UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

IARA VIEIRA FERREIRA

ASPECTOS CLINICOPATOLÓGICOS E MOLECULARES DOS SARCOMAS DA REGIÃO ORAL E MAXILOFACIAL

CLINICOPATHOLOGICAL AND MOLECULAR ASPECTS OF SARCOMAS IN THE ORAL AND MAXILLOFACIAL REGION

Piracicaba
2025

IARA VIEIRA FERREIRA

ASPECTOS CLINICOPATOLÓGICOS E MOLECULARES DOS SARCOMAS DA REGIÃO ORAL E MAXILOFACIAL

CLINICOPATHOLOGICAL AND MOLECULAR ASPECTS OF SARCOMAS IN THE ORAL AND MAXILLOFACIAL REGION

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 Oral Pathology and Oral Medicine, in the Oral Pathology area.

Orientadora: Profa. Dra. Fernanda Viviane Mariano Brum Corrêa

Este exemplar corresponde à versão final da dissertação defendida pela aluna Iara Vieira Ferreira e orientada pela Profa. Dra. Fernanda Viviane Mariano Brum Corrêa.

Piracicaba
2025

Ficha catalográfica
Universidade Estadual de Campinas (UNICAMP)
Biblioteca da Faculdade de Odontologia de Piracicaba
Marilene Girello - CRB 8-6159

Ferreira, Iara Vieira, 1999-
F413a Aspectos clinicopatológicos e moleculares dos sarcomas da região oral e maxilofacial / Iara Vieira Ferreira. – Piracicaba, SP : [s.n.], 2025.

Orientador: Fernanda Viviane Mariano Brum Corrêa.
Dissertação (mestrado) – Universidade Estadual de Campinas (UNICAMP), Faculdade de Odontologia de Piracicaba (FOP).

1. Sarcoma. 2. Osteossarcoma. 3. Neoplasias maxilomandibulares. 4. Neoplasias bucais. I. Mariano, Fernanda Viviane, 1984-. II. Universidade Estadual de Campinas (UNICAMP). Faculdade de Odontologia de Piracicaba (FOP). III. Título.

Informações complementares

Título em outro idioma: Clinicopathological and molecular aspects of sarcomas in the oral and maxillofacial region
Palavras-chave em inglês:
Sarcoma
Osteosarcoma
Jaw neoplasms
Mouth neoplasms
Área de concentração: Patologia
Titulação: Mestra em Estomatopatologia
Banca examinadora:
Fernanda Viviane Mariano Brum Corrêa [Orientador]
Sibele Nascimento de Aquino
Larissa Bastos Eloy da Costa
Data de defesa: 25-02-2025
Programa de Pós-Graduação: Estomatopatologia

Objetivos de Desenvolvimento Sustentável (ODS)
ODS: 3. Saúde e bem-estar

Identificação e informações acadêmicas do(a) aluno(a)
- ORCID do autor: https://orcid.org/0000-0001-7443-7190
- Currículo Lattes do autor: http://lattes.cnpq.br/3583957889303762

PROFª. DRª. FERNANDA VIVIANE MARIANO BRUM CORRÊA

PROFª. DRª. SIBELE NASCIMENTO DE AQUINO

PROFª. DRª. LARISSA BASTOS ELOY DA COSTA

A Ata da defesa, assinada pelos membros da Comissão Examinadora, consta no SIGA/Sistema de Fluxo de Dissertação/Tese e na Secretaria do Programa da Unidade.

AGRADECIMENTOS

Este trabalho foi realizado com o apoio da **Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) - código de financiamento 001**. Sou imensamente grata pelo suporte financeiro e pelo investimento em minha formação, fundamentais para o meu crescimento acadêmico e profissional.

Agradeço à **Universidade Estadual de Campinas (UNICAMP)** e à **Faculdade de Odontologia de Piracicaba (FOP)**. Minha gratidão também à Coordenação **Geral da Pós-Graduação da FOP**, e ao **Programa de Pós-Graduação em Estomatopatologia**, pela oportunidade de integrar este programa.

Agradeço à minha orientadora, **Profa. Dra. Fernanda Viviane Mariano**, por sua acessibilidade, empatia e orientação ao longo de toda esta jornada. Sua confiança e apoio ao longo do meu mestrado foram essenciais para aproveitar as oportunidades e superar desafios. Admiro sua liderança em um grupo grande e diverso, criando um ambiente acolhedor e colaborativo.

A todos os **professores**, **alunos** e **colaboradores do Programa de Pós-Graduação em Estomatopatologia**, minha gratidão pelos conhecimentos compartilhados ao longo do curso.

Agradeço de forma especial à **Profa. Dra. Sibele Nascimento de Aquino**, minha primeira orientadora na graduação e uma fonte de inspiração fundamental em minha trajetória. Sua orientação atenta, incentivo constante e generosidade foram essenciais para meu desenvolvimento pessoal e profissional.

À **Profa. Dra. Eliane Maria Ingrid Amstalden**, agradeço a oportunidade de participar de suas disciplinas durante dois semestres no programa de estágio docente. Tenho grande admiração pela sua paixão e dedicação ao ensino, que se refletem nos valiosos ensinamentos que recebi, os quais foram fundamentais para o meu crescimento nesta etapa da minha formação.

Aos **professores** e **funcionários** do **Departamento de Patologia, Área de Anatomia Patológica da Faculdade de Ciências Médicas da UNICAMP** e do **Hospital de Clínicas da UNICAMP**, meus sinceros agradecimentos, em especial à **Carla**, pelo acolhimento e constante disponibilidade.

Aos meus **amigos** e à família **LAPMOL**, sou imensamente grata pela convivência e parceria. A rede de apoio que conseguimos construir foi, sem dúvida, essencial para meu crescimento pessoal e profissional. Agradeço, especialmente, a **Tayná Maciel**, **Moisés Willian**,

Maria Clara Falcão, **Talita Kimura**, **Luccas Lavareze**, **João Scarini** e **Nívia Binda**. Com todos vocês, minha trajetória acadêmica se tornou mais leve e repleta de significados.

Agradeço de forma especial ao meu amigo **Reydson Souza**. Sua ajuda e incentivo foram essenciais nesse processo. Sou imensamente grata pelo seu carinho, paciência e generosidade.

Aos meus pais, **Marisa Vieira** e **Antônio Ferreira Junior**, expresso minha gratidão pelo apoio incondicional e por sempre estarem ao meu lado em todas as minhas escolhas. O amor, incentivo e a confiança que me oferecem são essenciais para que eu possa seguir em frente e lutar por meus sonhos.

Aos meus avós, **Maria Goretti** e **Antônio Ferreira**, sou imensamente grata pelo suporte, orações e por serem uma fonte constante de inspiração e força em minha vida.

Agradeço a **Deus**, por fortalecer minha fé nos momentos de incerteza e desafios. Encontro paz e serenidade em Sua presença, que me oferece conforto e esperança, especialmente nas horas de distâncias e saudades daqueles que sempre estiveram ao meu lado.

RESUMO

Sarcomas são tumores sólidos raros e heterogêneos originados de células progenitoras mesenquimais, englobando mais de 50 subtipos histológicos distintos e associados a diversos fatores de risco. Acometem predominantemente as extremidades, enquanto sua ocorrência na região oral e maxilofacial é incomum. Apesar da raridade, esses tumores apresentam alta morbidade e mortalidade, representando um desafio significativo no manejo clínico. Este estudo, estruturado em três capítulos, teve como objetivos: (1) analisar as características clínico-patológicas, abordagens terapêuticas e taxas de sobrevida dos sarcomas da região oral e maxilofacial; (2) relatar um caso de osteossarcoma induzido por radiação na região de cabeça e pescoço, acompanhado de revisão da literatura; e (3) mapear as alterações moleculares associadas ao osteossarcoma oral e maxilofacial. No primeiro capítulo, uma revisão sistemática revelou que fatores como idade, subtipo histológico, classificação T, estágio clínico, margens cirúrgicas, recorrência local e metástases à distância impactam significativamente a sobrevida dos pacientes. O segundo capítulo descreve um caso de osteossarcoma induzido por radiação em um paciente jovem com histórico de craniofaringioma, ressaltando a importância do diagnóstico precoce e do monitoramento de indivíduos expostos à radioterapia, devido à longa latência e ao prognóstico reservado dessa condição. O terceiro capítulo, por meio da revisão clinicopatológica e molecular de 68 casos de osteossarcomas orais e maxilofaciais, evidenciou o predomínio de formas agressivas e de alto grau. Diversas alterações genéticas foram identificadas, refletindo a complexidade molecular do osteossarcoma, com o gene *TP53* sendo o mais frequentemente alterado. Os achados deste estudo contribuem para a compreensão da complexidade clinicopatológica dos sarcomas orais e maxilofaciais. Além de reforçar a necessidade de um acompanhamento rigoroso de pacientes submetidos à radioterapia, os resultados ampliam as perspectivas para investigações futuras que aprofundem o conhecimento sobre a patogênese molecular desses tumores, possibilitando avanços no diagnóstico e no desenvolvimento de novas estratégias terapêuticas.

Palavras-chave: Sarcoma; Osteossarcoma; Neoplasias da Mandíbula; Neoplasias Bucais; Oral e Maxilofacial; Análise Molecular.

ABSTRACT

Sarcomas are rare and heterogeneous solid tumors originating from mesenchymal progenitor cells, encompassing over 50 distinct histological subtypes and associated with various risk factors. They predominantly affect the extremities, while their occurrence in the oral and maxillofacial region is uncommon. Despite their rarity, these tumors exhibit high morbidity and mortality, representing a significant challenge in clinical management. This study, structured in three chapters, aimed to: (1) analyze the clinicopathological characteristics, therapeutic approaches, and survival rates of sarcomas in the oral and maxillofacial region; (2) report a case of radiation-induced osteosarcoma in the head and neck region, accompanied by a literature review; and (3) map the molecular alterations associated with oral and maxillofacial osteosarcoma. In the first chapter, a systematic review revealed that factors such as age, histological subtype, T classification, clinical stage, surgical margins, local recurrence, and distant metastasis significantly impact patient survival. The second chapter describes a case of radiation-induced osteosarcoma in a young patient with a history of craniopharyngioma, highlighting the importance of early diagnosis and monitoring individuals exposed to radiotherapy due to the long latency and poor prognosis of this condition. The third chapter, through the clinicopathological and molecular review of 68 cases of oral and maxillofacial osteosarcomas, revealed the predominance of aggressive, high-grade forms. Several genetic alterations were identified, reflecting the molecular complexity of osteosarcoma, with the *TP53* gene being the most frequently altered. The findings of this study contribute to the understanding of the clinicopathological complexity of oral and maxillofacial sarcomas. In addition to emphasizing the need for strict follow-up of patients undergoing radiotherapy, the results broaden perspectives for future investigations to deepen the understanding of the molecular pathogenesis of these tumors, enabling advancements in diagnosis and the development of new therapeutic strategies.

Keywords: Sarcoma; Osteosarcoma; Jaw Neoplasms; Mouth Neoplasms; Oral and Maxillofacial; Molecular Analysis.

SUMÁRIO

1 INTRODUÇÃO

1.1. Sarcomas da região oral e maxilofacial

Os sarcomas correspondem a um grupo raro e heterogêneo de tumores sólidos derivados de células progenitoras mesenquimais, podendo surgir tanto de tecidos moles, como músculos, gordura, tecido vascular, tecido neural, quanto de tecidos duros, como os ossos e cartilagem (de Carvalho et al., 2020; Kotecha et al., 2021). Essas neoplasias mesenquimais frequentemente acometem as extremidades em 12% a 28% dos casos, seguidas pelas vísceras abdominais, com uma incidência de 22% (Hui, 2016; Mannelli et al., 2024; Tran et al., 1992).

Na região de cabeça e pescoço são menos comuns, representando 5-15% dos casos (Hui, 2016; Mannelli et al., 2024; Tran et al., 1992). Sarcomas orais são ainda mais raros, representando apenas 1% das neoplasias malignas dessa localização (Alishahi et al., 2015; de Carvalho et al., 2020). Embora incomuns nessas regiões, essas neoplasias estão associadas a elevada morbidade e mortalidade, o que torna seu diagnóstico e tratamento desafiadores (Kotecha et al., 2021; Makary et al., 2017).

A etiopatogênese da maioria dos sarcomas ainda é pouco elucidada, mas estudos sugerem que fatores genéticos e ambientais desempenham um papel crucial, incluindo mutações congênitas ou adquiridas, exposição à radiação e infecções virais (Sturgis and Potter, 2003; Wreesmann et al., 2022). Os principais fatores de risco incluem síndromes hereditárias como Li-Fraumeni e retinoblastoma, com frequente mutações no gene *TP53* e *RB1*, respectivamente.

A exposição à radiação ionizante na região da cabeça e pescoço também representa um risco significativo, podendo induzir sarcomas, geralmente com um período de latência de 10 a 12 anos (Coca-Pelaz et al., 2021; Giannini et al., 2018; Liao et al., 2023; Williams et al., 2018; Zhu et al., 2016). Além disso, infecções virais como Vírus da Imunodeficiência Humana (HIV), Herpesvírus Humano 8 (HHV-8) e Vírus de Epstein-Barr (EBV) estão associadas a determinados subtipos tumorais (Makary et al., 2017).

Os sarcomas manifestam sinais e sintomas pouco específicos, o que pode dificultar o diagnóstico diferencial com outras neoplasias dos tecidos moles (Sturgis and Potter, 2003). A expansão tumoral pode afetar estruturas adjacentes, como a base do crânio, trato nasossinusal e laringe (Makary et al., 2017), sendo caracterizada, frequentemente, por crescimento tumoral com ou sem dor, mobilidade dentária, disfunção dos nervos cranianos, sinusite unilateral, lesões vasculares nodulares, manchas arroxeadas disseminadas, sangramento nasal recorrente e disfagia dolorosa (Kalavrezos and Sinha, 2020).

A classificação mais recente da Organização Mundial da Saúde (OMS) agrupa os sarcomas em três categorias principais: sarcomas de tecidos moles, sarcomas ósseos e sarcomas indiferenciados de pequenas células redondas, abrangendo mais de 50 subtipos histológicos distintos (OMS, 2020). Na cavidade oral, os sarcomas ósseos e cartilaginosos são os mais frequentes (Alishahi et al., 2015). Em um estudo brasileiro, o osteossarcoma foi identificado como o subtipo mais prevalente na região oral (de Carvalho et al., 2020), além de ser considerado o subtipo mais comum relacionado a sarcomas induzidos por radiação (Giannini et al., 2018; Kumari et al., 2022; Liao et al., 2023; Williams et al., 2018; Zhu et al., 2016).

O tratamento depende do subtipo histológico do tumor (Grünewald et al., 2020) e a abordagem padrão envolve a ressecção cirúrgica do tumor primário, frequentemente combinada com quimioterapia neoadjuvante e/ou adjuvante e radioterapia. A recorrência local progressiva é a principal causa de mortalidade, frequentemente precedendo a disseminação sistêmica (Makary et al., 2017). De maneira geral, os sarcomas da cabeça e pescoço têm um prognóstico menos favorável em comparação com os sarcomas de outras partes do corpo, possivelmente devido à concentração de estruturas vitais nessa região, o que pode dificultar o tratamento eficaz (Wreesmann et al., 2022). Entre eles, os sarcomas radioinduzidos estão associados a uma menor sobrevida, possivelmente devido à supressão imunológica local, alterações genéticas induzidas pela radiação, desafios no tratamento de tecidos previamente irradiados e diagnósticos tardios (Patel, 2000; Wreesmann et al., 2022).

Dentre os sarcomas que acometem a região oral e maxilofacial, o osteossarcoma se destaca como a neoplasia óssea primária mais comum. Embora compartilhe algumas características clínico-patológicas com outros sarcomas, sua prevalência e comportamento clínico apresentam particularidades que merecem destaque.

1.2 Osteosarcomas da região oral e maxilofacial

O osteossarcoma é uma neoplasia óssea maligna rara, caracterizada pela produção de osso imaturo pelas células tumorais (OMS, 2022). Os maxilares, especialmente a mandíbula, representam o quarto local mais comum de acometimento, sendo precedidos pelos ossos longos, como fêmur, tíbia e úmero (Haefliger et al., 2022). Sua incidência global na região maxilofacial é de aproximadamente 4 a 5 casos por milhão de pessoas por ano (OMS, 2022), com predomínio entre a terceira e quarta décadas de vida, sem predileção por sexo (Ottaviani and Jaffe, 2009; Tran et al., 2020).

A etiologia do osteossarcoma permanece desconhecida, embora esteja frequentemente associada a fatores genéticos, incluindo síndromes como Li-Fraumeni, Werner, Bloom,

Rothmund-Thomson e retinoblastoma. No entanto, o envolvimento dos maxilares nesses casos é raro (Makary et al., 2017; OMS, 2022). Outros fatores de risco incluem exposição à radioterapia local, histórico de retinoblastoma e, mais raramente nos maxilares, doença óssea de Paget (OMS, 2022).

O cenário molecular do osteossarcoma ainda não é totalmente elucidado. Embora poucas mutações recorrentes tenham sido identificadas, *TP53* e *RB1* estão entre os genes mais frequentemente alterados, contribuindo para a instabilidade genômica característica desse tumor (OMS, 2022). O *TP53*, conhecido como o "guardião do genoma", regula a parada do ciclo celular, a reparação do DNA e a apoptose, e sua mutação compromete esses processos, favorecendo a proliferação tumoral. Já o *RB1* controla a transição da fase G1 para S, e sua inativação resulta em replicação celular desregulada (Tang et al., 2019).(Tang et al., 2019).

Nos osteossarcomas de baixo grau, a amplificação dos genes *CDK4* e *MDM2*, localizados no cromossomo 12q13-15, é frequente, sendo a amplificação de *MDM2* altamente específica e útil para diferenciá-los de lesões fibro-ósseas benignas (Haefliger et al., 2022; Luk et al., 2019). O *CDK4* atua na fosforilação do *RB1*, promovendo a progressão do ciclo celular, e sua superexpressão pode acelerar a proliferação celular. Já o *MDM2*, ao inibir o *TP53*, reduz sua resposta ao estresse celular, facilitando o desenvolvimento tumoral (Mejia-Guerrero et al., 2010; Zhou et al., 2018). Por outro lado, os osteossarcomas de alto grau apresentam cariótipos altamente complexos, com múltiplas anormalidades estruturais e numéricas, frequentemente associadas à cromotripse, um fenômeno de cromoanagênese que envolve rearranjos cromossômicos maciços e possivelmente resulta de erros na segregação cromossômica durante a divisão celular (Kansara et al., 2014).

Clinicamente, o osteossarcoma manifesta-se como um aumento de volume local, frequentemente acompanhado de dor e ulceração. Outros sinais podem incluir mobilidade dentária e fratura patológica (Barosa et al., 2014; Kalavrezos and Sinha, 2020; Makary et al., 2017). Radiograficamente, a lesão apresenta características agressivas, com crescimento destrutivo e infiltração nos tecidos adjacentes. A reação periosteal pode exibir padrões característicos, como "raios de sol" e "casca de cebola" (Haefliger et al., 2022; Luo et al., 2020). Quanto à localização, o osteossarcoma pode ser classificado em intraósseo, de superfície óssea (parosteal e periosteal) ou, menos frequentemente, extraósseo (Makary et al., 2017).

Microscopicamente, o osteossarcoma pode ser subdividido em diferentes variantes conforme o componente estromal predominante, incluindo as formas: osteoblástica, condroblástica, fibroblástica, rica em células gigantes, de células pequenas e telangiectásica (Grünewald et al., 2020; Makary et al., 2017). Nos maxilares, a variante condroblástica é a mais

comum (Cleven et al., 2020; Haefliger et al., 2022). Além disso, os osteossarcomas são classificados em baixo, intermediário ou alto grau, de acordo com o grau de atipia celular e a quantidade de mitoses atípicas (Grünewald et al., 2020).

O tratamento padrão para o osteossarcoma na região oral e maxilofacial é a ressecção cirúrgica completa, embora o papel da quimioterapia neoadjuvante ainda seja debatido (Khadembaschi et al., 2022; Weber et al., 2023). Na região maxilofacial, o osteossarcoma apresenta uma taxa de metástase menor em comparação aos casos extracranianos, mas um alto índice de recorrência. Essa recorrência elevada se deve à complexidade anatômica da região, que dificulta a ressecção completa do tumor (Kämmerer et al., 2012; Weber et al., 2023). O prognóstico é ainda mais reservado nos osteossarcomas secundários à irradiação (OMS, 2022).

