

UNIVERSIDADE DE BRASÍLIA
Faculdade de Ciências da Saúde
Departamento de Odontologia



Trabalho de Conclusão de Curso

**Variações morfológicas no canal da mandíbula em pacientes com
linfoma: uma revisão sistemática**

Bianca de Almeida Azevedo

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Trabalho de Conclusão de Curso apresentado ao Departamento de Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília, como requisito parcial para a conclusão do curso de Graduação em Odontologia.

Orientador: Prof^a. Dr^a. Nilce Santos de Melo

Co-orientador: Prof^a. Dr^a. Cristine Miron Stefani

Brasília

2023

Bianca de Almeida Azevedo

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Banca examinadora:

Prof^a. Dr^a. Carla Ruffeil Moreira Mesquita

Prof^a. Dr^a. Nilce Santos de Melo

Prof. Dr. Sérgio Bruzadelli Macedo

Aos pacientes com câncer.

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"Do mesmo modo que o metal enferruja com a ociosidade e a água parada perde sua pureza, assim a inércia esgota a energia da mente. "

Leonardo da Vinci

RESUMO

DE ALMEIDA AZEVEDO, Bianca. Variações morfológicas no canal da mandíbula em pacientes com linfoma: uma revisão sistemática. 2023. Trabalho de Conclusão de Curso (Graduação em Odontologia) – Departamento de Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília.

Introdução: Variações anatômicas no canal da mandíbula (CM) ocorrem com frequência e podem sugerir alterações causadas por condições locais e/ou sistêmicas, apresentando, inclusive, neoplasias malignas. Entre as possíveis malignidades que podem estar associadas às variações morfológicas no CM, estão os linfomas. Embora os linfomas constituam apenas 3,5% de todas as neoplasias intraorais, eles ainda são a segunda neoplasia mais comum de cabeça e pescoço. **Objetivo:** Este estudo visa identificar e relacionar alterações radiográficas morfológicas no canal da mandíbula em pacientes com linfoma, facilitando a suspeição clínica por parte dos dentistas, levando ao diagnóstico precoce, no que é configurado um screening de oportunidade. **Métodos:** O acrônimo PEOS (Participantes, Exposição, Resultados, Estudos) foi utilizado para formular a questão desta RS. Estratégias de busca foram desenvolvidas para as bases de dados PubMed/MedLine, EMBASE, SCOPUS, Web of Science e LILACS. Também realizada na literatura cinzenta no LIVIVO (exceto MedLine), ProQuest Dissertations & Theses Global: Health & Medicine e Google Scholar. A busca ocorreu em 24 de março de 2022, incluindo pacientes submetidos a exames radiológicos odontológicos apresentando variações morfológicas no CM associadas ao linfoma. Foram excluídos estudos que incluíam exclusivamente crianças; variações morfológicas no CM associadas a doenças locais ou neoplasias que não o linfoma; pacientes com diagnóstico ou suspeita de linfoma que não apresentassem variações morfológicas no CM; pacientes sem diagnóstico de linfoma; pacientes sem possibilidade de avaliação do CM; revisões, opiniões, capítulos de livros, protocolos de estudos, estudos pré-clínicos e ensaios clínicos. O processo de seleção dos artigos foi realizado em duas fases. Na primeira, dois revisores aplicaram os critérios de elegibilidade aos títulos e resumos de todas as referências e, na segunda, os critérios foram aplicados aos textos completos. O primeiro revisor coletou as informações necessárias dos estudos selecionados - características do estudo

e da população, avaliação e diagnóstico - e o segundo revisor confirmou a precisão das informações. Quaisquer controvérsias foram discutidas e decididas entre os dois revisores. Um protocolo de estudo foi elaborado e registrado no Open Science Framework (OSF) sob o identificador: DOI 10.17605/OSF.IO/XS9T2.

Resultados: 19 pacientes com linfoma foram considerados relevantes para esta RS. Foram incluídos dezesseis relatos de casos, uma série de caso e dois estudos de prevalência publicados entre 1992 e 2022. A variação morfológica mais visualizada radiograficamente foi o alargamento do CM, em cerca de 58% dos pacientes. Outras alterações relatadas foram: lesões líticas envolvendo o forame e/ou o CM, perda dos limites do CM, lesão expansiva do corpo direito da mandíbula, envolvendo canal e nervo mandibulares, reabsorção marginal do CM e envolvimento linfomatoso do nervo mandibular direito. Os sinais e sintomas mais frequentes foram hipoestesia em 68% dos pacientes, edema em 42% e dor em 36%.

Conclusão: Alterações radiográficas morfológicas no CM foram encontradas em pacientes com linfoma, em destaque o seu alargamento. Dos dezenove estudos incluídos nesta RS, dezesseis obtiveram o diagnóstico de linfoma após a avaliação odontológica, o que sugere que as alterações morfológicas no CM devem sempre ser procuradas para que o cirurgião dentista suspeite e incite um diagnóstico precoce.

Palavras-chave:

Canal da mandíbula; Radiografia dentária; Linfoma.

ABSTRACT

DE ALMEIDA AZEVEDO, Bianca. Morphological changes in the mandibular canal in patients with lymphoma: a systematic review. 2023. Undergraduate Course Final Monograph (Undergraduate Course in Dentistry) – Department of Dentistry, School of Health Sciences, University of Brasília.

Introduction: Anatomical variations in the mandibular canal (MC) occur frequently and may suggest alterations caused by local and/or systemic conditions, including malignant neoplasms. Among the possible malignancies that may be associated with morphological variations in the MC are lymphomas. Although lymphomas constitute only 3.5% of all intraoral neoplasms, they are still the second most common neoplasm of the head and neck. **Objective:** This study aims to identify and relate morphological radiographic changes in the mandibular canal in patients with lymphoma, facilitating clinical suspicion on the part of the dental general practitioner, leading to early diagnosis, which is configured as opportunity screening. **Methods:** The acronym PEOS (Participants, Exposition, Outcomes, Studies) was used to formulate the question of this SR. Search strategies were developed for PubMed/MedLine, EMBASE, SCOPUS, Web of Science and LILACS databases. It was also performed in the gray literature in LIVIVO (except MedLine), ProQuest Dissertations & Theses Global: Health & Medicine and Google Scholar. The search was performed on March 24, 2022, including patients undergoing dental radiological examinations showing morphological variations in the MC associated with lymphoma. Studies that exclusively included children were excluded; morphological variations in the mandibular canal associated with local diseases or neoplasms other than lymphoma; patients with diagnosis or suspicion of lymphoma who did not present morphological variations in the MC; patients without a diagnosis of lymphoma; patients with no possibility of MC evaluation; reviews, letters, opinions, book chapters, study protocols, preclinical studies, and clinical trials. The article selection process was carried out in two phases. In the first, two reviewers applied the eligibility criteria to the titles and abstracts of all references and, in the second, the criteria were applied to the full texts. The first reviewer collected the necessary information from the selected studies - study and population characteristics, assessment and

diagnosis - and the second reviewer confirmed the accuracy of the information. Any disputes were discussed and resolved between the two reviewers. A study protocol was elaborated and registered in the Open Science Framework (OSF) under the identifier: DOI 10.17605/OSF.IO/XS9T2. **Results:** 19 patients with lymphoma were considered relevant for this SR. Sixteen case reports, one case series and two prevalence studies published between 1992 and 2022 were included. The most visualized morphological variation was MC enlargement, in about 58% of patients. Other changes reported were: lytic lesions involving the foramen and/or MC, loss of the limits of MC, expansive lesion of the right body of the mandible, involving the mandibular canal and nerve, marginal reabsorption of the MC and lymphomatous involvement of the right mandibular nerve. The most frequent signs and symptoms were hypoesthesia in 68% of patients, edema in 42% and pain in 36%. **Conclusion:** morphological radiographic changes in the mandibular canal were found in patients with lymphoma, highlighting its enlargement. Of the nineteen studies included in this SR, sixteen were diagnosed with lymphoma after dental evaluation, which suggests that morphological alterations in the MC should always be looked for the dentist to suspect and encourage an early diagnosis.

Keywords:

Mandibular canal; Radiography, Dental; Lymphoma.

