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Original research article

Treatment of pure uterine sarcoma at the *Institut Català D'Oncologia*

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ABSTRACT

Aim: The aim of this retrospective study was to investigate the clinical and histopathological characteristics of the disease and treatment outcome of patients with pure uterine sarcomas.

Background: Uterine sarcomas are especially rare tumours, comprising only 3–5% of uterine cancers. They are characterized by histopathological diversity, rapid clinical progression, and poor prognosis. Optimal management consists of complete surgical removal and adjuvant radiotherapy may improve the prognosis.

Materials and methods: All patients with pure uterine sarcoma histology treated at our centre, the *Institut Català D'Oncologia* in Barcelona Spain, between 2002 and 2010 were reviewed.

Results: Records of 17 patients treated at our hospital over an 8-year period were obtained. Nine patients (53%) had leiomyosarcoma, 7 (41%) had endometrial stromal sarcoma, and 1 patient had unclassified sarcoma. All patients were treated with external beam radiation after surgical excision. Mean age was 62 years (range, 51–69 years). Of the 17 patients, 13 (76%) presented with stage I disease, 2 (12%) were stage II, and 2 (12%) stage III. The overall actuarial 2-year survival estimate was 82.5%. Two patients experienced local relapse. The 2-year local control rate was 90%. A total of 5 patients experienced either local or metastatic relapse. The 2-year progression free survival rate was 58%.

Conclusion: In our experience, combined treatment (surgery and adjuvant radiation therapy) is effective with acceptable side effects. Larger and multicenter studies are needed to assess treatment outcome for pure uterine sarcoma histology.

1. Background

Uterine sarcomas are especially rare tumours, comprising only 3–5% of uterine cancers.[1] Because of their low incidence and the existence of various pathologic types, little is known about the characteristics of these neoplasms. Despite the rarity of this tumour, significant progress has been made in recent years in improving classification, staging and management of patients with uterine sarcoma.[2]

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The current World Health Organization classification of tumours of the female genital tract divides uterine mesenchymal tumours into two types: smooth muscle tumours and endometrial stromal tumours.[3] Leiomyosarcoma (LMS) is the most common uterine sarcoma arising within the myometrium. LMS is a malignant smooth muscle tumour, and typically presents with prominent necrosis, high mitotic index, and moderate to severe cytological atypia. Diagnosis is based on a combination of some or all of these features.[4] Endometrial mesenchymal tumours are considerably rarer than smooth muscle uterine tumours. Endometrial stromal sarcoma (ESS) is a densely cellular tumour whose classification has been changed in recent years. Since the extent of mitotic activity within the tumour is more closely correlated with prognosis than the degree of cellular atypism, it became apparent that such tumours should be separated into two different clinicopathological entities: endometrial stromal sarcoma (ESS) and undifferentiated endometrial sarcoma (UES).[5,6] ESS is a 'low grade' tumour, behaving in an indolent fashion irrespective of its mitotic index. In contrast, UES is a 'high grade', rapidly growing tumour, characterized by aggressive behaviour and poor outcomes.[7,8]

In the last decade, the pathological description of uterine sarcomas has experienced numerous changes. Carcinosarcoma (CS), also called malignant mixed Müllerian tumour, had traditionally been considered a sarcoma. CS is a biphasic tumour, consisting of both carcinomatous epithelial and malignant mesenchymal components.[9] These two components used to be assumed as separate, resulting in a 'collision' tumour. However, it is now clear that the epithelial and mesenchymal components derive from a single stem cell, with the epithelial element of the tumour dominant in determining the biological behaviour. CS has therefore been re-classified as a dedifferentiated/metaplastic endometrial carcinoma,[10] and for this reason it is not included in our study.

