UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

CARLA ISABELLY RODRIGUES FERNANDES

LINFOMA DIFUSO DE GRANDES CÉLULAS B, SOE DE CAVIDADE ORAL E OROFARINGE: UM ESTUDO CLÍNICO-PATOLÓGICO

ORAL AND OROPHARYNGEAL DIFFUSE LARGE B-CELL LYMPHOMA, NOS: A CLINICOPATHOLOGIC STUDY

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Patologia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Stomatopathology, in Pathology area.

Orientador: Prof. Dr. Felipe Paiva Fonseca

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RESUMO

O linfoma difuso de grandes células B sem outra especificação (LDGCB SOE) é o subtipo mais comum dos linfomas não-Hodgkin encontrados na cavidade oral e região maxilofacial. As informações disponíveis atualmente na literatura acerca dos aspectos clínicopatológicos do LDGCB SOE oral e orofaríngeo são limitadas a relatos de caso e pequenas séries de casos. O primeiro capítulo deste estudo teve como objetivo revisar sistematicamente a literatura para determinar o perfil clinicopatológico do LDGCB oral e avaliar seus fatores prognósticos. Uma busca eletrônica foi executada utilizando as bases de dados *PubMed/MEDLINE*, *Web of Science* e *Science Direct* e 63 publicações foram incluídas no estudo, totalizando 122 casos. O LDGCB oral foi mais prevalente em homens mais velhos (61.5%), e a maioria dos tumores afetaram a gengiva, manifestando-se como um tumor assintomático. Oito casos apresentaram sintomas B e a maioria foi classificada em estágio I ou II de Ann Arbor (48.4%). Apenas 4 casos (3.3%) reportaram positividade para o vírus Epstein-Barr (EBV). Uso do CHOP foi considerado a principal opção de tratamento (24.5%) e a taxa de sobrevida global em 5 anos foi de 83%. Homens e pacientes com estágio Ann Arbor avançado apresentaram taxas de sobrevida significativamente mais baixas na análise univariada. Essa revisão sistemática demonstrou que apesar de o LDGCB SOE ser uma neoplasia agressiva, apresenta taxas de sobrevida altas. O segundo capítulo deste estudo teve como finalidade descrever os aspectos clinicopatológicos, imunoistoquímicos (IHQ) e status de EBV no LDGCB oral/orofaríngeo, e determinar o índice de sobrevida dos pacientes. Os casos foram recuperados de 6 instituições brasileiras. As características microscópicas e de IHQ dos casos foram revisadas por dois patologistas orais, bem como o diagnóstico. Hibridização in situ (ISH) foi realizada para detectar EBV. Cinquenta e dois casos foram incluídos neste estudo. Homens mais velhos foram os mais acometidos pelo LDGCB oral/orofaríngeo (57.7%). A maioria dos casos apresentou-se como um tumor doloroso na cavidade oral. Centroblastos foram o tipo celular predominante (63.5%) e 34 casos foram classificados no subgrupo celular do tipo centro germinativo. EBV foi detectado em 3 casos, os quais foram caracterizados como LDGCB EBV-positivo SOE. CHOP foi o esquema de quimioterapia mais utilizado (17.3%) e a sobrevida global após 5 anos foi de 53.7%. A análise univariada evidenciou que pacientes mais novos que apresentaram lesões dolorosas foram significativamente associados a um prognóstico ruim, bem como os casos que exibiram um alto índice de Ki67 e predominância de imunoblastos. Entretanto, essas variáveis perderam significância na análise multivariada. Este capítulo mostrou que o LDGCB SOE oral/orofaríngeo apresenta uma taxa alta de sobrevida alta, e que idade, dor, alto índice de Ki67 e a predominância de imunoblastos podem caracterizar fatores prognósticos adversos, apesar de não terem representado determinantes independentes.

Palavras-chave: Linfoma difuso de grandes células B. Linfoma não Hodgkin. Boca. Orofaringe.

ABSTRACT

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS) is the most frequent subtype of non-Hodgkin lymphomas found in the oral cavity and maxillofacial area. The current available data in the literature regarding the clinicopathological aspects of oral and oropharyngeal DLBCL NOS are limited to single case reports and small case series. The first chapter of this study aimed to systematically review the literature in order to determine the clinicopathologic profile of oral DLBCL NOS, and assess its prognostic factors. An electronic search was performed using PubMed/MEDLINE, Web of Science and Science Direct databases, and 63 publications were included in the study, comprising 122 cases. Oral DLBCL NOS was more prevalent in elderly males (61.5%), and most tumors affected the gingiva, presenting as an asymptomatic swelling. Eight cases presented B-symptoms and most cases were classified as Ann Arbor stage I or II (48.4%). Only 4 cases (3.3%) reported positivity for Epstein-Barr virus (EBV). CHOP therapy was the primary treatment choice (24.5%), and the overall 5-year survival rate was 83%. Males and patients with advanced Ann-Arbor stage presented significantly lower survival rates in the univariate analysis. This systematic review showed that although Oral DLBCL NOS is an aggressive malignancy, it presents high survival rates. The second chapter of this study aimed to describe the clinicopathological, immunohistochemical (IHC) and EBV status of oral/oropharyngeal DLBCL NOS, and determine the patients' survival rate. The cases were retrospectively retrieved from 6 Brazilian institutions. The microscopic description and diagnosis through analysis of hematoxylin-eosin sections and IHC reactions were reviewed by two oral pathologists. In situ hybridization (ISH) was performed to detect EBV. Fifty-two cases were included in the study. Elderly males were mostly affected by oral/oropharyngeal DLBCL NOS (57.7%). Most cases were presented as a painful swelling in the oral cavity. Centroblasts were the predominant cell type (63.5%) and 34 cases were classified into the germinal center B-cell type subgroup. EBV was detected by ISH in 3 cases, which characterized them as EBV-positive DLBCL NOS. CHOP was the most used chemotherapeutic scheme (17.3%), and the overall survival after 5 years was 53.7%. Univariate analysis found that younger patients with painful lesions were significantly associated with a poor prognosis, as well as the cases that showed a high Ki67 index and immunoblasts predominance. However, these variables lost their significance in the multivariate analysis. This chapter showed that oral/oropharyngeal DLBCL NOS presents a high survival rate, and age, pain, high Ki67 index, and predominance of immunoblasts may characterize adverse prognostic factors, although they did not represent independent determinants.

Keywords: Diffuse large B-cell lymphoma. Non-Hodgkin lymphoma. Mouth. Oropharynx.

SUMÁRIO

1 INTRODUÇÃO

Os tecidos linfoides são locais onde células precursoras sofrem maturação e diferenciação em células imunocompetentes e onde as reações de resposta aos antígenos ocorrem. Esses tecidos são divididos em dois grupos principais, de acordo com estágios de diferenciação celular e suas funções. O tecido linfoide primário abrange a medula óssea e o timo que, além de darem suporte ao processo inicial de diferenciação celular antígeno-independente, contêm as células precursoras linfoides. Já o tecido linfoide secundário corresponde aos linfonodos, baço e os tecidos linfoides associados à mucosa (MALT), onde as células linfoides maduras encontram os antígenos e desenvolvem diferentes tipos de resposta imunológica (Campo; Jaffe; Harris, 2017; Naeim et al, 2018).

Na medula óssea encontram-se populações de células tronco pluripotentes e autorrenováveis, incluindo os progenitores do sistema hematopoiético, bem como os precursores comuns de linhagem celular linfoide B, cujo processo de diferenciação continua na medula, e a linhagem T, cujas células indiferenciadas migram para o timo a fim de concluir seu processo de maturação. Os linfonodos possuem compartimentos celulares compostos por células B, células T, macrófagos e células dendríticas. Já o MALT é um tipo de tecido especializado, encontrado em associação com alguns epitélios, como o do trato gastrointestinal, placas de Peyer, naso e orofaringe – anel de Waldeyer, adenoides e tonsilas, contendo populações de células T e B, plasmócitos, macrófagos e linfócitos maduros (Wahed; Dasgupta, 2015; Campo; Jaffe; Harris, 2017).

Os linfomas resultam de mutações somáticas envolvendo uma célula progenitora linfoide, e correspondem a um grupo heterogêneo de neoplasias malignas monoclonais, as quais apresentam diferentes aspectos clínico-patológicos. A progênie das células afetadas pode apresentar os fenótipos B, T, ou *Natural Killer* (NK), recapitulando estágios normais de diferenciação dessas células, podendo originar-se tanto nos órgãos linfoides primários, quanto nos secundários (Szumera-Ciećkiewicz et al, 2014; Jaffe et al, 2017). Essas neoplasias são classificadas em dois grandes grupos: linfoma de Hodgkin (LH) e linfoma não-Hodgkin (LNH) (Campo; Jaffe; Harris, 2017).

O LH é considerado uma neoplasia de origem fundamentalmente linfonodal, sendo a manifestação primária fora dos linfonodos extremamente rara. Corresponde a aproximadamente 15-25% dos linfomas e geralmente apresenta melhor prognóstico que o LNH. Em contraste com a maioria dos linfomas, o componente celular maligno do LH

usualmente representa uma pequena parcela do total de células dos tecidos envolvidos (0.1%-2%) (Triantafillidou et al, 2012; Campo; Jaffe; Harris, 2017; Jaffe et al, 2017).

Já os LNH ocorrem em sítios extranodais em até 48% dos casos, ocupando a terceira posição entre as neoplasias malignas mais comuns da região oral e maxilofacial, sendo superado apenas pelo carcinoma espinocelular e pelas neoplasias malignas de glândula salivar (van der Waal et al, 2005; Triantafillidou et al, 2012; Szumera-Ciećkiewicz et al, 2014; De Castro et al, 2018). Estimativas demonstraram que em 2018 509.590 casos de LNH foram diagnosticados no mundo, ocupando a 13ª posição entre 36 tipos diferentes de câncer. Para o Brasil, estima-se 5.370 novos casos de LNH para cada ano do biênio 2018-2019, sendo a 11ª neoplasia maligna mais frequente (Bray et al, 2018; INCA, 2017). Cerca de 85%-90% dos LNH são de linhagem celular do tipo B, sendo o linfoma difuso de grandes células B sem outra especificação (LDGCB SOE) o subtipo mais comum, correspondendo a mais de 50% dos casos (Kolokotronis et al, 2005; Bhattacharyya et al, 2010; Triantafillidou et al, 2012; Walter et al, 2015).

O LDGCB SOE corresponde a uma proliferação de células B neoplásicas de tamanho médio a grande, com núcleo maior ou igual ao de um histiócito, ou com o dobro do tamanho do núcleo de um linfócito, distribuídas difusamente no tecido comprometido. Apesar de apresentar uma maior prevalência em indivíduos da 7ª década de vida, uma ampla faixa etária pode ser afetada, incluindo adultos jovens. Uma leve predileção pelo sexo masculino tem sido relatada (Ott, 2017; Li; Young; Medeiros, 2018). Através de um rápido crescimento tumoral, as localizações mais comumente afetadas pelo LDGCB SOE na região de cabeça e pescoço incluem o anel de Waldeyer, seios paranasais e cavidade oral, onde a gengiva e o palato têm sido relatados como os sítios mais envolvidos. (Cabeçadas; Martinez; Andreasen, 2019; Rodrigues-Fernandes et al, 2019). A maioria dos pacientes diagnosticados não apresenta fatores de risco associados ao LDGCB SOE (Martelli et al, 2013; Gascoyne; Campo; Jaffe, 2017).

Mudanças na última classificação da Organização Mundial de Saúde (2017) definiram estratégias para distinção e avaliação do prognóstico do LDGCB SOE, as quais incluem: classificação da célula de origem, análise da co-expressão de Bcl2 e Myc, bem como do rearranjo dos genes MYC com BCL2 e/ou BCL6, além da avaliação da positividade do linfoma para o vírus Epstein-Barr (EBV) (Hsi, 2017; Grimm; O'Malley, 2019).

Considerando que as informações disponíveis na literatura acerca dos aspectos clínico-patológicos do LDGCB SOE de cavidade oral/orofaringe são baseadas em

relatos de caso ou pequenas séries de casos que frequentemente incluem vários sítios da região de cabeça e pescoço, este trabalho tem como objetivo revisar a literatura sobre o LDGCB SOE de cavidade oral e descrever as características clínicas, imaginológicas, histológicas, imunoistoquímicas, e presença do EBV de uma amostra de 52 casos de LDGCB SOE de cavidade oral e orofaringe, determinando possíveis fatores prognósticos que afetem os índices de sobrevida dos pacientes.

2 ARTIGOS

2.1 Clinicopathological analysis of Oral Diffuse Large B-cell Lymphoma, NOS: a systematic review.

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Abstract

Background: Diffuse large B-cell lymphoma, NOS (DLBCL NOS) is the commonest extranodal non-Hodgkin lymphoma diagnosed in the oral and maxillofacial region. However, few studies are currently available and its prognostic determinants still remain undefined.

Purpose: To analyze the available data on oral DLBCL NOS and to describe its clinicopathological features, identifying potential prognostic factors.

Methods: An electronic systematic search was performed using multiple databases with a specific search strategy in April 2018. All reports describing DLBCL NOS involving the oral cavity and jaw bones with sufficient clinicopathological information were assessed.

Results: Sixty-three publications were included in the study, comprising 122 cases. Oral DLBCL NOS was found predominantly in elderly males (61.5%), and most often presented as an asymptomatic swelling of the gingiva. Patients were commonly HIV-negative (36.1%), with few reports describing EBV-positive cases (4 cases/3.3%). Only 8 cases presented B-symptoms and most cases were classified as stage I or II (48.4%). CHOP therapy was the main treatment option (24.5%) and the overall 5-year survival rate achieved 83%. Males and advanced Ann-Arbor stage patients presented significantly lower survival rates in the univariate analysis, but no significance was found in the multivariate model.

Conclusion: Oral DLBCL NOS is an aggressive malignancy, but with a high survival rate.

Key-words: Diffuse large B-cell lymphoma NOS, lymphoma, oral cavity, maxilla, mandible.

Introduction

Non-Hodgkin lymphomas (NHLs) are malignant lymphoproliferative disorders that uncommonly arise in the oral cavity and maxillofacial region, although the head and neck itself is the second most commonly affected site following the gastrointestinal tract[1,2]. Among all NHL subtypes affecting the oral cavity and jaw bones, diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS) is the most frequent[3].

Diffuse large B cell lymphoma, not otherwise specified (DLBCL NOS) is an aggressive neoplasm of medium to large B lymphoid cells that comprises 30% to 35% of adult NHL worldwide, but its etiology remains uncertain[3,4]. Although most patients do not have underlying risk factors and the tumors may arise *de novo*, some cases represent a high-grade transformation of a less aggressive lymphoma or may occur in the setting of an immunodeficiency[4,5].

Recent changes in the WHO classification of hematolymphoid tumors have defined new entities that are now classified separately from DLBCL NOS. Those cases demonstrating positivity to Epstein-Barr virus (EBV) are now categorized as EBV-positive DLBCL NOS, whereas genetic studies of DLBCL NOS that have mutations in Bcl2, Bcl6 and/or MYC, now give rise to the so-called double-hit and triple-hit high grade lymphomas[6,7,8]. These new definitions make the diagnosis of DLBCL NOS more specific, and may alter its currently known clinicopathological characteristics.

Currently, only single case reports and few small series of oral DLBCL NOS are available, impairing an appropriate understanding of its clinicopathological features. Moreover, the prognostic factors that may affect the patients' survival are also largely unknown and deserves to be better documented and understood. Therefore, the aim of this study was to evaluate the published data regarding oral DLBCL NOS, considering its clinicopathological features and potential prognostic factors.

Material and Methods

This study followed the PRISMA (Preferred Report Items for Systematic reviews and Meta-Analyses) Statement guidelines[9].

Search strategies

An electronic search was performed on April 2018, with dates between 2001 and 2018, to decrease the diagnostic variability caused by different classification schemes and a more difficult access to immunohistochemical analyses. The following databases

were assessed: PubMed/MEDLINE, Web of Science and Science Direct. The search strategy used in all databases consisted of the following key-words: (diffuse large b cell lymphoma OR large b cell lymphoma) AND (oral OR oral cavity OR mandible OR maxilla OR tongue OR palate OR maxillofacial OR gnathic OR jaw OR oral mucosa OR buccal). Assessment of previous literature reviews regarding oral DLBCL NOS and the reference list of the articles included was also done to obtain possible supplementary cases.

Inclusion and exclusion criteria

Inclusion criteria comprised cases diagnosed as DLBCL NOS of the oral cavity and/or the jaws, with sufficient clinical, microscopical and immunohistochemical information. Randomized and controlled clinical trials, cohort studies, cross-sectional studies, case control studies, case series and case reports, which were published in English, Portuguese or Spanish languages were screened for individual cases. Exclusion criteria comprised DLBCL NOS located in different sites other than the oral cavity or jaws, other subtypes of lymphomas, publications without detailed clinical and histological information, and studies without minimal immunohistochemistry panel to corroborate the diagnosis of DLBCL NOS (at least one positive B-cell antibody, such as CD20, CD79a, or PAX5). Review studies were also excluded, except those that had reported cases of oral DLBCL NOS with sufficient clinicopathological information.

Study selection

The titles and abstracts of all publications in the electronic searches were individually read by two authors. The studies that fulfilled the inclusion criteria, and also those that did not present sufficient information in the title or in the abstract, were fully assessed. These studies were cross-checked by another author to guarantee that the suitable ones were properly selected according to the inclusion and exclusion criteria.

Data extraction

All relevant data were independently extracted using a specific extraction form. For each selected study, the following information were extracted (when available): year and country of publication, number of cases, patients' sex and age, tumor location, patients' HIV status, oral signs and/or symptoms, duration of the oral manifestations, presence of B symptoms, immunohistochemistry panel used, patients' EBV status, Ann

Arbor staging, treatment employed, chemotherapy regimen, follow-up time and status of the patient at last follow-up.