SUMMARY

TITLE PAGE	12
ABSTRACT	13
1. INTRODUCTION	14
2. MATERIALS AND METHODS	15
2.1 PROTOCOL AND REGISTRATION	15
2.2 ELIGIBILITY CRITERIA	15
2.3 INFORMATION SOURCES AND SEARCH STRATEGY	16
2.4 SELECTION PROCESS	17
2.5 DATA COLLECTION PROCESS AND DATA ITEMS	17
2.6 METHODOLOGICAL QUALITY ANALYSIS	18
3. RESULTS	18
3.1 STUDY SELECTION	18
3.2 STUDY CHARACTERISTICS	18
3.3 METHODOLOGICAL QUALITY ANALYSIS	26
4. DISCUSSION	26
5. CONCLUSION	30
6. ACKNOWLEDGEMENTS	30
REFERENCES	31
APPENDIX I – DATABASE SEARCH STRATEGY	35
APPENDIX II – EXCLUDED ARTICLES AND REASONS FOR EXCLUSION	41
APPENDIX III – METHODOLOGICAL QUALITY ANALYSIS IN INDIVIDUAL STUDIES	45
ANNEX I– GUIDE FOR AUTHORS	48

TITLE PAGE

Variações morfológicas no canal da mandíbula em pacientes com linfoma: uma revisão sistemática

Morphological changes in the mandibular canal in patients with lymphoma: a systematic review

Bianca de Almeida Azevedo¹

Yuri Silvestre Barbosa¹

Paulo Tadeu de Souza Figueiredo²

Carla Ruffeil Moreira Mesquita²

André Ferreira Leite²

Adriano de Almeida de Lima²

Cristine Miron Stefani²

Nilce Santos de Melo²

¹ Health Sciences Faculty, University of Brasília, Brasília, Brazil.

² PhD, Professor at Department of Dentistry, Health Sciences Faculty, University of Brasília, Brasília, Brazil.

Correspondence author: Dr^a Nilce Santos de Melo, Health Sciences Faculty, University of Brasília, Asa Norte, Brasilia, 70910-900 DF, Brazil.

Email: nilcesantosmelo@gmail.com

ABSTRACT

Objective: This study aims to identify and relate morphological radiographic changes in the mandibular canal in patients with lymphoma, facilitating clinical suspicion on the part of the dental general practitioner.

Materials and Methods: The acronym PEOS (Participants, Exposition, Outcomes, Studies) was used to formulate the question of this Systematic Review. Search strategies were developed for PubMed/MedLine, EMBASE, SCOPUS, Web of Science and LILACS databases. It was also performed in the gray literature. The search was performed on March 24, 2022. The article selection process was carried out in two phases. A study protocol was elaborated and registered in the Open Science Framework (OSF).

Results: Sixteen case reports, one case series and two prevalence studies published between 1992 and 2022 were included. The most visualized morphological variation was enlargement of the mandibular canal, in about 58% of patients. The most frequent symptom was hypoesthesia in 68% of patients.

Conclusion: morphological radiographic changes in the mandibular canal were found in patients with lymphoma, highlighting its enlargement. Of the nineteen studies included in this SR, sixteen were diagnosed with lymphoma after dental evaluation, which suggests that morphological alterations in the MC should always be looked for the dentist to suspect and encourage an early diagnosis.

1. INTRODUCTION

Mandibular canals (MC) are anatomical structures that extend bilaterally from the mandibular foramen to the mental foramen carrying the inferior alveolar nerves, arteries, and veins. Anatomical variations in the path of the MC are not rare and may suggest changes caused by local and / or systemic conditions (1). Some lesions associated with mandibular canal variations are of a neoplastic nature; therefore, a prompt diagnosis is quite important (2). Lymphomas are among the possible malignant lesions associated with morphological changes in the MC.

The immune system malignancies are a heterogeneous group of malignant lymphomas (3), classified into two types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL mainly involves the lymph nodes, whereas 20%-30% of NHLs occur in extranodal sites (4). Of the non-Hodgkin's lymphomas in the oral cavity, 15% to 45% occur in the maxilla and mandible (5). Although lymphomas constitute only 3.5% of all intraoral malignancies, they still are the second most common neoplasms of the head and neck, second to squamous cell carcinoma (6). These tumors affect individuals of any age (7). Considering head and neck sites, primary NHL occurs more often in male patients than female, in the fifth to seventh decades of life(8).

Patients with NHL are treated with radiation therapy, chemotherapy, or a combination of the two. Higher clinical stage and higher histopathologic grade indicate a poorer prognosis. Therefore, it is important to detect the presence of these lesions in their earliest stage and differentiate them from other neoplastic or inflammatory lesions. For this purpose, radiologists should be familiar with the imaging characteristics of NHL (4).

Identifying anatomical changes in the mandibular canal strengthen dentist's role in the multidisciplinary team contributing to the interdisciplinarity of the health care network. Diagnosing a systemic pathology through oral alterations strengthens the patient's care in an integral, holistic way and enables the early establishment of a treatment. Therefore, this study aims to identify and relate morphological radiographic changes in the mandibular canal in patients with lymphoma, facilitating clinical suspicion on the part of the dental general

practitioner, leading to early diagnosis of the malignant disease, which is configured as opportunity screening.

2. MATERIALS AND METHODS

2.1 PROTOCOL AND REGISTRATION

A study protocol was elaborated based on PRISMA for systematic review protocols (PRISMA-P) (9), PROSPERO (10), University of Alberta Library guidelines (11) and COBE protocol model (12), and registered at the Open Science Framework (OSF) under the Identifier: DOI 10.17605/OSF.IO/XS9T2. This SR was reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (13).

2.2 ELIGIBILITY CRITERIA

The PEOS acronym (Participants, Exposition, Outcomes, type of Studies) was used to formulate the focused question in this SR, in which: P) Patients undergoing dental radiological examinations; E) Anatomical variations in the mandibular canal; O) Lymphoma diagnosis; S) Cohorts, Case Control, Cross-sectional, Case series and Case reports.

Inclusion criteria consisted of adolescents, adults or aged patients undergoing dental radiological examinations, such as intraoral, panoramic, cephalometric radiographs and computed tomography, presenting anatomical variations in the mandibular canal associated with lymphoma. The studies included were Cohort, Case Control, Cross-sectional, Case series and Case reports published in all languages.

The following exclusion criteria were applied: (a) Studies including exclusively children, and those including all ages for which exclusive adults/aged data extraction was not possible; (b) Anatomical variations in the mandibular canal associated with local diseases, such as odontogenic or jaw disorders or neoplasms other than lymphoma; (c) Studies including exclusively local manifestation of diseases; (d) Patients with diagnosis or suspicion of lymphoma without description of anatomical variations in the mandibular canal; (e) Patients with no lymphoma diagnosis; (f) No possibility of evaluating the

inferior alveolar nerve; (g) Reviews, letters, opinions, book chapters, conference abstracts, studies protocols (with no data available), pre-clinical studies (in vitro and in animals), clinical trials.

2.3 INFORMATION SOURCES AND SEARCH STRATEGY

Electronic search strategies were developed for five databases: PubMed (including MedLine), EMBASE, SCOPUS, Web of Science and Latin American and Caribbean Center on Health Sciences (LILACS). An additional grey literature search was performed on LIVIVO (except MedLine), ProQuest Dissertations & Theses Global: Health & Medicine and Google Scholar. Furthermore, hand-searches were performed on the reference list of included articles (Figure 1).

MeSH Terms and free terms were based on the PEOS acronym, wherein “P” referred to dental radiological examination: Radiography, Dental; Cone-Beam Computed Tomography; Radiography, Panoramic. The “E” was referred to mandibular canal: Mandibular canal; Inferior alveolar nerve. The “O” was referred to lymphoma: Lymphoma; Lymphoma, Non-Hodgkin. The types of studies (“S”) were not used as terms for the search. Between each term the Boolean Operator “OR” was used, and to connect the different topics the Boolean Operator “AND” was used.

More information concerning MeSH Terms, free terms used, and word combinations are available in Appendix 1. A reference manager software (Mendeley) was used to collect references and exclude duplicates.

