SYSTEMATIC REVIEW OF LYMPHOMA IN ORAL CAVITY AND MAXILLOFACIAL REGION

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Abstract
The aim of this paper is to determine, compare and summarize presentation characteristics of patients with lymphoma of the oral cavity and maxillofacial region using the results of different primary studies. Articles from the PubMed database published between 1990 and 2010 were reviewed. The key words “Lymphoma” and “Oral” were used to search for titles, identifying 215 articles, of which 178 were excluded and 37 were used for this review. After evaluation, the researchers agreed to include 15 of the papers in the study. This paper describes the author, year published, number of cases, sex, age, location, signs and symptoms, classification, diagnosis, staging and treatment reported in each of the 15 studies. A total 714 patients are described. In 11 out of 13 studies, there were more cases in males than females. Ages ranged from 3 to 96 years. Presentation was most frequently the gingiva and the main sign was swelling. Staging was described for only 177 cases and treatment was described for only 110 cases. It is concluded that the presentation of most of the lymphomas of the oral cavity and maxillofacial region is extranodal, non-Hodgkin’s. The most common locations are gingiva in the oral cavity and Waldeyer’s ring in the maxillofacial region. Although these lymphomas are rare pathological entities, it is important to describe the complete manifestation of their natural history in order to provide knowledge of their development.

Key words: lymphoma, mouth, review.

Introduction
Simply defined, lymphomas are malignant neoplasms of lymphocytes and their cell precursors¹. They are classified mainly as Hodgkin’s or non-Hodgkin’s lymphoma² according to differences in their histology and behavioral patterns.

Hodgkin’s lymphoma often appears as a nodal disease with a preference for cervical and mediastinal nodes, while over 40% of non-Hodgkin’s are extranodal³. Lymphoma is the second most common malignant neoplasm in head and neck, after epithelial malignant tumors in the oral cavity and maxillofacial

Résumé
L’objectif de ce travail a été déterminer, comparer et résumer les caractéristiques de présentation des patients avec lymphome de la cavité orale et la région maxillofaciale en utilisant les résultats de différentes études primaires. Des articles de la base de données PubMed publiés entre 1990 et 2010 ont été examinés. Les mots clés “Lymphome” et “Oral” ont été utilisés pour rechercher des titres, identifiant 215 articles, d’où 178 ont été exclus et 37 ont été utilisés pour cette revue. Après évaluation, les chercheurs ont convenu d’inclure 15 des papier dans l’étude. Cet article décrit l’auteur, l’année publiée, le nombre de cas, le sexe, l’âge, la localisation, les signes et les symptômes, la classification, le diagnostic, l’étape et le traitement rapportés dans chaque de ces 15 études. Un total de 714 patients sont décrits. Dans 11 des 13 études, il y avait plus de cas chez les hommes que chez les femmes. L’âge a varié de 3 à 96 ans. La présentation a été la plus fréquemment la gencive et le signe principal était la gonflement. L’étape a été décrite pour seulement 177 cas et le traitement a été décrit pour seulement 110 cas. Il est conclu que la présentation de la majorité des lymphomes de la cavité orale et la région maxillofaciale est extranodale, non-Hodgkin’s. Les emplacements les plus communs sont la gencive dans la cavité orale et le cercle de Waldeyer dans la région maxillofaciale. Même si ces lymphomes sont des entités pathologiques rares, il est important de décrire la manifestation complète de leur histoire naturelle afin de fournir des connaissances sur leur développement.

Mots clés : lymphome, bouche, revue.
Lymphoma represents 2.2% of all malignant neoplasms of head and neck, 3.5% of malignant intraoral neoplasms, 5% of tumors of salivary glands and 2.5% of all lymphomas on head and neck. 85% of the lesions affect tonsils and palate. Waldeyer’s ring takes second place for the incidence of extranodal non-Hodgkin lymphoma. In the oral cavity it includes palate, gingiva, tongue, cheek, floor of the mouth and lips as primary sites in approximately 2% of extranodal lymphomas.