Apesar dos avanços no tratamento do osteossarcoma em ossos longos, a raridade da neoplasia na região da cabeça e pescoço dificulta uma compreensão aprofundada de seu comportamento, resultando em desfechos terapêuticos ainda limitados devido à sua agressividade biológica (Hassanain et al., 2024; Lopes et al., 2001). Nos últimos anos, avanços no estudo das alterações moleculares têm permitido uma melhor estratificação das lesões, auxiliando no diagnóstico, na predição prognóstica e no desenvolvimento de terapias-alvo (Demicco, 2013). Uma compreensão mais detalhada dos mecanismos moleculares que influenciam o comportamento clínico e a resistência ao tratamento desses tumores é essencial para melhorar os desfechos dos pacientes. O mapeamento genético dessas lesões é fundamental para identificar correlações prognósticas, orientar estratégias terapêuticas e aprimorar o acompanhamento clínico a longo prazo.

Assim, o presente trabalho teve como objetivo:

- Analisar, por meio de uma revisão sistemática da literatura, as características clínico-patológicas e de sobrevida dos sarcomas da região oral e maxilofacial;
- Relatar um caso de osteossarcoma induzido por radiação na região de cabeça e pescoço, acompanhado de uma revisão da literatura;
- Mapear, por meio de uma revisão de escopo, as alterações moleculares do osteossarcoma oral e maxilofacial.

2 ARTIGOS

2.1 ARTIGO: Clinicopathologic Analysis of Sarcomas in the Oral and Maxillofacial Region: A Systematic Review

Submetido no periódico: *Oral Diseases* **(Anexo 1)**

Running title

Oral and Maxillofacial Sarcoma Review

Keywords

Sarcoma; Jaw Neoplasms; Mouth Neoplasms; Oral and Maxillofacial; Systematic Review

Iara Vieira Ferreira[1,2], Reydson Alcides de Lima Souza[1,2], Talita de Carvalho Kimura[1,2], Alfio José Tincani[3], Marcelo Elias Schempf Cattan[2], Arthur Antolini-Tavares[2], Albina Altemani[2], Fernanda Viviane Mariano[2*]

[1]Oral Diagnosis Department, Piracicaba Dental School, State University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil.
[2]Pathology Department, School of Medical Sciences, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.
[3]Head and Neck Surgery Department, School of Medical Sciences, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.

***Correspondence**

Fernanda Viviane Mariano
Department of Pathology
School of Medical Sciences - State University of Campinas (UNICAMP)
Tessália Vieira de Camargo, 126 - Barão Geraldo, Cidade Universitária
Campinas-SP, Brazil, Zip Code: 13083-887
Email: fevimariano@gmail.com
Phone: +55 (19) 3521-8215

ABSTRACT

Objective: This study aimed to systematically review primary sarcomas in the oral and maxillofacial region, with a focus on patient demographics and sarcoma-specific characteristics, including clinical presentation, histopathology, treatment approaches, follow-up outcomes, and survival rates.

Materials and Methods: A systematic review was conducted using the PECOS framework, including observational studies on primary oral and maxillofacial sarcomas. An electronic search in five databases identified eligible studies, and outcomes were analyzed via Kaplan–Meier and Cox regression.

Results: The review included 34 studies comprising 650 cases of sarcomas in the oral and maxillofacial region. The mean patient age was 35.1 years, with a slight male predominance. The lesions predominantly involved the mandible with osteosarcoma being the most common histological subtype. Surgery was the primary treatment, with 5-year overall survival and disease-specific survival (DSS) rates of 54.3% and 60.4%, respectively. Through univariate Cox analysis for DSS, factors such as age, histological subtype, T stage, clinical stage, surgical margins, recurrence, and metastases were found to significantly influence patient survival ($p < 0.05$).

Conclusion: This study provides an overall overview of oral and maxillofacial sarcomas, offering data to understand the clinicopathological characteristics of these lesions in a rare location, helping to improve their diagnosis and management.

1 INTRODUCTION

Sarcomas are rare and heterogeneous solid tumors derived from mesenchymal progenitor cells. They can originate in both soft tissues, such as muscle, fat, blood vessels, neural tissue, and cartilage, and hard tissues, such as bone (de Carvalho *et al*, 2020; Kotecha *et al*, 2021). The current World Health Organization (WHO) classification of soft tissue and bone tumors divides sarcomas into three main groups: soft tissue sarcomas, bone sarcomas, and undifferentiated round cell sarcomas. This classification includes more than 50 distinct histologic subtypes (WHO, 2020).

These mesenchymal tumors most commonly affect the extremities, with an incidence ranging from 12% to 28%, followed by the abdominal viscera with 22%. However, sarcomas in the head and neck region are less common, with an incidence ranging from 5% to 15% (Tran *et al*, 1992; Hui, 2016; Mannelli et al, 2024) Oral sarcomas are even rarer, accounting for approximately 1% of all malignancies found in this anatomical region (Alishahi *et al*, 2015; de Carvalho *et al*, 2020).

Despite their rarity, sarcomas of the oral and maxillofacial region are associated with high morbidity and mortality rates, posing significant challenges in the management of these neoplasms (Kumar *et al*, 2019). To the best of our knowledge, no systematic review has been performed to synthesize the available data on oral and maxillofacial sarcomas. Therefore, the aim of this study is to comprehensively evaluate the clinicopathologic characteristics, therapeutic approaches, and survival rates associated with this condition. The guiding question of this review is: "What is the clinicopathologic profile and survival outcomes of primary sarcomas of the oral and maxillofacial region?"

2 MATERIALS AND METHODS

2.1 Information sources and search strategies

Electronic searches were conducted without publication date or language restriction in June 2024 across the following databases: MEDLINE by PubMed, Web of Science, Scopus, Embase, and Lilacs. Additionally, gray literature was searched in Google Scholar, Open Gray, and ProQuest. The search strategy is detailed in **Table S1**. Manual searches were also performed by cross-referencing the reference lists of the included articles to identify additional publications that may have been missed during the electronic searches. The retrieved studies were imported into the reference manager Rayyan® (Ouzzani *et al*. 2016), where duplicate references were removed.

2.2 Eligibility criteria

The PECOS acronym (Population, Exposure, Comparison, Outcomes, and Study Design) was adapted to guide the formulation of the systematic review question. The following criteria were defined: P: Patients diagnosed with primary sarcoma in the oral and maxillofacial region; E: Diagnosis of sarcoma by histopathologic examination; C: Not applicable; O: Clinicopathologic findings and survival analysis; and S: Observational studies (cohort studies, case-control studies, or cross-sectional studies) and case series with at least 10 cases.

Exclusion criteria were as follows: (1) studies that did not specifically investigate the clinicopathologic profile of oral and maxillofacial sarcomas; (2) studies with incomplete or insufficient clinicopathological data for analysis, particularly regarding follow-up information; (3) studies that did not use histopathology as the reference standard for diagnosis; (4) reviews, case reports, protocols, short communications, personal opinions, letters, conference abstracts, book chapters, and in vitro or in vivo studies; (5) studies that did not include primary oral and maxillofacial sarcomas, excluding cases of recurrence and metastasis; (6) studies that included other anatomic site; (7) studies where the full text was not available; (8) studies with duplicate samples; and (9) studies with fewer than 10 cases were excluded to ensure statistical robustness, minimize bias, and enhance the reliability of the findings.

2.3 Study selection and data collection process

The selection process was then conducted in two phases by three independent authors (IVF, MESC, and TCK). The first phase involved reading the titles and abstracts of studies selected in Rayyan® (Ouzzani *et al*. 2016). Studies that met all inclusion criteria proceeded to the second stage of the selection process through full-text review and confirmation of eligibility criteria. Disagreements between the initial three reviewers were resolved by a fourth reviewer (RALS).

Data were extracted by three reviewers (IVF, MESC, and TCK) and validated by the entire research team. The following key data were extracted, when available: study characteristics (author/year, country, and study design); population characteristics (sample size, sex, age and conditions/comorbidities of the patients); sarcoma characteristics (location, size, clinical appearance, symptoms, histological subtype, molecular profile, staging, recurrence/metastasis, treatment, margin status, patient condition, follow-up); and survival analysis.

2.4 Risk of bias assessment

The risk of bias in individual studies was independently assessed by three authors (IVF, MESC, and TCK) using the Joanna Briggs Institute critical appraisal tool for each study. The risk of bias was classified as high if the study reached up to 49% “yes”; moderate if the study reached 50% to 69% “yes”; and low if the study reached at least 70% “yes”. Disagreements were resolved first by discussion and then by consulting a fourth author (RALS).

2.5 Data analysis

The collected data were organized using Microsoft Excel 2019 (Microsoft®) and presented descriptively. For statistical analysis, only cases with individually reported follow-up times and patient status were included. Sample size varied according to clinicopathological variables. The correlation between clinicopathologic characteristics and patient status was assessed by chi-square test. Survival rates were estimated using Kaplan-Meier method, and differences between survival curves were analyzed using the univariate log-rank test. To identify potential prognostic factors, the univariate Cox proportional hazards regression model was used to determine the hazard ratio (HR) and its 95% confidence interval. Statistical analyses were performed using GraphPad Prism (version 9.3.0, Dotmatics) and the Statistical Package for the Social Sciences (SPSS, version 22.0, IBM Corporation), with a $P\ Value < 0.05$ considered statistically significant.

2.6 Protocol and registration

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page *et al*., 2021) and was registered on the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42024608805).

3 RESULTS

3.1 Study selection and characteristics of the studies

The initial electronic search yielded 9015 references, of which 3532 duplicates were excluded. After applying the inclusion and exclusion criteria, 996 studies were selected for analysis. Additionally, 231 articles were identified through gray literature and manual reference checking of the selected studies, from which 46 were included in the analysis. In total, 34 articles were selected, covering 650 cases of oral and maxillofacial sarcoma, published between 1982 and 2024. The flowchart illustrates the study selection process in detail **(Figure S1)**.

The selected studies were from 23 countries, as shown below: United States (9), China (7), India (4), Spain (2), France (2), Germany (1), Canada (1), Japan (1), Egypt (1), Brazil (1), Greece and Germany (1), Taiwan (1), Italy (1), United Kingdom (1) and Mexico (1).

3.2 Description of individual studies

3.2.1 Clinical features

The summarized data is presented in **Table 1**, with detailed descriptions of the 650 cases analyzed available in **Table S2**. Oral and maxillofacial sarcomas were more frequent in males, representing 56.96% of cases (364/639), with a male-to-female ratio of 1.32:1. Age information was available for 411 cases, with an average patient age of 35.11 years (±21.79), ranging from 0.3 to 91 years. In our study, rhabdomyosarcoma was the most common histological subtype among children and adolescents, with a mean age of 10.12 years (0.3–77 years). This was followed by Ewing sarcoma, with a mean age of 16.8 years (4–30 years).

Anatomically, the mandible was the most frequently affected site, accounting for 38.92% of cases (253/650), followed by the maxilla at 30.77% (200/650). Histopathologic subtypes were updated according to the (*WHO,2020)* classification, revealing over 16 distinct variants. Osteosarcoma was the most common subtype, representing 36% of cases (235/650), followed by radiation-associated sarcomas (13.7%, 89/650), rhabdomyosarcoma (9.2%, 60/650), and chondrosarcoma (9.2%, 60/650).

Fourteen studies, covering 276 cases, reported clinical characteristics and/or symptoms, with some patients presenting multiple symptoms. In some studies, symptoms were grouped together, making it difficult to precisely identify each one. Overall, most lesions were described as swelling or mass formation, with pain being the most common symptom, followed by numbness or loss of sensation. Other observed symptoms included difficulty opening the mouth, nasal obstruction, and Garrington's sign. Less frequent symptoms included epistaxis, bleeding, weight loss, proptosis, dysphagia, ocular signs, and, in rare cases, facial paralysis.

Tumor dimensions were assessed in 150 cases, based on the largest diameter reported for each lesion. Sizes ranged from 0.6 cm to 15 cm, with a mean of 4.22 cm (±2.67). Among the cases analyzed, three patients with osteosarcoma had a history of Li-Fraumeni syndrome, while one patient with osteosarcoma had polyostotic fibrous dysplasia. Furthermore, a history of trauma was reported in one osteosarcoma patient and one Ewing sarcoma patient.

Radiotherapy was associated with the development of 89 out 650 cases of radiation-induced sarcoma: osteosarcoma (65 cases, 73%), undifferentiated pleomorphic sarcoma (16 cases, 18%), fibrosarcoma (7 cases, 7.9%), and spindle cell sarcoma (1 case, 1.1%). These

patients had previously received radiotherapy to treat conditions such as nasopharyngeal carcinoma, melanoma, Hodgkin's lymphoma, squamous cell carcinoma, adenoid cystic carcinoma, basal cell carcinoma, mucoepidermoid carcinoma, malignant teratoma, and non-Hodgkin lymphoma. According to three studies, the latency period for the development of sarcomas ranged from 2.5 to 34 years.

3.2.2 Staging

The T, N, and M stage classifications were reported in a limited number of cases: 67 for T stage, 53 for N stage, and 33 for M stage, out of 650 total cases. Among the 67 cases with T stage information, 57 (85.1%) were classified as T1/T2, and 10 (14.9%) as T3/T4. For the 53 cases with N stage data, 43 (81.1%) showed no lymph node involvement (N0), while 10 (18.9%) had lymph node metastasis (N1). Regarding the M stage, 30 out of 33 cases (90.9%) had no distant metastasis (M0), while 3 (9.1%) presented distant metastasis at diagnosis (M1).

Out of the 221/650 cases analyzed for stage grouping, 158 (71.5%) were classified as stages I/II, while 63 (28.5%) were classified as stages III/IV. Two studies that examined 37 cases of rhabdomyosarcoma classified the patients according to the IRS Group (Intergroup Rhabdomyosarcoma Study Group). Most cases were assigned to Group III (84.2%), while groups II and IV accounted for 13.2% and 2.6%, respectively.

3.2.3 Molecular analysis

Molecular testing was performed in only 18 of the 650 cases analyzed. The presence of the *PAX3::FOXO1* or *PAX7::FOXO1* gene fusion was assessed by fluorescence in situ hybridization (FISH) in 17 patients diagnosed with rhabdomyosarcoma, being positive in 14 and negative in 3. Furthermore, the molecular characteristics of a case of undifferentiated pleomorphic sarcoma were investigated through whole exome sequencing. Cancer driver genes analysis identified *GBP4* as a potential driver gene associated with primary undifferentiated pleomorphic sarcoma of the oral and maxillofacial region. A missense mutation in the *PIK3CA* gene (p.E545K) was also detected.

3.2.4 Treatment, tumor behavior, and follow-up

The treatment modality was available in 513 out of 650 cases analyzed. Surgery alone was the primary treatment modality, used in 175 of the 513 cases (34.11%). This was followed by the combination of surgery and chemotherapy in 125/513 cases (24.37%), while the combination of surgery, radiotherapy, and chemotherapy was employed in 88/513 cases

(17.15%). Tumor margins data were available for 248/650 cases. Among them, 156/248 cases (62.9%) had tumor-free (negative) margins, 91/248 cases (36.7%) had compromised (positive) margins, and 1/248 case (0.4%) underwent marginal resection.

Information on local recurrence was reported in 291 cases, nodal metastases in 128 cases, and distant metastases in 192 cases out of the 650 analyzed. Local recurrence was observed in 186 of 291 cases (63.9%). Nodal metastases occurred in 19 of 128 cases (14.8%), while distant metastases were reported in 52 of 192 cases (27.1%). Metastatic sites were described in 18 cases and included 4 in bones, 2 in the brain, and 12 in the lungs.

Median follow-up time was available for 385/650 cases, with a mean of 59.46 months (± 80.8), ranging from 0.8 to 479 months. Regarding patient status, the majority of patients were alive at the time of analysis (332/584, 56.8%). Among the surviving patients, 190 (57.2%) were disease-free, while 21 (6.3%) were living with the disease. On the other hand, 251 of 584 patients (43.2%) had died. Of these, 186 (74.1%) died due to the disease, and 20 (8.0%) died from other causes.

3.3 Synthesis of the results and statistical analysis

A total of 369 out of 650 cases, which had follow-up time and patient status data, were included in the statistical analysis. The 5-, 10-, and 15-year overall survival (OS) rates were 54.3%, 47.2%, and 42.9%, respectively, and the disease-specific survival (DSS) rates for the same intervals were 60.4%, 56.9%, and 54.7%. The Log-rank analysis revealed significant correlations between decreased OS (**Table S3** and **Figure S4**) and DSS (**Figure 1**) and factors such as age, histological subtype, T stage, N stage, clinical stage, margin status, local recurrence, and distant metastases. However, nodal metastases were significantly associated only with OS, whereas anatomical location was specifically associated with DSS. The univariate Cox regression analysis for DSS indicated that variables such as age, histological subtype, T stage, clinical stage, margin status, local recurrence, and distant metastases influenced the patient survival rate (**Table S4)**.

3.4 Risk of bias within studies

The risk of bias assessment, using the Joanna Briggs Institute tool, was conducted for 33 cross-sectional studies and 1 case series. Among these, 18 (54.5%) demonstrated a low risk of bias, while 14 (42.4%) showed a moderate risk. Further details regarding the individual risk of bias can be found in **figures S2** and **S3**.

4 DISCUSSION

Sarcomas of the oral and maxillofacial region constitute a diverse group of cancers (O'Neill *et al*, 2013). Due to the low frequency of cases diagnosed specifically in the oral and maxillofacial region, there are few studies that investigate their characteristics in detail. In this systematic review, we analyzed 650 cases reported in 34 articles published between 1982 and 2024. This study consolidates information on the demographic, clinical, pathologic, and therapeutic aspects of these sarcomas, as well as data on patient follow-up and related survival rates.

This review found that oral and maxillofacial sarcomas are slightly more common in men. Given the inclusion of various histologic subtypes, sex predilection may vary depending on the subtype, also reflecting the broad age range observed, from 0.3 to 91 years. These findings are consistent with the literature, as rhabdomyosarcoma predominantly occurs in children and adolescents (Gallagher *et al*., 2022), while Ewing sarcoma primarily affects children and young adults, with a slight male predominance (Tran *et al*., 2020). Osteosarcoma, in contrast, was the most frequent subtype among young adults, with a mean age of 35.25 years (4–84 years). This is in line with its reported occurrence in the third and fourth decades of life, without significant sex predilection (Ottaviani & Jaffe, 2009; Tran *et al*., 2020).

Oral and maxillofacial sarcomas can originate from any non-epithelial tissue in these regions (Wreesmann *et al*, 2022). In the oral and maxillofacial region, sarcomas are more commonly derived from soft tissues rather than bone or cartilage (Kumar *et al*, 2019). However, studies indicate that bone and cartilage sarcomas are more common in the oral cavity (Alishahi *et al*, 2015). In this study, the majority of cases (70.46%) involved the bones of the oral and maxillofacial region. Anatomical location was found to be statistically significant in relation to DSS, with sarcomas affecting the nasal region and maxillary sinuses showing a poorer 5-year prognosis (43.6%). Regarding histological subtypes, osteosarcoma represented the majority of cases. A recent Brazilian study, however, highlighted that osteosarcoma, Kaposi sarcomas, and chondrosarcomas are the most frequent (de Carvalho *et al*, 2020).

Oral and maxillofacial sarcomas often present with nonspecific signs and symptoms, that can be mistaken for benign or malignant soft tissue neoplasms (Sturgis and Potter, 2003). These symptoms may also be associated with the involvement of adjacent structures, such as the skull base, nasosinus tract, and larynx (Makary *et al*, 2017). The most common clinical signs include mass growth, with or without pain, tooth mobility, cranial nerve dysfunction, unilateral sinusitis, frequent nasal bleeding, voice changes, and difficulty or pain in swallowing

(Kalavrezos and Sinha, 2020). The symptomatic findings reported in the literature are consistent with those observed in our study.

