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Dissertação

Perfil clínico-histopatológico do carcinoma ex adenoma pleomórfico de glândulas salivares: uma revisão sistemática

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O presente trabalho de dissertação foi redigido segundo o Manual de Normas para Dissertações, Teses e Trabalhos Científicos da Universidade Federal de Pelotas de 2013, adotando o Nível de Descrição em Capítulos, descrito no referido manual. <http://sisbi.ufpel.edu.br/?p=documentos&i=7> Acesso em: <20/04/2023>.

Resumo

CEPEDA, Isadora Vilas Boas. **Perfil clínico-histopatológico do carcinoma ex adenoma pleomórfico de glândulas salivares: uma revisão sistemática.** 2023. 74f. Trabalho Dissertação em Clínica Odontológica, com ênfase em Diagnóstico Bucal – Pós-Graduação em Odontologia. Universidade Federal de Pelotas, Pelotas, 2023.

As neoplasias epiteliais de glândulas salivares são um grupo heterogêneo de doenças que têm características clinicopatológicas complexas e comportamentos distintos. O carcinoma ex adenoma pleomorfico (CXAP) é definido como uma neoplasia maligna que se origina a partir de um adenoma pleomorfico primário (de novo) ou de recorrências, compreendendo um grupo heterogêneo de aspectos histológicos malignos, com graus de invasividade e agressividade distintos. O objetivo deste estudo é realizar uma revisão sistemática para analisar o perfil clínico-patológico dos pacientes acometidos por Carcinoma ex adenoma pleomórfico de glândulas salivares. Uma revisão sistemática da literatura foi feita e 141 artigos foram incluídos, 111 casos desagregados (CD) e 30 agregados (CA). Os dados foram analisados usando o Excel v16 (Microsoft Office) e o software MedCalc (MedCalc Software bv, versão 19.2.6, Ostend, Bélgica). O CXPA foi mais frequente no sexo masculino (56,4% - CD e 58,8% - CA), na sexta década de vida, estadiamento T2 (34,5% - CD, 36,8% - CA), N0 (67,4% - CD, 68% - CA), M0 (89,4% - CD, 92,5% - CA), nas glândulas salivares maiores (89,9% - CD e 95,0% - CA), sendo a parótida (71,9% - CD e 82,7% - CA) a mais acometida. Adenocarcinoma (28,9%, 34,4%), carcinoma do ducto salivar (20,8%, 20,8%) e carcinoma mioepitelial (19,1%, 25,2%) foram os subtipos histológicos mais frequentes. O tempo de evolução médio foi de 99.67 meses. A curva de sobrevivência caiu drasticamente em 10 anos de acompanhamento no grupo CD, refletindo a agressividade desse tumor. Revisões sistemáticas facilitam e sintetizam as informações disponíveis na literatura, entretanto, novas pesquisas, seguindo os protocolos de reporte, são necessárias para melhor elucidar as características desta complexa entidade.

Palavras-chave: carcinoma ex adenoma pleomorfico, epidemiologia, revisão sistemática, glândulas salivares

Abstract

CEPEDA, Isadora Vilas Boas. **Clinical-histopathological profile of patients affected by Carcinoma ex pleomorphic adenoma of the salivary glands**. 2023. 74f. Work Dissertation in Clinical Dentistry, with emphasis on Oral Diagnosis Post-Graduation in Dentistry. Federal University of Pelotas, Pelotas, Year.

Salivary gland epithelial neoplasms are a heterogeneous group of diseases that have complex clinicopathological characteristics and distinct behaviors. Carcinoma ex pleomorphic adenoma (CXAP) is defined as a malignant neoplasm that originates from a primary pleomorphic adenoma (de novo) or from recurrences, comprising a heterogeneous group of malignant histological aspects, with different degrees of invasiveness and aggressiveness. The objective of this study is to carry out a systematic review to analyze the clinical-pathological profile of patients affected by Carcinoma ex pleomorphic adenoma of the salivary glands. A systematic review of the literature was performed, and 141 articles were included, 111 cases disaggregated (DC) and 30 aggregated (AC). Data were analyzed using Excel v16 (Microsoft Office) and MedCalc software (MedCalc Software bv, version 19.2.6, Ostend, Belgium). CXPA was more frequent in males (56.4% - DC and 58.8% - AC), in the sixth decade of life, stage T2 (34.5% - DC, 36.8% - AC), N0 (67.4% - DC, 68% - AC), M0 (89.4% - DC, 92.5% - AC), in the major salivary glands (89.9% - DC and 95.0% - AC), the parotid gland (71.9% - DC and 82.7% - AC) the most affected. Adenocarcinoma (28.9% - DC, 34.4% - AC), salivary duct carcinoma (20.8% - DC, 20.8% - AC) and myoepithelial carcinoma (19.1% - DC, 25.2% - AC) were the most frequent histological subtypes. The mean evolution time was 99.67 months. The survival curve down dramatically over 10 years of follow-up in the DC group, reflecting the aggressiveness of this tumor. Systematic reviews facilitate and summarize the information available in the literature, however, new research, following the reporting protocols, are necessary to better elucidate the characteristics of this complex entity.

Key-words: carcinoma ex pleomorphic adenoma, epidemiology, systematic review, salivary glands

Sumário

1 Introdução

As neoplasias epiteliais de glândulas salivares são um grupo heterogêneo de doenças que têm características clinicopatológicas complexas e comportamentos distintos (PINKSTON, et al. 1999). De acordo com a classificação dos tumores de glândulas salivares da Organização Mundial da Saúde (OMS) de 2017, existem 41 tipos de tumores de glândulas salivares, sendo 22 considerados malignos, 11 benignos e 8 que se encaixam em outras categorias. Em 2022, a classificação da OMS foi atualizada e mais três neoplasias benignas e duas malignas foram introduzidas (SKÁLOVÁ et al. 2022). São consideradas lesões incomuns, e representam de 3-6% de todos os tumores encontrados na região de cabeça e pescoço (EL-NAGGAR, et al. 2017), sendo que destes somente 10-15% ocorrem em glândulas salivares menores (POORTEN, et al. 2014).

Descrito pela primeira vez por Billroth em 1859, o adenoma pleomórfico (AP) é a neoplasia benigna mais comum de glândulas salivares (TIAN, et al. 2008; VASCONCELOS, et al. 2016), com a incidência anual de 2-3.5 casos/100.000 habitantes (SOOD et al. 2014). Podem ocorrer em qualquer idade, mas preferencialmente acometem pacientes entre a quarta e sétima década de vida (CUNHA, et al. 2023), com uma leve preferência pelo sexo feminino (ARAYA, et al. 2015; CUNHA, et al. 2020) e 60%-85% acometem a glândula parótida (SPIRO, 1986). Clinicamente, se apresenta como uma massa firme, com histórico de crescimento lento e assintomático, o que faz com que o diagnóstico seja feito com a lesão já evoluída (SEOK, et al. 2019).

