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VITÓRIA MARIA SOUSA CRUZ

ESTUDO CLINICOPATOLÓGICO E ANÁLISE DE SOBREVIDA DO SIALOBLASTOMA: UMA REVISÃO SISTEMÁTICA

CLINICOPATHOLOGICAL STUDY AND SURVIVAL OUTCOMES OF SIALOBLASTOMA: A SYSTEMATIC REVIEW

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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. Danyel Elias da Cruz Perez

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A Comissão Julgadora dos trabalhos de Defesa de Dissertação de Mestrado, em sessão pública realizada em 28 de fevereiro de 2023, considerou a candidata VITÓRIA MARIA SOUSA CRUZ aprovada.

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“É justo que muito custe o que muito vale”

Santa Teresa de Jesus

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RESUMO

Os tumores das glândulas salivares são lesões incomuns e desafiadoras. Indivíduos com tumores malignos raros enfrentam muitos desafios associados ao diagnóstico tardio e incorreto, além de interesse mínimo de pesquisa. O objetivo deste estudo foi sintetizar os dados por meio de uma revisão sistemática a fim de integrar as informações clínico-patológicas e os resultados de sobrevida desses tumores. Uma extensa pesquisa foi realizada usando os bancos de dados MEDLINE/PubMed, EMBASE, Scopus, Web of science e literatura cinza. O risco de viés estava disponível em todos os artigos incluídos. A busca eletrônica identificou 613 referências. Após a remoção de duplicatas, restaram 366 artigos, 264 das bases de dados principais e 102 da literatura cinza. Na fase de triagem, 103 artigos foram selecionados para avaliação do texto completo. Destes, 52 estudos selecionados preencheram os critérios de elegibilidade. No total, foram avaliados 62 pacientes. Não houve predileção por sexo. A maioria das lesões acometeu a glândula parótida (n=28; 45,2%). Quanto à presença de tumor ao nascimento, 38 (77,6%) eram congênitos. Sintomas foram relatados por 8 pacientes (17,9%), apresentando-se como parestesia, paralisia ou disfagia. Vinte e três (82,1%) indivíduos eram assintomáticos. As principais suspeitas clínicas foram lesões benignas (n=15; 42,8%), sendo o hemangioma a lesão mais referida (n=5; 14,2%). Todas as lesões se apresentaram clinicamente como aumento de volume no local, medindo em média 4,5 cm. A associação síncrona com outros tumores foi observada em 8 pacientes (16,0%), 4 casos (50%) com hepatoblastomas e 4 casos (50%) com nevo organoide. O principal tratamento de escolha foi a ressecção cirúrgica (n=53; 86,9%) e a recidiva tumoral ocorreu em 20 indivíduos (35,7%). O intervalo entre o tratamento do tumor primário e a recidiva foi em média de 10,2 meses. A metástase ocorreu em 10 indivíduos (18,9%), sendo o pulmão o local mais acometido (n=6; 60,0%). No teste de log-rank, houve uma diferença significativa aumento na sobrevida associada à doença em pacientes com menos de 1 ano de idade (82,8%; [IC:317–493,7]; p=0,003), indivíduos com tumores em glândulas salivares maiores (79,4%; [IC:280,1–467,3]; p= 0,005), pacientes sem metástases (77,8%; [IC: 95,9 – 151,2]; p= 0,011), lesões encapsuladas (85,7%; [IC: 285,3 - 541,6]; p=0,0001), tumores congênitos (83,3%; [IC: 283,0 - 488,8]; p= 0,0001) e lesões sem invasão perineural

(89,5%; [IC: 117,2 - 161.1]; p= 0,035). As curvas de Kaplan-Meier estimaram a sobrevida global e a sobrevida livre de doença em 5 anos de 95,5% e 68,1%, respectivamente. No modelo multivariado de regressão de Cox, apenas a presença de metástase foi identificada como um fator prognóstico independente (hazard ratio [FC]=9,81; p=0,010). Em conclusão, os sialoblastomas são lesões raras, que usualmente apresentam bom prognóstico. Entretanto, cerca de 35% dos tumores recidivam. Histologicamente, esses tumores são caracterizados pela proliferação de células de morfologia basalóide. A principal modalidade de tratamento é a ressecção cirúrgica, contudo lesões localmente invasivas, podem provocar extensa mutilação cirúrgica.

Palavras-chave: Neoplasias de glândulas salivares; Glândula parótida; Neoplasia de Cabeça e Pescoço; Análise de Sobrevida.

ABSTRACT

Salivary gland tumors are uncommon and challenging lesions. Individuals with uncommon or rare malignant tumors face many challenges associated with late and incorrect diagnosis, in addition to minimal research interest. The aim of this study was to synthesize data through a systematic review in order to integrate clinicopathological information and survival outcomes of these tumors. An extensive search was performed using MEDLINE/PubMed, EMBASE, Scopus, Web of science, and gray literature databases. Risk of bias was available for all included articles. The electronic search identified 613 references. After removing duplicates, 366 articles remained, 264 from the main databases and 102 from the gray literature. In the screening phase, 103 articles were selected for full-text evaluation. Of these, 52 selected studies met the eligibility criteria. In total, 62 patients were evaluated. There was no sex predilection. Most lesions affected the parotid gland (n=28; 45.2%). As for the presence of tumor at birth, 38 (77.6%) were congenital. Symptoms were reported by 8 patients (17.9%), presenting as paresthesia, paralysis or dysphagia. Twenty-three (82.1%) individuals were asymptomatic. The main clinical suspicions were benign lesions (n=15; 42.8%), with hemangioma being the most referred lesion (n=5; 14.2%). All lesions presented clinically as an increase in volume at the site, measuring an average of 4.5 cm. The synchronous association with other tumors was observed in 8 patients (16.0%), 4 cases (50%) with hepatoblastomas and 4 cases (50%) with organoid nevus. The main treatment of choice was surgical resection (n=53; 86.9%) and tumor recurrence occurred in 20 individuals (35.7%). The interval between treatment of the primary tumor and recurrence was on average 10.2 months. Metastasis occurred in 10 individuals (18.9%), with the lung being the most affected site (n=6; 60.0%). In the log-rank test, there was a significant increase in disease-associated survival in patients younger than 1 year of age (82.8%; [CI: 317–493.7]; p=0.003), individuals with tumors in major salivary glands (79.4%; [CI: 280.1–467.3]; p= .005), patients without metastases (77.8%; [CI: 95.9 – 151.2]; p= .011), encapsulated lesions (85.7%; [CI: 285.3 - 541.6]; p=0.0001), congenital tumors (83.3%; [CI: 283.0 - 488.8]; p= 0.0001) and lesions without perineural invasion (89.5%; [CI: 117.2 - 161.1]; p= 0.035). Kaplan-Meier curves estimated overall survival and disease-free survival at 5 years of 95.5% and 68.1%,

respectively. In the multivariate Cox regression model, only the presence of metastasis was identified as an independent prognostic factor (hazard ratio [HR]=9.81; p=0.010). In conclusion, sialoblastomas are rare lesions that usually have a good prognosis. However, about 35% of tumors recur. Histologically, these tumors are characterized by the proliferation of cells of basaloid morphology. The main modality of treatment is surgical resection, however locally invasive lesions can cause extensive surgical mutilation.

Keywords: Sialoblastoma; Salivary glands tumors; Parotid; Head and Neck Neoplasm; Survival Analysis.

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INTRODUÇÃO

As neoplasias de glândulas salivares (NGSs) compõem um grupo de lesões distintas que possuem consideráveis sobreposições de características clínicas, histológicas e imuno-histoquímicas (Fonseca et al. 2012). As NGSs são incomuns e representam aproximadamente 3% a 5% das neoplasias que acometem a região de cabeça e pescoço (Luksic et al. 2012; Ellies et al. 2006; Vargas et al. 2002). As diversas estruturas que compõem as glândulas salivares originam um grupo diverso e multifacetado, com características clínicas quem se sobrepõem, embora possuam comportamento biológico distinto, tornando os dados moleculares amplamente necessários, uma vez que diversas lesões apresentam rearranjos específicos, possibilitando maior acurácia no diagnóstico e no manejo clínico dos pacientes (World Health Organization 2020).

Independente das oscilações nas taxas de incidências dessas neoplasias observadas em estudos ao redor do mundo, a maioria mostra que mais de 60% das lesões ocorrem em glândulas salivares maiores (Alsanie et al. 2022; da Silva et al. 2018; Jones et al. 2008). A parótida é a localização anatômica mais comum, sendo afetada em 59% dos casos, seguida pelo palato, lábio superior e glândula submandibular (Fonseca et al. 2019). A International Agency for Research on Cancer (IARC) estimou 52.799 novos casos de NGSs malignas em todo o mundo. Número que evidencia a importância da qualificação dos profissionais de saúde, cirurgiões-dentistas e médicos, para diagnóstico precoce desses tumores (Zanella et al. 2021).

As diversas estruturas que compõem as glândulas salivares possibilitam originar um diversificado grupo de lesões com comportamento biológico distinto (da Silva et al. 2018). Sendo assim, algumas NGSs podem apresentar aspectos clínicos semelhantes, o que exige cautela ao estabelecer um diagnóstico preciso. Alguns aspectos clínicos são preditores de neoplasias malignas de glândula salivar, como presença de dor, ulceração, colocação azulada e telangiectasia. Portanto, o exame completo da cavidade oral é fundamental para estabelecer um diagnóstico precoce, diminuindo a morbidade e mortalidade dos pacientes (Mariz et al. 2019).

A biópsia incisional ou punção aspirativa por agulha fina são mandatórias para o diagnóstico de NGSs, permitindo maior acurácia no diagnostico final (Melo et al., 2012; Ogawa et al. 2008). Com relação à etiopatologia das neoplasias de glândulas salivares, ainda há poucos estudos. A ampla maioria dos estudos mostra que 50-70% dos tumores são de origem benigna. Fonseca et al. (2012) realizaram um estudo clínico-patológico de 493 casos de tumores de glândulas salivares em uma população do sul do Brasil. Observaram que o adenoma pleomórfico foi o tipo histológico mais frequente (72,5%), seguido do tumor de Warthin (10,8%). O tumor maligno mais comum foi o carcinoma mucoepidermóide (7,9%%), seguido por adenocarcinoma NOS (6,6%) e carcinoma adenóide cístico (3,0%). Em um estudo multicêntrico realizado no Brasil em 2019, observou-se que a sintomatologia dolorosa estava principalmente presente em tumores malignos. Em contrapartida, os tumores benignos eram indolentes, apresentando-se assintomáticos e com crescimento lento (Fonseca et al. 2019).

As NGSs possuem maior predileção pelo sexo feminino. Entretanto, quando se considera apenas neoplasias malignas, algumas pesquisas ressaltam pequena predileção pelo sexo masculino (Torabina et al. 2014; de Oliveira et al. 2009). Em relação à idade dos pacientes, o pico de incidência de tumores de glândulas salivares é principalmente na sexta década de vida, sendo incomum em crianças e adolescentes (Silas et al. 2009). A literatura cientifica é bastante restrita quando se estuda a epidemiologia de tumores de glândula salivar, principalmente na população pediátrica. O sialoblastoma é uma doença extremamente rara, originada das células epiteliais das glândulas salivares. Na região de cabeça e pescoço, o tumor geralmente se origina nas glândulas salivares maiores, comumente na parótida, seguida das glândulas submandibulares e salivares menores (Sultan et al. 2011; Di micco et al., 2019). Embora mais de 69% dos casos descritos estejam localizados na parótida, um caso incomum afetando a pálpebra também foi relatado (Di micco et al., 2019). A apresentação clínica clássica na maioria dos casos foi um edema indolente, de expansão lenta, sem sintomatologia dolorosa (Prigent et al. 2010).

Os sialoblastomas geralmente são congênitos, afetando menos frequentemente pacientes adultos jovens (Sultan et al. 2011; Di micco et al., 2019). Morfologicamente, as

lesões apresentam proliferação neoplásica de células semelhantes às encontradas durante a embriogênese das glândulas salivares (Di micco et al., 2019; Saravakos et al. 2016). Nessa neoplasia, observam-se ninhos sólidos de células basalóides com espaços ductais e pseudoductais parcialmente formados, separados por finas bandas fibrosas (Taylor et al. 1988; Saravakos et al. 2016). As células basalóides são caracterizadas por alta relação núcleo/citoplasma, núcleos redondos a ovais, cromatina nuclear frouxa e nucléolos proeminentes, demonstrando alta atividade mitótica, além do esperado ou presumido epitélio embrionário (Cristofaro et al. 2008). O estudo de Batsakis e colaboradores em 1992 propôs critérios histológicos que se associam como preditores de mau prognóstico; estes incluíram invasão de nervos ou espaços vasculares, áreas focais de necrose, células anaplásicas e altos níveis de Ki-67.