Exposure to external beam ionizing radiation in the oral and maxillofacial region has been linked to the development of sarcomas, as it can cause DNA damage and disrupt the cell cycle (Coca-Pelaz *et al*, 2021). These sarcomas are rare and often have a poor prognosis (Liao *et al*, 2023), with a latency period of 10 to 12 years after radiation exposure (Giannini *et al*, 2018; Williams *et al*, 2018). In our review, we found that radiation-induced sarcomas have the worst prognosis, with a 5-year overall survival rate of 20.4%. These sarcomas show lower survival rates, likely due to factors such as local immune system suppression in the irradiated area, the effect of radiotherapy on the genetic makeup of tumor cells, challenges in effectively treating the irradiated area, and diagnostic delays due to anatomic and histologic changes in the affected area (Patel, 2000; Wreesmann *et al*, 2022). Additionally, Li-Fraumeni syndrome, caused by mutations in the p53 gene, increases the risk of soft tissue and bone sarcomas, which account for approximately one-quarter of the tumors in affected individuals (Malkin *et al*, 1990; Zahm and Fraumeni, 1997; Sturgis and Potter, 2003; Makary *et al*, 2017). In our study, three patients with osteosarcoma were diagnosed with this syndrome.

Sarcomas exhibit significant complexity in their classification and subtyping (Bovée and Hogendoorn, 2010). Molecular tests such as FISH enable the identification of genetic rearrangements and specific mutations, aiding in the diagnosis and classification of these tumors. This is essential for determining appropriate treatments, identifying prognostic biomarkers, and personalizing therapies, improving clinical outcomes while minimizing side effects (Bovée and Hogendoorn, 2010; Demicco, 2013; Luk *et al*, 2019; Wreesmann *et al*, 2022). Despite the increased use of genetic analyses, only 18 cases have undergone molecular testing, 17 of which were rhabdomyosarcomas. The embryonal subtype cannot be assessed by FISH, but approximately 80% of alveolar subtype cases present specific chromosomal translocations: t(2;13)(q35;q14) and t(1;13)(p36;q14), resulting in *FOXO1::PAX3* fusions in about 55% of cases and *FOXO1::PAX7* in around 20% (Mehra *et al*, 2008; Downs-Kelly *et al*, 2009; Luk *et al*, 2019).

The standard treatment for sarcomas is surgical resection of the primary tumor, often combined with chemotherapy and/or radiotherapy, depending on the histologic subtype (de Bree *et al*, 2010; Barosa *et al*, 2014; Grünewald *et al*, 2020). Bone tumors such as osteosarcoma and Ewing's sarcoma are typically chemosensitive and treated with multimodal therapy, including radiotherapy (Grünewald *et al*, 2020). In contrast, chondrosarcomas show no significant survival benefit from these therapies (Tudor-Green *et al*, 2017). Oral and

maxillofacial sarcomas present therapeutic challenges due to the anatomic complexity, making it difficult to achieve adequate surgical margins (de Bree *et al*, 2010; Barosa *et al*, 2014). Cox regression analysis showed that patients with negative margins had a 73% lower risk of disease-specific mortality.

The prognosis of oral and maxillofacial sarcomas is generally less favorable compared to sarcomas originating in other anatomic locations (Wreesmann *et al*, 2022). Progressive local recurrence emerges as a major cause of mortality in these patients, often occurring before systemic dissemination. This pattern underscores the adverse impact of positive resection margins on prognosis. Additionally, other prognostic factors, such as tumor size, histological grade, disease stage, nodal involvement, and history of prior radiotherapy, are also crucial determinants of patients' clinical outcomes (Makary *et al*, 2017). The current systematic review revealed that patients with advanced tumor stages (T3/T4) have a 6.2-fold higher risk of mortality compared to those with early stages (T1/T2). Similarly, patients with clinical stage III/IV have a 9.3-fold higher mortality risk than those with stage I/II disease. The presence of local recurrence increases the risk of death by 5.5-fold, while the presence of distant metastases increases the risk of death by 1.7-fold.

This study has some important limitations that should be highlighted. First, many of the included articles did not provide clear demographic information or individualized clinical analyses and presented data in an aggregated form, making it difficult to assess specific characteristics. Additionally, there was a significant lack of essential clinicopathological information, such as TNM classification, staging, surgical margins, presence of recurrences, or metastases, which substantially reduced the amount of data available in these categories. Finally, although sarcoma subtypes have distinct etiologies and clinical behaviors, this work chose to approach the cases primarily by anatomic location rather than prioritizing histological aspects, which may limit the detailed understanding of each specific subtype. However, despite these limitations, the work makes a significant contribution to the clinical understanding of oral and maxillofacial sarcomas, providing a valuable overview of the disease patterns and their potential clinical outcomes, which may guide future research and improve the management of these cases in clinical practice.

5 CONCLUSION

In summary, oral and maxillofacial sarcomas show a slight male predominance, affect a wide age range (0.3 to 91 years), and predominantly affect the mandible, followed by the maxilla. Osteosarcoma is the most common histologic subtype, and surgery remains the primary

treatment, with 5-year overall survival and disease-free survival rates of 54.3% and 60.4%, respectively. Factors such as age, histologic subtype, T stage, clinical stage, surgical margins, local recurrence, and distant metastases significantly impact patient survival. This study provides valuable data to understand the clinicopathologic characteristics of these lesions in a rare location, helping to improve their diagnosis and management.

AUTHOR CONTRIBUTIONS

Iara Vieira Ferreira: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; data curation; formal analysis. **Reydson Alcides de Lima Souza**: Investigation; writing – original draft; methodology; data curation; formal analysis. **Talita de Carvalho Kimura:** Investigation; methodology; data curation. **Alfio José Tincani:** Investigation; methodology; data curation. **Marcelo Elias Schempf Cattan:** Writing – review and editing; formal analysis. **Arthur Antolini:** Writing – review and editing. **Albina Altemani:** Writing – review and editing. **Fernanda Viviane Mariano:** Conceptualization; supervision; Writing – review and editing.

ACKNOWLEDGMENTS

The authors would like to gratefully acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES, Brasilia, Brazil, finance code 001) and the São Paulo Research Foundation (FAPESP, São Paulo, Brazil, grant numbers: 20/08431-4 and 23/13091-6) for the scholarships.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Iara Vieira Ferreira https://orcid.org/0000-0001-7443-7190

Reydson Alcides de Lima-Souza https://orcid.org/0000-0001-5045-6960

Talita de Carvalho Kimura https://orcid.org/0000-0001-8406-7947

Alfio José Tincani https://orcid.org/0000-0001-6193-2686

Arthur Antolini-Tavares https://orcid.org/0000-0001-5964-4407

Albina Altemani https://orcid.org/0000-0002-9944-9734

Fernanda Viviane Mariano https://orcid.org/0000-0003-3694-5025

REFERENCES

Alishahi B, Kargahi N, Homayouni S (2015). Epidemiological Evaluation of Head and Neck Sarcomas in Iran (the Study of 105 Cases Over 13 Years). *Iran J Cancer Prev* 8. 10.17795/ijcp-3432

Barosa J, Ribeiro J, Afonso L, Fernandes J, Monteiro E (2014). Head and neck sarcoma: Analysis of 29 cases. *Eur Ann Otorhinolaryngol Head Neck Dis* 131: 83–86.

Bovée JVMG, Hogendoorn PCW (2010). Molecular pathology of sarcomas: concepts and clinical implications. *Virchows Arch* 456: 193–199.10.1007/s00428-009-0828-5

de Bree R, van der Waal I, de Bree E, René Leemans C (2010). Management of adult soft tissue sarcomas of the head and neck. *Oral Oncol* 46: 786–790.10.1016/j.oraloncology.2010.09.001

de Carvalho WRS, de Souza LL, Pontes FSC, *et al* (2020). A multicenter study of oral sarcomas in Brazil. *Oral Dis* 26: 43–52. 10.1111/odi.13211

Coca-Pelaz A, Mäkitie AA, Strojan P, *et al* (2021). Radiation-Induced Sarcomas of the Head and Neck: A Systematic Review. *Adv Ther* 38: 90–108. 10.1007/s12325-020-01556-y

Demicco EG (2013). Sarcoma Diagnosis in the Age of Molecular Pathology. *Adv Anat Pathol* 20: 264–274. 10.1097/PAP.0b013e31829c2c7b

Downs-Kelly E, Shehata BM, López-Terrada D, *et al* (2009). The Utility of FOXO1 Fluorescence In Situ Hybridization (FISH) in Formalin-fixed Paraffin-embedded Specimens in the Diagnosis of Alveolar Rhabdomyosarcoma. *Diagnostic Mol Pathol* 18: 138–143.10.1097/PDM.0b013e31818c2ea4

Gallagher KPD, van Heerden W, Said-Al-Naief N, *et al* (2022). Molecular profile of head and neck rhabdomyosarcomas: A systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 134: 354–366. 10.1016/j.oooo.2021.12.128

Giannini L, Incandela F, Fiore M, *et al* (2018). Radiation-Induced Sarcoma of the Head and Neck: A Review of the Literature. *Front Oncol* 8. 10.3389/fonc.2018.00449

Grünewald TG, Alonso M, Avnet S, *et al* (2020). Sarcoma treatment in the era of molecular medicine. *EMBO Mol Med* 12. 10.15252/emmm.201911131

Hui JYC (2016). Epidemiology and Etiology of Sarcomas. *Surg Clin North Am* 96: 901–914.10.1016/j.suc.2016.05.005

Kalavrezos N, Sinha D (2020). Head and neck sarcomas in adulthood: current trends and evolving management concepts. *Br J Oral Maxillofac Surg* 58: 890–897. 10.1016/j.bjoms.2020.05.015

Kotecha S, Williams M, White HB, Graystone J, Gibbons M, Cosker T (2021). Head and neck sarcoma: three-year data from a tertiary referral centre. *Ann R Coll Surg Engl* 103: 762–767. 10.1308/rcsann.2021.0119

Kumar P, Surya V, Urs AB, Augustine J, Mohanty S, Gupta S (2019). Sarcomas of the Oral and Maxillofacial Region: Analysis of 26 Cases with Emphasis on Diagnostic Challenges. *Pathol Oncol Res* 25: 593–601. 10.1007/s12253-018-0510-9

Liao Y, Hsu C, Leu C, *et al* (2023). Radiation-induced sarcoma of head and neck: Clinical characteristics and molecular signatures. *Head Neck* 45: 638–646. 10.1002/hed.27279

Luk PP, Selinger CI, Cooper WA, *et al* (2019). Clinical Utility of In Situ Hybridization Assays in Head and Neck Neoplasms. *Head Neck Pathol* 13: 397–414. 10.1007/s12105-018-0988-1

Makary RF, Gopinath A, Markiewicz MR, Fernandes R (2017). Margin Analysis. *Oral Maxillofac Surg Clin North Am* 29: 355–366. 10.1016/j.coms.2017.04.002

Malkin D, Li FP, Strong LC, *et al* (1990). Germ Line p53 Mutations in a Familial Syndrome of Breast Cancer, Sarcomas, and Other Neoplasms. *Science (80-)* 250: 1233–1238. 10.1126/science.1978757

Mannelli G, Bassani S, Cosi G, *et al* (2024). Global frequency and distribution of head and neck sarcomas in adulthood: a systematic review. *Eur Arch Oto-Rhino-Laryngology* 281: 2553–2567. 10.1007/s00405-024-08477-4

Mehra S, de la Roza G, Tull J, Shrimpton A, Valente A, Zhang S (2008). Detection of FOXO1 (FKHR) Gene Break-apart by Fluorescence In Situ Hybridization in Formalin-fixed, Paraffin-embedded Alveolar Rhabdomyosarcomas and Its Clinicopathologic Correlation. *Diagnostic Mol Pathol* 17: 14–20.10.1097/PDM.0b013e3181255e62

O'Neill JP, Bilsky MH, Kraus D (2013). Head and Neck Sarcomas. *Neurosurg Clin N Am* 24: 67–78. 10.1016/j.nec.2012.08.010

Ottaviani G, Jaffe N (2009). The Epidemiology of Osteosarcoma. Cancer Treat Res. 2009; 152:3-13. 10.1007/978-1-4419-0284-9_1

Ouzzani, Mourad, Hossam Hammady, Zbys Fedorowicz, and Ahmed Elmagarmid. 2016. "Rayyan—a Web and Mobile App for Systematic Reviews." Systematic Reviews 5(1):210. 10.1186/s13643-016-0384-4

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer,

L., Tetzlaff, J. M., Akl, E. A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... McKenzie, J. (2021). PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. British Medical Journal, 372, n71. 10.1136/bmj.n160

Patel SR (2000). Radiation-induced sarcoma. *Curr Treat Options Oncol* 1: 258–261. 10.1007/s11864-000-0037-6

Sturgis EM, Potter BO (2003). Sarcomas of the head and neck region. *Curr Opin Oncol* 15: 239–252. 10.1097/00001622-200305000-00011

Tran N-A, Guenette JP, Jagannathan J (2020). Soft Tissue Special Issue: Imaging of Bone and Soft Tissue Sarcomas in the Head and Neck. *Head Neck Pathol* 14: 132–143. 10.1007/s12105-019-01102-5

Tran LM, Mark R, Meier R, Calcaterra TC, Parker RG (1992). Sarcomas of the head and neck. Prognostic factors and treatment strategies. *Cancer* 70: 169–177. 10.1002/1097-0142(19920701)70:1<169::aid-cncr2820700127>3.0.co;2-f

Tudor-Green B, Gomez R, Brennan PA (2017). Current update on the diagnosis and management of head and neck soft tissue sarcomas. *J Oral Pathol Med* 46: 674–679. 10.1111/jop.12555

WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 3). https://publications.iarc.fr/588.

Williams L, Tmanova L, Mydlarz WK, *et al* (2018). Radiation-Associated Sarcoma of the Neck: Case Series and Systematic Review. *Ann Otol Rhinol Laryngol* 127: 735–740. 10.1177/0003489418789966

Wreesmann VB, Oomen KP, Brennan PA (2022). Angiosarcomas of the head and neck: Impact of large data analysis on clinical management. *J Oral Pathol Med* 51: 904–910.10.1111/jop.13354

Zahm SH, Fraumeni JF (1997). The epidemiology of soft tissue sarcoma. *Semin Oncol* 24: 504–14.

Table 1: Summary of 650 Sarcoma Cases in the Oral and Maxillofacial Region.

Variables	**n (%)**
Sex (n=639)	

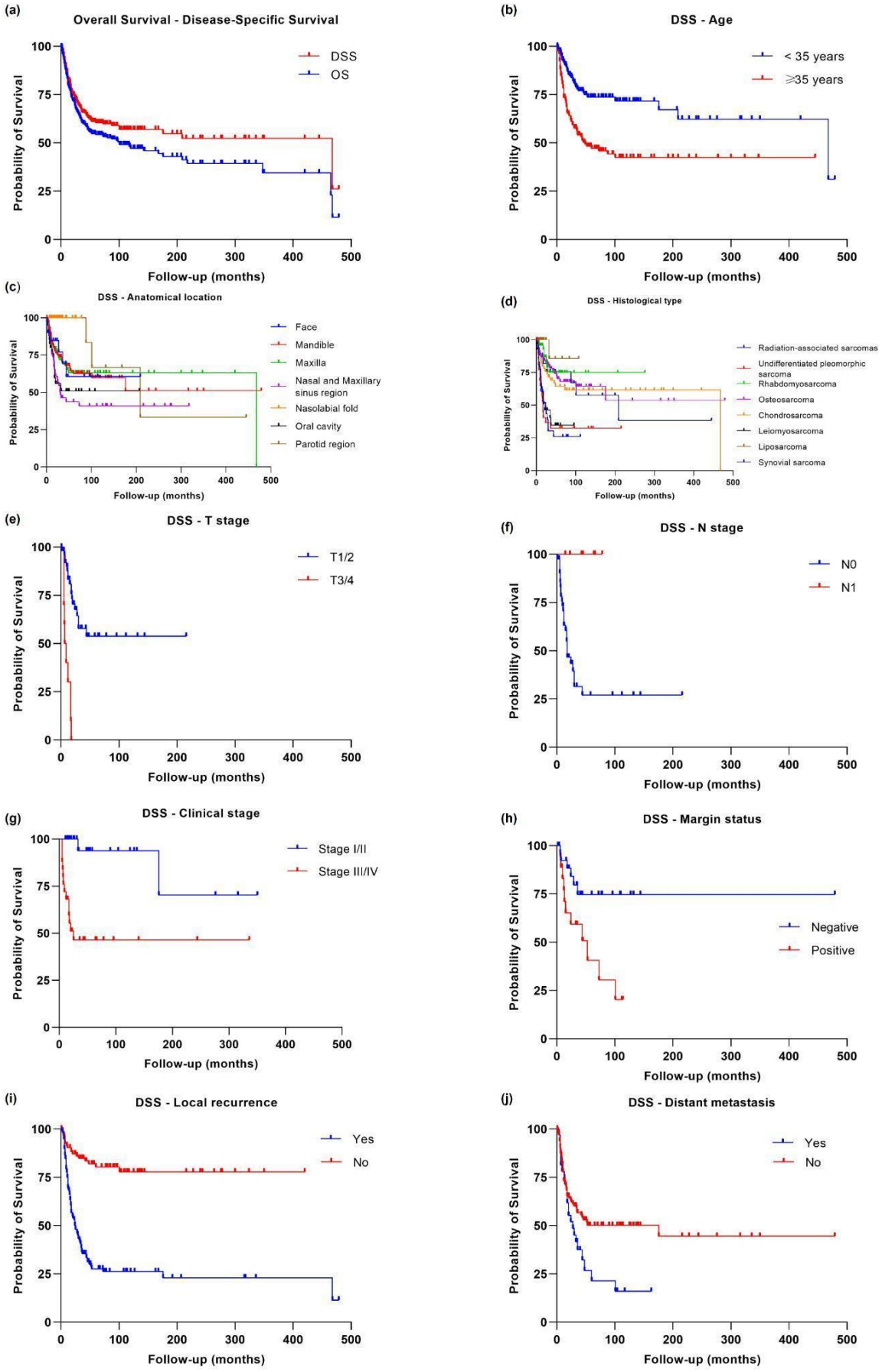
Male	364 (57%)
Female	275 (43%)
Age (years, n=411)	
Mean	35.11
Standard deviation	21.79
Range	0.3-91
Anatomical location (n=650)	
Mandible	253 (38.92%)
Maxilla	200 (30.77%)
Nasal and Maxillary Sinus Region[a]	53 (8.15%)
Oral Cavity[b]	51 (7.85%)
Nasolabial Fold	38 (5.85%)
Face[c]	31 (4.77%)
Parotid Region	17 (2.62%)
Others[d]	7 (1.08%)
Histological type (n=650)	
Osteosarcoma	235 (36.15%)
Radiation-associated sarcomas[e]	89 (13.69%)
Rhabdomyosarcoma	60 (9.23%)
Chondrosarcoma	60 (9.23%)
Synovial sarcoma	52 (8.00%)
Ewing's Sarcoma	39 (6.00%)
Leiomyosarcoma	35 (5.38%)
Undifferentiated pleomorphic sarcoma	32 (4.92%)
Liposarcoma	27 (4.15%)
Spindle cell sarcoma	5 (0.77%)
Fibrosarcoma	4 (0.62%)
Angiosarcoma	4 (0.62%)
Malignant Peripheral Nerve Sheath Tumor	4 (0.62%)
Myeloid Sarcoma	2 (0.31%)
Dermatofibrosarcoma protuberans	1 (0.15%)
Low grade sarcoma	1 (0.15%)
Tumor size (cm, n=150)	

Mean	4.22
Standard deviation	2.67
Range	0.5-15
T stage (n=67)	
T1/T2	57 (85.1%)
T3/T4	10 (14.93%)
N stage (n=53)	
N0	43 (81.1%)
N1	10 (18.9%)
M stage (n=33)	
M0	30 (90.9%)
M1	3 (9.1%)
Clinical Stage (n=221)	
I/II	158 (71.5%)
III/IV	63 (28.5%)
Treatment (n=513)	
S alone	175 (34.1%)
S+CT	125 (24.4%)
S+RT+CT	88 (17.2%)
S+RT	71 (13.8%)
CT alone	19 (3.7%)
RT+CT	18 (3.5%)
None	7 (1.4%)
S+RT+CT/Target Therapy	6 (1.2%)
RT alone	3 (0.6%)
S+CT/Target Therapy	1 (0.2%)
Margin status (n=248)	
Negative	156 (62.9%)
Positive	91 (36.7%)
Marginal resection	1 (0.4%)
Local Recurrence (n=291)	
Yes	186 (63.9%)
No	105 (36.1%)

Nodal metastasis (n=128)	
Yes	19 (14.8%)
No	109 (85.2%)
Distant metastasis (n=192)	
Yes	52 (27.1%)
No	140 (72.9%)
Follow-up (months) (n=385)	
Mean	59.46
Standard deviation	80.8
Range	0.8-479
Status (n=583)	
Alive	332 (56.9%)
Dead	251 (43.1%)

Note: S: Surgery; RT: Radiation therapy; CT: Chemotherapy.
[a] Maxillary sinus (35), Nasal Cavity (14), Nasal fossa (2), Nasal septum (2).
[b]Tongue (19), Gingiva (7), Palate (6), Lip (4), Floor of mouth (4), Buccal mucosa (4), Alveolus (2), Retromolar trigone (2), Oral cavity NOS (1), Buccal area (1), Buccal vestibule (1).
[c]Cheek (20), Chin (1), Face NOS (5), Facial buccal pad (1), Zygomatic area (1), Submental (1), Submaxillary region (1), Submandibular region (1),
[d]Temporomandibular (5), Tonsil (2).
[e]Osteosarcoma (65), Undifferentiated pleomorphic sarcoma (16 cases), Fibrosarcoma (7 cases), Spindle cell sarcoma (1).

