INTRODUCTION

Myxofibrosarcoma (MFS) is one of the most common STS of elderly patients. Histologically, it is classified as a spectrum of fibroelastic lesions with variable myxoid stroma, pleomorphism and a distinctive curved-shaped vascular pattern. It was classified as a unique entity by the World Health Organization (WHO) in 2002, due to its own clinical pattern and pathological behavior. Commonly they rise in the extremities, but they can be found in the abdomen, retroperitoneum and in the head as well. Surgery continues to be the gold standard treatment for MFS. To achieve wide surgical margins during the procedure, is not only the desirable goal of every surgeon, but also remains a challenge due to its poorly understood behavior. Chemotherapy (CT) and radiotherapy (RT) can be used as adjuvant or neoadjuvant settings, but the definitive role of both are not totally defined. They can be also used as palliative therapies for metastatic patients. But still, little have been investigated and documented about the clinical treatment of the disease. Given the lack of randomized trials for MFS, the definitive role of both are not totally defined. They can be also used as palliative therapies for metastatic patients.
the creation of treatment guidelines, the outcomes and prognostic factors for MFS, remain uncertain. They exhibit a relatively better OS rate than other STS, however, their propensity for LR, which can be as high as 60%, still remains as an important issue. Also, LR is directly associated with tumor grade and DM. Some studies, with poor casuistry, suggest that tumor size, positive surgical margins at resection and necrotic percentage, are possible prognostic factors for OS. Nevertheless, an advantage in the prognosis of MFS, is a low risk of DM with reports in between 20-30% and an OS with reports in between 70-80% in five years. However, no large publications have yet totally investigated or defined the prognostic factors of MFS. Then, in an effort to improve the understanding of the clinical outcomes and the prognosis of appendicular MFS, we conducted a retrospective study, evaluating a series of 75 patients, with the purpose of describing the factors associated with the poor prognosis of the disease after surgical treatment.

**MATERIALS AND METHODS**

A retrospective study was performed after we obtained the approval from the ethical committee review board from our institute. We identified the clinical records from every patient diagnosed with MFS that underwent surgery, in the division of orthopedic oncology, in the last 25 years. A total of 75 patients with MFS in the extremities were included in this study. All the patients with incomplete data in the medical files, with the tumor located in the trunk or the head and that didn’t received surgery as treatment, were excluded from our investigation. Diagnoses were performed by the pathology division of our institute, based on the WHO classification of STS. Demographic data including: gender, age, tumor location, surgery and number of surgeries, surgical margins, histologic grade, adjuvant or neoadjuvant therapy, LR and time to develop LR, DM and time to develop DM, follow up and oncologic status were collected. Histologic grade was determined based on French Federation of Cancer Centers (FNCLCC). The decision on using CT and RT for each patient was studied in multidisciplinary meetings. Of these patients, 44 were female and 31 were male, with a mean age of 53 (range, 1-88 years). Most of the tumors (56%) appeared on the right side of the body. The thigh was the most affected anatomical location with 31 cases, followed by the calf 16 cases, forearm 10 cases, pelvis 6 cases, shoulder 4 cases and arm and foot with 3 cases each (Table 1). The size of the tumor was divided in four groups in accordance with the American Joint Committee on Cancer (AJCC) staging system. Group II had 32 patients, group III had 19 patients, group IV had 14 patients and group I had 10 patients reported (Table 1). Sixty four (85.3%) patients received tumor wide resection surgery, while 11 (14.7%) patients underwent limb amputation.Margins were microscopically positive in 18 (24%) cases and negative in 57 (76%) cases. Most cases, 35 (46.7%), had grade 3 (FNCLCC) tumor report. LR was found in 20 (26.7%) cases, of which, 16 (80%) underwent multiple surgical procedures (MSP). Also, we had 27 (36%) reports of DM, being the lungs 25 (95%), lymph nodes 5 (18.5%), abdominal cavity 2 (7.4%) and brain 1 (3.7%) the affected sites (Table 1). Twenty (26.7%) patients received neoadjuvant RT. Median follow up in this study was 30.7 months (range, 1.8-383.8 months among surviving patients). Median survival time was 29 months, OS rate was 59.3%. Twenty three (30.7%) patients died of the disease (Table 1). Pathology reports of surgical margins, LR and OS after the first surgery, were considered the principal objectives of this study. Time for LR, single or multiple, was calculated from the first surgical procedure. OS was estimated using the Kaplan-Meier method. The relation between single surgical procedure (SSP), LR, DM and oncologic status were investigated using the log-rank test for categorical variables. Differences of the p < 0.05 were considered statistically significant.