Many risk factors for uterine sarcoma have been reported in the literature. The most common factors associated with higher risk for these sarcomas are previous pelvic irradiation (most commonly more than 10 years before tumour development and reported in 10–25% of cases); black women; and the use of long-term adjuvant tamoxifen for breast cancer.[11,13] The clinical presentation of uterine sarcomas is non-specific. Peak incidence is between 50 and 65 years of age. Uterine sarcomas typically present as a rapidly growing uterine mass, and additional symptoms may include pelvic or abdominal pain and vaginal bleeding.[14]

Radiological diagnosis prior to hysterectomy is difficult, with diagnosis frequently made post-operatively.[15] Current staging systems have been unsatisfactory, although a FIGO staging system created specifically for uterine sarcomas is available, and may allow better grouping of patients according to expected prognosis.[16] The reported prognostic factors in uterine sarcomas are as follows: stage, age, residual tumour after surgery, positive peritoneal cytology, lymph node involvement, vascular and lymphatic space invasion, myometrial invasion, degree of advanced differentiation or mitotic index, large tumour size, and pathologic type.[17] Because these tumours are so aggressive, the incidence rate of distant metastases is quite high.[18] Typically, disease spread occurs locally; lymphatic spread is unusual in uterine sarcoma,

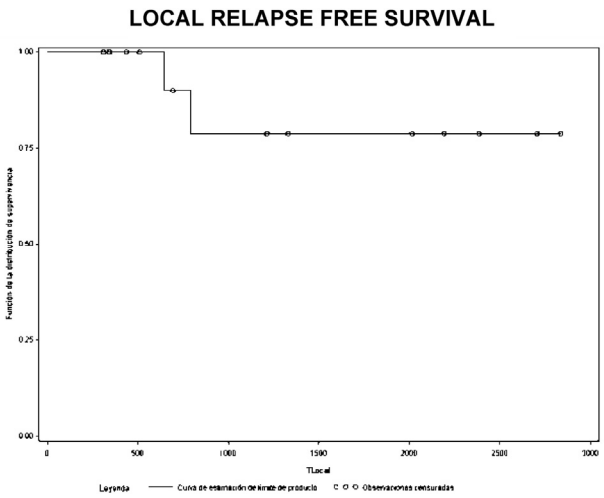

Fig. 1 – Kaplan–Meier estimates of local relapse free survival among patients treated with surgery and adjuvant external beam radiotherapy.

in which dissemination usually occurs in the peritoneum and early haematogenous spread with distant metastases (Figs. 1 and 2).[19]

Treatment of uterine sarcomas is a considerable challenge. The primary treatment of early stage disease is total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) and peritoneal washings; however, it is not clear whether routine lymphadenectomy is necessary. External pelvic irradiation has been employed as adjuvant treatment, and most authors report that this therapy decreases local recurrence rates without any significant impact on survival, given that most patients with relapsed disease have distant failures.[20–22] A number of early reports showed improved local control when post-operative adjuvant radiation was administered, and in some of these early series this seemed to give an

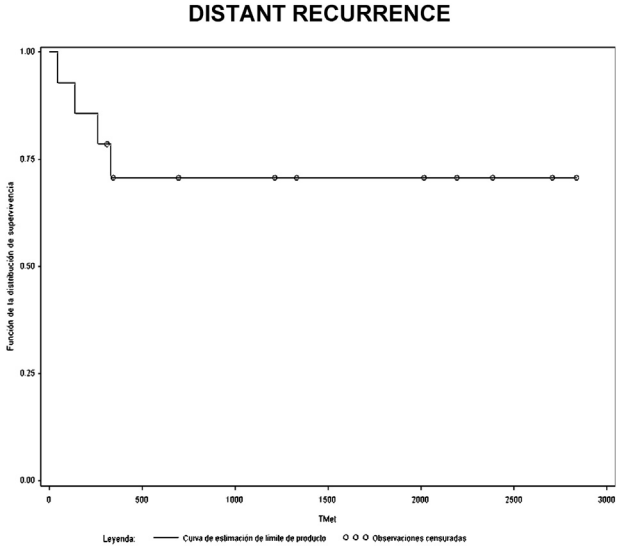

Fig. 2 – Kaplan–Meier estimates of distant recurrence failure among patients treated with surgery and adjuvant external beam radiotherapy.

Table 1 – International Federation of Gynaecology and Obstetrics (FIGO, 2009) staging system for *Leiomyosarcoma and Endometrial Stromal Sarcoma*.

