

Extremity soft tissue sarcoma: does surgical margin impact survival?

Sarcomas de tejidos blandos en las extremidades: ¿el margen quirúrgico impacta la supervivencia?

Rafael Medrano-Guzmán*, Moises Brener-Chaoul, Luis E. García-Ríos, and Marisol Luna-Castillo

Department of Sarcomas and Upper Digestive Tract, Hospital of Oncology, Centro Médico Nacional Siglo XXI, Mexico City, Mexico

Abstract

Objective: To define the impact of surgical margins on local recurrence (LR), distant recurrence (DR) and overall survival (OS) in patients with soft tissue sarcomas of the extremities (eSTS). **Method:** Patients treated for a primary eSTS from 2006 to 2010 were analyzed. Rates of local recurrence, distant recurrence, and overall survival were estimated using the KaplanMeier method. The association of possible prognostic factors such as local recurrence, metastasis, and survival was performed using the Cox proportional hazards model. **Results:** 128 patients were analyzed. The surgical margins were positive (R1 resection) in 22.7% and negative in 77.3%. The LR was 27%, the DR was 13% (70% of the population was free of disease at 5 years) and OS at 5 years was 84%. The prognostic factors for OS at 5 years were clinical stage, type and histological grade. The surgical margin had no impact on OS. **Conclusions:** Although an adequate oncological resection cannot be underestimated, this should be considered in the decision of the optimal treatment of eSTS when amputation or significant functional impairment of the limb is required to obtain negative surgical margins.

Keywords: Extremities soft tissue sarcoma. Surgical margins. Overall survival.

Resumen

Objetivo: Definir el impacto de los márgenes quirúrgicos sobre la recurrencia local (RL), la recurrencia a distancia (RD) y la supervivencia global (SG) en pacientes con sarcomas de tejidos blandos de las extremidades (STBe). **Método:** Se analizaron pacientes tratados por un STBe primario desde 2006 hasta 2010. Las tasas de recurrencia local, recurrencia a distancia y supervivencia global se estimaron mediante el método de Kaplan-Meier. La asociación de posibles factores pronósticos como recidiva local, metástasis y supervivencia se realizó mediante el modelo de riesgos proporcionales de Cox. **Resultados:** Se analizaron 128 pacientes. Los márgenes quirúrgicos fueron positivos (resección R1) en el 22.7% y negativos en el 77.3%. La RL fue del 27% y la RD fue del 13% (el 70% de la población está libre de enfermedad a 5 años) y la SG a 5 años fue del 84%. Los factores pronósticos para la SG a 5 años fueron el estadio clínico, el tipo y el grado histológico. El margen quirúrgico no tuvo impacto en la SG. **Conclusiones:** Aunque no se puede subestimar una resección oncológica adecuada, esto se debe considerar en la decisión del tratamiento óptimo de los STBe cuando se requiere una amputación o un deterioro funcional significativo de la extremidad para obtener márgenes quirúrgicos negativos.

Palabras clave: Sarcoma de tejidos blandos de extremidades. Márgenes quirúrgicos. Supervivencia global.

*Correspondence:

Rafael Medrano-Guzmán

E-mail: dr.rafaelmedranoguzman@gmail.com

2444-0507/© 2022 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 03-04-2022

Date of acceptance: 10-08-2022

DOI: 10.24875/CIRUE.M22000711

Cir Cir (Eng). 2023;91(6):792-797

Contents available at PubMed

www.cirugiaycirujanos.com

Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare solid tumors of mesenchymal origin with variable clinical and pathological characteristics, representing 1% of malignant tumors in adults. It is estimated that in the United States, approximately 13,130 new cases were diagnosed in 2020, and 5350 people died from the disease (2870 men and 2480 women)¹.

There are more than 100 different histological subtypes of soft tissue tumors, most of which are STS. The most common histotypes are liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma². The most frequently affected anatomical sites are the extremities (43%), followed by the viscera (19%), retroperitoneum (15%), trunk (10%), and head and neck (9%)³.

Surgery is the primary treatment for extremity STS (ESTS). It is necessary to circumferentially resect healthy tissue around the tumor because the surgical margin is the reference for defining the quality of the surgery and has a clear impact on local recurrence (LR), although the impact on overall survival (OS) remains controversial⁴⁻⁷.