Existem relatos na literatura demonstrando a associação sincrônica de sialoblastoma e hepatoblastoma, que é um evento extremamente incomum (Rodríguez et al. 2021). Tal ocorrência pode ser explicada devido à origem embrionária comum da glândula parótida e do fígado. Como resultado, a anormalidade afetaria as células de ambos os órgãos, levando ao surgimento de dois tumores sincrônicos, produtores de alfa-fetoproteína (AFP), em locais diferentes no mesmo paciente (Rodríguez et al. 2021). Embora ambos os tumores sejam extremamente incomuns, deve-se lembrar que podem ocorrer no mesmo paciente e que investigações apropriadas devem ser feitas para excluir hepatoblastoma em recém-nascidos com diagnóstico de sialoblastoma. Devido à sua raridade e significativa sobreposição de achados clínicos e patológicos, o diagnóstico diferencial do sialoblastoma é desafiador. Como a maioria das células tumorais apresenta aspecto basalóide, os principais diagnósticos diferenciais são o adenoma de células basais e o carcinoma adenóide cístico (CAC) (Dardick et al. 2010). No entanto, os CACs ocorrem principalmente em pacientes adultos. Além disso, o diagnóstico histológico deve excluir outros tumores malignos comuns na infância, como linfoma ou rabdomiossarcoma (Zanella et al. 2021). O painel imuno-histoquímico do sialoblastoma mostra positividade para citoqueratina em células ductais, bem como para vimentina, actina e proteína S-100 (Williams et al. 2006).

Observa-se, portanto, que a literatura é limitada devido à raridade da lesão, e o tratamento de escolha para o sialoblastoma permanece controverso. Em geral, a ressecção cirúrgica com margens livres de tumor é o tratamento de primeira linha, embora possa ser mutilante em casos de tumores grandes ou localmente invasivos. As sequelas podem ser extensas e vão desde defeitos estéticos até paralisia do nervo facial (Prigent et al. 2010; Di micco et al., 2019). Assim, torna-se relevante revisar todos os casos bem documentados de sialoblastoma já publicados, para estabelecer de forma mais clara o comportamento biológico da doença, a sobrevida dos pacientes, assim como fatores clínicos e histopatológicos preditivos de prognóstico. A seguir apresentaremos os resultados da dissertação na forma de artigo científico, que consistiu em uma revisão sistemática para estudar os aspectos clínico-patológicos e sobrevida dos casos de sialoblastoma previamente descritos.

2 ARTIGO: TITLE: Clinicopathological study and survival outcomes of sialoblastoma: a systematic review

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CONFLICT OF INTEREST STATEMENT

None.

AUTHORSHIP CONTRIBUTION STATEMENT

Vitória Maria Sousa Cruz: Conceptualization; Data curation; methodology; writing – original draft. **Éder Gerardo dos Santos Leite:** Data curation; methodology; writing – review and editing. **Brendo Vinicius Rodrigues Louredo:** Data curation; methodology; writing – review and editing. **Hélen Kaline Farias Bezerra:** Data curation; methodology; writing – review and editing. **Maria Eduarda Pérez-de-Oliveira:** Formal analysis; Investigation; methodology; writing – review and editing. **Márcio Ajudarte Lopes:** Writing – review and editing. **Pablo Agustin Vargas:** Writing – review and editing. **Alan Roger Santos-Silva**: Writing – review and editing. **Luiz Paulo Kowalski:** Writing – review and editing. **Danyel Elias da Cruz Perez:** Project administration; Supervision; Validation; Writing-review & editing.

ABSTRACT

Sialoblastoma is a rare malignant salivary gland tumor. The aim of this study was to review the available published data on sialoblastoma in a comprehensive analysis of its clinicopathologic characteristics, treatment, and outcomes. An unrestricted electronic search was performed in the following databases: MEDLINE/PubMed, EMBASE, Scopus, Web of science and gray literature databases. Eligibility criteria included publications with sufficient clinical, imaging, and histopathological information to confirm the diagnosis of sialoblastoma. Data were evaluated descriptively and analytically. A total of 52 studies met the eligibility criteria. In total, 62 patients were evaluated. There was no gender predilection, with the parotid being the most affected primary site (n=28; 45.2%). Sialoblastoma mainly affects patients at or shortly after birth (N=38; 61.3%). Congenital lesions (p=0.014), tumors located in the major salivary glands (p=0.043), patients older than 1 year (p=0.018) and occurrence of metastasis (p=0.008) were associated with the risk of recurrences. Histological features such as focal necrosis (p<0.001), presence of mitotic figures (p=0.031), perineural invasion (p=0.034) and non-encapsulated lesions (p=0.012) were also associated with recurrence. Kaplan-Meier survival curves estimated overall survival (OS) and disease-free survival (DFS) rates at 5 years of 95.5% and 68.1%, respectively. In the multivariate Cox regression model, only the presence of metastasis was identified as an independent prognostic factor (hazard ratio [HR]=9.81; p=0.010). In conclusion, no sex predilection was observed, and most cases occurred in the parotid glands. Although sialoblastoma presents good prognosis, the tumor has a high recurrence rate.

Keywords: Prognostic factors; Review; Sialoblastoma, Salivary gland neoplasm; Neoplasms.

1 INTRODUCTION

Salivary gland tumors (SGTs) are uncommon and challenging lesions because they comprise a heterogeneous group of neoplasms, with large spectrum of clinical and histopathological features and different outcomes [1]. It is estimated that around 5% of SGTs occur in the pediatric population, with neoplasms of epithelial origin being the most frequent during the first 20 years of life [2].

Sialoblastomas are rare malignant SGTs, diagnosed mainly in the neonatal period or in early childhood, originating from the epithelial cells of the salivary glands [3]. Like other rare neoplasms, they face challenges related to delay in diagnosis, nomenclature, and management, especially when associated with systemic conditions. First described in 1966 as “embryoma” by Vawter and Tefft [4], they have since undergone numerous changes in their nomenclature until Taylor suggested in 1988 the term sialoblastoma [5]. In 1996, sialoblastoma was classified as a benign tumor, but in 2005 the World Health Organization (WHO) regrouped it into a malignant tumor of the salivary glands, despite its uncertain malignant potential, remaining so until today [6].

The clinical presentation of sialoblastoma is broad and this makes difficult to distinguish it from other more frequent tumors diagnosed in this age group, such as hemangioma, lymphangioma or nerve sheath tumors [7]. Sialoblastomas most commonly affect the parotid glands and are histologically characterized by the proliferation of basaloid tumor cells [3,8]. Yet, the overall prognosis of this tumor remains controversial. About one third of sialoblastomas tends to evolve with local invasion, risk of recurrence at the primary site, and occasional regional lymph node metastasis or distant metastasis, presenting an extremely challenging course [9,10].

Individuals with uncommon malignancies face many challenges associated with late and incorrect diagnosis, limited clinical experience, and minimal research interest. As far as we know, the scientific literature lacks a critical and comprehensive analysis of sialoblastomas. It raises the question: “What are the clinicopathological profile and survival outcomes of sialoblastoma?”.

2 MATERIALS AND METHODS

2.1 Eligibility criteria

The acronym PECOS (Population, Exposure, Comparison, Outcomes and Study design) was used to formulate the focused question of this review. It considered (P) Patients of any age group, gerden, race, ethnicity, geographic location, and systemic condition; (E) Sialoblastoma located in minor or major salivary glands diagnosed by histopathological examination; (C) not applicable; (O) Clinicopathological data of sialoblastomas; and (S) observational studies (cross-sectional, cohort, case series, and case reports) evaluating the clinicopathological features of sialoblastomas published in any language.

Exclusion criteria were as follows: (1) Studies that did not evaluate the clinicopathological features of sialoblastoma; (2) Studies in which sialoblastoma data were not available for data extraction because of grouping with other diseases or other sites than salivary glands; (3) Review, protocols, short communications, personal opinions, letters, conference abstracts, and laboratory research; (4) Studies whose full texts were not available; (5) Studies with duplicate sample and (6) Studies in which the histopathological data of the sialoblastoma were not available, making it impossible to confirm the diagnosis.

2.2 Information sources and search strategy

Specific search strategies were implemented on December 17th, 2022, for each of the following databases: PubMed, Scopus, EMBASE and Web of Science. The gray literature was also screened and encompassed Google Scholar and ProQuest **(Supplementary Table S1)**. Duplicated references were removed using a reference management software (EndNote, Thomson Reuters, Toronto, Canada). No limits were applied regarding to the date and language of publications in the search strategy.

2.3 Selection process

Study selection was completed individually by two authors (VMSC and EGSL) in 2 phases. The first phase consisted in reading the titles and abstracts of screened studies on Rayyan® [11]. The studies that appeared to meet all inclusion criteria went to the second phase, in which full texts were independently read by the same two authors and the eligibility criteria were confirmed. Disagreements between the 2 initial reviewers were solved by a third reviewer (MEPO) with experience in systematic reviews.

2.4 Data collection process and data items

The information that would be extracted from the selected articles was agreed with the entire research team. Therefore, the data that best delineated the sample, as well as the outcomes were: (a) publication data (first author, year, country, journal of publication and study design); (b) Population and exposure data (sample size, patients' sex and age, anatomical location, clinical presentation, symptomatology, imaging exam, clinical diagnostic hypothesis, histopathological, immunohistochemical and genetic features, type of biopsy, occurrence of recurrence/metastasis, recurrence time, synchronous association with other tumors, treatment, follow-up time, and patients’ current status).

2.5 Risk of bias assessment

The risk of bias of individual studies was independently assessed by 2 authors (VMSC and EGSL) using Joanna Briggs Institute – University of Adelaide tool for case reports [12]. There was a calibration of the researchers before the individual evaluation of the manuscripts using 5 studies. The risk of bias was categorized as high when the study reached up to 49% “yes”; moderate when the study reached from 50% to 69% “yes”; and low when the study reached at least 70% “yes.”

2.6 Effect measures

The primary outcome of this systematic review was to assess the clinicopathological profile of sialoblastoma, which was evaluated by grouping similar features in order to provide their frequencies by percentage. Secondary outcomes were to identify potential prognostic factors and survival outcomes of sialoblastoma by Kaplan-Meier method an Cox regression analysis.

2.7 Statistical analysis

Statistical analyzes were performed using the SPSS software (IBM Corporation, Armonk, NY), version 22. Initially, a descriptive analysis of clinicopathological characteristics was performed using absolute numbers, with the respective relative frequencies distributed in percentages. The existence of associations between all variables was assessed using Pearson's chi-square test or Fisher's test. Kaplan-Meier cumulative disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) were generated. The DFS rate was calculated based on the period between the time of diagnosis and the last follow-up (disease-free) or time of disease recurrence (local recurrence). The DSS was calculated based on the time from diagnosis to the last follow-up (alive without disease) or time of death (died from disease) and the OS was based on the

time from diagnosis to the last follow-up (alive, not otherwise specified [NOS]) or time of death (died, NOS). The difference between the survival curves was investigated using the Log-Rank test. The univariate Cox proportional hazards regression model was employed to identify potential prognostic factors. A multivariate Cox regression model was created using all variables that achieved a p-value ≤ 0.10. For all tests, a significance level of 5% was used.

3 RESULTS

3.1 Study selection

The electronic search identified 613 references. After removing duplicates, 366 articles remained, 264 from the main databases and 102 from the gray literature. In the screening phase, 103 articles were selected for full-text evaluation. Of these, 51 selected studies [3,5,7–10,13–57] met the eligibility criteria. Additionally, 1 article [58] was added from a manual search of the reference lists of included studies, resulting in the inclusion of 52 articles in the qualitative synthesis. The study selection process is illustrated in **Figure S1** and the reasons for exclusion of each full-read article in phase 2 are described in **Supplementary Table S2.**

3.2 Study characteristics

The detailed data collected from each included study are described in **Supplementary Tables S3, S4 and S5.** The 52 studies were published between 1980 and 2022, 47 case reports and 5 case series. Asia concentrated the largest number of studies (n = 18 articles; 34.6%), followed by North America (n = 16 articles; 30.7%) and Europe (n = 11 articles; 21.1%). The studies were reported in 20 different countries: United States (n=15; 24.1%), Turkey (n=6; 9.6%), India (n=5; 8.0%), Mexico (n=3; 4.8%), France (n=3; 4.8%), China (n=3; 4.8%), Germany (n=2; 3.2%),

England (n=2; 43.2%), Australia (n=2; 3.2%), Argentina, Canada, Singapore, South Africa, Israel, Italy, Sweden, Switzerland, Thailand, United Kingdom and South Korea (1 case each; 1.6%). The distribution of cases by country is shown in **Figure 1.**

3.3 Clinical characteristics

The clinical characteristics are summarized in **Table 1.** In total, 62 patients were evaluated. No sex predilection was observed, with 31 (50.8%) cases occurring in females and 30 (49.2%) in males. In one case the sex was not reported [50]. Anatomical location was reported in all included cases. Most of the lesions affected the parotid gland (n = 28; 45.2%), followed by the submandibular gland (n= 18; 29.0%) **(Figure 2)**. Regarding to the presence of tumor at birth, most cases (n = 38; 77.6%) were congenital. However, this data was not reported in 13 (21.0%) cases. The mean patients' age at diagnosis was 1.46 years ± 2.87 years, ranging from 0 days (intrauterine life) to 15 years.