Analysis

The clinicopathological data was presented descriptively. Chi-square test was used to compare clinicopathological variables and the patients' status (alive or dead). Kaplan-Meier method was used to calculate survival rates, whereas the difference between survival curves was investigated using the Log-Rank univariate test to identify potential prognostic factors. To investigate what clinicopathological feature would represent an independent prognostic factor, a multivariate Cox regression model was created including the parameters that were statistically significant in the univariate analysis. The software SPSS version 22.0 was used and a p-value ≤ 0.05 was considered statistically significant.

Results

Literature search

The screening procedure is summarized in **Figure 1**. The initial search resulted in 886 publications. After checking the databases, 213 records were excluded because of duplication. Further assessment of the titles and abstracts resulted in the exclusion of 578 publications, since they were not associated to the subject and 7 articles could not be assessed (**Supplementary Table 1**). Analysis of the remaining 88 articles resulted in the exclusion of 25 papers, which did not meet the inclusion criteria or provide sufficient clinical, histological and immunohistochemical information to confirm the diagnosis of oral DLBCL NOS. Finally, a total of 63 studies were included in the descriptive and statistical analyses (**Supplementary Table 2**).

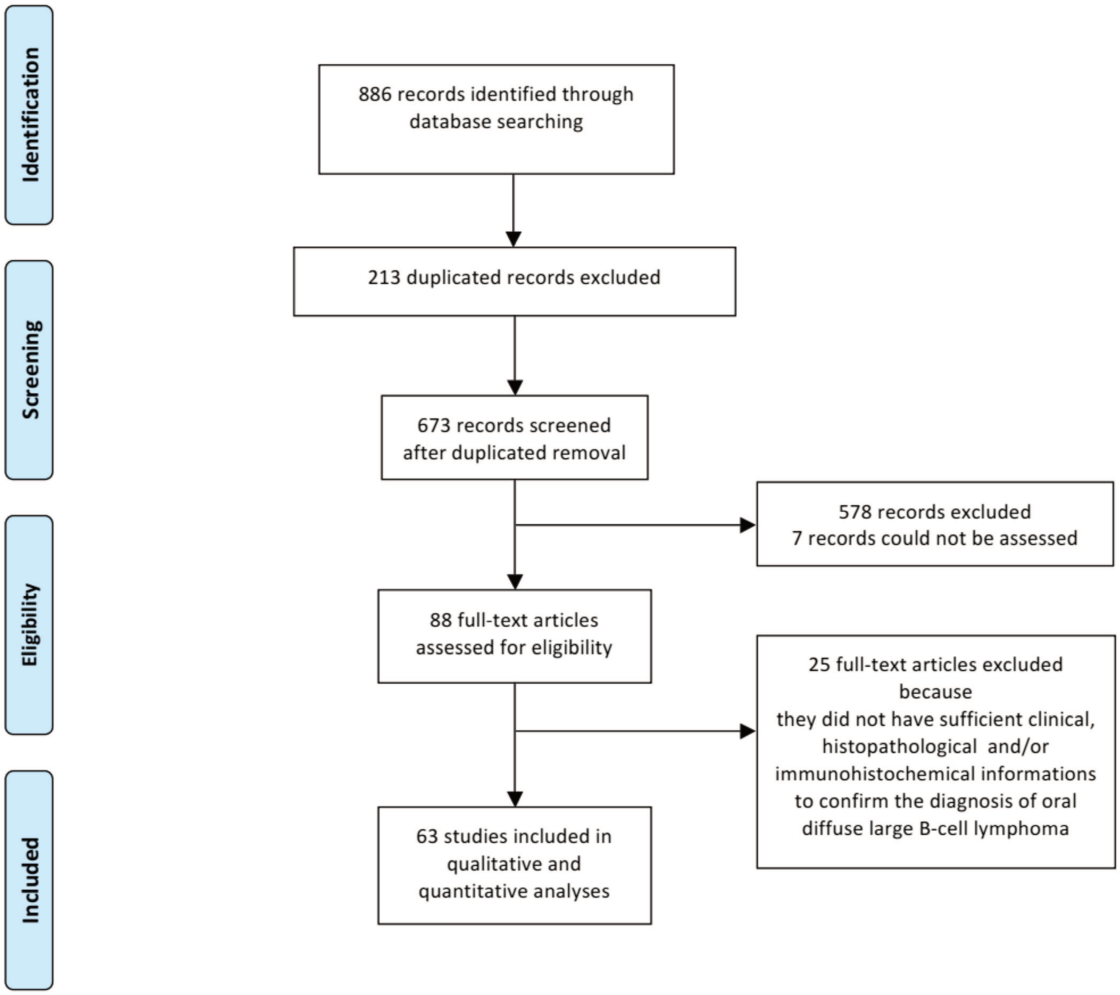
Risk of bias

The selection criteria included available information about immunohistochemistry analysis to confirm the diagnosis of oral DLBCL NOS, which reduced the risk of bias, as well as the publications with sufficient clinical and histological data. Of the 25 excluded papers fully assessed, 16 did not present any immunohistochemistry panel, or presented incoherent antibodies for oral DLBCL NOS diagnosis, not showing any positivity to a B-cell marker. Nine papers were also excluded because tumors were located in the tongue base, and therefore better classified

as oropharyngeal. A higher risk of bias comprised the low and widely variable follow-up time of most of the cases, loss of clinical information including the status of the patients at their last follow-up, and the use of data acquired from very different medical/dental centers' that were standardized in one same group.

Some EBV positive cases were also diagnosed as DLBCL NOS, but instead of removing them we evaluated the importance of EBV to the clinicopathological characteristics of the tumors. None of the cases were investigated for Bcl2, Bcl6 and/or MYC translocations, and therefore, it was not possible to determine if these cases could represent the more recent entities double and triple-hit high grade lymphomas.

Figure 1. Study selection process according to PRISMA guidelines.



Description of the studies and statistical analysis

The 63 papers included in this study comprised 122 cases, ranging from single case reports to a series of oral NHLs that included 21 cases of oral DLBCL NOS[10], and originated from 17 countries: Argentina; Australia; Brazil; Canada; Chile; Croatia; Greece; India, Ireland; Italy; Israel; Japan; Serbia; Switzerland; Tunisia; Turkey, and USA.

The demographic and clinicopathological features of the 122 cases of oral DLBCL NOS are summarized in **Table 1**. Tumors were more predominant in males (75 cases; 61.5%) with a mean age of 58.7 years (range of 8 to 96 years). The gingiva was the most frequently affected location (33 cases; 27%), followed by the maxillary mucosa (31 cases; 25.4%), and the most common clinical sign was a swelling (51 cases; 41.8%). Pain was the most common reported symptom (31 cases), followed by local numbness (19 cases); tooth loosening/mobility (6 cases); nasal obstruction and/or discharge (3 cases); foreign body sensation in the throat (2 cases); sore throat (1 case); dysphagia (2 cases), and odynophagia (1 case). The duration of these manifestations lasted from less than a month to over a year.

The presence of B-symptoms was described in 8 cases (6.6%), while HIV status was positive in 10 cases (8.2%), and EBV in 4 cases only (3.3%). According to the Ann Arbor staging system, 59 cases were classified as stages I or II (48.4%), and 6 as stages III and IV (4.9%). The most common treatment option was chemotherapy (36 cases; 29.5%), in which the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was the leading scheme for chemotherapy (30 cases; 24.5%). Sixty-five patients (53.3%) were alive at their last follow-up, 21 were dead (17.2%) and this information was not available for 36 cases (29.5%). The mean follow-up time was 33.8 months, which ranged from 1 to 177 months.

Table 1. Demographic and clinicopathological features of 122 oral DLBCL NOS cases published in the literature.

Clinicopathological variables	n = 122	%
Sex		
Male	75	*61.5*
Female	47	*38.5*
Age (mean age: 58.7 yrs)		
< 58.7yrs	53	*43.4*
> 58.7yrs	69	*56.6*
Location		
Gingiva	33	*27.0*
Palate	17	*14.0*
Maxillary mucosa	31	*25.4*
Mandibular mucosa	19	*15.6*
Tongue	5	*4.0*
Buccal mucosa	6	*4.9*
Others*	11	*9.0*
Clinical presentation		
Swelling	51	*41.8*
Ulcer	3	*2.5*
Swelling and ulcer	20	*16.4*
NA	48	*39.3*
HIV status		
Negative	44	*36.1*
Positive	10	*8.2*
NA	68	*55.7*
EBV status		
Negative	30	*24.6*
Positive	4	*3.3*
NA	88	*72.1*
Ann Arbor stage		
Stages I and II	59	*48.4*
Stage III and IV	6	*4.9*
NA	57	*46.7*
Presence of B-symptoms		
No	22	*18.0*
Yes	8	*6.6*
NA	92	*75.4*
Treatment		
Chemotherapy	36	*29.5*
Chemot.+Radiot.	33	*27.0*
Others	5	*4.1*
No treatment	4	*3.3*
NA	44	*36.1*
Chemotherapy scheme**		
CHOP	30	*24.5*
R-CHOP	17	*13.9*
CHOP+R-CHOP	1	*0.8*
Others	12	*9.8*
No treatment	5	*4.0*
NA	58	*47.5*
Status		
Alive	65	*53.3*
Dead	21	*17.2*
NA	36	*29.5*

* Labial comissure: 1 case; Mandible: 2 cases; Maxilla: 6 cases; Alveolus: 1 case; Gingiva/Jaw: 1 case. NA: Not available. ** CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP: rituximab+CHOP.

Statistical analysis showed that male patients were significantly associated with a higher death rate (p = 0.039), but no other clinicopathological variables presented significant association with patients' status at last follow-up **(Table 2)**. The overall 5-years survival rate of patients included in this review was 83% (**Figure 2**). By using the Log-rank univariate analysis, we observed that only the patients' categorized as Ann Arbor's stages III and IV were significantly associated with a lower survival rate (p = 0.019) (**Table 3 and Figure 2**). However, according to our multivariate Cox regression model, this variable lost its significance and could not be considered an independent prognostic determinant of a lower survival (**Table 4**).

Table 2. Association analysis between the clinicopathological features of 122 oral DLBCL NOS cases and the patients' status at last follow-up.

Clinicopathological variables	**Alive** N *(%)*	**Dead** N *(%)*	***p*-value**
Sex			
Male	35 (53.9)	17 (81)	*0.039*
Female	30 (46.1)	4 (19)	
Age (mean age: 58.7 yrs)			
< 58.7yrs	32 (49.2)	6 (54.5)	*0.13*
> 58.7yrs	33 (50.8)	15 (45.5)	
HIV status			
Negative	17 (85)	16 (88.9)	*1.00*
Positive	3 (15)	2 (11.1)	
Ann Arbor stage			
Stages I and II	42 (93.3)	10 (90.9)	*1.00*
Stages III and IV	3 (6.7)	1 (9.1)	
Presence of B-symptoms			
No	17 (73.9)	2 (50)	*0.56*
Yes	6 (26.1)	2 (50)	
Treatment			
Chemotherapy	25 (47.2)	4 (57.1)	*0.70*
Chemotherapy + Radiotherapy	28 (52.8)	3 (42.9)	

Figure 2. Survival curves. A) Kaplan-Meyer curve demonstrating the overall survival of patients affected by oral DLBCL NOS. B) Using Log-Rank univariate analysis, Ann Arbor stage was the only parameter to significantly affect the survival rate of patients affected by oral DLBCL NOS.

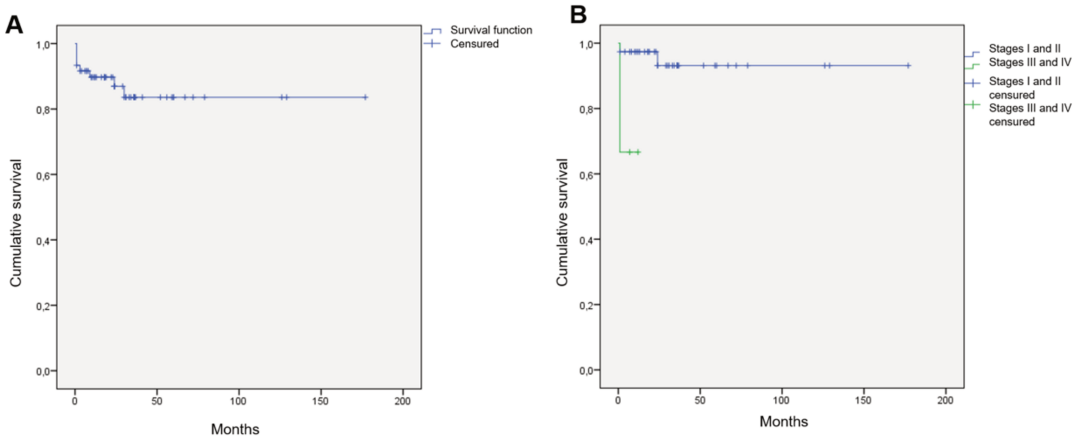


Table 3. Log-rank univariate analysis of the clinicopathological features of oral DLBCL NOS cases.

Clinicopathological variables	Log-rank univariate analysis			
	5-years survival (%)	Estimative (95% CI)	Chi-square	*p*-value
Sex				
Male	75.6	98.4 (80 – 116.8)	2.75	*0.097*
Female	95.8	169.7 (155.6 – 183.7)		
Age (mean age: 58.7 yrs)				
< 58.7yrs	85.0	68.5 (59 – 78.1)	0.00	*0.99*
> 58.7yrs	83.1	149.5 (124.1 – 174.9)		
HIV status				
Negative	64.0	24.7 (14.1 – 35.2)	0.39	*0.53*
Positive	50.0	18.5 (1.4 – 36.7)		
Ann Arbor stage				
Stages I and II	93.1	165.9 (150.7 – 181.0)	5.51	*0.019*
Stages II and IV	66.7	8.3 (2.5 – 14.2)		
Presence of B-symptoms				
No	81.0	62.5 (50.2 – 74.8)	2.30	*0.13*
Yes	66.7	24.3 (11.1 – 37.5)		
Treatment				
Chemotherapy	78.9	59.2 (47.9 – 70.6)	2.22	*0.13*
Chemotherapy+Radiotherapy	96.0	170.0 (156.7 – 183.4)		

CI: Confidence interval.

Table 4. Multivariate Cox regression model created using all variables that achieved a p-value < 0.10 in the univariate analysis.

Variables	Hazard ratio	95% CI		*p*-value
		Lower	Upper	
Sex	164,231.4	< 0.01	2.901	0.97
Ann Arbor staging I *vs* IV	11.000	0.688	175.863	0.90

CI: Confidence interval.

Discussion

DLBCL is clinically and pathologically diverse, consequently, new entities are frequently recognized and subsequently removed from this group, as happened with plasmablastic lymphoma (PBL), EBV-positive DLBCL NOS and the more recent high grade double and triple-hit lymphomas[4,6,7,11]. Although DLBCL NOS represents the most common lymphoma that can arise in the oral cavity[2,12], there is scarce information in the literature regarding its clinical course and prognosis, with only few small series currently available[13,14,15]. Therefore, we attempted in this study to systematically review the available data on oral/maxillofacial DLBCL NOS to better determine the clinicopathological features of this neoplasm and of the affected patients. We observed that despite its aggressiveness, oral DLBCL NOS is associated with a high survival rate and that an advanced Ann-Arbor stage may negatively impact the patients' prognosis.

DLBCL NOS most commonly affects males and the elderly population, although it may occasionally occur in children and young adults[11,15], a finding consistent with our results, although the significant association between patients' sex and the occurrence of deaths has not been described before[14-16]. Approximately 40% of cases of DLBCL NOS are extranodal, predominantly affecting the gastrointestinal tract, followed by the bone, testes, spleen, thyroid, liver, kidneys, and adrenal glands. In the orofacial region, the most frequently affected sites include the Waldeyer's ring (tonsils, nasopharynx, and base of tongue) and the salivary glands[4,13,17]. Considering only the oral cavity and the jaw bones, we found that the gingiva was the most affected location, although Mian et al. (2014)[15], found that the palate represented the predominant site for early-staged oral DLBCLs.

Clinically, DLBCL NOS presents as a rapidly growing tumor, with or without ulceration, resembling squamous cell carcinoma, soft tissue malignancies, minor salivary glands tumors and osteosarcomas, therefore, the list of clinical differential diagnoses is large[12,13,17]. The low frequency of B-symptoms was consistent with the

number of cases classified as Ann Arbor stage I and II, as previously reported that also included cases affecting the Waldeyer's ring and parotid glands[13]. The significant association between advanced stage diseases and a lower survival observed in our univariate analysis is consistent with previous studies that included oral cavity cases[14,16]. The lack of significance in the multivariate analysis possibly is due the small number of cases investigated in this review.

The risk of developing various types of lymphomas is increased in the setting of HIV, especially in the context of AIDS stage, usually manifesting as aggressive and disseminated tumors[5]. DLBCL NOS is the second most common HIV-associated NHL, which also includes PBL, Burkitt's lymphoma (BL) and primary effusion lymphoma[16,18]. Although data regarding the HIV status was not provided for most of the cases investigated in our study (55.7%), it needs to be considered in the clinical investigation when patients are diagnosed with oral DLBCL NOS.

In contrast to PBL[19], the association between EBV and DLBCL is uncommon, and confirmed in our results. According to the current WHO classification of hematolymphoid tumors, EBV-positive cases should be diagnosed as either EBV-positive DLBCL NOS or as another type of EBV-positive lymphoma, such as DLBCL associated with chronic inflammation or lymphomatoid granulomatosis[4]. Initially termed as EBV-positive DLBCL of the elderly, the updated WHO revision has modified this terminology to EBV-positive DLBCL NOS given the reported cases affecting younger individuals[20]. This distinct neoplasm is mostly extranodal, with aggressive course and poor prognosis[11]. In this review, we were unable to evaluate the importance of EBV for the outcome of patients affected by oral DLBCL NOS due to the very small number of cases reported. However, we observed that all patients were alive at their last follow-up (mean of 14.7 months), and most of them were males with a mean age of 69.8 years old. Information regarding HIV-infection was not available in most cases.