In a study conducted by Bonvalot et al.⁸, margin status and local recurrence were not correlated with survival, while in a retrospective study by Zagars et al.⁹, it was demonstrated that a negative margin improved disease-specific survival.

The known predictive factors that affect OS are histological grade, age, tumor size, and histological subtype¹⁰. Ten-year OS ranges from approximately 96% for grade 1 tumors down to 60% for grade 3 tumors¹¹.

Although adequate oncological resection cannot be overemphasized, it is also important to balance the negative surgical margin with functional outcomes, making it essential to have a better understanding of what is adequate in the local treatment of ESTS and its impact on OS. Therefore, we decided to conduct this retrospective analysis to determine whether patient and tumor characteristics, as well as LR, have an impact on OS in patients with intermediate and high-risk eSTS treated at a single institution in Mexico.

Method

Data were collected from patients with primary ESTS treated at the oncology hospital of Centro Médico Nacional Siglo XXI in Mexico from January 2006 through December 2010. All patients had histological confirmation of ESTS, no metastasis at the time of diagnosis,

and were initially treated with surgery. Patients with recurrent or metastatic disease, those treated outside our hospital, and those on neoadjuvant chemotherapy or radiotherapy were excluded. The data retrieved included tumor size, histological type, surgical margin, and grade.

LR, distant recurrence (DR), and OS rates were estimated using the Kaplan-Meier method. The association of potential prognostic factors, such as LR, metastasis, and survival, was analyzed using the Cox proportional hazards model. Multivariate analysis was initially performed on all potential risk factors, such as sex, age, histology, grade, stage according to the American Joint Committee on Cancer, tumor size, and margin. LR and DR were analyzed as risk factors for decreased OS, incorporating these results into the Cox model as time-dependent covariates.

Results

A total of 128 patients were analyzed, with a sex ratio of 1:1. The lower extremities were the most affected location (85.2% of cases). The most frequent histology was liposarcoma (43.8%), followed by myxofibrosarcoma (14.1%), undifferentiated pleomorphic sarcoma (11.7%), synovial sarcoma (10.9%), malignant peripheral nerve sheath tumor (6.3%), and others (13.3%).

Regarding size, 53.9% of the tumors were > 16 cm, 33.6% were between 11 cm and 15 cm, 8.6% were between 6 cm and 10 cm, and 3.9% were < 5 cm. Lymphovascular invasion was present in only 4.7% of cases. Histological grade 1 was found in 45.3% of cases, grade 2 in 24.2%, and grade 3 in 25%; histological grade could not be determined in 5.5% of cases. Regarding clinical stage, the most frequent were IB, with 44.5%, and IIB, with 26.6%. Surgical margins were positive (R1 resection) in 22.7% of cases and negative in 77.3%. All patients underwent surgery; 36 patients (28.1%) also received adjuvant radiotherapy, and only 1 received adjuvant chemotherapy and radiotherapy.

The characteristics of the patients are summarized in Table 1.

Local recurrence

Lymphovascular invasion (odds ratio [OR], 15.333; $p = 0.014$), grade 3 histology (OR, 4.804; $p = 0.002$), and surgical margin (OR, 15.937; $p = 0.000$) were significant factors for LR. In grade 3 histology, the risk is up to 3.8 times higher, and for lymphovascular invasion or positive surgical margin, up to 14 times higher.