Twenty-three (82.1%) individuals were asymptomatic, with 8 (17.9%) patients reporting a painful lesion. Clinical diagnostic hypotheses were presented in 35 (56.4%) cases, with some of them presenting more than one hypothesis. However, only the first suggested diagnosis was considered in the analysis. The main clinical suspicions were benign lesions (n = 15; 42.8%), with hemangioma being the most reported lesion (n = 5; 14.2%). Sialoblastoma was the clinical hypothesis in only 1 case (2.8%). All lesions presented clinically as a swelling, with mean size of 4.58 ± 3.11 cm in their largest diameter, ranging from 1 cm to 15.0 cm. The tumor appeared with color alteration in 8 (50.0%) patients, ulcerated or telangiectatic surface in 11 (61.1%) cases, and firm consistency in all individuals (n = 32; 51.6%).

The type of biopsy was described in 51 (82.3%) out of the 62 cases. Excisional biopsy was the most performed (n = 29; 56.9%), followed by incisional biopsy, which was performed in 13 (25.5%) cases, of which 4 were performed in the parotid region. Fine needle aspiration (FNA) was done in just 7 (13.7%) individuals. Two (3.9%) cases had only confirmed the diagnosis of sialoblastoma by autopsy [27,34]. Synchronous association with other tumors was observed in 8 (16.0%) patients, being 4 (50.0%) cases occurring with hepatoblastomas and 4 (50.0%) cases with organoid nevus. Surgical resection (n=53; 86.9%) was the most common treatment, and tumor recurrence was reported in 20 (35.7%) individuals. The recurrence occurred after a mean time of 10.60 ± 7.37 (ranging from 3 to 31 months) of the initial treatment. In all cases of recurrence (n=20), patients underwent salvage treatment. The most common salvage treatment was surgery alone in 7 (35%) cases, followed by surgery and chemotherapy in 5 (25.5%), surgery associated with chemoradiotherapy in 5 (25%), chemotherapy alone in 2 (10%), and surgery associated with radiotherapy in 1 (5%) case.

Metastasis occurred in 10 (18.9%) patients, with the lung being the most affected site (n=6; 60.0%), followed by neck lymph nodes (n=2; 20.0%). Facial paralysis was reported in 17 (68.0%) patients because of tumor invasion of the facial nerve or sequelae resulting of surgical procedures. The follow-up time was available in 45 (72.5%) cases, ranging from 3 months to 43 years, with a mean time of 51.8 months. The patients' status was reported in 50 (80.6%) cases, showing that 4 (8.0%) individuals died of disease and 1 (2.0%) patient died of other causes.

3.4 Histopathological characteristics

Histopathological features were described in all cases **(Table 2)**. Lesions were encapsulated in 17 (27.4%) individuals and showed two main distinct histopathological patterns: cribriform (n

= 17; 27.4%) and solid (n = 14; 22.6%). The presence of basaloid cells was clearly mentioned in 61 (96.7%) cases. In addition, different microscopic features were simultaneously present in some lesions, such as: ductal structures (n=48; 77.4%), perineural invasion (n=6; 9.7%), nuclear pleomorphism (n=11; 17.7%), focal necrosis (n=20; 32.3%) and mitotic figures (n=35; 56.5%). The fibromyxoid stroma was the most observed, occurring in 28 (45.2%) tumors. Immunohistochemical markers were used in 35 (56.4%) cases, being positive for cytokeratin in 34 (54.8%) lesions, smooth-muscle actin in 23 (37.0%), and S-100 protein in 22 (35.4%) cases. The Ki-67 cell proliferation index was evaluated in 22 (35.4%) cases, with the positivity ranging from 3% to 80% of the tumor cells.

3.5 Statistical analysis

The statistical analysis showed that congenital lesions (p=.014), tumors located in the major salivary glands (p=.043), patients older than 1 year (p=.018), and occurrence of metastasis (p=.008), were associated with the risk of recurrences. Patients more than 1 year old were associated with a higher percentage of metastasis (p=.039). In addition, tumors with ill-defined borders (p=.014) and recurrence (p=.030) were associated with a higher percentage of deaths. Histological characteristics, such as focal necrosis (p<.001), presence of mitotic figures (p=.031), perineural invasion (p=.034), and non-encapsulated lesions (p=.012) were also associated with recurrence. Furthermore, there was a higher incidence of congenital tumors located in the major salivary glands (p=0.033), and the presence of nuclear pleomorphism (p=.011) in tumors from minor salivary glands.

Kaplan-Meier survival curves estimated a 5-year OS, DSS, and DFS rates of 95.5%, 95.3%, and 68.1%, respectively **(Figure 3)**. Based on the log-rank test, there was a significant increase in

DSS in patients younger than 1 year of age (82.8%; CI: 405.4 (317–493.7); p=.003), individuals with lesions in major salivary glands (79.4%; CI: 280.1–467.3); p= .005), patients without metastases (77.8%; CI: 95.9 – 151.2), p=.011), encapsulated lesions (85.7%, ICD: 285.3 - 541.6) p=0.0001), congenital lesions (83.3%, CI: 283.0 - 488.8) p= 0.0001) and lesions that do not show perineural invasion (89.5%, CI: 117.2 - 161.1) p= 0.035) **(Supplementary Table S6) (Supplementary Image S2)**. In the univariate Cox regression, patients diagnosed with more than 1 year of age (hazard ratio [HR] = 4.31; *p*=.008), non-congenital lesions (hazard ratio [HR] = 6.85; *p*=.002), tumors located in the minor salivary glands (hazard ratio [HR] = 3.80; *p*=.010) and presence of metastasis (hazard ratio [HR] = 3.56; *p*=.019) have a lower DFS rate **(Table 3)**. However, when created a multivariate cox regression model, only the presence of metastasis was identified as an independent prognostic factor (hazard ratio [HR] = 9.81; *p*=.010) **(Table 3)**.

3.6 Risk of bias in studies

Most articles provided clear descriptions of the patients' characteristics, history, and condition, being classified as low risk (n=48; 92.3%) or moderate risk (n=4; 7.7%) of bias. Several studies did not correctly describe the adverse events, harm or unforeseen events (n= 18; 34.6%) as well as the clinical condition of the patient at presentation (n=11; 21.1%). However, all articles had valid criteria and methods to be included. Several case reports lacked information about proposed treatment and follow-up. All case series lacked appropriate statistical analysis information (n=5; 100%). The risk of bias assessment of all studies is summarized in **Figure 4** and detailed in **Supplementary Tables S7 and S8.**

4 DISCUSSION

The various structures from the salivary glands allow the origin of a wide and diverse group of tumors with different biological behaviors [59]. The annual incidence of salivary glands neoplasms is low, being even rarer in the pediatric population, representing about 3 to 4 cases per 100,000 individuals [60]. It is observed, therefore, that due to the rarity of these tumors, some clinical and microscopic characteristics may mimic aspects similar to other lesions, which requires caution in establishing an accurate diagnosis. Indeed, the present systematic review confirms that sialoblastomas are rare salivary gland tumors. Therefore, due to the lack of consistent clinicopathological information about these tumors, a systematic approach to the subject was carried out.

Sialoblastoma can manifest congenitally or not, occurring with a higher incidence in early childhood patients [3,31]. The lesions can be detected by obstetric ultrasound. However, as this test is operator-dependent, the diagnosis is related to the professional's experience [61]. Another important point is the frequency of ultrasounds that are performed during prenatal care, interfering with the early diagnosis of facial anomalies [62]. In this systematic review, only 5 (8.0%) cases of sialoblastoma were diagnosed in the intrauterine period [19,20,25,45,52]. A total of 21 cases (33.8%) was diagnosed only on the first day of life, despite already having tumors with considerable diameters. Nevertheless, attention should be paid to the bias associated with publication, where this information may not have been reported adequately. Thus, it is difficult to accurately estimate the percentage of patients who could have been diagnosed during neonatal screening.

No significant gender predilection was observed, with a female to male ratio of 1.03:1, and mean age of 1.4 years. Most cases occurred in patients with less than 1 year-old. A study reported cases of sialoblastomas in adult patients. Certainly, the cases described are salivary gland neoplasms, but there are not sufficient histological data or image to confirm the diagnosis of sialoblastoma in any of these patients [63]. Therefore, we excluded this study from this systematic review.

Major salivary glands are the most affected sites for sialoblastomas, with the parotid gland being more affected than the submandibular gland [9]. The present study showed that only 16 (25.0%) patients lesions affecting the minor salivary glands, with the buccal mucosa being the most common location (n = 14; 87.5%). Although the number of lesions that affected this region was low, it is assumed that they are even smaller. Yet, a structure named as accessory parotid gland (GPA) is present in about 56.0% of the general population [64]. It is located in the lateral region of the face behind the zygomatic process, usually anterior to the parotid gland and parallel to Stensen's duct. Thus, the GPA can be easily confused with the minor salivary glands and may represent a diagnostic challenge when its existence is unknown by the practitioners [65]. None of the cases included in our study reported the GPA involvement, which may raise the hypothesis that some GPA cases may have been mistakenly recorded as buccal mucosa origin.

Sialoblastomas are clinically nonspecific, and their clinical appearance may overlap with other lesions of higher incidence [10]. The differential diagnosis included other neoplasms of glandular origin [27], vascular lesions [45] and infectious diseases [40]. According to Mariz et al. [66], symptomatic lesions, color change and presence of telangiectasia may be predictors of malignancy for palatine salivary gland tumors. Although the intraoral presentation of sialoblastoma is nonspecific, such features may be useful to support the decision to perform an incisional or

excisional biopsy, even in lesions located in extraoral sites. In the present study, 17.9% of the patients had painful symptoms, 50% color alteration and 61.1% altered surface, presenting with an ulcerated or telangiectatic appearance. However, the clinical appearance of the lesions was not reported in detail in most of the included cases.

The diagnosis was confirmed by excisional biopsy in 29 (56.9%) individuals, followed by incisional biopsy, which was performed in 13 (25.5%) cases, of which 4 were performed in the parotid region. However, iatrogenic paresthesia triggered by this clinical approach should not be overlooked [48]. Currently, the FNAB has been applied with high accuracy in the diagnosis of salivary gland tumors, with the Milan system being a useful tool to predict potential risks of malignancy [67,68]. Morphologically, the lesions present neoplastic proliferation of cells similar to those found during the embryogenesis of the salivary glands [8,10]. In this neoplasm, solid nests of basaloid cells are observed with partially formed ductal and pseudoductal spaces, separated by fibromyxoid stroma [5,10]. Basaloid cells are characterized by a high nucleus/cytoplasm ratio, round to oval nuclei, loose nuclear chromatin and prominent nucleoli, demonstrating high mitotic activity [31]. The tumor can sometimes show infiltrative growth with vascular [19] and perineural invasion [10]. Mitoses are usually frequent and focal necrosis can be observed [41]. The immunohistochemistry can be used to elucidate the diagnosis but not as a tool for definitive diagnosis. Thirty-five articles included in this review reported immunohistochemistry analysis. The percentage of ki-67 positivity ranged from 3.0% [27] to 80% [36].

There are four reports in the literature demonstrating the synchronic association of sialoblastoma and hepatoblastoma, which is an extremely uncommon event [20,34,50,52]. Such occurrence can be explained due to the common embryonic origin of the parotid gland and the liver. As a result, the abnormality would affect the cells of both organs, leading to the appearance

of two synchronous tumors producers of alpha-fetoprotein (AFP) in different sites in the same patient [57]. Although both tumors are extremely uncommon, it should be remembered that they can occur in the same patient and that appropriate investigations should be performed to exclude hepatoblastoma in newborns diagnosed with sialoblastoma.

Wide local resection with negative margins is the first-line treatment, although it can be mutilating in cases of large or locally invasive tumors. Sequelae can be extensive and vary from aesthetic defects to facial nerve paralysis [5,9,48]. The clinical characteristics that were most associated with recurrence were non-congenital lesions, tumors located in the minor salivary glands, patients older than 1 year of age and individuals who had metastatic lesions. It was identified that only the presence of metastasis was an independent prognostic factor ($p=0.010$). SGTs in children/adolescents have milder features. The 5-year OS of malignant SGTs for pediatric patients ranges from 81.6% to 98% compared to 59% for adults [69–72] In this review, it was found that the OS of patients affected by sialoblastoma is 95.5% in 5 years. Nevertheless, the 5-year DFS was 68%. Albeit most patients were alive without disease, sialoblastoma was shown to be a tumor associate with a high risk of recurrence.

Despite the relevant information presented in the selected studies, there are some limitations that should be highlighted. In some cases, there was a lack of follow-up information and description of the clinical features of the tumors. These data are essential to carry out prognostic and survival analyzes of patients affected by the disease. All case reports, with confirmed histopathological diagnosis, were included in this review, but further studies are needed, mainly cohort studies, to define precise prognostic factors of sialoblastomas.