Histologically, DLBCL NOS exhibits a mixture of centroblasts and immunoblasts that grow in a diffuse pattern, partially or totally effacing the architecture of the affected organ[11,17]. Immunohistochemically, neoplastic cells express pan B-cell markers, such as CD19, CD20 and PAX5, and are negative for pan T-cell markers[17]. Cyclin D1 and SOX11 negativity rules out the blastoid variants of mantle cell lymphoma; the lack of plasma cell markers helps to differentiate the neoplasm from PBL, and the use of CD10, Bcl2 and Bcl6 associated with morphological features contribute to distinguish DLBCL NOS from BL and follicular lymphoma. Ki67

proliferative index is usually high, but it is lower than the observed in PBLs and BLs[4]. In this review only cases with positivity to at least one B-cell marker were included as an attempt to decrease the risk of misdiagnoses, however, the high variability in the immunohistochemical panels among the reports is still considered a potential limitation.

DLBCL NOS should also be differentiated from the recently described high-grade B-cell lymphomas (HGBCL), characterized by rearrangements of the MYC proto-oncogene along with Bcl2 and/or Bcl6, identified as double-hit or triple-hit lymphomas, accounting for between 5 and 10% of the cases of DLBCL, but in the oral cavity this incidence is unknown[7,8].

Despite its clinical aggressiveness, DLBCL NOS is potentially curable[3]. The introduction of rituximab (a monoclonal anti-CD20 antibody) in combination with CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) has significantly improved patients' outcome[3,17,21]. Nevertheless, only 17% of the oral DLBCL NOS cases in this study were treated with R-CHOP and we could not investigate the importance of this therapy to the patients' prognosis.

Different from the low survival rate observed in other high-grade lymphomas like PBL[19], we observed a much higher rate for oral DLBCL NOS. Similarly, Rayess et al. (2017)[16] also observed an overall 5-year survival of 84% for oropharyngeal DLBCL, whereas a study with 48 oral DLBCL NOS reported a lower 5-year survival rate of 45%[14].

It is important to highlight that the results obtained in our study need to be further validated, given the methodological limitations of this systematic review that retrieved clinicopathological data from cases diagnosed and treated in different dental and medical centers.

In conclusion, oral DLBCL NOS is an aggressive neoplasm that presents a high survival rate, and that disease stage may contribute to a lower survival rate, although it did not represent an independent prognostic determinant for these patients.

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Supplementary Table 1. List of articles that could not be fully assessed to be used in this review.

Number	Articles that could not be assessed
1	Robledo J, Roach B. Tex Dent J. 2010 Mar;127(3):317, 322-3.
2	Naidu A, Kovach TA, Wright JM, Schow SR. Tex Dent J. 2013
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4	Ketheeswaranathan V, Smith G. Dent Update. 2016 Jul-Aug;43(6):591.
5	Someya M, Sakata K, Nagakura H, Itou K, Nakata K, Oouchi A, Satoh M, Hareyama M. Radiat Med. 2005 Jun;23(4):296-302.
6	Alderson GL, Jones AC, McGuff HS, Tiner BD. Tex Dent J. 2006 Mar;123(3):300, 304.
7	Hassona Y, Almuhaisen G, Almansour A, Scully C. BMJ Case Rep. 2017 Jan 24;2017.

Supplementary Table 2. Clinicopathological data of all 122 cases (63 articles) that were considered in this study after the exclusion of the articles that did not meet the inclusion criteria.

Number	Author	Year	Country	Sex	Age	HIV status	Location	Oral and maxillofacial clinical signs (ulcer/swelling/reddish/purple/bleeding/etc)	Oral and maxillofacial clinical Symptoms (pain/etc)	Systemic symptoms (fever/headache/weight loss/etc)	Duration of the oral manifestations (months)	Immunohistochemistry panel used	EBER ISH	Ann Arbor Classification	Treatment employed	Chemotherapy regimen	Follow-up time (months)	Status at last follow-up (Alive/Dead)
1	Castellano et al.	2002	Italy	F	61	ND	Labial comissure	Ulcer	Not presented	Not presented	12	Positive: CD20, CD30; Negative: CD15	ND	IA	Chemotherapy	ACOP-B: adriblastine, cyclophosphamide, vincristine, prednisone, bleomycin	10	Alive
2	Mealey et al.	2002	USA	M	66	ND	Maxillary gingiva	Swelling	ND	Not presented	ND	Positive: LCA, CD20, CD79a (weak); Negative: CD3, CD45RO, kernix, S100, HMB-45.	ND	I-AE	Chemotherapy and radiotherapy	CHOP	ND	Alive
3	Pazoki et al.	2003	USA	F	58	ND	Mandibular mucosa	Swelling	Lip numbness, teeth loosening	Not presented	5	Positive: LCA, CD20, Bcl-2; T-cell antigens	ND	IAE	Chemotherapy	CHOP	72	Alive
4	Pazoki et al.	2003	USA	M	58	ND	Maxillary gingiva	Purple swelling, Proptosis of the left eye	ND	Not presented	ND	Positive: CD20; Negative: CD3	ND	IAE	Chemotherapy and radiotherapy	CHOP	30	Alive
5	Pazoki et al.	2003	USA	F	45	ND	Mandible	Swelling	Pain and lip numbness	Not presented	4	Positive: CD20,CD3; Negative: pan-cytokeratins	ND	IAE	Chemotherapy and radiotherapy	CHOP	24	Alive
6	Pazoki et al.	2003	USA	F	33	ND	Mandibular gingiva	Purple swelling	Lip numbness, teeth loosening	Not presented	ND	Positive: LCA, CD20, CD43; Negative: T-cell markers	ND	IAE	Chemotherapy	ND	36	Alive
7	Longo et al.	2004	Italy	M	45	ND	Mandibular mucosa	Swelling	Lip paraesthesia	ND	ND	Positive: CD20, LCA	ND	I-E	Chemotherapy and radiotherapy	CEOP: vincristine, cyclophosphamide, epirubicin, prednisone	36	Alive
8	Kobler et al.	2005	Croatia	M	63	ND	Maxillary gingiva	Reddish swelling	ND	ND	ND	Positive: CD20, CD79a	ND	IIE	Chemotherapy and radiotherapy	CHOP	11	Alive
9	Angiero et al.	2006	Italy	M	56	ND	Mandibular gingiva	Reddish swelling	ND	ND	ND	Positive: CD20, Ki67; Negative: CD3, CD10, CD30, ALK-1	ND	IIE	Chemotherapy	CHOP	24	Dead
10	Corti et al.	2007	Argentina	M	38	Positive	Hard palate and gingiva	Reddish swelling and ulcer	Pain, odynophagia, dysphagia	Fever, weight loss and night sweats	1	Positive: CD20; Negative: CD3	Negative	ND	Chemotherapy	CHOP	ND	Alive
11	Hamza et al.	2009	Tunisia	M	67	ND	Palate	Swelling, erosion	Not presented	ND	9	Positive: CD20, vim; Negative: CK, CD3, S100	ND	ND	ND	ND	ND	ND
12	Kini et al.	2009	India	M	55	ND	Mandibular buccal vestibule (intraosseous)	Facial asymmetry, intraoral swelling	Not presented	ND	4	Positive: CD45, CD20; Negative: CD3	ND	ND	Chemotherapy	CHOP	18	Alive
13	Martinelli-Kläy et al.	2009	Brazil	F	46	ND	Mandibular gingiva	Reddish swelling and ulcer	Pain, foreign-body sensation in the throat	ND	ND	Positive: CD20; Negative: CD30, CD3, ALK	ND	IE	Chemotherapy	CHOP	36	Alive
14	Niscola et al.	2009	Italy	M	33	ND	Left mandible (intraosseous)	Swelling	Pain	ND	1	Positive: CD30, CD20, CD10, Ki-67 (>60%); Negative: ALK, CD45R, CD3, other T-cell markers	ND	IE	Chemotherapy and radiotherapy	R-CHOP, CHOP	60	Alive
15	Sato et al.	2009	Japan	M	69	ND	Hard palate	ND	ND	ND	ND	Positive: CD20, MUM1, Bcl-2 and Ki-67 (50%); Negative: CD3, CD5, CD10, CD138, BCL-6	Negative	IE	Chemotherapy and radiotherapy	CHOP	59	Alive
16	Sato et al.	2009	Japan	F	57	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, MUM1, Ki-67 (85%); Negative: CD3, CD5, CD10, CD138, BCL-6, Bcl-2	Negative	IE	Radiotherapy	Not performed	79	Alive
17	Sato et al.	2009	Japan	F	65	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, MUM1, Bcl-2, Ki-67 (75%); Negative: CD3, CD5, CD10, CD138 and BCL-6	Positive	IE	Chemotherapy and radiotherapy	R-CHOP	13	Alive
18	Sato et al.	2009	Japan	F	68	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, MUM1, Ki-67 (60%); Negative: CD3, CD5, CD10, CD138, BCL-6, Bcl-2	Negative	IE	Chemotherapy and radiotherapy	CHOP	22	Alive
19	Sato et al.	2009	Japan	M	60	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, BCL-6, MUM1, Bcl-2, Ki-67 (90%); Negative: CD3, CD5, CD10, CD138	Negative	IE	Chemotherapy and radiotherapy	R-CHOP	16	Alive
20	Sato et al.	2009	Japan	F	68	ND	Gingiva	ND	ND	ND	ND	Positive: CD10, CD20, BCL-6, Bcl-2, Ki-67 (80%); Negative: CD3, CD5, CD138, MUM1	Negative	IE	ND	ND	ND	ND
21	Sato et al.	2009	Japan	M	62	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, BCL-6, MUM1, Bcl2, Ki-67 (70%); Negative: CD3, CD5, CD10, and CD138	Positive	IE	Chemotherapy	R-CHOP	19	Alive
22	Sato et al.	2009	Japan	F	74	ND	Hard palate	ND	ND	ND	ND	Positive: CD20, MUM1, Bcl-2 , Ki-67 (60%); Negative: CD3, CD5, CD10, CD138, BCL-6	Negative	IE	Chemotherapy and radiotherapy	CHOP	129	Alive
23	Sato et al.	2009	Japan	M	85	ND	Soft palate	ND	ND	ND	ND	Positive: CD20, MUM1, Bcl-2 and Ki-67 (80%); Negative: CD3, CD5, CD10, CD138, BCL-6	Negative	IE	ND	ND	ND	ND
24	Sato et al.	2009	Japan	M	76	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, BCL-6, MUM1, Bcl-2, Ki-67 (80%); Negative: CD3, CD5, CD10, CD138	Negative	IE	Chemotherapy and radiotherapy	Rituximab+doxorubicin; vincristine; prednisolone+cyclophosphamide	33	Alive
25	Sato et al.	2009	Japan	M	53	ND	Hard palate	ND	ND	ND	ND	Positive: CD20, MUM1, Ki-67 (90%); Negative: CD3, CD5, CD10, CD138, BCL-6, Bcl-2	Negative	IE	Chemotherapy	CHOP	ND	ND
26	Sato et al.	2009	Japan	F	72	ND	Gingiva	ND	ND	ND	ND	Positive: CD10, CD20, BCL-6, MUM1, Ki-67 (50%); Negative: CD3, CD5, CD138, Bcl-2	Negative	IE	ND	ND	ND	ND
27	Sato et al.	2009	Japan	M	85	ND	Hard palate	ND	ND	ND	ND	Positive: CD10, CD20, BCL-6, Bcl-2 and Ki-67 (55%); Negative: CD3, CD5, CD138, MUM1	Negative	IE	Chemotherapy	R-CHOP	37	Alive
28	Sato et al.	2009	Japan	M	86	ND	Soft palate	ND	ND	ND	ND	Positive: CD20, MUM1, Ki-67 (90%); Negative: CD3, CD5, CD10, CD138, BCL-6, Bcl-2	Negative	IE	Chemotherapy and radiotherapy	CHOP	126	Alive
29	Sato et al.	2009	Japan	M	71	ND	Buccal mucosa	ND	ND	ND	ND	Positive: CD20, MUM1, Bcl-2, Ki-67 (90%); Negative: CD3, CD5, CD10, CD138, BCL-6	Negative	IE	Chemotherapy and radiotherapy	CHOP	67	Alive
30	Sato et al.	2009	Japan	F	63	ND	Hard palate	ND	ND	ND	ND	Positive: CD10, CD20, BCL-6, Ki-67 (50%); Negative: CD3, CD5, CD138, MUM1, Bcl-2	Negative	IE	Chemotherapy and radiotherapy	CHOP	4	Alive

Supplementary Table 2. Clinicopathological data of all 122 cases (63 articles) that were considered in this study after the exclusion of the articles that did not meet the inclusion criteria (Continuation).

31	Sato et al.	2009	Japan	F	62	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, BCL-6, MUM1, Ki-67 (65%); Negative: CD3, CD5, CD10, CD138, Bcl-2	Negative	IE	Chemotherapy and radiotherapy	CHOP	177
32	Sato et al.	2009	Japan	F	77	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, BCL-6, MUM1, Ki-67 (80%); Negative: CD3, CD5, CD10, CD138, Bcl-2	Negative	IIE	Surgery and chemotherapy	CHOP	31
33	Sato et al.	2009	Japan	M	57	ND	Gingiva	ND	ND	ND	ND	Positive: CD20, MUM1, Ki-67 (90%); Negative: CD3, CD5, CD10, CD138, BCL-6, Bcl-2	Negative	IIE	Chemotherapy	R-CHOP	52
34	Sato et al.	2009	Japan	F	71	ND	Tongue	ND	ND	ND	ND	Positive: CD20, BCL-6, MUM1, Bcl-2, Ki-67 (40%); Negative: CD3, CD5, CD10, CD138	Negative	IIE	Chemotherapy	THP-COP: cyclophosphamide, doxorubicin (pirarubicin), vincristine, prednisolone	34
35	Sato et al.	2009	Japan	M	67	ND	Hard palate	ND	ND	ND	ND	Positive: CD20, MUM1, Bcl-2, Ki-67 (60%); Negative: CD3, CD5, CD10, CD138, BCL-6	Negative	IIE	Chemotherapy and radiotherapy	CHOP	29
36	Bhattacharyya et al.	2010	USA	F	91	Negative	Crest of maxillary alveolus	Ulcer and swelling	ND	ND	>1	Positive: CD20, Bcl-6, MUM1 and Ki67 (40-50%); Negative: CD10, CD3, CD5 and Bcl-2	ND	ND	Declined treatment	Declined treatment	ND
37	Bhattacharyya et al.	2010	USA	M	76	Negative	Mandibular mucosa	ND	Pain, chin and lip numbness	ND	1	Positive: CD20, Bcl-2, MUM1, Ki67 (80–95%); Negative: CD10, CD3, CD5, Bcl-6	ND	ND	Chemotherapy and radiotherapy	ND	ND
38	Bhattacharyya et al.	2010	USA	M	80	Negative	Facial aspect of maxillary tuberosity	Swelling	ND	ND	<1	Positive: CD20, Bcl-2, Bcl-6, MUM1, Ki 67 (>75%); Negative: CD10, CD3	ND	ND	Declined treatment	Declined treatment	ND
39	Bhattacharyya et al.	2010	USA	F	77	Negative	Maxillary mucosa	Swelling	ND	ND	ND	Positive: CD20, CD3, Bcl6, MUM1, Ki 67 (60-70%); Negative: CD10, CD5, Bcl2	ND	ND	ND	ND	ND
40	Bhattacharyya et al.	2010	USA	M	38	Negative	Maxillary vestibule	Swelling	Pain	ND	1.5	Positive: CD10, CD20, Bcl-6, Ki 67 (40-50%); Negative: CD3, CD5, Bcl2, MUM-1	ND	ND	Chemotherapy and radiotherapy	ND	ND
41	Bhattacharyya et al.	2010	USA	F	51	Negative	Right maxillary buccal vestibule	Swelling	ND	ND	>6	Positive: CD20, Bcl-2, Bcl-6, Ki 67 (90%); Negative: CD10, CD3, CD5, MUM-1	ND	ND	Chemotherapy	ND	ND
42	Bhattacharyya et al.	2010	USA	M	60	Negative	Right mandibular buccal vestibule	Swelling	Numbness	ND	2.5	Positive: CD20, Bcl-6, MUM-1, Ki67 (50-70%); Negative: CD10, CD3, Bcl-2	ND	ND	ND	ND	ND
43	Bhattacharyya et al.	2010	USA	M	56	Negative	Maxillary mucosa	ND	Pain	ND	<1	Positive: CD10, CD20, Bcl-2, Bcl-6, Ki67 (>80%); Negative: CD3, CD5, MUM-1	ND	ND	Chemotherapy and radiotherapy	ND	ND
44	Bhattacharyya et al.	2010	USA	F	45	Negative	Right mandibular body	Facial enlargement	ND	ND	3	Positive: CD20, Bcl-6, Ki67 (>80%); Negative: CD10, CD3, CD5, Bcl-2, MUM-1	ND	ND	Chemotherapy	ND	ND
45	Bhattacharyya et al.	2010	USA	M	54	Negative	Maxilla	Swelling	ND	ND	ND	Positive: CD20, Bcl-6, MUM1, Ki67 (80%); Negative: CD10, CD3, CD5, Bcl-2	ND	ND	ND	ND	ND
46	Bhattacharyya et al.	2010	USA	M	72	Negative	Maxillary alveolus	Swelling and necrosis	ND	ND	ND	Positive: CD20, Bcl-2, Bcl-6, MUM1, Ki67 (40-50%); Negative: CD10, CD3, CD5	ND	ND	Died before treatment	Died before treatment	ND
47	Bhattacharyya et al.	2010	USA	F	89	Negative	Right maxillary vestibule	Swelling and ulcer	Discomfort in denture wearing	ND	<1	Positive: CD20, Bcl-2, Bcl-6, Ki 67 (>80%); Negative: CD10, CD3, CD5, MUM1	ND	ND	Chemotherapy	ND	ND
48	Bhattacharyya et al.	2010	USA	F	74	Negative	Right maxillary tuberosity	Swelling	Mass sensation	ND	>1	Positive: CD20, Bcl-2, Bcl-6, MUM1, Ki67 (40-60%); Negative: CD10, CD3, CD5	ND	ND	Chemotherapy and radiotherapy	ND	ND
49	Frei et al.	2012	Switzerland	M	76	ND	Right palate and buccal mucosa	Facial asymemetry, intraoral reddish swelling	Pain, hypoesthesia of maxillary nerve	Not presented	ND	Positive: CD20, CD79a, CD10, Pax-5, BCL-2 and BCL-6 (weak), Mib-1 (90%); Negative: MUM-1	ND	IIIA	Chemotherapy	R-CHOP	12
50	Mnejja et al.	2010	Tunisia	F	17	ND	Mandibular vestibule (intraosseous)	Swelling	Dental pain	Not presented	12	Positive: CD20	ND	ND	Chemotherapy and transplant	RACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisolone	24
51	Ojha et al.	2010	USA	M	51	Positive	Maxillary gingiva	Infraorbital swelling, maxillary swelling with necrosis	Pain	Weight loss, night sweats	ND	Positive: CD79a, kappa light chain, Bcl6, Ki-67 (80%); Negative: CD10, CD20, CD138, TdT	ND	II	Chemotherapy	hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone	1
52	Corti et al.	2011	Argentina	M	32	Positive	Gingiva, palate	ND	ND	ND	ND	Positive: CD20	ND	ND	ND	ND	1
53	Corti et al.	2011	Argentina	M	38	Positive	Gingiva, jaw		ND	ND	ND		ND	ND	ND	ND	36
54	Corti et al.	2011	Argentina	M	43	Positive	Palate, gingiva		ND	ND	ND		ND	ND	ND	ND	ND
55	Matsuzaki et al.	2011	Japan	F	68	ND	Left maxillary gingiva	Swelling	Epistaxis and nasal obstruction	Weight loss	ND	Positive: CD20, CD79, CD10; Negative: AE1/AE3, vim, S100, CD3, CD5	ND	IVB	Chemotherapy	Pirarubicin, cyclophosphamide, vincristine, prednisolone, and rituximab	ND
56	Terada et al.	2011	Japan	F	96	ND	Tongue	Swelling	ND	ND	ND	Positive: CD45, CD20, p53, Ki-67 (100%); Negative: cytokeratins, EMA, CD3, CD30, CD45RO, TdT	ND	ND	Chemotherapy and radiotherapy	R-CHOP	60
57	Chi et al.	2012	USA	F	40	ND	Mandibular gingiva	Swelling	Pain and paresthesia	ND	ND	Positive: CD45, CD20, Bcl-6, CD10 (scarce), vimentin (scarce), Ki-67 (~80%); Negative: CD3, myeloperoxidase, MUM-1, S100, AML, AE1/AE3.	ND	IIE	Chemotherapy and radiotherapy	R-CHOP	1
58	Ürün et al.	2012	Turkey	M	53	ND	Mandibular gingiva	Swelling	Teeth/gingival pain and chin paresthesia	ND	3	Positive: CD45, CD20, vim; Negative: S100, SMA, keratin	ND	IE	Chemotherapy and radiotherapy	R-CHOP	18
59	Zadik et al.	2012	Israel	F	66	ND	Mandibular mucosa	Facial Swelling, non-healed extraction site	Pain,chin paresthesia	Not presented	8	Positive: LCA, CD20, MIB-1 (>50%); Negative: CD3, Bcl-1	ND	I	Chemotherapy and radiotherapy	R-CHOP	ND
60	Vinoth et al.	2012	India	F	14	Negative	Maxillary gingiva	Multiple gingival swellings	ND	Not presented	2	Positive: CD45, CD20; Negative:CD3	ND	ND	Chemotherapy	LMP-96 group B protocol	10

