CLINICS

CLINICAL SCIENCE

Comparative study of planned and unplanned excisions for the treatment of soft tissue sarcoma of the extremities

Carlos E. H. Hanasilo,[I] Marcelo S. Casadei,[I] Leandro Auletta,[I] Eliane M. I. Amstalden,[II] Silvia R. F. Matte,[I] Mauricio Etchebehere[I]

[I]Universidade Estadual de Campinas (UNICAMP), Faculdade de Ciências Médicas, Orthopedics, Campinas/SP, Brazil. [II]Universidade Estadual de Campinas (UNICAMP), Pathology, Campinas/SP, Brazil.

OBJECTIVE: Unplanned excision of soft tissue sarcomas is common because benign soft tissue lesions are very frequent. This study evaluated the impact of unplanned resections on overall survival, local recurrence and distant metastasis in patients with soft tissue sarcomas of the extremities.

METHODS: In total, 52 patients who were diagnosed with soft tissue sarcomas between May 2001 and March 2011 were analyzed in a retrospective study. Of these patients, 29 (55.8%) had not undergone previous treatment and the remaining 23 (44.2%) patients had undergone prior resection of the tumor without oncological planning. All subsequent surgical procedures were performed at the same cancer referral center. The follow-up ranged from 6 to 122 months, with a mean of 39.89 months. Age, lesion size and depth, histological grade, surgical margins, overall survival, local and distant recurrence and adjuvant therapies were compared.

RESULTS: Residual disease was observed in 91.3% of the re-resected specimens in the unplanned excision group, which exhibited greater numbers of superficial lesions, low histological grades and contaminated surgical margins compared with the re-resected specimens in the planned excision group. No differences were observed in local recurrence and 5-year overall survival between the groups, but distant metastases were significantly associated with planned excision after adjustment for the variables.

CONCLUSIONS: There was no difference between patients undergoing unplanned excision and planned excision regarding local recurrence and overall survival. The planned excision group had a higher risk of distant metastasis, whereas there was a high rate of residual cancer in the unplanned excision group.

KEYWORDS: Sarcoma; Prognosis; Surgery; Extremities.

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E-mail: marcelocasadei@yahoo.com.br, mscthet@yahoo.com.br

Tel.: 55 19 99842-9067

INTRODUCTION

Soft tissue sarcomas (STSs) are rare primary malignant neoplasms that originate from the mesoderm and account for less than 1% of all malignant tumors. STSs may appear at any age and with virtually any localization (1-3) but predominantly occur in the extremities (in approximately two-thirds of cases) (3). According to the World Health Organization (WHO), the incidence of STSs is 30 cases per million people per year (4). Most STSs have no clearly defined etiology, but multiple associated and predisposing factors, such as genetic mutations in pluripotent mesenchymal stem cells and exposure to radiation and certain herbicides, have been described (3,4).

The ability of surgeons and radiotherapists to accurately assess the extent of the disease from clinical examinations and images, and especially magnetic resonance imaging (MRI) has improved local control of the disease in 95% of cases (8,9). Prompt diagnosis and treatment at an oncology center using biopsies, planned wide resections and adjuvant therapy have increased the 5-year survival rate from 62% to 84% (2,10-12).

Certain STSs are inadvertently and inappropriately resected prior to correct diagnosis following an anatomopathologic examination because although STSs are rare, benign tumors are very common in soft tissues (3,000 new cases per million per year, compared with 30 cases of STSs) (4). Oversight in STS management is associated with the inexperience of surgeons at non-oncology institutions (2,13).

No potential conflict of interest was reported.

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Giuliano and Eilber (7) introduced the term ''unplanned total excision'' for the macroscopic removal of STSs without consideration of preoperative images or the surgical margins of the normal tissue around the tumors. Noria et al. (11) further described this term with respect to STS as unplanned resection of a lesion without taking advantage of the benefits of preoperative diagnostic modalities and without the intention to achieve tumor-free margins.

