RIC

ARTÍCULO ORIGINAL

Serum albumin is an independent prognostic factor for survival in soft tissue sarcomas

Juan Camilo Barreto-Andrade,* Heriberto Medina-Franco*

* Dirección de Cirugía. Sección de Cirugía Oncológica. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

ABSTRACT

Background. Soft tissue sarcomas are rare tumors with a wide clinical spectrum. Prognostic factors for survival have been identified, but they have been focused in the characteristics of the tumor. Patient related variables have not usually been considered in previous analysis. **Methods.** We analyzed a group of 61 patients with soft tissue sarcomas. Tumor related variables and patient related ones were recorded. Overall and disease free survival were calculated according to the Kaplan and Meier method. Prognostic factors for survival were determined by the log-rank method for univariate analysis and the Cox method for multivariate analysis. **Results.** Clinical and demographic characteristics are comparable to those of previous reports. Adverse prognostic factors for overall survival in multivariate analysis were advanced stage, high tumor grade, irresecability, and serum albumin. Size, high surgical risk (ASA III-IV) and a low performance status (Karnofsky less than 70) were predictive of overall survival only in univariate analysis. For disease free survival, only high tumor grade had statistical significance. **Conclusions.** Besides the usual tumor related prognostic factors, such as grade and stage, patient related factors, such as performance status and surgical risk should be considered when predicting survival. Specifically, serum albumin was an independent prognostic factor for overall survival.

Key words. Soft tissue sarcoma. Survival. Prognostic factors. Serum albumin.

La albúmina sérica es un factor pronóstico independiente para sobrevida en sarcomas de tejidos blandos

RESUMEN

Introducción. *Los sarcomas de tejidos blandos son tumores raros con un amplio espectro clínico. Se han identificado diversos factores de pronóstico para supervivencia centrados fundamentalmente en las características del tumor, mientras que las variables asociadas con el paciente no han sido consideradas en análisis previos.* ***Métodos.*** *Se analizó en forma retrospectiva un grupo de 61 pacientes con sarcomas de tejidos blandos. Se identificaron variables relacionadas al tumor, así como aquellas relacionadas con el paciente. Se calcularon la sobrevida global y la sobrevida libre de enfermedad con el método de Kaplan y Meier. Se determinaron los factores de pronóstico para sobrevida de acuerdo con el método de log-rank para el análisis univariado y el método de Cox para el análisis multivariado.* ***Resultados.*** *Las características demográficas y clínico-patológicas fueron similares a reportes previos de la literatura. Factores pronósticos negativos para sobrevida global en el análisis multivariado fueron el estadio avanzado de la enfermedad, tumor de alto grado, enfermedad no resecable y albúmina sérica. El tamaño del tumor, riesgo quirúrgico elevado (ASA III-IV) y pobre estado general (Karnofsky igual o menor de 70) fueron predictores de sobrevida global sólo en el análisis univariado. Para sobrevida libre de enfermedad, sólo el grado tumoral tuvo significancia estadística.* ***Conclusiones.*** *Además de los factores usuales asociados con el tumor como grado y estadio, cuando se busca determinar pronóstico se deben considerar factores asociados con el paciente como estado general y riesgo quirúrgico. Específicamente, la albúmina sérica se encontró como factor independiente para predecir sobrevida global.*

Palabras clave. *Sarcoma de partes blandas. Sobrevida. Factores de pronóstico-albúmina sérica.*

INTRODUCTION

Soft tissue sarcomas are rare tumors that arise in mesenchymal tissues, representing less than 1% of all malignancies. They have a wide clinical spectrum, and can be suffered in any range of age and almost equally in both sexes.[1] The small number of cases seen make the understanding of these entities

difficult, and large series in tertiary care centers are required to draw conclusions about their natural history and the results of treatment.

Due to their rarity, a high suspicion index is important when a soft tissue tumor is resected or a biopsy is taken, since the maximum benefit for the patient can be obtained when they are referred to specialized centers. Early and adequate treatment is determinant in the prognosis of these tumors.