Supplementary Table 2. Clinicopathological data of all 122 cases (63 articles) that were considered in this study after the exclusion of the articles that did not meet the inclusion criteria (Continuation).

101	Tina et al.	2014	India	M	50	Negative	Right mandibular vestibule	Swelling	Dysphagia	Not presented	3	Positive: CD20, LCA; Negative: CD3, cytokeratin	ND	IA-E	ND	ND	ND	ND
102	Buchanan et al.	2015	USA	M	35	ND	Buccal and maxillary vestibule	Swelling and bleeding	Pain	ND	2	Positive: CD20, CD3, Ki-67 (35–50%)	Negative	ND	ND	ND	ND	ND
103	Bugshan et al.	2015	USA	M	54	ND	Mandibular gingiva and buccal mucosa	Swelling and necrosis	Lip numbness, tooth mobility	ND	>1	Positive: CD20, CD3 (scattered positivity for T-cells), CD79a, CD10 (weak), Bcl-6; Negative: CD34, TdT, Cyclin D1, CD23.	ND	ND	ND	ND	ND	ND
104	Kaibuchi et al.	2015	Japan	M	87	ND	Left mandibular gingiva	Reddish swelling, ulcer	ND	Not presented	ND	Positive: LCA, CD79a (partial), CD10,MIB-1 (>95%); Negative: EMA, MPO, CD3, CD5, CD43, CD45RO, CD20, LMP1, CD138, CyclinD1, kappa,lambda, Bcl2	ND	ND	No treatment	Not performed	30	Dead
105	Kobayashi et al.	2015	Japan	M	71	ND	Right buccal mucosa	Swelling, necrosis, ulcer	Pain	ND	2	Positive: CD20, CD79a; Negative: ck, CD5	Positive	I	ND	ND	12	Alive
106	Mittal et al.	2015	India	M	50	Negative	Mandibular gingiva	Reddish swelling, mandible body pathological fracture	Not presented	Fever	<1	Positive: CD20, bcl-2, CD3/CD5 (scattered lymphocytes), CD10 (focal), Ki67 (30%)	ND	III-A	ND	ND	1	Dead
107	Patil et al.	2015	India	M	79	Negative	Maxillary buccal vestibule	Facial asymetry, intraoral swelling	Pain, numbness of cheek mucosa	ND	1	Positive: LCA, CD20, CD3 (weak), Ki-67	ND	ND	ND	ND	ND	ND
108	Pereira et al.	2015	Brazil	M	48	Negative	Mandibular vestibule and bone (intraosseous)	Swelling	Lip numbness, teeth cold sensitivity	ND	5	Positive: LCA, CD20, CD79a, Ki-67 (>80%); Negative: CD3, CD138, MUM-1, v538c	Negative	I	Chemotherapy	R-CHOP	7	Alive
109	Tomioka et al.	2015	Japan	F	8	ND	Tongue	Swelling	ND	Not presented	1	Positive: CD20, CD79a	ND	ND	Chemotherapy	COPAD: cyclophosphamide, vinblastine, pirarubicin, prednisolone	41	Alive
110	Webber et al.	2015	USA	M	55	ND	Maxilla (Intraosseous)	Not presented	Pain	Not presented	ND	Positive: CD20, CD79a, CD10	ND	ND	Chemotherapy	ND	6	Alive
111	Goto et al.	2016	Japan	M	81	Negative	Right mandibular gingiva and lower buccal vestibule	Reddish swelling	Gingival pain and lip numbness	ND	ND	Positive: CD20	Positive	IV	ND	ND	ND	ND
112	Jayapalan et al.	2016	India	M	60	ND	Maxillary vestibule and hard palate	Reddish swelling and ulcer	Pain	Not presented	<1	Positive: CD45, CD20; Negative: CK, desmin, S100, HMB-45, CD3, Bcl-6, CD138	ND	ND	Chemotherapy and radiotherapy	ND	3	Dead
113	Khandelwal et al.	2016	Canada	F	55	ND	Palate	Swelling	Not presented	ND	<1	Positive: CD20, Bcl2, Bcl6 (weak), MUM1, Ki67 (90-95%); Negative: CD3, CD10, CD5, CD30	ND	IV	Chemotherapy and Radiotherapy	R-CHOP and methotrexate	7	Alive
114	Kumar et al.	2016	India	F	41	Negative	Maxillary labial sulcus	Swelling	Teeth pain, discomfort	ND	5	Positive: LCA, CD20, Bcl-2, CD3 (focal), Ki-67 (<50%); Negative: CK, CD5	ND	ND	Chemotherapy	CHOP	1	Dead
115	Sepulveda et al.	2016	Chile	F	40	ND	Mandibular gingiva	Swelling	Not presented	Not presented	6	Positive: CD20, CD79a, CD45, BCL6; Negative: CD3, CD5, CD30	ND	IE	Chemotherapy and Radiotherapy	R-CHOP	18	Alive
116	Syed et al	2016	USA	M	81	ND	Maxillary gingiva	Swelling	Numbness, pain	ND	<1	Positive: CD20, CD79a	ND	ND	ND	ND	ND	ND
117	Syamala et al.	2016	India	M	62	Negative	Mandibular gingiva	Reddish swelling and ulcer	Pain and teeth mobility	ND	<1	Positive: Ki-67 (90%), CD-20, CD10, Bcl-6; Negative: CD3, MUM-1	ND	ND	ND	ND	ND	ND
118	Jawanda et al.	2017	India	M	19	ND	Left posterior mandible	Swelling	Pain, teeth mobility	ND	1	Positive: LCA, CD20, CD3; Negative: CD31, CD138, TdT	ND	ND	ND	ND	ND	ND
119	Rai et al.	2017	India	F	40	ND	Maxillary mucosa and hard palate	Facial swelling, intraoral swelling and ulcer	ND	ND	1,5	Positive: LCA, PAX5, Bcl2, CD138 (focal), Ki67 (100%); Negative: CD20, CD3, CD30,CD10.	ND	ND	ND	ND	ND	ND
120	Vrbic et al.	2017	Serbia	M	44	Positive	Palate	Reddish swelling and ulcer	Pain	Not presented	4	Positive: CD20, CD10, MUM1, Bcl6, Ki67 (90%); Negative: CD3, CD5, Bcl2	ND	I-EA	Chemotherapy + HAART	R-CHOP	24	Alive
121	Wang et al.	2017	China	M	73	ND	Tongue	ND	Sore throat	Not presented	ND	Positive: CD20, CD79a,MUM1, CD10 (focal); Negative: CD3, CD2	ND	ND	Chemotherapy and radiotherapy	ND	56	Alive
122	Donaduzzi et al.	2018	Brazil	M	72	Negative	Mandibular gingiva	Reddish swelling	ND	ND	1	Positive: CD20 and Ki67 (100%); Negative: CD3, CD30, and CD15	ND	ND	Chemotherapy	ND	9	Dead

2.2 Artigo: Oral and Oropharyngeal Diffuse Large B-cell Lymphoma, NOS: a clinicopathologic study of 52 cases.

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Abstract

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS) is a heterogeneous malignancy, with variable clinical presentation and outcome. Very few is understood regarding prognosis and survival in oral/oropharyngeal cases. Therefore, the aim of this study is to describe the clinicopathological, immunohistochemical (IHC) and EBV-status of oral/oropharyngeal DLBCL NOS, and to assess the patients' survival rate. The cases were retrospectively retrieved from six Brazilian pathology institutions. The microscopic description/diagnosis and IHC reactions were reviewed by two oral pathologists. In situ hybridization (ISH) was done to detect EBV. Statistical analysis was performed to compare the clinicopathological features with the patients' status at last follow up, as well as to calculate survival curves, and to identify potential prognostic factors. Fifty-two cases were included in this study. Elder males were the most affected patients by oral/oropharyngeal DLBCL NOS, which frequently manifested as a painful swelling in the oral cavity. Centroblasts were the predominant cell type in the majority of the tumors (63.5%), and 34 cases were classified into the Germinal center B-cell type (GCB). EBV was detected in 3 cases. CHOP was the most used chemotherapeutic scheme (17.3%), and the overall survival after 5 years achieved 53.7%. Patients younger than 62 years-old, presence of pain, a Ki67 proliferative index higher than 48.3%, and the predominance of immunoblasts were associated with a lower survival in the univariate analysis ($p = 0.005$; $p = 0.001$; $p = 0.024$; $p = 0.04$, respectively). However, these variables lost their significance in the multivariate model. In conclusion, oral/oropharyngeal DLBCL NOS is an aggressive malignancy. Age, pain, high Ki67 index, and predominance of immunoblasts may represent adverse prognostic factors, although they were not independent determinants of lower survival.

Key-words: Diffuse large B-cell lymphoma, non-Hodgkin lymphoma, oral cavity, oropharynx.

Introduction

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS) is a neoplasm of large B-cells arranged in a diffuse growth pattern (Li; Young; Medeiros, 2018). It is characterized as a heterogeneous malignancy, since its clinical presentation and outcome are remarkably variable, reflecting its biological and pathogenetic diversity (Cozzolino et al, 2016; Reddy et al, 2017). DLBCL NOS has an annual incidence of over 100,000 cases worldwide, representing 25-35% of adult non-Hodgkin lymphomas (NHL) in developed countries, and 42.5% in developing countries (Perry; Diebold; Nathwani, 2016; Reddy et al, 2017; Gascoyne; Campo; Jaffe, 2017). Different etiologies have been postulated with no consensus, although some cases develop in an underlying immunodeficiency basis and the Epstein-Barr virus (EBV) infection was shown to be present in a varying number of cases (Gascoyne; Campo; Jaffe, 2017).

Clinically, DLBCL NOS usually manifests as a rapidly growing tumor, affecting extranodal sites in over 40% of the cases (Li; Young; Medeiros, 2018; Cabeçadas; Martinez; Andreasen, 2019). In the head and neck region, the most common site of DLBCL NOS is the Waldeyer's ring, followed by the paranasal sinuses and the oral cavity, where the gingiva and palate are the most affected locations (Cabeçadas; Martinez; Andreasen, 2019; Rodrigues-Fernandes et al, 2019).

Recently, we have reviewed the literature to describe the clinicopathological features of DLBCL NOS of the oral cavity, but most of the currently available data is based on individual case reports or small series that include cases affecting many areas of the head and neck, none of them detailed evaluating the survival aspects of the patients (Rodrigues-Fernandes et al, 2019). Therefore, the aim of this study is to comprehensively describe the clinicopathological, immunohistochemical (IHC) and EBV-status of a large sample of oral and oropharyngeal DLBCL NOS and to determine the survival rate of the patients affected by this malignancy.

Materials and Methods

This study was approved by the Ethical Committee of the Piracicaba Dental School, University of Campinas, Piracicaba, Brazil (process no. 67128417.4.0000.5418).

Study population

All cases diagnosed as DLBCL NOS between January 2004 and May 2019 were retrospectively retrieved from the pathology files of six Brazilian institutions [Piracicaba Dental School of the University of Campinas (Piracicaba); School of Dentistry of the Universidade Federal de Minas Gerais (Belo Horizonte); Oral Pathology Service of the João de Barros Barreto University Hospital (Belém); Federal University of Rio Grande do Sul (Porto Alegre); School of Dentistry of the State University of Rio de Janeiro (Rio de Janeiro); Private Pathology Service (Natal)]. Formalin-fixed, paraffin-embedded tissues were obtained and new histological sections were stained with hematoxylin-eosin to be used for microscopic description and diagnosis confirmation by two oral pathologists following the current World Health Organization Classification of Lymphoid Neoplasms (2017). The clinicopathological features that were retrieved from patients' medical files included age, sex, tumor location, clinical presentation, time of evolution, imaging features, treatment, status at last follow-up (dead or alive), and time of follow-up. Overall survival rate was defined as the period from the date of diagnosis to the date of the patients' death or last follow-up.

Immunohistochemistry

Immunohistochemical reactions were performed in 3 μm sections of formalin-fixed, paraffin-embedded tissues that were dewaxed with xylene and then hydrated in a descending ethanol series. The endogenous peroxidase activity was blocked with 10% hydrogen peroxide in a single bath during 15 minutes. After washing in PBS buffer (pH 7.4), the sections were incubated for 2 hours with primary antibodies, and then exposed to high-sensitive horseradish peroxidase reagents (ADVANCE, Dako, Capinteria, CA, USA) and diaminobenzidine tetrahydrochloride (DAB, Sigma-Aldrich, St Louis, MO, USA). The slides were counterstained with Carazzi hematoxylin for 3 minutes. Positive control histological sections were used for each antibody, while the negative control was acquired by omitting the specific primary antibody.

All cases were submitted to one same IHC panel necessary for the diagnosis of DLBCL NOS and included the cytoplasmatic antibodies LCA, CD3 and CD20 for an initial screening, followed by CD10, Bcl6, MUM1, Bcl2 and Ki67. The cases were considered positive for Bcl2 when more than 50% of the cells showed a cytoplasmatic staining. The proliferative index was obtained by calculating the percentage of

malignant cells with nuclear staining for Ki67 among 500 to 1000 cells from randomly selected high-power fields. The subclassification of the cases according to the Hans algorithm for DLBCL NOS (2004) was performed considering the positivity of CD10 within the cytoplasm, and the nuclear staining of Bcl6 and MUM1, with a minimum expression of 30%.

Moreover, some additional antibodies were used in the IHC analysis always that necessary, in order to elucidate the diagnosis of some cases, and included pan-cytokeratin (AE1/AE3), vimentin, plasma cell, CD138, CD79a, PAX5, TdT, CD45RO, CD56, CD68, CD30, CD43, and CD5. Detailed information about immunohistochemistry antibodies and methods applied in the reactions are available in **Table 1**.

Table 1. Set of antibodies used in this study.