5 CONCLUSION

In summary, this systematic review showed that sialoblastoma mainly affect patients in at birth or shortly afterwards. There was no gender predilection, with the parotid gland being the most affected region. The clinical behavior is broad, and most cases appear as slow and indolent growth lesions. Microscopically, the lesions were usually encapsulated and showed proliferation of basaloid cells that can be organized into two distinct main histopathological patterns: cribriform and solid. Sialoblastoma can present recurrence and locally aggressive behavior, with regional and distant metastases. Furthermore, genetic analysis studies are needed to elucidate the causes of the tumor and compare with other salivary gland neoplasms.

OTHER INFORMATION

Protocol and registration

The methods of this study were established prior to the initiation of the review and the resulting protocol was written following PRISMA-P [40], which was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) database under registration number: CRD42023389338. Furthermore, this systematic review was reported based on the Preferred Reporting Items Statement for Systematic Reviews and Meta-analyses (PRISMA) guidelines [73].

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LEGENDS FOR FIGURES

Figure 1. Worldwide distribution of included cases of sialoblastomas in salivary glands.

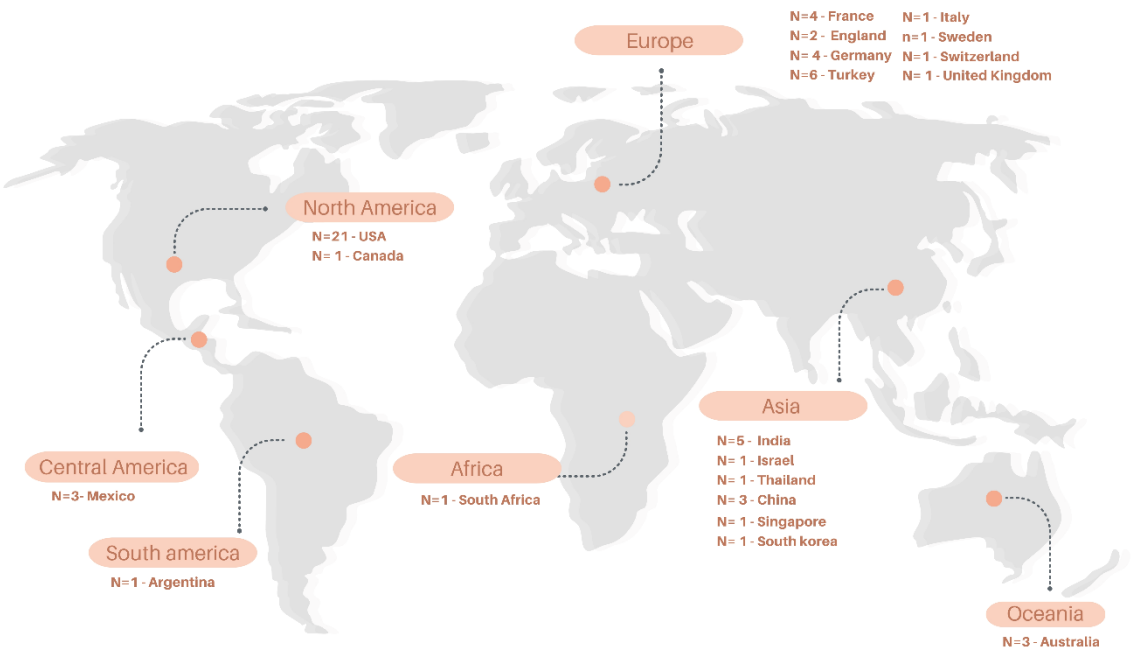

Figure 2. Anatomical sites according to the clinical presentation of sialoblastomas in salivary glands.

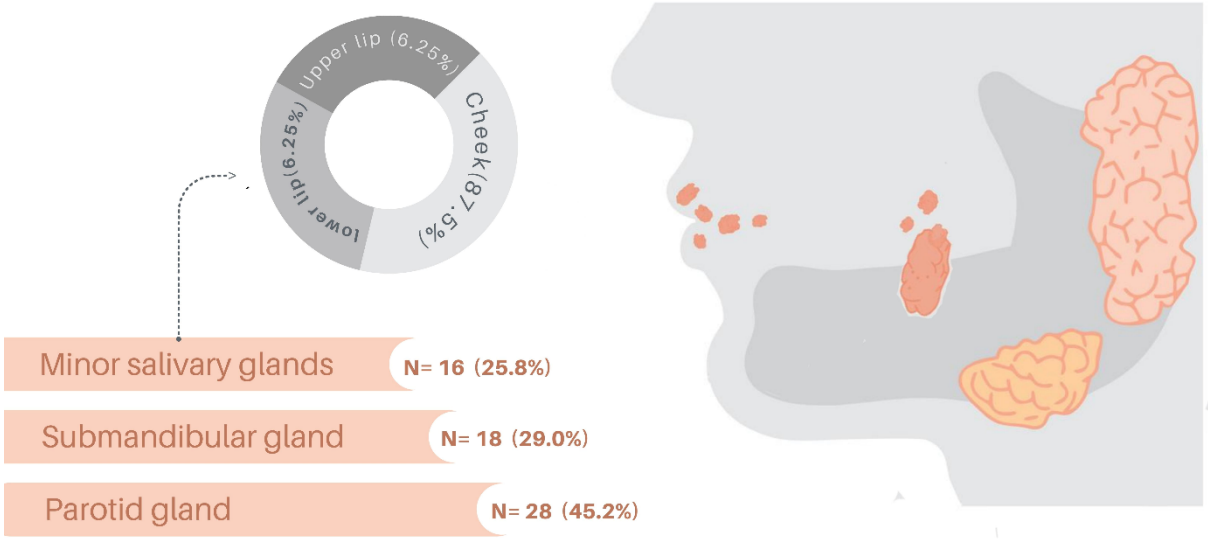

Figure 3. Kaplan-Meier survival curves estimating the 5-year overall survival (A), Disease-specific survival (B), and Disease-free survival (C).

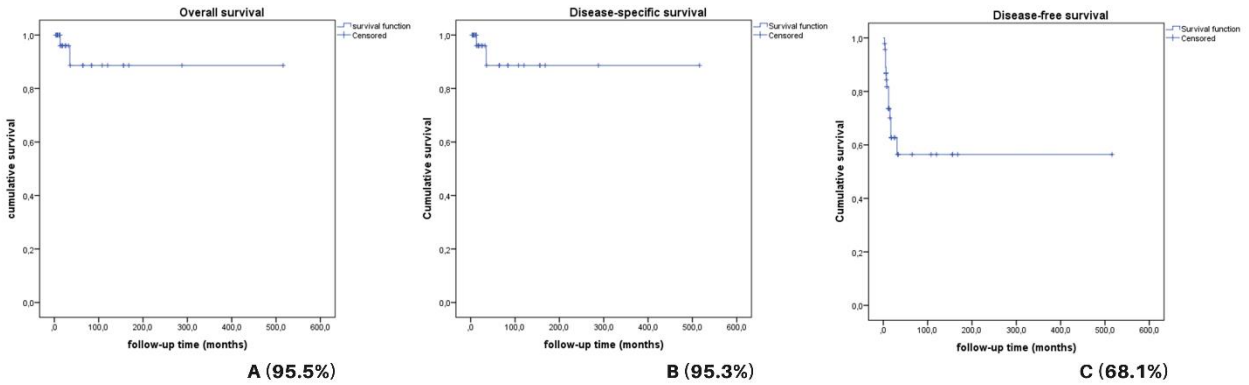

Figure 4. Risk of bias summary reviewers' judgments about each checklist item presented as percentages according to each study design**. Graph A** shows a summary of the risk of bias for the case reports. **Graph b** Graph b shows a summary risk of bias for the case series. **Graphs C:** Risk of bias was categorized as high when the study reached up to 49% yes ratings, moderate for 50% to 69% yes ratings, and low for >70% yes rating.

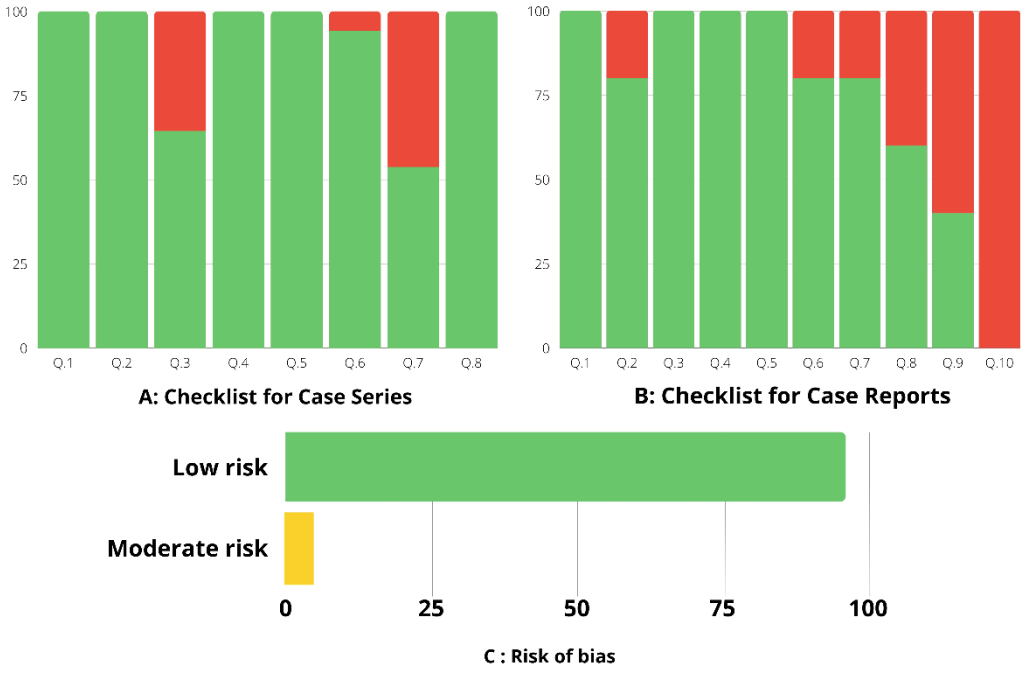

Figure S1. Flow diagram of literature search and selection criteria adapted from PRISMA [73].

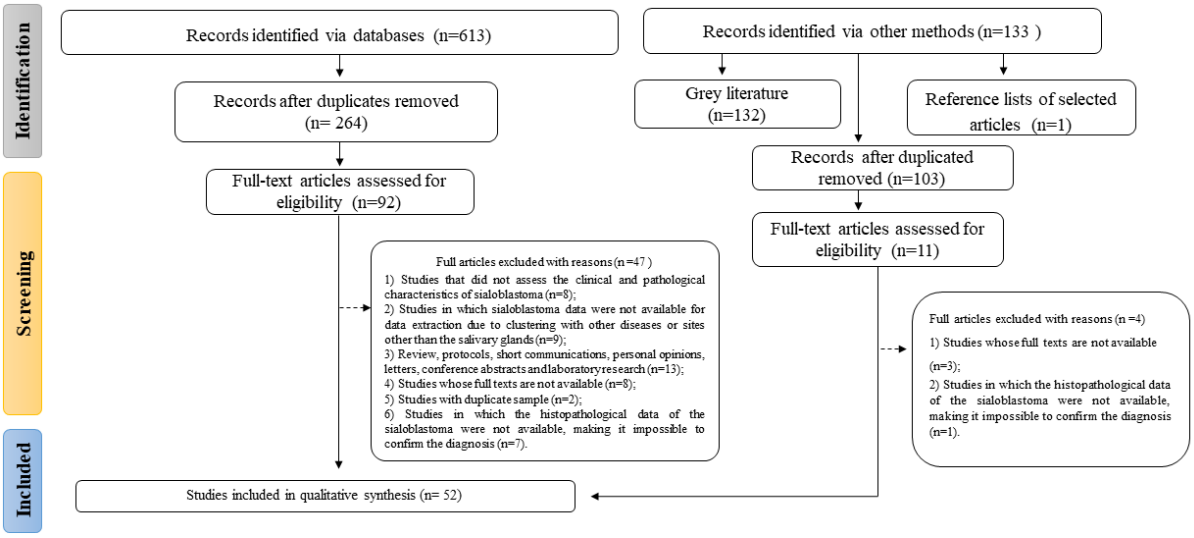

Figure S2. Univariate log-rank analysis revealed that age (p = 0.003), location (p = 0.005), metastases (p=0.011), presence of capsule (0.0001), congenital lesions (p= 0.0001) and perineural invasion (p= 0.035) significantly affect the survival rate (disease-free survival) of patients with sialoblastoma.