Unplanned excision (Unpex) of STSs occurs often, but the negative effects of this manipulation on definitive local and systemic treatments and prognosis remain controversial (14). The prognostic factors for Unpex are not as well defined as the prognostic factors for STSs that are removed exclusively at oncology centers. The prognostic factors for patient survival in STS cases include clinical stage, histological grade and subtype, size, depth, metastasis at diagnosis and the location of the primary disease. These factors differ from the most important factors in local disease control: surgical margins and adjuvant radiotherapy (5,14).

The objective of this study was to evaluate the impact of these unplanned resections on overall survival, local recurrence and distant metastasis in patients with STSs of the extremities.

MATERIALS AND METHODS

The records of patients who were treated at the Orthopedic Oncology Service of Hospital de Clínicas of the University of Campinas (HC-UNICAMP) were assessed. Only patients over 14 years old who had a diagnosis of an STS in the extremities and who were initially treated at another institution or directly referred to HC-UNICAMP for initial treatment from May 2001 to March 2011 were included. Patients without neoplasms in the extremities (e.g., the head, neck, trunk or retroperitoneum) and patients who had not undergone definitive surgical treatment were excluded. The Institutional Review Board of the Faculty of Medical Sciences of UNICAMP (FCM-UNICAMP) approved this study.

A total of 52 patients with STSs (Table 1), comprising 30 (57.7%) males and 23 (42.3%) females with a mean age of 44.96±17.23 years (16.92 to 80.69) at admission, were included. Of these patients, 29 (55.8%) have undergone surgeries exclusively at our center (i.e., planned surgeries (Pex)). The remaining 23 (44.2%) patients had undergone prior unplanned resection (Unpex) and were treated with definitive planned resection at our center.

The patients were divided into high- and low-grade sarcoma groups based on histological grade, which was determined by a single specialist in musculoskeletal tumors in the Department of Anatomopathology at FCM-UNICAMP using a three-level scale: grade I was considered as low grade, and grades II and III were considered as high grade (3).

Lesion size was assessed by MRI or specimen resection using the larger diameter or axis as a reference.

Sarcoma depths were divided into superficial (above the muscle fascia) and deep (below the muscle fascia) lesions.

The surgical margins of the specimens resected during definitive surgery were divided into groups based on Enneking's classification (15,16): 1. a positive margin with the presence of neoplasms at any portion of the borders previously marked, 2. a negative margin with neoplasms less than 10 mm from the edges of the resection, and 3. a negative margin with neoplasms at a distance equal to or greater than 10 mm from the edges of the resection.

Table 1 - Descriptive statistics.

Variable	N	%
Gender		
Female	22	42.3%
Male	30	57.7%
Mean age (years)	44.96±17.23	
Follow-up (months)	39.9±29.3	
Type of resection		
Planned	29	55.8%
Unplanned	23	44.2%
Histological grade		
Low	4	7.7%
High	48	92.3%
Size		
<5 cm	6	11.5%
≥5 cm	46	88.5%
Depth		
Superficial	5	9.6%
Deep	47	90.4%
Surgical margins		
Positive	5	9.6%
Negative, <10 mm	18	34.6%
Negative, ≥10 mm	29	55.80%
Radiotherapy	29	55.7%
Chemotherapy	33	63.4%
Amputations/disarticulations	21	40.4%
Postoperative complications	10	19.2%
Soft tissue reconstruction	2	4%
Positivity for residual disease (Unpex group)	21	91.3%
Local recurrence (months)	4 (14.4±4.7)	7.7%
Distant metastases (months)	23 (10 at admission) (13 after admission 14.4±10.5)	44.2%
Death (months)	10 (31±3.8)	19.2%

The rate of residual disease (i.e., the presence of viable neoplasms) was evaluated for the re-resected specimens from the Unpex group.

Amputations or disarticulations and complications after definitive surgery, chemotherapy and radiotherapy were assessed in both groups. Local recurrence was verified after definitive surgery using clinical examinations and MRI during the follow-up exams. Distant metastases were identified using computed tomography examinations and/or bone scintigraphy. The overall survival time was measured from the date of patient admission to patient death. Patients who left prior to the end of the 5-year follow-up were punctually censored on 5-year survival curves.