Antibody	Manufacturer	Clone	Dilution	Antigen retrieval	Positive control
LCA	Dako, Carpinteria, CA, USA	2B11+PD7/26	1:200	Citrate buffer (pH 6.0)	Tonsil
CD3	Dako, Carpinteria, CA, USA	F7.2.38	1:100	Citrate buffer (pH 6.0)	Tonsil
CD10	Dako, Carpinteria, CA, USA	56C6	1:100	EDTA/TRIS (pH 9.0)	Tonsil
CD20	Dako, Carpinteria, CA, USA	L 26(1,2)	1:300	Citrate buffer (pH 6.0)	Tonsil
Bcl-2	Dako, Carpinteria, CA, USA	124	1:50	Citrate buffer (pH 6.0)	Lymph node
Bcl-6	Santa Cruz, Santa Cruz, CA, USA	PG-B6p	1:300	EDTA/TRIS (pH 9.0)	Tonsil
MUM1	Dako, Carpinteria, CA, USA	MUM1p	1:500	EDTA/TRIS (pH 9.0)	Tonsil
Ki67	Dako, Carpinteria, CA, USA	MIB-1	1:100	EDTA/TRIS (pH 9.0)	Squamous cell carcinoma
AE1/AE3	Dako, Carpinteria, CA, USA	AE1/AE3	1:300	Citrate buffer (pH 6.0)	Fibrous hyperplasia
Vimentin	Dako, Carpinteria, CA, USA	Vim 3B4	1:400	Citrate buffer (pH 6.0)	Uterus
Plasma cell	Dako, Carpinteria, CA, USA	Vs38c	1:400	Citrate buffer (pH 6.0)	Tonsil
CD138	Dako, Carpinteria, CA, USA	MI 15	1:100	Citrate buffer (pH 6.0)	Fibrous hyperplasia
CD79a	Dako, Carpinteria, CA, USA	JCB 117	1:1000	Citrate buffer (pH 6.0)	Tonsil
PAX5	Novocastra, Newcastle, UK	1EW	1:50	EDTA/TRIS (pH 9.0)	Tonsil
TdT	Dako, Carpinteria, CA, USA	Policlonal	1:50	EDTA/TRIS (pH 9.0)	Lymphoblastic lymphoma
CD45RO	Dako, Carpinteria, CA, USA	UCHL 1	1:200	Citrate buffer (pH 6.0)	Tonsil
CD56	Novocastra, Newcastle, UK	1B6	1:50	EDTA/TRIS (pH 9.0)	Intestine
CD68	Dako, Carpinteria, CA, USA	KP-1	1:300	Citrate buffer (pH 6.0)	Mucocele
CD30	Dako, Carpinteria, CA, USA	Ber-H2	1:500	EDTA/TRIS (pH 9.0)	Tonsil
CD43	Dako, Carpinteria, CA, USA	DF-T1	1:200	EDTA/TRIS (pH 9.0)	Tonsil
CD5	Dako, Carpinteria, CA, USA	CD5/54/F6	1:300	EDTA/TRIS (pH 9.0)	Tonsil

In situ hybridization (ISH) for EBV

ISH reaction was performed to detect EBV. A fluorescein-labelled peptide nucleic acid probe (PNA) complementary to 2 nuclear encoded RNAs (EBER) (Y5200, Dako, Glostrup, Denmark) was hybridized at 55°C for 90 minutes, and then labelling

was performed by using the PNA ISH detection kit (K5201, Dako). A sample of Extranodal NK/T-cell lymphoma, nasal type was used as a positive control. Carazzi hematoxylin was used for subsequent counterstaining. Cases considered positive for EBV presented a dark blue mark within the nuclei of the tumor cells.

Statistical analysis

Chi-square and Fisher's exact tests were used to compare clinicopathological features and the patients' status (alive or dead). Kaplan-Meier method was used to calculate survival curves, whereas differences between the curves were investigated using the Log-Rank univariate test to identify potential prognostic factors. All variables that achieved significance in the univariate analysis and treatment modality used for the patients were included in a multivariate model created by Cox proportional harzard test to identify potential independent prognostic factors. The software SPSS version 22.0 was used and a p-value ≤ 0.05 was considered statistically significant.

Results

Demographic characteristics

Seventy-six cases diagnosed as DLBCL NOS were initially retrieved from the pathology files assessed; however, 24 cases were excluded due to lack of clinical information to confirm the location of the neoplasm, lack of available immunohistochemical sections to confirm the diagnosis, or absence of paraffin blocks or histological sections to perform the necessary immunohistochemical reactions. Therefore, 52 cases remained in the present study for analysis.

The clinicopathological features of all 52 cases included in this study are summarized in **Table 2**. The cases were more predominant in males (30 cases; 57.7%). Most of the patients was diagnosed in the 7th decade of life (mean age: 62.8 years; range 23 – 88 years). The majority of our sample consisted of oral cavity lymphomas (42 cases; 80.8%), whereas oropharyngeal cases accounted for 10 cases (19.2%). The hard palate and the jaw bones were the most frequently affected sites (14 and 9 cases, respectively), followed by the gingiva (3 cases), retromolar trigone (3 cases), alveolar ridge (2 cases), lips (2 cases), floor of the mouth (2 cases), and buccal mucosa (2 cases). Moreover, 2 cases presented extension to the maxillary sinus. The cases that involved the oropharynx comprised the soft palate (4 cases), palatine tonsil (1 case), and base of tongue (1 case), whereas 4 cases did not report the specific oropharyngeal site.

Clinical features

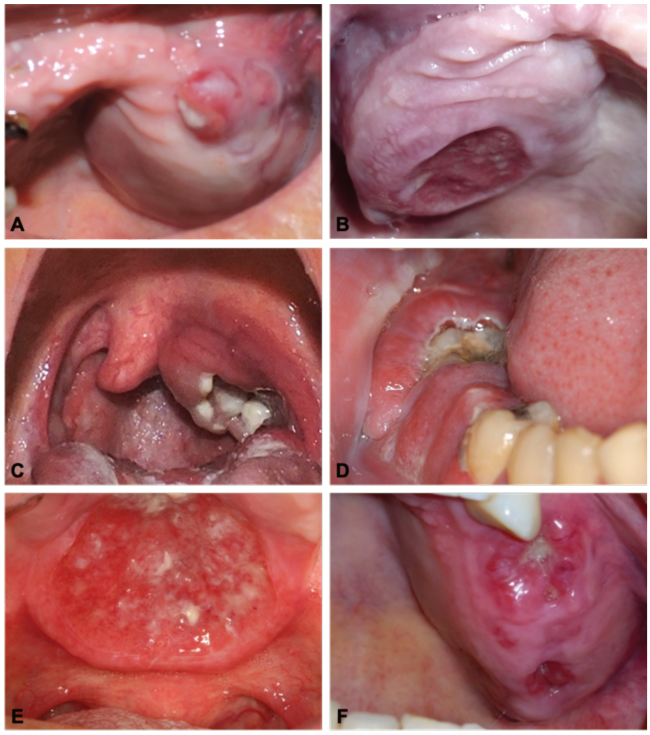
The main clinical findings of oral/oropharyngeal DLBCL NOS are illustrated in **Figure 1**. The most common clinical presentation was an asymptomatic swelling (40 cases; 76.9%), although pain was reported in 14 cases (26.9%). Additional clinical signs also included bleeding (3 cases; 5.8%) and bone destruction (10 cases; 19.2%) (**Table 2**). When radiograph and/or computed tomography were available for intra-osseous lymphomas, these cases demonstrated ill-defined radiolucid/hypodense images causing cortical bone expansion and destruction. Two cases were shown to obliterate the maxillary sinus, and one case showed extension to the orbital cavity (**Figure 2**). Patients more frequently reported rapidly growing tumors, with less than a month of duration, although some cases (4 cases; 7.7%) were reported with almost one year of evolution.

Table 2. Demographic and clinicopathological features of the 52 cases investigated in this study.

Clinicopathological variables	n = 52	%
Sex		
Female	22	42.3
Male	30	57.7
Age (mean age: 62.8 yrs)		
< 62.8 yrs	20	38.5
> 62.8 yrs	32	61.5
Site		
Oral cavity	42	80.8
Oropharynx	10	19.2
Symptoms		
Pain	14	26.9
Asymptomatic	21	40.4
ND	17	32.7
Swelling		
Presence	40	76.9
Absence	6	11.5
ND	6	11.5
Ulcer		
Presence	24	46.2
Absence	22	42.3
ND	6	11.5
Bleeding		
Presence	3	5.8
Absence	19	36.5
ND	30	57.7
Bone destruction		
Presence	10	19.2
Absence	15	28.8
ND	27	51.9
Treatment		
CT	4	7.7
CHOP	9	17.3
R-CHOP	3	5.8
RT	1	1.9
CT+RT	4	7.7
No treatment applied	5	9.6
ND	26	50
Status		
Alive	15	28.8
Dead	13	25.0
ND	24	46.2

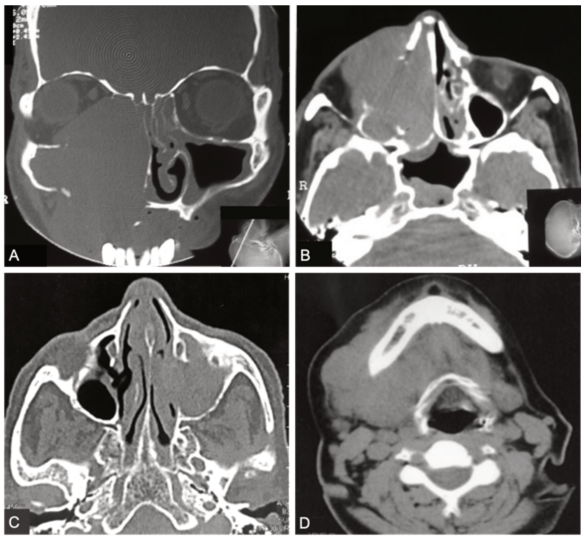
CT: Chemotherapy; RT: Radiotherapy; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP: rituximab+CHOP. ND: Information not described.

Figure 1. Clinical findings of oral/oropharyngeal DLBCL NOS.



A: A 66-year-old male presenting a diffuse swelling involving both vestibular and palatal surfaces of the left maxillary alveolar ridge, with extension to the soft palate. A small area of ulceration is also observed. **B:** A 57-year-old male presenting a large swelling in the right hard palate, extending to the midline, with the presence of a large ulceration. **C:** A 57-year-old female with an ulcerated swelling involving the left palatine tonsil, causing deviation of the uvula. **D:** A gingival swelling embracing and covering the right mandibular molars of a 33-year-old male. **E:** An 84-year-old female with a large ulceration in the palate, presenting elevated borders with foci of necrosis. **F:** A diffuse swelling involving the left maxillary gingiva/alveolar ridge, with extension to the buccal vestibule of a 77-year-old female patient. Areas of ulceration are also observed.

Figure 2. Imaging characteristics of oral/oropharyngeal DLBCL NOS.

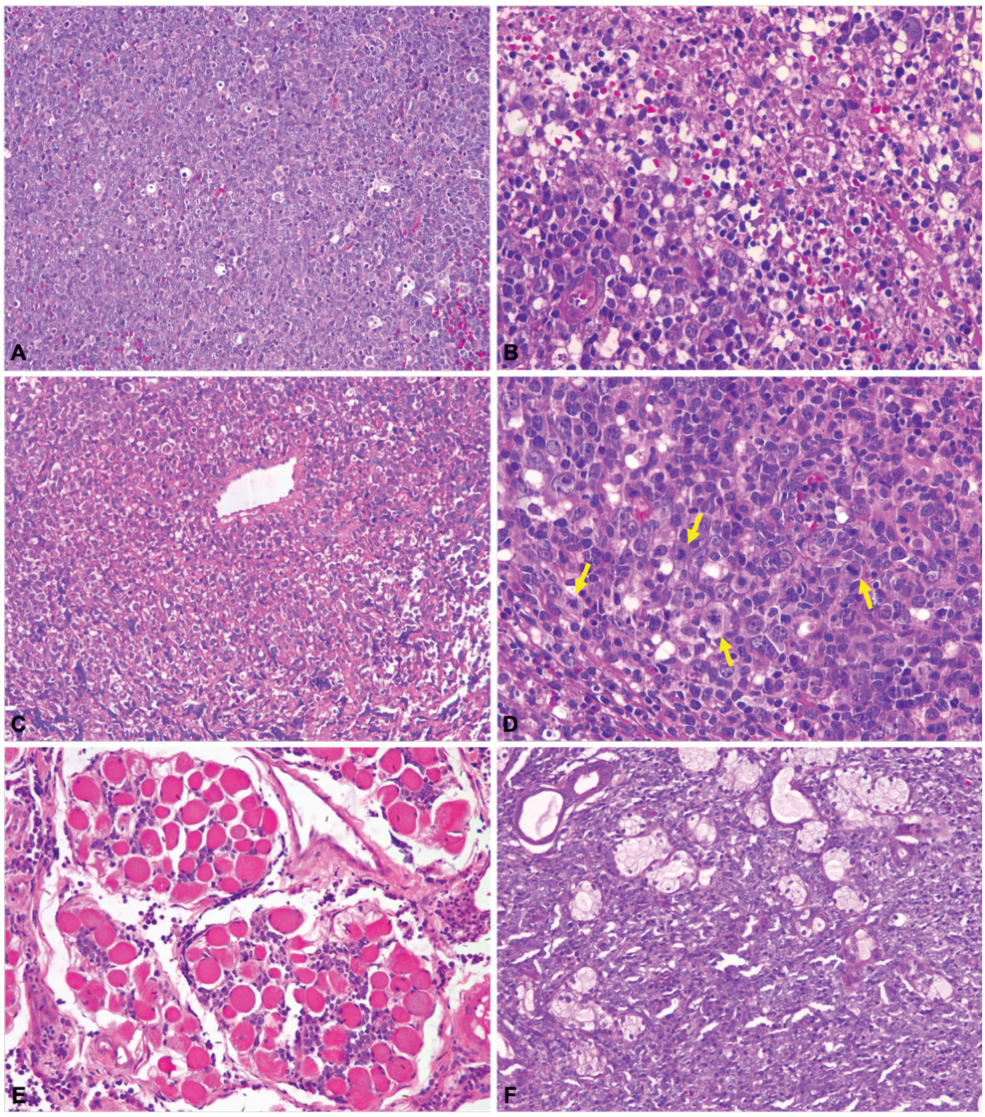


A-B: Computed tomography (CT) scans of a 57-year-old male exhibiting involvement of the right nasal cavity, maxillary and ethmoid sinuses, with tumor invasion into the orbital cavity (**A:** coronal section; **B:** axial section). **C:** Axial section of a CT scan of an 84-year-old female showing obliteration of the right maxillary sinus (CT scan). **D:** CT scan of a 63-year-old female presenting a large tumor involving the right mandible, with extension to the submandibular space (axial section).

Microscopic findings

The affected tissues exhibited effacement of their architecture by the diffuse infiltration of neoplastic cells, which permeated the surrounding structures, such as muscles, vessels, bone, and adipose tissue, exhibiting extensive areas of necrosis in most of the cases (44 cases; 84.6%). Ulceration of the overlying mucosa was also a common finding (24 cases). Fourteen cases presented the so-called "starry sky" appearance demonstrating variable number of tingible body macrophages with phagocytosed cell debris (26.9%) (**Figure 3**).

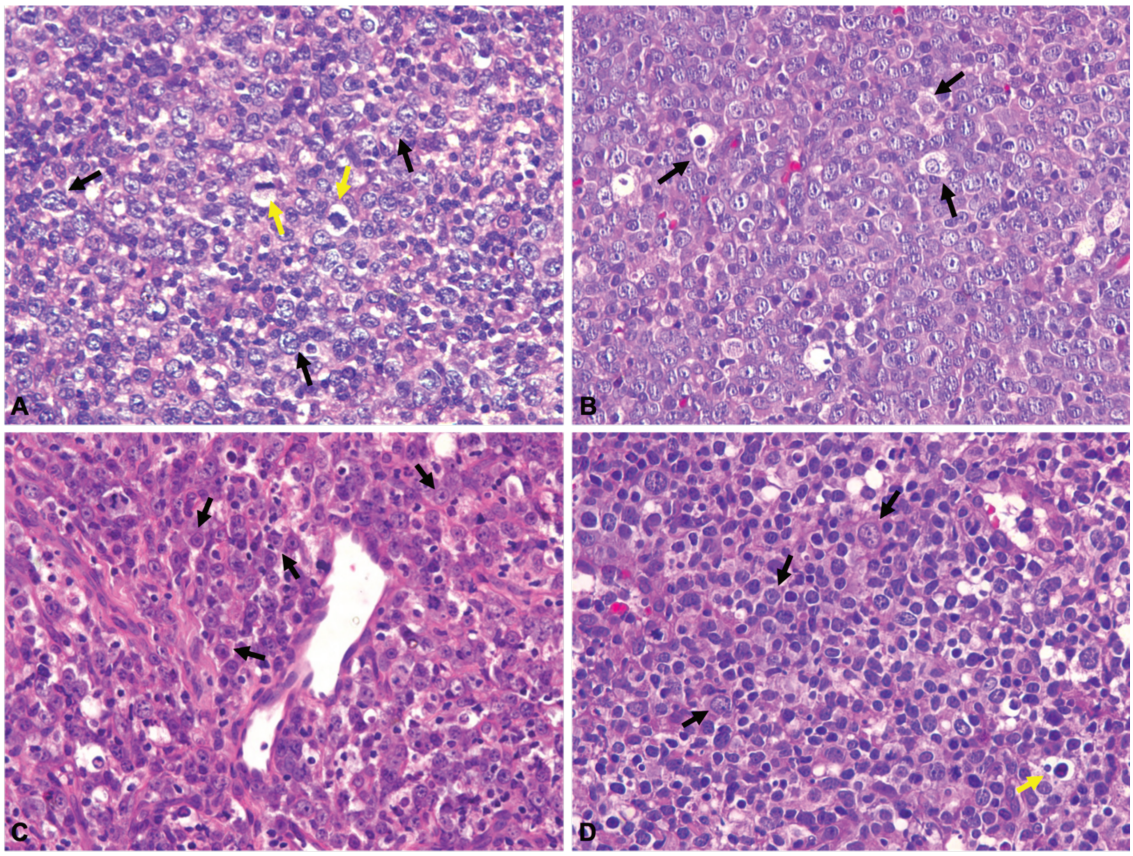
Figure 3. Microscopic features of oral/oropharyngeal DLBCL NOS.