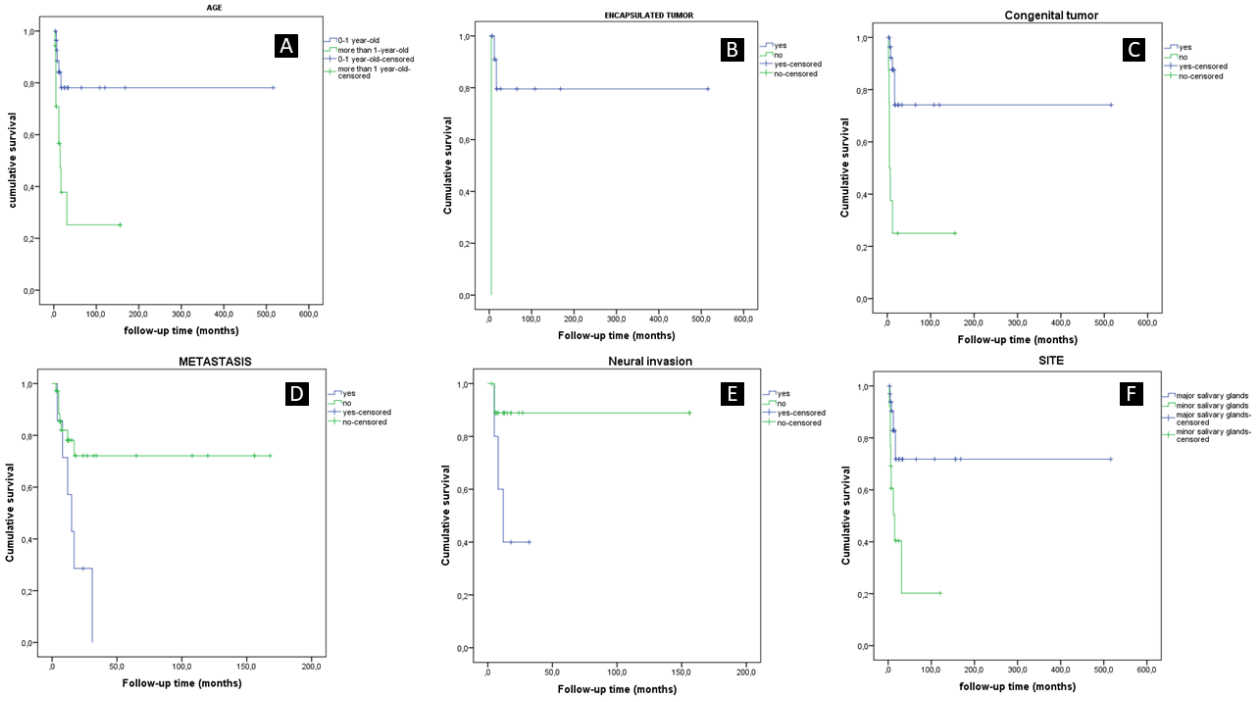

Table 1. Clinical characteristics of 62 sialoblastomas included in this systematic review.

Clinical variables	Number of patients (%)
Sex (n=61)	
Male	30 (49.2)
Female	31 (50.8)
Congenital (n=49)	
Yes	38 (77.6)
No	11 (22.4)
Age group (n=62)	
0-1 year	38 (61.3)
> 1 year	24 (38.7)
Range	0 day – 15 years
Mean ± SD	1.46 years ± 2.87 years
Site (n=62)	
Major salivary glands	46 (74.2)
Minor salivary glands	16 (25.8)
Symptomatology (n=28)	
Painful	5 (17.9)
Painless	23 (82.1)
Clinical diagnostic hypothesis (n=27)	
Salivary gland tumors	8 (29.7)
Tumors of vascular origin	7 (25.9)
Infectious diseases	3 (11.1)
Carcinomas	2 (7.4)
Teratoma	2 (7.4)
Other	5 (18.5)
Size of the lesions, cm (n=53)	
Range (cm)	1.0 – 15.0
Mean ± SD	4.58 ± 3.11
Color (n=16)	
Normochromic	8 (50.0)
Color alteration	8 (50.0)
Surface (n=18)	
Smooth	7 (38.9)
Surface alteration	11 (61.1)
Synchronous association with other tumors (n=50)	
Yes	8 (16.0)
No	42 (84.0)
Types of synchronous association (n 8)	
Hepatoblastoma	4 (50.0)
Organoid nevus	4 (50.0)
Treatment (n=61)	
Surgery	53 (86.9)
Surgery + CT	5 (8.2)
No treatment	3 (4.9)
Recurrence (n=56)	
Yes	20 (35.7)

No	36 (64.3)
Recurrence time, months (n=15)	
Range (months)	3 – 31
Mean ± SD	10.60 ± 7.37
Salvage treatment (n=20)	
Surgery	6 (30.0)
Surgery + CT	5 (25.0)
Surgery + CT + RT	5 (25.0)
Lymph node resection	4 (20.0)
Metastasis	
Yes	10 (16.1)
No	43 (81.1)
Metastasis site (n=10)	
Neck lymph nodes	2 (20.0)
Lung	6 (60)
Neck lymph nodes and lung	1 (10.0)
Neck lymph nodes and bone	1 (10.0)
Facial paralysis (n=25)	
Yes	17 (68.0)
No	8 (32.0)
Follow-up time, months (n=46)	
Range (months)	3 – 516
Mean ± SD	51.84 ± 90.21
Patients' status (n=49)	
Alive	44 (89.7)
Dead	5 (10.3)

Abbreviations: SD – standard deviation; RT – radiotherapy; CT – chemotherapy

Table 2. Histological characteristics of 62 sialoblastomas included in this systematic review.

Variables	**Number of cases (%)**

Capsule (n=20)	
Yes	17 (85.0)
No	3 (15.0)
Solid pattern (n=19)	
Yes	14 (73.7)
No	5 (26.3)
Cribriform pattern (n=29)	
Yes	14 (58.6)
No	12 (41.4)
Ductal structure formation (n=51)	
Yes	48 (94.1)
No	3 (5.9)
Perineural invasion (n=30)	
Yes	6 (20.0)
No	24 (80.0)
Nuclear pleomorphism (n=15)	
Yes	11 (73.3)
No	4 (26.7)
Focal necrosis (n=35)	
Yes	20 (57.1)
No	15 (42.9)
Mitotic figures (n=43)	
Yes	35 (81.4)
No	8 (18.6)
Stroma (n=44)	
Fibrous	9 (20.5)
Fibromyxoid	28 (63.6)
Myxoid	6 (13.6)
Desmoplastic	1 (2.3)

Table 3. Hazard ratio associated to disease-free survival in sialoblastomas

	Univariate analysis*	***Multivariate analysis***

Variables	HR± (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Male	Reference	.111	-	**-**
Female	2.80 (0.79-9.92)		-	
Age group				
< 1 year	Reference		Reference	.139
> 1 year	4.31 (1.47-12.64)	**.008**	3.11 (0.69-13.99)	
Congenital				
Yes	Reference	**.002**	Reference	.057
No	6.85 (2.08-22.63)		5.2 (0.95-28.60)	
Site				
Major salivary glands	Reference	**.010**	Reference	.077
Minor salivary glands	3.80 (1.37-10.52)		5.1 (8.4-31.07)	
Size				
<3.0 cm	Reference	.183	-	-
>3.0 cm	2.14 (0.70-6.54)		-	
Limits of the lesion				
Well defined	Reference		-	-
Undefined	1.71 (0.76-3.8)	.193	-	
Symptoms				
Painful	2.38 (0.59-9.56)	.223	-	**-**
Painless	Reference		-	
Facial paralysis				
Yes	2.30 (0.28-19.16)	.441	-	**-**
No	Reference		-	
Synchronous association with other tumors				
Yes	Reference		-	**-**
No	1.37 (0.30-6.29)	.690	-	
Metastasis				
Yes	3.56 (1.23-10.31)	**.019**	9.81 (1.73-55.60)	**.010**
No	Reference		Reference	
Perineural invasion				
Yes	5.31 (0.89-31.80)	.067	-	**-**
No	Reference		-	
Cribriform pattern				
Yes	Reference	.205	-	**-**
No	2.35 (0.63-8.79)		-	

Solid pattern				
Yes	3.41 (0.73-15.82)	.117	-	**-**
No	Reference		-	
Myoepithelial cells				
Yes	1.12 (0.13-9.69)	.918	-	**-**
No	Reference		-	
Nuclear pleomorphism				
Yes	2.85 (0.34-23.80)	.333	-	**-**
No	Reference		-	
Ductal structures				
Yes	Reference	.117	-	**-**
No	3.41 (0.73-15.82)		-	

* univariate and multivariate Cox regression – model was created using all variables that achieved a *P*-value > .10

±HR: hazard ratio; CI: confidence interval.

Table S1. Search strategies with appropriated key words and number of references retrieved from each database.

Database	Search strategy (search date: December, 2022)	Results
PUBMED	(sialoblastoma OR “congenital basal cell adenoma” OR “congenital hybrid basal cell adenoma-adenoid cystic carcinoma” OR “basaloid adenocarcinoma” OR embryoma)	**168**
SCOPUS	TITLE-ABS-KEY(sialoblastoma OR “congenital basal cell adenoma” OR “congenital hybrid basal cell adenoma-adenoid cystic carcinoma” OR “basaloid adenocarcinoma” OR embryoma)	**214**
EMBASE	('sialoblastoma'/de OR 'congenital basal cell adenoma' OR 'congenital hybrid basal cell adenoma-adenoid cystic carcinoma' OR 'basaloid adenocarcinoma' OR 'embryoma'/de)	**83**
WEB OF SCIENCE	TS=(sialoblastoma OR “congenital basal cell adenoma” OR “congenital hybrid basal cell adenoma-adenoid cystic carcinoma” OR “basaloid adenocarcinoma” OR embryoma)	**130**
GOOGLE SCHOLAR	First 100 more relevant hits. No patents and no citations. (“sialoblastoma” OR “congenital basal cell adenoma” OR “congenital hybrid basal cell adenoma-adenoid cystic carcinoma”)	**100**
ProQUEST	TI,AB(“sialoblastoma” OR “congenital basal cell adenoma” OR “congenital hybrid basal cell adenoma-adenoid cystic carcinoma” OR “basaloid adenocarcinoma” OR “embryoma”)	**32**

Table S2. Excluded articles and reasons for exclusion (n= 47)

	References	Reasons for exclusion
1.	**Pediatric salivary gland tumors and tumor-like lesions**	1
2.	**Dysembryoma of the little lip**	1
3.	**The woman with unexplained anaemia**	1
4.	**The gastrulation of parthenogenetic embryoma in humans**	1
5.	**Malignant mediastinal embryoma. A case with pulmonary metastasis. Complete remission after chemotherapy**	2
6.	**Bilateral Wilms' tumor; a case report**	2
7.	**Embryoma (sialoblastoma) of salivary glands.**	1
8.	**Head and neck tumors in children and adolescents: Impact of a multidisciplinary tumor board**	3
9.	**Malignant mixed epithelial-mesenchymal neoplasms of the lung**	2
10.	**Sialoblastoma: A literature review from 1966-2011**	3
11.	**Paediatric head and neck pathology**	1
12.	**An embryoma of large dimensions**	4
13.	**What's new in the AFIP fascicle on salivary gland tumors: a few highlights from the 4th Series Atlas**	3
14.	**Adamanto-odontoblastic embryoma associated with follicular cysts of the maxilla**	4
15.	**The odontoblastic embryomas of the jaw. Clinical and anatomic pathological contribution**	4
16.	**Salivary Gland Tumors**	3
17.	**The spectrum of pediatric tumors in infancy, childhood, and adolescence: A comprehensive review with emphasis on special techniques in diagnosis**	1
18.	**SOX10-positive salivary gland tumors: a growing List, including mammary analogue secretory carcinoma of the salivary gland, sialoblastoma, Low-grade salivary duct carcinoma, basal cell adenoma/adenocarcinoma, and a subgroup of mucoepidermoid carcinoma**	3
19.	**Hamartoma, teratoma, dermoid cyst, embryoma, heteroplasia**	4
20.	**Sialoblastoma: case report**	2
21.	**Disorders and tumors of the salivary glands in children**	3
22.	**Myb Immunohistochemical Staining and Fluorescencein situHybridization in Salivary Rare Basaloid Lesions**	3
23.	**Tumours in childhood: The embryomas**	3
24.	**Immunohistochemical and molecular profile of salivary gland cancer in children.**	1
25.	**Basaloid adenocarcinoma. A new variant of pulmonary adenocarcinoma**	2
26.	**Pediatric salivary gland lesions**	3
27.	**Normal fetal salivary glands at 14-16 weeks of gestation as observed by transvaginal ultrasound imaging**	3
28.	**Selective pathologies of the head and neck in children: A developmental perspective**	3
29.	**Observations of two cases of monomorphic monodermal embryomas**	3
30.	**Congenital sialoblastoma in a newborn: diagnostic challenge of a rare entity**	4
31.	**Juvenile pleomorphic adenoma of the parotid gland with embryonal structure**	2
32.	**An eyelid sialoblastoma-like tumor with a sarcomatoid myoepithelial component**	2
33.	**Pediatric cancer in the head and neck**	3
34.	**Diffuse embryoma with intratubular germ-cell neoplasia**	2
35.	**Sialoblastoma (embryoma): MR findings of a rare pediatric salivary gland tumor.**	5
36.	**Sialoblastoma: a case report and review of the literature on congenital epithelial tumors of salivary gland origin.**	5
37.	**Sialoblastoma: MRI findings**	6
38.	**Management of sialoblastoma with surgery and brachytherapy**	6
39.	**Progressive metastatic sialoblastoma in a young child: Challenges in treatment.**	6
40.	**Sialoblastoma and Hepatoblastoma in an Infant: A Case Report and Review of the Literature**	6
41.	**A fetus with a huge neck mass and a large abdominal circumference–a rare case of sialoblastoma and hepatoblastoma**	6
42.	**How to manage an unresectable or recurrent sialoblastoma.**	6
43.	**Surgical excision of sialoblastoma in the parotid gland in newborn**	2

44.	**Recurrent sailoblastoma in female child after a 12-month course of chemotherapy**	4
45.	**Sialoblastoma, a rare salivary gland neoplasm: a case report and review of literature**	4
46.	**Juvenile pleomorphic parotid adenoma of embryonal structure**	4
47.	**Sialoblastoma in adults: distinction from adenoid cystic carcinoma.**	6

1) Studies that did not assess the clinical and pathological characteristics of sialoblastoma.