Figure 1 Disease-specific survival (DSS) curves were analyzed for 319 cases. (a) Kaplan-Meyer curve demonstrating the comparative curve between OS and DSS of patients affected by oral and maxillofacial sarcomas. Using Log-Rank univariate analysis, (b) age (P<0.0001), (c) anatomical location (P=0.0065), (d) histological type (P<0.0001), (e) T stage (P<0.0001), (f) N stage (P=0.0066), (g) clinical stage (P=0.0004), (h) margin status (P=0.0107), (i) local recurrence (P<0.0001) and (j) distant metastasis (P=0.0224) significantly impact the survival rate of oral and maxillofacial sarcoma.


(a)
Overall Survival - Disease-Specific Survival
DSS
OS
Probability of Survival
Follow-up (months)
(b)
DSS - Age
< 35 years
≥35 years
Probability of Survival
Follow-up (months)
(c)
DSS - Anatomical location
Face
Mandible
Maxilla
Nasal and Maxillary sinus region
Nasolabial fold
Oral cavity
Parotid region
Probability of Survival
Follow-up (months)
(d)
DSS - Histological type
Radiation-associated sarcomas
Undifferentiated pleomorphic sarcoma
Rhabdomyosarcoma
Osteosarcoma
Chondrosarcoma
Leiomyosarcoma
Liposarcoma
Synovial sarcoma
Probability of Survival
Follow-up (months)
(e)
DSS - T stage
T1/2
T3/4
Probability of Survival
Follow-up (months)
(f)
DSS - N stage
N0
N1
Probability of Survival
Follow-up (months)
(g)
DSS - Clinical stage
Stage I/II
Stage III/IV
Probability of Survival
Follow-up (months)
(h)
DSS - Margin status
Negative
Positive
Probability of Survival
Follow-up (months)
(i)
DSS - Local recurrence
Yes
No
Probability of Survival
Follow-up (months)
(j)
DSS - Distant metastasis
Yes
No
Probability of Survival
Follow-up (months)

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1 Search strategies in databases and grey literature.

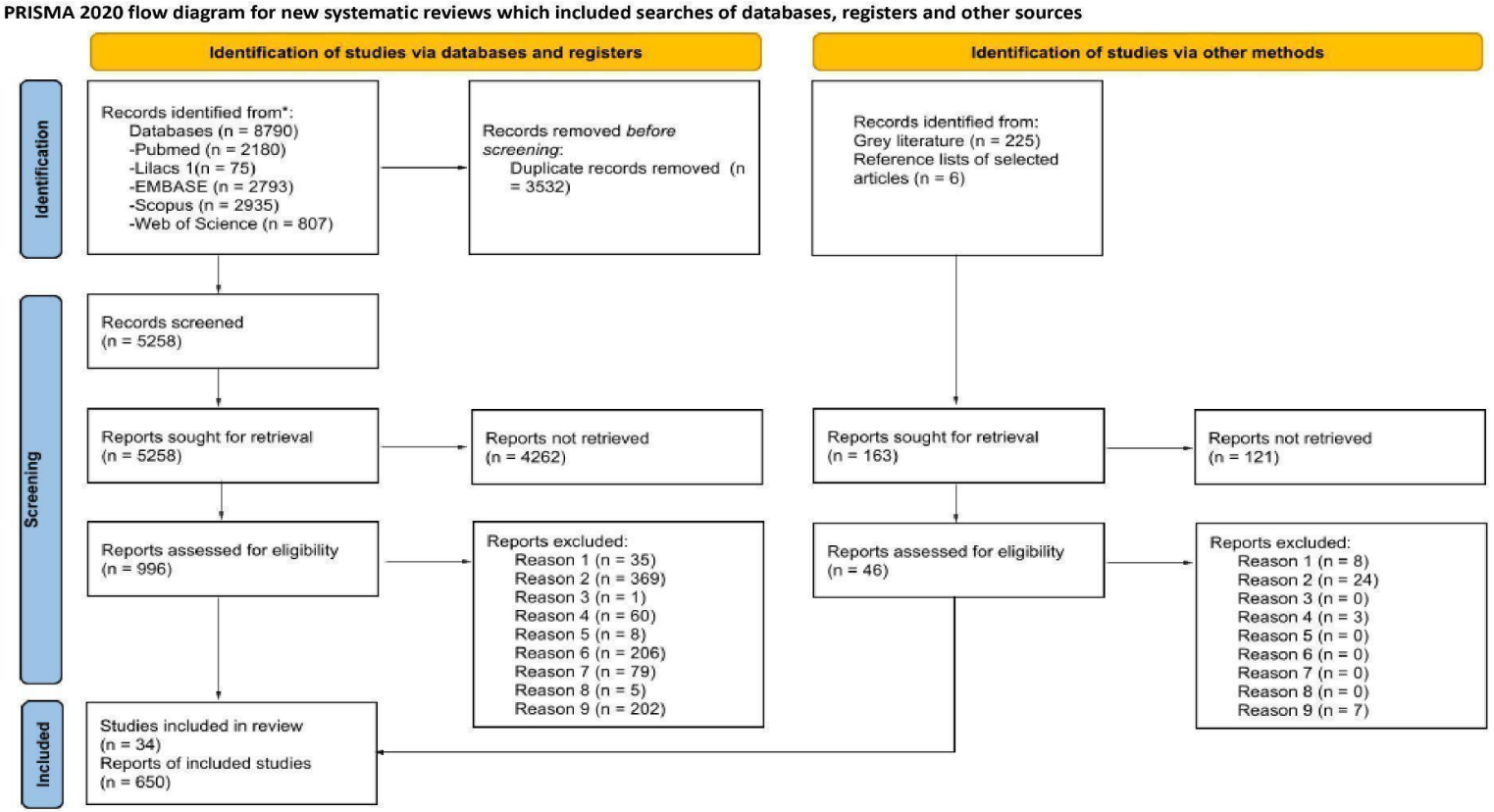
Database	(Search date: June 27th, 2024)	**Results**
PubMed	("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma s"[All Fields] OR "sarcoma soft tissue"[All Fields] OR "sarcomas soft tissue"[All Fields] OR "Soft Tissue Sarcoma"[All Fields] OR "Soft Tissue Sarcomas"[All Fields] OR "sarcoma epithelioid"[All Fields] OR "Epithelioid Sarcoma"[All Fields] OR "Epithelioid Sarcomas"[All Fields] OR "sarcomas epithelioid"[All Fields] OR "sarcoma spindle cell"[All Fields] OR "sarcomas spindle cell"[All Fields] OR "Spindle Cell Sarcoma"[All Fields] OR "Spindle Cell Sarcomas"[All Fields]) **AND** ("head and neck" OR "oral and maxillofacial"[All Fields]) **AND** (prevalence[MeSH Terms] OR prevalence OR frequency OR frequencies OR epidemiology[MeSH Terms] OR epidemiology[MeSH Subheading] OR epidemiology OR epidemiologic OR epidemiological OR occurrence OR occurrences OR incidence[MeSH Terms] OR incidence OR "cross-sectional studies"[MeSH Terms] OR "cross-sectional studies" OR "cross-sectional study" OR "cross sectional study" OR "cross sectional studies" OR "cross-sectional analysis" OR "cross-sectional analyses" OR "cross sectional analysis" OR "cross-sectional analyses" OR survey OR surveys OR "retrospective studies"[MeSH Terms] OR "retrospective studies" OR "retrospective study" OR "prospective studies"[MeSH Terms] OR "prospective studies" OR "prospective study" OR "observational study" OR "observational studies" OR nationwide OR populational OR population OR populations OR database OR databases)	**2180**

Scopus	TITLE-ABS-KEY (sarcomas OR "Sarcoma, Soft Tissue" OR "Sarcomas, Soft Tissue" OR "Soft Tissue Sarcoma" OR "Soft Tissue Sarcomas" OR "Sarcoma, Epithelioid" OR "Epithelioid Sarcoma" OR "Epithelioid Sarcomas" OR "Sarcomas, Epithelioid" OR "Sarcoma, Spindle Cell" OR "Sarcomas, Spindle Cell" OR "Spindle Cell Sarcoma" OR "Spindle Cell Sarcomas") **AND** TITLE-ABS-KEY ("head and neck" OR "oral and maxillofacial") **AND** TITLE-ABS-KEY (prevalence OR frequency OR frequencies OR epidemiology OR epidemiologic OR epidemiological OR occurrence OR occurrences OR incidence OR "cross-sectional studies" OR "cross-sectional study" OR "cross sectional study" OR "cross sectional studies" OR "cross-sectional analysis" OR "cross-sectional analyses" OR "cross sectional analysis" OR "cross-sectional analyses" OR survey OR surveys OR "retrospective studies" OR "retrospective study" OR "prospective studies" OR "prospective study" OR "observational study" OR "observational studies" OR nationwide OR populational OR population OR populations OR database OR databases)	**2935**
Embase	(sarcomas OR 'sarcoma, soft tissue'/exp OR 'sarcoma, soft tissue' OR 'sarcomas, soft tissue' OR 'soft tissue sarcoma'/exp OR 'soft tissue sarcoma' OR 'soft tissue sarcomas' OR 'sarcoma, epithelioid' OR 'epithelioid sarcoma'/exp OR 'epithelioid sarcoma' OR 'epithelioid sarcomas' OR 'sarcomas, epithelioid' OR 'sarcoma, spindle cell'/exp OR 'sarcoma, spindle cell' OR 'sarcomas, spindle cell' OR 'spindle cell sarcoma'/exp OR 'spindle cell sarcoma' OR 'spindle cell sarcomas') **AND** ('head and neck' OR 'oral and maxillofacial') **AND** (prevalence OR frequency OR frequencies OR epidemiology OR epidemiologic OR epidemiological OR occurrence OR occurrences OR incidence OR 'cross-sectional studies' OR 'cross-sectional study' OR 'cross sectional study' OR 'cross sectional studies' OR 'cross-sectional analysis' OR 'cross sectional analysis' OR 'cross-	**2793**

	sectional analyses' OR survey OR surveys OR 'retrospective studies' OR 'retrospective study' OR 'prospective studies' OR 'prospective study' OR 'observational study' OR 'observational studies' OR nationwide OR populational OR population OR populations OR database OR databases)	
Web of Science	TS=(sarcomas OR "Sarcoma, Soft Tissue" OR "Sarcomas, Soft Tissue" OR "Soft Tissue Sarcoma" OR "Soft Tissue Sarcomas" OR "Sarcoma, Epithelioid" OR "Epithelioid Sarcoma" OR "Epithelioid Sarcomas" OR "Sarcomas, Epithelioid" OR "Sarcoma, Spindle Cell" OR "Sarcomas, Spindle Cell" OR "Spindle Cell Sarcoma" OR "Spindle Cell Sarcomas") **AND** TS=("head and neck" OR "oral and maxillofacial") **AND** TS=(prevalence OR frequency OR frequencies OR epidemiology OR epidemiologic OR epidemiological OR occurrence OR occurrences OR incidence OR "cross-sectional studies" OR "cross-sectional study" OR "cross sectional study" OR "cross sectional studies" OR "cross-sectional analysis" OR "cross-sectional analyses" OR "cross sectional analysis" OR "cross-sectional analyses" OR survey OR surveys OR "retrospective studies" OR "retrospective study" OR "prospective studies" OR "prospective study" OR "observational study" OR "observational studies" OR nationwide OR populational OR population OR populations OR database OR databases)	**807**
Lilacs (via VHL)	(sarcomas) **AND** ("head and neck" OR "cabeza y cuello" OR "cabeça e pescoço" OR "oral and maxillofacial" OR "oral y maxilofacial" OR "oral e maxilofacial") **AND** (“prevalence” OR “prevalência” OR “prevalencia” OR “epidemiology” OR “epidemiologia” OR “epidemiología” OR “incidence” OR “incidência” OR “incidencia”)	**75**
Grey Literature		
Google Scholar	First 100 more relevant hits.	**100**

	(sarcoma) **AND** ("head and neck" OR "oral and maxillofacial") **AND** (prevalence OR incidence OR frequency)	
Open Gray	(sarcoma) **AND** ("head and neck" OR "oral and maxillofacial") **AND** (prevalence OR incidence OR frequency)	**0**
ProQuest	TI,AB(sarcoma) **AND** TI,AB("head and neck" OR "oral and maxillofacial") **AND** TI,AB(prevalence OR incidence OR frequency)	**125**
Total		**9015**

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



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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.

Table S2 Demographic and clinicopathological characteristics of the 34 studies (650 cases) of oral and maxillofacial sarcomas included in the systematic review.

Author/ Year	C	N	Age (y)	Sex	Site	Size (cm)	Conditions/ comorbidities of patients	Clinical apperance and symtoms	Histological Type	MA	T	N	M	Stg	Other stg	Treat	Margin	LR	NM	DM	St	Follow-up (m)
Shmookler et al. 1982	USA	10	27	F	Cheek	4	NI	Gradually enlarging mass 4 Gradually enlarging mass associated pain or tenderness 3 Cervical lymphadenopathy 1 Distinct polypoid shape 1 Pediclelike surface attachment 1 Exophytic mass 1 Hemoptysis and respiratory stridor 1	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	15.6
			35	F	Facial Buccal pad	2.4	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	48
			36	M	Cheek	4.5	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	Yes	NI	NI	Dead	25.2
			26	M	Cheek	NI	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	Yes	NI	NI	Dead	31.2
			19	M	Parotid region	1	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	Yes	NI	NI	Dead	34.8
			49	M	Parotid region	4	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	No	NI	NI	NED	27.6
			36	M	Submental	5	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			35	M	Tonsil	4	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			34	M	Tonsil	NI	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	No	NI	NI	NED	36
			16	M	Tongue	1.2	NI		Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	96
Finn et al. 1984	USA	10	48	F	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	348
			47	M	Nasal cavity	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	240
			49	F	Mandible	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	168
			44	F	Palate	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	72
			71	F	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	132
			40	M	Nasal septum	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	36
			50	M	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	6
			34	F	Mandible	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Dead	12
			58	M	Mandible	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	None	NI	NI	NI	NI	Dead	4
			23	F	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	NI	NI	NI	NED	24
Fernandez Sanroman et al. 1982	Spain	13	12	M	Maxilla	Mean 4.5	NI	Swelling, pain and tooth mobility	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	NI	NI	NI	NED	24
			17	M	Mandible		NI	Swelling and pain	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Pos	Yes	NI	Yes (Lung)	DOD	6

			84	M	Maxilla		NI	Swelling and ingival bleeding	Osteosarcoma	NI	NI	NI	NI	NI	NI	RT	NI	NI	NI	NI	DOD	5
			59	M	Mandible		NI	Swelling and Pain	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	NI	DOD	6
			43	F	Maxilla		NI	Swelling	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	Yes	NI	NI	DOD	24
			60	M	Cheek		NI	Swelling	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	Yes	NI	Yes (Lung)	DOD	36
			33	F	Chin		NI	Swelling	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S	Neg	Yes	NI	NI	DOC	120
			16	F	Mandible		NI	Swelling, pain and tooth mobility	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	Yes (Brain)	DOD	13
			20	F	Mandible		NI	Swelling	Fibrosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	NI	NI	NI	NED	60
			22	M	Mandible		NI	Swelling and pain	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	NI	NI	NI	DOC	96
			9	M	Mandible		NI	Swelling and pain	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	NI	NI	NI	NED	72
			11	M	Mandible		NI	Swelling	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	NI	NI	NI	NED	60
			5	M	Maxilla		NI	Swelling	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	NED	72
Ruark et al. 1982	USA	15	45	F	Maxilla	NI	NI	Nasal obstruction & discharge	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	Yes	NI	NI	DOD	49
			28	M	Mandible	NI	NI	Chin numbness and painful teeth	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	Yes	NI	Yes (Lung)	DOD	9
			31	F	Mandible	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	Yes (Sternum)	DOD	28
			26	M	Maxilla	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	NI	NED	420
			29	F	Maxilla	NI	NI	Nasal obstruction and sinusitis	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	DOD	9
			46	F	Nasal septum	NI	NI	Nasal obstruction and loss of smell	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	NI	DOD	73
			56	F	Maxilla	NI	NI	Nasal obstruction and mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	NI	NI	DOD	46

			53	F	Maxilla	NI	NI	Painless enlargement	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	NI	NED	324
			10	M	Maxilla	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	DOD	23
			44	M	Maxilla	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	NI	NED	300
			18	M	Maxilla	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	NI	NED	240
			36	M	Maxilla	NI	NI	Enlarging space between incisors	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	Yes	NI	NI	NED	192
			51	M	Mandible	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	132
			48	M	Maxilla	NI	NI	Progressive cheek swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	NI	NI	Alive	120
			18	M	Maxilla	NI	NI	Painless mass	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	NI	NED	84
Dry et al. 2000	USA	10	31	M	Maxilla	NI	NI	Swelling	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	61
			58	M	Maxilla	2.5	NI	Pain and swelling	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	55
			88	F	Floor of mouth	1	NI	Inspiratory stridor	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	DOD	0.8
			28	M	Maxilla	NI	NI	Pain	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	DOD	37
			74	F	Mandible	3.5	NI	Pain and swelling	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	DOC	2
			15	F	Tongue	NI	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	NED	50
			34	F	Palate	5	NI	Pain	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	Yes	NI	Yes (Lung)	DOD	14
			91	F	Upper lip	1.5	NI	Swelling	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	Yes	NI	DOC	46
			27	F	Mandible	2	NI	Pain	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	28
			NI	M	Gingiva	NI	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Gadwal et al. 2001	USA	21	7	F	Mandible	1.2	NI	Swelling, tenderness and paresthesias of the lip	Osteosarcoma	NI	NI	NI	NI	III	NI	S+CT	NI	No	No	No	NED	140
			9	M	Mandible	2.5	NI	Swelling and painless	Osteosarcoma	NI	NI	NI	NI	I	NI	None	NI	No	No	No	DOC	20
			16	M	Mandible	2.5	NI	Mass and Pain	Osteosarcoma	NI	NI	NI	NI	I	NI	S	NI	No	No	No	NED	137
			10	M	Mandible	2.5	NI	Mass and paresthesia of lower lip	Osteosarcoma	NI	NI	NI	NI	III	NI	S+RT+CT	NI	Yes	No	No	DOC	348
			13	F	Mandible	3	NI	Mass and malocclusion of teeth	Osteosarcoma	NI	NI	NI	NI	I	NI	CT	NI	No	No	No	NED	48