Stage	Definition
I	Tumour limited to the uterus
IA	≤5 cm
IB	>5 cm
II	Tumour extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumour invades abdominal tissues (not just protruding into abdomen)
IIIA	1 Site
IIIB	>1 Site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumour invades bladder/or Rectum
IVB	Distant metastases

improved survival benefit compared to surgery alone.[10,23] The role of complementary brachytherapy in these patients is unclear and somewhat controversial, given the lack of available data on local outcome.

Most of the previous studies of uterine sarcomas included patients with CS. Given the recent changes in the classification, it is apparent that new studies are needed to evaluate and characterize pure uterine sarcomas, especially considering how rare they are. For this reason, we decided to undertake the present study.

The objective of our study was to assess the clinical evolution of a group of patients from our centre who had undergone surgery and adjuvant radiotherapy to treat uterine sarcomas (LMS, ESS, UES). We assessed local control, distant metastasis, and overall and progression-free survival.

2. Materials and methods

The study included all 17 patients treated at our hospital for uterine sarcoma between May 2002 and July 2010. Patient medical records were reviewed, and information regarding patient medical history, tumour characteristics, treatment modalities, and follow-up was recorded. Survival information was obtained by personal consultation. All patients were staged retrospectively according to the 2009 FIGO staging classification (Table 1).

Follow-up examinations were usually performed every 3 months during the first 2 years, every 4 months during the third year, every 6 months until the fifth year, and annually thereafter. Follow-up visits included a physical examination and, depending on the treatment protocol and the existence of clinical symptoms, chest X-ray and/or abdominal and pelvic computed tomography to rule out recurrent or metastatic disease.

2.1. *Statistical analysis*

The data were analysed using SAS software version 9.2 (SAS Institute, Cary, NC). The main endpoints were overall survival, local control, and progression free-survival. All estimates were calculated using the Kaplan–Meier estimator. We were unable to evaluate the prognostic factors due to the small sample size. Frequency table are present for prognostic factors, treatment, efficacy and toxicity.

Table 2 – Baseline characteristics.

	N (%)
Menopausal status	
Median age/range	62 (51–69)
Post-menopausal	17 (100%)
Medical history	
HTA	9 (53%)
DM	0
Median between symptom and evaluation (days)	34 (5–122)
First symptom: menorrhagia	14 (85.7%)
Type of surgery	
TAH and BSO	7 (41%)
TAH and BSO and node sampling	10 (59%)
FIGO stage	
I	13 (76%)
II	2 (12%)
III	2 (12%)
Histological type	
Leiomyosarcoma (LMS)	9 (53%)
Endometrial stromal sarcoma (ESS)	7 (41%)
Unclassified	1 (7%)
Tumour grade	
Moderately differentiated (G2)	5 (29%)
Poorly differentiated (G3)	8 (47%)
Unknown	4 (24%)
Myometrial invasion	
Inner third	6 (35%)
Middle third	2 (12%)
Outer third	9 (53%)

3. Results

The clinical characteristics of all patients are presented in Table 2. Mean age was 62 years (range, 51–69). Nine patients (53%) had leiomyosarcoma, seven (41%) had endometrial stromal sarcoma and one patient had unclassified sarcoma. All patients were post-menopausal.

Family history was mostly of breast cancer, although some patients also had a family history of uterine adenocarcinoma and gastrointestinal malignancies. Half of the patients had arterial hypertension (HTA). The main presenting symptom was abnormal uterine bleeding (metrorrhagia), although other symptoms, including abdominal pain or discomfort, were also described. Time from symptom presentation to diagnosis was highly variable, ranging from 5 to 122 days, although in cases of postmenopausal bleeding, the time to diagnosis was substantially shorter (median, 33 days).

All 17 patients were treated surgically with curative intent; of these, 7 patients (41%) underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and peritoneal washings, without pelvic lymphadectomy. Node sampling was performed in 10 patients (59%), and in 4 cases lymph nodes were dissected laparoscopically. Postoperative evaluation revealed no additional malignancy, although 1 patient had a positive peritoneal washing. Remarkably, the

Table 3 – Radiation therapy details.

	N (range)
Whole pelvis RT	
Total dose	50.4 (45–50.4)
Duration of WPRT (days)	38 (34–55)
Duration of WPRT + BT (days)	53 (32–86)
Dose (Gy) per fraction	1.8 (1.8–2.0)
Four fields	17 (100%)
Energy	15 (15–18 MV)
Brachytherapy	
LDR	7 (50%)
PDR	4 (28.6%)
HDR	3 (21.4%)

histological analysis showed that the surgical margins were free of disease in all cases (R0).

