Prognostic factors in patients with jaw sarcomas

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Abstract: The aim of this study was to identify the prognostic factors related to the survival of patients with sarcomas of the jaw treated in the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru. Age, gender, delay in consultation, diagnostic delay, therapeutic delay, tumor size, tumor location, facial asymmetry, pain, treatment type, and histopathological diagnosis were all evaluated as possible prognostic factors that would influence survival in those with jaw sarcomas. In the analysis, the following was used: mortality tables, Kaplan-Meier's product-limit method, log-rank, and Breslow and Tarone-Ware tests; for the prognostic factors, Cox's Regression Model was used. The overall survival rate, with the patient being free from disease at two years, was 55%, and that at five years was 45%. In the independent analysis of the prognostic factors, four variables were statistically significant in influencing survival: gender (p = 0.043), histopathologic diagnosis (p = 0.019), tumor location (p = 0.019), and treatment type (p = 0.030). According to Cox's Regression Model for the multivariate analysis, statistically significant prognostic factors were: gender (p = 0.086), tumor location (p = 0.020), and treatment type (p = 0.092). Thus, the variables of gender, tumor location, and treatment type were determined to be predictive factors for prognosis of survival.

Descriptors: Sarcoma; Jaw; Survival; Prognosis.

Introduction

Sarcomas of the jaws (JS) are infrequent, accounting for about 1% of all the malignant tumors that occur in the oral and maxillofacial region.[1] These sarcomas are highly aggressive and as such require an accurate diagnosis and therapy to be treated effectively.[2]

Prognostic factors for sarcomas are not well-known,[3] specifically regarding the jawbones. There are some studies that present data on osteosarcomas of the jawbones or data on head and neck sarcomas, but these studies are far from comprehensive.

Studies such as that by Patel *et al.*[4] reviewed the records of 44 patients with osteogenic head and neck sarcomas and found, at 3 and 5 years, overall survival rates of 81% and 70%, respectively. In this study, only the surgical margins were correlated significantly to survival prognosis.

In 2008, Singh *et al.*[5] examined 36 cases of soft-tissue sarcomas of the head and neck, and Penel *et al.*[6] analyzed 45 similar cases and found overall survival rates at 5 years of 49% and 52% (± 8%), respectively.

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The size of the tumor was the most important prognostic factor in the former study, and in the second study, which performed a univariate analysis, the prognostic factors that were statistically significant included high levels of malignancy, early infiltration of lymph nodes, absence of surgery, and number of surgical procedures. In the multivariate analysis, the level of malignancy ($p = 0.006$) and the absence of surgery ($p = 0.005$) were still significant.

The 10-year retrospective research of Ketabchi *et al.*[7] analyzed 25 cases of hard- and soft-tissue sarcomas of the head and neck and found a 76% overall survival rate for hard-tissue sarcomas (osteosarcomas in jawbones) and 80% for soft-tissue sarcomas within a follow-up time of 12 to 108 months (60 months on average).

The aim of this study was to identify the prognostic factors related to the survival of patients with jaw sarcomas, using univariate and multivariate analyses to assess prognostic factors associated with survival, and to determine survival rates at 2 and 5 years for patients with JS treated in the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases (INEN), Lima, Peru, over the period of 1952 to 2007.

Methodology

The present study is a longitudinal, retrospective case series focusing on 155 patients with a diagnosis of JS and registered in the Statistics Department of the INEN, Lima, Peru, from 1952 to 2007. Of these 155 patients, however, 20 had to be excluded due to incomplete case information that could not be analyzed accurately.

Statistical analysis

Descriptive statistics of frequency were developed for each variable. For the percentage of survival at 2 and 5 years, the mortality table was used, and for the univariate survival analysis, Kaplan-Meier's product-limit method was used. For the bivariate analysis, the log-rank, Breslow and Tarone-Ware tests were used to compare a variable and other survival variables. The multivariate analysis of the prognostic factors was obtained when Cox's Regression Model, also called the proportional risks model, was applied. Values of $p \leq 0.05$ (5%) were considered significant. The analysis was developed with the SPSS statistical package (15.0 version for Windows, SPSS Inc., Chicago, USA) with Windows XP® Operating System (Microsoft, Inc., Seattle, USA).