A: "Starry sky" appearance composed by tingible-body macrophages with phagocytosed cell debris (HE, 200x). **B:** Area of coagulative necrosis with neoplastic cells and karyorrhetic debris (HE, 400x). **C:** Lymphoid infiltrate with an angiocentric distribution and presence of necrosis (HE, 200x). **D:** Presence of atypical mitotic figures is observed (yellow arrows) (HE, 400x). **E-F:** Infiltration of neoplastic cells into the surrounding normal muscle fibers and minor salivary glands.

Centroblasts were the predominant cell type (33 cases; 63.5%), and consisted of large non-cleaved cells with round to oval vesicular nuclei and multiple small nucleoli (**Figures 4A-B**). The immunoblasts predominated in 19 cases (36.5%) and exhibited round to oval vesicular nuclei with a single prominent and centred-located nucleolus (**Figure 4C**). Nevertheless, the admixture of these two cell types was observed in all tumours, together with smaller and more hyperchromatic centrocytes. Moreover, cellular atypia, such as irregular nuclear foldings, coarse chromatin and giant or bizarre nuclei was also frequently present (**Figure 4D**). Atypical mitotic figures were commonly observed, and the mean mitotic ratio in our sample was 4.2 mitosis per high power field (HPF), ranging from 1 to 13.4 mitoses/HPF (**Table 3**).

Figure 4. Neoplastic cell types observed in oral/oropharyngeal DLBCL NOS.



A: Centroblasts: large non-cleaved cells with round and vesicular nuclei, and multiple small nucleoli (black arrows). Atypical mitoses are also visualized (yellow arrows). **B:** Tingible-body macrophages among centroblasts (black arrows). **C:** Immunoblasts exhibiting oval and round vesicular nuclei with a prominent central nucleolus (black arrows). **D:** Admixture of cells presenting intermediate features with variation in nuclei size and shape, as well as chromatin arrangement (black arrows). Apoptotic bodies are also noted (yellow arrow) (HE, 400x).

Table 3. Microscopic features, main immunohistochemical findings, and EBV-status of the 52 cases investigated in this study.

Microscopic variables	n = 52	%
Bcl2 expression		
Positive	34	65.4
Negative	18	34.6
Ki67 index (mean: 48.3%)		
< 48.3%	19	36.5
> 48.3%	33	63.5
CD10 expression		
Positive	20	38.5
Negative	32	61.5
Bcl6 expression		
Positive	37	71.2
Negative	15	28.8
MUM1 expression		
Positive	29	55.8
Negative	23	44.2
Hans algorithm		
GCB	34	65.4
ABC	18	34.6
EBV status		
Positive	3	5.8
Negative	49	94.2
Predominant cell type		
Centroblast	33	63.5
Immunoblast	19	36.5
Starry sky pattern		
Presence	14	26.9
Absence	38	73.1
Necrosis		
Presence	44	84.6
Absence	8	15.4
Mitotic ratio (mean: 4.2 mit/HPF)		
< 4.2 mit/HPF	32	61.5
> 4.2 mit/HPF	20	38.5

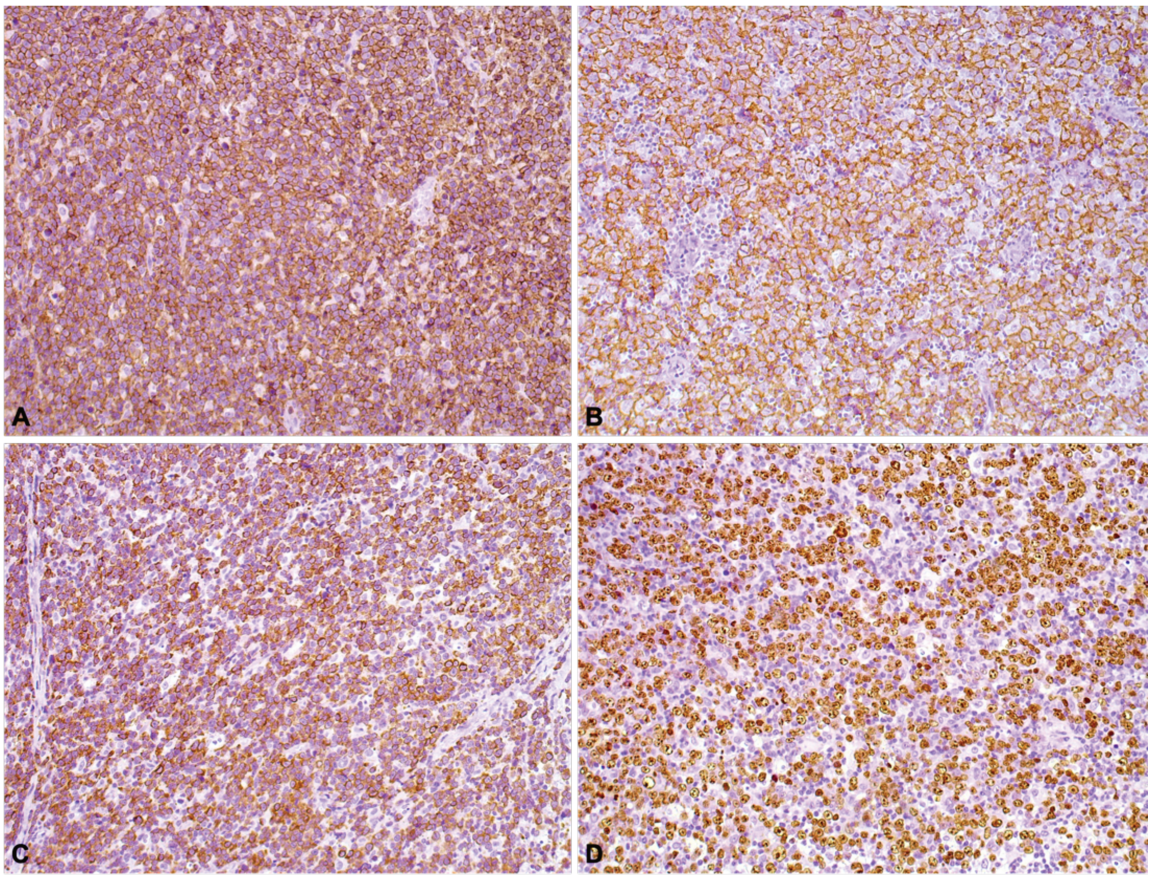
GCB: Germinal center B-cell type; ABC: Activated B-cell type. HFP: high power field.

Immunohistochemical and EBV ISH findings

All cases showed positivity for LCA and CD20 antibodies, whereas CD3 was negative in the tumor cells, exhibiting focal positivity in a variable number of small reactive lymphocytes (**Figures 5A-B**). Bcl2 cytoplasmic staining was positive in 34 cases (65.4%) (**Figure 5C**). Twenty cases were positive for CD10 antibody (38.5%); MUM-1 was expressed in 29 cases (55.8%), and Bcl6 was positive in 37 cases (71.2%). According to the Hans algorithm for DLBCL NOS (2004), 34 cases were classified into the germinal center B-cell (GCB) type group (65.4%), and 18 cases were categorized into the activated B-cell (ABC) type group (34.6%) (**Table 3**; **Figure 6**). The mean proliferative index obtained with Ki67 staining was 48.3%, ranging from 19.5% to 90%

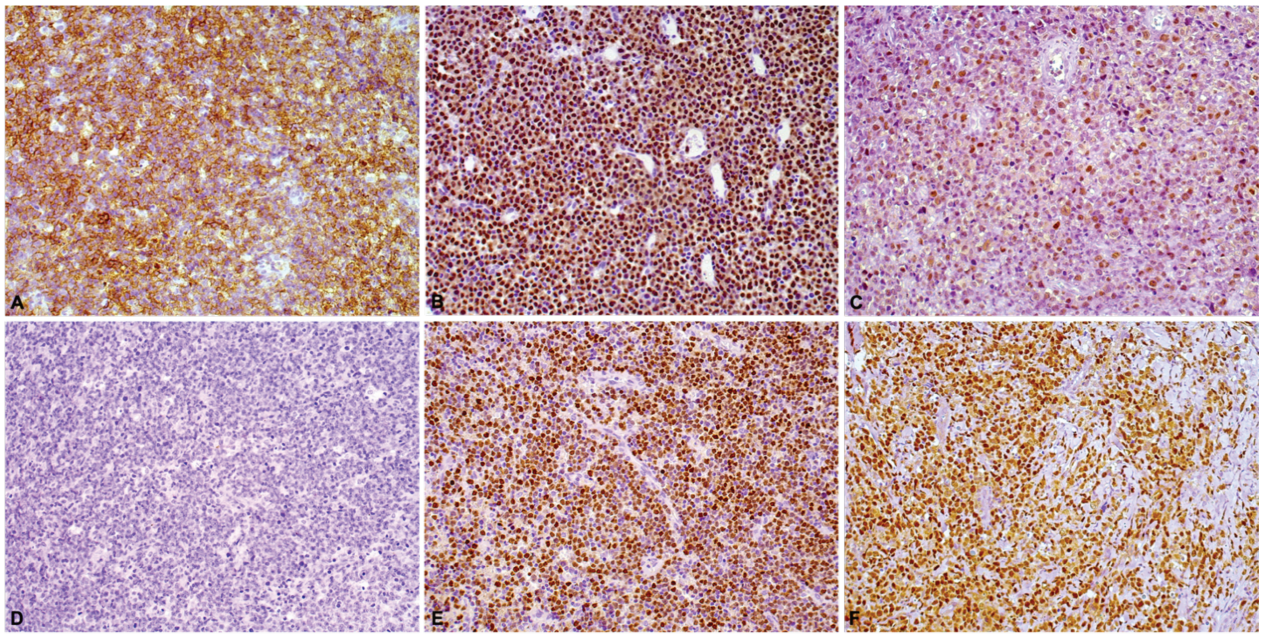
(**Figure 5D**). EBV was detected in 3 cases only, all located in the oral cavity (5.8%), which sub-categorized them as EBV-positive DLBCL NOS (**Figure 7**).

Figure 5. Immunohistochemical findings in oral/oropharyngeal DLBCL NOS cases.



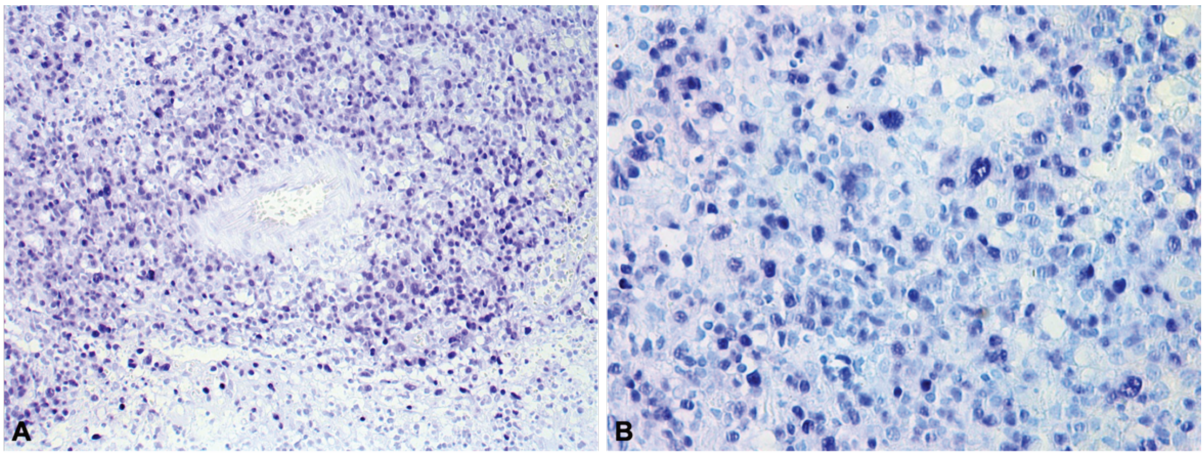
A: Expression of tumor cells for LCA, demonstrating their lymphoid origin. **B:** CD20 antibody was expressed in the neoplastic B-cells, corroborating this cell lineage for diagnosis. **C:** Diffuse expression of Bcl2 within the tumor cells. **D:** High proliferative index demonstrated by nuclear Ki67 staining (IHC, 200x).

Figure 6. Immunohistochemical findings in oral/oropharyngeal DLBCL NOS cases, according to the Hans algorithm.



A: Diffuse expression of CD10 within the membranes of the tumor cells. **B-C:** Nuclear staining of MUM1 and Bcl6 antibodies, respectively. These findings represent a case of DLBCL NOS, germinal center B-cell type. **D:** Negative expression for CD10 antibody. **E-F:** Expression of MUM1 and Bcl6 within the cell nuclei, respectively. These findings represent a case of DLBCL NOS, activated B-cell type (IHC, 200x).

Figure 7. *In situ* hybridization analysis to investigate the presence of EBV-positive DLBCL NOS cases.



A-B: Positivity of EBV within the nuclei of the tumor cells. Perivascular arrangement of the positive cells and areas of coagulative necrosis are also observed (ISH-EBV, 200x; 400x, respectively).

Treatment and outcome

Detailed treatment data was unavailable for 26 cases (50%); however, those with available information showed that chemotherapy was applied in virtually all cases (20 cases), whereas one case was submitted to radiotherapy only, and 5 cases were not submitted to any sort of treatment. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), with or without the use of rituximab was the main chemotherapeutic scheme used (9 cases; 17.3%). Twenty-eight patients had their survival status available, in which 15 patients (28.8%) were alive at their last follow-up, whereas 13 patients were dead (25.0%) (**Table 2**). The mean follow-up time for 24 cases was 27 months, ranging from 1 to 83 months.

Clinicopathological correlation and survival-rate analysis

Statistical analysis revealed that patients younger than 62.8 years old were significantly associated with a higher death rate ($p = 0.02$), as well as the patients who presented painful lesions ($p = 0.05$). However, none of the microscopic, IHC, and EBV findings showed significant association with patients' status at last follow-up **(Table 4)**. The overall survival rate of our sample was 53.7% after 5 years of follow-up (**Figure 8**).

Figure 8. Kaplan-Meyer curve demonstrating the overall survival of patients affected by oral/oropharyngeal DLBCL NOS.

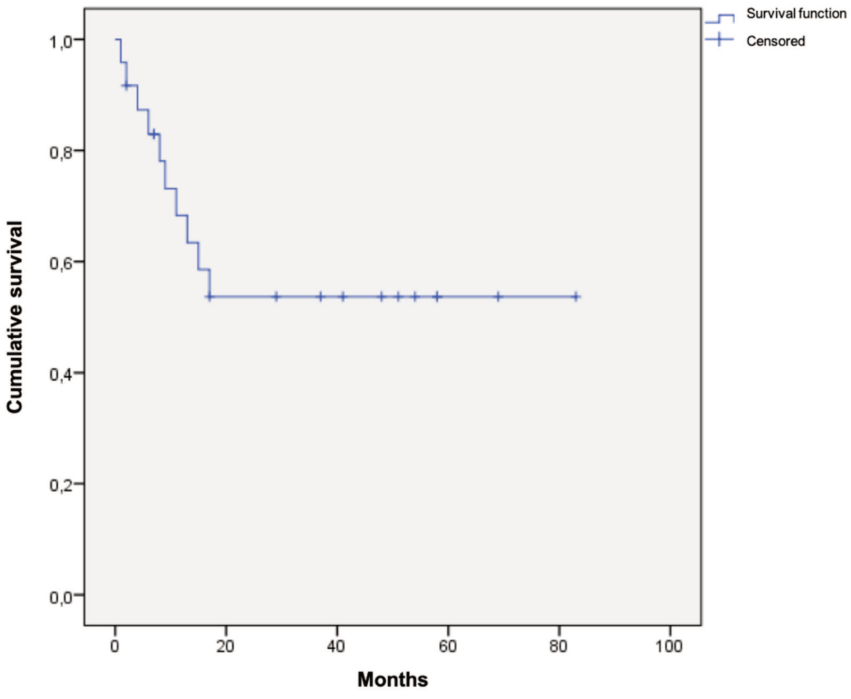


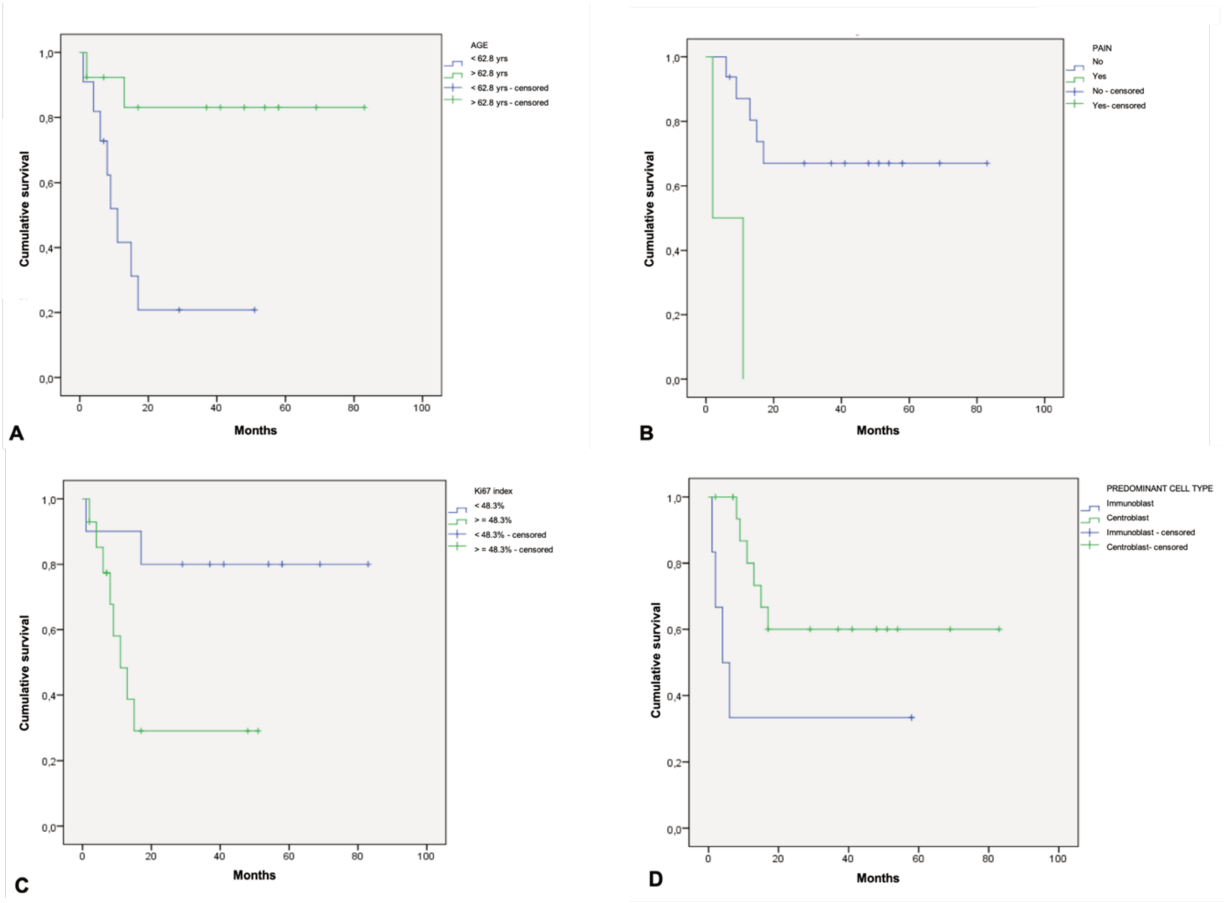
Table 4. Association analysis of the clinicopathological features, microscopic, immunohistochemical and in situ hybridization findings, with the status of the patients affected by oral/oropharyneal DLBCL NOS at their last follow-up.