			13	M	Mandible	3	NI	Swelling	Osteosarcoma	NI	NI	NI	NI	III	NI	S+CT	NI	Yes	No	No	NED	336
			17	M	Mandible	3.5	NI	Mass	Osteosarcoma	NI	NI	NI	NI	I	NI	S	NI	No	No	No	NED	90
			9	M	Mandible	3.5	NI	Mass	Osteosarcoma	NI	NI	NI	NI	I	NI	None	NI	No	No	No	NED	104
			14	F	Mandible	4	NI	Mass and loosening of teeth	Osteosarcoma	NI	NI	NI	NI	I	NI	S	NI	No	No	No	NED	31
			14	M	Mandible	4.5	NI	Mass and weight loss	Osteosarcoma	NI	NI	NI	NI	II	NI	S+CT	NI	Yes	No	No	NED	51
			4	F	Mandible	5.5	NI	Mass	Osteosarcoma	NI	NI	NI	NI	II	NI	S+RT+CT	NI	Yes	No	No	DOD	176
			10	F	Mandible	6	NI	Mass	Osteosarcoma	NI	NI	NI	NI	II	NI	None	NI	No	No	No	NED	137
			15	F	Mandible	7	NI	Mass	Osteosarcoma	NI	NI	NI	NI	II	NI	S+RT	NI	No	No	No	NED	350
			15	F	Maxilla	7	NI	Mass and loosening of teeth	Osteosarcoma	NI	NI	NI	NI	I	NI	NI	NI	NI	No	No	LFU	NI
			17	F	Mandible	7	NI	Mass	Osteosarcoma	NI	NI	NI	NI	I	NI	S	NI	Yes	No	No	AWD	15
			11	F	Mandible	8	NI	Swelling and weight loss	Osteosarcoma	NI	NI	NI	NI	III	NI	CT	NI	No	No	No	NED	244
			17	M	Mandible	10	NI	Mass	Osteosarcoma	NI	NI	NI	NI	II	NI	NI	NI	NI	No	No	LFU	NI
			18	M	Mandible	NI	NI	Mass	Osteosarcoma	NI	NI	NI	NI	I	NI	S	NI	No	No	No	NED	54
			16	F	Mandible	NI	NI	Swelling	Osteosarcoma	NI	NI	NI	NI	I	NI	S	NI	Yes	No	No	NED	316
			13	F	Mandible	NI	NI	Swelling	Osteosarcoma	NI	NI	NI	NI	II	NI	None	NI	No	No	No	DOC	465
			1	M	Nasal cavity	NI	NI	Mass and ptosis of eyelid	Osteosarcoma	NI	NI	NI	NI	II	NI	NI	NI	Yes	No	No	LFU	NI
Nascimento et al. 2002	USA	23	36	M	Tongue	0.6	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	108
			48	F	Cheek	3	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			50	M	Tongue	1.2	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	48
			76	M	Tongue	1	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	14
			47	F	Tongue	2.2	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	16
			29	M	Cheek	5	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	5
			74	M	Tongue	NI	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	Yes	NI	NI	AWD	17
			77	F	Tongue	0.6	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	20
			43	M	Tongue	1	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	11
			45	M	Gingiva	1.5	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	10
			72	M	Tongue	0.7	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	24
			83	F	Tongue	2.5	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			NI	NI	Cheek	NI	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			49	F	Floor of mouth	8	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	66
			80	M	Tongue	1	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	2
			35	F	Floor of mouth	4	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	25
			49	F	Cheek	3	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NED	24
			51	F	Lip	0.9	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	3
			53	M	Tongue	0.8	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	2

			47	M	Cheek	6	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	Yes	NI	NI	AWD	84
			28	F	Lip	2	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	9
			55	F	Palate	1	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			53	M	Tongue	2	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Pandey et al. 2003	India	16	42	F	Face NOS	NI	NI	NI	Spindle cell sarcoma	NI	T2	NI	NI	NI	NI	S+CT	NI	Yes	NI	No	AWD	43
			54	M	Maxilla	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	NI	NI	NI	NI	S+RT	NI	Yes	NI	No	AWD	65
			53	F	Check	NI	NI	NI	Spindle cell sarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	No	NI	No	NED	5
			22	M	Mandible	NI	NI	NI	Spindle cell sarcoma	NI	T2	NI	NI	NI	NI	S+RT	NI	NI	NI	NI	DOD	19
			40	M	Parotid region	NI	NI	NI	Malignant Peripheral Nerve Sheath Tumor	NI	T2	NI	NI	NI	NI	S+RT	NI	NI	NI	Yes	AWD	36
			15	M	Tongue	NI	NI	NI	Spindle cell sarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	No	NI	No	NED	44
			16	F	Check	NI	NI	NI	Angiosarcoma	NI	T2	NI	NI	NI	NI	S+RT	NI	No	NI	No	NED	96
			34	M	Mandible	NI	NI	NI	Liposarcoma	NI	T2	NI	NI	NI	NI	S+RT	NI	Yes	NI	No	NED	48
			17	M	Lip	NI	NI	NI	Rhabdomyosarcoma	NI	T2	NI	NI	NI	NI	S+RT+CT	NI	No	NI	Yes (Lung)	DOD	20
			68	M	Tongue	NI	NI	NI	Spindle cell sarcoma	NI	T1	NI	NI	NI	NI	S	NI	Yes	NI	No	AWD	5
			28	F	Maxilla	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	NI	NI	NI	NI	S	NI	No	NI	No	LFU	2
			15	M	Alveolus	NI	NI	NI	Malignant Peripheral Nerve Sheath Tumor	NI	T1	NI	NI	NI	NI	S	NI	Yes	NI	No	AWD	14
			54	F	Face NOS	NI	NI	NI	Liposarcoma	NI	T2	NI	NI	NI	NI	S+CT	NI	Yes	NI	Yes (Lung)	AWD	8
			15	M	Alveolus	NI	NI	NI	Rhabdomyosarcoma	NI	T2	NI	NI	NI	NI	S+RT+CT	NI	Yes	NI	No	NED	13
			52	M	Face NOS	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	NI	NI	NI	NI	S+RT	NI	Yes	NI	No	AWD	8
			13	M	Mandible	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T1	NI	NI	NI	NI	S+RT+CT	NI	No	NI	No	NED	1
Knott et al. 2003	USA	11	11	F	Nasal cavity	NI	NI	Epistaxis and nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	LFU	NI

			15	F	Maxillary sinus	5	NI	Epistaxis and nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	135
			23	F	Maxillary sinus	9	NI	Swelling and pain	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	No	NI	NI	NED	264
			24	M	Nasal cavity	3.4	NI	Mass and nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	No	NI	NI	NED	96
			24	M	Maxillary sinus	4.2	NI	Epistaxis	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	DOD	31
			29	F	Maxillary sinus	4.1	NI	Epistaxis and headache	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	Yes	NI	NI	NED	318
			30	M	Maxillary sinus	5	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	NI	NI	DOD	12
			36	F	Maxillary sinus	3.8	NI	Nasal obstruction and pain	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	278
			60	F	Maxillary sinus	3.2	NI	Epistaxis and nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	Yes	NI	NI	DOD	20
			75	M	Nasal cavity	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	LFU	NI
			83	F	Nasal cavity	5.5	NI	Nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	DOD	4
Yamaguchi et al. 2004	Japan	24	25	M	Temporo-mandibular	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	No	NI	NED	85
			34	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	No	NI	NED	114
			40	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	NED	76
			46	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	No	Yes	DOD	60
			50	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	Yes	AWD	163
			50	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	No	No	NI	NED	39
			29	M	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	Yes	No	NI	DOD	16
			43	M	Mandible	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	Yes	DOD	24
			45	M	Submandibular region	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	No	No	NI	NED	97
			56	M	Maxilla	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	No	NI	NED	140
			57	M	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	Yes	NI	DOD	9

			63	M	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	No	NI	NED	60
			11	M	Buccal mucosa	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	NED	207
			27	F	Buccal mucosa	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	Yes	NI	DOD	18
			55	M	Maxilla	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	No	No	NI	DOD	27
			58	M	Maxilla	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	RT+CT	NI	No	No	Yes	DOD	4
			77	M	Mandible	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	No	Yes	NED	33
			0.4	F	Mandible	NI	NI	NI	Fibrosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	No	Yes	Yes	NED	117
			10	F	Mandible	NI	NI	NI	Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	No	NI	NED	138
			16	F	Mandible	NI	NI	NI	Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	No	NI	NED	228
			43	M	Mandible	NI	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	No	NI	AWD	96
			34	M	Temporo-mandibular	NI	NI	NI	Angiosarcoma	NI	NI	NI	NI	NI	NI	CT+RT	NI	No	No	Yes	DOD	48
			53	M	Maxilla	NI	NI	NI	Angiosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	Yes	NI	DOD	8
			33	F	Buccal mucosa	NI	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	DOD	32
Canadian Society of Otolaryngology-Head and Neck Surgery Oncology Study Group 2004	Canada	35	15	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	NED	31
			37	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	No	NI	No	NED	34
			62	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	No	NI	No	NED	110
			36	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	DOD	42
			26	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	Yes	NI	No	DOD	46
			33	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Pos	Yes	NI	No	DOD	53
			53	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	Yes	NED	24
			30	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	NED	78
			23	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	Yes	NI	No	NED	108
			19	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	DOC	47
			76	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	Yes	NI	No	DOD	9
			20	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	No	NI	No	NED	77
			59	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	CT	NI	Yes	NI	No	DOD	34
			35	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	No	NI	No	NED	78
			55	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	Yes	NI	No	DOD	18
			14	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	NED	28
			61	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	Yes	NI	No	DOD	6
			35	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	NED	57
			65	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	CT	NI	Yes	NI	No	DOD	3
			25	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	Yes	NED	104
			36	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	NED	70
			20	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	Yes	NI	No	NED	48
			58	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	Yes	NI	No	DOC	118

			64	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	Yes	NI	No	AWD	127
			58	M	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	No	NI	No	NED	3
			26	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	No	NI	No	NED	80
			56	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	Yes	NI	No	DOD	35
			29	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Pos	No	NI	Yes	AWD	35
			59	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	Yes	NI	Yes	DOD	6
			73	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	Yes	NI	No	DOD	52
			31	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	CT+RT	NI	Yes	NI	No	DOD	9
			23	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Pos	Yes	NI	Yes	DOD	18
			42	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	No	NI	No	DOC	143
			33	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Pos	No	NI	Yes	DOD	101
			25	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	No	NI	No	NED	109
Fernandes et al. 2007	USA	16	Mean 41 Range 14-51	M6/ F10	Mandible 9 Maxilla 7	NI	Li-Fraumani Syndrome 1 Polyostotic fibrous dysplasia 1 Previous RT 1	Swelling 14 Loosening og the teeth 3 Pain 2 Hypoesthesia 1 Garrington's sign 5	Osteosarcoma	NI	NI	NI	NI	NI	NI	S 10 S+CT 4 NI 2	NI (16)	Yes 1	NI	Yes 1 (Lung)	NED 12 DOD 2 LFU 2	Mean 46 (14-108)
Thiele et al. 2008	German y	12	Mean 42 +/- 16 Range 16-68	M8/ F4	Mandible 5 Maxilla 7	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S 3 S+RT 2 S+CT 7	NI (12)	Yes 3	No 12	No 12	DOD 2 NED 10	NI
Wang et al. 2009	Taiwan	22	49	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 9.5 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S	Neg	Yes	No	No	DOD	18
			45	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 10.9 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Pos	Yes	No	No	DOD	11
			32	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 9 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S	Pos	Yes	No	No	DOD	28

			62	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 8.9 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Pos	Yes	No	No	DOD	30
			48	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 7.3 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Neg	Yes	No	No	DOD	44
			43	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 5.7 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Pos	Yes	No	No	DOD	12
			70	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 15 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Pos	Yes	No	No	DOD	6
			53	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 14 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S+RT	Pos	Yes	No	No	DOD	12
			45	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 2.25 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S	Neg	Yes	No	No	DOD	7
			51	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 17 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Pos	Yes	No	No	DOD	2
			54	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 8.5 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S	Neg	Yes	No	No	DOD	18
			43	M	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 8.6 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S+RT	Pos	Yes	No	No	AWD	112
			37	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 10 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S+RT	Pos	Yes	No	No	DOD	24
			62	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 9 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Neg	Yes	No	Yes (Brain)	DOD	30

			59	F	Maxillary sinus	NI	Nasopharyngeal carcinoma Latency 23.6 years	NI	RAS Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Neg	No	No	Yes (Lung)	DOD	7
			46	F	Nasal cavity	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S+RT	Neg	No	No	No	NED	96
			26	M	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S+RT	Neg	No	No	No	NED	144
			64	F	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S+RT	Pos	Yes	No	No	DOD	15
			11	F	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S	Neg	No	No	No	NED	216
			59	M	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S	Neg	No	No	No	NED	132
			64	F	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T2	N0	NI	NI	NI	S+RT	Pos	Yes	No	No	DOD	10
			39	F	Maxillary sinus	NI	NI	NI	Undifferentiated pleomorphic sarcoma	NI	T1	N0	NI	NI	NI	S+RT	Neg	No	No	No	NED	4
Al-Daraji et al. 2009	Egypt	26	61	M	Temporo-mandibular	1	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	17
			9	F	Mandible	1.3	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			72	F	Check	1.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	NED	209
			12	F	Nasolabial fold	1.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	218
			49	M	Parotid region	2.2	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	98
			41	M	Submaxillary region	2.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			39	F	Parotid region	2.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	101
			49	F	Parotid region	2.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			19	M	Parotid region	3	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	33
			27	F	Check	3	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			85	F	Parotid region	3	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	80
			49	M	Parotid region	3.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	NI	NI	NI	NED	445
			41	M	Parotid region	3.6	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	NI	NI	NI	NED	132

			35	F	Temporo-mandibular	4	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	NI	NI	NI	NED	200
			54	F	Zygomatic area	4.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	Yes	NI	NI	DOC	168
			26	F	Parotid region	4.9	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	Yes	NI	NI	NED	168
			55	F	Check	5.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	2
			39	M	Parotid region	5.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	88
			22	M	Temporo-mandibular	5.4	NI	Mass	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	8
			64	M	Parotid region	5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	8
			23	F	Parotid region	5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			27	M	Parotid region	6.5	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	39
			36	M	Check	7	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	27
			7	M	Parotid region	NI	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOD	209
			27	M	Maxillary area	NI	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			33	M	Parotid region	NI	NI	NI	Synovial Sarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	DOC	41
Prado et al. 2009	Brazil	13	32	F	Maxilla	9	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	NI	NI	DOD	468
			45	M	Mandible	3	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	NI	NI	DOD	36
			25	F	Maxilla	7	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	None	NI	NI	NI	NI	DOD	2
			25	M	Mandible	10	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	RT	NI	NI	NI	NI	DOD	3
			58	M	Maxilla	7	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	DOD	12
			37	M	Mandible	NI	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
			52	M	Maxilla	9.5	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	DOC	72
			38	M	Mandible	4.5	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	144
			47	F	Maxilla	8	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	DOD	16
			15	M	Maxilla	3	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	NI	NI	NED	96
			55	F	Maxilla	3.5	NI	Swelling	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	60
			22	F	Nasal fossa	6	NI	Nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	No	NI	NI	NED	36
			11	F	Nasal fossa	4.2	NI	Nasal obstruction	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	NI	NI	NED	36
Fyrmpas et al. 2009	Greece and Germany	10	2	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	III	NI	CT+RT	NI	Yes	No	No	DOD	25
			8	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	II	NI	S+RT+CT	Neg	No	No	No	NED	132
			7	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	II	NI	S+RT+CT	NI	No	No	No	NED	276
			3	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	III	NI	CT+RT	NI	No	No	No	NED	96

			17	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	III	NI	CT+RT	NI	Yes	Yes	Yes	DOD	20
			18	NI	Maxillary sinus	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	II	NI	CT+RT	NI	Yes	No	Yes	DOD	33
			17	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	III	NI	S+RT+CT	Pos	Yes	Yes	No	DOD	7
			13	NI	Maxillary sinus	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	II	NI	S+RT+CT	Neg	Yes	No	No	NED	16
			3	NI	Maxillary sinus	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	III	NI	S+CT	Neg	No	No	No	NED	36
			3	NI	Nasal cavity	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	II	NI	CT	NI	No	No	No	NED	125
Yan et al. 2010	China	20	55	M	Palate	5	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	No	No	No	NED	20
			33	F	Palate	1	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	7
			42	M	Maxilla	2	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	No	Yes	No	DOD	6
			11	F	Cheek	4	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	Yes	No	No	AWD	20
			40	M	Mandible	4	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	No	LFU	NI
			34	M	Mandible	4	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	No	No	NED	53
			21	F	Cheek	2	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	No	No	No	NED	48
			13	M	Mandible	4	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	No	No	DOD	11
			25	M	Maxilla	7	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	No	LFU	NI
			16	F	Cheek	4	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	No	LFU	NI
			46	F	Mandible	2	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	No	No	DOD	21
			63	F	Maxilla	6	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	5
			48	M	Floor of mouth	3	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	17
			12	F	Cheek	5	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	No	No	DOD	8
			56	M	Mandible	6	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	15
			6	F	Cheek	10	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	None	NI	No	No	No	DOD	3
			47	F	Mandible	6	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	16
			19	M	Mandible	4	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	No	No	DOD	35
			52	M	Mandible	3.5	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	11
			49	M	Maxilla	6	NI	NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	No	DOD	12
Luna-Ortiz et al. 2010	Mexico	21	75	M	Maxilla	5	NI	Swelling 10 Pain 8 Gingival tumor 7 hard palate tumor 4 gingival ulceration in 4 bleeding 2 proptosis 2 paresthesia/	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	NI	NI	NI	NED	24
			28	M	Maxilla	13	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	CT+RT	Pos	NI	NI	NI	LFU	2
			28	F	Maxilla	5	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Neg	Yes	NI	NI	LFU	33
			16	F	Maxilla	NI	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	RT	Neg	Yes	NI	NI	LFU	21
			49	F	Maxilla	NI	NI			NI	NI	NI	NI	NI	NI	S+CT	Neg	NI	NI	NI	LFU	12
			32	M	Maxilla	10	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Pos	NI	NI	NI	NED	134
			39	F	Maxilla	6	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	LFU	34
			23	M	Maxilla	7	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	NI	LFU	90
			25	M	Maxilla	4	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	NI	NI	NI	NED	45
			49	F	Maxilla	9	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	NI	NI	NI	NED	9
			32	F	Maxilla	6	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	NI	LFU	17

			63	M	Maxilla	9	NI	dysesthesia V2 2 dysphagia 2 weight loss 2 nasal cavity tumor 1 teeth mobility 1 trismus 1 epiphora 1	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	NI	LFU	17
			17	M	Maxilla	5	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	Yes	NI	NI	LFU	17
			31	M	Maxilla	11	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	Yes	NI	NI	DOD	29
			40	M	Maxilla	8	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	NI	NI	NI	LFU	10
			76	F	Maxilla	5	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	NI	NI	NI	NED	44
			28	F	Maxilla	3	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	NI	NI	NI	NED	44
			16	F	Maxilla	15	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	NI	NI	NI	NED	43
			29	F	Maxilla	4	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	NI	NI	NI	NED	21
			28	M	Maxilla	3	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S	Neg	Yes	NI	NI	NED	72
			66	F	Maxilla	10	NI		Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	NI	NI	NI	NED	2
Debnam et al. 2012	USA	11	34	F	Mandible	NI	Melanoma Latency NI	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Dead	9
			45	M	Mandible	NI	Hodgkin lymphoma Latency 9 years	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	Dead	13
			50	M	Maxilla	NI	Squamous cell Latency NI	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	68
			48	M	Mandible	NI	Squamous cell Latency 57.6	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	Dead	14
			52	M	Maxilla	NI	Basal cell Latency 25 years	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	77
			50	F	Mandible	NI	Adenoid cystic Latency 20 years	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Dead	9
			67	M	Mandible	NI	Squamous cell Latency 12.8 years	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	16
			74	M	Mandible	NI	Squamous cell Latency NI	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	3
			83	F	Right maxillary mass	NI	Squamous cell Latency NI	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	Dead	12
			65	M	Retromolar trigone	NI	Squamous cell Latency 10 years	NI	RAS Spindle cell sarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Alive	16
			47	F	Retromolar trigone	NI	Mucoepidermoid tumor Latency NI	NI	RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Dead	14