Histologicamente, embora já tenha sido chamado de tumor misto, o AP tem origem puramente epitelial (HELLQUIST, et al. 2019). É caracterizado pela presença de células ductais e mioepiteliais, dispostas em um estroma condromixoide, no qual a parte mesenquimal se origina de um processo metaplásico das células mioepiteliais neoplásicas (HERNANDEZ-PRERA, et al. 2021). Podem apresentar um padrão microscópico variado dependendo do arranjo epitelial e da quantidade de estroma presente (ITO, et al. 2009), sendo, eventualmente, um desafio diagnóstico para o patologista (HELLQUIST, et al. 2019).

O tratamento é cirúrgico e o tumor possui uma taxa de recorrência entre 3,4% e 6,3% (ANTONY, et al. 2011), estando associada a diversos fatores, dentre eles, a remoção do tumor por enucleação, ruptura do tumor durante a cirurgia, abundância de estroma condromixoide e indíviduos jovens (ROOKER, et al. 2021; ALZUMAILI, et al. 2022). Após a primeira recorrência, há um risco de novas recorrências e da transformação maligna, estimada em 3,3% (KATAS, 2018). Idade avançada (EGAL, et al. 2018) e tamanho do tumor são alguns dos fatores associados a essa transformação (YIN, et al. 2020).

O carcinoma ex adenoma pleomorfico (CXAP) é definido como uma neoplasia maligna que se origina a partir de um adenoma pleomorfico primário (de novo) ou de uma recorrência (GNEPP, 1993). A sua patogênese não é clara, e duas hipóteses têm sido levantadas na literatura ao longo dos anos: a primeira, mais antiga, de que o tumor poderia ser maligno desde o começo (GERUGHTY, et al. 1969) ou a segunda possibilidade, de que ocorra uma transformação carcinomatosa em um adenoma pleomórfico, pois a média de idade para PA era 10 anos menor que para CXPA, sendo a maioria dos pacientes atendidos inicialmente com história de massa de longa duração, com crescimento abrupto e novos sintomas (OLSEN, et al. 2001).

O CXPA tem uma leve predileção pelo sexo feminino (ANTONY, et al. 2012) e normalmente ocorre entre a sexta e a sétima década de vida (SEOK, et al. 2019; KHANNA, et al. 2019). A apresentação clínica clássica é uma massa firme na parótida (NOURAEI, et al. 2005; ANTONY, et al. 2012), que pode ser confundida com o AP, mas um crescimento rápido e repentino em uma lesão que antes apresentava crescimento lento deve levantar suspeita de uma transformação maligna (GUPTA, et al. 2019). O CXAP tem preferência pelas glândulas salivares maiores, em especial na parótida, e, quando em glândulas menores, se dá principalmente no palato (DAMM, et al. 2001; YOSHIHARA, et al. 1995). Usualmente se apresenta assintomático, podendo ser sintomático com o passar do tempo, à medida que o tumor vai crescendo e pressionando outras estruturas, como por exemplo, o nervo facial (ZBAREN, 2018).

Microscopicamente, o CXPA é composto da mistura de um adenoma pleomorfico com um carcinoma, sendo o adenocarcinoma, o carcinoma de ducto salivar e o carcinoma mioepitelial as variações histológicas mais encontradas (LEWIS, et al. 2001; KATABI, et al. 2010; BHARDWAJ, et al. 2018). O diagnóstico

do CXPA é muitas vezes difícil e desafiador, porque o seu componente maligno é com frequência pequeno e negligenciado (OLSEN, et al. 2001).

De acordo com a classificação mais recente da Organização Mundial da Saúde (SKÁLOVÁ et al. 2022), histologicamente é subdividido em intracapsular (proliferação anormal dentre/entre os ductos), mínimamente invasivo (rompimento da cápsula do AP por células carcinomatosas, <4-6mm de extensão além da borda do AP) e amplamente invasivo (estendendo-se na glândula e nos tecidos adjacentes) (EL-NAGGAR, et al. 2017).

De forma prática, carcinomas que se originam a partir do AP podem ser classificados em dois grupos: carcinomas com diferenciação mioepitelial, como por exemplo, carcinoma adenóide cístico, adenocarcinoma e carcinoma mioepitelial, e carcinomas sem diferenciação mioepitelial, como por exemplo, carcinoma mucoepidermoide, carcinoma de células escamosas e carcinoma do ducto salivar (NAGAO, et al. 2012).

O seu tratamento é cirúrgico, normalmente associado com radioterapia e quimioterapia (ANTONY, et al. 2012; ZUREK, et al. 2022). A taxa de metástase local ou à distância é de aproximadamente 70% e a taxa de sobrevivência em 5 anos varia de 25%-65%, sendo as variantes intracapsular e a minimamente invasiva as que apresentam um melhor prognóstico (EL-NAGGAR, et al. 2017; KEY, et al. 2022).

Devido à sua raridade, os CXPAs ainda são tumores de glândulas salivares pouco compreendidos e não há dados em larga escala sobre sua caracterização clínico-patológica. Essas neoplasias frequentemente surgem a partir de uma lesão benigna, mas compreendem um grupo heterogêneo de aspectos histológicos malignos, com graus de invasividade distintos. Portanto, o objetivo deste estudo é realizar uma revisão sistemática a fim de melhor compreender o perfil clínico-patológico dos pacientes acometidos por Carcinoma ex adenoma pleomórfico de glândulas salivares.

2 Capítulo 1 - Artigo

O seguinte artigo será enviado para publicacação e está formatado de acordo com as normas da revista Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology – Qualis A2 e Fator de Impacto 2.538.

Clinicopathological profile of carcinoma ex pleomorphic adenoma of the salivary glands - a systematic review

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Abstract

Objective: this study aims to perform a systematic review (SR) to better understand the demographic and clinicopathological profile of Carcinoma ex pleomorphic adenoma (CXPA) of the salivary glands. Study design: SR of the literature was made and 141 articles were included, 111 disaggregated cases (DC), which were individualized information and 30 aggregated cases (AC), which were pooled cases from large series. The data were extracted and analyzed using Excel v16 (Microsoft Office) and the MedCalc software. Results: CXPA was most frequent, for DC and AC, respectively, in males (56.4%, 58.8%), in the sixth decade of life, T2 (34.5%, 36.8%), N0 (67.4%, 68%), M0 (89.4%, 92.5%) staging, in major salivary glands (89.9%, 95.0%), being the parotid (71.9%, 82.7%) the most affected. Adenocarcinoma (28.9%, 34.4%), salivary duct carcinoma (20.8%, 20.8%) and myoepithelial carcinoma (19.1%, 25.2%) were the most frequent histological subtype. Conclusion: The current SR demonstrates CXPA is a rare entity that affects older males, being the parotid gland its main site, predominantly T2N0M0. The most common histological subtypes of CXPA are adenocarcinoma, salivary duct carcinoma and myoepithelial carcinoma. SR facilitates and synthesizes information. However, more research following the guidelines are necessary, to better elucidate the characteristics of this complex tumor.

Key words: carcinoma ex pleomorphic adenoma, epidemiology, systematic review, salivary glands

Introduction

Carcinoma ex pleomorphic adenoma (CXPA) is defined as carcinoma arising from a primary or recurrent pleomorphic adenoma (PA)[1]. This rare malignant neoplasm accounts for 11.6% of all malignant salivary gland neoplasms and has a prevalence rate of 5.6 cases per 100,000 malignant neoplasms[1]. CXPA has a slight female predilection[2], and commonly affects individuals aged between 6th and 7th decades of life[3,4]. The classic clinical feature of CXPA is a firm mass in parotid[2,5,6], when it involves major salivary glands, or in palate, when the minor salivary glands are affected by it[7].