2) Studies in which sialoblastoma data were not available for data extraction due to clustering with other diseases or sites other than the salivary glands.

3) Review, protocols, short communications, personal opinions, letters, conference abstracts and laboratory research.

4) Studies whose full texts are not available.

5) Studies with duplicate sample.

6) Studies in which the histopathological data of the sialoblastoma were not available, making it impossible to confirm the diagnosis.

Table S3. Sociodemographic features of the fifity-two studies (62 cases) of Sialoblastoma included in the systematic review.

Study	Country	Sample	Sex	Age	Anatomical location	Cong	Symptoms	Clinical hypothesis	Biopsy	Synchronous association with other tumors	Treatment	Recurrence	Secondary treatment	Metastasis	DFI (months)	Follow-up (months)
CANALIS et al., 1980.	USA	1	M	1 day	Submandibular gland	YES	NO	Neoplasm	Ex	NI	Surgical excision	NO		NI	-	18
ROTH et al., 1986.	France	2	M	1 day	Parotid gland	YES	NO	NI	Ex	NO	Total parotidectomy	NO		NO	-	108
			M	1 day	Cheek	YES	NO	NI	Ex	NO	Total parotidectomy	NO		NO	-	120
SIMPSON et al., 1986.	USA	1	F	1 day	Parotid gland	YES	Facial paralysis	NI	Ex	NO	Surgical resection	YES	Total parotidectomy + chemotherapy	YES (cervical lymph nodes)	8	64
TAYLOR et al., 1988.	Canada	1	F	1 day	Cheek	YES	NO	Teratoma	Ex	NO	Surgical excision	YES (Twice in the same region)	Surgical excision + Radioactive gold implants	NO	6	NI
BATSAKIS et al.,1988.	USA	1	M	1 day	Parotid gland	YES	NI	NI	Ex	NO	Parotidectomy	NO		NO	-	12
ADKINS et al., 1990.	Australia	2	M	2 months	Parotid gland	YES	NI	Chronic lymphadenitis	In	NO	Surgical resection	NO	-	NO	-	8
			F	2.8 years	Parotid gland	NI	NI	NI	Ex	NO	Superficial parotidectomy and right cervical	NO	-	NO	-	156

											lymph node					
HARRIS et al., 1990.	England	1	F	1 day	Submandibular gland	YES	NI	Congenital salivary gland tumour	E	NO	Partial submandibulectomy	NO		NO	-	15
SEIFERT et al., 1997.	Germany	3	M	1 day	Parotid gland	YES	NI	NI	Ex	NO	Surgical excision	NO		NO	-	NI
			F	1 day	Submandibular gland	YES	NI	NI	Ex	NO	Surgical excision	NO		NO	-	NI
			M	1 day	Submandibular gland	YES	NI	NI	NI	NI	NI	NI		NI	NI	NI
LUNA et al., 1999.	USA	1	F	21 months	Cheek	NO	NO	NI	Ex	NO	Surgical resection	YES	Surgical excision	NO	5	12
BRANDWEIN et al., 1999.	USA	1	F	1.7 years	Cheek	NI	NI	NI	Trans	Extensive congenital nevus	Parotidectomy	YES	Surgical excision + maxillectomy + Chemotherapy + radiotherapy	NO	5	12
ALVAREZ et al., 1999.	Mexico	1	F	5 years	Parotid gland	NO	NO	Lymphangioma	NI	NO	Surgical excision	YES	Parotidectomy and complete resection of local lymph nodes	NO	5	12
GARRIDO et al., 2000.	UK	1	M	0 day	Parotid gland	YES	NO	NI	Ex	NO	Surgical excision	NO	-	NO	-	24

SIDDIQI et al., 2000.	USA	1	F	0 day	Parotid gland	YES	NI	NI	Ex	Hepathoblastoma	Surgical resection + chemotherapy	NO		NO	NA	65
GREEN et al., 2000.	USA	1	M	11 months	Submandibular gland	YES	NO	NI	Ex	Organoid Nevus	Submandibulectomy	NO		NO	-	18
MOSTAFAPOUR et al., 2000.	USA	1	M	1 day	Submandibular gland	YES	NO	NI	Ex	NI	Surgical resection with free margins	NI	-	NI	NI	NI
ORTIZ et al., 2001.	Mexico	1	M	3 months	Parotid gland	YES	NI	NI	NI	NO	Surgical excision	NO		NO		6
HUANG et al., 2003.	USA	1	F	21 months	Cheek	NI	NI	NI	Trans	Congenital nevus	Surgical resection	YES	Parotidectomy with facial nerve resection chemotherapy and radiation	YES (lung)	31	74
OZDEMIR et al., 2005.	Turkey	1	F	0 day	Parotid gland	YES	NI	Teratoma	Ex	NO	Surgical resection with free margins	NO		NO	-	6
VERRET et al., 2006.	USA	1	M	15 months	Submendibular gland	NO	NO	NI	Ex	NO	Surgical excision + level I cervical lymph nodes	NI	-	NI	NA	12
TATLIDEDE et al., 2006.	Turkey	1	F	4 years	Cheek	NI	NO	Hemangioma	In		Surgical resection	YES	Surgical resection and chemotherapy	YES (Submandibular lymph nodes	15	NI
	USA	6	F	10 days	Parotid gland	YES	NI		Auto	NI		NI	-	-	-	-

							Tumor de células mistas			Removed at autopsy					
			M	7 days	Submandibular gland	YES	NI	Basal cell embryoma	Ex	NI	Surgical resection	NO	-	NI	NI	516
WILLIAMS et al., 2006.			M	5 months	Parotid gland	NI	NI	sebaceus carcinoma	NI	NI	Surgical resection	YES	Submandibular nodes + chemotherapy + Radiotherapy	YES (Submandibular lymph nodes and lung)	NI	NI
			M	2 months	Parotid gland	NI	NI	adenocarcinoma NOS	NI	NI	Surgical resection	YES	Surgical excision	NO	NI	36
			F	6 months	Submandibular gland	NI	NI	CAC	NI	NI	Surgical resection	NO		NO	NI	168
			M	1 day	Parotid gland	YES	NI	SCC undifferentiated	NI	NI	Surgical resection	YES	Surgical excision	NO	NI	NI
VIDYADHAR et al., 2008.	Singapore	1	M	3 months	Parotid gland	YES	NI	Lymphoma	Ex	NO	Surgical excision	NO	-	NO	-	13
MOON et al., 2008.	South Korea	1	F	1 day	Submandibular gland	YES	NO	Neurogenic tumor	Ex	NO	Surgical excision	NO	-	NO	-	13
CRISTOFARO et al., 2008.	Italy	1	F	6 months	Submandibular gland	NI	NO	NI	NI	No	Surgical resection	NO		NO	NA	12
SCOTT et al., 2008.	Australia	1	F	4 years	Cheek	NO	NO	Hemangioma	In	Cutaneous hamartoma	Chemotherapy + surgery	NO	-	YES (lung)	NI	NI

											(subtotal parotidectomy)					
MARUCCI et al., 2009.	England	1	F	1 day	Cheek	YES	NI	Hemangioma	In	NO	Surgical excision	NO		NO	-	6
STONES et al., 2009.	South Africa	1	M	1 day	Parotid gland	YES	NI	NI	Auto	Hepatoblastoma	The patient died before performing the procedure		-	-	NA	NA
MERTENS et al., 2009.	Sweden	1	F	1 month	Submandibular gland	Yes	NI	NI	Ex	NO	Surgical removal	NO		NO	-	18
ERSOZ et al., 2010.	Turkey	1	M	4 years	Parotid gland	NO	NI	Parotiditis	Ex	NO	Surgical excision (with compromised margins)	YES	Surgical excision + quimioterapia	YES (lung)	4	-
PATIL et al., 2010.	USA	2	F	1 day	Parotid gland	YES	NI	NI	Ex	NO	Surgical resection	YES	Surgical excision	NO	17	84
			M	15 years	Parotid gland	NO	NO	NI	In	NO	Lost follow-up	NI	-	YES (Lymph nodes, temporal bone and vertebrae)	NI	Lost follow-up
EKEN et al., 2010.	Turkey	1	F	3 years	Cheek	NI	NO	NI	FNAC	NO	Surgical resection	NO	-	NO		NI
PRIGENT et al., 2010.	France	1	F	1 day	Parotid gland	YES	YES	Pleomorphic adenoma	FNAC	NO	Superficial parotidectomy	YES	Chemotherapy and total parotidectomy	YES (lung)	12	12

KARAMAN et al., 2010.	Turkey	1	M	5 years	Cheek	NO	YES	Mumps	Ex	NO	Surgical resection	YES	Surgical resection + chemotherapy	NO	3	NI
KATTOOR et al., 2010.	India	1	M	1 year	Cheek	NI	NO	NI	In	NO	Surgical resection	YES	Partial right maxillectomy AND removal of residual parotid AND resection of the facial nerve AND chemotherapy followed by radiotherapy	NO	-	12
SAFFARI et al., 2011.	USA	1	M	1 day	Cheek	YES	NO	NI	In	NO	Surgical excision with compromised margins	NO		NO	-	7
FAROOQI et al., 2011.	USA	1	F	3 months	Parotid gland	YES	NI	NI	NI	NI	Surgical resection	YES	Surgical resection + chemotherapy + radiotherapy)	YES (lung)	17	84

FUCHSMANN et al., 2011.	France	1	F	0 day	Submandibular gland	YES	NI	Hemangioma	NI	NO	surgical resection	NO	-	NO	NA	12
BROWN et al., 2012.	Mexico	1	F	4 months	Upper lip	YES	NO	Vascular/lymphatic malformation	NI	NO	Surgical excision	NO	-	NI		18
AGGARWAL et al., 2013	India	1	F	I day	Submandibular gland	YES	NI	NI	FNAC	NO	Surgical excision	NO	-	NO	-	8
DEMIRÖZ et al., 2014	Turkey	1	M	4 years	Cheek	NI	NI	NI	Ex	NO	Surgical excision	YES	Surgical excision	NI	12	NI
SHARMA et al., 2014	India	1	M	5 year	Parotid gland		NO	NI	FNAC	NO	Total parotdectomy and lymph node excision	NO	-	NO	NO	6
KATARIA et al., 2015	India	1	M	8 years	Parotid gland	YES	NI	Salivary gland tumor	FNAC	NO	Surgical excision with free margins	NO	-	NO	-	12
SICHEL et al., 2016	Israel	1	M	1 day	Submandibular gland	YES	NI	NI	FNAC	NO	Submandibulectomia	NO	-	NO	-	27
IRACE et al., 2016	USA	1	M	5 months	Parotid gland	YES	Dysphagia and facial paralysis	Hemangioendothelioma	In	NO	Neoadjuvant chemotherapy and total parotidectomy + adjuvant chemotherapy	YES	Chemotherapy	NO	NI	35

SARAVAKOS et al., 2016	Germany	1	F	13 years	Parotid gland	NO	NO	NI	Ex	NO	Total parotidectomy	YES	Surgical excision	NO	12	288
WANI et al., 2016	India	1	M	1 day	Submandibular gland	YES	NI	NI	FNAC	NO	Surgical excision	NO	-	NO	-	4
SITTHICHAIYAKUL et al., 2016	Thailand	1	F	1 year	Cheek	NO	NI	NI	In	NO	Surgical excision with free margins	NO	-	NO	NA	24
WANG et al., 2018	China	1	F	1 year	Lower lip	NO	NO	Neuroendocrine tumor of the salivary gland	In	NO	Excision	YES	Chemotherapy	NO	7	13
DI MICCO et al., 2019	Switzerland	1	F	1,5 year	Submandibular gland	NO	YES	NI	E	NO	Surgical excision	NO	-	NO	-	156
RODRÍGUEZ et al., 2021	Argentina	1	M	0 day	Parotid gland	YES	NI	Hemangioma	I	Hepatoblastoma	Neoadjuvant chemotherapy + surgical resection	NO	-	YES (lung)	-	24
YANG et al., 2022	China	1	NI	6 months	Parotid gland	NI	NI	NI	Ex	Hepatoblastoma	neoadjuvant chemotherapy parotid sialoadenectomy	NO	-	NO	-	32
HE et al., 2022	China	1	F	2 years	Submandibular gland	YES	NO	Submandibular tumor	Ex	NI	Submandibulectomy (free margins)	NO	-	NO	-	3

Cong: Congential; F: Female; M: Male; FNAC: Fine Needle Aspiration Cytology; Ex: escisional; In: Incisional; NI: not informed; Trans: Transoral surgery; DFI: Disease free intern.

