Survival in patients with oral and maxillofacial diffuse large B-cell lymphoma

Abstract: The purpose of this study was to determine the survival and prognostic factors of patients with diffuse large B-cell lymphoma (DLBCL) of the oral cavity and maxillofacial region. Retrospectively, the clinical records of patients with a primary diagnosis of DLBCL of the oral cavity and maxillofacial region treated at the A.C. Camargo Hospital for Cancer, São Paulo, Brazil, between January 1980 and December 2005 were evaluated to determine (A) overall survival (OS) at 2 and 5 years and the individual survival percentage for each possible prognostic factor by means of the actuarial technique (also known as mortality tables), and the Kaplan Meier product limit method (which provided the survival value curves for each possible prognostic factor); (B) prognostic factors subject to univariate evaluation with the log-rank test (also known as Mantel-Cox), and multivariate analysis with Cox’s regression model (all the variables together). The data were considered significant at \( p \leq 0.05 \). From 1980 to 2005, 3513 new cases of lymphomas were treated, of which 151 (4.3\%\) occurred in the oral cavity and maxillofacial region. Of these 151 lesions, 48 were diffuse large B-cell lymphoma, with 64\% for OS at 2 years and 45\% for OS at 5 years. Of the variables studied as possible prognostic factors, multivariate analysis found the following variables have statistically significant values: age (\( p = 0.042 \)), clinical stage (\( p = 0.007 \)) and performance status (\( p = 0.031 \)). These data suggest that patients have a higher risk of mortality if they are older, at a later clinical stage, and have a higher performance status.

Descriptors: Lymphoma, Large B-Cell, Diffuse; Survival; Mouth Neoplasms; Prognosis.

Introduction

Lymphomas represent a heterogeneous group of malignant clonal diseases. The characteristic they share is that they arise as a result of somatic mutation of a lymphocyte progenitor.1 Although lymphomas represent less than 5\% of all oral cancers,2 they are the most frequent non-epithelial malignant tumors in the oral cavity and maxillofacial region (OC-MR).3 Further, lymphoma is a general term for a complex group of malignant neoplasms of the lymphoreticular system,4 traditionally defined as either Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL).5 The current classification of lymphoma subtypes was proposed by the World Health Organization in 2008.6
NHL occurs mainly in the lymph nodes, though approximately 24% of cases affect extra-nodal locations,7,8 such as stomach, skin, lung, central nervous system, orbit, salivary glands and oral cavity. The type of NHL most frequently diagnosed is DLBCL, which is in turn the most frequent type of primary lymphoma of the oral cavity.10,11 Factors which have been shown to have significant influence on the survival of patients with NHL include:

- age,
- presence or absence of constitutional symptoms,
- performance status,
- serum lactate dehydrogenase (LDH),
- Ann Arbor stage,
- tumor size,
- number of nodal and extranodal disease sites, and
- bone marrow involvement.12,13

It is important to identify, measure, and interpret the characteristics of alterations which have prognostic implications and influence in a DLBCL patient’s survival. This is important to predict patient survival, and to understand the natural history of the disease in order to provide an appropriate treatment plan according to the response to therapy. Thus, the purpose of the study was to determine the survival and prognostic factors of patients with DL-BCL of the oral cavity and maxillofacial region.

Methodology

An observational, descriptive, cross-sectional, retrospective research design was followed. The patients included in this study were treated at A.C. Camargo Hospital for Cancer, São Paulo, Brazil, between January 1980 and December 2005 and their clinical histories contained a primary diagnosis of DLBCL of the OC-MR. Clinical records with incomplete data were excluded.

Overall survival was defined as the percentage of patients remaining alive during the period from the beginning of treatment to the last visit or date of death (in years). The following variables were considered for the analysis of prognostic factors:

- size of lesion,
- increased volume,
- pain,
- local symptoms,
- general symptoms,
- histologic malignancy grade (according to The International Working Formulation for Clinical Usage),14
- clinical stage (based on the Ann Arbor staging system),15-17
- International Prognostic Index (IPI),18
- performance status evaluated according to the Eastern Cooperative Oncology Group (ECOG),19
- serum concentration of LDH,
- extranodal involvement,
- treatment,
- follow-up state and
- follow-up time.

The collected data were transferred to the Microsoft Excel program (Microsoft, Inc., Redmond, USA), and the analysis was conducted with the Statistical Package for Social Sciences - SPSS (version 18.0 for Windows, IBM Inc., Chicago, USA).

Survival analysis was calculated using two statistical tests:

1. the actuarial technique (also known as mortality tables) to determine the percentage of OS at 2 and 5 years and the percentage of individual survival for each possible prognostic factor and
2. the Kaplan Meier product limit method, a test that provides the curves or lines for the survival value for each possible prognostic factor.

Prognostic factors were evaluated in two ways:

1. univariate analysis, with the log-rank test (also known as Mantel-Cox) which provides the statistical significance of the differences between the survival curves or lines of the Kaplan Meier product limit individually for each variable and
2. multivariate analysis, using the Cox regression model, considering all variables and possible prognostic factors together.