Patients have signs of localized or diffuse swelling, ulceration of mucosa, paresthesia, anesthesia and tooth loss. Diagnosis includes a combination of physical examination, blood tests, diagnostic imaging and selective biopsies.

The most widely used system for classifying lymphoma stages is the Ann Arbor staging classification, which was initially introduced for Hodgkin’s lymphoma and later adopted for classifying non-Hodgkin lymphoma.

Lymphoma malignancy prognosis is revealed by the following factors: age, performance status, number of extranodal sites involved, Ann Arbor stage and serum level of lactate dehydrogenase (LDH), all of which make up the International Prognostic Index. Treatment of non-Hodgkin’s lymphoma in the head and neck region is complex due to the many variables involved.

The main aim of this systematic review was to determine, from a series of cases, the presentation characteristics of patients with lymphoma in the oral cavity and maxillofacial region. The systematic review was proposed in order to compare these presentations and summarize results from various primary studies using strategies to minimize bias and random error.

### MATERIALS AND METHODS

#### Search strategy for studies
Articles from the PubMed database published between 1990 and 2010 were included. The search was performed 72 days after the deadline for article inclusion. The key words “Lymphoma” and “Oral” in article titles were entered in the field “advanced search” field.

#### Selection of studies
215 studies were identified. After reading the abstracts, 178 were excluded for the reasons shown in Table 1. The 37 remaining full papers were read independently by 3 researchers.

#### Study assessment criteria
It was decided that at least two researchers should agree to include each article in this study, according to the abovementioned criteria. The most frequent reason for exclusion was insufficient data for evaluation. The Kappa values for agreement among researchers were as expected (K≥0.67). In the end, 15 papers were selected which had different designs, but all contained information on the clinical characteristics of the lymphoma in the oral cavity and maxillofacial region: age, sex, location, signs and symptoms, classification, diagnosis, staging and treatment; even if not all the data were reported in every article.

#### Data extraction
The data on the characteristics found and all the documented results are summarized in a general table.

### RESULTS

Table 2 summarizes the information from the articles that were included. For the 15 studies it provides author, year published, number of cases, gender, age, location, signs and symptoms, classification, diagnosis, staging and treatment (certain data were not included in some of the articles).