Table 1. Patient characteristics

	n	%
Sex		
Female	64	50
Male	64	50
Course of the disease		
< 3 months	4	3.1
3-6 months	17	13.3
> 6 months	107	83.6
Affected Limb		
Upper	19	14.8
Lower	109	85.2
Histological type		
Liposarcoma	56	43.8
Myxofibrosarcoma	18	14.1
Malignant peripheral nerve sheath tumor	8	6.3
Synovial sarcoma	14	10.9
MFH	15	11.7
Others	17	13.3
Treatment		
Surgery	91	71.1
Surgery and radiotherapy	36	28.1
Surgery, radiotherapy, and chemotherapy	1	0.8
Size (cm)		
1-5	5	3.9
6-10	11	8.6
11-15	43	33.6
> 16	69	53.9
Lymphovascular Invasion		
Present	6	4.7
Absent	122	95.3
Histological grade		
1	58	45.3
2	31	24.2
3	32	25
Undetermined	7	5.5
Surgical margin (mm)		
< 5	28	21.9
5.1-10	36	28.1
11-20	22	17.2
> 20	13	10.2
Positive	29	22.7
CS		
IA	5	3.9
IB	57	44.5
IIA	5	3.9
IIB	34	26.6
III	24	18.8
IV	3	2.3
DFI		
< 60 months	39	30.5
> 60 months	89	69.5
Local recurrence		
No	93	72.7
Yes	35	27.3

(Continues)

Table 1. Patient characteristics (continued)

	n	%
Distant recurrence		
No	111	86.7
Yes	17	13.3
Five-year survival		
Yes	108	84.4
No	20	15.6

CS: clinical stage; MFH: malignant fibrous histiocytoma; DFI: disease-free interval.

Distant recurrence

Risk factors for DR are similar to those for LR: lymphovascular invasion (OR, 16.769; $p = 0.002$), grade 3 histology (OR, 12.727; $p = 0.002$), and surgical margin (OR, 5.119; $p = 0.003$). Synovial sarcoma was found to be a high-risk histological subtype (OR, 13.250; $p = 0.001$).

Overall survival

Five-year OS was affected by the same risk factors as DR, except for positive surgical margin (OR, 2.105; $p = 0.157$). Statistical significance was observed in histological subtypes, malignant peripheral nerve sheath tumor (OR, 16.20; $p = 0.007$), synovial sarcoma (OR, 15.00; $p = 0.003$), and undifferentiated pleomorphic sarcoma (OR, 18.00; $p = 0.001$); also, when adjuvant radiotherapy was administered (OR, 3.504; $p = 0.014$), when lymphovascular invasion was present (OR, 13.250; $p = 0.004$), and with histological grade 2 (OR, 6.720; $p = 0.025$) or 3 (OR, 14.667; $p = 0.001$).

Overall survival analysis

In the statistical analysis, patients treated and followed for 5 years had an LR rate of 27% (35 cases), with 80% of these occurring within the first 2 years of follow-up, and a DR rate of 13% (17 cases), leaving only 70% of patients disease-free at 5 years. The 5-year OS was 84% (Fig. 1). Surgical margin did not affect OS, as shown in Fig. 2.

Univariate analysis

We found that clinical stage, histological grade, and R1 resection are prognostic factors for LR, as shown in Fig. 3. For DR, surgical margin, histological grade,

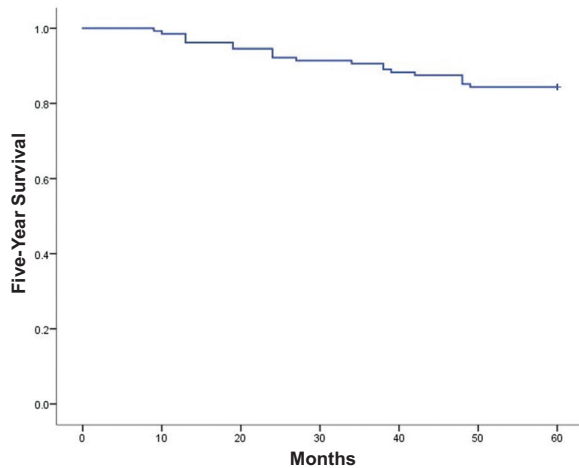


Figure 1. 5-year survival.