| Variable Description (n=75) | Variable | Description (n=75) |
|----------------------------|----------|-------------------|
| Gender                     |          | Gender            |
| female                     |          | female            |
| male                       |          | male              |
| Follow up (months)         |          | Follow up (months) |
| mean ± SD                  |          | mean ± SD         |
| OS                          |          | OS                |
| Grade, n (%)               |          | Grade, n (%)      |
| I                          |          | I                 |
| II                         |          | II                |
| III                        |          | III               |
| Local, n (%)               |          | Local, n (%)      |
| shoulder                   |          | shoulder          |
| arm                        |          | arm               |
| forearm                    |          | forearm           |
| hand                       |          | hand              |
| pelvis                     |          | pelvis            |
| thigh                      |          | thigh             |
| calf                       |          | calf              |
| foot                       |          | foot              |
| Size, n (%)                |          | Size, n (%)       |
| < 5cm                      |          | < 5cm             |
| 5cm to 9.99cm              |          | 5cm to 9.99cm     |
| 10cm to 14.9cm             |          | 10cm to 14.9cm    |
| >15cm                      |          | >15cm             |
| Side, n (%)                |          | Side, n (%)       |
| right                      |          | right             |
| left                       |          | left              |
| Surgery, n (%)             |          | Surgery, n (%)    |
| resection                  |          | resection         |
| amputation                 |          | amputation        |
| Margins, n (%)             |          | Margins, n (%)    |
| negative                   |          | negative          |
| positive                   |          | positive          |
| Adjuvance, n (%)           |          | Adjuvance, n (%)  |
| yes                        |          | yes               |
| no                         |          | no                |
| Local Recurrence, n (%)    |          | Local Recurrence, n (%) |
| yes                        |          | yes               |
| no                         |          | no                |
| Multiple Surgeries, n (%)  |          | Multiple Surgeries, n (%) |
| yes                        |          | yes               |
| no                         |          | no                |
| Distant Metastasis, n (%)  |          | Distant Metastasis, n (%) |
| yes                        |          | yes               |
| no                         |          | no                |
| Local for Distant Metastasis, n(%)* |          | Local for Distant Metastasis, n(%)* |
| abdomen                    |          | abdomen           |
| brain                      |          | brain             |
| lung                       |          | lung              |
| lymph nodes                |          | lymph nodes       |
| Death, n (%)               |          | Death, n (%)      |
| yes                        |          | yes               |
| no                         |          | no                |
| Overall Survival, n(%)**   |          | Overall Survival, n(%)** |
| median (min., max.)        |          | median (min., max.) |
| mean ± SD                  |          | mean ± SD         |

* Based on patients with metastasis; ** For the 23 patients that died.

Estimated using the Kaplan-Meier method. MSP, DM and deaths were considered the secondary objectives of this study. Also, we calculated the OS, time to LR and DFOS using Kaplan-Meier functions and log-rank tests to compare the outcomes of the qualitative variables. The influence of age on the outcomes of the patients was tested using the Cox bivariate regression. The not adjusted HR with their respective confidence interval of 95%, were calculated using the Cox bivariate regression. The selected variables that when together presented significant level of 5% in the final model,
were tested in multiple models also. For all the statistical analyses, we used the IBM-SPSS software for Windows version 20.0. For tables and charts, we used the Microsoft Excel 2008 version software. All the tests were realized with a significant level of 5%.

RESULTS

LR was statistically influenced by tumor margins, MSP and DM (p < 0.001) (Figures 1-3). FDOS was statistically influenced by tumor grade (FNCLCC), tumor margins, MSP and DM (p < 0.05). LR suffered statistical influence by MSP alone or by tumor margins and DM together. Patients with MSP had 18.82 times a higher risk of LR than patients that had SSP. Positive microscopically margins with DM had 2.84 times a higher risk of LR than negative microscopically margins. Patients with DM had 6.59 times a higher risk of LR than patients without metastasis. DFOS was statistically influenced by MSP and DM. Patients with MSP had 3.11 times a higher risk of diminished DFOS, and patients with reports of DM had 8.17 times a higher risk of diminished DFOS (Figure 4). OS was statistically influenced by tumor grade (FNCLCC), LR, MSP and DM (p < 0.05) (Table 2-3) (Figure 5-6). Together, tumor grade (FNCLCC) and LR had a negative influence in the OS of the patients, being grade III (FNCLCC) 5.79 times a higher risk of death than grade I (FNCLCC) (p = 0.022), and patients with LR had 3.72 times a higher risk of death than patients with no report of LR (p = 0.003). DM is probably the most important prognostic factor to explain OS in patients with MFS, but we were not able to use this variable since none of the patients without metastasis died.