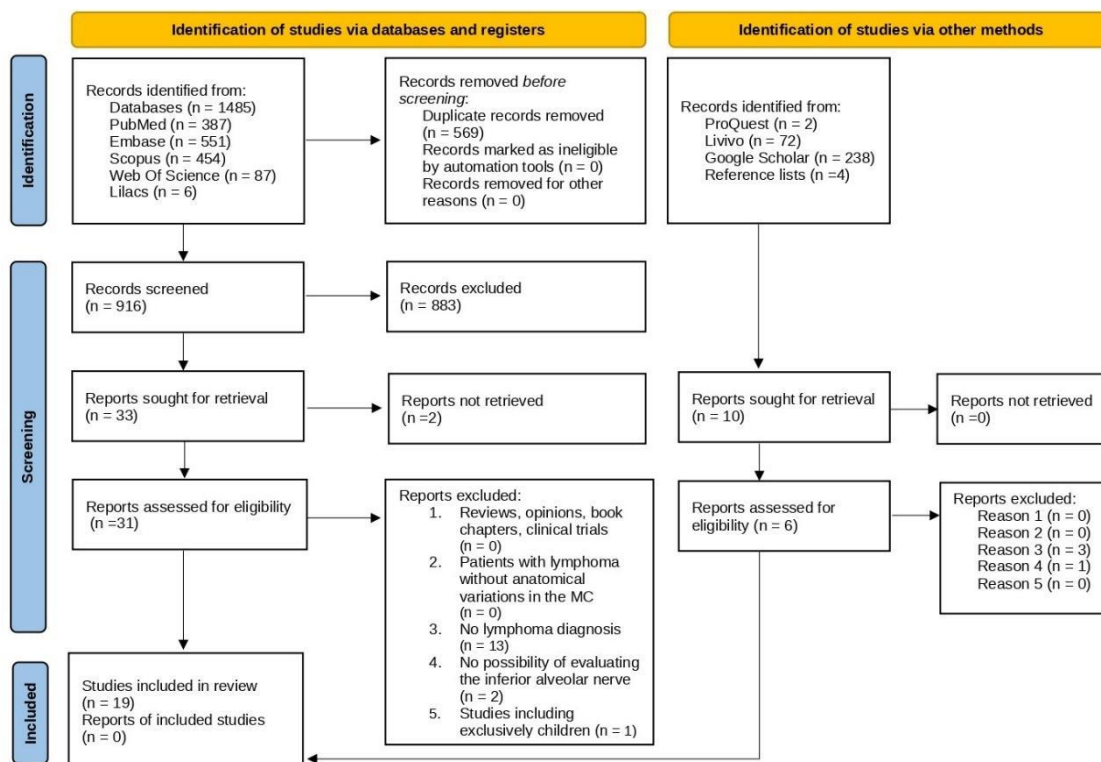


Figure 1: flow diagram of literature search and selection criteria. Based on PRISMA 2020 flow diagram for new systematic reviews.

2.4 SELECTION PROCESS

The selection process was conducted in two phases. In phase one, two reviewers (BAA and YSB) independently screened titles and abstracts of all identified references. The studies that did not fulfill the eligibility criteria were excluded. In phase two, the same two reviewers applied the eligibility criteria to the full-text of the studies selected in phase 1. A third reviewer (PTSF) was consulted in the event of a disagreement not solved by a consensus discussion. The reference manager software Rayyan was used in this process.

2.5 DATA COLLECTION PROCESS AND DATA ITEMS

The first reviewer (BAA) collected the required information from the selected studies. A second reviewer (YSB) confirmed the accuracy of the information collected. Any controversies were discussed and decided between the two reviewers. Data collected consisted of study characteristics (authors, year of publication, country, study design), population characteristics (sample

size, age range of participants, gender), case evaluation (radiographic examination, anatomical variations in the mandibular canal, clinical signs and symptoms) and diagnosis (previous diagnosis of lymphoma, posterior diagnosis of lymphoma, differential diagnosis).

2.6 METHODOLOGICAL QUALITY ANALYSIS

The methodological quality analysis of individual studies was assessed through the Joanna Briggs Institute Critical Appraisal Checklist (14) for Case Reports (15), Checklist for Case Series (16) and Checklist for Prevalence Studies (17). Two reviewers (BAA; YSB) separately performed the appraisal assigning “yes”, “no”, “unclear” or “not applicable” to each question of the checklist. A conference between the two reviewers was made, and any discordance was discussed and decided between themselves. Detailed information concerning the appraisal of the included studies quality is available in Appendix 3.

3. RESULTS

3.1 STUDY SELECTION

From 1485 references identified from main electronic databases, 916 studies remained after removing duplicated records. In addition, 312 studies were identified from the grey literature, and 4 were included by hand-searching reference lists. All database searches were performed on 24th March 2022. At the end of phase 1, 43 references were considered for eligibility, of which 19 were finally included after full-text reading. The excluded studies list with reasons for exclusion is available in Appendix 2.

3.2 STUDY CHARACTERISTICS

Sixteen case reports, one case series and two prevalence studies published between 1992 and 2022 were included, of which three were conducted in Brazil(8)(7)(18), one in Greece(6), two in India(19)(20), one in Iran(21), two in Italy(22)(23), three in Japan(4)(24)(25), one in Serbia(3), one in Singapore(26), two in the UK(27)(28) and three in the USA(5)(29)(30).

Overall, 51 participants with lymphoma were analyzed in these studies; however, 19 were considered relevant to this RS. Michi et al.(24) had a sample size of 2748 patients with malignant tumors of the mouth and jaws, of which 27 were diagnosed with lymphoma and only one patient (patient number 25, a 45 years old male) presented the characteristics of the inclusion criteria. Imaizumi et al.(4) and Pazoki et al.(30) had a sample size of 4 patients each, yet only one of each (patient number 2 – a 19 years old male- and case 1 – a 58 years old female-, respectively) was included in the analysis in accordance to the eligibility criteria.

The mean age of the examined patients was 49,6 years (19-91) and the proportion between male and female genders was 2,6:1, respectively.

The most used radiographic exams for evaluation of the maxillomandibular complex were Panoramic Radiograph (25)(26)(18)(30)(7)(8)(21)(24)(4)(6)(23)(3)(22)(5) and Computed Tomography Scan (19)(5)(22)(3)(23)(29)(6)(4)(24)(21)(8)(7)(30)(25) equally requested (fourteen cases each), followed by magnetic resonance imaging (4)(25)(28)(20)(27)(23) (six cases) and Neurography (20) and lateral teleradiography (8) with one case each.

The anatomical variations in the mandibular canal radiographically visualized were: widening/enlargement of the mandibular canal and/or foramen(8)(20)(21)(22)(25)(3)(26)(27) (5)(29)(30), lytic lesions involving the foramen and/or the mandibular canal (18)(6)(19), loss of the limits of the mandibular canal (7)(4), expansive lesion of the right body of the mandible, involving the mandibular canal and nerve (23), marginal resorption of the mandibular canal (24) and lymphomatous involvement of the right mandibular nerve (28).

Regarding the clinical signs and symptoms, hypoesthesia (18)(19)(22)(20)(21)(4)(24)(26)(27)(28)(5)(29)(30), swelling (7)(18)(21)(24)(25)(3)(27)(30) and pain (7)(20)(21)(23)(4)(24)(3) were the dominant complaint. Lymphadenopathy(5), fatigue and malaise(29) and mobile teeth(18)(6) was also conditions found in the patients reported.

Three patients presented a previous diagnosis of lymphoma(19)(20)(5), which means that the anatomical variations in the mandibular canal were found later

on, with the disease already installed and diagnosed. Sixteen patients had a posterior diagnosis of lymphoma (8)(7)(18)(6)(21)(22)(23)(4)(24)(25)(3)(26)(27)(28)(29)(30), meaning that the finding of a variation of normality in the mandibular canal may have been a key factor for the diagnosis of a malignant systemic disease.

Jaws lymphomas do not have any specific clinical and radiological features therefore, some authors have reported some differential diagnoses when facing patients with lymphomas, such as jaw metastases and intracranial involvement of the mandibular nerve by lesions at the base of the skull(19), leptomenigeal seeding(19), dental infection(19)(23), periodontal disease(6), Bell's palsy(27), benign and malignant neoplasms of the inferior mandibular nerves(20), osteosarcoma(7)(20), systemic infiltrative disorders(20), malignant tumor(18)(24), benign tumor(24)(25), Neurofibromatosis(8)(21), malformations(8)(21)(25), endocrine neoplasia(8)(21), hemangioma(8), malignant lymphangioma(8), osteomyelitis(26).