Table S4. Clinicoradiographic features of the fifity-two studies (62 cases) of Sialoblastoma included in the systematic review.

Study	Facial paralysis	Diameter (cm)	Consistency	Color	Surface	Fundamental lesion	Limits	Edges	Primary histopathological diagnosis
CANALIS et al., 1980.	NI	3	Firm	Normochromic	Smooth	Nodule	NI	NI	Sialoblastoma
ROTH et al., 1986.	YES (3months)	NI	NI	NI	NI	Nodule	Well circumscribed	NI	Sialoblastoma
	YES (4months)	NI	NI	NI	NI	Nodule	NI	NI	Sialoblastoma
SIMPSON et al., 1986.	YES	1,5	Firm	NI	NI	Nodule	NI	NI	Sialoblastoma
TAYLOR et al., 1988.	YES	15	Firm	NI	NI	Nodule	NI	NI	Sialoblastoma
BATSAKIS et al., 1988.	NI	4,5	NI	Normochromic	Smooth	Nodule	NI	NI	Sialoblastoma
ADKINS et al., 1990.	YES	2,5	NI	NI	NI	Nodule	NI	NI	NI
	YES	2	NI	NI	NI	Nodule	NI	NI	NI
HARRIS et al., 1990.	NI	NI	Solid	NI	NI	NI	NI	NI	Sialoblastoma
SEIFERT et al., 1997.	NI	3	NI	NI	NI	Nodule	NI	NI	NI
	NI	2	NI	NI	NI	Nodule	NI	NI	NI
	NI	5	NI	NI	NI	Nodule	NI	NI	NI

LUNA et al., 1999.	NI	2	Firm	NI	NI	Nodule	NI	NI	Sialoblastoma
BRANDWEIN ., 1999.	YES	2	Firm	NI	NI	Nodule	Well circumscribed	well borders	Sialoblastoma
ALVAREZ et al., 1999.	NO	5	Firm	Red-violaceous	NI	Nodule	Well circumscribed	irregular	Adenoid cystic carcinoma
GARRIDO et al., 2000.	YES	9	NI	Reddish	Ulcerated	Nodule	NI	NI	Sialoblastoma
SIDDIQI et al., 2000.	NI	14	Variable consistency	NI	Telangiectasia	Nodule	Well circumscribed	NI	Sialoblastoma
GREEN et al., 2000.	NO	4,3	Firm	NI	NI	Nodule	NI	NI	
MOSTAFAPO UR et al., 2000.	NI	2	NI	NI	NI	Nodule	NI	NI	Sialoblastoma
ORTIZ et al., 2001.	NI	2,2	NI	NI	NI	Nodule	NI	NI	
HUANG et al., 2003.	YES	NI	Firm	NI	NI	Nodule	NI	NI	Sialoblastoma
OZDEMIR et al., 2005.	NI	8	Firm	Reddish	Telangiectatic	Nodule	NI	NI	Sialoblastoma
VERRET et al., 2006.	NO	3	NI	NI	NI	Nodule	Well circumscribed	NI	
TATLIDEDE et al., 2006.	YES	5	Firm	Bluish	NI	Nodule	Indefinite	Undefined	
WILLIAMS et al., 2006.	-	6	NI	NI	NI	Nodule	NI	NI	Cellular mixed tumor

	NI	3	NI	NI	NI	Nodule	NI	NI	NI
	NI	6	NI	NI	NI	Nodule	NI	NI	NI
	NI	2	NI	NI	NI	Nodule	NI	NI	NI
	NI	5	NI	NI	NI	Nodule	NI	NI	NI
	NI	5	NI	NI	NI	Nodule	NI	NI	NI
VIDYADHAR et al., 2008.	NI	5	NI	NI	NI	Nodule			Sialoblastoma
MOON et al., 2008.	NI	3	Firme	NI	NI	Nodule	Well circumscribed	NI	Sialoblastoma
CRISTOFARO et al., 2008.	NI	3	NI	NI		Nodule	Well circumscribed		
SCOTT et al., 2008.	NO	3	Firm	Normochromic	Smooth	Nodule	Well circumscribed	bem definidas	Mucoepidermoid carcinoma
MARUCCI et al., 2009.	NI	1	Firm	Bluish	Telangiectatic	Nodule	NI	NI	Sialoblastoma
STONES et al., 2009.	NI	4	Firm	Normochromic	Telangiectatic	Nodule	NI	NI	Sialoblastoma
MERTENS et al., 2009.	NO	3	NI	NI	NI	Nodule	NI	NI	NI
ERSOZ et al., 2010.	NI	2,4	NI	NI	NI	Nodule	Well circumscribed	Undefined	
PATIL et al., 2010.	NI	2,2	NI	NI	NI	Nodule	NO	NO	
	NI	NI	NI	NI	NI	Nodule	Difused	NI	
EKEN et al., 2010.	NI	3	Firm	Normochromic	Smooth	Nodule	NI	NI	Sialoblastoma
PRIGENT et al., 2010.	YES	7	Firm	NI	Telangiectatic	Nodule	Well circumscribed		

KARAMAN et al., 2010.	NI	1,3	NI	NI	NI	Nodule	Well circumscribed	BEM DELIMITADAS	
KATTOOR et al., 2010.	YES	NI	NI	NI	NI	NI	NI	NI	
SAFFARI et al., 2011.	NO	4,5	Firm	Bluish	Telangiectatic	Nodule	Well circumscribed	Well delimited	
FAROOQI et al., 2011.	NI	NI	NI	NI	NI	NI	NI	NI	
FUCHSMAN N et al., 2011.	Transitory paresthesia	6	Firm	Normocromic	Integrated surface	Nodule	Well circumscribed		
BROWN et al., 2012.	NI	3	Firm	Blue hue and increased vascularity	Ulcerated	Nodule	Well circumscribed	NI	
AGGARWAL et al., 2013.	NI	8	Firm	Normocromic	Telangiectatic	Nodule	Well circumscribed		Sialoblastoma
DEMIRÖZ et al., 2014.	NI	2	NI	NI	NI	Nodule	NI	NI	
SHARMA et al., 2014.	NI	6	Firm	NI	NI	Nodule	Well circumscribed	NI	Sialoblastoma
KATARIA et al., 2015.	NI	4	Firm	NI	NI	Nodule	Well circumscribed	NI	
SICHEL et al., 2016.	NO	3,5	Firm	NORMOCROMICA	Integrated surface	Nodule	Well circumscribed	NI	

IRACE et al., 2016.	YES	12	Friable	NI	NI	Nodule	Well circumscribed	Well circunscribed	
SARAVAKOS et al., 2016.	Transitory paresthesia	2	Firm	NI	NI	Nodule	Well circumscribed	NI	
WANI et al., 2016.	NI	NI	Firm	Reddish	Telangiectatic	Nodule	NI	NI	Sialoblastoma
SITTHICHAIYAKUL et al., 2016.	NI	NI	NI	NI	NI	Nodule	NI	NI	
WANG et al., 2018.	NI	7	Firm	NI	NI	Nodule	Undefined	Undefined	Salivary gland neuroendocrine tumor
DI MICCO et al., 2019.	YES - transient due to biopsy	4	Firm	NI	NI	Nodule	NI	NI	
RODRÍGUEZ et al., 2021.	NO	11,4	Firm	NI	Telangiectatic	Nodule	Well circumscribed	NI	Sialoblastoma
YANG et al., 2022.	YES	6,6	Firm	NI	NI	Nodule	Well circumscribed	well borders	
HE et al., 2022.	NI	3	NI	NI	Smooth	Nodule	NI	NI	Submandibular gland tumor

NI: not informed

Table S5. Microscopical and immunohistochemical characteristics of the fifity-two studies (62 cases) of Sialoblastoma included in the systematic review.

Study	Focal necrosis	Myoepithelial cell	Stroma	Mitoses	cytokeratins +	actin	s-100 +	p63	c-kit	Ki-67
CANALIS et al., 1980.	NI	NI	Fibrous	NO	NI	NI	NI	NI	NI	NI
ROTH et al., 1986.	NO	NI	YES	NI	NI	NI	NI	NI	NI	NI
	NO	NI	YES	NO	NI	NI	NI	NI	NI	NI
SIMPSON et al., 1986.	YES	YES	Fibrous	YES	NI	NI	NI	NI	NI	NI
TAYLOR et al., 1988.	YES	YES	YES	YES	YES	YES	NI	NI	NI	NI
BATSAKIS et al., 1988.	NI	NI	NI	YES	YES	NI	NI	NI	NI	NI
ADKINS et al., 1990.	NI	NI	NI	YES	NI	NI	NI	NI	NI	NI
	NI	NI	NI	YES	NI	NI	NI	NI	NI	NI
HARRIS et al., 1990.	NO	YES	Fibrous	NO	YES	YES	YES	NI	NI	NI
SEIFERT et al., 1997.	NI	NI	Loose	NO	YES	YES	NI	NI	NI	NI
	NI	NI	Loose	NI	YES	YES	NI	NI	NI	NI
	YES	NI	Loose	YES	YES	YES	NI	NI	NI	NI
LUNA et al., 1999.	YES	NI	NI	YES	YES	NI	YES	NI	NI	YES
BRANDWEIN et al., 1999.	YES	YES	NI	YES	YES	NI	YES	NI	NI	YES (30%)
ALVAREZ et al., 1999.	YES	NO	NI	YES	YES	YES	YES	NI	NI	NI

GARRIDO et al., 2000.	YES	NI	Vascularized	YES	NI	NI	NI	NI	NI	NI
SIDDIQI et al., 2000.	YES	NI	NI	NI	NI	NI	NI	NI	NI	NI
GREEN et al., 2000.	YES	YES	Desmoplastic	YES	YES	YES	NI	NI	NI	YES (50%)
MOSTAFAPOUR et al., 2000.	NO	YES	Fibromyxoid	NO	NI	NI	YES	NI	NI	NI
ORTIZ et al., 2001.	NO	NI	YES	NO	NI	NI	NI	NI	NI	NI
HUANG et al., 2003.	NI	YES	YES	NI	NI	NI	NI	NI	NI	NI
OZDEMIR et al., 2005.	NI	NI	NI	NI	YES	YES	YES	NI	NI	NI
VERRET et al., 2006.	NO	NI	YES	YES	NI	NI	NI	NI	NI	NI
TATLIDEDE et al., 2006.	YES	YES	Fibrous	NI	YES	YES	YES	NI	NI	NI
WILLIAMS et al., 2006.	NI	NI	YES	NI	NI	NI	NI	NI	NI	NI
	NI	NI	NI	YES	YES	YES	YES	YES	NI	YES (3%)
	NI	NI	YES	YES	NI	NI	NI	NI	NI	NI
	NI	NI	NI	YES	YES	YES	YES	YES	NI	YES (80%)
	NI	NI	YES	YES	NI	NI	NI	NI	NI	NI
	YES	NI	NI	YES	YES	YES	YES	YES	NI	YES (40%)
VIDYADHAR et al., 2008.	NO	NI	Fibrous	YES	NI	YES	YES	NI	NI	YES (10%)
MOON et al., 2008.	NO	NI	Fibrous	YES	YES	NI	NI	NI	NI	YES (3%)
CRISTOFARO et al., 2008.	NI	NI	YES	NI	YES	YES	YES	NI	NI	NI
SCOTT et al., 2008.	YES	NI	YES	YES	YES	YES	NI	NI	NI	NI
MARUCCI et al., 2009.	NI	YES	Fibrovascular	NI	NI	NI	NI	NI	NI	NI
STONES et al., 2009.	NI	NI	Fibrous	NI	NI	NI	NI	NI	NI	NI