Statistical analyses were performed. Categorical variables were analyzed using frequency tables and quantitative variables were analyzed using descriptive measures (e.g., the mean and standard deviation). Chi-squared association tests (e.g., Fisher's exact test and Pearson's Chi-square test) were used for bivariate analyses. Multivariate analyses were performed using Cox multivariate and logistic regression, with a confidence interval (CI) of 95%. An analysis of survival was performed using Kaplan-Meier curves. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

The distribution of histological STS subtypes revealed synovial sarcoma in 11 patients (21.2%) and liposarcoma,

malignant fibrous histiocytoma and myxofibrosarcoma in six patients each (11.5%) (Table 2).

The majority (92.3%) of lesions were high grade. The remaining 7.7% of lesions were classified as low grade and these lesions were only identified in patients in the Unpex group.

Among all sarcomas, 11.5% were smaller than 5 cm and 88.5% were greater than or equal to 5 cm.

Deep sarcomas represented the majority (90.4%) of cases. Among superficial STSs, four were in the Unpex group and only one was in the Pex group.

In addition, the surgical margins of the definitive surgical resection specimens revealed positive margins in five patients (9.6%), negative margins of less than 10 mm in 18 patients (34.6%) and negative margins greater than or equal to 10 mm in 29 patients (62% and 55.80%, respectively). Eighteen (62%) of these last 29 patients with negative margins had undergone amputations or disarticulations.

Radiotherapy treatment was prescribed for 29 (55.7%) of 52 patients in the study, regardless of the size ($p = 0.39$), histological grade ($p = 0.06$) or depth ($p = 0.64$) of the lesion; the condition of the surgical margins ($p = 0.06$); or the incidence of local recurrence ($p = 0.12$).

Chemotherapy was initiated in 33 patients (63.4%) in the sample. This therapy was prescribed significantly more often for STSs that were greater than or equal to 5 cm ($p = 0.02$), high grade ($p = 0.01$) and deep ($p = 0.01$) and that had distant metastases ($p = 0.01$).

In total, 21 patients underwent amputation or disarticulation procedures in this study (40.4%), with 13 (44.8%) in the Pex group and eight (34.8%) in the Unpex group.

Among the 10 patients diagnosed with postoperative complications (19.2%), we found five cases of infection (9.6% of the subjects), two cases of phantom pain after amputation, one case of dehiscence of the surgical wound and two cases of pathologic fracture. One fracture occurred after radiotherapy, without evidence of recurrent neoplasms and the other occurred during local recurrence.

Two patients (4%), both of whom belonged to the Unpex group, underwent procedures for the reconstruction of soft tissue due to inappropriate coverage of the surgical wound.

We analyzed the rate of residual disease as part of re-resection, such as the expansion of surgical margins and positivity was found in 91.3% of patients (21/23). Of the 23 patients in the Unpex group, only four arrived without apparent disease, based on either physical examination or imaging at baseline at HC-UNICAMP. After undergoing margin expansion, two of these four patients had residual disease upon pathologic evaluation.

Table 2 - Histological type.

Synovial sarcoma	11(21%)
Liposarcoma	6(11%)
Malignant fibrous histiocytoma	6(11%)
Myxofibrosarcoma	6(11%)
Clear-cell sarcoma	4(8%)
Malignant schwannoma	3(6%)
Rhabdomyosarcoma	3(6%)
Dermatofibrosarcoma protuberans	3(6%)
Chondrosarcoma	2(4%)
Leiomyosarcoma	2(4%)
Pleomorphic sarcoma	2(4%)
Fibrosarcoma	1(2%)
Alveolar Sarcoma	1(2%)
Soft tissue Ewing sarcoma/PNET	1(2%)
Fibromyxoid sarcoma/Evans	1(2%)