A summary of the descriptive characteristics of included articles is presented in Table 1.

Table 1: Summary of descriptive characteristics of included studies

Study characteristics		Sample			Evaluation			Diagnosis		
Author/Year/ Country	Study design	N	Age range	Gender	Radiographic examination	Anatomical variations in the mandibular canal	Clinical signs and symptoms	Previous diagnosis of lymphoma	Posterior diagnosis of lymphoma	Differential diagnosis
Balamurugan et. al 2017 India	Case report	1	61	M	CT	Lytic lesions involving the foramen and the mandibular canal	Hypoesthesia in mandibular division of Trigeminal Nerve	Yes Non-Hodgkin lymphoma	-	Jaw metastases; leptomeningeal seeding; dental infection
Barber et. al 1992 USA	Case report	1	40	M	PR CT	Widening of the right inferior alveolar canal and mental foramen	Numbness of the lower lip and jaw; bilateral cervical lymphadenopathy	Yes Non-Hodgkin lymphoma	-	-
Bertolotto et. al 1996 Italy	Case report	1	32	NR	PR CT	Widening of the right mandibular canal with ill-defined margins	Numbness of the jaw and paresthesia in the region of the right mandibular nerve	No	Diffuse large-cell Non-Hodgkin lymphoma of the B-line	-
Burić et. al 2010 Serbia	Case report	1	57	M	PR CT	Uniform enlargement of the mandibular canal	Painful and rapidly progressive swelling involving the left mandible	No	Primary B-cell non-Hodgkin's lymphoma	-

Study characteristics		Sample			Evaluation			Diagnosis		
Author/Year/ Country	Study design	N	Age range	Gender	Radiographic examination	Anatomical variations in the mandibular canal	Clinical signs and symptoms	Previous diagnosis of lymphoma	Posterior diagnosis of lymphoma	Differential diagnosis
Catania et. al 2021 Italy	Case report	1	91	F	PR CT MRI	Expansive lesion of the right body of the mandible, involving the mandibular canal and nerve	Right mandibular pain	No	Diffuse large B-cell lymphoma	Odontogenic abscess
Fan et. al 2011 USA	Case report	1	51	F	CT	Larger right-side mandibular foramen	Numb sensation in right lower lip and right chin region; generalized fatigue, malaise and vague diffuse aching all over the body	No	Non-Hodgkin lymphoma	-
Goutzanis et. al 2020 Greece	Case report	1	20	M	PR CT	Extensive osteolytic lesion of the right mandibular retromolar region including the right alveolar nerve	Mobile right lower second molar	No	T-cell lymphoblastic lymphoma	Periodontal disease
Hammond et. al 2011 UK	Case report	1	80	M	PR MRI	Widening of the inferior dental nerve canal and signs of bony resorption	Soft tissue swelling emanating from parotid, and extending buccally towards the mental foramen; palsies of 7 of the 12 cranial nerves	No	Non-Hodgkin lymphoma	Bell's palsy

Study characteristics		Sample			Evaluation			Diagnosis		
Author/Year/ Country	Study design	N	Age range	Gender	Radiographic examination	Anatomical variations in the mandibular canal	Clinical signs and symptoms	Previous diagnosis of lymphoma	Posterior diagnosis of lymphoma	Differential diagnosis
Imaizumi et. al 2012 Japan	Cohort	4	6-43	F/M 2:2	PR CT MRI	Loss of the mandibular canal wall (case 2)	Pain of the left posterior mandible, numbness of the left lower lip (case 2)	No	Non-Hodgkin Lymphoma	-
Jain and Sankhe 2021 India	Case report	1	56	M	MRI Neurography	Abnormal thickened and enhancing left inferior alveolar nerve with adjacent soft tissue	Numbness, tingling sensation, and pain in the left side of jaw; numbness in the left lower lip and chin region	Yes Testicular lymphoma	-	Benign and malignant neoplasms of the inferior mandibular nerves, osteosarcoma, systemic infiltrative disorders
Michi et. al 2022 Japan	Cohort	27	37-95	F/M 8:19	PR CT	Marginal resorption of the mandibular canal Case 1 (Patient n°. 25)	Pain in the mandibular left molar area; paralysis of the left mentum region; swelling of the left side of the mandible	No	Diffuse large B-cell lymphoma	Malignant tumor, benign tumor, and inflammation
Mojaver et. al 2005 Iran	Case report	1	38	F	PR CT	Enlarged inferior alveolar canal	Pain in left mucobuccal fold and paresthesia of tongue; swelling on the left mandibular first and second premolar region.	No	B-cell lymphoma	Neurofibromatosis; arteriovenous malformation; endocrine neoplasia

Study characteristics		Sample			Evaluation			Diagnosis		
Author/Year/ Country	Study design	N	Age range	Gender	Radiographic examination	Anatomical variations in the mandibular canal	Clinical signs and symptoms	Previous diagnosis of lymphoma	Posterior diagnosis of lymphoma	Differential diagnosis
Munhoz et. al 2017 Brazil	Case report	1	39	M	PR LT CT	Enlargement of mandibular canal and mental foramen bilaterally	None	No	Non- Hodgkin lymphoma	bilateral hemangioma; malignant lymphangioma; neurofibromatosis; multiple endocrine neoplasia; arteriovenous malformation; vascular leiomyoma
Oliveira et. al 2020 Brazil	Case report	1	56	M	PR CT	Loss of the limits of the mandibular canal	Swelling and pain in left side of jaw; discrete asymmetry in mandible angle region	No	Diffuse large B-cell lymphoma	Osteosarcoma
Pazoki et. al 2003 USA	Case series	4	33 - 58	F/M 3:1	PR CT	Right mental foramen enlarged; bone trabeculation on the right side appeared relatively less dense than on the left side	Intermittent numbness of the right lower lip; swelling in the mandibular buccal vestibule in the lower right premolar region	No	B-cell malignant lymphoma	Abnormal lymphoid proliferation
Siqueira et. al 2019 Brazil	Case report	1	51	M	PR	Osteolytic lesion around the mandibular canal and the mental foramen	Mandibular swelling and paresthesia in the right body of mandible, and extensive mass and teeth mobility	No	Diffuse large B-cell lymphoma	Malignant tumor

Study characteristics		Sample			Evaluation			Diagnosis		
Author/Year/ Country	Study design	N	Age range	Gender	Radiographic examination	Anatomical variations in the mandibular canal	Clinical signs and symptoms	Previous diagnosis of lymphoma	Posterior diagnosis of lymphoma	Differential diagnosis
Teh and Saigo 2012 Singapore	Case report	1	57	M	PR	Inferior dental canal enlarged	Numbness at right lower teeth, lower lip and chin; tenderness at lower right wisdom tooth	No	B-cell Lymphoma and Follicular Lymphoma	Osteomyelitis
Vora et. al 2017 UK	Case report	1	34	M	MRI	Lymphomatous involvement of the right mandibular nerve	Right-sided perioral numbness;	No	Burkitt lymphoma	-
Yamada et. al 2000 Japan	Case report	1	59	F	PR CT MRI	Right mandibular canal widely enlarged	Swelling of the hard palate without pain; similar lesion 20 mm in length on the left floor of the mouth	No	B-cell-type extranodal non- Hodgkin's lymphoma	Malformations; benign tumors

3.3 METHODOLOGICAL QUALITY ANALYSIS

For case reports, patient's demographic characteristics were clearly described only in 7 studies, about 43%. Data presentation, such as patient's age, gender, race, medical history, diagnosis, prognosis, previous treatments, past and current diagnostic test results, and medications is quite important. Collecting this information and trying to find out which demographic characteristics can lead to a greater suspicion for the diagnosis of lymphoma is a key point in this study. The fact that only 7 studies clearly reported these characteristics may bring a bias to the data found.

All case reports presented a clear description of the current clinical condition, which is fundamental to understand the manifestation of the disease and its signs and symptoms, and all except one described in detail the diagnostic tests or methods and the results.

The interventions or treatment procedures, post-intervention clinical conditions and adverse events were considered not applicable for this RS, as the dentist does not perform treatments for malignant diseases.

For the two prevalence studies, one did not have a great sample and study participants have not been sampled appropriately, as the other one had a big sample and sampled the participants appropriately.