It has been demonstrated that with current therapy, soft tissue sarcomas diagnosed at an early stage are frequently curable. While it is clear that surgery remains the main modality of treatment, there are still areas of controversy regarding adjuvant therapy. Chemotherapy and radiation therapy, have a positive, but modest effect in survival and recurrence, and they are associated with considerable toxicity.[2,3] It is necessary to identify prognostic factors for survival, because these results can be used to select candidates that are more likely to benefit from adjuvant therapy. Much has been written about the prognostic factors for survival, and large size, high histologic grade, positive margins of resection and recurrent disease have been identified as predictors of an adverse outcome.[4-7] The literature regarding patient related factors that are predictors for survival in soft tissue sarcomas is scarce. The purpose of the current study is to identify prognostic factors in a tertiary care center, with an emphasis of considering not only tumor related factors, but patient related factors as well.

METHODS

Patients with a diagnosis of soft tissue sarcoma were retrospectively identified at the National Institute of Medical Sciences and Nutrition Salvador Zubiran, from January 1986 to May 2006. Data was collected from a review of the patients' files, written records, and imaging and pathology records. We included in the analysis patients with primary disease, and also patients that were initially diagnosed and treated outside our Institution, but that continued their further treatment and follow-up in our Department. Histological confirmation was made in every case; and re-evaluation of biopsy material taken outside was performed by our pathologists. Routine clinical and demographic data were recorded, plus specific variables that included preoperative Karnofsky score, surgical risk according to the American Society of Anesthesiologists (ASA) classification, presentation symptoms, haemoglobin level, serum albumin and body mass index (BMI). Age was analyzed as continuous variable as well as categorical one: young patients were considered those 40 years old or less and old patients those > 70 years, as categorized in an arbitrary form in the literature.

Tumor related variables were registered, including histopathologic subtype, size, grade, site, stage at presentation, and whether a previous biopsy was performed. The treatment each patient received (complete or incomplete resection, radiotherapy and/or chemotherapy) was noted. A tumor was deemed as resectable when at least gross negative margins could be accomplished.

Patients treated with radiation or chemotherapy were those with adverse prognostic factors, therefore, inclusion of treatment-related variables in the analysis was considered to be misleading, and these factors were not included in the multivariate analysis.

Total follow-up, time elapsed for recurrence, type of recurrence (local or systemic), status of the patient in the last presentation were recorded. Hypoalbuminemia was defined as preoperative serum albumin of less than 3.5 g/dL; a Karfnofsky score less than 80 was considered as poor performance status; a high surgical risk patient was registered when he or she had an ASA grade of III or IV; obesity was defined as an BMI greater than 30 kg/m^2.

Summary statistics were obtained by using standard methods. The aim of the statistical analysis was to determine tumor and patient-related factors associated with overall survival and disease-free survival. Life-table curves were constructed by the Kaplan-Meier method.[8] Analysis of the prognostic value of each variable was examined with the log-rank test.[9] Comprehensive analysis of the effect of all covariates jointly was performed by using the Cox proportional hazards model.[10] Covariates were selected into the model only if they had significance in the univariate analysis. Statistical significance was defined as a $p < 0.05$.

RESULTS

Patients

Sixty-one patients with soft tissue sarcoma were identified during the period from 1986 to 2006 at the National Institute of Medical Sciences and Nutrition Salvador Zubiran. The median age was 48 years (range, 16-81 years). There were 35 females (57%) and 26 males (43%). Most tumors were larger than 5 cm (87%), and high grade (63%). The most common histology was liposarcoma (39%). The rest of

Table 1. Clinical and demographic features of 61 patients with soft-tissue sarcomas.