Santamaría et al. 2012	Spain	12	Median 30.5	M8/F4	Mandible 12	NI	NI	NI	Ewing's sarcoma 2 Chondrosarcoma 2 Osteosarcoma 4 Low-grade sarcoma 1 Synovial sarcoma 1 Rhabdomyosarcoma 2	NI	NI	NI	NI	NI	NI	S+RT 2 S+CT 2 S+RT+CT 7 S 1	Neg 10 Pos 2	NI	NI	Yes 2	NED 5 Dead 5 AWD 2	45.25 (6-76)
Mazeron et al. 2014	France	16	3	M	Nasolabial fold	2.5	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	IRS: II	S+RT+CT	NI	NI	NI	NI	Alive	33
			3	M	Nasolabial fold	4	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	CT+RT	NI	NI	NI	NI	Alive	30.3
			2	F	Nasolabial fold	2	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	CT+RT	NI	NI	NI	NI	Alive	24.5
			1	F	Nasolabial fold	1.8	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	CT+RT	NI	NI	Yes	NI	Alive	26.3
			1	M	Nasolabial fold	4.5	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	Yes	Yes	NI	Dead	1.7
			2	M	Nasolabial fold	2.5	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	Yes	Yes	Dead	2
			1	M	Nasolabial fold	1.1	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	NI	NI	Alive	11
			13	M	Nasolabial fold	2.4	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	Yes	Yes	NI	Dead	2.8
			13	F	Nasolabial fold	NI	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	NI	NI	Alive	8.3
			0.3	F	Nasolabial fold	3	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	Yes	NI	NI	Dead	3.3
			1	F	Nasolabial fold	2	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	NI	Yes	Dead	2.3
			0.3	M	Nasolabial fold	0.6	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	II	CT+RT	NI	NI	Yes	NI	Dead	3.7
			6	F	Nasolabial fold	1.5	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	NI	NI	Alive	8.9
			6	F	Nasolabial fold	2.8	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	Yes	NI	Dead	2.1
			1	F	Nasolabial fold	1.7	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	Yes	NI	NI	Dead	1.8
			1	M	Nasolabial fold	2	NI	NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	III	S+RT+CT	NI	NI	NI	NI	Alive	6.4

Qureshi et al. 2014	India	11	<10 6 >10 5 Median 10 Range 5-16	M7/F4	Mandible 6 Maxilla 5	NI	NI	NI	Ewing's sarcoma	NI	NI	NI	NI	NI	NI	S+CT 11	Neg 10 Pos 1	Yes 1	NI	1 (Bone)	NED 9 AWD 1 DOD 1	Median 63 (12-109)
Liu et al. 2015	China	15	Mean 35 Median 38 Range 14-62	M5/F10	Mandible 8 Maxilla 7	≤5 8 >5 7	NI	Swelling 12 Numbness 6 Pain 5 Trismus 5 Tooth motility 3	Synovial Sarcoma	NI	NI	NI	NI	IIA 10 IIB 4 IV B 1	NI	S 15 RT 9 CT 6	Pos 3 Neg 12	Yes 6	Yes 1	Yes 1 (Lung)	DOD 4 Alive 11	Mean 42 (12-90)
Quereshi et al. 2016	India	21	≤12 11 >12 10 Median 11.6 Range 5–17	M11/F10	Mandible 8 Maxilla 13	≤5 7 >5 14	NI	NI	Ewing's Sarcoma	NI	NI	NI	NI	NI	NI	CT 21 S 17 RT 4	Neg 14 Pos 3	NI	NI	NI	NED 14 AWD 1 DOD 6	Mean 36 (7-123m)
Zhu et al. 2016	China	15	50	F	Maxilla	NI	Nasopharyngeal carcinoma Latency 7 years		RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	LFU	NI
			55	F	Maxilla	NI	Nasopharyngeal carcinoma Latency 5 years		RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	DOD	25

			31	F	Mandible	NI	Nasopharyngeal carcinoma Latency 13 years	Mass 13 Trismus 9 Pain 7 Osteoradionecrosis 5 Numbness 2 Bleeding 2 Ocular signs 2 Facial paralysis 1	RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	NI	LFU	NI
			26	M	Mandible	NI	Nasopharyngeal carcinoma Latency 12 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	NI	LFU	NI
			43	F	Maxilla	NI	Malignant teratoma Latency 12 years		RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	NI	No	NI	NED	80
			10	M	Mandible	NI	Nasopharyngeal carcinoma Latency 5 years		RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	NI	NED	77
			41	F	Mandible	NI	Non-Hodgkin lymphoma Latency 4 years		RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	NED	67
			35	M	Maxilla	NI	Nasopharyngeal carcinoma Latency 9 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	NI	DOD	12
			42	M	Maxilla	NI	Nasopharyngeal carcinoma Latency 3 years		RAS Fibrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	NI	No	NI	DOC	11
			54	M	Mandible	NI	Nasopharyngeal carcinoma Latency 10 years		RAS Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	NI	DOD	5
			56	M	Mandible	NI	Nasopharyngeal carcinoma Latency 8 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	DOD	10
			32	M	Mandible	NI	Nasopharyngeal carcinoma Latency 10 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	NI	No	NI	NED	7
			57	F	Mandible	NI	Nasopharyngeal carcinoma Latency 20 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	AWD	8

			46	F	Mandible	NI	Nasopharyngeal carcinoma Latency 21 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	No	NI	NED	5
			51	F	Maxilla	NI	Nasopharyngeal carcinoma Latency 12 years		RAS Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	Yes	No	NI	DOD	7
Liao et al. 2016	China	45	≤49 21 >49 24 Median 49 Range 18–69	M33/F12	Mandible 12 Maxilla 33	≤5 22 >5 23	Nasopharyngeal carcinoma Median latency 8 years (3–34 years) ≤8 23 >8 22	NI	RAS Osteosarcoma	NI	NI	NI	M 1 2	I/II 19 III/IV 26	NI	S 30 S+CT 8 S+RT+CT 1 CT 6	Pos 24 Neg 15	Yes 10	NI	NI	DOD 45	Mean 17.9 (2.1-56.5)
Seng et al. 2019	China	55	≤32 19 >32 16 Mean 32.5 Range 14–66	M35/F20	Mandible 55	NI	No	Swelling 55 Pain 10 Lower lip numbness 6 Trismus 3 Cachexia 15	Osteosarcoma	NI	NI	NI	NI	IA 11 IB 12 IIA 21 IIB 8 NI 3	NI	S+CT 50 S+RT+CT 5	Pos 5	Yes 11	NI	Yes 8	LFU 8 DOD 12 Alive 35	Mean 63.3 (10-163)

Bouaoud et al. 2019	France	35	Median 36.8 Range 18.5 - 84.4	M23 /F12	Mandible 21 Maxilla 14	Median 4 (1.5-9.9)	NI	Evolving mass syndrome 29 Pain 6	Osteosarcoma	NI	NI	NI	NI	IIA 24 IIB 2 IV A 4 IV B 3 NI 2	NI	S 31 CT 40 RT 8	Neg 17 Pos10 NI 8	Yes 8	NI	Yes 3	Dead 8 Alive 27	Median 43.6 (1-160.7)
Kumar et al. 2019	India	26	18	M	Mandible	NI	Trauma 2	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	Alive	90
			65	M	Mandible	NI		NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	Yes	NI	NI	Dead	19
			21	M	Maxilla	NI		NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	38
			22	M	Maxilla	NI		NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	NI	NI	NI	Alive	61
			60	M	Maxilla	NI		NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	Dead	26
			18	M	Maxilla	NI		NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Dead	12
			14	F	Maxilla	NI		NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	11
			17	M	Maxilla	NI		NI	Ewing's Sarcoma	NI	NI	NI	NI	NI	NI	RT+CT	NI	NI	NI	NI	Alive	119
			30	M	Mandible	NI		NI	Ewing's Sarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	Yes	NI	NI	Alive	120
			18	M	Mandible	NI		NI	Ewing's Sarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	Alive	54
			4	M	Mandible	NI		NI	Ewing's Sarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	NI	NI	NI	Alive	33
			15	F	Mandible	NI		NI	Ewing's Sarcoma	NI	NI	NI	NI	NI	NI	S+CT	NI	NI	NI	NI	Alive	50
			75	M	Maxilla	NI		NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	Dead	25
			40	M	Mandible	NI		NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU	NI
			21	M	Buccal Vestibule	NI		NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	Alive	78
			21	F	Maxilla	NI		NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT	NI	Yes	NI	NI	Dead	24
			20	F	Mandible	NI		NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	Alive	12
			17	M	Gingiva	NI		NI	Leiomyosarcoma	NI	NI	NI	NI	NI	NI	S	NI	NI	NI	NI	LFU	NI
			55	M	Maxillary Alveolus	NI		NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Dead	8
			20	M	Maxilla	NI		NI	Undifferentiated pleomorphic sarcoma	NI	NI	NI	NI	NI	NI	RT+CT	NI	NI	NI	NI	Dead	23
			59	M	Maxillary Tuberosity	NI		NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	NI	NI	NI	Alive	59
			23	F	Buccal Mucosa	NI		NI	Rhabdomyosarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Alive	13
			38	F	Mandible	NI		NI	Malignant Peripheral Nerve Sheath Tumor	NI	NI	NI	NI	NI	NI	S+RT	NI	NI	NI	NI	Alive	18

			60	F	Maxilla	NI		NI	Malignant Peripheral Nerve Sheath Tumor	NI	NI	NI	NI	NI	NI	S+RT+CT	NI	NI	NI	NI	Alive	25
			28	M	Mandible	NI		NI	Myeloid Sarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Alive	30
			5	M	Mandible	NI		NI	Myeloid Sarcoma	NI	NI	NI	NI	NI	NI	CT	NI	NI	NI	NI	Alive	28
Cassoni et al. 2020	Italy	15	Mean 38.53 +/- 18.91	M4/ F11	Mandible 7 Maxilla 8	NI	NI	NI	Osteosarcoma 12 RAS Osteosarcoma 3	NI	NI	NI	NI	IA 2 IIA 11 IIB 1	NI	S 8 Multimodality 7	Neg 12 Pos 2 Margina l resection 1	Yes 4	NI	NI	Dead 3 NI 12	Mean 7.46 +/- 4.59
You et al. 2021	China	10	45	M	Gingiva	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M 0	IV	NI	S	NI	Yes	NI	No	DOD	9
			42	M	Tongue	NI	Previous RT: yes Squamous cell carcinoma	NI	Undifferentiated pleomorphic sarcoma	NI	T3	N0	M 0	III	NI	S+CT/Target therapy	NI	Yes	NI	No	DOD	5
			46	F	Gingiva	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M 0	IV	NI	S+RT+CT /Target therapy	NI	No	NI	Yes (Lung)	DOD	18
			63	F	Gingiva	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M 0	IV	NI	S+RT	NI	Yes	NI	No	DOD	5
			39	M	Tongue	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M 0	IV	NI	S+RT+CT /Target therapy	NI	Yes	NI	No	DOD	5
			79	F	Buccal area	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	Missense mutation in gene PIK3CA (p.E545K).	T4	N0	M 0	IV	NI	S	NI	No	NI	Yes (Lung)	DOD	6.5
			49	M	Tongue	NI	Previous RT: yes Squamous cell carcinoma	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M 0	IV	NI	S+RT+CT /Target therapy	NI	Yes	NI	No	DOD	6

			20	F	Palate	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M0	IV	NI	S+RT+CT /Target therapy	NI	Yes	NI	No	DOD	17
			59	M	Gingiva	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M0	IV	NI	S+RT+CT /Target therapy	NI	Yes	NI	No	DOD	12
			40	F	Maxillary sinus	NI	Previous RT: no	NI	Undifferentiated pleomorphic sarcoma	NI	T4	N0	M0	IV	NI	S+RT+CT /Target therapy	NI	Yes	NI	Yes (Lung)	DOD	17
Kotecha et al. 2021	UK	14	16	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	Yes	No	No	NED	479
			69	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Neg	No	NI	Yes	DOD	7
			47	F	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	No	No	No	NED	228
			75	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Neg	No	No	No	NED	35
			63	F	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+RT	Pos	No	No	No	NED	33
			72	M	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Pos	Yes	No	No	DOD	12
			60	M	Oral cavity NOS	NI	NI	NI	Liposarcoma	NI	NI	NI	NI	NI	NI	RT+CT	NI	No	No	No	NED	33
			21	M	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	S+CT	Pos	No	No	No	NED	92
			67	F	Maxilla	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	RT+CT	NI	No	No	No	NED	25
			28	M	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	RT+CT	Neg	Yes	NI	Yes	NED	40
			88	M	Face NOS	NI	NI	NI	Dermatofibrosarcoma protuberans	NI	NI	NI	NI	NI	NI	S+RT+CT	Pos	Yes	No	No	NED	114
			71	F	Face NOS	NI	NI	NI	Angiosarcoma	NI	NI	NI	NI	NI	NI	S+RT+CT	Pos	Yes	NI	Yes	DOD	44
			76	F	Mandible	NI	NI	NI	Osteosarcoma	NI	NI	NI	NI	NI	NI	RT+CT	NI	No	No	No	DOD	11
			50	M	Maxilla	NI	NI	NI	Chondrosarcoma	NI	NI	NI	NI	NI	NI	NI	NI	No	No	No	DOD	10
Zhang et al. 2024	Chin a	21	0.8	F	Nasolabial fold	<5 17 >5 4	NI	NI	Rhabdomyosarcoma		T1a	N1	M0	III	IRS: III	S+RT+CT	NI	Yes	NI	NI	Alive	42.5
			9	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	NI	NI	Alive	10.9
			0.8	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	NI	NI	Alive	20.6
			4	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N1	M0	III	III	S+RT+CT	NI	NI	Yes	NI	Alive	64.1
			1	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2b	N1	M0	III	III	S+RT+CT	NI	NI	NI	NI	Alive	45.2
			3	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	NI	NI	Alive	58.1
			1	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	Yes	NI	Alive	24.8
			0.6	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2b	N0	M0	II	III	S+RT+CT	NI	NI	NI	NI	Alive	18.1

			3	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma	PAX3/7FOXO1 gene fusion positive in 14 patients and negative in 3	T2b	N1	M0	III	III	S+RT+CT	NI	NI	Yes	Yes (Zygomatic and paerietal bones)	Dead	32.5
			5	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	NI	NI	Alive	26.6
			3	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2b	N1	M0	III	III	S+RT+CT	NI	NI	NI	NI	Alive	78.3
			0.7	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	NI	NI	Alive	20.6
			2	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2a	N1	M0	III	III	S+RT+CT	NI	NI	NI	NI	Alive	14.9
			1	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	II	S+RT+CT	NI	NI	NI	NI	Alive	15.6
			1	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2a	N1	M0	III	III	S+RT+CT	NI	NI	Yes	NI	Alive	22.7
			10	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	III	S+RT+CT	NI	NI	NI	NI	Alive	12.7
			1	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N0	M0	I	II	S+RT+CT	NI	Yes	NI	NI	Alive	34.3
			3	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T1a	N1	M1	IV	IV	S+RT+CT	NI	NI	NI	Yes (Zygomatic and paerietal bones)	Dead	24.5
			4	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2a	N1	M0	III	III	S+RT+CT	NI	Yes	NI	NI	Dead	13.8
			1	F	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2a	N0	M0	II	III	S+RT+CT	NI	Yes	NI	NI	Dead	23.9
			10	M	Nasolabial fold		NI	NI	Rhabdomyosarcoma		T2a	N1	M0	III	III	S+RT+CT	NI	NI	NI	NI	Alive	66

Note: C: country; N: number of cases; F: female; M: male; y: years; m: months; NI: not informed; MA: molecular alteration; Stg: stage; Neg: negative; Pos: positive; Treat: treatment; RT: radiotherapy; CT: chemotherapy; St: status; NED: no evidence of disease; AWD: alive with disease; LFU: lost follow-up; DOD: died of disease; DOC: died of other cause; RAS: radiation-associated sarcoma, LR: local recurrence; NM: nodal metastasis; DM: distant metastasis.

Figure S2 Summary of the risk of bias in cross-sectional studies, assessed using the Joanna Briggs Institute Critical Appraisal Checklist.

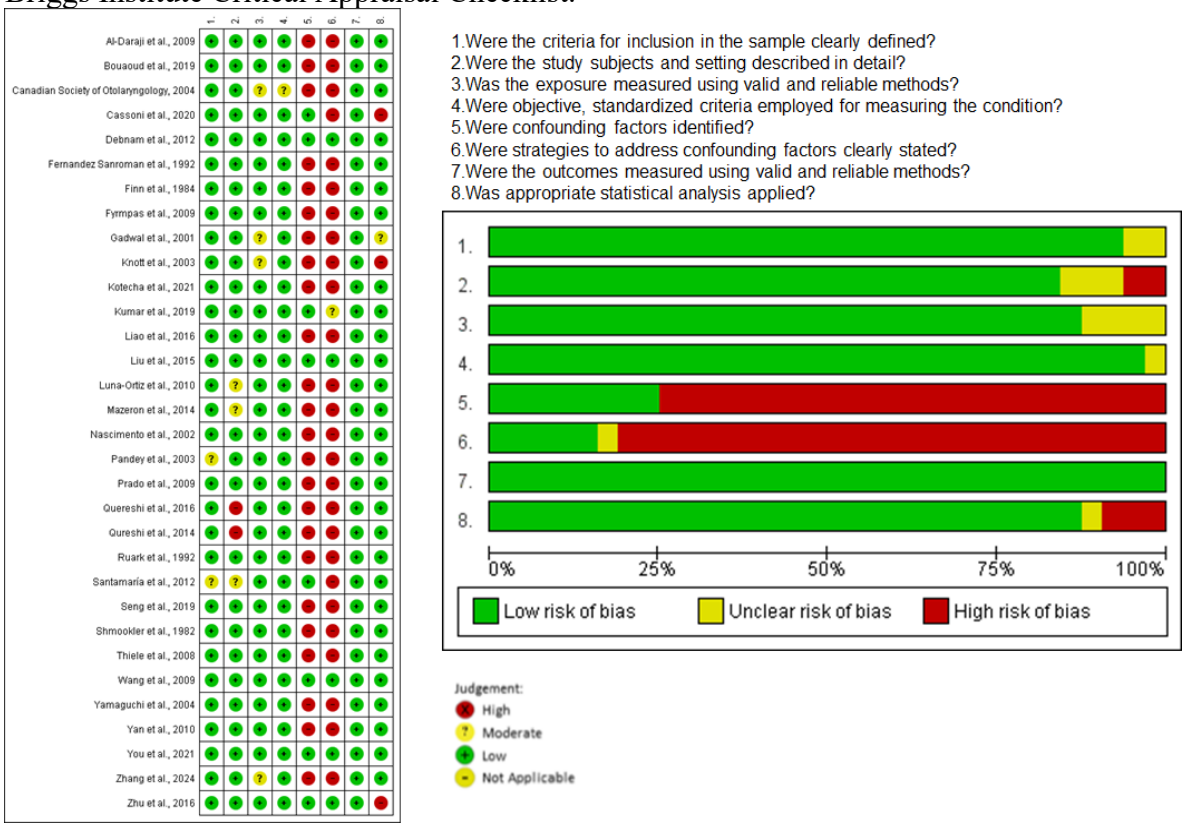


Figure S3 Summary of the risk of bias in case report study, assessed using the Joanna Briggs Institute Critical Appraisal Checklist.

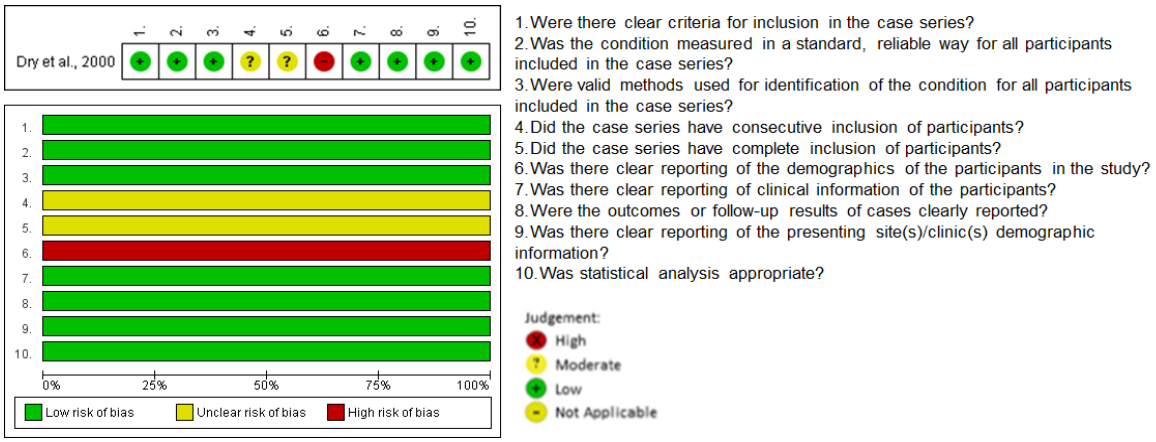


Table S3 Univariate Log-rank analysis of the clinicopathological characteristics in 369 cases of oral and maxillofacial sarcomas.