DISCUSSION

MFS it’s a rare tumor that represents 5% of all STS. Considered as the most frequent STS in elderly patients, it has a high rate of LR when compared with other sarcomas. MFS is usually reported as a high grade tumor, with an important potential of DM. It is also often inappropriate excised, due to its variable presentation, infiltrative growth pattern and multiple onset location. The reasons of the high rates of LR are not completely understood. Some authors believe that MFS cause an extensive invasion on the neighbor tissues, fact that is not visible during surgery. Reports of small superficial MFSs, excised in not oncologic centers, treated as benign tumors, which end up being referred to specialized center with LR, is a common finding. Some facts, described in few studies, can be considered to be important for the prognosis of MFS: tumor grade, surgical inadequate or positive margins, LR and DM. To our knowledge, this is the first study that describes MFS as a unique entity, in a Latin American hospital, and the casuistry in this case series, is among the largest found in the investigated studies. In our study, 75 patients with pathologically confirmed diagnosis of MFS, and a median follow up of 30.7 months presented: 25% had positive surgical margins, 46.7 % had high grade tumors, 26.7 % had reports of LR and 36% presented DM. This study had a number of limitations. First, the lack of studies on this disease as a unique entity becomes a major difficulty on the research for information. Also the publications are
Table 2. Analysis of the estimated overall survival of patients according to the different characteristic.

| Variable | Estimated mean time (months) | CI 95% | HR not adjusted | IC 95% | Death | Total N | % | p |
|----------|------------------------------|-------|-----------------|-------|-------|---------|---|---|
| Gender   |                              |       |                 |       |       |         |   |   |
| female   | 246.82                       | 181.85| 311.78          | 1.00  | 11    | 44      | 25.0| 0.166 |
| male     | 162.55                       | 111.93| 213.17          | 1.77  | 0.78  | 4.02    | 12 | 31 | 38.7 |
| Age (years) |                              |       |                 |       |       |         |   |   |
| Grade    |                              |       |                 |       |       |         |   |   |
| I        | 340.98                       | 285.18| 396.77          | 1.00  | 2     | 22      | 9.1 | 0.002 |
| II       | 183.11                       | 107.12| 259.10          | 3.54  | 0.68  | 18.31   | 5  | 18 | 27.8 |
| III      | 121.71                       | 70.09 | 173.34          | 8.70  | 1.96  | 38.17   | 16 | 35 | 45.7 |
| Local    |                              |       |                 |       |       |         |   |   |
| shoulder | 200.73                       | 89.87 | 311.58          | 0.98  | 0.11  | 8.74    | 1  | 4  | 25.0 |
| arm      | 160.23                       | 46.08 | 274.39          | 0.96  | 0.11  | 8.58    | 1  | 3  | 33.3 |
| forearm  | 102.93                       | 67.52 | 138.35          | 1.02  | 0.19  | 5.62    | 2  | 10 | 20.0 |
| hand     | 65.57                        | 65.57 | #                | #     | 0     | 2       | 0   | 0.0 |
| thigh    | 176.07                       | 123.67| 228.47          | 1.22  | 0.31  | 9.63    | 2  | 6  | 33.3 |
| calf     | 258.64                       | 157.97| 352.31          | 1.00  | 0.57  | 17.39   | 4  | 16 | 25.0 |
| Size     |                              |       |                 |       |       |         |   |   |
| <5cm     | 337.53                       | 252.75| 422.31          | 1.00  | 1     | 10      | 10  | 10.0 |
| 5 to 9.9cm | 158.06                      | 111.70| 204.42          | 3.56  | 0.45  | 27.82   | 10 | 32 | 31.3 |
| 10 to 14.9cm | 177.91                     | 112.21| 243.61          | 4.04  | 0.50  | 32.87   | 7  | 19 | 36.8 |
| >15cm    |                              |       |                 |       |       |         |   |   |
| Side     |                              |       |                 |       |       |         |   |   |
| right    | 165.80                       | 118.40| 213.20          | 1.00  | 0.21  | 1.24    | 7  | 33 | 21.2 |
| left     | 272.38                       | 203.31| 341.65          | 0.51  | 0.21  | 1.24    | 7  | 33 | 21.2 |
| Surgery  |                              |       |                 |       |       |         |   |   |
| resection| 234.23                       | 182.39| 286.08          | 1.00  | 0.38  | 4.35    | 3  | 11 | 27.3 |
| amputation| 173.94                     | 76.66 | 271.02          | 1.28  | 0.38  | 4.35    | 3  | 11 | 27.3 |
| Margins  |                              |       |                 |       |       |         |   |   |
| negative | 274.12                       | 222.67| 325.36          | 1.00  | 0.93  | 4.87    | 10 | 18 | 55.6 |
| positive | 73.44                        | 49.32 | 97.57           | 2.13  | 0.93  | 4.87    | 10 | 18 | 55.6 |
| Adjuvance|                              |       |                 |       |       |         |   |   |
| yes      | 185.10                       | 122.67| 247.34          | 0.91  | 0.38  | 2.22    | 7  | 20 | 35.0 |
| no       | 239.95                       | 182.96| 296.95          | 1.00  | 1.25  | 7.24    | 16 | 55 | 29.1 |
| L. Recurrence |                          |       |                 |       |       |         |   |   |
| yes      | 31.11                        | 30.73 | 31.87           | 1.00  | 5.04  | 58120.3 | 23 | 27 | 85.2 |
| no       | 383.77                       | 383.77| 383.77          | 1.00  | 0     | 0.0     | 0  | 0  | 0.0 |
| Total    | 236.82                       | 189.17| 285.47          | 1.00  | 24    | 75      | 32.0|   |