Results

Distribution of the variables

An analysis was performed on 135 clinical records, with appropriate consent having been obtained from patients with confirmed diagnosis of JS. The age range was from 1 to 80 years, with the average being 31 years. Most individuals (48.1%) were between 0 and 30 years old. In the analysis regarding gender, a slight predominance in the female gender (55.6%) (ratio of 1.25 to 1) was observed. Osteosarcoma was the most frequent diagnosis (51.1%), followed by chondrosarcoma (17.8%) (Table 1). Within a range from 1 to 26 cm, the average tumor size was 5 cm, with most patients (66.7%) having a tumor bigger than 4 cm. The most frequent location was in the upper jaw (maxillary) (53.3%). Facial asymmetry was observed in 87.4%, and the symptom of pain in 62.2%. The two treatment classifications were designated as "combination of treatments" and "surgical treatment" in a total of 114 cases. It was not possible to classify treatments

Table 1 - Survival rates for diagnoses of jaw sarcomas in patients at the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru (1952-2007).

Diagnosis	N	%	Survival 2 years	Survival 5 years
Osteosarcoma	69	51.1	63%	53%
Chondrosarcoma	24	17.8	70%	63%
Malignant fibrous histiocytoma	16	11.9	31%	15%
Fibrosarcoma	08	05.9	57%	38%
Rhabdomyosarcoma	07	05.2	36%	36%
Ewing's sarcoma	04	03.0	_*	_
Leiomyosarcoma	01	00.7	_	_
Undifferentiated sarcoma	06	04.4	_	_
	135	100		

* The statistical calculation could not be made.

more specifically, since specific data on the types of treatment were not described clearly in the clinical records. The delay in making an appointment averaged 91 days (3 months), the diagnostic delay averaged 138 days (4.5 months), and the therapeutic delay was shown to be 122 days (4 months) on average. The survival time of patients ranged from 12 to 12,205 days (33.42 years), with an average of 355 days.

Survival analysis

The survival rate at 2 and 5 years, based on mortality tables, was 55% and 45%, respectively (Figure 1).

Analysis of relative impact of the prognostic factors of survival

In the univariate analysis, gender (p = 0.043), histopathological diagnosis (p = 0.019), tumor location (p = 0.019), and treatment type (p = 0.030) were found to be statistically significant. Using the Kaplan-Meier survival curve, we observed that female patients had 1.8 times more risk of death than males (Figure 2). By using the log-rank test of survival curves to compare survival rates between osteosarcomas and other types of jaw sarcomas, we found that a statistically significant difference existed between these two groups (p = 0.019). Patients with osteosarcomas were found to have a better survival rate than those with diagnoses of other sarcomas. When analyzing the survival curves regarding the location of the JS, we found a significant difference (p = 0.019), demonstrating that patients with sarcomas in the lower jaw (mandibular) had a better survival prognosis than those with maxillary sarcomas (Figure 3). A statistical difference in survival (p = 0.030) was also found in the type of treatment. It was observed that patients who received surgical treatment (the "surgical treatment" group) had a reduced risk of death by 0.5 times compared with other treatments (the "combined treatment" group) (Figure 4).

Analysis of the influence of the prognostic factors on survival

Univariate and multivariate analyses of all prognostic factors were carried out, and three predictive variables were seen to influence survival: male gender (p = 0.086), mandibular tumor location (p = 0.020), and surgical treatment (p = 0.092). Per the results, the female gender presented 1.8 times more risk of death due to this neoplasia than did the male gender. Likewise, it was observed that the maxillary tumor location also had a negative impact on survival, since it caused 2.2 times increased risk of death due to JS compared with the mandibular

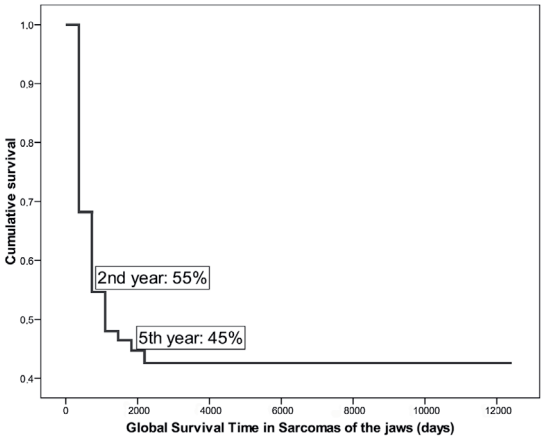

Figure 1 - Overall survival curve according to the actuarial model (in years) for patients with sarcomas of the jaw, seen at the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru (1952-2007) (Analysis of Mortality Table).

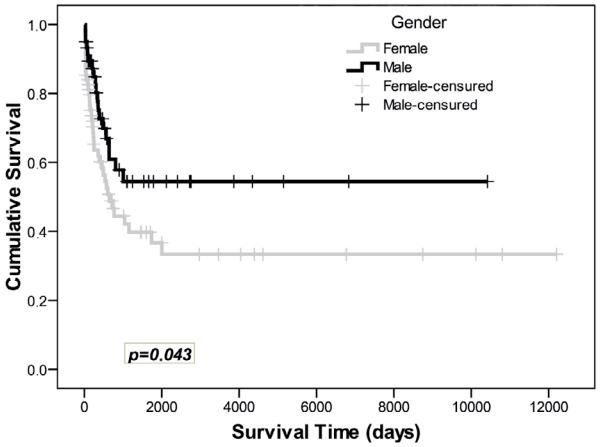

Figure 2 - Comparison of survival curves according to gender for patients with sarcomas of the jaw, seen at the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru (1952-2007) (comparison: Kaplan-Meier's test) ($p \leq 0.05$).

