between centers but nearly 80% of patients had early Stage I–II. Only histologic grade, chemotherapy, and brachytherapy showed significant differences. Proportion of high grade at one center was significantly different when compared with other ones. This center showed 14 cases, while only 13 cases were observed in all of the remaining ones. In this particular center, chemotherapy was administered more frequently. The clinico-pathological and treatment characteristics of the series are summarized in Table 1, together with LRFI, DFI, and OS.

During the time of observation, 46 patients had loco-regional relapses, 31 cases of distant metastases occurred and 48 patients died (16 were treated with radiation and 32 without), 2 of them not directly due to the tumor and 23 with disseminated disease. Overall recurrence rate was 53.4% (55/103). Eighty-four percent (46/55) of failures were loco-regional (14 with radiotherapy and 32 without), while distant failure accounted only for 56.4% (31/55) and both were seen in 40% (22/55). The OS for the entire group was 63.7% and 56% at 2 and 5 years, respectively. Probability of LRFI reached 59.8% at 2 years and 57.4% at 5 years. The DFI at 2 and 5 years were 52.9% and 48.7%, respectively.

In an univariate analysis of LRFI, age, stage, pathology, grade, and external radiotherapy showed significant differences. When Mullerian and leiomyosarcoma tumors were studied, excluding stromal sarcomas, the age significance disappeared. Stages were grouped by early (I–II) vs. advanced (III–IVa) with 36% (30/82) and 76% (16/21) of loco-regional relapses, respectively. Three out of 17 patients

Table 1. Univariate analysis for LRFI, DFI, and OS

		Loco-regional disease-free interval			Disease-free interval			Specific overall survival		
Prognostic features	N	2 y (%)	5 y (%)	*p*	2 y (%)	5 y (%)	*p*	2 y (%)	5 y (%)	*p*
Age:										
< 60	52	71	66.5	0.04	65.4	59	0.026	72.6	68	0.034
≥ 60	51	48	48		40	38		57	44.6	
Stage:										
I	66	70	66	0.003	67	62	<0.0001	74	69	<0.0001
II	16	67	67		47	47		69	50	
III	12	33	33		17	8		28	28	
IVa	9	11	—		11	—		22	11	
Pathology:										
Mullerian	40	54	54	0.02	49	43.6	0.006	64	50.6	0.008
Leiomyosarcoma	43	58	55.4		46.5	44		58.6	50.3	
Stromal sarcoma	17	88	81.4		88	81.4		88.2	88.2	
Others	3	—	—		—	—		—	—	
Histologic grade										
Low	25	96	92	0.0006	88	84	0.0006	96	86.6	<0.0001
Intermediate + High	40	50	50		40	40		60	56	
Multicentricity										
Yes	14	43	43	0.2043	43	43	0.6658	43	43	0.2189
No	78	65	62		56	50		69	58	
Vascular-lymphatic invasion										
Yes	13	69	69	0.3588	61.5	61.5	0.3973	69.2	61.5	0.7178
No	60	57	54		52	49		62	53	
Myometrial invasion										
No	38	61.5	55	0.8728	51.3	45.8	0.7416	61.5	53	0.6316
≤ 50%	24	58	58		54	54		67	62	
> 50%	39	58	58		53	48		67	56	
Necrosis										
Yes	52	52	50	0.3408	40	38	0.1231	56	45	0.1576
No	37	74	67		67	52		74	65	
External radiotherapy										
Yes	55	76	76	<0.0001	68.5	63	0.0004	76	73	0.0003
No	48	41	36.4		35	33		51	37	
External RT ± brachytherapy										
Yes	24	71	71	0.334	62.5	58	0.476			
No	30	83	83		76	67				
Chemotherapy (Intermediate + High grades)										
Yes	20				30	30	0.2	45	40	0.3715
No	20				50	50		55.6	50	