Pex compared with unpex

The Pex and Unpex groups did not differ in gender, age at admission, length of follow-up, lesion size, radiotherapy, chemotherapy, amputation, postoperative complications, soft tissue reconstruction procedures, local recurrence, distant metastasis or death (Table 3). The Unpex group had a higher proportion of superficial sarcomas ($p = 0.013$), low histological grades ($p = 0.033$) and positive margins after re-resection at HC-UNICAMP ($p = 0.034$) compared with the Pex group. Survival curves were calculated using 5-year Kaplan-Meier analysis with a Cox model and they showed no difference for local recurrence-free survival (96.5% *versus* 86.2% for Pex *versus* Unpex, respectively; $p = 0.31$), metastasis-free survival (51.9% *versus* 74.9% for Pex *versus* Unpex, respectively; $p = 0.07$) or overall survival (46.1% *versus* 82.7% for Pex *versus* Unpex, respectively; $p = 0.16$) (Figures 1 to 3). In the multivariate analysis, the occurrence of local recurrence ($p = 0.17$) and death ($p = 0.17$) remained not significantly different between the groups. However, after performing the multivariate analysis, we verified that patients undergoing Pex had an 8.17 times higher risk of developing distant metastases compared with the Unpex group ($p = 0.03$).

Local recurrence

Four (7.7%) local relapses were observed: three in the Unpex group and one in the Pex group (Table 1). The mean

Table 3 - Comparison between planned and unplanned resections.

Variables	Pex	Unpex	*p*
Gender			
Female	13 (44.8%)	9 (39.1%)	0.449
Male	16 (55.2%)	14 (60.9%)	
Age			
<50 years	18 (62.1%)	15 (65.2%)	0.523
≥50 years	11 (37.9%)	8 (34.8%)	
Follow-up			
< 40 weeks	21 (72.4%)	14 (60.9%)	0.279
≥ 40 weeks	8 (27.6%)	9 (39.1%)	
Size			
<5 cm	3 (10.3%)	3 (13.0%)	1.00
≥5 cm	26 (89.7%)	20 (87.0%)	
Depth			
Superficial	0	5 (21.7%)	0.013*
Deep	29 (100.0%)	18 (78.3%)	
Histological grade			
Low	0	4 (17.4%)	0.033*
High	29 (100.0%)	19 (82.6%)	
Surgical margins (definitive)			
Positive	1 (3.4%)	4 (17.4%)	0.034*
Negative, <10 mm	14 (48.3%)	4 (17.4%)	
Negative, ≥10 mm	14 (48.3%)	15 (65.2%)	
Radiotherapy	18 (62%)	11 (47.8%)	0.4
Chemotherapy	21 (72.4%)	12 (52.1%)	0.16
Amputations/disarticulations	13 (44.8%)	8 (34.8%)	0.57
Postoperative complications	5 (17%)	5 (21.7%)	0.47
Soft tissue reconstruction	0	2 (8.7%)	0.19
Local recurrence	1 (3.4%)	3 (13%)	0.750
Distant metastases	15 (51.7%)	8 (34.8%)	0.772
Death	7 (24.1%)	3 (13%)	0.667

*$p<0.05$, indicating that the test result confirms a statistically valid association between the tested variables.

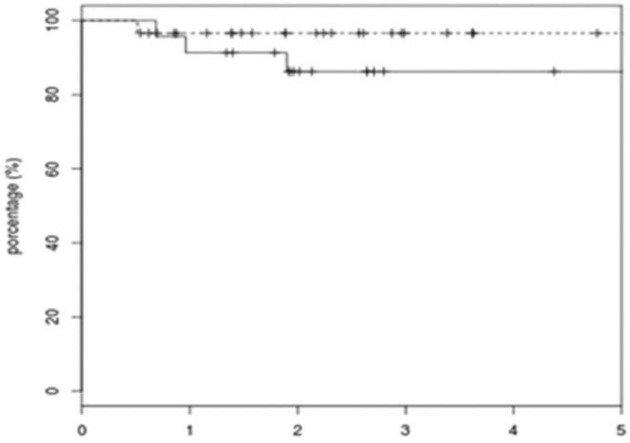

Figure 1 - Kaplan-Meier analysis of 5-year survival free of local recurrence comparing Pex (---) with Unpex (—). Pex: 96.5% ×Unpex: 86.2% ($p = 0.31$).