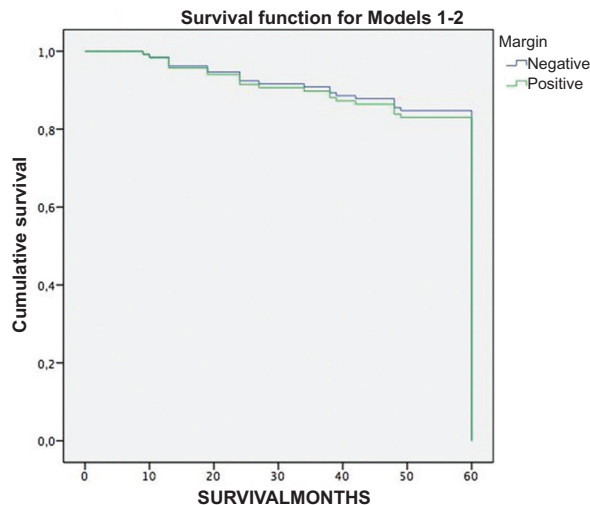


Figure 2. 5-year survival for patients with positive and negative surgical margins.

and subtype were the prognostic factors found in our analysis (Fig. 4). The prognostic factors for 5-year OS were clinical stage, grade, and histological type (Fig. 5).

Discussion

The diagnosis of ESTS can be challenging. The most common presentation is a palpable tumor, and time from symptom onset to treatment usually exceeds 6 months, which clearly impacts the achievement of a negative surgical margin, which was achieved in 78% of cases due to the size and depth of the tumor (in 71.1% of cases, the tumor was located deep to the fascia). In more than 80% of our population, the lower

limb was affected, which could explain why 53.9% presented with tumors > 16 cm.

The LR rate was 27.3%, higher than the 20% usually reported in the literature^{12,13}, with 80% of these recurrences occurring within the first 2 years after surgery. The DR rate was 13.3%, lower than reported in other studies¹⁴, with a disease-free survival of 69.5%, well below the 85%-90% reported by Weitz et al.¹⁵ in their study.

Histological subtypes such as epithelioid sarcoma and myxofibrosarcoma, and a surgical margin < 1 mm, are well-known predictors of LR, as previously demonstrated¹⁶⁻¹⁹; in our analysis, histological grade 2, lymphovascular invasion, and R1 resection were factors associated with LR.

We found that high-grade tumors, synovial sarcoma, and positive surgical margin were predictors of DR, unlike previous studies where tumor size was not a predictive factor, suggesting that it may be a less important predictor^{9,15,20}.

In a study conducted by Pisters et al.²¹, factors such as tumor size ≥ 10 cm, high histological grade, deep location, local recurrence, and positive microscopic surgical margin were found to affect disease-specific mortality²¹. The predictors of OS found in this study were histological type (malignant peripheral nerve sheath tumor, synovial sarcoma, undifferentiated pleomorphic sarcoma), lymphovascular invasion, and histological grades 2 and 3. Surgical margin status did not affect OS.

We cannot retrospectively conclude that achieving negative margins would improve OS. Despite a 27% LR rate, 5-year OS was 84%, which could be influenced by the relatively small sample size, the limited number of deaths, and the short follow-up time in our study. Nevertheless, we found that high histological grade and lymphovascular invasion are factors that can increase the risk of LR, DR, and poor OS.

We cannot retrospectively conclude that achieving negative margins would have improved the OS. When the goal of obtaining negative surgical margins requires amputation or significant functional impairment, decisions should be made on a case-by-case basis, considering the disease biology, the patient's health status, and their informed decision.

Understanding the characteristics and biology of ESTS is complex due to the wide variety of histological subtypes. However, to establish a unified criterion, various centers have worked to identify prognostic factors that healthcare professionals can rely on to guide