Most patients (13 of 17; 76%) presented with stage I disease: 11 of these patients were diagnosed with stage IA and 2 patients with stage 1B. The other 4 patients were stage II (2 cases) or stage III (2 cases). No stage IV patients were included in this sample. Eight patients (47%) had a Grade 3/poorly differentiated tumour, 5 (29%) a Grade 2/moderately differentiated tumour, and 4 patients (24%) had unknown tumour grading.

All patients underwent external beam radiotherapy (EBRT) with linear accelerator and a mean dose of 50.4 Gy (45–50.4 Gy) in several daily fractions (Table 3). In addition, 14 patients received intracavitary vaginal brachytherapy after EBRT. The mean dose of brachytherapy was 25.5 Gy (10–36 Gy). High-dose-brachytherapy was used in only 3 patients. One patient also received chemotherapy (combined ifosphamide and adriamycin) due to positive peritoneal malignancy.

Side-effects and toxicity were as expected in such cases, with no grade 3 (RTOG/EORTC acute and late toxicity morbidity scoring criteria) gastro-intestinal or genito-urinary toxicity during treatment or follow-up.[16,17] The most common acute side effects were grade 2 gastro-intestinal toxicity, reported in 6 patients during treatment. Eight patients experienced acute urinary toxicity ($\leq$ grade 2) during treatment. There were no cases requiring interruption of adjuvant radiotherapy due to treatment toxicity. Possible late side effects of radiotherapy were observed in 3 patients who reported gastro-intestinal pain (one of which was scored as a RTOG/EORTC grade 3 toxicity). Notably, all 3 of these patients had undergone adjuvant low-dose rate brachytherapy, although the total cumulative dose delivered to the rectum and bowel was $\leq$70 Gy in all 3 cases.

Median follow-up was 43 months during which one case of local recurrence and 4 cases of distant metastasis in the lung were observed.

The overall 2-year actuarial survival estimate was 82.5%. Two patients suffered a local relapse. The 2-year local control rate was 90%. A total of 5 patients experienced either local or metastatic relapse. Progression free survival at 2 years was 58%.

4. Discussion

Uterine sarcoma is a rare and lethal disease. The data presented here are derived from a small series of patients treated at our department over a 10-year period. Carcinosarcomas, which account for approximately half of uterine sarcomas in other studies, are no longer considered pure sarcomas due to recent changes in histological classification.[10,13,23,24] As a result of the exclusion of this histological sub-group, our series consists of only 17 patients. However, to our knowledge, ours is one of the first studies to evaluate and characterize pure sarcomas and treatment outcome under this new classification system.

Age distribution was similar regardless of histological subtype, since all the women were post-menopausal. One woman had a history of breast cancer treated by tamoxifen for 5 years. As previous studies have described, the use of tamoxifen is associated with an increased risk for uterine sarcoma, mainly CS.[11,12] None of the patients in our sample had previously undergone pelvic irradiation.

Time between first symptom and first medical evaluation was highly variable (between 5 and 122 days). Despite this wide range, the median time elapsed between first symptom and diagnosis was only 34 days, probably because the most common initial symptom in our study was vaginal bleeding (85%), which usually leads to a faster diagnosis.

We cannot draw any conclusions about the efficacy of chemotherapy in this group because only 1 patient received this adjuvant treatment.

As described in previous studies, the only factor that was significantly correlated with prognosis was disease stage at diagnosis.[12,14] However, we should point out that the limited number of patients in our study made it difficult to find a significant correlation between risk factors and prognosis. In our study, 76% of patients were stage I, a bit lower than the 84.8% reported in the EORTC study.[24] The good response to treatment observed in our sample was likely to be related to the early stage disease, and this is supported by the relatively small number of patients who experienced local recurrence (2 cases) and/or distant metastasis to the lung (4 patients). Notably, all 4 of the patients with distant metastasis had a poor histological prognosis (more than 20 mitoses/field) and presence of vascular invasion.