The one case series did not specify the inclusion criteria clearly nor reported the demographic's characteristics of the participants. On the other hand, it clearly described the clinical information of the participants and the outcomes or follow up results of cases. Additionally, the condition was measured in a reliable way.

4. DISCUSSION

This is the first systematic review searching morphological changes in the mandibular canal in patients with lymphoma aiming for screening opportunities and early diagnosis of this systemic disease in the dental general practitioner's office.

The oral and maxillofacial complex contains multiple structures that can be secondarily affected by some systemic diseases. Pachêco-Pereira et al. (31)

demonstrated that the complex trabecular microarchitecture of the mandible could be affected by systemic diseases, such as osteoporosis, osteogenesis imperfecta, diabetes mellitus and primary hyperparathyroidism, which alter the bone structure and turn over.

The morphological changes caused by the involvement of MC in Non-Hodgkin lymphoma can be given by two mechanisms: it may arise from the bone, wrap around the mandibular canal, and infiltrate into it later, or it may arise from the lymphoid tissue of the mandibular canal, grow with neural and perineural spreading, and slowly expand or destroy the surrounding bone over time. (3)

This description helps us understand the most frequent sign and symptoms in this SR. About 58% of the patients presented radiographic enlargement of the MC, 68% presented hypesthesia, 42% presented swelling and 36% presented pain, which may be related to compression caused by lymphoma infiltration in the MC with neural and perineural spreading. Concerning other radiographic signs beyond the expansion of the mandibular canal path walls, such as lytic lesions in 16% of cases, loss of the limits in 10% and marginal resorption in 5%, may be related to the arise of the lymphoma primary on the bone marrow, causing nonspecific bone erosion in the mandibular canal region.

Radiographic enlargement of the MC is a rare finding typically caused by a benign or malignant neoplastic process, especially when associated with neuropathy along the sensory distribution of the inferior alveolar nerve.(32) Nevertheless in this SR it was the most common radiographic finding in the studied patients, suggesting a possible association.

The existing literature corroborates the results found in this SR. According to Mortazavi et al. (2) oral non-Hodgkin lymphomas are often characterized by a bony swelling, which can be symptomatic or asymptomatic, as well sensory disturbance. This entity has no pathognomonic radiographic feature, but it usually manifests as a radiolucency with poorly-defined margins, loss of cortical definition, widening of the periodontal ligament, mental foramen widening, and dilation of the mandibular canal.

The enlargement of the MC must be seen as and it has to light up an alert: it can be associated with a systemic disease. The enlargement itself is not an anatomic variation, and not a pathognomonic sign, however the radiographic finding should raise the suspicion of the existence of an underlying disease, whether malignant or not (2).

The differential diagnosis for an enlarged MC includes benign or malignant tumors (NHL, osteosarcoma, schwannoma, perineurinoma, and solitary neurofibroma), osteomyelitis, lipoma, vascular malformations and hamartomatous lesions (hemangioma), iatrogenic causes, defects of bone, reactive lesions, perineural invasion or metastases from malignancies (squamous cell carcinoma, adenoid cystic carcinoma, acinic cell adenocarcinoma), or idiopathic causes. MC enlargement can also manifest as part of certain syndromes (multiple endocrine neoplasia syndromes, Proteus syndrome, acromegaly, Noonan syndrome). (32)

Despite the fact that enlargement usually results from neoplastic causes, not every malignant lesion will cause enlargement of the MC, as the other radiographic signs showed by this RS, such as lytic lesions involving the foramen and/or the mandibular canal (18)(6)(19), loss of the limits of the mandibular canal (7)(4), expansive lesion of the right body of the mandible, involving the mandibular canal and nerve (23), marginal resorption of the mandibular canal (24) and lymphomatous involvement of the right mandibular nerve (28).

Sixteen patients, about 84% of those studied, had a posterior diagnosis of lymphoma (8)(7)(18)(6)(21)(22)(23)(4)(24)(25)(3)(26)(27)(28)(29)(30), meaning that the diagnosis of the disease was only performed after evaluation by the dentist. Although we did not find a temporal agreement, our results reinforce the importance of analyzing the morphological changes of the MC, as a key element in the suspicion of systemic diseases. The early diagnosis and treatment of a malignant disease can provide the patient with money-saving, fewer disease symptoms, fewer treatment side effects, and increased survival rates since it was reported a 5-year survival rate of 50% for isolated lymphoma cases (3). Due to the severity of the disease and the great possibility of a fatal outcome, it is important to avoid delaying to a definitive diagnosis. (8)

Thereby, opportunistic screening of some systemic disorders that affect bone density via routinely obtained dental imaging is potentially a beneficial practice, since dental images are valuable diagnostic sources as these are routinely administered and relatively low-dose exposures to patients with anatomical and pathological features, being a beneficial practice (31).

Dentistry has increasingly evolved in the sense of participating in the multidisciplinary care of the patient in an integral way, that is, considering the individual as a whole, and not just examining the oral cavity. Therefore, the screening for medical conditions in a dental setting is a novel approach that could be an effective component of a disease prevention/ control strategy. Implementing screening for systemic conditions in a dental setting should be encouraged not only from a public health perspective but also as an approach to provide additional patient information that could affect the delivery of oral health care and should be an integral component of dental practice (33).

In pursuit of new methods of detecting pathological conditions and differentiating them from variations of normality, artificial intelligences have emerged to perform these analyzes automatically. Automatic tracing of the MC can provide advantages over manual tracing, as it might be more accurate and save time (34).

On the present SR we have a limitation in the evaluation of dental images, strongly influenced only by dental issues and not as a general view of the jaws. There is usually an overlap of the evaluator's focus of interest for odontogenic diseases. Additionally, the sample of patients was small, and the reporting of patients' demographic characteristics was not complete in most cases, regarding their medical, family, and psychosocial histories (including relevant genetic information), as well as the relevant past interventions and their outcomes. The fact that only 7 studies clearly reported these characteristics may bring a bias to the data found.

The number of studies found for this review and the data found suggest an association between morphological changes in the mandibular canal and lymphoma, and reinforce the importance of early diagnosis of systemic diseases. These factors can provide future diagnostic protocols in case there is a suspicion of lymphoma in a patient assisted by the dental general practitioner.

Morphological changes in the mandibular canal should always be looked for, especially its enlargement, because they may indicate the presence of serious systemic diseases, such as lymphoma. We believe that the establishment of automated CM segmentations, with the use of artificial intelligence, will be the way for the future in diagnosis.

5. CONCLUSION

The main morphological radiographic change in the mandibular canal found in this SR was the widening/enlargement of the mandibular canal and/or foramen. Of the nineteen evaluated patients included in this SR, sixteen were diagnosed with lymphoma after dental evaluation, strengthening the role of the dental general practitioner in the systemic diseases' suspicious and diagnosis, and highlighting the importance of screening opportunities in the dentist's office.

6. ACKNOWLEDGEMENTS

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APPENDIX I – DATABASE SEARCH STRATEGY