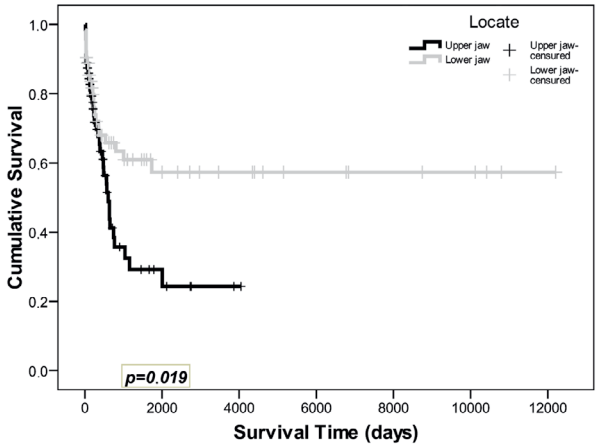

Figure 3 - Comparison of survival curves according to tumor location in patients with sarcomas of the jaw, seen at the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru (1952-2007) (Comparison: Kaplan-Meier's test) ($p \leq 0.05$).

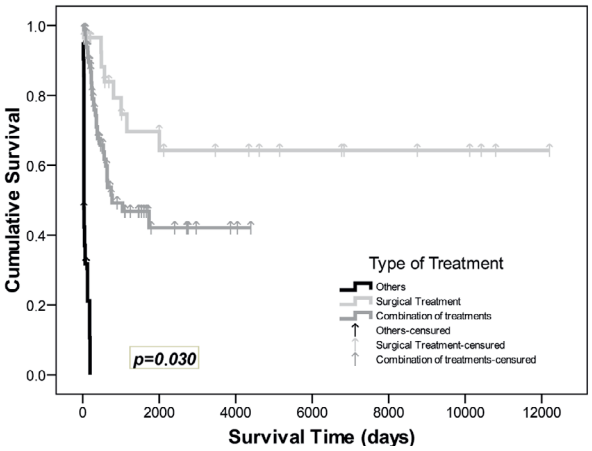

Figure 4 - Comparison of survival curves according to type of treatment in patients with sarcomas of the jaw, seen at the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru (1952-2007) (Comparison: Kaplan-Meier's test) ($p \leq 0.05$).

Table 2 - Comparison between the univariate and the multivariate analyses of the prognostic factors for survival in JS patients at the Dr. Eduardo Caceres Graziani National Institute for Neoplastic Diseases, Lima, Peru (1952-2007).

Risk Factor	Univariate Analysis (p value)	Multivariate Analysis (p value)
Age (years)	0.544	0.729
Gender	0.043*	0.086 (*f*)
Histopathologic diagnosis	0.019*	0.679
Delay in consulting	0.180	0.377
Diagnostic delay	0.200	0.651
Therapeutic delay	0.143	0.490
Tumor size	0.776	0.993
Location	0.019*	0.020* (*f*)
Facial asymmetry	0.631	0.436
Pain	0.686	0.790
Treatment type	0.030*	0.092 (*f*)

The p-value of the univariate analysis was calculated by means of the log-rank analysis ($p \leq 0.05$). The p-value of the multivariate analysis was calculated by means of Cox's Regression Model ($p \leq 0.05$). * Values indicating statistical significance; the variable is according to the model. (*f*)Variable present in the risk function.

tumor location. Conversely, it was observed that a surgical treatment reduced by half the risk of death compared with the use of a combination of treatments, even though, according to the confidence interval, we could not statistically ensure that it behaves as a protection factor (Table 2).

Risk function of the prognostic factors in survival

The final model for measurement of the influence of various variables on survival was the risk function, which is comprised of the multivariate analysis of prognostic factors and Cox's Regression Model. Overall, 3 of the 4 variables that had a statistical significance in the univariate analysis were selected:

$$Ht = h_0(t)\ Exp\ (0.563 \times \text{Female Gender} + 0.8 \times \text{Upper Jaw Location} - 0.696 \times \text{Surgical Treatment})$$

Discussion

Regarding the survival risks for patients with JS, Cox's Regression Model selected 3 of the 4 variables that had a statistical significance in the independent analysis: gender, sarcoma location, and treatment type. The fourth variable, histopathological diagnosis, which was not found to be significant in the Cox Regression Model, loses statistical significance when analyzed as a whole. It is explained by the joint intervention of the other variables, but the specific reason for the occurrence of this phenomenon cannot be determined. Nevertheless, according to the litera-

ture, it is suspected that the delays in consultation and diagnosis, combined with treatment location, lead to similar outcomes for those with a diagnosis of osteosarcoma and those with different types of JS.