time to the onset of local recurrence was 14.4 ± 4.7 months after definitive surgery performed at HC-UNICAMP. Five-year recurrence-free survival was determined based on the Kaplan-Meier survival curve and was 91.2%. The bivariate analysis revealed no relationship between local recurrence and size ($p = 0.548$), depth ($p = 0.794$), histological grade ($p = 0.835$), the presence of residual lesions ($p = 0.203$), surgical margins ($p = 0.224$), radiotherapy ($p = 0.089$) or chemotherapy ($p = 0.096$). The multivariate analyses also did not show any differences.

Distant metastasis

Ten patients (19.2%), six in the Pex group and four in the Unpex group, had metastases at admission. Moreover, 13 patients, 9 in the Pex group and 4 in the Unpex group, exhibited metastases at the follow-up (25% of all patients and 31% of non-metastatic patients at admission). The average time to the development of metastasis after admission was 10.5 ± 14.4 months. Therefore, 23 patients

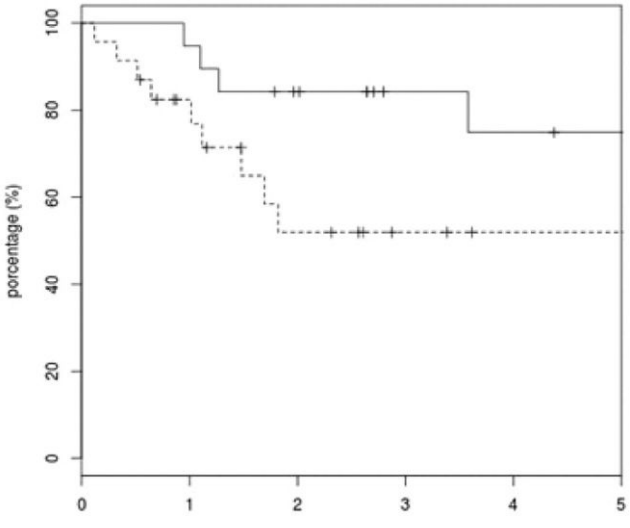

Figure 2 - Kaplan-Meier analysis of 5-year survival free of distant metastases comparing Pex (---) with Unpex (—). Pex: 51.9% ×Unpex: 74.9% ($p = 0.07$).

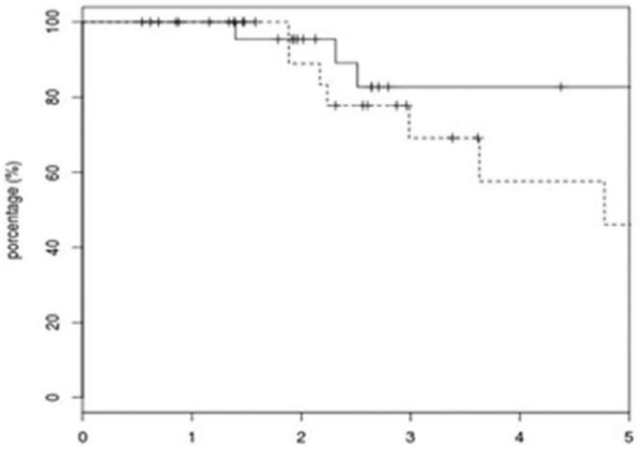

Figure 3 - Kaplan-Meier analysis of 5-year overall survival comparing Pex (---) with Unpex (—). Pex: 46.1% × Unpex: 82.7% ($p = 0.16$).

(44.2%) were diagnosed with distant metastases during the follow-up. Distant metastasis-free survival over 5 years, obtained from the Kaplan-Meier curve, was 62.7%. The bivariate analysis revealed that sarcoma depth and a size greater than 5 cm were prognostic factors that increased the risk of distant metastases ($p<0.05$). Histological grade, residual tumor and surgical margins were not related to the incidence of distant metastases. In the multivariate analysis, in which all variables were adjusted for positive margins ($p = 0.02$) and the implementation of Pex ($p = 0.03$) were significantly associated with the appearance of distant lesions, with odds ratios of 115.58 and 8.17, respectively.