Database	Search (2022-03-24)	References (n)
<p style="text-align: center;">PubMed</p>	<p>Search: (((("Alveolar canal inferior"[All Fields] OR "Alveolar canal"[All Fields] OR "Alveolar nerve"[All Fields] OR "Inferior Alveolar Canal"[All Fields] OR "Inferior Alveolar Foramen"[All Fields] OR "Inferior alveolar nerve canal"[All Fields] OR "Inferior alveolar nerve"[All Fields] OR "Inferior dental canal"[All Fields] OR "Jaw bone neurovascularization"[All Fields] OR "jaw diseases"[All Fields] OR "jaw diseases"[MeSH Terms] OR "Jaw"[All Fields] OR "Jaw"[MeSH Terms] OR "mandible abnormalities"[All Fields] OR "mandible"[All Fields] OR "mandible"[MeSH Terms] OR "Mandibular canal"[All Fields] OR "Mandibular canal"[MeSH Terms] OR "Mandibular nerve"[All Fields] OR "Mandibular nerve"[MeSH Terms] OR "Retromolar canal"[All Fields])) AND (("African Lymphoma"[All Fields] OR "Burkitt Cell Leukemia"[All Fields] OR "Burkitt Leukemia"[All Fields] OR "Burkitt Lymphoma"[All Fields] OR "Burkitt Lymphoma"[MeSH Terms] OR "Burkitt Tumor"[All Fields] OR "Burkitts Leukemia"[All Fields] OR "Burkitt's Leukemia"[All Fields] OR "Burkitts Lymphoma"[All Fields] OR "Burkitt's Tumor"[All Fields] OR "Diffuse Histiocytic Lymphoma"[All Fields] OR "Diffuse Large Cell Lymphoma"[All Fields] OR "Diffuse Large Lymphoid Lymphoma"[All Fields] OR "Diffuse Lymphoma"[All Fields] OR "Diffuse Mixed Cell Lymphoma"[All Fields] OR "Diffuse Mixed Small and Large Cell Lymphoma"[All Fields] OR "Diffuse Small Cleaved Cell Lymphoma"[All Fields] OR "Diffuse Undifferentiated Lymphoma"[All Fields] OR "High Grade Lymphoma"[All Fields] OR "Histiocytic Lymphoma"[All Fields] OR "Hodgkin disease"[All Fields] OR "Hodgkin disease"[MeSH Terms] OR "Intermediate Grade Lymphoma"[All Fields] OR "L3 Lymphocytic Leukemia"[All Fields] OR "Low Grade Lymphoma"[All Fields] OR "Lymphatic hyperplasia"[All Fields] OR "lymphoma B-Cell"[All Fields] OR "Lymphoma Large B-Cell Diffuse"[All Fields] OR "lymphoma Non hodgkin"[All Fields] OR "Lymphoma Nonhodgkin"[All Fields] OR "lymphoma"[All Fields] OR "lymphoma"[MeSH Terms] OR "Malignant Lymphoma"[All Fields] OR "Mixed Cell Lymphoma"[All Fields] OR "Mixed Lymphocytic Histiocytic Lymphoma"[All Fields] OR "Mixed Lymphoma"[All Fields] OR "Non-Hodgkin lymphoma"[All Fields] OR "Pleomorphic Lymphoma"[All Fields] OR "Small Non Cleaved Cell Lymphoma"[All Fields] OR "Undifferentiated Lymphoma"[All Fields]))) AND (("Bitewing radiography"[All Fields] OR "Computed tomography"[All Fields] OR "cone beam computed tomography"[All Fields] OR "cone beam computed tomography"[MeSH Terms] OR "dental digital radiography"[All Fields] OR "Dental radiography"[All Fields] OR "dento maxillofacial radiology"[All Fields] OR "diagnostic imaging"[All Fields] OR "diagnostic imaging"[MeSH Terms] OR "digital dental radiography"[All Fields] OR "digital radiography dental"[All Fields] OR "magnetic resonance"[All Fields] OR "panoramic radiography"[All Fields] OR "radiograph"[All Fields] OR "radiographic"[All Fields] OR "radiographies"[All Fields] OR "radiography digital dental"[All Fields] OR "radiography"[All Fields] OR "radiography"[MeSH Terms] OR "radiographys"[All Fields] OR</p>	<p style="text-align: center;">387</p>

	"radiological"[All Fields] OR "radiology"[All Fields] OR "radiology"[MeSH Terms] OR "radiology's"[All Fields] OR "spiral cone beam computed tomography"[All Fields] OR "spiral cone beam computed tomography"[MeSH Terms] OR "x-ray tomography"[All Fields]))	
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<p>Scopus</p>	<p>TITLE-ABS-KEY (("Alveolar canal inferior" OR "Alveolar canal" OR "Alveolar nerve" OR "Inferior Alveolar Canal" OR "Inferior Alveolar Foramen" OR "Inferior alveolar nerve canal" OR "Inferior alveolar nerve" OR "Inferior dental canal" OR "Jaw bone neurovascularization" OR "jaw diseases" OR "Jaw" OR "mandible abnormalities" OR "mandible" OR "Mandibular canal" OR "Mandibular nerve" OR "Retromolar canal") AND ("African Lymphoma" OR "Burkitt Cell Leukemia" OR "Burkitt Leukemia" OR "Burkitt Lymphoma" OR "Burkitt Tumor" OR "Burkitts Leukemia" OR "Burkitt's Leukemia" OR "Burkitts Lymphoma" OR "Burkitt's Tumor" OR "Diffuse Histiocytic Lymphoma" OR "Diffuse Large Cell Lymphoma" OR "Diffuse Large Lymphoid Lymphoma" OR "Diffuse Lymphoma" OR "Diffuse Mixed Cell Lymphoma" OR "Diffuse Mixed Small and Large Cell Lymphoma" OR "Diffuse Small Cleaved Cell Lymphoma" OR "Diffuse Undifferentiated Lymphoma" OR "High Grade Lymphoma" OR "Histiocytic Lymphoma" OR "Hodgkin disease" OR "Intermediate Grade Lymphoma" OR "L3 Lymphocytic Leukemia" OR "Low Grade Lymphoma" OR "Lymphatic hyperplasia" OR "lymphoma B-Cell" OR "Lymphoma Large B-Cell Diffuse" OR "lymphoma Non hodgkin" OR "Lymphoma Nonhodgkin" OR "lymphoma" OR "Malignant Lymphoma" OR "Mixed Cell Lymphoma" OR "Mixed Lymphocytic Histiocytic Lymphoma" OR "Mixed Lymphoma" OR "Non-Hodgkin lymphoma" OR "Pleomorphic Lymphoma" OR "Small Non Cleaved Cell Lymphoma" OR "Undifferentiated Lymphoma") AND ("Bitewing radiography" OR "Computed tomography" OR "cone beam computed tomography" OR "dental digital radiography" OR "Dental radiography" OR "dento maxillofacial radiology" OR "diagnostic imaging" OR "digital dental radiography" OR "digital radiography dental" OR "magnetic resonance" OR "panoramic radiography" OR "radiograph" OR "radiographic" OR "radiographies" OR "radiography digital dental" OR "radiography" OR "radiographys" OR "radiological" OR "radiology" OR "radiology's" OR "spiral cone beam computed tomography" OR "x-ray tomography"))</p>	<p>454</p>
<p>Web of Science</p>	<p>TS=(("Alveolar canal inferior" OR "Alveolar canal" OR "Alveolar nerve" OR "Inferior Alveolar Canal" OR "Inferior Alveolar Foramen" OR "Inferior alveolar nerve canal" OR "Inferior alveolar nerve" OR "Inferior dental canal" OR "Jaw bone neurovascularization" OR "jaw diseases" OR "Jaw" OR "mandible abnormalities" OR "mandible" OR "Mandibular canal" OR "Mandibular nerve" OR "Retromolar canal") AND ("African Lymphoma" OR "Burkitt Cell Leukemia" OR "Burkitt Leukemia" OR "Burkitt Lymphoma" OR "Burkitt Tumor" OR "Burkitts Leukemia" OR "Burkitt's Leukemia" OR "Burkitts Lymphoma" OR "Burkitt's Tumor" OR "Diffuse Histiocytic Lymphoma" OR "Diffuse Large Cell Lymphoma" OR "Diffuse Large Lymphoid Lymphoma" OR "Diffuse Lymphoma" OR "Diffuse Mixed Cell Lymphoma" OR "Diffuse Mixed Small and Large Cell Lymphoma" OR "Diffuse Small Cleaved Cell Lymphoma" OR "Diffuse Undifferentiated Lymphoma" OR "High Grade Lymphoma" OR "Histiocytic Lymphoma" OR "Hodgkin disease" OR "Intermediate Grade Lymphoma" OR "L3 Lymphocytic Leukemia" OR "Low Grade Lymphoma" OR "Lymphatic hyperplasia" OR "lymphoma B-Cell" OR "Lymphoma Large B-Cell Diffuse" OR "lymphoma Non hodgkin" OR "Lymphoma Nonhodgkin" OR "lymphoma" OR "Malignant Lymphoma" OR "Mixed Cell Lymphoma" OR "Mixed Lymphocytic Histiocytic Lymphoma" OR "Mixed Lymphoma" OR "Non-Hodgkin lymphoma" OR</p>	<p>87</p>