Although the CXPA can be clinically similar to PA, a recent and sudden growth in a previously slow-growing lesion may be suspicious for malignant transformation[8]. Overall, PA has an incidence of malignant change of 6.2%[9]. Factors such as incomplete removal of PA by enucleation, tumor rupture during surgery, abundant amount of condromixoid stroma and young age are strongly associated with PA recurrence [10, 11]. After the first recurrence of PA, there is a risk of new recurrences [10, 11] and also for malignant change, which is estimated at 3.3%[15].

Microscopically, CXPA is composed of a mixture of regions of pleomorphic adenoma (or degenerated PA) with different histological variants of carcinoma [13, 14, 15, 16]. The epithelial malignant tumor may be exclusively or predominantly one tumor type or may present as a mixed type. They are most often diagnosed as adenocarcinoma not otherwise specified, salivary ductal carcinomas, and myoepithelial carcinoma as well [13,15]. Moreover, tumor grading and invasion are important histopathological characteristics of CXPA [12]. According to the last WHO classification (2022) tumor invasion in CXPA is subtyping in intracapsular (*in situ* or abnormal proliferation within/between the ducts), minimally invasive (disruption of PA capsule by tumor cells, extending beyond its margins), and widely invasive (tumor cells present into the gland and adjacent tissues) [12]. Another histological high-risk aspect are positive margins, perineural invasion, and lymph node metastasis [18]. Widely invasive and high-grade CXPA have been associated with poor prognoses [13,20].

Surgery is the gold standard treatment for CXPA, usually associated with radiotherapy and chemotherapy [13,19]. CXPA rate of local or distant metastasis is as many as 70% and its 5-year survival rate ranges from 25% to 65% [17, 21].

Due to the rarity of CXPAs, they are still poorly understood salivary gland tumors and no large-scale data on their clinicopathological characterization are available. These neoplasms arise in the settings of a benign PA, but they comprise a very heterogeneous group of malignant histologies, grade and invasiveness. Therefore, the aim of this study is to perform a systematic review in order to better understand the clinicopathological profile of Carcinoma ex pleomorphic adenoma of the salivary glands.

Methods

This review was conducted following the guidelines for reporting systematic reviews of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [178]. A protocol was delineated and registered in National Institute for Health Research´s International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42022380495.

1. Information sources and search strategies

Electronic searches on Pubmed, Embase, Scopus, and Web of Science databases for articles published in English prior to September 2022 and without date publication restrictions were undertaken. The keywords and Booleans used in PubMed were “carcinoma ex-pleomorphic adenoma OR carcinoma ex-benign mixed tumor AND salivary gland OR parotid gland OR submandibular gland OR sublingual gland OR minor salivary gland”. This search strategy was adapted to the other databases.

2. Eligibility criteria

The main purpose of the present systematic review was to answer the following question: “What is the clinicopathological profile of Carcinoma ex pleomorphic adenoma of the salivary glands?”

Inclusion criteria: retrospective, prospective, case-control, case series, and case reports that related cases of carcinoma ex pleomorphic adenoma in all salivary

glands (major and minor), with enough descriptions of clinical and histopathological information. When there was more than one study with the same population, we included the paper where more data were available.

Exclusion criteria: reviews, meta-analyses, letter to editor, book chapters, personal comments, abstracts published in conference proceedings, animal research or in vitro studies.

3. Selection process

The search was conducted by one independent author (IVBC) and the eligibility criteria were evaluated by two independent authors (IVBC and FAC). The agreement between reviewers in the assessment of the first 50 references was determined. Kappa was calculated. A value of Kappa ≥ 0.80 indicated a very good agreement between reviewers [174]. Any discrepancies were resolved by a third author (SBCT). Articles were first selected by their title and abstract and then, after reading full text the authors decided if they met de inclusion criteria. The Rayyan software was used to remove duplicates and to organize the references.

The data were extracted by one independent author (IVBC) who made analysis using Excel v16 (Microsoft Office). Datasets were crosschecked by a second author (SBCT) and any discrepancies were solved by consensus. The studies were separated into two categories: *disaggregated cases (DC)*, when the information for each case was individualized, and *aggregated cases (AC)*, when the data were pooled and the information about the studied disorder was taken together in case series. The data extracted were the last name of the authors and publication year, country, number of cases, age (years), sex (male and female), size (according to TNM grade system), nodes (presence/absence), metastasis (presence/absence), site 1 (major salivary gland or minor salivary gland), site 2 (lesion location), symptom (presence/absence), evolution time (in months), image exam (ultrasound, Magnetic Resonance Imaging (MRI), Tomography (CT)) , CXPA type (histological malignant variants), perineural invasion (presence/absence), lymphovascular invasion (presence/absence), necrosis (presence/absence), atypical mitosis (presence/absence), hyalinization (presence/absence), positive margin (yes/no), positive lymph nodes (yes/no), treatment, death (yes/no) and follow up (in months).

4. Study risk of bias assessment

Critical appraisal of the studies were carried out by two independent authors (IVBC and FAC) using the Joanna Briggs Institute, University of Adelaide tool for case report, case series, and cross sectional studies [175]. Any discrepancies were solved by a third author (SBCT).

5. Statistical analysis

The MedCalc software was used (MedCalc Software bv, version 19.2.6, Ostend, Belgium). Descriptive analyses were performed. For the outcome of death, survival analysis was carried out with the Kaplan-Meier test ($p > 0.05$).

Results

Study selection

The electronic search yielded 2,061 articles and 141 [22-163] were included in this review as shown in flowchart in Figure 1. A total of 111 considered as DC and 30 as AC. Kappa indicating the agreement between reviewers in the assessment of the first 50 references was 0.85.

Critical appraisal of the included articles

For the case reports and case series, all 90 (100%) included articles provided a clear description of the patients' demographic characteristics and current clinical status and the patient history as a timeline. Diagnostic tests or assessment methods were reported in 89 (98.8%) studies. Most articles provided intervention data (n = 78; 86.7%) and the post-intervention (n = 60; 66.6%) clinical condition of affected individuals. All articles (100%) provided take-away lessons (Table S1).

For the cross-sectional studies, all 51 (100%) provided satisfying information regardless of the inclusion criteria, study subjects, exposure, condition, confounding factors, outcomes, and statistical analysis (Table S2).

General characteristics of the included studies

The results of the descriptive analyses of the DC are summarized in Table 1 and the ones of the AC in Table 2. The three countries with more reports of DC were Japan (21.5%), followed by Brazil (17.0%), and the United States (13.9%). For the AC, cases in the United States (19.4%), China (19.4%), and Brazil (12.9%) were the countries with more publications.

Demographic aspects

Regarding the sex of the individuals, the CXPA was more frequent in males (56.4% for DC and 58.8% for AC). The mean age was 58.82 years for the DC and 57.64 for the AC.