Death

Ten deaths occurred during the follow-up period, comprising three patients in the Unpex group and seven patients in the Pex group, with an average time to the occurrence of the event of 31 ± 3.8 months. The global 5-year survival calculated from the Kaplan-Meier curve was 65.5%.

Sarcoma size, depth, histological grade and residual tumor were not related to death. Positive surgical margins ($p = 0.009$) and the presence of distant metastasis ($p = 0.001$) appeared to be significant variables in the occurrence of death in the bivariate analysis. In the multivariate analysis, a high histological grade ($p = 0.01$) and positive margins ($p = 0.01$) were identified as independent prognostic factors for the occurrence of death, with odds ratios greater than 1000 and 383.75, respectively.

DISCUSSION

STSs continue to be inappropriately resected due to the rarity of this disease and the lack of experience of surgeons who work outside cancer centers, leading to high rates of residual disease. We also believe that the clinical problems associated with unplanned resection of a sarcoma are applicable to surgical procedures without consideration of potential malignancy, such as transverse skin incisions, excessive postoperative hematomas, insults to uninvolved joints, drainage away from a skin incision and broad mattress skin sutures (17).

First, we analyzed the entire group (52 patients) to identify prognostic factors for the development of local recurrence, distant metastasis and death.

Local recurrence occurred in only four patients (7.7%) in this study, similar to the 4.1% observed by Novais et al. (18) and the 13% reported by Lewis et al. (19). Local recurrence was not associated with any of the studied variables, in contrast to published data, which showed that surgical margins and radiotherapy affect local tumor recurrence (6,14,20,21,22,23).

Excluding the patients with metastasis at the beginning of this study, the rate of distant metastasis was 31% (13/42), similar to the 32.1% found by Novais et al. (18) and above the 18% and 22% reported by Lewis et al. (19) and Pisters et al. (21), respectively. After adjusting the data through multivariate analysis, affected surgical margins ($p = 0.02$) and planned resection ($p = 0.03$) were considered to be unfavorable prognostic factors for the occurrence of distant metastases. Regarding positive surgical margins, what was observed in this study is not consistent with the data of Novais et al. (18) but agrees with the analysis of 2,084 STSs in adults conducted by Stojadinovic et al. (25). In this group, lesions that were larger than 5 cm, high grade or deep did not correlate with distant metastasis, as described by Lewis et al. (19).

The present study revealed that 44.2% of the patients treated for STSs at this oncology center underwent Unpex, which is within the range of 18% to 64.6% found in the literature (1,2,6,9,11,14,26-28).

When comparing the groups, the Pex group showed a higher frequency of superficial lesions. By comparing subcutaneous STSs with deep STSs, Peabody et al. (30) showed that 94% of patients with superficial lesions had surgery prior to treatment at a referral center, whereas only approximately half (52%) of patients with deep lesions were operated on outside of the sarcoma center. Based on these findings, we can assume that superficial lesions are less challenging than deeply located lesions are for surgeons who are willing to operate on soft tissue tumors without oncological planning and to treat synovial cysts. However, Umer et al. (24) found no significant difference between the baseline characteristics of these two groups.

A significant difference was also found in the Unpex group, with a greater presence of positive margins and expected re-manipulation due to major technical difficulties, such as difficulty in differentiating neoplastic tissue scarring. These findings are in contrast to the results reported by Fiore et al. (26). These researchers showed a higher incidence of positive surgical margins in their Pex group ($p<0.001$). A plausible hypothesis justifying this significant predominance of positive margins in the Pex group in the study by Fiore et al. (26) is that the anatomical location of an STS in relation to the neurovascular bundle or adjacent bone hinders the achievement of adequate margins.