Log-rank test; *Cox bivariate regression results.

Table 3. Results of the adjusted models for overall survival, local recurrence and disease free overall survival.

| Outcome Model | Variable | HR adjusted | CI (95%) | p |
|---------------|----------|-------------|----------|---|
| Grade (ref.: I) | II       | 2.38        | 0.45 12.74 | 0.031 |
| Initial   | III      | 5.59        | 1.22 25.51 | 0.026 |
| Margins (positive) | III     | 5.59        | 1.22 25.51 | 0.026 |
| Overall   | Multiple Surgeries | 0.47 | 1.15 2.14 | 0.214 |
| Survival  | Multiple Surgeries | 0.47 | 1.15 2.14 | 0.214 |
| Grade (ref.: I) | Final   | II          | 2.54    | 0.48 13.41 | 0.027 |
| Recurrence | Metastasis | 1.59        | 0.44 4.82 | 0.692 |
| Local     | Multiple Surgeries | 18.82 | 4.35 81.38 | <0.001 |
| Metastasis | Multiple Surgeries | 6.59 | 2.17 20.02 | 0.001 |
| Disease   | III      | 2.15        | 0.52 8.98 | 0.294 |
| Free      | Initial | 0.75        | 0.30 1.90 | 0.546 |
| Overall   | Multiple Surgeries | 0.82 | 2.07 6.68 | 0.668 |
| Survival  | Multiple Surgeries | 3.91 | 1.35 10.06 | 0.004 |
| Metastasis | Metastasis | 6.04 | 1.99 19.09 | 0.002 |
| Final     | Metastasis | 3.11 | 1.32 7.34 | 0.009 |
| Metastasis | Metastasis | 8.17 | 2.68 24.92 | <0.001 |

Cox multiple regression.
specifically when they are inadequate. But evidence supports that positive margins, in fact, increases LR, affecting the DFS. As for DM, most of the studies report low rates with a range varying from 15% to 30%. The most common affected organ is the lung. In accordance to the findings in literature, our rate of DM was 36%, also being the lung the predominant affected organ. Although, the prognostic factors for MFS haven’t been totally defined, there are some facts about the disease that have a direct connection with OS. Authors agree that tumor grade and surgical margins have a close relation with LR, being grade III tumors and reports of positive or not adequate margins, important factors for increasing the rates of LR. Another important fact is that the LR also increases the potential for DM, which has a direct effect on follow up time and consequently OS. In our study, we identified that high grade tumors and positive margins, alone or together, directly increase the rates of LR. Also, we observed that LR has a principal role on the DM appearance. Interestingly, these facts separately or in group affect directly the OS of the patient with MFS. Anyhow, future studies are needed, to see whether these results are similar or not to the new information obtained.

CONCLUSION
In this institutional series of MFS, positive margins and DM were significantly associated with a higher risk of LR. Tumor grade, positive margins LR and DM are significant predictors of OS poor prognosis.

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