LRFI = loco-regional disease-free interval; DFI = disease-free interval; OS = specific overall survival

with stromal sarcomas had local relapse vs. 43 of the 46 remaining patients. No differences were found between leiomyosarcoma and Mullerian tumors for local control. LRFI probability reached by external radiation in 55 patients was 76% at 2 and 5 years, whereas this probability was 41% and 36.4% in the group of 48 patients without treatment (Fig. 1). A multivariate analysis for LRFI in the global series, external radiation treatment, and stage showed to be of value in prognosis (Table 2). Locally advanced stages show an increase in risk of loco-regional relapse by a factor of 5.7 when compared with early Stages I–II. When external radiotherapy was administered, the risk of loco-regional relapse decreased 8.6 times.

In relation to the univariate study for DFI (Table 1), the same variables that showed significant differences for LRFI became significant. The probability for being disease-free for the group treated with radiotherapy reached 68.5% and 63% at 2 and 5 years, and the probability for patients without external radiation was 35% and 33% at 2 and 5 years, respectively (Fig. 2).

Multivariate analysis showed three factors as being of value in DFI (Table 2). Advanced stages increased progression risk by a factor of 4.9, while radiotherapy decreased this risk 2.5 times.

Mullerian tumors or leiomyosarcoma have 9.5 times more risk of disease-progression than stromal sarcoma.

For OS, the univariate study showed significant differences for age, stage, pathology, histologic grade, and radiotherapy. The OS probability for patients treated with radiotherapy was 76% and 73% at 2 and 5 years, respectively. The probability decreased to 51% and 37% (Fig. 3) for those patients who were not irradiated. Only stage and radiation

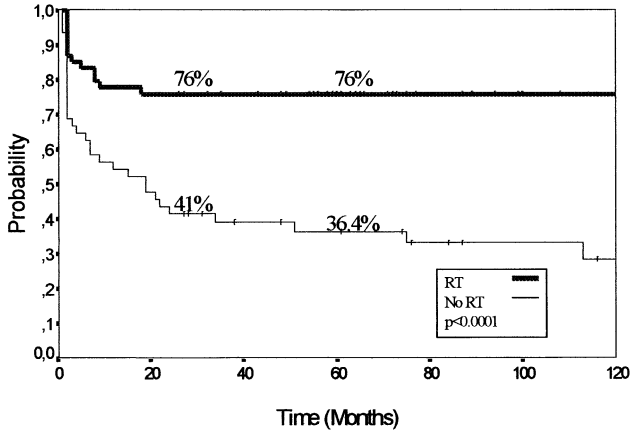

Fig. 1. Kaplan-Meier estimates of loco-regional disease-free interval among patients treated with or without radiotherapy (RT).

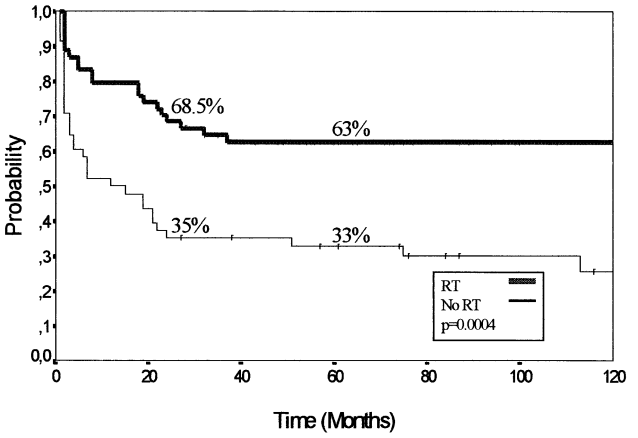

Fig. 2. Kaplan-Meier estimates disease-free interval among patients treated with or without radiotherapy (RT).

therapy became significant in the multivariate analysis. Death caused by disease increased nearly 2 times for advanced stages, and decreased 3.6 times when radiation was given.