TNM grade system and other clinical features (anatomic location and evolution time)

Considering the TNM grade system for cancer staging elaborated by the American Cancer Society [176], T2 (34.5%, 36.8%), N0 (67.4%, 68%), and M0 (89.4%, 92.5%) were more frequent in the DC and AC, respectively.

Regarding the anatomic location, the major salivary glands were more affected in both analyses, DC and AC (89.9% and 95.0%), being the parotid gland the most frequent location (71.9% - DC and 82.7% - AC). Considering the minor salivary glands, the specific site was informed only for the DC, involving six different anatomic locations for the development of CXPA, with the palate being the most common affected region (4.9%)

The variable evolution time (in months - mean, standard deviation) was mentioned only for DC, being 99.67 (±121.23). When analyzing the association between evolution time and sex, the mean evolution time for females was 88.97 months and 109.07 months for males, with no significant statistical difference between male and female individuals (p=0.221) (Table 3). Comparing the evolution time and site, the mean evolution time for major salivary glands was 100.47 months, and 99.26 for minor salivary glands (Table 4), also with no statistical significance (p = 0,950).

Imaging exams

Considering the type of image exam, data were available only in 68 DC, being the Computed Tomography (CT) (47.0%) the most used complementary diagnostic exam, follow by Magnetic Resonance Imaging (MRI) (33.9%) and by the combination of CT and MRI (14.8%).

Histological features

For the CXPA type, a total of 23 different malignant subtypes were listed in the range of histological variants for CXPA (20 for DC and 15 for AC). The three most

common variants in the DC were: adenocarcinoma (28.9%), salivary duct carcinoma (20.8%), and myoepithelial carcinoma (19.1%). For the DCs, the adenocarcinoma was the most frequent malignancy in males (25%) and the myoepithelial carcinoma in females (19,5%) (Table 5). In the AC, adenocarcinoma (34.4%), myoepithelial carcinoma (25.2%), and salivary duct carcinoma (20.8%) were the most frequent variants for CXPA.

Still on the histological analysis of the DCs, despite the amount of missing data, the results showed that perineural and lymphovascular invasion were absent in a significant number of cases (53.0% and 60.0%, respectively). When informed, necrosis (83.1%/59), atypical mitoses (86.4%/37), and hyalinization (85.7%/56), negative margins (56.5%/23) and positive lymph nodes (55.6%/54) were the most cited histological features (Table 1).

Considering AC data, perineural and lymphovascular invasion were absent in most cases that this data was available (82.7%/587 and 89.1%/587, respectively). Necrosis (63.3%/87), atypical mitosis (60.2%/68), negative margins (77.4%/1578), and negative lymph nodes (71.1%/589) were the most frequent histological features (Table 2).

Regarding the treatment, surgery was the most common therapeutic modality in both analyses (65.4% for DC and 53.2% for AC), followed by the combination of surgery and radiotherapy (26.2% - DC and 36.3% - AC) (Table 1 and Table 2).

For the outcome of death in the DCs, data of 185 individuals were collected. Among them, 53 died during the follow-up period. The mean time of follow-up was 113.52 months (standard error = 8.77). At 12 months of follow-up, the survival probability was 91.7%. However, within the 115-months of follow-up, the survival probability dropped to 45.0%. Figure 2 shows the curve for survival probability.

Discussion

CXPA is a complex disease with poorly understood pathogenesis. They arise from a pleomorphic adenoma, being composed by a heterogeneous group of histological subtypes with different degrees of invasiveness and aggressiveness. This neoplasm has a prevalence rate of 5.6 cases in 100.000 malignant neoplasms and an incidence rate of 0.17 tumor per 1 million person [1].

Geographic differences are seen in the prevalence of CXPA. In the present systematic review, the most frequent country for the aggregated cases was Japan,

where the prevalence of the CXPA was 10% of the primary parotid's malignant neoplasms [134], and the most frequent country for the disaggregated cases was the United States, where the prevalence of CXPA is of 12% [158]. We tend to agree with Alsanie et al. (2022), who recently mentioned that there are several limitations in evaluating the distribution and frequency of salivary gland tumors, in general, around the world. Fact that is also observed for CXPA, given the significant variability in the literature about its incidence, with data obtained from small and unicentric cohorts could not be safely extrapolated [159].

Althought literature shows a slight female prevalence [3], as seen in previous studies [61, 64, 113], ours showed that CXPA is more prevalent in males (56.4% - DC and 58.8% - AC), and the reason for this is unclear, as primary and recurrent pleomorphic adenoma, from which this malignant neoplasm originates, are more common in women [152]. The overall mean age found was 57.92 years old which agrees with the literature where the average age varies between 55-61 years old [3, 110; 134]. Recent studies that evaluated the malignant transformation in PA found that male sex [160] and older age are risk factors for developing CXPA [148, 160].

Most of the lesions were found in the parotid gland (71.9% - DC and 82.7% - AC), which agrees with the literature [161, 162]. Analyzing the minor salivary glands (n=48), data available only in the disaggregated cases, the most frequent site was the palate (47.9%), emphasizing that a careful examination of the oral mucosa is very important to prevent an early diagnosis of this lesion, as there is a great chance of diagnosing a malignant neoplasm in minor salivary glands [163].

Patients with malignant salivary gland tumors usually complain of a swelling that may or may not be accompanied by pain [2], which can justify the fact that most of the lesions found in our study were classificate as T2 (tumor larger than 2cm but smaller than 4cm) (34.5% - DC, 36.8% - AC). It is important to emphasize that the pT staging [176] includes the PA parts of the tumor, which are usually larger than the CXPA parts, therefore pT system does not necessarily reflects the invasiveness of the tumor [15, 164], as seen in our study, where most of the patients also has no lymph node affected or metastasis (N0 and M0, respectively).

In the disaggregated cases, when analyzing the evolution time in an isolated view it was noted that in fact, the found period is a very long time for a malignant neoplasm development (99.67 months +- 121.23). The fact is that the CXPA arises from a benign neoplasm that has a slow and painless growth pattern [2] and it must be

taken in account when interpreting this result, given that the evolution time reported by the patients frequently includes PA growth before malignant change. Because of that, it may no reflet the real time of the malignant growth. In regard to the symptoms, described in 76 DC cases, and present in 82.8% of them, is one of the factors that leads the patient to seek medical care [123] and it is also an indication of malignancy of the tumor [64].

We tried to make a correlation between sex and evolution time and between site and evolution time. When analyzing sex, men tend to report a larger evolution time of the lesions (109.7 x 88.97 mouths), which can be explained by their delay in seeking medical care when compared to women [167], but there was no statistical difference in the analysis. When analyzing the site, the major salivary gland showed a larger evolution time than the minor (100.47 months x 99.26 months, respectively). Although there was no statistical difference found in this analysis, it is easily understandable that a tumor developing inside a major salivary gland such as the parotid, for example, takes longer to appear than the same lesion on the palate.

In the present review, 68 cases reported the use of imaging exams, with the computed tomography (47.0%) and the magnetic resonance imaging (33.9%) the most cited. Due to the heterogeneity of types of salivary gland tumors, it is important to aggregate techniques of diagnosis, and imaging exams are very useful in distinguishing between benign and malignant masses and to help the surgery planning [168].

