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Is adjuvant treatment in early-stage uterine sarcomas beneficial?

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Summary

Objective: To compare overall survival (OS) and disease-free period (DFP) in patients with uterine sarcomas (US) in early stages with and without adjuvant treatment. *Materials and Methods:* One hundred sixteen clinical files with a diagnosis of US were reviewed. These were distributed into two groups: those who received adjuvant treatment with chemotherapy (CT) and/or radiotherapy (RT), and those who did not. Chi-square test was utilized for qualitative and the Mann–Whitney *U* test for quantitative variables. OS and the DFP were calculated with the Kaplan–Meier method and compared with the log-rank test. *Results:* Forty-seven patients were identified with clinical Stages I and II, of whom 25 patients (53.1%) received adjuvant treatment and 22 (46.8%) did not. Of the first group, 18 (72%) were treated with RT and 12 (48%) received CT. Five-year OS in patients who received adjuvant treatment was 68.05% (CI: 41.27–84.58) in comparison with those who did not, which was 78.41% (CI: 51.99–91.36, $p = 0.41$). Five-year DFP in the group that received adjuvant treatment was 46.88% (95% CI, 25.21–65.94), and in the group that did not it was 52.89% (95% CI, 30.00–71.39, $p = 0.56$). *Conclusion:* In early stage US, the benefit in OS and DFP using adjuvant management is limited, therefore, it has to be offered cautiously or not offered to this particular group of patients. Larger number of patients needs to be evaluated and collaborative phase III trial conducted in order to establish the role of adjuvant CT or RT for these neoplasms.

Key words: Sarcomas; Uterine neoplasm; Radiotherapy; Chemotherapy; Adjuvant; Cytoreduction.

Introduction

Uterine sarcomas (US) comprise a heterogeneous group of infrequent mesenchymal tumors that represent 8% of all uterine neoplasms and not more than1% of gynecological neoplasms in general [1]. In Mexico, US constitute 2.16% of all malignant neoplasms, with age-of-presentation most frequently at 40–60 years [2].

US are divided histologically into leiomyosarcomas (LMS), undifferentiated sarcomas (UNS), and endometrial stromal sarcomas (ESS) as the most prevalent [3]. Carcinosarcomas are now considered as endometrial carcinomas with sarcomatoid differentiation; thus, they are stratified and treated as such [4]. US are characterized by aggressive behavior, with a tendency toward local recurrence and distant metastasis; their prognosis is poor and there are few studies that report their incidence, behavior, treatment, and clinical response [5].

The standard treatment-of-choice is hysterectomy, for staging as well as for local control of the disease [1]. There is controversy regarding adjuvant treatment in US, in patients with a diagnosis of LMS in early stages, radiotherapy (RT) does not offer benefit in the disease-free period (DFP) or in overall survival (OS).[6] On the other hand, in a retrospective study on patients with US, those treated with pelvic RT had a lower local recurrence rate in comparison to patients treated with surgery alone (28% *vs*. 48%, $p = 0.0002$), but five-year OS rates (36% *vs*. 27%, $p = 0.10$) and distant metastasis rates (57% *vs*. 54%, $p = 0.96$) were not statistically significant [7]. In terms of the use of chemotherapy (CT), a proposal exists that there should be standard adjuvant treatment, because the risk of having distant disease could be as high as 50% in early stages up to 90% in locally advanced disease, reporting a diminution in the relapse rate of 62% in Stages III and IV in those with adjuvant chemotherapy [8].

The objective of the present study was to compare OS and DFP in patients with US in early stages with and without adjuvant treatment.

Materials and Methods

This is a retrospective study conducted at the Instituto Nacional de Cancerología de México (INCan), where the clinical files of patients with a diagnosis of a uterine neoplasm were reviewed treated between January 2000 and December 2014. All of the patients with a diagnosis of US according to the World Health Organization (WHO) were included, who were in Stages I and II according to International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria, and who were submitted to an initial surgical procedure. Patients were excluded who had another malignant uterine neoplasm including carcinosarcoma and who had

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Table 1. — *General characteristics of patients with early-stage uterine sarcomas.*