Clinicopathological variables	**Log-rank univariate analysis**			
	5-Year disease-free survival (%)	**Estimate (95% CI)**	**Chi-square**	***p*-value**
Sex				
Male	53.851	0.9740 (0.7127-1.331)	0.02788	0.8674
Female	55.064	1.027 (0.7512-1.403)		
Age (years)				
<35	63.843	0.5309 (0.3901-0.7226)	16.76	**<0.0001**
≥35	44.573	1.883 (1.384-2.563)		
Anatomical location				
Mandible	58.533	NC	4.528	0.6056
Maxilla	56.945	NC		
Nasal and Maxillary Sinus Region	43.688	NC		
Oral Cavity	45.233	NC		
Nasolabial Fold	60.081	NC		
Face	57.619	NC		
Parotid Region	63.179	NC		
Histological type				
Osteosarcoma	65.744	NC	49.19	**<0.0001**
Radiation-associated sarcomas	20.456	NC		
Rhabdomyosarcoma	56.669	NC		
Chondrosarcoma	61.338	NC		
Synovial sarcoma	58.105	NC		
Leiomyosarcoma	29.690	NC		
Undifferentiated pleomorphic sarcoma	32.512	NC		
Liposarcoma	85.714	NC		

Tumor size (cm)				
<4	61.158	0.9139 (0.5387-1.550)	0.1145	0.7350
≥4	55.649	1.094 (0.6450-1.856)		
T Stage				
T1/T2	47.858	0.1501 (0.03638-0.619)	35.51	**<0.0001**
T3/T4	0.000	6.664 (1.615-27.49)		
N Stage				
N0	25.979	3.337 (1.491-7.467)	4.628	**0.0314**
N1	64.286	0.2997 (0.1339-0.6708)		
Clinical Stage				
I/II	85.901	0.2011 (0.08586-0.470)	12.88	**0.0003**
III/IV	42.779	4.973 (2.124-11.65)		
Treatment				
Surgery	52.957	NC	3.653	0.1609
Multimodal	57.665	NC		
RT and/or CT	36.125	NC		
Margin				
Positive	28.039	3.267 (1.700-6.277)	18.13	**<0.0001**
Negative	70.407	0.3061 (0.1593-0.5882)		
Local recurrence				
Yes	27.624	4.565 (3.186-6.541)	54.01	**<0.0001**
No	79.083	0.2191 (0.1529-0.3139)		
Nodal metastasis				
Yes	19.444	2.611 (1.104-6.174)	10.55	**0.0012**
No	52.656	0.3829 (0.1620-0.9054)		
Distant metastasis				
Yes	18.824	1.996 (1.160-3.436)	9.470	**0.0021**
No	51.921	0.5010 (0.2910-0.8624)		

Note: The significance of the bolded values is < 0.05 (p-value < 0.05). S: Surgery; RT: Radiation therapy; CT: Chemotherapy; NC: Not Computed.

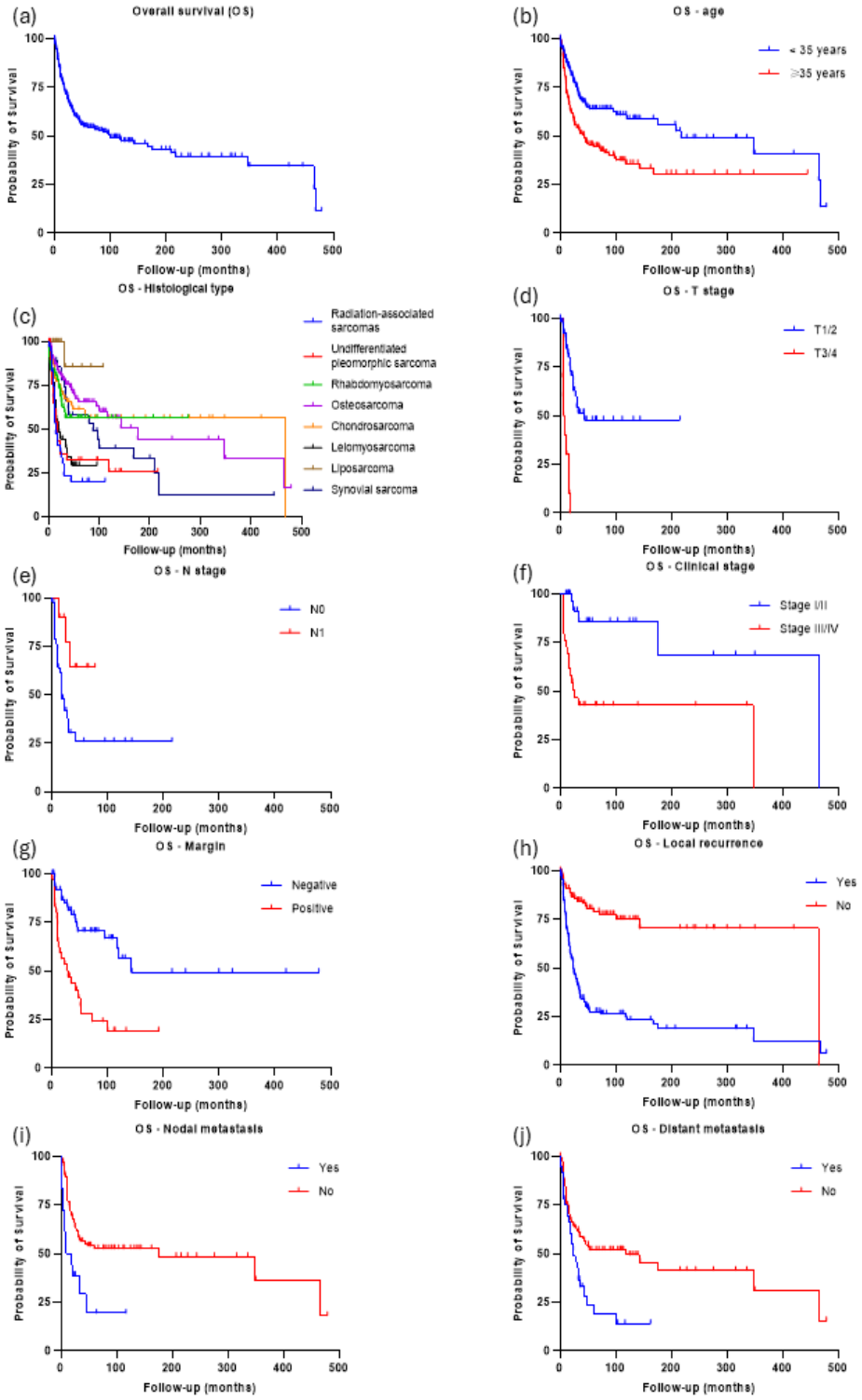


Figure S4 Overall Survival (OS) curves. (a) Kaplan-Meyer curve demonstrating the OS of patients affected by oral and maxillofacial sarcomas. Using Log-Rank univariate analysis, (b) age (P<0.0001), (c) histological type (P<0,0001), (d) T stage (P<0.0001), (e) N stage (P=0.0314), (f) clinical stage (P=0.0003), (g) margin status (P<0.0001), (h) local recurrence (P<0.0001), (i) nodal metastasis (P=0.0012) and (j) distant metastasis (P=0.0021) significantly impact the survival rate of oral and maxillofacial sarcoma.

Table S4 Clinical and Tumor Characteristics Influencing Disease-Specific Survival in Oral and Maxillofacial Sarcomas: Univariate Cox Analysis

	HR (95% CI)	**p-value**
Sex		
Male	1	0.594
Female	1.107 (0.761 – 1.611)	
Age		
< 35	0.372 (0.251 – 0.551)	**<0.001**
≥ 35	1	
Anatomical Location		
Soft tissue	1	0.788
Intraosseous	0.951 (0.657 – 1.375)	
Histological Subtype		
Soft tissue	0.373 (0.216–0.643)	**<0.001**
Bone	0.081 (0.161-0.493)	
RAS	1	
T Stage		
T1/T2	0.162 (0.072 – 0.366)	**<0.001**
T3/T4	1	
N Stage		
N0	29.299 (0.477 – 1798.258)	0.108
N1	1	
Clinical Stage		
I/II	0.108 (0.024 – 0.481)	**0.003**
III/IV	1	
Treatment		
CT and/or RT	1	
Surgery	0.854 (0.451 – 1.619)	0.629
Multimodal	0.574 (0.305 – 1.082)	0.086
Margins status		
Positive	1	**<0.001**
Negative	0.270 (0.142 – 0.514)	

Local Recurrence		
Yes	1	**<0.001**
No	0.182 (0.109 – 0.304)	
Nodal Metastasis		
Yes	1	0.525
No	0.758 (0.322 – 1.782)	
Distant Metastasis		
Yes	1	**0.029**
No	0.575 (0.350 – 0.945)	

Note: S: Surgery, RT: Radiation Therapy, CT: Chemotherapy, HR:Hazard Ratio, RAS: radiation-associated sarcoma; CI:Confidence Interval. Ref Reference categories are indicated by 1 in the corresponding row.

2.2 ARTIGO: Radiation-induced osteosarcoma in the head and neck region: Case report and literature review

Publicado no periódico: *Oral Oncology* **(Anexo 2)**

Iara Vieira Ferreira[1,2], Marcelo Elias Schempf Cattan[2], Carlos Takahiro Chone[3], Arthur Antolini[2], Erika Said Abu Egal[4], Albina Altemani[2], Fernanda Viviane Mariano[1,2*]

[1]Oral Diagnosis Department, Piracicaba Dental School, State University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil.

[2]Pathology Department, School of Medical Sciences, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.

[3]Department of Ophthalmology and Otorhinolaryngology, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.

[4]Biorepository and Molecular Pathology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, United States.

***Corresponding author:**
Fernanda Viviane Mariano – fmariano@unicamp.br
Department of Pathology, School of Medical Sciences - State University of Campinas (UNICAMP).
Tessália Vieira de Camargo, 126 – Barão Geraldo, Cidade Universitária, Campinas, SP, Brazil, Zip code: 13083-887

Abstract

Radiation-induced sarcoma (RIS) is a rare but highly aggressive complication of radiotherapy, especially in the head and neck region (RIS-HN). This report describes a case of radiation-induced osteosarcoma (RIOS) in a 32-year-old woman with a history of craniopharyngioma treated with surgery and radiotherapy 13 years prior. The patient exhibited symptoms including epistaxis, diplopia, and ptosis of the right eyelid. Imaging revealed a large, inoperable tumor in the area that had received prior radiotherapy. A biopsy confirmed the diagnosis of osteosarcoma, and the patient initiated palliative chemotherapy. Unfortunately, the treatment was unsuccessful, and the patient passed away. A review of 148 RIOS cases published in the last 25 years in the literature shows that the maxilla and mandible are the most affected sites (68.86%), with an average latency of 11.79 years. The most common primary tumor was nasopharyngeal carcinoma, treated with an average radiation dose of 61.69 Gy. The prognosis remains poor, with 72.3% of patients dying within an average of 23 months of follow-up. This study highlights the clinical and pathological characteristics of RIOS, the importance of long-term monitoring of irradiated patients to detect and treat these tumors early, with the aim of improving patient outcomes.

Introduction

Radiotherapy is an essential treatment for head and neck cancer, with recent advancements leading to significant improvements in patient survival and quality of life [1–3]. However, this increase in survival rates has been accompanied by a rise in the incidence of secondary neoplasms, including radiation-induced sarcoma (RIS), a rare and highly lethal complication, particularly when located in the head and neck region (RIS-HN) [2–4]. The diagnosis of RIS-HN is based on well-defined criteria, including the emergence of the tumor in a previously irradiated area, histological distinction between the primary and secondary tumors, absence of the secondary tumor during radiotherapy, and a latency period after radiotherapy [5,6]. The most prevalent histological variants include malignant fibrous histiocytoma, osteosarcoma, chondrosarcoma, and fibrosarcoma, all of which are associated with a poor prognosis [3,7].

This article reports a case of RIS-HN, along with a literature review of radiation-induced osteosarcoma (RIOS) in this region.

Case report

A 32-year-old female patient from Itatiba, Brazil, presented to the clinic with a 20-day history of epistaxis, purulent nasal discharge, and severe frontal headache. Over the past seven days, she developed diplopia, right eye ptosis, and episodes of nausea and vomiting. The patient had a history of craniopharyngioma, diagnosed 13 years prior, treated via transsphenoidal craniotomy. The pathological examination at that time revealed a residual tumor in the dorsum sellae, adhered to the cavernous sinus. Following surgical resection, the patient underwent adjuvant radiotherapy, receiving 55.80 Gy in 31 fractions of 1.80 Gy each, delivered through three fields (right temporal, left temporal, and frontal) using 9 MV energy on an Al-Netuno device. Since then, the patient has been under clinical follow-up due to panhypopituitarism secondary to surgery, with continuous hormone replacement therapy. However, the emergence of new symptoms necessitated further investigation. Magnetic resonance imaging revealed an extensive lesion in the previously irradiated region, invading the clivus, cavernous sinus, maxillary sinus, and nasal cavity. A biopsy of the lesion in the nasopharynx was performed via an endoscopic nasal approach. Microscopic examination revealed a predominantly spindle-cell malignant neoplasm composed of atypical cells, including multinucleated cells, with numerous mitoses, both typical and atypical. The presence of high cellularity and the production of osteoid material by the neoplastic cells were observed, establishing the diagnosis of osteosarcoma (**Figure 1**). Given the unresectable nature of the neoplasm, the patient was referred for palliative

treatment with cisplatin and doxorubicin-based chemotherapy. Despite the implementation of these therapeutic measures, the clinical course was unfavorable, and the patient died of the disease after 16 months of follow-up.

Discussion

The etiopathogenesis of most sarcomas remains poorly understood, but genetic and environmental factors, including genetic alterations, radiation exposure, and infections, have been implicated in their development [8,9]. Ionizing radiation, particularly through external beam radiation in the head and neck, is a recognized risk factor, causing DNA damage and cell cycle dysregulation [10,11]. RIS-HN has a worse prognosis due to factors such as local immunosuppression, genetic alterations in tumor cells from radiotherapy, difficulties in treating irradiated areas, and diagnostic delays from anatomical and histological changes [9,12]. Among histological subtypes, osteosarcoma is the most prevalent [10,40]. This rare, aggressive neoplasm typically arises at least five years after radiation exposure [36,41]. The study presents a case of RIOS in a female patient, emphasizing diagnostic challenges and poor prognosis associated with this condition.

A comprehensive review on radiation-induced osteosarcoma revealed 148 cases published in PubMed over the past 25 years (**Table 1**) [4,10,13–39]. Most patients were male (66%) with a mean age of 45.65 years. The maxilla was the most affected site for RIOS, accounting for 39.04% of cases. In our review, the mean latency period was 11.79 years (range: 3–36 years), aligning with the literature, which reports a median latency of 8 years (range: 3–34 years) [36]. In our case, the latency period was slightly longer, at 13 years.

Table 1. Summary of 148 cases of radiation-induced osteosarcoma published in PubMed over the last 25 years.

Clinicopathological variables	Value %
Sex (n=147)	
Male	97 (66%)
Female	50 (34%)
Age (years) (n=88)	
Mean	45.65

Standard deviation	17.73
Range	9-83
Primary tumor histology (n=145)	
Nasopharyngeal carcinoma	86 (59.3%)
Squamous cell carcinoma	12 (8.3%)
Lymphoma	7 (4.8%)
Retinoblastoma	7 (4.8%)
Rhabdomyosarcoma	4 (2.8%)
Adenoid cystic carcinoma	4 (2.8%)
Others[a]	25 (17.2%)
Primary tumor location (n=139)	
Nasopharynx	90 (64.7%)
Oral cavity	9 (6.5%)
Intraocular	6 (4.3%)
Parotid	5 (3.6%)
Others[b]	29 (20.9%)
Total Dose of Radiotherapy (Gy) (n=76)	
Mean	61.69
Standard deviation	12.06
Range	30-96
Latency period (years) (n=91)	
Mean	11.79
Standard deviation	6.71
Range	3-36

Location of Radiation-Induced Osteosarcoma (n= 146)	
Maxilla	57 (39.04%)
Mandible	45 (30.82%)
Others[c]	44 (30.14%)
Treatment (n=140)	
Surgery	74 (52.9%)
Surgery + chemotherapy	35 (25.0%)
Chemotherapy	15 (10.7%)
Surgery + radiotherapy	5 (3.6%)
Surgery + radiotherapy + chemotherapy	4 (2.9%)
Multimodal therapy NOS	4 (2.9%)
Radiotherapy + chemotherapy	1 (0.7%)
Radiotherapy	1 (0.7%)
Refused treatment	1 (0.7%)
Status (n=137)	
Died of the disease	65 (47.4%)
Died	34 (24.8%)
Alive	28 (20.4%)
No evidence of disease	4 (2.9%)
Alive with disease	3 (2.2%)
Lost follow-up	3 (2.2%)
Time of follow-up (months) (n=88)	
Mean	23
Standard deviation	22.65

Range	1-143

[a]Others: Oligodendroglioma (3), Meningioma (2), Astrocytoma (2), Mucoepidermoid carcinoma (2), Medulloblastoma (2), Renal metastasis (1), Tonsillar carcinoma (1), Ewing sarcoma (1), Adenocarcinoma (1), Carcinoma (1), Nasopharyngeal angiosarcoma (1), Ependymoma (1), Acute lymphoblastic leukemia (1), Craniopharyngioma (1), Melanoma (1), Basal cell carcinoma (1), Glioma (1), Liposarcoma (1), Papillary carcinoma (1).

[b]Others: Neck (3), Paranasal sinus (3), Central nervous system (2), Larynx (2), Nasal ala (2), Nasal cavity (2), Posterior fossa (2), Sinonasal (2), Brainstem (1), Frontoparietal (1), Head and neck (1), Lip (1), Masticator space (1), Maxilla (1), Orbit (1), Parieto-occipital (1), Temporal (1), Temporoparietal (1), Thyroid (1).
[c]Others: Paranasal sinus (6), Nasal cavity/Nose (5), Oral cavity (5), Cranium (4), Neck (4), Sinonasal (3), Temporal bone (3), Frontal bone (2), Mastoid (2), Occipital bone (2), Skull base (2), Parieto-occipital (1), Orbit (1), Postnaris (1), Sphenoid ridge (1), Zygoma (1), Frontoparietal (1).

Nasopharyngeal carcinoma (NC) was the most common histological subtype of the primary tumor, representing 86 cases (59.3%), with the nasopharynx being the most frequent location, found in 64.7% of cases. Radiotherapy, the standard treatment for NC, often targets the skull base, maxilla, mandible, and pterygoid bone. RIOS may develop as a late complication in these irradiated areas [4]. This emphasizes the importance of long-term monitoring of patients treated for NC due to the risk of secondary neoplasms in radiation-exposed sites [42]. Our patient, however, had a history of craniopharyngioma, rarely associated with RIOS, adding rarity to this case.

The management of RIOS typically involves surgery, radiotherapy, chemotherapy, or a combination [36]. In this review, surgery alone was the most common approach, used in 52.9% of cases, followed by combined surgery and chemotherapy in 25%. While complete surgical excision remains the cornerstone of RIOS management, its feasibility in advanced cases is often limited by the tumor's location in complex regions and the risk of damaging vital structures [19]. Prognosis is extremely poor, as evidenced by a study of 45 cases of RIOS in the maxilla and mandible, where all patients died within a median survival of 17.9 months (range: 2.1–56.5 months) [36]. Similarly, in our case, the patient died after 16 months, and our review showed a mortality rate of 72.3% within a mean follow-up of 23 months (range: 1–143 months).

In summary, this article presents a case of RIOS in the head and neck region in a young patient. A review of the literature from the past 25 years, based on cases published in English on PubMed, reveals that most cases involve males (mean age: 45.65 years). The most common histological type and primary tumor location were, respectively, nasopharyngeal carcinoma

(59.3%) and nasopharynx (64.7%). The latency period was 11.79 years, with the maxilla being the most affected site by RIOS (39.04%). Despite predominantly surgical treatment (52.9%), 72.3% of patients died during the mean follow-up period of 23 months. These findings highlight the importance of early diagnosis and monitoring of radiation-exposed patients due to the long latency period and poor prognosis associated with this rare yet aggressive condition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to gratefully acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES, Brasilia, Brazil, finance code 001).

References

[1] Zenga J, Pipkorn P, Adkins DR, Thorstad WL, Nussenbaum B. Trials in head and neck oncology: Evolution of perioperative adjuvant therapy. Oral Oncol 2017;72:80–9. https://doi.org/10.1016/j.oraloncology.2017.07.012.