Histologically, CXPA is characterized by the coexistence of benign and malignant areas [155]. CXPA can be divided into those with only epithelial (luminal) malignancy, this being the most found [169], and those with myoepithelial (non-luminal) malignancy [2]. The lesions with myoepithelial differentiation can be further subdivided into those that exhibit both epithelial and myoepithelial malignancies and those with exclusive myoepithelial malignancy [170]. The most common histological malignant subtypes found in our study were adenocarcinoma, salivary duct carcinoma and myoepithelial carcinoma, which is in agreement with recent publications [18, 19]. This systematic review gets together under the name of adenocarcinomas the cases diagnosed in this general definition, but also adenocarcinomas NOS (not otherwise specified), which were reported in four manuscripts [94,121, 146, 177]. Since the CXPA first identification by Eneroth et al. (1968) [179], this entity has been increasingly recognized, under the growing knowledge from the WHO classifications. However, as this SR

included papers published in different timepoints, some misdiagnosis may be present, requiring re-examination of histological samples of CXPA, which is logistically not feasible.

Thus, a question arises: is there a correlation between the overall-survival (OS) and the histological subtype in CXPA? The literature is contradictory about the value of the histologic subtype of CXPA in their prognosis. Katabi et al. (2010) found that the presence of mioepithelial histology increases the risk of recurrence in CXPA, even within the group of intracapsular/minimally invasive (IC/MI) tumors. The myoepithelial carcinomas were mostly invasive (43%) [15]. Key et al. (2022), performed a systematic review with focus on the overall survival and the prognostic factors in CXPA. Due to their inconsistent reporting of histological subtype and categorisation methods, median OS was not calculated. These authors concluded that the prognostic value of the histological subtype of CXPA is still to be established, providing a broad spectrum of future research in this field, with the objective of better characterizing the malignant component of CXPA [21].

Moreover, considering the histopathological parameters for the malignancy such as perineural/lymphovascuilar invasion, necrosis, atypical mitoses, presence of positive margins after tumor excision and also evidence of positive lymph nodes after neck dissection, that have been documented for DC and AC cases, although there are important limitations due to the significant lack of this information in both, some points should be highlighted. For both DC and AC cases, the absence of clinical regional metastasis in the TNM grade system (67.3%/245 and 68%/2364), was somewhat confirmed by the negative histological analysis of lymph nodes (44.4%/54 and 71.1%/589). The predominance of the negative neck metastasis could be justified, at least in part, for the size and biologic behavior of most of the lesions in the present study, mainly classified as T2, as previously cited. Recently, Key et al. (2022) analyzed prognostic factors in CXPA and observed that the median OS-3 years, OS-5 years, and OS-10 years for N0 disease was 81.2 %, 72.7 %, and 50.0 %, respectively [21].

As shown in this review, the treatment of choice for CXPA is surgery (65.4% - DC and 53.2% - AC), and a complete resection with margin is very important to the prognosis of the disease [93, 134]. Additional therapy depends on some factors, such as: positive margins (43.5% - DC and 22.6% - AC), lymph node (55.6% - DC and 28.9% - AC) or distant metastasis (10.6% - DC and 7.5% - AC) and histopathological

subtype of tumor [93, 171]. Associating surgery with radiotherapy is usually the treatment of choice for these cases [113].

Finally, regarding the outcome of death, we were able to evaluate only the DC group data, which had 185 individuals, with a total of 53 deaths during the follow up period. Analyzing the Kaplan-Meier curve, we could confirm that CXPA presented from the OS 1 year (91.7%) an important decline to 45.0%, through a period of almost 10 years (115-months) of follow up, reflecting the high aggressiveness of this malignant neoplasm along the time.

The present review has some limitations, and due to the heterogeneity of the methodologies and results data, we couldn't perform a meta-analysis. Also, there was a lot of missing information regarding the clinical and histological characteristics of the lesions, which made it difficult to explore statistical correlation between data. Said that, there must be highlighted the importance of following the CARE checklist [172] for case reports and case series and the STROBE checklist [173] for cross sectional studies.

To the best of our knowledge, this is the first systematic review that evaluated the clinical and pathological aspects of the CXPA together. The fact that we found a higher male frequency must be highlighted and new studies are required to study this aspect in depth, once the original benign lesion is more common in women [152]. Also, the higher evolution time of the lesion present in this study should be taken into account, once the risk of malignization increases with time [110]. Because of its different malignant components, we emphasize the need for future research to analyze the molecular biological behavior of this kind of tumor, in order to better understand its etiopathogenesis.

Conclusion

The most important clinical findings about CXPA in this review were: male frequency, sixth decade of life, major prevalence of T2N0M0, major salivary glands, being the parotid the most affected. Regarding the histological findings, the most common histological subtypes were adenocarcinoma, salivary duct carcinoma and myoepithelial carcinoma; lymphovascular and perineural invasion were usually absent. The OS of CXPA dropped down drastically in 10 years of follow-up in the DC group, reflecting the aggressiveness of this tumor. Systematic reviews are important because they aggregate data from different studies and facilitate the synthesis of

information. That said, we emphasize the need for more research, following the guidelines, to better elucidate the characteristics of this complex tumor.

Declaration of interest

None.

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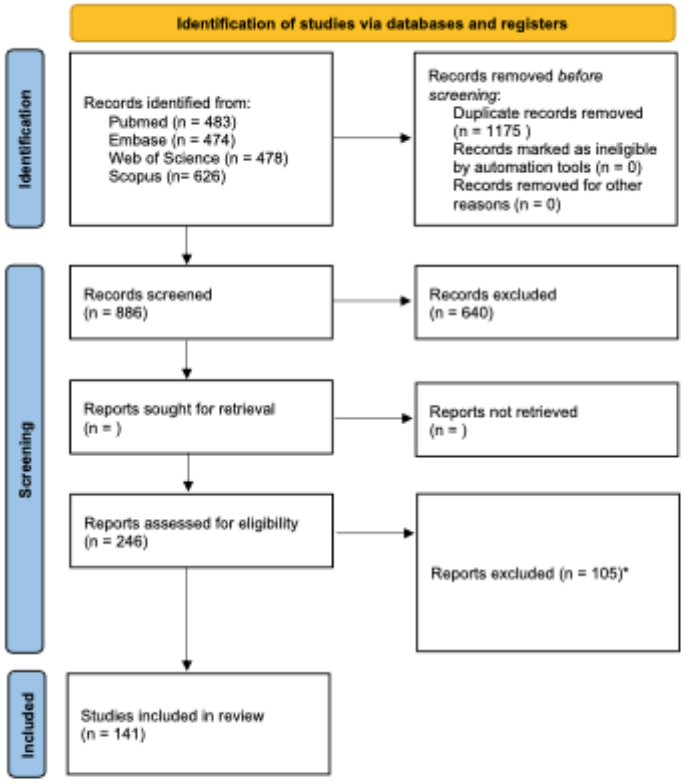
FIGURES



*The list of reason is exposed in the Appendix 1.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure 1: PRISMA 2020 flow chart describing the search and selection process of this systematic review