The studies presented 7 to 361 cases each and were published between 1990 and 2010. Altogether they described 714 patients, and in 11 out of 13 studies there were more males than females. Ages ranged from 3 to...
Table 2: Characteristics of the selected studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Nº</th>
<th>Gender</th>
<th>Age</th>
<th>Location</th>
<th>Signs and Symptoms</th>
<th>Classification</th>
<th>Diagnosis</th>
<th>Staging</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolvius 1994</td>
<td>34</td>
<td>M</td>
<td>59</td>
<td>Soft tissue of palate</td>
<td>24 Swelling 06 Pain 03 Numness 10 Ulceration</td>
<td>Kiel</td>
<td>12 Centroblastic lymphoma 01 Immunoblastic lymphoma 02 Large cell anaplastic</td>
<td>20 Stage I</td>
<td>05 Cht + Rt</td>
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<td>F</td>
<td>14</td>
<td>Gingiva</td>
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<td>01 Burkitt's lymphoma 02 Lymphoblastic 08 Centroblastic-centrocytic lymphoma</td>
<td>01 Stage III</td>
<td>11 Stage IV</td>
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<td></td>
<td>Tongue</td>
<td></td>
<td></td>
<td>06 Centrocytic lymphoma</td>
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<td>01 Stage II</td>
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<td></td>
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<td>Maxilla</td>
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<td>02 Palate 05 Mandible</td>
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<tr>
<td>Shindoh 1997</td>
<td>31</td>
<td>M</td>
<td>52.83</td>
<td>Gingiva</td>
<td>29 Swelling 09 Pain 06 Paresthesia 03 Disturbed healing of an extraction wound</td>
<td>WF</td>
<td>05 Lymphoma, large cell, immunoblastic 05 Lymphoma, small non-cleaved cell</td>
<td>14 Stage I</td>
<td>03 Stage II 03 Stage II 10 Stage IV</td>
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<td></td>
<td>F</td>
<td>23</td>
<td>Buccal mucosa</td>
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<td></td>
<td>01 Burkitt's lymphoma 01 Lymphoblastic 15 Diffuse lymphoma, large cell type</td>
<td>01</td>
<td>10 Stage IV Of 33 cases</td>
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<td></td>
<td>Tongue</td>
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<td>01 Diffuse lymphoma, mixed small and large cell</td>
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<td>Palate</td>
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<td>02 Diffuse lymphoma, small cleaved cell</td>
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<td></td>
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<td>REAL</td>
<td>02 Unclassified</td>
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<td>03 Mandible 03 Soft palate 01 Submandibular gland 01 Parotid gland 03 Tongue</td>
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<td>Tongue</td>
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<td>03 Nasal cavity 03 Maxillary sinus</td>
<td>06</td>
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<td>Ardekian 1999</td>
<td>13</td>
<td>M</td>
<td>15.3</td>
<td>Mandible and mandibl</td>
<td>5 Swelling 7 Pain 2 Paresthesia</td>
<td>REAL</td>
<td>Burkitt's lymphoma</td>
<td>06 Stage I</td>
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<td>02 Palate 05 Maxilla</td>
<td>07</td>
<td>03 Cht + Rt</td>
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<td>37</td>
<td>M</td>
<td>65</td>
<td>Palate</td>
<td></td>
<td>WF</td>
<td>31 Intermediate grade lymphoma 06 High grade lymphoma</td>
<td>24 Stage IE</td>
<td>13 Stage III 23 Rt</td>
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<td></td>
<td>Gingiva inferior</td>
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<td>Buccal mucosa</td>
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<td>02 Tongue 01 Floor of mouth 01 Lip</td>
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<tr>
<td>Yor 2001</td>
<td>27</td>
<td>M</td>
<td>61</td>
<td>Gingiva</td>
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<td>REAL</td>
<td>01 Small lymphocytic</td>
<td>08 Stage I</td>
<td>09 Stage II 09 Stage IV Of 26 cases</td>
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<td>Buccal mucosa</td>
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<td>Leong 2001</td>
<td>58</td>
<td>M</td>
<td>56.96</td>
<td>Palate</td>
<td></td>
<td>REAL</td>
<td>25 Swelling 02 Loosening of the teeth 03 Extensive bone destruction</td>
<td>26</td>
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<td>13 Immunoblastic lymphoma</td>
<td>01</td>
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<td>Epstein 2001</td>
<td>361</td>
<td>M</td>
<td>62.5</td>
<td>Tongue</td>
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<td>118 Tonsil 58 Parotid gland 40 Nasopharynx 34 Maxillary sinus 32 Nasal cavity</td>
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<td>Maxilla</td>
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<td>36 Tongue 17 Palate 07 Submandibular lymph nodes 07 Gingiva 18 Other</td>
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<td>Tongue</td>
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<td>Palate</td>
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<td></td>
<td>82 Lymphoma NOS 03 Hodgkin's disease</td>
<td>07</td>
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</table>
96 years, and in 7 out of 13 studies patients were in their seventies, on average. The most frequent intra-oral location was gingiva, with 111 cases, followed by palate with 64 cases, while the most frequent location for the maxillofacial region was tonsil, with 126 cases, followed by parotid gland, with 63 of the cases described. In all the studies describing local signs and symptoms, the main feature is swelling. Diagnoses varied, but they were all non-Hodgkin lymphoma, mostly of B cells. Of the 177 cases for which staging is described, 100 were at stage IE, 39 were at stage IIE, 5 were at stage IIIE and 33 were at stage IV. The treatments of the cases presented in 8 of the 15 studies shown are: chemotherapy plus radiotherapy for 41 cases, chemotherapy for 28 cases, radiotherapy for 27 cases, chemotherapy plus surgery for 9 cases and surgery for 5 cases.