Variable	n (%)
Tumor Size	
≤ 5 cm	8 (13)
> 5 cm	52 (87)
Site	
Extremities	40 (66)
Truncal	13 (21)
Intraabdominal	5 (8)
Head and neck	2 (3)
Intrathoracic	1 (2)
Histopathology	
Liposarcoma	24 (39)
MPNT	10 (16)
Leiomyosarcoma	9 (15)
MFH	5 (8)
Fibrosarcoma	4 (7)
Other	9 (15)
Stage	
I	15 (25)
II	13 (21)
III	11 (18)
IV	22 (36)
Grade	
Low	22 (36)
High	38 (62)
Intermediate	1 (1.5)
Previous biopsy performed	36 (59)
Received chemotherapy	26 (43)
Received radiotherapy	32 (52)
Presenting symptoms	
Palpable mass	54 (88.5)
Pain	39 (64)
Organ compression	14 (23)
Weight loss	12 (20)
Fever	6 (10)

MPNT: Malignant peripheral nerve tumor. MFH: Malignant fibrous histiocytoma.

the clinical and demographic features are presented in table 1.

Surgical mansagement

Thirty-nine patients had localized disease, versus 22 patients that had metastatic disease, which were rendered unsuitable for a surgical resection of any type. In 35 of the patients with localized disease (90%), complete surgical resection of the tumor was performed.

Analysis of prognostic factors

The median follow-up was 20 months (range, 1-185 months). No patient was lost to follow-up. A total of

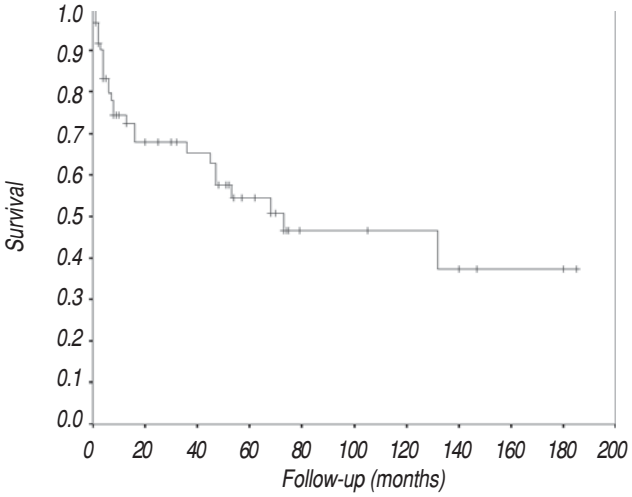

Figure 1. *Overall survival of the entire patient population.*

26 patients (43%) died of disease-related causes during the follow-up period. Median overall survival was 73 months (95% CI 5-141). The 1-year, 5-year and 10-year actuarial overall survival was 74%, 54% and 46%, respectively, as it is shown in figure 1.

For analysis, intermediate grade was included in the low grade category. Variables that were predictors of decreased overall survival in the univariate analysis were high histologic grade ($p < 0.00001$), advanced stage ($p < 0.00001$), unresectable tumors ($p < 0.00001$), size > 5 cm ($p = 0.04$), poor performance status ($p = 0.0002$), high surgical risk ($p < 0.00001$), and a serum albumin less than 3.5 mg/dL ($p = 0.03$). Variables that were not significant for survival in the univariate analysis were age, sex, obesity, previous biopsy performed, histology, and site (Table 2). For some of these variables, the median survival was not reached.

In multivariate analysis, the variables that maintained their significance as prognostic factors were high histologic grade ($p = 0.002$), advanced stage ($p = 0.026$), unresectable tumors ($p = 0.0001$) and hypoalbuminemia ($p = 0.02$) (Table 2). Figure 2 shows the effects of these variables on overall survival.

Median disease-free survival was 52 months (95% CI 33-71, SE 9.9). On univariate analysis, only high histologic grade was found to be a significant predictor for disease-free survival ($p = 0.02$).

DISCUSSION

The clinical and demographic features in this group of patients were similar to what has been re-

Table 2. Analysis of prognostic factors.