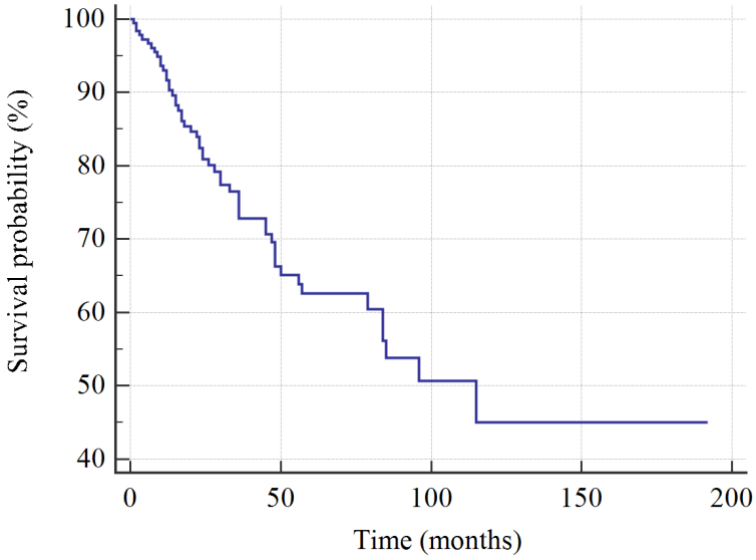


Figure 2: Curve for survival probability of CXPA

TABLES

Table 1: Descriptive analysis of demographic and clinicopathologic aspects of the disaggregated cases

Variable	N (%)
Country (n = 481)	
Australia	01 (0.2)
Brazil	82 (17.0)
Canada	07 (1.4)
China	53 (11.1)
France	01 (0.2)
Germany	41 (8.5)
Greece	01 (0.2)
India	24 (5.0)
Iran	01 (0.2)
Israel	01 (0.2)
Italy	04 (0.8)
Japan	104 (21.5)
Korea	01 (0.2)
Malaysia	02 (0.4)
Portugal	01 (0.2)
Republic of Korea	03 (0.6)
Romania	01 (0.2)
Saudi Arabia	28 (5.8)
Singapore	01 (0.2)
South Korea	02 (0.4)
Spain	02 (0.4)
Sweden	10 (2.1)
Switzerland	01 (0.2)
Syria	27 (5.6)
Taiwan	01 (0.2)
Tunisia	01 (0.2)
Turkey	02 (0.4)
United Kingdom	11 (2.3)
United States	67 (13.9)
Sex (n = 482)	
Female	210 (43.6)
Male	272 (56.4)
Age (years) – Mean (±) [Min – Max]	58.82 (±14.98) [19 – 98]

Size (n = 319)	
T1	41 (12.9)
T2	110 (34.5)
T3	115 (36.1)
T4a	33 (10.3)
Tis	20 (6.3)
Nodes (n = 245)	
N + (non-specified)	37 (15.1)
N0	165 (67.4)
N1	13 (5.4)
N2	06 (2.4)
N2b	19 (7.8)
N2c	03 (1.2)
N3a	01 (0.4)
N3b	01 (0.4)
Metastasis (n = 188)	
M0	168 (89.4)
M1	20 (10.6)
Site (n = 479)	
Major salivar gland	431 (89.9)
Minor salivar gland	48 (10.1)
Site (n = 462)	
Alveolar ridge and retromolar trigone	01 (0.2)
Tongue	02 (0.5)
Buccal mucosa	08 (1.8)
Floor of the mouth	01 (0.2)
Lip	05 (1.0)
Palate	23 (4.9)
Parotid	332 (71.9)
Sublingual	01 (0.2)
Submandibular	89 (19.2)
Symptom (n = 76)	
No	13 (17.2)
Yes	63 (82.8)

Imaging exam (n = 68)	
Ultrasound	02 (3.0)
Magnetic Resonance Imaging (MRI)	23 (33.9)
Tomography	32 (47.0)
Ultrasound and MRI	01 (1.5)
Tomography and MRI	10 (14.8)
CXPA type (n = 350)	
Adenocarcinoma	101 (28.9)
Adenoid cystic carcinoma	04 (1.2)
Carcinoma ex pleomorphic adenoma	15 (4.2)
Carcinosarcoma	04 (1.2)
Epidermoid carcinoma	01 (0.3)
Epithelial-myoepithelial carcinoma	15 (4.2)
Intraductal carcinoma	08 (2.2)
More than one malignant neoplasm	12 (3.5)
Mucoepidermoid carcinoma	06 (1.8)
Myoepithelial carcinoma	67 (19.1)
Salivary duct carcinoma	73 (20.8)
Salivary gland carcinosarcoma	01 (0.3)
Sarcomatoid carcinoma	02 (0.6)
Small cell carcinoma	01 (0.3)
Squamous cell carcinoma	08 (2.2)
Undifferentiated carcinoma	32 (9.5)
Perineural invasion (n = 34)	
No	18 (53.0)
Yes	16 (47.0)
Lymphovascular invasion (n = 30)	
No	18 (60.0)
Yes	12 (40.0)
Necrosis (n = 59)	
No	10 (16.9)
Yes	49 (83.1)
Atypical mitoses (n = 37)	
No	05 (13.6)
Yes	32 (86.4)
Hyalinization (n = 56)	
No	08 (14.3)
Yes	48 (85.7)

Margin + (n = 23)	
No	13 (56.5)
Yes	10 (43.5)
Lymph nodes + (n = 54)	
No	24 (44.4)
Yes	30 (55.6)
Treatment (n = 130)	
Surgery	85 (65.4)
Quimiotherapy	01 (0.8)
Surgery and radiotherapy	34 (26.2)
Surgery and quimiotherapy	02 (1.6)
Surgery, radiotherapy and quimiotherapy	08 (6.1)
Death (n = 195)	
No	141 (72.3)
Yes	54 (27.7)
Death (months) – Mean (±) [Min – Max]	41.34 (±37.3) [1 – 192]

Table 2: Descriptive analysis of demographic and clinicopathologic aspects of the aggregated studies

Variable	Results
Country (n = 30)	
Australia	01 (3.2)
Brazil	04 (12.9)
Canada	01 (3.2)
China	06 (19.4)
Germany	02 (6.4)
Japan	02 (6.4)
Portugal	01 (3.2)
Singapore	01 (3.2)
South Korea	03 (9.6)
Switzerland	01 (3.2)
Turkey	01 (3.2)
United Kingdom	01 (3.2)
United States	06 (19.4)
Sex – (n = 3236)	
Female	1338 (41.2)
Male	1908 (58.8)
Age (years) – Mean (±) [Min – Max]	57.64 [46 – 67]
Size – (n = 1903)	
T1	415 (21.8)
T2	700 (36.8)
T3	564 (29.6)
T4	224 (11.8)

Nodes – (n = 2364)	
N	573 (32.0)
N0	1791 (68.0)
Metastasis – (n = 1783)	
M0	1650 (92.5)
M1	133 (7.5)
Site – (n = 3238)	
Major salivary gland	3073 (95.0)
Minor salivary gland	165 (5.0)
Site – (n = 2976)	
Parotid	2461 (82.7)
Sublingual	01 (0.03)
Submandibular	514 (17.2)