There was no difference in amputations or disarticulations between the Pex and the Unpex groups, similar to the observation by Teixeira et al. (31) in a total of 30 cases of STSs. Only two cases (13.3% of non-amputees) belonged to the Unpex group, in contrast to the findings of Arai et al. (32), who reported 47% with grafts or flaps in the Pex group compared with 71% in the Unpex group ($p = 0.002$).

The presence of residual disease in patients re-operated on after Unpex was demonstrated in 21 of 23 specimens (91.3%). Studies that excluded obvious local recurrence upon physical examination and imaging studies from their samples reported a percentage of residual tumor ranging from 35% to 59% (1,2,11,25). Authors who evaluated every case of Unpex, regardless of the presence of local disease, showed a residual disease rate varying from 23.6% to 91% (7,9,14,26,28), designating our study as one with a higher rate of residual tumor after Unpex and showing the ineffectiveness of unplanned pretreatment. The local recurrence rate in patients undergoing Unpex ranges from 5% to 34% in the literature (1,2,14) and the present study is within this range for the three cases diagnosed during follow-up (13%). In this sample, no difference was found between the Pex and the Unpex groups in local tumor recurrence ($p = 0.17$), as reported by Teixeira et al. (31), Arai et al. (32), Lewis et al. (28) and others (6,26). In contrast, Potter et al. (14) showed that those patients undergoing Unpex had a 34% recurrence rate, compared with only 6% of patients undergoing Pex ($p<0.0001$), even after extensive resection of the tumor and radiation in two-thirds of cases.

Unexpectedly, after adjustment for other variables, the group that underwent Pex showed a greater risk of distant lesions ($p = 0.03$), with an odds ratio of 8.17 (95% CI: 0.81 to 29), and was approximately eight times more likely to develop distant metastases compared with the Unpex group. Similar results were obtained by Lewis et al. (28), with survival without distant metastasis of 83% for Unpex and only 63% for Pex and $p = 0.005$ after adjustment for other risk factors. Arai et al. (32), Qureshi et al. (33) and Fiore et al. (26) showed no differences in the occurrence of distant metastases with respect to the variable ''planned resection.'' There was no relationship between distant metastasis and local recurrence ($p = 0.088$) during follow-up, as reported by Gustafson et al. (29).

For Lewis et al. (28), whose study included a total of 1,092 individuals and was conducted at MSKCC, those patients who underwent Pex (70%) showed worse 5-year survival than did the Unpex group (88%) ($p = 0.005$), suggesting that re-resection, or margin amplification, is a predictor of improved survival and the occurrence of distant metastases. Possible explanations, according to Lewis et al. (28), are as follows: a) the re-resection or expansion of the resection margins removes residual tumor that extends beyond the primary tumor and pseudocapsule, which obviously would not be noted by the pathologist in the specimen initially resected during Pex; b) complete removal of the tumor site during Pex means a loss of inhibition of satellite lesions and subsequent diagnosis of metastasis; and c) Unpex promotes immunity, with marked activation of dendritic cells, which recognize antigens in the residual tumor, resulting in an immune response with long-term memory and protecting patients from future local recurrence and distant metastasis.

The results of this study may have been affected by a certain bias due to the small sample size, as observed in the descriptive statistics and the wide CIs obtained in the multivariate analysis.

Unplanned surgical procedures for the treatment of STSs in limbs are related to superficial, low-grade tumors and even after expansion of the surgical margins, these procedures show a higher frequency of positive surgical margins. There was no difference between the patients undergoing Unpex and Pex with respect to local recurrence and 5-year overall survival. The Pex group had a higher risk of distant metastasis in this series, whereas the Unpex group had a high rate of residual cancer.

AUTHOR CONTRIBUTIONS

Hanasilo CE conceived the study, wrote the manuscript and participated in the surgical treatment and follow-up of the analyzed patients. Casadei MS searched medical records and organized the database. Auletta L participated in the surgical treatment and follow-up of the analyzed patients. Amstalden EM was responsible for the histological studies of the patients. Matte SR searched medical records and organized the database. Etchebehere M reviewed the manuscript and participated in the surgical treatment and follow-up of the analyzed patients.

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