Vascular and lymphatic invasion is a well-known prognostic factor in several diseases because the penetration gives tumour cells the opportunity to metastasize to other sites. In general terms, invasion of vascular spaces by a tumour is indicative of an aggressive neoplasm that has a marked tendency to metastasize and to recur locally.[18] In a study of 60 patients diagnosed with uterine neoplasms with sarcomatous component, Rovirosa et al.[19] found that vascular and lymphatic space invasion is the most relevant prognostic factor after staging.

We found that, based on histological group, LMS patients had a worse outcome than ESS patients. Patients with uterine LMS accounted for 3 of the 4 cases of distant metastasis and 1 of the 2 cases with local recurrence. Ferrer et al.[25], in a study that included 103 patients, found that uterine LMS patients had a poorer prognosis when adjusted for age. The other patient with lung metastasis had uterine ESS, which also recurred locally, but the presence of a positive peritoneal washing in surgery could have contributed to that patient's poor outcome. All patients with specific disease recurrence were classified initially as FIGO stage III, which

may have contributed to the poor clinical outcome in our series. It should be noted that the distant lung metastases all occurred shortly after the end of treatment (between 60 and 160 days after radiotherapy), a fact that appears to support the aggressive behaviour of these tumours.

The low treatment toxicity rate reported in our series is also notable, although it is important to remember that this was a retrospective study. That said, we believe that toxicity could be further reduced with the use of newer radiotherapy techniques such intensity modulated radiotherapy (IMRT) or helical tomotherapy (HT). Yang et al. found that IMRT and HT deliver better conformity and lower dose to organs at risk vs. 3D conformal radiotherapy in postoperative whole pelvic radiotherapy (WPRT) for endometrial cancer. Nevertheless, the impact of these radiotherapy techniques on toxicity has yet to be assessed in a prospective study.[26]

Surgery is the primary treatment for localized uterine sarcomas. The use of lymphadenectomy is a bit more controversial, especially in pure uterine sarcomas (LMS and ESS), which tend not to spread to the lymph nodes. In one series of 275 women with uterine LMS, only 3 of 37 patients who underwent nodal sampling had positive nodes,[27] suggesting that lymphadenectomy should be performed only for CS histology. In our study, in which 10 patients underwent nodal sampling, all the nodal biopsies were negative.

The only randomized study of adjuvant radiotherapy in uterine sarcomas was published by the EORTC.[24] In that study, patients underwent surgery and were randomized either to observation or pelvic radiation. Adjuvant chemotherapy was not administered. There were almost as many patients with LMS as those with CS (103 and 91, respectively). The initial analysis showed a reduction in local relapse in the radiotherapy arm (22% vs. 40%). Local recurrence was low (2.7% of patients) while 44.5% of patients had distant metastasis during follow-up. Compared to our study, the local recurrence rate was lower but distant metastasis higher. The EORTC study found no difference in overall or disease-free survival between the groups, although a subgroup analysis revealed improved local control for CS patients who had undergone radiotherapy, but no benefit for the LMS radiotherapy subgroup. This result may be due to increased radiotherapy effectiveness on carcinomatose component of the CS.

Most patients (82%) in our series underwent adjuvant brachytherapy after completing external pelvic irradiation, but the use of brachytherapy in vaginal fundus is highly variable depending on the centre. To our knowledge, no study published to date has been able to demonstrate better local control with brachytherapy; notwithstanding this lack of date, we recommend its use as a boost technique because it provides improved localized dose distribution with the potential to destroy sub-clinical disease with minimal early and late morbidity.[28–30]

5. Conclusion

Although our study was too small to obtain statistically significant results, we believe the findings presented here contribute to the growing body of evidence in this rare tumour type. However, it is clear that large multicenter studies will be necessary to gain a better understanding of uterine sarcoma. Nevertheless, with the exclusion of CS even less patients will contribute for future studies. In our experience, disease stage, LMS histology, and vascular invasion all seem to be relevant for prognosis. As described in literature, no other treatment modality seems to be as effective as hysterectomy with bilateral oophorectomy and adjuvant radiation therapy. Side effects of combined surgery and irradiation are acceptable, since severe side effects are rare.

Conflict of interest

I certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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None declared.

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