	<p>"Pleomorphic Lymphoma" OR "Small Non Cleaved Cell Lymphoma" OR "Undifferentiated Lymphoma") AND ("Bitewing radiography" OR "Computed tomography" OR "cone beam computed tomography" OR "dental digital radiography" OR "Dental radiography" OR "dento maxillofacial radiology" OR "diagnostic imaging" OR "digital dental radiography" OR "digital radiography dental" OR "magnetic resonance" OR "panoramic radiography" OR "radiograph" OR "radiographic" OR "radiographies" OR "radiography digital dental" OR "radiography" OR "radiographys" OR "radiological" OR "radiology" OR "radiology's" OR "spiral cone beam computed tomography" OR "x-ray tomography"))</p>	
<p>LILACS (Portuguese and Spanish)</p>	<p>("Alveolar canal inferior" OR "Alveolar canal" OR "Alveolar nerve" OR "Inferior Alveolar Canal" OR "Inferior Alveolar Foramen" OR "Inferior alveolar nerve canal" OR "Inferior alveolar nerve" OR "Inferior dental canal" OR "Jaw bone neurovascularization" OR "jaw diseases" OR "Jaw" OR "mandible abnormalities" OR "mandible" OR "Mandibular canal" OR "Mandibular nerve" OR "Retromolar canal" OR "Doenças Maxilomandibulares" OR "Enfermedades Maxilomandibulares" OR "Arcada Osseodentária" OR "Mandíbula" OR "Nervo Mandibular" OR "Nervio Mandibular") AND ("African Lymphoma" OR "Burkitt Cell Leukemia" OR "Burkitt Leukemia" OR "Burkitt Lymphoma" OR "Burkitt Tumor" OR "Burkitts Leukemia" OR "Burkitt's Leukemia" OR "Burkitts Lymphoma" OR "Burkitt's Tumor" OR "Diffuse Histiocytic Lymphoma" OR "Diffuse Large Cell Lymphoma" OR "Diffuse Large Lymphoid Lymphoma" OR "Diffuse Lymphoma" OR "Diffuse Mixed Cell Lymphoma" OR "Diffuse Mixed Small and Large Cell Lymphoma" OR "Diffuse Small Cleaved Cell Lymphoma" OR "Diffuse Undifferentiated Lymphoma" OR "High Grade Lymphoma" OR "Histiocytic Lymphoma" OR "Hodgkin disease" OR "Intermediate Grade Lymphoma" OR "L3 Lymphocytic Leukemia" OR "Low Grade Lymphoma" OR "Lymphatic hyperplasia" OR "lymphoma B-Cell" OR "Lymphoma Large B-Cell Diffuse" OR "lymphoma Non hodgkin" OR "Lymphoma Nonhodgkin" OR "lymphoma" OR "Malignant Lymphoma" OR "Mixed Cell Lymphoma" OR "Mixed Lymphocytic Histiocytic Lymphoma" OR "Mixed Lymphoma" OR "Non-Hodgkin lymphoma" OR "Pleomorphic Lymphoma" OR "Small Non Cleaved Cell Lymphoma" OR "Undifferentiated Lymphoma" OR "Linfoma de Burkitt" OR "Doença de Hodgkin" OR "Enfermedad de Hodgkin" OR "Linfoma") AND ("Bitewing radiography" OR "Computed tomography" OR "cone beam computed tomography" OR "dental digital radiography" OR "Dental radiography" OR "dento maxillofacial radiology" OR "diagnostic imaging" OR "digital dental radiography" OR "digital radiography dental" OR "magnetic resonance" OR "panoramic radiography" OR "radiograph" OR "radiographic" OR "radiographies" OR "radiography digital dental" OR "radiography" OR "radiographys" OR "radiological" OR "radiology" OR "radiology's" OR "spiral cone beam computed tomography" OR "x-ray tomography" OR "Tomografia Computadorizada de Feixe Cônico" OR "Tomografía Computarizada de Haz Cónico" OR "Diagnóstico por Imagem" OR "Diagnóstico por Imagen" OR "Radiografía" OR "Radiografia" OR "Radiología" OR "Radiología" OR "Tomografia Computadorizada de Feixe Cônico Espiral" OR "Tomografía Computarizada de Haz Cónico Espiral")</p>	<p>6</p>

Grey Literature		
<p>LIVIVO (except Medline)</p>	<p>("Alveolar canal inferior" OR "Alveolar canal" OR "Alveolar nerve" OR "Inferior Alveolar Canal" OR "Inferior Alveolar Foramen" OR "Inferior alveolar nerve canal" OR "Inferior alveolar nerve" OR "Inferior dental canal" OR "Jaw bone neurovascularization" OR "jaw diseases" OR "Jaw" OR "mandible abnormalities" OR "mandible" OR "Mandibular canal" OR "Mandibular nerve" OR "Retromolar canal" OR "Doenças Maxilomandibulares" OR "Enfermedades Maxilomandibulares" OR "Arcada Osseodentária" OR "Mandíbula" OR "Nervo Mandibular" OR "Nervio Mandibular") AND ("African Lymphoma" OR "Burkitt Cell Leukemia" OR "Burkitt Leukemia" OR "Burkitt Lymphoma" OR "Burkitt Tumor" OR "Burkitts Leukemia" OR "Burkitt's Leukemia" OR "Burkitts Lymphoma" OR "Burkitt's Tumor" OR "Diffuse Histiocytic Lymphoma" OR "Diffuse Large Cell Lymphoma" OR "Diffuse Large Lymphoid Lymphoma" OR "Diffuse Lymphoma" OR "Diffuse Mixed Cell Lymphoma" OR "Diffuse Mixed Small and Large Cell Lymphoma" OR "Diffuse Small Cleaved Cell Lymphoma" OR "Diffuse Undifferentiated Lymphoma" OR "High Grade Lymphoma" OR "Histiocytic Lymphoma" OR "Hodgkin disease" OR "Intermediate Grade Lymphoma" OR "L3 Lymphocytic Leukemia" OR "Low Grade Lymphoma" OR "Lymphatic hyperplasia" OR "lymphoma B-Cell" OR "Lymphoma Large B-Cell Diffuse" OR "lymphoma Non hodgkin" OR "Lymphoma Nonhodgkin" OR "lymphoma" OR "Malignant Lymphoma" OR "Mixed Cell Lymphoma" OR "Mixed Lymphocytic Histiocytic Lymphoma" OR "Mixed Lymphoma" OR "Non-Hodgkin lymphoma" OR "Pleomorphic Lymphoma" OR "Small Non Cleaved Cell Lymphoma" OR "Undifferentiated Lymphoma" OR "Linfoma de Burkitt" OR "Doença de Hodgkin" OR "Enfermedad de Hodgkin" OR "Linfoma") AND ("Bitewing radiography" OR "Computed tomography" OR "cone beam computed tomography" OR "dental digital radiography" OR "Dental radiography" OR "dento maxillofacial radiology" OR "diagnostic imaging" OR "digital dental radiography" OR "digital radiography dental" OR "magnetic resonance" OR "panoramic radiography" OR "radiograph" OR "radiographic" OR "radiographies" OR "radiography digital dental" OR "radiography" OR "radiographys" OR "radiological" OR "radiology" OR "radiology's" OR "spiral cone beam computed tomography" OR "x-ray tomography" OR "Tomografia Computadorizada de Feixe Cônico" OR "Tomografía Computarizada de Haz Cónico" OR "Diagnóstico por Imagem" OR "Diagnóstico por Imagen" OR "Radiografía" OR "Radiografia" OR "Radiologia" OR "Radiología" OR "Tomografia Computadorizada de Feixe Cônico Espiral" OR "Tomografía Computarizada de Haz Cónico Espiral")</p>	72
<p>ProQuest Dissertations & Theses Global: Health & Medicine</p>	<p>noft(("Alveolar canal inferior" OR "Alveolar canal" OR "Alveolar nerve" OR "Inferior Alveolar Canal" OR "Inferior Alveolar Foramen" OR "Inferior alveolar nerve canal" OR "Inferior alveolar nerve" OR "Inferior dental canal" OR "Jaw bone neurovascularization" OR "jaw diseases" OR "Jaw" OR "mandible abnormalities" OR "mandible" OR "Mandibular canal" OR "Mandibular nerve" OR "Retromolar canal") AND ("African Lymphoma" OR "Burkitt Cell Leukemia" OR "Burkitt Leukemia" OR "Burkitt Lymphoma" OR "Burkitt Tumor" OR "Burkitts Leukemia" OR "Burkitt's Leukemia" OR "Burkitts Lymphoma" OR "Burkitt's Tumor" OR "Diffuse Histiocytic Lymphoma" OR "Diffuse Large Cell Lymphoma" OR "Diffuse Large Lymphoid Lymphoma" OR "Diffuse Lymphoma" OR "Diffuse Mixed Cell Lymphoma" OR "Diffuse Mixed Small and Large Cell</p>	2