Variables	Alive N *(%)*	Dead N *(%)*	*p*-value
Sex			
Male	9 (60.0)	6 (46.2)	0.46
Female	6 (40.0)	7 (53.8)	
Age (mean age: 62.8 yrs)			
< 62.8 yrs	3 (20.0)	9 (69.2)	0.02
> 62.8 yrs	12 (80.0)	4 (30.8)	
Site			
Oral cavity	12 (80.0)	10 (76.9)	1.00
Oropharynx	3 (20.0)	3 (23.1)	
Symptoms			
Pain	0 (0)	3 (37.5)	0.05
Asymptomatic	12 (100)	5 (62.5)	
Swelling			
Presence	13 (86.7)	10 (83.3)	1.00
Absence	2 (13.3)	2 (16.7)	
Ulcer			
Presence	7 (46.7)	7 (58.3)	0.58
Absence	8 (53.3)	5 (41.7)	
Bleeding			
Presence	0 (0)	1 (11.1)	0.47
Absence	10 (100)	8 (88.9)	
Bone destruction			
Presence	2 (22.2)	2 (28.6)	1.00
Absence	7 (77.8)	5 (71.4)	
Treatment			
CHOP	5 (41.7)	4 (50.0)	0.93
R-CHOP	2 (16.6)	1 (12.5)	
Others*	5 (41.7)	3 (37.5)	
Bcl2 expression			
Positive	12 (80.0)	6 (46.2)	0.11
Negative	3 (20.0)	7 (53.8)	
Ki67 index (mean: 48.3%)			
< 48.3%	8 (53.3)	3 (23.1)	0.14
> 48.3%	7 (46.7)	10 (76.9)	
Cell of origin			
GCB	11 (73.3)	7 (53.8)	0.43
ABC	4 (26.7)	6 (46.2)	
EBV status			
Positive	1 (6.7)	1 (7.7)	1.00
Negative	14 (93.3)	12 (92.3)	
Predominant cell type			
Centroblast	13 (86.7)	7 (53.8)	0.10
Immunoblast	2 (13.3)	6 (46.2)	
Starry sky pattern			
Presence	3 (20)	5 (38.5)	0.41
Absence	12 (80)	8 (61.5)	
Necrosis			
Presence	12 (80)	12 (92.3)	0.60
Absence	3 (20)	1 (7.7)	
Mitotic ratio (mean: 4.2 mit/HPF)			
< 4.2 mit/HPF	9 (60)	9 (69.2)	0.71
> 4.2 mit/HPF	6 (40)	4 (30.8)	

*Cases that neither specified the chemotherapy scheme, or did not perform any treatment. GCB: Germinal center B-cell type; ABC: Activated B-cell type. HFP: high power field.

By using Log-rank univariate analysis, we also observed that patients younger than 62.8 years-old and symptomatic patients were significantly associated with a lower survival rate (p = 0.005 and p = 0.001, respectively). The cases that presented a high proliferative index and a predominance of immunoblasts were also significantly associated with a lower survival (p = 0.024 and p = 0.04, respectively) (**Table 5**; **Figure 9**). Although we did not find a significant association between the treatment modality and the patients' survival rate by using the univariate analysis, we also included this variable in our Cox regression model, given its well-known importance to the patients' prognosis. In the multivariate model created, none of the variables included achieved statistical significance and, therefore, could not be considered independent determinants of a lower survival (**Table 6**).

Figure 9. Parameters that significantly affected the survival rate using Log-rank univariate analysis.



A: Age (p = 0.005). **B:** Pain (p = 0.001). **C:** Ki67 index (p = 0.024). **D:** Predominant cell type (p = 0.04).

Table 5. Log-rank univariate analysis of the clinicopathological features, microscopic and immunohistochemical findings, and EBV-status.

Clinicopathological variables	Log-rank univariate analysis			
	5-years survival (%)	Estimative (95% CI)	Chi-square	*p*-value
Sex				
Male	60.0	54.8 (33.4 – 76.2)	1.31	*0.25*
Female	45.5	29.6 (14.2 – 45.0)		
Age (mean age: 62.8 yrs)				
< 62.8 yrs	20.8	17.8 (6.9 – 28.8)	7.60	*0.005*
> 62.8 yrs	83.1	70.3 (8.2– 54.2)		
Site				
Oral cavity	54.1	41.7 (27.7 – 55.8)	0.08	*0.78*
Oropharynx	50.0	44.5 (6.7 – 82.3)		
Symptoms				
Pain	0	6.5 (0 – 15.3)	10.1	*0.001*
Asymptomatic	67.0	59.6 (42.7 – 76.4)		
Swelling				
Presence	54.3	49.6 (32.4 – 66.8)	0.09	*0.76*
Absence	66.7	30 (12.4 – 47.6)		
Ulcer				
Presence	55.0	49.3 (27.3 – 71.3)	0.09	*0.76*
Absence	56.8	44.2 (25.6 – 62.7)		
Bleeding				
Presence	0	11 (11 – 11)	1.92	*0.17*
Absence	58.0	44.5 (29.4 – 59.6)		
Bone destruction				
Presence	50.0	31 (14.2 – 47.8)	0.04	*0.83*
Absence	63.6	55.5 (34 – 77.1)		
Treatment				
CHOP	17.7	34.6 (18.0 – 51.0)	1.02	*0.60*
R-CHOP	27.2	35.5 (10.3 – 60.4)		
Others*	17.1	63.6 (40.8 – 86.3)		
Bcl2 expression				
Positive	62.2	56.2 (37.5 – 74.8)	2.58	*0.10*
Negative	37.5	25.1 (7.3 – 42.9)		
Ki67 index (mean: 48.3%)				
< 48.3%	80.0	68.2 (49.7 – 86.7)	5.13	*0.024*
> 48.3%	29.0	21.1 (9.6 – 32.7)		
Cell of origin				
GCB	54.1	49.6 (31.2 – 67.9)	0.11	*0.74*
ABC	53.6	33.8 (13.3 – 54.2)		
EBV status				
Positive	50.0	22.0 (12.3 – 31.7)	0.02	*0.90*
Negative	54.2	48.8 (32.1 – 65.4)		
Predominant cell type				
Centroblast	60.0	54.7 (37.1 – 72.3)	4.10	*0.04*
Immunoblast	33.3	21.5 (0.81 – 42.2)		
Starry sky pattern				
Presence	22.2	15.8 (3.33 – 28.2)	3.02	*0.08*
Absence	63.2	55.9 (38.5 – 73.3)		
Necrosis				
Presence	51.1	33.8 (38.5 – 73.3)	0.40	*0.53*
Absence	66.7	59.0 (22.3 – 45.3)		
Mitotic ratio (mean: 4.2 mit/HPF)				
< 4.2 mit/HPF	51.4	46.7 (27.2 – 66.2)	0.16	*0.69*
> 4.2 mit/HPF	58.3	35.8 (19.9 – 51.7)		

*Cases that neither specified the chemotherapy scheme, or did not perform any treatment. GCB: Germinal center B-cell type; ABC: Activated B-cell type. HFP: high power field. CI: confidence interval.

Table 6. Multivariate Cox regression model, including the variables that were statistically significant in the univariate analysis, and the treatment strategy used.

Variables	Hazard ratio	95% CI		*p*-value
		Lower	Upper	
Age	8.32	0.38	180.4	0.18
Pain	0.37	0.03	5.43	0.47
Ki67 index	0.11	0.008	1.65	0.11
Predominant cell type	8.80	0.37	207.9	0.18
Treatment	0.77	0.17	3.58	0.74

CI: confidence interval.

Discussion

DLBCL NOS is the most common subtype of non-Hodgkin lymphomas; however, most of the clinical and pathological information regarding its oral and oropharyngeal manifestations is limited to single case reports or scarce small case series, which precludes a better understanding regarding the biological behaviour of this malignant neoplasm when affecting these anatomic regions (van der Waal et al, 2005; Kemp et al, 2008; Sato et al, 2009; Scherfler et al, 2012; Triantafillidou et al, 2012; Guevara-Canales et al, 2013). Therefore, we attempted to investigate the clinicopathological data, immunohistochemical features, and EBV-status of 52 patients affected by oral/oropharyngeal DLBCL NOS in order to better comprehend the influence of these features in the patients' prognosis and survival. We observed that age and symptomatic tumors are likely to represent poor prognostic determinants, as well as a high proliferative index and the predominance of immunoblasts in the microscopic findings.

As previously described, we observed that males are the most commonly affected patients by oral/oropharyngeal DLBCL NOS, suggesting a higher male susceptibility in these locations, in comparison to other extranodal sites, such as breast and thyroid, which usually affects more females (Sato et al, 2009; Castillo; Winer; Olszewski, 2014; Owosho et al, 2014; Takano et al, 2015). Although the lymphoid tissue that comprise the Waldeyer's ring are the most frequently involved sites of head and neck DLBCL NOS (Han et al, 2017; Rayess et al, 2017), our cases demonstrated a higher prevalence in the oral cavity. In this location, the gingiva and palate are most commonly affected (Sato et al, 2009; Triantafillidou et al, 2012; Mian et al, 2014; Rodrigues-Fernandes et al, 2019), although we have also observed a high involvement of the jaw bones, as demonstrated in other studies (van der Waal et al, 2005; Kemp et

al, 2008). These variations in the ratio value of oral:oropharyngeal cases are likely related to our sample source, which mostly comprised cases retrieved from oral pathology services.

Advanced age has been associated with an unfavourable outcome for DLBCL NOS when considering a cut-off higher than 60 years old (Martelli et al, 2013; Gascoyne; Campo; Jaffe, 2017). Møller; Pedersen; Christensen (2003) analysed 177 cases of nodal and extranodal DLBCL NOS and demonstrated a significant association between patients older than 50 years old and a lower survival rate. Similar results have also been previously reported for oral and oropharyngeal tumors (Guevara-Canales et al, 2013; Rayess et al, 2017). Conversely, we found a significant association between patients younger than 62.8 years and a decreased survival rate, which could be explained by the presence of some patients younger than 62.8 years not submitted to any therapeutic modality, possibly decreasing the survival rate of this group.

Oral/oropharyngeal DLBCL NOS is a rapidly growing neoplasm, with 32.3% of our cases reporting 2 months of duration or less, which demands an efficient diagnostic and therapeutic approach (van der Waal et al, 2005; Li; Young; Medeiros, 2018). In line with the literature, the majority of our cases manifested as an asymptomatic tumor, what may contribute to delay the diagnosis (Sato et al, 2009; Triantafillidou et al, 2012; Picard et al, 2015). Meanwhile, the presence of pain was significantly associated with a lower survival rate in the univariate analysis, which has not been previously described (Guevara-Canales et al, 2013). Given that the presence of symptoms highly depends on the site of extranodal involvement, the local manifestation of pain may represent a characteristic of oral/oropharyngeal DLBCL NOS, specially in the cases with ulceration, not necessarily present in nodal or other extranodal DLBCL NOS, reflecting its biological diversity. Current staging protocols associate the presence of systemic B-symptoms with an adverse prognosis, but we were unable to obtain this data for analysis (Martelli et al, 2013; Gascoyne; Campo; Jaffe, 2017).

The histologic presentation of DLBCL NOS comprises a diffuse proliferation of medium to large-size lymphoid cells with diverse morphology and, consistently with our results, the centroblasts are the most common cell type (Xie; Pittaluga; Jaffe, 2015; Ott et al, 2017; Li; Young; Medeiros, 2018). Immunoblasts may occasionally exhibit plasmacytoid appearance, which may be challenging to differentiate these cases from plasmablastic lymphoma without immunohistochemical investigation (Rodrigues-Fernandes et al, 2018). Previous studies suggested that tumors with immunoblastic

morphology would be associated with a lower survival rate (Engelhard et al, 1997; Bernd et al, 2009; Ott et al, 2010), which is in accordance with our results. However, these findings should be carefully assessed, considering the lack of a clear cut-off value to consider the predominance of one given cellular type, as well as the inter-observer reproducibility variation (Xie; Pittaluga; Jaffe, 2015).

The immunophenotype for DLBCL NOS includes positivity to pan B-cell markers and negativity to T-cell ones (Gascoyne; Campo; Jaffe, 2017). CD20 is used not only for diagnostic purposes, but it is also very important to determine the therapeutic management, since its expression allows the use of rituximab monoclonal therapy (Martelli et al, 2013; Coleman et al, 2016).

As an attempt to obtain an additional prognostic determinant for DLBCL NOS cases, Hans et al. (2004) recommended the use of CD10, Bcl6 and MUM1 immunoexpression pattern to categorize the tumors as either Germinal center B-cell type (GCB) or Activated B-cell type (ABC), which would be more accessible than classifying them according to their genetic profile. It was previously shown that GCB DLBCL NOS is more frequent than the activated B-cell type (ABC) subgroup, which is in accordance to the present study (Owosho et al, 2014; Sanchéz et al, 2015). Regarding the prognostic importance of this classification, the ABC subtype has been associated with a worse outcome in both nodal and extranodal sites (Lu et al, 2016), although Sato et al. (2009) observed a high survival rate in patients with ABC DLBCL NOS involving the oral cavity. Bhattacharyya et al. (2010) described in their series (N= 13) that only half of the cases classified as ABC DLBCL NOS presented a mean survival rate of 16 months (4 cases). We did not find a significant prognostic potential of this algorithm, as described by other authors, suggesting that it may not be a reliable instrument to stratify patients according to their risk of death (Ott et al, 2010; Benesova et al, 2012; Castillo et al, 2012; Coutinho et al, 2013).

The expression of Bcl2 in DLBCL NOS is highly variable, ranging from 47 to 84% (Gascoyne; Campo; Jaffe, 2017), and it has been associated with poor overall survival, particularly in cases classified into the GCB subgroup (Iqbal et al, 2011; Sanchéz et al, 2015). In our study, most cases categorized into the GBC subgroup expressed Bcl2 (23 cases), however, we could not determine whether this immunoexpression would represent an adverse prognostic factor for this sub-type of oral/oropharyngeal DLBCL NOS, due to the limited number of cases with available follow-up data, but we observed that Bcl2 did not impact the survival of the patients

affected by this oral/oropharyngeal malignancy, as also described by other authors (Obermann et al, 2009; Sato et al, 2009; Ott et al, 2010).

The proliferative index of DLBCL NOS is typically high, but lower than other aggressive lymphomas, such as plasmablastic lymphoma and Burkitt's lymphoma. The presence of the so-called "starry sky" pattern can be found in some cases and the presence of mitotic figures is easily observed, consequently leading to a rapid clinical growth (Li; Young; Medeiros, 2018; Rodrigues-Fernandes et al, 2018). Therefore, the Ki67 immunostaining is also high, usually more than 40% (Owosho et al, 2014; Sanchéz et al, 2015; Gascoyne; Campo; Jaffe, 2017), as demonstrated in our study. Although Ki67 expression did not retain its significance as prognostic determinant in our multivariate model, it may have some importance given its significance in the univariate analysis. Divergent results have been described in the literature, since some studies demonstrated a significant association between a high Ki67 index and a poorer outcome (Li et al, 2012; Sanchéz et al, 2015), while others failed to obtain this association (Sato et al, 2009; Ott et al, 2010).

EBV-positive DLBCL NOS comprises < 5-15% of all DLBCLs, frequently occurring in males older than 50 years old, although sporadic cases are also reported in younger patients in the third decade of life (Nakamura; Jaffe; Swerdlow, 2017), as observed in our sample that included patients' with 23, 29, and 54 years old. EBV exhibits different types of latency, resulting in latent membrane gene products, such as LMP1, and nuclear antigens, like EBV-encoded RNA (EBER) (Battle-Lopez et al, 2016). Immunohistochemistry may be used to detect EBV in DLBCL NOS, which can be positive for LMP1; however, ISH is the most sensitive method, with more than 80% of the atypical cells being positive for the virus (Auerbach; Aguilera, 2015; Battle-Lopez et al, 2016; Nakamura; Jaffe; Swerdlow, 2017). The prognosis of EBV-positive DLBCL NOS differs significantly regarding the age of the affected patient. By using a cut-off value of 45 years, younger patients are likely to present a better prognosis in comparison with older individuals (Oyama et al, 2007; Dojcinov et al, 2011; Nicolae et al, 2015; Uccini et al, 2015). We were unable to assess the role of EBV in the patients' outcome due to the small number of EBV-positive cases in our sample, nevertheless, we observed that the 23-year old patient was alive after 29 months of follow-up, whereas the 54-year-old patient died less than one month after the diagnosis. The 29-year-old patient was lost to follow-up.