	With adjuvant treatment *n* = 25 (53%)	Without adjuvant treatment *n* = 22 (47%)	*p*
Age* (years)	54 (45-58)	47 (39-50)	0.096
Oncological FH**	6 (24)	5 (22.7)	0.918
Smoking**	1 (4)	2 (9.09)	0.593
Menopause*	13 (12-14)	13 (12-13)	0.311
Presentation*			
Bleeding	15 (60)	7 (32)	0.223
Pain	5 (20)	5 (23)	
Pelvic tumor	2 (8)	2 (9)	
Other	3 (12)	8 (36)	
FHR*			
Endometrial stromal sarcoma (ESS)			0.001
Undifferentiated Sarcoma	0 (0)	7 (32)	
Leiomyosarcoma		0 (0)	
Other	9 (36)	13 (59)	
	12 (48)	2 (9)	
	4 (16)		
Stage*			
I	9 (36)	8 (36.3)	0.979
II	16 (64)	14 (63.6)	

*FH: family history; FHR: final histopathological report. *Median (InterQuartile Range [IQR]); **Absolute frequency (relative frequency).*

Table 2. — *Characteristics of the treatment of patients with uterine sarcomas in Stages I and II who received and who did not receive adjuvant treatment.*

	With adjuvant treatment *n* = 25 (53%)	Without adjuvant treatment *n* = 22 (47%)	*p*
Surgery type	19 (76)	19 (86)	0.718
Simple hysterectomy			
Radical hysterectomy	3 (12)	2 (9)	
Cytoreduction	2 (8)	1 (5)	
Pelvic exenteration	1 (4)	0 (0)	
Complete cytoreduction	25 (100)	20 (91)	0.123
Site of the surgery			0.205
INCan	10 (40)	5 (23)	
OINC	15 (60)	17 (77)	
RT	18 (72)	NA	NA
No	7 (28)		
External RT	5 (20)	NA	NA
Combined	13 (52)		
CT	12 (48)	NA	NA
Recurrence and/or progression	13 (52)	11 (50)	0.891
Type of recurrence			
Local	1 (4)	2 (9)	0.814
Regional	1 (4)	1 (5)	
Distant	11 (44)	8 (36)	

BSO: bilateral salpingo-oophorectomy; BPL: bilateral pelvic lymphadenectomy; PAL: para-aortic lymphadenectomy; INCan: Instituto Nacional de Cancerología de México; FINC: outside of the INCan, RT: radiotherapy; CT: chemotherapy. Absolute frequency (relative frequency). NA: not applicable.

Table 3. — *Overall survival and disease-free period between patients with uterine sarcomas who received and who did not receive adjuvant treatment.*

	Med-dian OS	Five-year OS	95% CI	Med-dian DFP	Five-year DFP	95% CI
General	NA	72.93%	55.09-84.61	31.1 mo-nths	49.67%	33.88-63.61
Without adjuvant	NA	78.41%	51.99-91-36	78.37	52.89%	30.00-71.39
With adjuvant	NA	68.05%	41.27-84.58	24.33	46.88%	25.21-65.94

OS: overall survival; DFP: disease-free period; NA: not achieved.

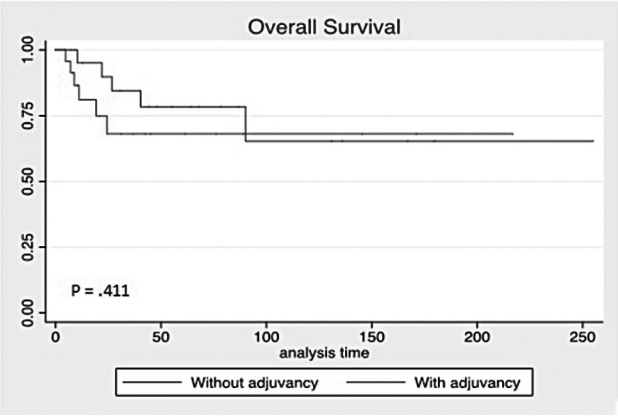

Figure 1. — OS in patients with uterine sarcomas who received and who did not receive adjuvant treatment.