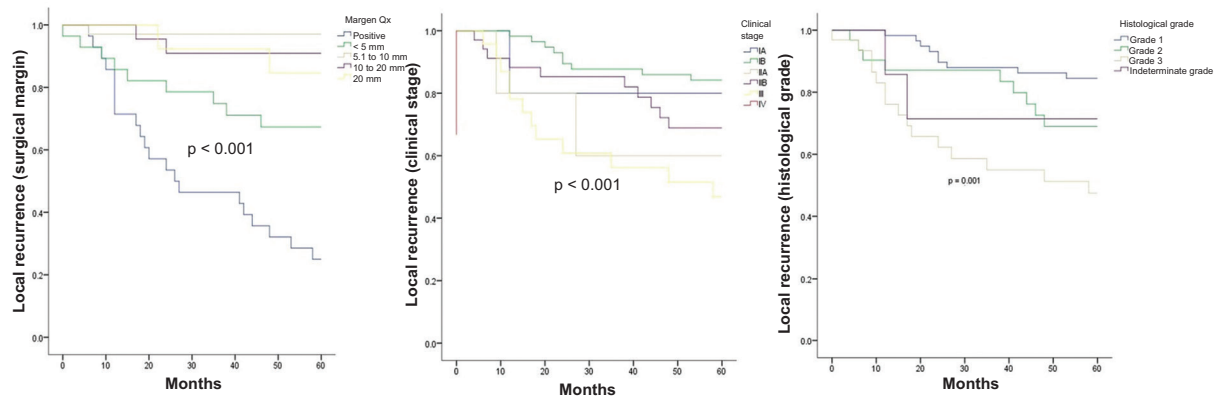


Figure 3. Prognostic factors for local recurrence.

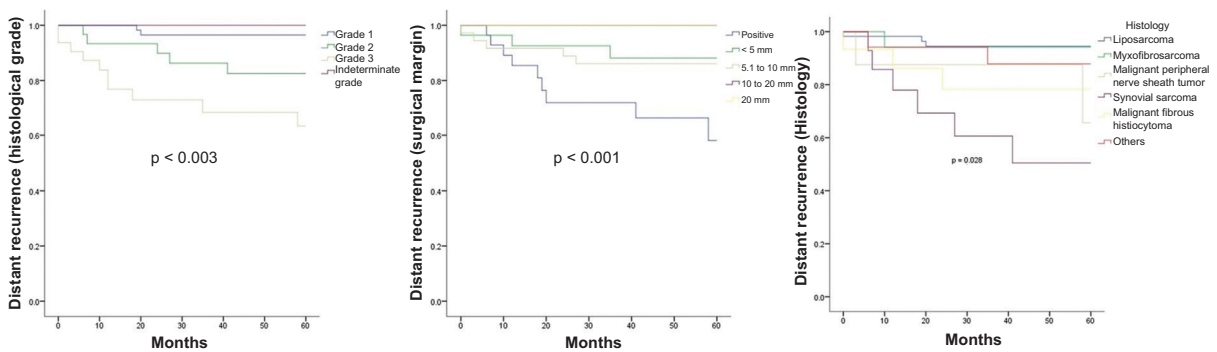


Figure 4. Prognostic factors for distant recurrence.

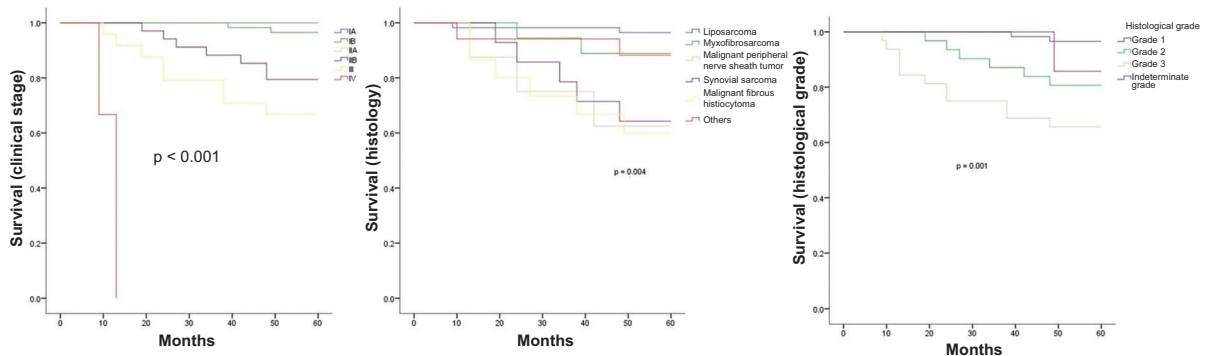


Figure 5. Prognostic factors for overall survival.

treatment. Among these factors, the surgical margin is controversial; in our study, it did not impact OS, which should be the primary goal of cancer treatment. We believe this is because the margin directly affects disease-free survival (DFS), which is not the same as overall survival. In our results, the surgical margin did not affect survival but did influence LR, DR, and DFS,

which in turn affect OS. The therapeutic principle of limb preservation will remain important, and future research should focus on impacting OS.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