In the present study, the age group distribution is from 1 to 80 years, with an average age of 31 years. This value is similar to that described by Brockstein.[8] In turn, Yoel[9] and co-workers report similar data, citing greater predominance of JS in the second, third, fourth, and fifth decades of life. The literature describes a bimodal age group distribution for osteosarcomas, in which the majority of patients are between 10 and 20 years old, with a secondary group over 50 years old. The present study did not find this type of distribution and, in fact, found a progressive decrease of cases occurring as age increased. When the diagnoses were compared in the current study, a 51.1% predominance of osteosarcomas was found, which is high compared with 24.6% reported by Yoel *et al.*[9] or 28% reported by Yamaguchi *et al.*[10]

Sarcomas are a heterogeneous group of tumors that present, are diagnosed, and are treated at different stages and therefore have different overall prognoses. The overall survival at 2 years of head and neck sarcomas in the current study was of 55%, a low value compared with studies by Penel *et al.*,[6] where survival was reported to be 71.7%. Also, Nagler *et al.*[11] reported a 72% survival rate for maxillofacial sarcomas, Mücke[12] and colleagues found a survival rate of 83.78%, and the cases studied by the Canadian Society of Otorhinolaryngology showed a survival rate of 79%.

At 5 years, the survival rate was 45%, a value close to that found by Singh *et al.*[5] (49%) in the United Kingdom and by Penel *et al.*[6] (52.3%) in France, while the value was low compared with that found by Mücke[12] and co-workers in Germany (60.81%) and by Ketabchi *et al.*[7] in the United Kingdom (80%). Overall, much of the literature reports a five-year survival rate between 57% and 86%.[4,6,11,13]

For osteogenic sarcomas, Kassir *et al.*[14] report a survival rate of 37%, and Ketabchi[7] and colleagues note an overall survival rate of 76%. The present study found a survival rate for osteosarcomas of 63% and 53% at 2 and 5 years, respectively. The survival rates for osteosarcomas are better than those for other sarcomas, since the former exhibit different biological behavior and different dissemination. It is assumed that the differences regarding survival rates are due to the different factors used in the treatment and development of the sarcomas.

In the univariate analysis of risk factors that influence survival, the only variables that were found to be statistically significant were: gender, histopathological diagnosis, tumor location, and treatment type. When all variables were analyzed by Cox's Regression Model (age, gender, delay in consulting, diagnostic delay, therapeutic delay, tumor size, tumor location, facial asymmetry, pain, treatment type, and histopathological diagnosis), the following prognostic factors emerged: gender, tumor location, and the treatment type received. Patel *et al.*[4] found that the only prognostic factor was the extension of surgical margins. de Bree[15] and colleagues concluded that the prognostic factors for sarcomas that reduce overall survival are: tumors in any anatomical location with a diameter greater than 5 cm, with many abnormalities found on histological examination, and with positive surgical margins. Penel[6] and co-workers found that the variables infiltration level and absence of surgery influenced survival. August *et al.*[16] describe the factors of age and surgical treatment as influencing survival. Ruiz[17] and co-workers refer to tumor size, tumor location, and histological level. Nagler[11] and colleagues report type of sarcoma and young age, and Harb *et al.*[18] mention that tumor size on presentation generally depends on the location of the tumor, with the location being of greater prognostic impact. Finally, Singh[5] and co-workers found that tumor size was the most important prognostic factor.

Fayda *et al.*[19] studied 30 cases and focused on the roles of surgery and radiotherapy in the treatment of soft-tissue sarcomas of the head and neck during an average follow-up time of 31 months. They found a statistically significant difference in the overall survival rate of patients who were treated with surgery and radiotherapy.

Osteosarcomas are less aggressive sarcomas compared with other jaw sarcomas. Many researchers refer to the importance of the diagnostic process as a prognostic factor, because treatments of osteo-

sarcomas differ from those for other types of sarcomas.[5] This difference eliminates this factor as an element in the prognosis of survival. In Peru, there are no data on survival of patients with sarcomas in the jawbones, and therefore prospective studies with more specific data about this topic are necessary.

Conclusion

In patients with JS, the factors independently related to survival are: histopathological diagnosis, gender, tumor location, and treatment type. On the whole, the positive prognostic factors were found to be male gender, tumor location in the mandible, and surgical treatment.

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