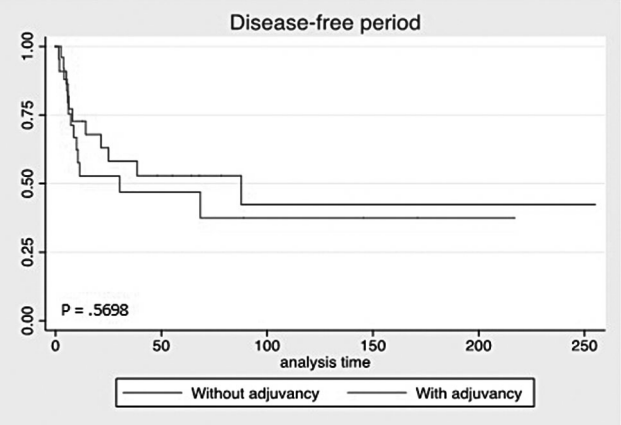

Figure 2. — DFP of patients with uterine sarcomas who received and who did not receive adjuvant treatment.

not been submitted to surgery initially, as well as those with double primaries and incomplete files.

The patients were distributed into two groups: patients who received adjuvant treatment with CT and/or RT, and the remaining group that did not. The following variables were studied: age, familiar history, smoking; menopause, symptom of initial presentation, final histopathological report, clinical stage, type of surgery, type of adjuvant treatment, recurrence, and the progression of each patient. Overall survival (OS) was defined as the period between diagnosis of the disease and death or last follow-up visit, while DFP was defined as the period between initiation of follow-up and the appearance of recurrence or the last follow-up visit. Complete cytoreduction of the surgery was defined as when no visible macroscopic disease was left.

Descriptive statistical analysis was carried out, including central tendency measurements. Inferential statistics were performed of the variables studied by dividing these into two groups: patients who received adjuvant treatment and those who did not, utilizing the chi-squared or the Fisher test for qualitative variables and the Mann–Whitney *U* or the Student *t*-test for quantitative variables, according to the case. OS and DFP were calculated with the Kaplan–Meier method and were compared with the log-rank test. A p value of < 0.05 was taken as statistically significant. The 2015 Stata V.12.0 statistical software program. This study was reviewed and approved by the local IRB according to Declaration of Helsinki statutes.

Results

A total of 116 clinical files of patients with a diagnosis of US between January 2000 and December 2014 were identified; 69 patients were excluded for the following reasons: for having carcinosarcoma, for not having completed their treatment with surgery, or for not being early stage. There were 47 patients with clinical Stages I and II, among whom 25 patients (53.1%) received adjuvant treatment and 22 (46.8%) did not. Median age was 47 years. Regarding type of histology, in the adjuvant treatment group, 12 (48%) were LMS, nine (36%) UNS, and four (16%), of another histology in comparison with the group that did not receive adjuvant treatment, in which 13 (59%) were LMS, seven (32%) EES, and two (9%), another histopathological origin, with a statistically significant difference ($p = 0.001$). According to clinical stage, in the group with adjuvant treatment, nine (36%) were Stage I and 16 (64%) were Stage II, in comparison with the group that did not receive adjuvant treatment, where eight (36.3%) and 14 (63.6%) patients were Stages I and II, respectively. On performing the comparison with the remainder of the demographic variables, no statistical differences were found between groups (Table 1).

Of patients in the adjuvant group, all were submitted to complete cytoreduction, in comparison with the group that did not receive it, where 20 (91%) patients had been submitted to complete cytoreduction. There was no statistically significant difference regarding the institution where the surgery was performed ($p = 0.205$). Of the group that received adjuvant treatment, 18 (72%) patients were treated with RT, including 13 (52%) with external RT and brachytherapy and seven (28%) with external RT alone; similarly, 12 (48%) received CT. Recurrence and/or disease progression was present in 24 patients. Of these, 13 (52%) were from the group with adjuvant treatment, with one (4%) local, one (4%) regional, and 11 (44%) distant. This was in contrast with the group that did not receive adjuvant management, where 11 (50%) presented recurrence and/or progression, as local, regional, and distant in two (9%), one (5%), and eight (36%), respectively, without finding statistical significance between the two groups ($p = 0.891$) (Table 2).

General five-year DFP was 49.67% (95% CI, 33.8–63.61) with a median of 31.1 months, while general five-year OS was 72.93% (95% CI, 55.09–84.61%), without reaching the median (Table 3). With regards to five-year OS in patients who received adjuvant treatment, this was

68.05% (95% CI, 41.27–84.58) in comparison with those who did not receive it, where this was 78.41% (95% CI, 51.9–991.36), without being statistically significant (p = 0.41) (Figure 1). Five-year DFP in the group that received adjuvant treatment was 46.88% (95% CI, 25.21–65.94) in contrast with the group that did not, where this was 52.89% (95% CI, 30.00–71.39), not being statistically significant (p = 0.56) (Figure 2).