**DISCUSSION**

Few researchers have conducted studies on lymphoma in the oral cavity and maxillofacial region. The highest number of cases was reported in the study by Epstein et al.5 in 2001, which reports 361 cases in oral cavity and paraoral region. Van der Waal et al.25 in 2004 and Kemp et al.21 in 2008 reported 40 cases of non-Hodg-
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kin lymphoma in the oral cavity in each study. This systematic review gathers 714 cases from 15 studies. Regarding gender in the studies of oral cavity lymphoma, Kemp et al.\textsuperscript{23} find 53\% female, although they say that the difference between sexes is not statistically significant, like Urquhart et al.\textsuperscript{29} in a review of 235 non-Hodgkin lymphomas of the head and neck in 2001, although Mawardi et al.\textsuperscript{10} say that gender is a risk factor because men are more often affected than women. In the review of 15 studies, there were 381 men and 278 women out of a total 659 cases for which gender was specified.

Regarding the age of patients with lymphoma of the oral cavity and maxillofacial region, the range in the studies reviewed was 3 to 96 years, and in most studies the average patient was in his/her seventies, in agreement with studies such as Urquhart et al.\textsuperscript{29} which reports that non-Hodgkin lymphoma is more frequently diagnosed for ages 70 to 80 years.

The most frequent location for lymphomas of the maxillofacial region is Waldeyer’s ring\textsuperscript{30}, which is similar to what was found in this review, even though some studies only refer to cases in the oral cavity while others specifically exclude Waldeyer’s ring\textsuperscript{4,24,25}. Within the oral cavity, gingiva was the most frequent location according to the 15 studies described. Highest frequency for gingival location found in the set of 13 out of 15 studies matches individual studies such as the one by Solomides et al.\textsuperscript{31}.

Swelling of the area involved and absence of pain were the two signs and symptoms most often described in the evaluated studies. Systemic signs and symptoms (fever of unknown origin (>38°C), inexplicable weight loss and night sweating) are usually more often described in patients with Hodgkin’s lymphoma than with non-Hodgkin lymphoma\textsuperscript{30}, and in the oral cavity there may be swelling only\textsuperscript{9}.

This review describes studies published between 1990 and 2010, so they use different versions of lymphoma classification, including the International Working Formulation for Clinical Usage\textsuperscript{32} of 1982, Kiel classification\textsuperscript{33} of 1988, the Revised European-American Lymphoma (REAL) classification\textsuperscript{34} of 1994, the World Health Organization (WHO) classification\textsuperscript{35} of 2001 and the latest update of the World Health Organization (WHO)\textsuperscript{36} of 2008.

Out of the 177 cases for which staging was described, most were in stages I and II. Early diagnosis can allow the disease to be treated in its early stages, providing better patient prognosis\textsuperscript{5}.

Chemotherapy with radiotherapy was the treatment of choice in 41 cases from the 15 studies describing treatment. Non-Hodgkin lymphomas located on head and neck were treated with radiotherapy alone or combined with chemotherapy\textsuperscript{37}. Based on a review of 53 patients, it was suggested that radiotherapy was the adequate treatment for localized lymphoma and that chemotherapy was preferable for patients with systemic complication\textsuperscript{37}. A retrospective study of 92 patients with intermediate- and high-grade lymphoma showed a good response to combined chemotherapy and radiotherapy\textsuperscript{38}.

To conclude, the presentation of lymphomas of the oral cavity and maxillofacial region is more often the extranodal, non-Hodgkin type. The most common locations are gingiva in the oral cavity and Waldeyer’s ring in the maxillofacial region. Although lymphomas of the oral cavity and maxillofacial region are rare pathological entities, it is important to describe the complete manifestation of their natural history in order to provide knowledge of their development.

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