	<p>Lymphoma" OR "Diffuse Small Cleaved Cell Lymphoma" OR "Diffuse Undifferentiated Lymphoma" OR "High Grade Lymphoma" OR "Histiocytic Lymphoma" OR "Hodgkin disease" OR "Intermediate Grade Lymphoma" OR "L3 Lymphocytic Leukemia" OR "Low Grade Lymphoma" OR "Lymphatic hyperplasia" OR "lymphoma B-Cell" OR "Lymphoma Large B-Cell Diffuse" OR "lymphoma Non hodgkin" OR "Lymphoma Nonhodgkin" OR "lymphoma" OR "Malignant Lymphoma" OR "Mixed Cell Lymphoma" OR "Mixed Lymphocytic Histiocytic Lymphoma" OR "Mixed Lymphoma" OR "Non-Hodgkin lymphoma" OR "Pleomorphic Lymphoma" OR "Small Non Cleaved Cell Lymphoma" OR "Undifferentiated Lymphoma") AND ("Bitewing radiography" OR "Computed tomography" OR "cone beam computed tomography" OR "dental digital radiography" OR "Dental radiography" OR "dento maxillofacial radiology" OR "diagnostic imaging" OR "digital dental radiography" OR "digital radiography dental" OR "magnetic resonance" OR "panoramic radiography" OR "radiograph" OR "radiographic" OR "radiographies" OR "radiography digital dental" OR "radiography" OR "radiographys" OR "radiological" OR "radiology" OR "radiology's" OR "spiral cone beam computed tomography" OR "x-ray tomography"))</p>	
Google Scholar	<p>("Alveolar canal" OR "Alveolar nerve" OR "Inferior dental canal" OR "Mandibular canal" OR "Mandibular nerve") AND ("lymphoma Non hodgkin" OR "lymphoma" OR "Malignant Lymphoma" OR "Non-Hodgkin lymphoma") AND ("Dental radiography" OR "panoramic radiography")</p>	238

**APPENDIX II – EXCLUDED ARTICLES AND REASONS FOR
EXCLUSION**

Author, Year exclusion	Reason	for
Ai et al., 2017		4
Al Mussaed, 2017		3
Ardekian et al., 1996		3
Baskaran et al., 2006		3
Benites et al., 2020		3
Bilodeau et al., 2012		3
Colella et al., 2019		3
Cortese et al., 2014		3
Dalirsani et al., 2015		5
Friedrich et al., 2019		4
Maeda et al., 2018		3
Mochizuki et al., 2015		3
Neerupakam et al., 2018		3
Okahata et al., 2014		3
Oueslati et al., 2020		3
Parker et al., 2021		3
Potier et al., 2016		3
Sodnom et al., 2021		3
Tseng et al., 2020		3
Vartiainen et al., 2008		4

- (1) Reviews letters, opinions, book chapters, conference abstracts, studies protocols (with no data available), pre-clinical studies (in vitro and in animals), clinical trials.
- (2) Patients with diagnosis or suspicion of lymphoma without description of anatomical variations in the mandibular canal;
- (3) No lymphoma diagnosis;
- (4) No possibility of evaluating the inferior alveolar nerve;
- (5) Studies including exclusively children, and those including all ages for which exclusive adults/aged data extraction is not possible.

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APPENDIX III – METHODOLOGICAL QUALITY ANALYSIS IN INDIVIDUAL STUDIES

Methodological quality analysis in case reports:

	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention or treatment procedures clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Balamurugan et. al,2017	N	N	Y	N	NA	NA	NA	Y
Barber et. al, 1992	Y	N	Y	Y	NA	NA	NA	Y
Bertolotto et. al, 1996	N	N	Y	Y	NA	NA	NA	Y
Buric' et. al, 2010	Y	Y	Y	Y	NA	NA	NA	Y
Catania et. al, 2021	N	Y	Y	Y	NA	NA	NA	Y
Fan et. al, 2011	Y	Y	Y	Y	NA	NA	NA	Y
Goutzanis et. al, 2020	N	Y	Y	Y	NA	NA	NA	Y
Hammond et. al, 2011	N	N	Y	Y	NA	NA	NA	Y

	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the interventions or treatment procedures clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Jain and Sankhe, 2021	N	Y	Y	Y	NA	NA	NA	Y
Mojaver et. al, 2005	N	N	Y	Y	NA	NA	NA	N
Munhoz et. al, 2017	Y	Y	Y	N	NA	NA	NA	Y
Oliveira et. al, 2020	N	N	Y	Y	NA	NA	NA	Y
Siqueira et. al, 2019	Y	Y	Y	Y	NA	NA	NA	Y
Teh and Saigo, 2012	Y	N	Y	Y	NA	NA	NA	Y
Vora et. al, 2017	Y	Y	Y	Y	NA	NA	NA	Y
Yamada et. al, 2000	N	N	Y	Y	NA	NA	NA	N

Yes (Y); No (N); Unclear (U); Not applicable (NA)

Methodological quality analysis in case series:

	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?
Pazoki et. al, 2003	N	Y	Y	N	N	N	Y	Y	N	NA

Methodological quality analysis in prevalence studies:

	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?
Imaizumi et. al, 2012	N	N	N	Y	N	Y	Y	NA	U
Michi et. al, 2022	Y	Y	Y	N	Y	Y	U	Y	U

ANNEX I– GUIDE FOR AUTHORS

Systematic reviews with or without meta-analyses must adhere to the PRISMA guidelines, and a PRISMA checklist and flowchart must be submitted with such papers. The word limit for Review Papers is 4,000 words, with a maximum of two tables or images and 50 references.

Language

Authors should write their manuscripts in British English using an easily readable style. Authors whose native language is not English should have a native English speaker read and correct their manuscript. Spelling and phraseology should conform to standard British usage and should be consistent throughout the paper. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

Presentation

Authors should pay special attention to the presentation of their findings so that they may be communicated clearly. The background and hypotheses underlying the study as well as its main conclusions should be clearly explained. Titles and abstracts especially should be written in language that will be readily intelligible to any scientist.

Abbreviations

Oral Diseases adheres to the conventions outlined in Units, Symbols and Abbreviations: A Guide for Medical and Scientific Editors and Authors. Non-standard abbreviations must be used three or more times and written out completely in the text when first used.

Structure

All papers submitted to *Oral Diseases* should include: Title Page, Structured Abstract, Main text, References, (Figures), (Figure Legends), (Tables)

Title Page

Should be part of the manuscript uploaded for review and include: A title of no more than 100 characters including spaces; A running title of no more than 50 characters; 3-6 keywords, Complete names and institutions for each author; Corresponding author's name, address, email address and fax number; Date of submission (and revision/resubmission)

Abstract

Limited to 200 words in length and should contain no abbreviations. The abstract should be included in the manuscript document uploaded for review as well as separately where specified in the submission process. The abstract should convey the essential purpose and message of the paper in an abbreviated form set out under: Objective(s), Subject(s) (or Materials) and Methods, Results, Conclusions(s).

References

References should be prepared according to the *Publication Manual of the American Psychological Association* (6th edition). This means in-text citations should follow the author-date method whereby the author's last name and the year of publication for the source should appear in the text, for example, (Jones, 1998). For references with three to five authors, all authors should be listed only on the first occurrence of the in-text citation, and in subsequent in-text occurrences only the first author should be listed followed by 'et al.'. The complete reference list should appear alphabetically by name at the end of the paper.

Figures

All figures and artwork must be provided in electronic format.

Unnecessary figures and parts (panels) of figures should be avoided: data presented in small tables or histograms, for instance, can generally be stated briefly in the text instead. Figures should not contain more than one panel unless the parts are logically connected.

Figures divided into parts should be labelled with a lower-case, boldface, roman letter, a, b, and so on, in the same type size as used elsewhere in the figure. Lettering in figures should be in lower-case type, with the first letter capitalized. Units should have a single space between the number and unit, and follow SI nomenclature common to a particular field. Unusual units and abbreviations should be spelled out in full or defined in the legend. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. In general visual cues (on the figures themselves) are preferred to verbal explanations in the legend (e.g. broken line, open red triangles etc).