CXPA type – (n = 1166)	
Acinar cell carcinoma	3 (0.2)
Adenocarcinoma	401 (34.4)
Adenoid cystic carcinoma	47 (4.0)
Basal cell adenocarcinoma	10 (0.9)
Carcinosarcoma	06 (0.5)
Clear cell carcinoma	05 (0.4)
Ductal carcinoma	08 (0.6)
Epidermoid carcinoma	01 (0.08)
Epithelial-myoepithelial carcinoma	34 (2.9)
Intraductal carcinoma	09 (0.7)
Large cell undifferentiated carcinoma	01 (0.08)
Mucoepidermoid carcinoma	47 (4.0)
Myoepithelial carcinoma	294 (25.2)
Oncocytic carcinoma	09 (0.7)
Papillary cystadenocarcinoma	06 (0.5)
Polymorphous low-grade adenocarcinoma	04 (0.3)
Salivary duct carcinoma	243 (20.8)
Squamous cell carcinoma	17 (1.4)
Undifferentiated carcinoma	21 (1.8)
Invasiveness – (n = 233)	
Non	48 (20.5)
Minimally	17 (7.3)
Frankly	168 (72.2)
Perineural invasion – (n = 587)	
No	486 (82.7)
Yes	101 (17.3)

Lymphovascular invasion – (n = 587)	
No	523 (89.1)
Yes	64 (10.9)
Necrosis – (n = 87)	
No	32 (36.7)
Yes	55 (63.3)
Atypical mitoses – (n = 68)	
No	27 (39.8)
Yes	41 (60.2)
Margin + – (n = 1578)	
No	1221 (77.4)
Yes	357 (22.6)
Lymph nodes + – (n = 589)	
No	419 (71.1)
Yes	170 (28.9)
Treatment – (n = 3663)	
Surgery	1950 (53.2)
Surgery and radiotherapy	1330 (36.3)
Surgery and quimiotherapy	237 (6.5)
Surgery, radiotherapy and chemotherapy	43 (1.1)
No treatment	15 (0.4)
Other	88 (1.1)
Death – (n = 147)	
Yes	147 (100)

Table 3: Correlation between sex and evolution time at the disaggregate cases of CXPA (Mann Whitney test)

	Female Mean Median (Min – Max)	Male Mean Median (Min – Max)	p value
Evolution time	88.97 24.0 (0.75 – 540.0)	109.07 48.0 (2.00 -504.0)	0.221

Table 4: Correlation between site and evolution time at the disaggregate cases of CXPA (Mann Whitney test)

	Major salivary gland Mean Median (Min – Max)	Minor salivary gland Mean Median (Min – Max)	p value
Evolution time	100.47 36.0 (0.75 – 540.0)	99.26 60.0 (3.00 - 360.0)	0.950

Table 5: Correlation between type of malignant component and sex at the disaggregate cases of CXPA

	Female N (%)	Male N (%)
CXPA type		
Adenocarcinoma	33 (15.7)	68 (25.0)
Adenoid cystic carcinoma	02 (1.0)	02 (0.7)
Carcinoma ex pleomorphic adenoma	08 (3.8)	07 (2.6)
Epidermoid carcinoma	01 (0.5)	00 (0.0)
Epithelial-myoepithelial carcinoma	08 (3.8)	07 (2.6)
Intraductal carcinoma	03 (1.4)	05 (1.8)
More than one malignant neoplasm	06 (2.9)	10 (3.7)
Mucoepidermoid carcinoma	01 (0.5)	05 (1.8)
Myoepithelial carcinoma	41 (19.5)	25 (9.2)
Salivary duct carcinoma	23 (11.0)	50 (18.4)
Salivary gland carcinosarcoma	0 (0.0)	01 (0.4)
Sarcomatoid carcinoma	02 (1.0)	00 (0.0)
Small cell carcinoma	01 (0.5)	00 (0.0)
Squamous cell carcinoma	02 (1.0)	06 (2.2)
Undifferentiated carcinoma	14 (6.7)	18 (6.6)
Missing	65 (31.0)	68 (25.0)

SUPPLEMENTARY MATERIAL

Appendix 1: list and justification of excluded articles after full reading

Hu YH, Li W, Zhang CY, Xia RH, Tian Z, Wang LZ, Xie L, Li J. Prognostic nomogram for disease-specific survival of carcinoma ex pleomorphic adenoma of the salivary gland. Head Neck. 2017 Dec;39(12):2416-2424. - same population as Hu, et al. 2016

Hu Y, Xia L, Zhang C, Xia R, Tian Z, Li J. Clinicopathologic Features and Prognostic Factors of Widely Invasive Carcinoma Ex Pleomorphic Adenoma of Parotid Gland: A Clinicopathologic Analysis of 126 Cases in a Chinese Population. J Oral Maxillofac Surg. 2020 Dec;78(12):2247-2257. - same population as Hu, et al. 2016

Xia L, Hu Y, Li J, Gu T, Zhang C, Wang L, Tian Z. A low percentage of HER-2 amplification whereas indicates poor prognosis in salivary carcinoma ex pleomorphic adenoma: a study of 140 cases. J Oral Pathol Med. 2017 Mar;46(3):167-174. - same population as Hu, et al. 2016

Andreasen S, Therkildsen MH, Bjørndal K, Homøe P. Pleomorphic adenoma of the parotid gland 1985-2010: A Danish nationwide study of incidence, recurrence rate, and malignant transformation. Head Neck. 2016 Apr;38 Suppl 1:E1364-9. - pleomorphic adenoma

Mariano FV, Costa AF, Gondak RO, Martins AS, Del Negro A, Tincani ÁJ, Altemani A, de Almeida OP, Kowalski LP. Cellular Proliferation Index between Carcinoma Ex-Pleomorphic Adenoma and Pleomorphic Adenoma. Braz Dent J. 2015 Jul-Aug;26(4):416-21. - same population as Soares, et al. 2011

Yau, W and Yu Wai Chan. “Management of malignant submandibular gland tumour: 20-year experience in a single institution.” *Surgical Practice* 24 (2020): 55 - 59.