For all cases, significance was considered as \( p \leq 0.05 \).
Results

From January 1980 to December 2005, 3513 new cases of lymphoma were treated at the A.C. Camargo Hospital, of which 151 (4.3%) occurred in the OC-MR. Of these 151 lymphomas, 48 (31.79%) were DLBCL. Of the 48 patients evaluated, OS was 64% at 2 years and 45% at 5 years (Figure 1).

Table 1 shows the survival percentage and significance value for each variable analyzed as a possible prognostic factor for survival.

Multivariate analysis of different variables studied as possible prognostic factors showed three sta-
### Table 1 - Percent survival at 2 and 5 years evaluated for possible prognostic factors for subjects with DLBCL of the OC-MR.

(continued on next page)
tistically significant factors:
• age (p = 0.042) (Figure 2),
• clinical stage (p = 0.007) (Figure 3) and
• performance status (p = 0.031) (Figure 4).

The mortality risk was found to be 0.603 times higher in patients over 60 years of age than in patients aged 60 years or less. Survival was found to be 0.789 times better in patients at clinical stage I than in those at clinical stage IV. Similarly, the mortality risk was 0.716 times less in patients with a performance status of 1 or lower compared to patients with performance status of 2 or higher (Table 2).

**Discussion**

In this study, the 48 DLBCLs evaluated corresponded to 31.79% of the NHL patients treated at Hospital A.C. Camargo for Cancer between 1980 and 2005, which is slightly lower than the DLBCL values reported in the case series studies performed by van der Wall et al., Kemp et al. and Solomides et al. in which they accounted for 50%, 58% and 68%, respectively of all oral NHL. Although DLBCL represents about 30% to 40% of NHL cases in general, its predominance is even higher in the oral cavity and this is probably explained by its propensity to occur at a single extranodal site.

Factors that have been found to influence survival significantly in patients with DLBCL include:
• the presence or absence of constitutional symptoms,
• LDH,
• Ann Arbor stage, and
• involvement of bone marrow.

Studies such as that of Møller et al. reported the survival of patients with DLBCL without specifying the location of the tumor, and found an overall survival rate of 85% at 5 years, which is much higher than the value determined in this study (45% at 5 years). This may be because in cases of OC-

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**Table 1 - (continued)**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Survival at 2 years (%)</th>
<th>Survival at 5 years (%)</th>
<th>p value according to log rank (Univariate)</th>
<th>p value according to Cox (Multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cht</td>
<td>61</td>
<td>43</td>
<td>0.694</td>
<td>0.310</td>
</tr>
<tr>
<td>Cht + Rt</td>
<td>69</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt</td>
<td>39</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cht + Rt + Sg</td>
<td>100</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cht + Sg</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sg + Rt</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sg</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant value. IPI: International Prognostic Index, LDH: lactate dehydrogenase, Cht: chemotherapy, Rt: radiotherapy, Sg: surgery.

**Table 2 - Potential risk factors associated with survival for subjects with DLBCL of the OC-MR, according to multivariate hazard ratio of Cox analysis.**

<table>
<thead>
<tr>
<th>Variable analyzed</th>
<th>Hazard ratio</th>
<th>Confidence interval 95%</th>
<th>p value according to Cox (multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>0.397</td>
<td>0.162–0.973</td>
<td>0.042*</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>0.211</td>
<td>0.220–2.028</td>
<td>0.007*</td>
</tr>
<tr>
<td>Stage II</td>
<td>1.392</td>
<td>0.421–4.602</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>4.387</td>
<td>1.209–15.921</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>0.284</td>
<td>0.900–0.894</td>
<td>0.031*</td>
</tr>
<tr>
<td>≥ 2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant value.
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MR, patients often take too long to seek medical attention, which results in more difficult treatment and poorer prognosis. Vose reported a survival rate of about 50% at 5 years, which is similar to the result found in our study.

Multivariate analysis of prognostic factors showed that factors having significant influence are age, clinical stage and performance status. This corresponds with the results reported by Møller et al., who also found that age and clinical stage influence the survival of patients with DLBCL. Ho et al. also report that the prognosis is influenced by clinical stage and histologic grade because large cell lymphomas are considered aggressive and have a poor prognosis.

Many variables have been studied with regards to the survival prognosis of patients with DLBCL, such as hematological and biochemical profiles. Even though these profiles are often normal, patients may have a reduction in the number of peripheral blood lymphocytes, reductions in serum albumin levels, and increases in LDH, which has been shown to correlate with a poor prognosis. Some authors have not found the expression of Bcl-2 protein, though it occurs in 30% to 60% of cases, and it has been found to have prognostic value. Nevertheless, other studies suggest that the expression of Bcl-2 is related to a significantly poorer survival rate. It has also been reported that multiple myeloma oncogene 1 (MUM1) expression is significantly associated to a lower survival rate. The study by Bhattacharyya et al. considered the type of DLBCL in the oral cavity as a prognostic factor. Similarly, Tibiletti et al. evaluated fluorescence in situ hybridization to detect the heterogeneity of DLBCL and identify alterations with prognostic implications.

**Conclusion**

According to the results of this study, it may be concluded that the mortality risk is significantly higher in patients with OC-MR DLBCL who are older, at a higher clinical stage, and have higher performance status suggesting these are survival prognosis factors.

**References**