Factor	Median survival in months (95% CI)*	Univariate P value	Multivariate P value
Age*			
< 40	1.03 (0.8-1.5)	P = 0.97	NS
> 70	1		
Sex			
Male	73 (0-165)	P = 0.59	NS
Female	68		
Grade*			
Low	1	P < 0.00001	P = 0.002
High	24 (10.1-32.5)		
Size			
≤ 5 cm	1	P = 0.04	NS
> 5 cm	4 (1.2-7.3)		
Serum albumin*			
< 3.5 mg/dL	5 (2.1-9.4)	P = 0.03	P = 0.02
≥ 3.5 mg/dL	1		
Stage			
I	1	P < 0.00001	P = 0.026
II	2.5 (1.7-6.8)		
III	3.3 (0.8-9.9)		
IV	23 (12.1-35.5)		
Performance status			
Karnofsky < 80	9 (6-20)	P = 0.0004	NS
Karnofsky ≥ 80	143		
Obesity*			
BMI < 30	1	P = 0.68	NS
BMI ≥ 30	1.4 (0.7-3.7)		
Surgical risk			
ASA I – II	132	P < 0.00001	NS
ASA III – IV	7 (3-11)		
Previous biopsy performed			
Yes	132 (19-245)	P = 0.1	NS
No	47 (9-85)		
Type of excision*			
Complete (R0 or R1)	1	P < 0.00001	NS
Incomplete (R2 o biopsy)	18 (8.3-31.5)		
Histology			
Liposarcoma	132 (9-255)	P = 0.65	NS
Other	68 (36-100)		
Site			
Extremities	73 (0-155)	P = 0.78	NS
Other	68 (0-142)		
Site			
Retroperitoneum	132 (8-256)	P = 0.85	NS
Other	68 (37-99)		

CI: Confidence interval. NS: Not significant. BMI: Body mass index.
* When the median survival of one variable has not been reached, the results are expressed as relative risk (95% CI).

ported in the literature, with some variations probably derived from to the size of the population studied.[11] The average tumor size was 14.5 cm, with most of the lesions (87%) measuring over 5 cm. This greater size of the tumors might show the delay in the search for medical attention that frequently occurs in developing countries. Another explanation, or contributing factor, is the relatively high percentage of retroperitoneal and intraabdominal tumors, making them undetectable in their initial phases.

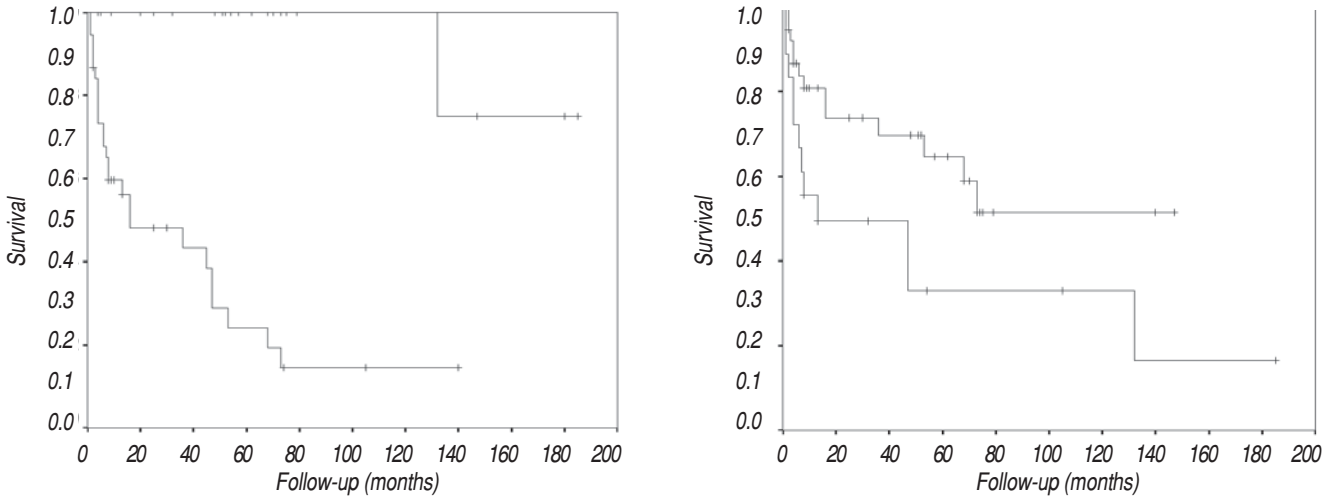

Figure 2. *Overall survival according to histologic grade and serum albumin.*

Nevertheless, as we mentioned earlier, the proportion of resectable tumors was high (90% of non-disseminated tumors), a figure that is close to the reported range of near 100% in extremities and 65% in retroperitoneum.[12]