When the initial Stage (I–II) subgroup was analyzed, external radiotherapy, pathology, and histologic grade were significant in the univariate study for LRFI, DFI, and OS. Only external radiation was an independent significant variable in the multivariate analysis for the early stages and increased the LRFI and DFI by factors of 3.4 and 2.5, respectively, and decreased specific death threefold when it was given. Chemotherapy had no impact on disease outcome either in the global series or in early stages. Stage I and stromal sarcoma were found in a significantly higher proportion in the radiotherapy group. When stromal sarcomas were left out of analyses, the proportion of Stage I was similar between radiotherapy and nonradiotherapy groups, and, in this case, radiotherapy was still significant in all parmeters studied (LRFI, DFI, and OS).

Surgical approach and radiotherapy proportion was not different depending on the treatment period, which has been classified in to early ($\leq$ 1989) and late (after 1989) periods.

DISCUSSION

Uterine sarcoma is a very rare tumor, accounting for 3% to 7% of uterine cancers, including complex histology patterns. It is characterized by an extremely agressive behavior leading to an early dissemination and death. Several studies have tried to find prognostic features, but treatment efficacity is difficult to evaluate because of the small number of patients, so the role of radiotherapy in the management of uterine sarcoma is still controversial. Local relapse benefit was generally found in literature (8–10, 17) and two studies showed significant improvement in survival; one with few patients (12) and the other when brachytherapy was added to external radiotherapy in Stage I of Mullerian sarcomas (18). In general, the impact of radiotherapy on survival could depend on patient selection for treatment, which reflects a tendency to select patients with a poor prognosis for radiotherapy, as well as the fact they are from a small series. The few patients with this diagnosis make it impossible to carry out randomized assays in only one institution to determine the efficacy of radiotherapy. Results of the multicentric, prospective trial EORTC-55874, which is ongoing at the present time, will be needed to know the exact impact of radiotherapy.

Table 2. Significant variables in multivariate analysis for LRFI, DFI, and OS

Prognostic features	e^{Beta}	Beta	Standard error	Chi-square value	*p* value
Loco-regional disease-free interval					
External radiation treatment	8.6	2.152	0.502	17.36	< 0.0001
Stage	5.71	1.743	0.357	16.5	< 0.0001
Disease-free interval					
Stage	4.89	1.589	0.331	20.28	< 0.0001
Pathology	9.48	2.250	1.015	13.927	< 0.0001
External radiation treatment	2.54	0.934	0.321	8.894	0.003
Overall survival					
External radiation treatment	3.62	1.287	0.345	14.895	< 0.0001
Stage	1.91	0.647	0.147	14.748	< 0.0001

Abbreviations as in Table 1.

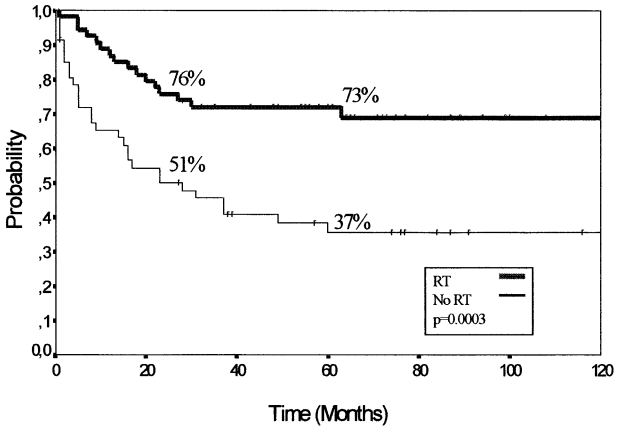

Fig. 3. Kaplan-Meier estimates of specific overall survival among patients treated with or without radiotherapy (RT).