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Malignant salivary gland tumours in South Tunisia: A clinicopathological study of 40 cases – conference summary

Simultaneous occurrence of an intraductal adenocarcinoma and an invasive myoepithelial carcinoma in a recurrent pleomorphic adenoma of the parotid gland - A case report – conference summary

Clinicopathologic analysis of 71 carcinomas ex pleomorphic adenoma- conference summary

Immunoprofiling of salivary duct carcinoma in a large cohort retrospective study of 170 patients from Japan: Significances of p53 and MUC6 – conference summary

Early carcinoma ex-pleomorphic adenoma, diagnostic and clinical implications: A case report – conference summary

A mixed adeno-neuroendocrine carcinoma ex-pleomorphic adenoma of soft palate: A heretofore undescribed occurrence – conference summary

A rare case report of sarcoma ex pleomorphic adenoma of parotid gland – article unavailable

Secretory carcinoma ex pleomorphic adenoma: A case report – conference summary

Partial Sternotomy Technique Allows Use of Intraoperative Flexible Bronchoscope for Diagnosis Tracheomacia - conference summary

Searching for Hodgkin-discovering a carcinoma ex pleomorphic adenoma – conference summary

Acantholytic squamous cell carcinoma (SCC) and salivary duct carcinoma ex-pleomorphic adenoma: Relationship to aberrant expression of E-cadherin – conference summary

Fine needle aspiration cytology of rare salivary gland tumor: Mucoepidermoid carcinoma ex pleomorphic adenoma – conference summary

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Salivary gland tumours-a study of 30 Romanian cases – conference summary

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Carcinoma ex pleomorphic adenoma of the parotid gland: A case report – conference summary

Carcinoma ex pleomorphic adenoma in a young woman – conference summary

Giant carcinoma ex pleomorphic adenoma of parotid-a case report – conference summary

Pleural metastasis from carcinoma ex pleomorphic adenoma diagnosed by effusion cytology: A case report –conference summary

Carcinoma (myoepithelial carcinoma) ex pleomorphic adenoma of the palate: A case report with cytologic and histopathologic dilema – conference summary

Carcinoma ex pleomorphic adenoma of the salivary glands: Clinico-pathological analysis – conference summary

Non invasive carcinoma ex pleomorphic adenoma of the sub mandibular salivary gland: A challenging case – conference summary

Fine needle aspiration cytology of carcinoma ex-pleomorphic adenoma: A study of 20 cases with correlating histopathology – conference summary

PLAG1 and HMGA2 abnormalities in differential diagnosis of carcinoma EX-pleomorphic adenoma and de-novo counterparts – conference summary

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Parotid gland carcinoma EX pleomorphic adenoma diagnosed by fine needle aspiration: A case report – conference summary

Carcinoma ex-pleomorphic adenoma of the base of tongue: A case report and review of malignant minor salivary gland tumors - conference summary

Myoepithelial carcinoma ex pleomorphic adenoma showing an exophytic growth at the uvula of palate. Report of a case – conference summary

Salivary duct carcinoma ex pleomorphic adenoma of the parotid gland: A case report – conference summary

Salivary duct carcinoma ex pleomorphic adenoma of the parotid gland: A case report – conference summary

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Carcinoma ex pleomorphic adenoma occurring in the sublingual gland: a case report – article unavailable

A clinical study of 37 cases of major salivary gland carcinomas – article unavailable

A case of carcinoma ex pleomorphic adenoma in the submandibular gland from which myoepithelial carcinomas have arisen with cervical and lung metasis – article unavailable

Carcinoma ex pleomorhic adenoma: Case report of a rare tumor – article unavailable

A rare case of carcinoma ex pleomorphic adenoma of the palate with cervical lymph node metastasis – article unavailable

SUPPLEMENTARY TABLES

Table S1: Joanna Briggs Institute critical appraisal for case reports and case series

Reference	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(s) or treatment procedure(s) 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?	Total
Nandini, et al. 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Zhang, et al. 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Zhang, et al. 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Agarwal, et al. 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Foschini, et al. 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Klijanienko, et al. 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Mighri, et al. 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included

Shetty, et al. 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Kusafuka, et al.2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Akaki, et al. 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Khanna, et al 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Kataoka, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Sun, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Li, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Chirico, et al. 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Kato, et al. 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Sugino, et al. 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Rahman, et al. 2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Gupta, et al. 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Naito, et al. 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included

Ho, et al. 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Deshmukh, et. al 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Zhu, et al. 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Chauhan, et al. 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Fukushima, et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Enokida, et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Goyal, et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Mok, et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Mariano, et al. 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Kong, et al. 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Daltoe, et al. 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Sedassari, et al. 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Magaki, et al. 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included

Bourell, et al. 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Raut, et al. 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Sedassari, et al. 2014	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Pamuk, et al. 2014	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Srivastava, et al. 2014	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Included
Iino, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Choi, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Muro, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Nakamura, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Juncar, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Bishop, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Nakajima, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Sano, et al. 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included

Ariyoshi, et al. 2012	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Dyalram, et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Karpowicz, et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Sharon, et al. 2010	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Chen, et al. 2010	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Included
McNamara, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Reichart, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Ide, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Nakamori, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Tamiolakis, et al. 2009	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Tsutsumi, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Kato, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Daneshbod, et al. 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included

Kunimura, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Park, et al. 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Hellin-Meseguer, et al. 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Parwani, et al. 2004	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Ilhan, et al. 2005	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Said, et al. 2003	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Felix, et al 2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Anand, et al. 1998	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
W. Heintz, et al. 1998	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Mee Kimm, et al. 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Yoshihara, et al. 1995	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Spencer, et al. 1991	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Included
Talmi, et al. 1990	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included

Lubamba, et al. 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Jeon, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Romano, et al. 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Chhikara, et al. 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Lau, et al. 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Mariano, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Ohba, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Sheedy, et al. 2006	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Included
Yagihara, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Takayamaa, et al. 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Kim, et al. 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Almubarak, et al. 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Bhat, et al. 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included

Nadershah, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Yamada, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Yong, et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Included
Patil, et al. 2010	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included
Ita, et al. 2005	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Included

Table S2: Joanna Briggs Institute critical appraisal for cross-sectional studies

Reference	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
Park, et al, 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ma, et al, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patel, et al, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xin, et al, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Okano, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gupta, et al, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Soares, et al, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seoak, et al, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Asahina, et al. 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AngAng, et al, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sedassari, et al, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ihrler, et al, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Valstar, et al, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brito, et al, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hu, et al, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Suzuki, et al, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ye, et al, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rito, et al, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nishijima, et al, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Katabi, et al. 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Altinay, et al, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Griffith, et al, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lim, et al, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Tarakji, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mariano, et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhu, et al, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hashimoto, et al. 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bahrami, et al. 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim, et al, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weiler, et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hu, et al. 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Martinez, et al. 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tarakji, et al. 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Katabi, et al, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nakajima, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Persson, et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Luers, et al, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Vargas, et al, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Araújo, et al. 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Genelhu, et al. 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Matsubayashi, et al. 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen, et al, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nouraei, et al, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palma, et al. 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nigam, et al. 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vargas, et al, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Olsen, et al, 2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Viqneswaran, et al. 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dardick, et al. 1986	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu, et al, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zbaren, et al, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

3 Considerações Finais

Os achados clínicos mais importantes sobre CXPA nesta revisão foram: frequência masculina, sexta década de vida, maior prevalência de T2N0M0, glândulas salivares maiores, sendo a parótida a mais acometida. Quanto aos achados histológicos, os subtipos histológicos mais comuns foram adenocarcinoma, carcinoma de ducto salivar e carcinoma mioepitelial; invasão linfovascular e perineural estavam geralmente ausentes. A curva de sobrevivência do CXPA caiu significativamente em 10 anos de acompanhamento no grupo de casos desagregados, refletindo a agressividade desse tumor. As revisões sistemáticas são importantes porque agregam dados de diferentes estudos e facilitam a síntese de informações. Posto isso, ressaltamos a necessidade de mais pesquisas, seguindo os devidos protocolos, para melhor elucidar as características desse tumor complexo, com vistas a preencher importantes lacunas de conhecimento ainda presente na literatura.

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