MERTENS et al., 2009.	NI	NI	YES	YES	YES	NI	NO	NI	NI	NI
ERSOZ et al., 2010.	YES	NI	YES	YES	YES	NI	YES	YES	NI	YES (80%)
PATIL et al., 2010.	NI	NI	Fibrous	NI	YES	YES	YES	YES	NO	YES (20%)
	NO	NI	YES	YES	YES	YES	YES	NO	NO	YES (70% - 80%)
EKEN et al., 2010.	NI	NI	Fibromyxoid	YES						
PRIGENT et al., 2010.	YES	NI	YES	YES	YES	NI	NO	NI	NO	NI
KARAMAN et al., 2010.	YES	NI	NI	YES	NI	NI	NI	NI	NI	NI
KATTOOR et al., 2010.	NI	NI	NI	YES	YES	NI	YES	NI	NI	NI
SAFFARI et al., 2011.	NO	NO	Fibromyxoid	YES	YES	NI	YES	YES	NI	YES (25% - 30%)
FAROOQI et al., 2011.	NI	NI	NI	YES	NI	NI	NI	NI	NI	NI
FUCHSMANN et al., 2011.	NO	NI	YES	YES	YES	NO	YES	NI	NI	YES (30%)
BROWN et al., 2012.	YES	NI	YES	NI	NI	NI	NI	YES	YES	NI
AGGARWAL et al., 2013..	NO	YES	Fibromyxoid	NI	YES	YES	NI	NI	NI	YES (4-6%)
DEMIRÖZ et al., 2014.	YES	NI	NI	YES	no	NO	NO	YES	NO	YES (40%)
SHARMA et al., 2014.	NO	YES	Fibrous		YES	NI	NI	NI	NI	NO
KATARIA et al., 2015.	NI	YES	YES	YES	YES	YES	YES	NI	NI	NI
SICHEL et al., 2016.	NO	NI	YES	YES	NI	NI	NI	NO	NI	YES(10-15%)
IRACE et al., 2016.	YES	NI	NI	NI	YES	NI	NI	NI	NI	NI

SARAVAKOS et al., 2016.	NI	YES	YES	NI	NI	NI	NI	NI	NI	NI
WANI et al., 2016.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
SITTHICHAIYAKUL et al., 2016.	YES	NO	YES	YES	YES	YES	YES	YES	NI	YES (70%)
WANG et al., 2018.	NI	NI	NI	YES	NI	NI	NI	NI	NI	YES (50%)
DI MICCO et al., 2019.	NI	NI	YES	NI	NI	NI	NI	NI	NI	YES
RODRÍGUEZ et al., 2021.	YES	YES	Fibrous	NO	YES	YES	YES	NI	NI	YES (20 - 30%)
YANG et al., 2022.	NI	NI	NI	NI	YES	YES	YES	YES	NO	YES (20%)
HE et al., 2022.	NO	YES	Fibromyxoid	NO	YES	YES	YES	YES	NI	YES (10%)

NI: not informed

Table S6. Univariate log-rank analysis of clinicopathological characteristics of cases of Sialoblastoma in salivary glands.

Variables	Recurrence/total	5-year survival (%)	Estimative (95% CI)	p-value
Age group				**<.003**
0-1 year old	5/29	82.8	405.4 (317.0 – 493.7)	
More than 1 year old	10/18	44.4	49.2 (11.6 – 86.7)	
Color				-
Normochromic	0/5	100.0	-	
Color alteration	2/8	75.0	-	
Cribriform pattern				<.198
Yes	4/13	69.2	104.9 (53.3 – 156.5)	
No	5/10	50.0	14.4 (7.9 – 20.9)	
Capsule				**<. 0001**
Yes	2/14	85.7	413.4 (285.2 – 541.6)	
No	1/1	0	5.0 (5.0 – 5.0)	
Congenital				**<. 0001**
Yes	5/30	83.3	385.9 (283.0 – 488.8)	
No	8/6	25.0	43.5 (0.0 – 88.5)	
Facial paralysis				<.420
Yes	7/15	53.3	83.3 (44.9 – 121.7)	
No	1/6	83.3	23.3 (16.7 – 29.8)	
Focal necrosis				-
Yes	16/10	37.5	-	
No	0/12	100.0	-	
Limits				<.166
Well defined	19/6	68.4	73.5 (50.8 – 96.2)	
Undefined	2/2	0.0	11.0 (3.1 – 18.8)	
Metastasis				**<.011**
Yes	6/7	14.3	16.8 (8.9 – 24.8)	
No	8/36	77.8	123.5 (95.9 – 151.2)	
Mitoses				-
Yes	11/26	57.7	-	
No	0/6	100	-	
Myoepithelial cells				<.917
Yes	6/14	57.1	20.8 (13,5 – 28.1)	

No	1/3	66.7	17.6 (7.5 – 27.8)	
Perineural invasion				**<.035**
Yes	3/5	40.0	17.8 (7.4 – 28.1)	
No	2/19	89.5	139.2 (117.2 – 161.1)	
Nuclear pleomorphism				<.292
Yes	7/9	22.2	14.9 (6.8 – 23.0)	
No	1/4	75.0	21.5 (12.1 – 30.8)	
Sex				<.091
Male	3/19	84.2	424.4 (328.6 – 520.3)	
Famele	12/27	55.6	74.7 (37.5 – 111.8)	
Site				**<.005**
Major salivary glands	7/34	79.4	373.7 (280.1 – 467.3)	
Minor salivary glands	8/13	38.5	35.2 (3.6 – 66.9)	
Solid pattern				<.285
Yes	6/10	40.0	14.0 (8.4 – 19.6)	
No	1/4	75.0	19.5 (13.2 – 25.7)	
Surface				-
Smooth	0/5	100.0	-	
Smooth alteration	1/10	90.0	-	
Symptomatology				<.201
Painful	3/4	25.0	44.7 (0.0 – 107.7)	
Painless	6/17	64.7	72.7 (43.1 – 102.3)	
Synchronous association with other tumors				<.684
Yes	2/6	66.7	45.5 (24.6 – 66.5)	
No	11/35	68.6	97.3 (68.5 – 126.1)	
Treatment				-
Surgery	15/44	65.9	-	
Surgery + CT	0/3	100.0	-	

Table S7. Description of the risk of bias of all studies in detail assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in Systematic Reviews of the JBI (case report).

Question	1-	2-	3-	4-	5-	6-	7-	8-	N (%)
CANALIS et al. 1980.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
SIMPSON et al. 1986.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
TAYLOR et al. 1988.	YES	YES	NO	YES	YES	YES	NO	YES	6/8 (75)
BATSAKIS et al. 1988.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
HARRIS et al. 1990.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
LUNA et al. 1999.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
BRANDWEIN et al. 1999.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
ALVAREZ et al. 1999.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
GARRIDO et al. 2000.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
SIDDIQI et al. 2000.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
GREEN et al. 2000.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
MOSTAFAPOUR et al. 2000.	YES	YES	NO	YES	YES	NO	NO	YES	5/8 (62,5)
ORTIZ et al. 2001.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
HUANG et al. 2003.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
OZDEMIR et al. 2005.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
VERRET et al. 2006.	YES	YES	YES	YES	YES	NO	NO	YES	6/8 (75)
TATLIDEDE et al. 2006.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
VIDYADHAR et al. 2008.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
MOON et al. 2008.	YES	YES	NO	YES	YES	YES	NO	YES	6/8 (75)
CRISTOFARO et al. 2008.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
SCOTT et al. 2008.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
MARUCCI et al. 2009.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
STONES et al. 2009.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
MERTENS et al. 2009.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
ERSOZ et al. 2010.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
PATIL et al. 2010.	YES	YES	NO	YES	YES	YES	NO	YES	6/8 (75)
EKEN et al. 2010.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
PRIGENT et al. 2010.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
KARAMAN et al. 2010.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
KATTOOR et al. 2010.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
SAFFARI et al. 2011.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
FAROOQI et al. 2011.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)

FUCHSMANN et al. 2011.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
BROWN et al. 2012.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
Aggarwal R et al. 2013	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
DEMIRÖZ et al. 2014.	YES	YES	NO	YES	YES	YES	YES	YES	7/8 (87,5)
SHARMA et al. 2014.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
KATARIA et al. 2015.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
SICHEL et al. 2016.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
IRACE et al. 2016.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
SARAVAKOS et al. 2016.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
WANI et al. 2016.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
SITTHICHAIYAKUL et al. 2016.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
WANG et al. 2018.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
DI MICCO et al. 2019.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
RODRÍGUEZ2021 et al. 2021.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
YANG et al. 2022.	YES	YES	YES	YES	YES	YES	YES	YES	8/8 (100)
HE et al. 2022.	YES	YES	YES	YES	YES	YES	NO	YES	7/8 (87,5)
%	52 (100%)	52 (100%)	41 (78.8%)	52 (100%)	52 (100%)	50 (96.1%)	34 (65.3%)	52 (100%)	

1- Were patient's demographic characteristics clearly described?

2- Was the patient's history clearly described and presented as a timeline?

3- Was the current clinical condition of the patient on presentation clearly described?

4- Were diagnostic tests or assessment methods and the results clearly described?

5- Was the intervention(s) or treatment procedure(s) clearly described?

6- Was the post-intervention clinical condition clearly described?

7- Were adverse events (harms) or unanticipated events identified and described?

8- Does the case report provide takeaway lessons?

Table S8. Description of the risk of bias of all studies in detail assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in Systematic Reviews of the JBI (series of cases).

Question	1	2	3	4	5	6	7	8	9	10	%
ROTH et al. 1986.	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	9 (90%)
ADKINS et al. 1990.	YES	YES	YES	YES	YES	YES	YES	NO	NO	NO	7 (70%)
SEIFERT et al. 1997	YES	NO	YES	YES	YES	YES	NO	NO	NO	NO	5 (50%)
WILLIAMS et al. 2006.	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	9 (90%)
PATIL et al. 2010.	YES	YES	YES	YES	YES	NO	YES	YES	NO	NO	7 (70%)
%	5 (100%)	4 (80%)	5 (100%)	5 (100%)	5 (100%)	4 (80%)	4 (80%)	3 (60%)	2 (40%)	0	

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?

3 CONCLUSÃO

- O sialoblastoma acomete principalmente pacientes durante a primeira década de vida, geralmente ao nascimento ou nos primeiros meses de nascimento. Não houve predileção por sexo, sendo a glândula parótida a região mais acometida.
- O comportamento clínico é amplo, e a maioria dos casos se apresentavam como lesões de crescimento lento e indolente. No entanto, algumas lesões podem se manifestar localmente agressivas, com metástases regionais e à distância.
- Microscopicamente, as lesões geralmente são encapsuladas e apresentavam proliferação de células basaloides que podem se organizar principalmente em dois padrões histopatológicos distintos: cribriforme e sólido. As lesões que apresentavam necrosem focal, presença de figuras mitóticas e invasão perineural estavam mais associadas à mais taxa de recorrência.
- O principal tratamento de escolha era a excisão cirúrgica.
- Ademais, para melhor entendimento dessa neoplasia, faz-se necessário estudos moleculares, a fim de identificar com maior acurácia características clínicas, histopatológicas ou moleculares que interfira diretamente no prognostico desse tumor.

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Anexo 1: Relatório de verificação de plágio

ESTUDO CLINICOPATOLÓGICO E ANÁLISE DE SOBREVIDA DO SIALOBASTOMA: UMA REVISÃO SISTEMÁTICA

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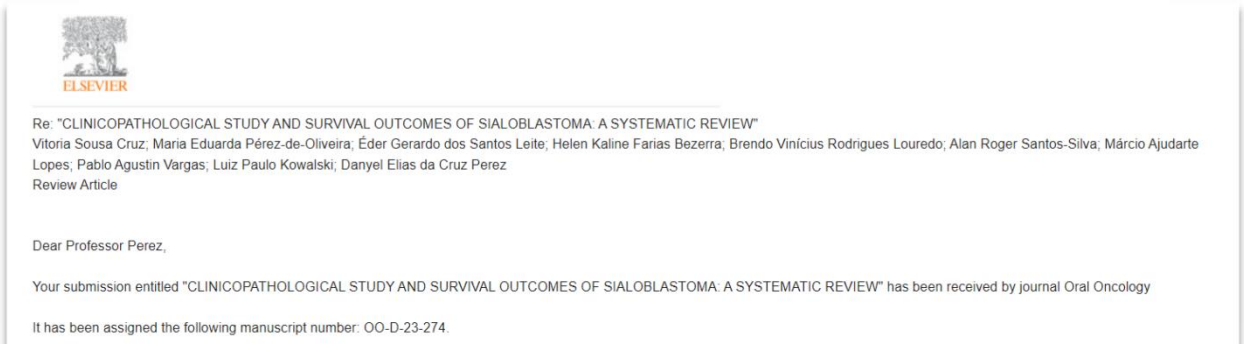
Anexo 2: Comprovante de submissão do artigo



Re: "CLINICOPATHOLOGICAL STUDY AND SURVIVAL OUTCOMES OF SIALOBLASTOMA: A SYSTEMATIC REVIEW"
Vitoria Sousa Cruz; Maria Eduarda Pérez-de-Oliveira; Éder Gerardo dos Santos Leite; Helen Kaline Farias Bezerra; Brendo Vinícius Rodrigues Louredo; Alan Roger Santos-Silva; Márcio Ajudarte Lopes; Pablo Agustin Vargas; Luiz Paulo Kowalski; Danyel Elias da Cruz Perez
Review Article

Dear Professor Perez,

Your submission entitled "CLINICOPATHOLOGICAL STUDY AND SURVIVAL OUTCOMES OF SIALOBLASTOMA: A SYSTEMATIC REVIEW" has been received by journal Oral Oncology

It has been assigned the following manuscript number: OO-D-23-274.