We have studied retrospectively 103 medical charts of patients diagnosed as having uterine sarcoma, from six different centers, examining the effect of radiotherapy on LRFI, DFI, and OS. In our series, radiation therapy showed a marked increase in the three parameters studied (LRFI, DFI, and OS) for all the groups in the univariate and multivariate analyses, even for early Stage (I–II). Radiation therapy significantly decreased loco-regional failure from 70% to 30% and deaths from 67% to 33%. It seems reasonable that loco-regional control could decrease the probability of micrometastase dissemination as well as improve survival, as related in breast cancer (19, 20) and as found with the impact of loco-regional control on OS in breast (21–23) and rectum cancer (24). In the literature, survival ranges from 48% to 54% and from 34% to 57.7% for 2 and 5 years, respectively (1, 3, 4, 9, 25). In our series, survival is increased up to 63.7% and 56%, probably due to a higher proportion of early stages than other series.

Stage has been found to be an important prognostic factor in different studies (3, 4, 10). This is also confirmed in our study, but no differences were seen between Stage I and II. We based stage classification on surgical approach, which does not differ in proportion or agressiveness between early and late periods, so we could assume that there is no significant stage migration. Proportion of radiation treatments is also similar between those periods. In the radiotherapy group there was a greater proportion of Stage I and stromal pathology, and these patients were younger. Nevertheless, when stromals sarcomas were left out of the analyses, the impact of radiotherapy is still significant. Therefore, we think that age factor is not a bias in this study.

We have seen that stromal sarcomas showed better prognosis than leiomyosarcoma and Mullerian sarcomas, but mean age of those patients was significantly lower than the other pathologies. Age is revealed as a prognostic factor in the univariate analysis of our study, but not in the case of a multivariate one, as recently reported by Nordal and Thorensen (4). We found that leiomyosarcomas have the same mean age and prognosis of Mullerian sarcomas, but it is reported that leiomyosaroma show better prognosis (10) and have higher incidence in younger patients. When adjusting for age, this effect disappeared, then leiomyosarcoma is thought to have poorer prognosis than Mullerian tumors (26). Menopausal status is not found to have a prognostic value as it is in a study of 209 patients (9). Probably young patients (nonmenopausal) with a high percentage of stromal sarcomas could have the best prognosis in our series.

In a large prospective study for Mullerian tumors, the principal factors related to progression-free interval were lymph node involvement, cell type, adnexal involvement, and sarcoma grade (6). A histologic finding that had a significant influence on all parameters studied univariately was the grade, although no effect was seen in multivariate analysis. The incidence of positive pelvic and para-aortic nodes was estimated in small series ranging from 20% to 45% (27, 28). Three of 18 patients (17%) with node sampling at operation were positive in our series.

Higher doses delivered to tumor volume are radiobiologically expected to give a better local disease control. Larson *et al.* (18) found better local control and survival when brachytherapy was added to external radiotherapy in Stage I of Mullerian sarcomas. In our series, brachytherapy together with external radiation did not show a significant effect on disease control, either in the Mullerian subgroup.

Overall relapse is 53.4%, which is similar to that reported by Major *et al.* (6). Distant metastases are thought to constitute the main failure pathway, leading to nearly the total amount of failures, and happened in 75% of loco-regional failures (8). We found that only 48% of the total loco-regional failures (22/46) were associated with distant relapses. Although the total amount of distant relapses was 56.4%, the greater failure pathway was loco-regional in our series (84%). This finding could be explained by higher proportion of early stages than other studies.

Performance status, not reflected in clinical charts in our series, has been found to be a prognostic feature in cancer patients, but in uterine sarcomas it has only been referred to in one study (9).

We could conclude that postoperative radiotherapy in our series has an impact on loco-regional, progression-disease, and survival. While these results encourage the use of radiation therapy in uterine sarcomas, we have to point out that our series is a retrospective, multicentric study; a fact that makes treatment criteria inhomogeneous and could produce imbalances of the variables between groups. Therefore, these results could be used as a hypothesis for future prospective, multicentric studies with a careful selection of patients, homogeneity of treatments, pathology and molecular findings, and an accurate register of performance status and radiation toxicity.

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