Currently, the standard therapy for patients with DLBCL NOS is the combination of rituximab and CHOP (R-CHOP), which is associated with 60–65% of cure, and an overall survival of about 50% after 5 years of follow-up for nodal and extranodal cases (Castillo; Winer; Olszewski, 2014; Coleman et al, 2016; Li; Young; Medeiros, 2018). Because of the limited number of cases treated with R-CHOP in our sample, we could not investigate whether patients affected by oral/oropharyngeal DLBCL NOS would be significantly benefited with this scheme when compared to CHOP therapy.

Previous studies reported an overall 5-year survival rate for oral/oropharyngeal DLBCL NOS of 45% and 84%, respectively (Guevara-Canales et al, 2013; Rayess et al, 2017). In our recent review on oral DLBCL NOS, we observed a 5-year survival rate of 83% (Rodrigues-Fernandes et al, 2019), higher than our current original sample (53.7%). This may be related to the presence of patients in our sample that were not submitted to any treatment due to health care assistance constraints, which may have negatively impacted the survival rate of our sample.

To investigate the clinicopathological and survival aspects of oral/oropharyngeal DLBCL NOS, we needed to gather cases from different pathology institutes. However, such methodology may represent a potential limitation of this study, considering the potential heterogeneity regarding the therapeutic management used by each center. In addition, the availability of more detailed clinical data, such as clinical manifestations, systemic alterations, and longer follow-up period, would have strengthened our results.

Finally, it would be recommended for future studies on DLBCL NOS the investigation of its genetic aspects as an effort to identify cases that would fit in the more recently described entity high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements (HGBL, R) (Hsi, 2017; Scott et al, 2018; Novo et al, 2019), determining whether this genetic categorization would impact the prognosis of patients affects by oral/oropharyngeal DLBCL. Because the diagnosis of HGBL, R may be highly laborious, cost and timely consuming, and very difficult to be systematically performed in all cases, especially in developing countries, it has been recommended that cases strongly expressing Myc and Bcl2 proteins by immunohistochemistry, and also exhibiting a high proliferative index should be considered for this genetic investigation, which would be applied for some of our cases. Consequently, no agreement on the most appropriate therapeutic approach has been obtained for this new entity (Novo et al., 2019; Liu; Barta, 2019).

In conclusion, this study confirmed that oral and oropharyngeal DLBCL NOS is an aggressive neoplasm, and that some clinical (age and pain) and microscopic (Ki67 expression and predominance of immunoblasts) features may be important to negatively influence the survival of the affected patients, although they do not represent independent prognostic determinants.

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3 DISCUSSÃO

O primeiro capítulo deste estudo consistiu em uma revisão da literatura acerca do LDGCB SOE de cavidade oral, a fim de determinar suas características clinicopatológicas, além de possíveis determinantes prognósticos, e observou-se que, apesar de apresentar um comportamento agressivo, o LDGCB SOE oral estaria associado a uma alta taxa de sobrevida após 5 anos de acompanhamento, a qual poderia ser influenciada negativamente pelo avançado estágio de Ann Arbor (Rodrigues-Fernandes et al, 2019). Já o segundo capítulo teve como objetivo avaliar os aspectos clínicos, microscópicos, imunoistoquímicos e a presença do vírus EBV em uma amostra de 52 pacientes afetados pelo LDGCB SOE de cavidade oral e orofaringe, através de uma análise retrospectiva, no qual observamos um índice de sobrevida após cinco anos de acompanhamento de 53.7%, inferior ao observado em nossa revisão de literatura. Além disso, observamos uma possível influência negativa da idade, presença de dor, de um alto índice de proliferação celular medido pela expressão da proteína Ki67 e do predomínio de imunoblastos no prognóstico desses pacientes, apesar de essas variáveis terem perdido significância estatística quando avaliados dentro de um modelo de análise multivariada.

Confirmamos em ambos os capítulos que o LDGCB SOE é mais prevalente em pacientes idosos do sexo masculino, assim como descrito anteriormente (Sato et al, 2009; Owosho et al, 2014; Takano et al, 2015; Gascoyne; Campo; Jaffe, 2017). Apesar de ainda não ter sido descrita uma associação significativa entre o sexo dos pacientes e a ocorrência de morte do paciente, pudemos observar a influência da idade destes indivíduos, concordando com estudos prévios (Møller; Pedersen; Christensen, 2003; Guevara-Canales et al, 2013; Rayess et al, 2017).

Aproximadamente 40% dos casos de LDGCB SOE envolvem sítios extranodais (Kolokotronis et al, 2005; Han et al, 2017; Li; Young; Medeiros, 2018); quando consideramos apenas os tecidos da cavidade oral, a revisão sistemática demonstrou que a gengiva foi o sítio mais acometido, seguido pelo palato, enquanto que em nossa amostra de 52 pacientes observamos uma maior incidência no palato, conforme descrito anteriormente em um estudo com LDGCB em estágio inicial (Mian et al, 2014; Rodrigues-Fernandes et al, 2019). Entretanto, vale ressaltar que muitos casos são diagnosticados apresentando grandes dimensões, podendo acometer tanto o palato quanto a gengiva/rebordo alveolar simultaneamente, o que poderia influenciar a

frequência específica de cada localização em nossos dados de revisão, uma vez que muitos casos relatados não exibiam as imagens clínicas.

Clinicamente, o LDGCB SOE apresenta-se como um tumor de crescimento rápido, com ou sem ulceração, e áreas de necrose tecidual, podendo simular a apresentação clínica de outras neoplasias malignas da cavidade oral e orofaringe (Li; Young; Medeiros, 2018). Como demonstrado na literatura, a maioria dos pacientes de nossa amostra apresentou tumores de rápido crescimento, assintomáticos ou com presença de dor, a qual foi correlacionada significativamente com um uma menor taxa de sobrevida, achado este que não havia sido descrito na literatura e que ainda carece de uma melhor compreensão do ponto de vista biológico (van der Waal et al, 2005; Sato et al, 2009; Guevara-Canales et al, 2013; Triantafillidou et al, 2012; Picard et al, 2015). Apesar de estudos prévios terem observado que a presença de sintomas B é incomum, porém associada a um prognóstico desfavorável no LDGCB SOE extranodal, tal informação clínica não estava disponível em nossa amostra de 52 casos, o que impossibilitou a realização de uma análise comparativa (Triantafillidou et al, 2012; Martelli et al, 2013; Rayess et al, 2017; Gascoyne; Campo; Jaffe, 2017).

O diagnóstico microscópico do LDGCB SOE consiste na combinação de achados histológicos, os quais incluem a presença de uma proliferação difusa de centroblastos e imunoblastos, e immunoistoquímicos, com positividade forte e difusa para marcadores de linfócitos B e negatividade para os de linfócitos T (Xie; Pittaluga; Jaffe, 2015; Ott et al, 2017; Li; Young; Medeiros, 2018). Haja vista a necessidade de um amplo painel imunoistoquímico para confirmação do diagnóstico de LDGCB SOE, bem como para exclusão de outros diagnósticos diferenciais, observamos que muitos dos casos relatados na literatura e que fizeram parte de nosso primeiro capítulo não exibiam todos os marcadores necessários para confirmação diagnóstica, o que diminui a confiabilidade de alguns casos relatados. Com o objetivo de diminuir esse viés, consideramos apenas os casos que relataram positividade para CD20 e negatividade para marcadores de células T, mesmo entendendo que outros marcadores necessitam estar relatados. (Rodrigues-Fernandes et al, 2019). Vale ressaltar a necessidade de se investigar a presença de translocações envolvendo os genes MYC, BCL2 e/ou BCL6, com o objetivo de determinar a possível presença de linfomas de células B de alto grau, o que não foi possível ser realizado em nossa amostra e que ainda não foi relatado na literatura no contexto de linfomas oral e de orofaringe (Merron; Davies, 2018; Scott et al, 2018).

Previamente designado como LDGCB EBV-positivo do idoso, a última atualização da Organização Mundial de Saúde (2017) modificou essa terminologia para LDGCB EBV-positivo SOE, dada a crescente quantidade de casos reportados envolvendo pacientes jovens (Nakamura; Jaffe; Swerdlow, 2017), o que também foi observado em nossa amostra, a qual incluiu dois pacientes com 23 e 29 anos, respectivamente. Observamos também a baixa frequência de casos de linfoma difuso oral/orofaríngeo associados ao EBV e, por conta disso, não foi possível determinar o papel desse vírus na sobrevida dos pacientes, apesar de a literatura relatar um melhor prognóstico envolvendo pacientes mais jovens (Oyama et al, 2007; Dojcinov et al, 2011; Nicolae et al, 2015; Uccini et al, 2015).

Graças à introdução do anticorpo monoclonal rituximabe, o padrão-ouro para o tratamento do LDGCB SOE consiste na combinação deste agente com o regime CHOP (ciclofosfamida, doxorrubicina, vincristina e prednisona), resultando em taxas de cura superiores a 60% (Castillo; Winer; Olszewski, 2014; Coleman et al, 2016; Li; Young; Medeiros, 2018). Por conta da pequena parcela de casos em nossa amostra que reportaram a utilização dessa modalidade terapêutica, não conseguimos investigar o valor prognóstico do R-CHOP nos casos de LDGCB SOE oral/orofaríngeo e seu potencial benefício em relação ao esquema composto apenas pelo CHOP (Rodrigues-Fernandes et al, 2019).

4 CONCLUSÃO

O presente estudo confirmou que o LDGCB SOE oral/orofaríngeo é uma neoplasia de alto grau agressiva, com sobrevida que varia de 53.7% a 83%. Características clínicas como idade, presença de dor e estadiamento podem influenciar negativamente a sobrevida dos pacientes, assim como o índice proliferativo e a predominância de imunoblastos presentes nos achados microscópicos.

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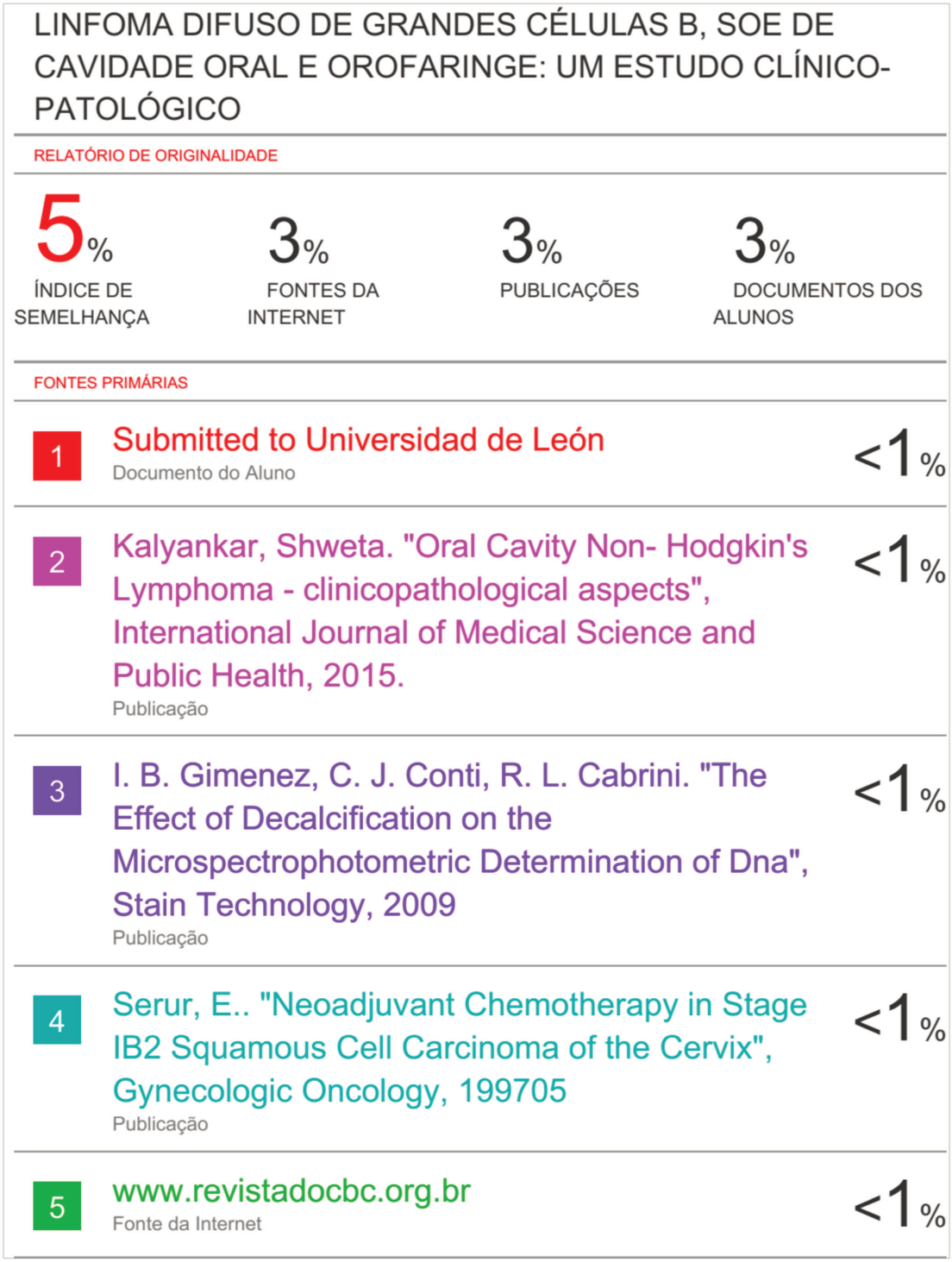
ANEXOS

Anexo 1 – Verificação de originalidade e prevenção de plágio



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CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa "Análise clinicopatológica e imunoistoquímica das hiperplasias linfoides e dos linfomas da cavidade oral", CAAE 67128417.4.0000.5418, dos pesquisadores Celeste Sánchez Romero, Oslei Paes de Almeida, Carla Isabelly Rodrigues Fernandes e Felipe Paiva Fonseca, satisfaz as exigências das resoluções específicas sobre ética em pesquisa com seres humanos do Conselho Nacional de Saúde – Ministério da Saúde e foi aprovado por este comitê em sua versão original 26/06/2017 e na versão emendada em 01/11/2017.

The Research Ethics Committee of the Piracicaba Dental School of the University of Campinas (FOP-UNICAMP) certifies that research project "Clinicopathological and immunohistochemical analysis of follicular lymphoid hyperplasias and lymphomas of the oral cavity", CAAE 67128417.4.0000.5418, of the researcher's Celeste Sánchez Romero, Oslei Paes de Almeida, Carla Isabelly Rodrigues Fernandes and Felipe Paiva Fonseca, meets the requirements of the specific resolutions on ethics in research with human beings of the National Health Council - Ministry of Health, and was approved by this committee on 26th of June of 2017 (original version) and 01nd of November of 2017 (amended version).

Profa. Fernanda Miori Pascon

Vice Coordenador
CEP/FOP/UNICAMP

Prof. Jacks Jorge Junior

Coordenador
CEP/FOP/UNICAMP

Nota: O título do protocolo e a lista de autores aparecem como fornecidos pelos pesquisadores, sem qualquer edição.
Notice: The title and the list of researchers of the project appears as provided by the authors, without editing.

Anexo 3 – Página inicial do artigo

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INVITED REVIEW

WILEY Journal of Oral Pathology & Medicine

Clinicopathological analysis of oral diffuse large B-cell lymphoma, NOS: A systematic review

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Background: Diffuse large B-cell lymphoma, NOS (DLBCL NOS) is the commonest extranodal non-Hodgkin lymphoma diagnosed in the oral and maxillofacial region. However, few studies are currently available and its prognostic determinants remain undefined.

Purpose: To analyse the available data on oral DLBCL NOS and to describe its clinicopathological features, identifying potential prognostic factors.

Methods: An electronic systematic search was performed using multiple databases with a specific search strategy in April 2018. All reports describing DLBCL NOS involving the oral cavity and jaw bones with sufficient clinicopathological information were assessed.

Results: Sixty-three publications were included in the study, comprising 122 cases. Oral DLBCL NOS was found predominantly in elderly males (61.5%), and most often presented as an asymptomatic swelling of the gingiva. Patients commonly were HIV-negative (36.1%), with few reports describing EBV-positive cases (four cases/3.3%). Only eight cases presented B symptoms and most cases were classified as stage I or II (48.4%). CHOP therapy was the main treatment option (24.5%) and the overall 5-year survival rate achieved 83%. Males and advanced Ann Arbor stage patients presented significantly lower survival rates in the univariate analysis, but no significance was found in the multivariate model.

Conclusion: Oral DLBCL NOS is an aggressive malignancy, but with a high survival rate.

KEYWORDS
diffuse large B-cell lymphoma NOS, lymphoma, mandible, maxilla, oral cavity

1 | INTRODUCTION

Among all non-Hodgkin lymphomas (NHL) subtypes affecting the oral cavity and the jaw bones, diffuse large B cell lymphoma, not otherwise specified (DLBCL NOS) is the most frequent,[1–3] representing an aggressive neoplasm of medium to large B lymphoid cells that comprises 30%-35% of adult NHL worldwide, but its etiology remains uncertain.[3,4] Although most patients do not have underlying risk factors and the tumors may arise *de novo*, some cases represent a high-grade transformation of a less aggressive lymphoma or may occur in the setting of an immunodeficiency.[4,5]

Recent changes in the WHO classification of hematolymphoid tumors have defined new entities that are now classified separately from DLBCL NOS. Those cases demonstrating positivity to

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