References

1. Siegel RL, Miller KD, Jemal A. *CA Cancer J Clin.* 2021;71:7-33.
2. Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, editores. *WHO Classification of tumours of soft tissue and bone.* 4th ed. IARC WHO Classification of Tumours. Vol. 5. WHO Press; 2013.
3. Puri A, Gulia A. Management of extremity soft tissue sarcomas. *Indian J Orthop.* 2011;45:301-6.
4. Trovik CS, Bauer HC, Alvegard TA, Anderson H, Blomqvist C, Berlin O, et al. Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group register. *Eur J Cancer.* 2000;36:710-6.
5. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2084 localized primary adult soft tissue sarcomas. *Ann Surg.* 2002;235:424-33.
6. Gronchi A, Casali PG, Mariani L, Miceli R, Fiore M, Lo Vullo S, et al. Status of surgical margins and prognosis in adult soft tissue sarcomas of the extremities: a series of patients treated at a single institution. *J Clin Oncol.* 2005;23:96-104.
7. Stoeckle E, Gardet H, Coindre JM, Kantor G, Bonichon F, Milbéo Y, et al. Prospective evaluation of quality of surgery in soft tissue sarcoma. *Eur J Surg Oncol.* 2006;32:1242-8.
8. Bonvalot S, Levy A, Terrier P, Tzanis D, Bellefqih S, Le Cesne A, et al. Primary extremity soft tissue sarcomas: does local control impact survival? *Ann Surg Oncol.* 2017;24:1940-1947.
9. Zagars GK, Ballo MT, Pisters PWT, Pollock RE, Patel SR, Benjamin RS, et al. Prognostic factors for patients with localized soft tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. *Cancer.* 2003;97:2530-43.
10. Callegaro D, Miceli R, Bonvalot S, Ferguson P, Strauss DC, Levy A, et al. Development and external validation of two nomograms to predict overall survival and distant metastases after surgical resection of localized soft tissue sarcomas of the extremities: a retrospective analysis. *Lancet Oncol.* 2016;17:671-80.
11. Mariani L, Miceli R, Kattan MW, Brennan MF, Colecchia M, Fiore M, et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. *Cancer.* 2005;103:402-8.
12. Khanfir K, Alzieu L, Terrier P, Le Péchoux C, Bonvalot S, Vanel D, et al. Does adjuvant radiation therapy increase locoregional control after optimal resection of soft-tissue sarcoma of the extremities? *Eur J Cancer.* 2003;39:1872-80.
13. Eilber FC, Rosen G, Nelson SD, Selch M, Dorey F, Eckardt J, et al. High-grade extremity soft tissue sarcomas: factor predictive of local recurrence and its effect on morbidity and mortality. *Ann Surg.* 2003;237:218-26.
14. Coindre JM, Terrier P, Bui NB, Bonichon F, Collin F, Le Doussal V, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. *J Clin Oncol.* 1996;14:869-77.
15. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. *J Clin Oncol.* 2003;21:2719-25.
16. Gronchi A, Lo Vullo S, Colombo C, Collini P, Stacchiotti S, Mariani L, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. *Ann Surg.* 2010;251:512-7.
17. Trovik CS, Skjeldal S, Bauer H, Rydholm A, Jebsen N. Reliability of margin. Assessment after surgery for extremity soft tissue sarcoma: the SSG experience. *Sarcoma.* 2012;2012:290698.
18. Levy A, Le Péchoux C, Terrier P, Bouaita R, Domont J, Mir O, et al. Epithelioid sarcoma: need for a multimodal approach to maximize the chances of curative conservative treatment. *Ann Surg Oncol.* 2014;21:269-76.
19. Sanfilippo R, Miceli R, Grosso F, Fiore M, Puma E, Pennacchioli E, et al. Myxofibrosarcoma: prognostic factors and survival in a series of patients treated at a single institution. *Ann Surg Oncol.* 2011;18:720-5.
20. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol.* 1996;14:859-68.
21. Pisters PWT, Leung DHY, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcoma of the extremities. *J Clin Oncol.* 1996;14:1679-89.