Median overall survival was 73 months for all stages. In a report by Pollock et al,[11] including long-term follow up of patients diagnosed in 1988, they found a survival of 75% at 1 year, and 50% at 5 years. The reported 5 year survival in the group of the Memorial Sloan-Kettering Cancer Center is 76%, with a median follow up of 4 years.[4] We found results similar to the former; with 74% survival at 1 year and 54% at 5 years. Our database includes a heterogenous population, some of them with a diagnosis made in 1987, and for this reason it is not possible to standardize the treatment received by the patients, mainly regarding adjuvant treatment. It must be considered that a substantial proportion of patients (36%) had stage IV disease.

The variables that were predictors of survival in the univariate analysis can be divided as patient related ones and tumor related ones. Patient related variables that were predictors of survival were a low serum albumin (less than 3.5 mg/dL), poor performance status (Karnofsky score less than 80), and high surgical risk (ASA III and IV). Tumor related variables were size, histologic grade, stage and unresectability.

A fundamental issue to underscore when evaluating a patient with a soft tissue sarcoma, and that finds support in this study is the relevance of the patient related factors that influence survival. The traditional approach to the clinical evaluation of soft tissue sarcoma has emphasized tumor size, tumor grade, the presence of recurrent disease, and positive surgical margins in the assesment for the risk of disease-specific mortality. In the present study, on multivariate analysis, serum albumin retained its statistical significance, thus demonstrating to be an independent prognostic factor for overall survival. Patients with a serum albumin lesser than 3.5 mg/dL, had a median survival of 13 months, whereas in patients with a serum albumin of 3.5 mg/dL or greater, the median survival has not been reached ($p = 0.03$).

The level of serum albumin is a reflect of the patient's nutritional status, and with a half-life of 14 to 18 days, it is not a sensitive indicator of rapid metabolic changes, but certain pathologies can induce a consistent descent. The causes of this descent are multiple. Cancer patients may suffer an important weight loss and generalized cachexy. Contributing factors are less oral intake of food, impaired metabolic rate, endocrine abnormalities, plus circulating cytokines that have been long identified. Specifically, interleukin 1 (IL-1), tumor necrosis factor (TNF) and interpheron-γ (IFN- γ) are produced in neoplastic diseases. They stimulate proteolysis, along with cortisol playing a role. IL-6 and IL-1 induce the synthesis of hepatic acute phase proteins while they inhibit the synthesis of albumin.[13] Anorexy is common in cancer patients, even with small tumors, a finding attributed to altered satiety mechanisms in the central nervous system mediated by cytokines.[14]

Serum albumin has been reported as a predictor of survival in other malignancies, like gastric cancer[15] and gallbladder cancer.[16] Serum albumin as an independent prognostic factor is not usually described in reports of soft tissue sarcomas. In one study it was found as an independent factor after multiple regression analysis in patients with Ewing sarcoma, and the authors conclude that the value of serum albumin warrants confirmatory studies,[17] serum albumin has been described as a marker of general performance so interventional nutrition maneuvres may not have an impact in patients' prognosis.

It might be predictable that a lower performance status and a higher surgical risk correlate with impaired survival, and these variables may associate with a more advanced stage. This was suggested when multivariate analysis was done and both variables lost their statistical significance. Even though, there are reports that associate the Karnofsky score with an independent effect in survival.[18]

The tumor-related variables were consistent with previous reports. In the current study, only stage, histologic grade and resectability retained their significance after multivariate analysis.

We did not find sex, age, site, histologic subtype, BMI or previous biopsies to have an effect in this population, although some of these variables have been reported as predictors, such as age [19] and histologic subtype.[4,20]

The only factor related to disease-free survival was histologic grade: patients with high grade lesions had an elevated risk of recurrence. It has been reported that certain features like histologic subtype (MPNT or fibrosarcoma), or age greater than 50 are associated with recurrence,[4] but this was not the case in the population analyzed. This may be attributed to the smaller size of the population.