Discussion

Evaluation of OS and DFP in US is difficult due to its scarce frequency, its histopathological variety with distinctive characteristics, and its aggressiveness. In this study, differences were not found when comparing OS and DFP in the groups studied. According to Mangioni *et al.*, in a multicenter study that included 219 patients in clinical Stages I and II, the patients were randomly assigned into two groups: 109 (49.7%) patients were assigned to the observation treatment arm and 110 (51%) patients to the adjuvant pelvic RT treatment arm; 99 (49.3%) were LMS, 92 (40.9%) were carcinosarcomas, and 30 (12.6%) were ESS. In the initial analysis, a local relapse rate and a distant metastasis rate were demonstrated in 24 (22%) and in 49 (46%) patients of the group that received adjuvant treatment, against 44 (40%) and 35 (32%) patients of the group that did not receive it, respectively. The difference in local or regional disease progression between the two treatment arms was statistically significant, being present in 24 (22%) patients of the group that received adjuvant management in comparison to 44 (40%) patients of the group that did not (p = 0.004) [8].

In the present study, the authors did not find that the group that received adjuvant treatment had more poor histology neoplasms, such as UNS or LMS, for which is an expected management due to the tumor biology in these particular groups. LMS is a very aggressive tumor that is associated with poor prognosis, even when it is found confined to the uterus. Even when diagnosed at early clinical stages, LMS recurrence rates range between 53% and 71%, and the OS rate ranges between 15% and 25%, depending on the tumor's characteristics [9, 10].

EES have a recurrence rate of up to 50%, localized to the pelvis as the most common, although pulmonary metastasis can occur (9–43% of the recurrent tumors and in even 10% of Stage I tumors). Five-year OS is 67–100%, with a median of 11 years. UNS, on the other hand, present rapid progression, with frequent, generally pelvic, prior to two years after the initial diagnosis [11].

In the present study, complete cytoreduction was performed in 100% of patients who received adjuvant treatment and in 91% of those who did not. It is very probable that the capacity to perform a surgical procedure without leaving residual tumor is related with the stage, because in the most advanced stages, above all when there is distant disease, procuring the resection of the whole tumor is difficult to achieve. The place or institution where the initial surgery was performed, whether outside a specialized center such as the Instituto Nacional de Cancerología de México (INCan) or not, does not exert an impact on the prognosis. This can be due to the stage at presentation were hysterectomy with or without salpingo-oophorectomy (SOP) is sufficient and does not require specialized surgeons or gynecologists for its performance.

In the present study, there was no statistical significance in terms of frequency or recurrence and/or progression (p = 0.891), or in recurrence type (p = 0.814) in the groups studied. The most frequent recurrence type in both groups was distant. This is expected for this type of neoplasm, because sarcomas tend to recur at a distance. In a multicentric study where patients were analyzed with sarcomas at Stages I and II, 72% presented distant recurrence.[12]

In terms of the strengths of the study, it is noteworthy that adequate patient selection was achieved, excluding carcinosarcomas, that all cases were at early clinical stages, and that, to the authors' knowledge, this is the first study with these characteristics in Mexican population. Among the study's limitations, they find the reduced number of patients evaluated, the retrospective characteristics, and a selection bias in the histology, that could have exerted an influence on the results, above all due to it being a heterogeneous group.

Conclusions

US are malignant heterogeneous neoplasms. In the patients analyzed at the INCan with this type of neoplasm, statistically significant differences were not found in OS and in DFP between the group of patients who received adjuvant treatment and the group that did not. This is a hypothesis generator study; thus, controlled and randomized prospective studies that will require interinstitutional collaboration to achieve having an adequate number of patients are needed, as well as the identification of the best adjuvant treatment scheme, in the case of the latter playing a role in the management of these patients.

However, with the evidence presented and at a site where there are insufficient resources for the administration of adjuvant treatment, it would be acceptable not to provide this type of management, because identification of a statistical advantage has not been feasible, either in OS or in DSF.

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