CONCLUSION

Soft tissue sarcomas are rare tumors, even in reference centers. The clinical and demographic characteristics found in this study are comparable to previous reports, although with a tendency towards larger tumor size and advanced stage at presentation. Serum albumin was an independent prognostic factor for survival, not usually considered in other studies. It should be emphasized that not only tumor related factors are determinant for survival in patients with soft tissue sarcomas. Other significant patient related factors found in the univariate analysis were the performance status and the surgical risk. We propose that these variables are included in future analysis of survival in sarcomas to further quantify their importance. The other prognostic factors were consistent with previous studies.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin* 2004; 54: 8-29.
2. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: metaanalysis of individual data. *Lancet* 1997; 350: 1647-54.
3. Bramwell V, Rouesse J, Steward W, et al. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma–reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1994; 12: 1137-49.
4. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol* 1996; 14: 1679-89.
5. Singer S, Corson JM, Demetri GD, Healey EZ, Marcus K, Eberlein T. Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. *Ann Surg* 1995; 221: 185-95.
6. Collin C, Godbold J, Hajdu S, et al. Localized extremity soft tissue sarcoma: an analysis of factors affecting survival. *J Clin Oncol* 1988; 5: 601-12.
7. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma. Analysis of 500 patients treated and followed at a single institution. *Ann Surg* 1998; 228: 355-65.
8. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457-81.
9. Armitage P, Berry G. Statistical Methods in Medical Research. 2nd. Ed. Oxford, UK: Blackwell Scientific Pub; 1987.
10. Cox D. Regression models and life-tables. *J R Stat Soc* 1972; 34(Ser. B):187-200.
11. Pollock RE, Karnell LH, Menck HR, Winchester DP. The National cancer database report on soft tissue sarcoma. *Cancer* 1996; 78: 2247-57.
12. Jaques DP, Coit DG, Hajdu SI, Brennan MF. Management of primary and recurrent soft tissue sarcoma of the retroperitoneum. *Ann Surg* 1990; 212: 51-9.
13. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; 340: 448-54.
14. Baracos VE. Regulation of skeletal-muscle protein turnover in cancer-associated cachexia. *Nutrition* 2000; 16: 1015-8.
15. Oñate-Ocaña LF, Aiello-Crocifoglio V, Gallardo-Rincón D, et al. Serum albumin is a significant prognostic factor for patients with gastric adenocarcinoma. *Ann Surg Onc* 2006; 13: S35.
16. Medina-Franco H, Ramos-Gallardo G, Orozco-Zepeda H, Mercado-Diaz MA. Factores pronósticos en cáncer de vesícula. *Rev Invest Clin* 2005; 57: 662-5.
17. Aparicio J, Munarriz B, Pastor M, et al. Long-term follow-up and prognostic factors in Ewing's sarcoma. A multivariate analysis of 116 patients from a single institution. *Oncology* 1998; 55: 20-6.
18. Rougraff B, Sandler A. Karnofsky performance score as a predictor of survival in soft tissue sarcoma. *Clin Orthop Relat Res* 2002; 397: 196-203.
19. Singer S, Corson JM, Gonin R, Labow B, Eberlein TJ. Prognostic factors predictive of survival and local recurrence for extremity soft tissue sarcoma. *Ann Surg* 1994; 219: 165-73.
20. Koea JB, Leung D, Lewis JJ, Brennan MF. Histopathologic type: an independent prognostic factor in primary soft tis-

sue sarcoma of the extremity? *Ann Surg Oncol* 2003; 10: 432-40.

Reimpresos:

Dr. Heriberto Medina-Franco
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.
Vasco de Quiroga 15.
Col. Sección XVI, Tlalpan.
14080, México, D.F.
Tel.: (55)5487-0900 Ext.: 2140.
E-mail: herimd@hotmail.com.

Recibido el 3 de septiembre de 2008.
Aceptado el 15 de enero de 2009.