[2] Giannini L, Incandela F, Fiore M, Gronchi A, Stacchiotti S, Sangalli C, et al. Radiation-Induced Sarcoma of the Head and Neck: A Review of the Literature. Front Oncol 2018;8. https://doi.org/10.3389/fonc.2018.00449.

[3] Liao Y, Hsu C, Leu C, Lai S, Huang Y, Hsieh M, et al. Radiation-induced sarcoma of head and neck: Clinical characteristics and molecular signatures. Head Neck 2023;45:638–46. https://doi.org/10.1002/hed.27279.

[4] Wei Z, Xie Y, Xu J, Luo Y, Chen F, Yang Y, et al. Radiation-induced sarcoma of head and neck: 50 years of experience at a single institution in an endemic area of nasopharyngeal carcinoma in China. Medical Oncology 2012;29:670–6. https://doi.org/10.1007/s12032-011-9828-9.

[5] Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma in irradiated bone. Report of eleven cases. Cancer 1948;1:3–29. https://doi.org/10.1002/1097-0142(194805)1:1<3::AID-CNCR2820010103>3.0.CO;2-.

[6] Murray EM, Werner D, Greeff EA, Taylor DA. Postradiation sarcomas: 20 cases and a literature review. International Journal of Radiation Oncology*Biology*Physics 1999;45:951–61. https://doi.org/10.1016/S0360-3016(99)00279-5.

[7] Thiagarajan A. Radiation-induced sarcomas of the head and neck. World J Clin Oncol 2014;5:973. https://doi.org/10.5306/wjco.v5.i5.973.

[8] Sturgis EM, Potter BO. Sarcomas of the head and neck region. Curr Opin Oncol 2003;15:239–52. https://doi.org/10.1097/00001622-200305000-00011.

[9] Wreesmann VB, Oomen KP, Brennan PA. Angiosarcomas of the head and neck: Impact of large data analysis on clinical management. Journal of Oral Pathology & Medicine 2022;51:904–10. https://doi.org/10.1111/jop.13354.

[10] Zhu W, Hu F, Zhao T, Wang C, Tao Q. Clinical Characteristics of Radiation-Induced Sarcoma of the Head and Neck: Review of 15 Cases and 323 Cases in the Literature. Journal of Oral and Maxillofacial Surgery 2016;74:283–91. https://doi.org/10.1016/j.joms.2015.07.013.

[11] Coca-Pelaz A, Mäkitie AA, Strojan P, Corry J, Eisbruch A, Beitler JJ, et al. Radiation-Induced Sarcomas of the Head and Neck: A Systematic Review. Adv Ther 2021;38:90–108. https://doi.org/10.1007/s12325-020-01556-y.

[12] Patel SR. Radiation-induced sarcoma. Curr Treat Options Oncol 2000;1:258–61. https://doi.org/10.1007/s11864-000-0037-6.

[13] KING AD, AHUJA AT, TEO P, TSE GMK, KEW J. Radiation Induced Sarcomas of the Head and Neck Following Radiotherapy for Nasopharyngeal Carcinoma. Clin Radiol 2000;55:684–9. https://doi.org/10.1053/crad.2000.0503.

[14] Lagrange J-L, Ramaioli A, Chateau M-C, Marchal C, Resbeut M, Richaud P, et al. Sarcoma after Radiation Therapy: Retrospective Multiinstitutional Study of 80 Histologically Confirmed Cases. Radiology 2000;216:197–205. https://doi.org/10.1148/radiology.216.1.r00jl02197.

[15] Galera-Ruiz H, Sanchez-Calzado JA, Rios-Martin JJ, DeMingo-Fernandez EJ, Muñoz Borge F. Sinonasal radiation-associated osteosarcoma after combined therapy for rhabdomyosarcoma of the nose. Auris Nasus Larynx 2001;28:261–4. https://doi.org/10.1016/S0385-8146(01)00056-6.

[16] Osipov V, Ho K-C, Krouwer HG, Meyer G, Shidham VB. Post-radiation dedifferentiation of meningioma into osteosarcoma. BMC Cancer 2002;2:34. https://doi.org/10.1186/1471-2407-2-34.

[17] Matsuyama A, Yonemitsu N, Hayashida S, Watanabe K, Sugihara H, Inokuchi A. Case of postradiation osteosarcoma with a short latency period of 3 years. Pathol Int 2003;53:46–50. https://doi.org/10.1046/j.1440-1827.2003.01427.x.

[18] Sale KA, Wallace DI, Girod DA, Tsue TT. Radiation-Induced Malignancy of the Head and Neck. Otolaryngology–Head and Neck Surgery 2004;131:643–5. https://doi.org/10.1016/j.otohns.2004.05.012.

[19] Wei-wei L, Qiu-liang W, Guo-hao W, Zhi-hua C, Zong-yuan Z. Clinicopathologic Features, Treatment, and Prognosis of Postirradiation Osteosarcoma in Patients with Nasopharyngeal Cancer. Laryngoscope 2005;115:1574–9. https://doi.org/10.1097/01.mlg.0000173166.48440.e4.

[20] Maghami EG, St-John M, Bhuta S, Abemayor E. Postirradiation sarcoma: a case report and current review. Am J Otolaryngol 2005;26:71–4. https://doi.org/10.1016/j.amjoto.2004.08.005.

[21] Valentí V, López-Pousa A, Gonzalez Y, Farré N. Radiation-Induced Mandibular Osteogenic Sarcoma: Report of a Case and Review of the Literature. Journal of Craniofacial Surgery 2005;16:452–6. https://doi.org/10.1097/01.SCS.0000147386.53251.97.

[22] Kasthoori JJ, Wastie ML. Radiation-induced osteosarcoma of the maxilla. Singapore Med J 2006;47:907–9.

[23] McHugh JB, Thomas DG, Herman JM, Ray ME, Baker LH, Adsay NV, et al. Primary versus radiation-associated craniofacial osteosarcoma. Cancer 2006;107:554–62. https://doi.org/10.1002/cncr.22019.

[24] Seethala RR, Sturgis EM, Raymond AK, Deavers MT. Postirradiation Osteosarcoma of the Mandible With Heterologous Differentiation. Arch Pathol Lab Med 2006;130:385–8. https://doi.org/10.5858/2006-130-385-POOTMW.

[25] Makimoto Y, Yamamoto S, Takano H, Motoori K, Ueda T, Kazama T, et al. Imaging findings of radiation-induced sarcoma of the head and neck. Br J Radiol 2007;80:790–7. https://doi.org/10.1259/bjr/20938070.

[26] Franco Gutiérrez V, Llorente Pendás JL, Coca Pelaz A, Cabanillas Farpón R, Suárez Nieto C. Radiation-Induced Sarcomas of the Head and Neck. Journal of Craniofacial Surgery 2008;19:1287–91. https://doi.org/10.1097/SCS.0b013e3181869df1.

[27] Chabchoub I, Gharbi O, Remadi S, Limem S, Trabelsi A, Hochlef M, et al. Postirradiation Osteosarcoma of the Maxilla: A Case Report and Current Review of Literature. J Oncol 2009;2009:1–4. https://doi.org/10.1155/2009/876138.

[28] Shao Z, He Y, Wang L, Hu H, Shi H. Computed tomography findings in radiation-induced osteosarcoma of the jaws. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2010;109:e88–94. https://doi.org/10.1016/j.tripleo.2009.10.049.

[29] Patel AJ, Rao VY, Fox BD, Suki D, Wildrick DM, Sawaya R, et al. Radiation-induced osteosarcomas of the calvarium and skull base. Cancer 2011;117:2120–6. https://doi.org/10.1002/cncr.25734.

[30] Brusić SK, Pusić M, Cvjetković N, Karnjus R, Candrlić B, Kukuljan M, et al. Osteosarcoma of the mastoid process following radiation therapy of mucoepidermoid carcinoma of the parotid gland--a case report. Coll Antropol 2012;36 Suppl 2:223–5.

[31] Matthew Debnam J, Guha-Thakurta N, Mahfouz YMM, Garden AS, Benjamin RS, Sturgis EM, et al. Radiation-associated head and neck sarcomas: Spectrum of imaging findings. Oral Oncol 2012;48:155–61. https://doi.org/10.1016/j.oraloncology.2011.08.017.

[32] Song MJ, Song JS, Roh J-L, Choi S-H, Nam SY, Kim SY, et al. Mdm2 and p53 Expression in Radiation-Induced Sarcomas of the Head and Neck: Comparison with <i>De Novo</i> Sarcomas. The Korean Journal of Pathology 2014;48:346–50. https://doi.org/10.4132/KoreanJPathol.2014.48.5.346.

[33] Wood J, Ver Halen J, Samant S, Florendo N. Radiation-induced sarcoma masquerading as osteoradionecrosis: case report and literature review. J Laryngol Otol 2015;129:279–82. https://doi.org/10.1017/S0022215114003326.

[34] Jones M, Chebib I, Deshpande V, Nielsen GP. Radiation-Associated Low-Grade Extraskeletal Osteosarcoma of the Neck Following Treatment for Thyroid Cancer. Int J Surg Pathol 2015;23:384–7. https://doi.org/10.1177/1066896915587757.

[35] Kim KS, Chang JH, Choi N, Kim H-S, Han I, Moon KC, et al. Radiation-Induced Sarcoma: A 15-Year Experience in a Single Large Tertiary Referral Center. Cancer Res Treat 2016;48:650–7. https://doi.org/10.4143/crt.2015.171.

[36] Liao L-Q, Yan H-H, Mai J-H, Liu W-W, Li H, Guo Z-M, et al. Radiation-induced osteosarcoma of the maxilla and mandible after radiotherapy for nasopharyngeal carcinoma. Chin J Cancer 2016;35:89. https://doi.org/10.1186/s40880-016-0153-8.

[37] Rashidghamat E, Calonje JE. A case of radiation-induced osteosarcoma of the skull presenting as a cutaneous epidermotropic tumor with a short latent period. J Cutan Pathol 2018;45:352–4. https://doi.org/10.1111/cup.13103.

[38] Lou J, Jiang L, Dai X, Wang H, Yang J, Guo L, et al. Radiation-Induced Sarcoma of the Head and Neck Following Radiotherapy for Nasopharyngeal Carcinoma: A Single Institutional Experience and Literature Review. Front Oncol 2021;10. https://doi.org/10.3389/fonc.2020.526360.

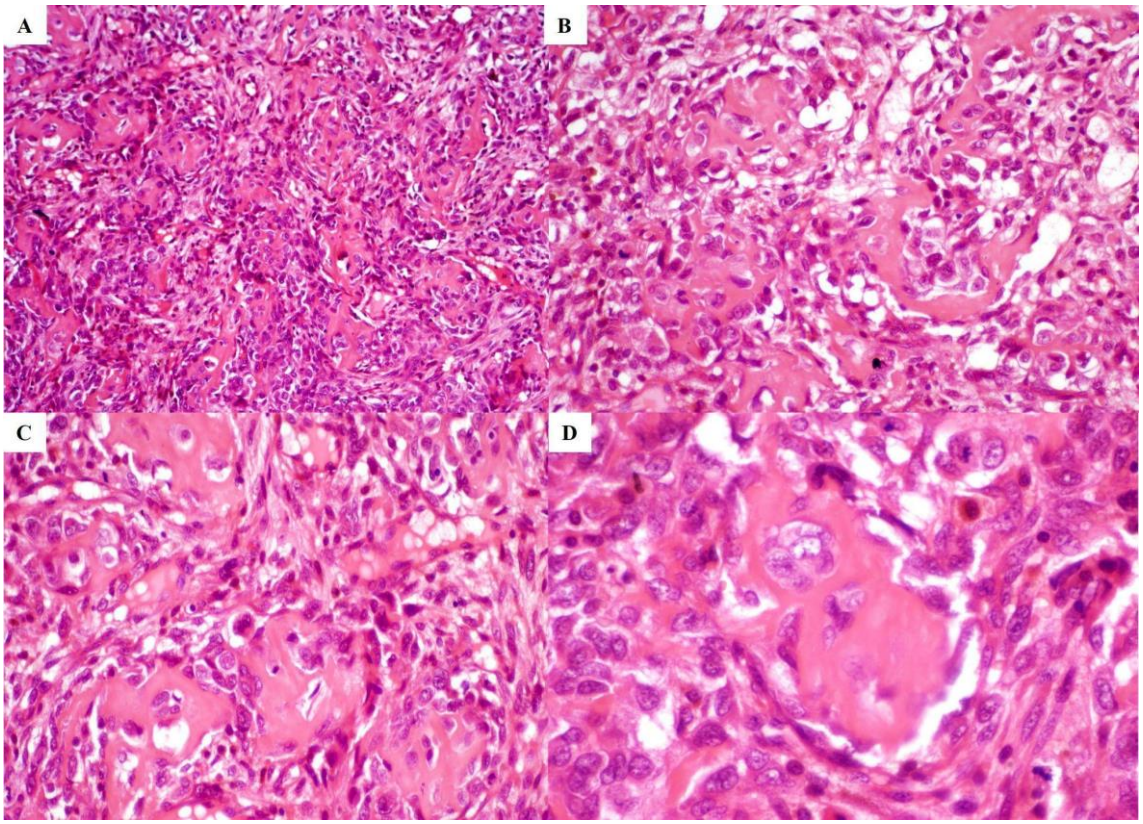
[39] Malik F, Gleysteen JP, Agarwal S. Osteosarcoma of the jaw: report of 3 cases (including the rare epithelioid variant) with review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e71–80. https://doi.org/10.1016/j.oooo.2020.03.044.

[40] Kumari N, Majumdar KS, Usmani SA, Agarwal SP. Radiation-induced synchronous mandibular osteosarcoma and papillary thyroid carcinoma. J Cancer Res Ther 2022;18:305–7. https://doi.org/10.4103/jcrt.JCRT_366_20.

[41] Wei-wei L, Qiu-liang W, Guo-hao W, Zhi-hua C, Zong-yuan Z. Clinicopathologic Features, Treatment, and Prognosis of Postirradiation Osteosarcoma in Patients with Nasopharyngeal Cancer. Laryngoscope 2005;115:1574–9. https://doi.org/10.1097/01.mlg.0000173166.48440.e4.

[42] Cai P, Wu Y, Li L, Zhang R, Xie C, Wu P, et al. CT and MRI of radiation-induced sarcomas of the head and neck following radiotherapy for nasopharyngeal carcinoma. Clin Radiol 2013;68:683–9. https://doi.org/10.1016/j.crad.2013.01.004.

Figure 1. Histopathological features of osteosarcoma. **(A)** Low-power view showing a predominantly spindle-cell neoplasm with atypical features (H&E, 10×). **(B-C)** Increased cellularity and osteoid production by neoplastic cells (H&E, 20×). **(D)** High-power view highlighting cellular pleomorphism and atypical mitotic figures (H&E, 40×).



2.3 ARTIGO: Molecular Alterations in Osteosarcomas of the Oral and Maxillofacial Region: A Scoping Review

Artigo a ser submetido ao periódico: *Oral Diseases*

Running title

Molecular Alterations in Osteosarcomas

Keywords

Osteosarcoma; Jaw Neoplasms; Molecular Analysis; Scoping Review.

Iara Vieira Ferreira[1,2], Reydson Alcides de Lima-Souza[1,2], Moisés Willian Aparecido Gonçalves[1,2], Luccas Lavareze[1,2], Erika Said Abu Egal[3], Albina Altemani[2], Fernanda Viviane Mariano[2*]

[1]Oral Diagnosis Department, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil.
[2]Pathology Department, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.
[3]Biorepository and Molecular Pathology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, United States.

***Correspondence**

Fernanda Viviane Mariano
Department of Pathology
School of Medical Sciences - State University of Campinas (UNICAMP)
Tessália Vieira de Camargo, 126 - Barão Geraldo, Cidade Universitária
Campinas-SP, Brazil, Zip Code: 13083-887
Email: fevimariano@gmail.com
Phone: +55 (19) 3521-8215

ABSTRACT

Objective: This study aimed to map molecular alterations associated with oral and maxillofacial osteosarcomas (OS), providing an overview of the genetic mechanisms involved in their development and progression.

Materials and Methods: A scoping review was performed following the PRISMA-ScR guidelines. Studies included observational research, case reports, and systematic reviews focusing on molecular alterations in oral and maxillofacial OS. A comprehensive search was conducted across four databases, and findings were synthesized and categorized by molecular characteristics.

Results: A total of 20 studies involving 68 maxillofacial OS cases were included. The average patient age was 39.4 years, with a slight male predominance. The mandible was the most commonly affected site, and chondroblastic OS was the most frequent histological subtype. Genetic alterations were predominantly observed in the TP53 gene, along with alterations in MDM2, CDK4, and other genes. Treatment primarily involved surgery, with or without chemotherapy. Local recurrence occurred in 11.1% of cases, and distant metastases in 16%. At the final follow-up, 69.7% of patients were alive.

Conclusion: This study emphasizes the value of molecular techniques in improving the diagnosis and management of maxillofacial OS. However, further research is needed to fully understand the molecular complexity and optimize therapeutic strategies.

1 INTRODUCTION

Osteosarcoma (OS) is a rare malignant bone neoplasm with a global incidence of approximately 4–5 cases per million people per year. It is characterized by the production of immature bone by tumor (WHO, 2023). While the femur, tibia, and humerus are the most common sites, the jaws - particularly the mandible - represent the fourth most common site (Haefliger *et al*, 2022). In contrast to OS affecting the long bones of the extremities, which display a bimodal incidence pattern with most cases occurring between 14 and 18 years and a smaller second peak in older adults, OS in the head and neck region typically develop in patients 10 to 20 years older than those with extragnathic OS, predominantly in the third to fourth decades of life, with no sex predilection (Ottaviani and Jaffe, 2009; Tran *et al*, 2020; WHO, 2023). This neoplasm can present as a primary tumor, associated with genetic factors such as Li-Fraumeni, Werner, Bloom, Rothmund-Thomson, and retinoblastoma syndromes. Additionally, it can occur as a secondary tumor, often related to previous radiation therapy, a history of retinoblastoma, or Paget's disease (Makary *et al*, 2017; WHO, 2023).

Craniofacial OS differs from axial skeleton OS in its distinct clinical and biological behavior (DeAngelis *et al*, 2012; Weber *et al*, 2023). In the craniofacial region, OS exhibits a reduced metastasis rate compared to cases originating from extracranial regions. Nevertheless, the recurrence rate remains elevated, primarily due to the challenges associated with achieving complete resection in anatomically complex areas (Kämmerer *et al*, 2012; Weber *et al*, 2023). The standard treatment remains complete surgical resection, though the role of neoadjuvant chemotherapy continues to be a topic of debate (Khadembaschi *et al*, 2022; Weber *et al*, 2023). Although progress has been made in the treatment of OS in long bones, its rare occurrence in the head and neck region hinders a comprehensive understanding of its behavior in this area, contributing to persistently unsatisfactory therapeutic outcomes due to its pronounced biological aggressiveness (Lopes *et al*, 2001; Hassanain *et al*, 2024).

In recent years, advances in the study of molecular alterations have allowed better stratification of lesions, aiding in diagnosis, prognostic prediction, and the development of targeted therapies (Demicco, 2013). Low-grade OS often show gene amplification in *CDK4* and *MDM2* located on chromosome 12q13–15. *MDM2* amplification is highly specific and distinguishes these tumors from benign fibro-osseous lesions (Luk *et al*, 2019; Haefliger *et al*, 2022). In contrast, high-grade OS are characterized by complex karyotypes with numerous structural and numerical abnormalities, often associated with chromothripsis (Kansara *et al*, 2014).

A deeper understanding of the molecular mechanisms underlying the clinical behavior and treatment resistance of these tumors is essential to improve patient outcomes. In this context, the present study aims to map the molecular alterations associated with prognosis in craniofacial OS, providing a basis for the development of targeted therapeutic strategies. The guiding question of this scoping review is: "What molecular alterations have been described in the literature for OS affecting the oral and maxillofacial region?"

2 MATERIAL AND METHODS

2.1 Protocol and registration

The methods of this scoping review were previously established according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Systematic Review Protocols (PRISMA-P) checklist (Moher *et al*, 2015). The resulting protocol was registered with the Open Science Framework (OSF; Center for Open Science, Charlottesville, United States) (Spies JR, 2013), and is available online with the registration number DOI 10.17605/OSF.IO/W35KZ. In addition, the present scoping review was conducted following the checklist of the PRISMA Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al, 2018; Page et al, 2021).

2.2 Eligibility criteria

The acronym PCC (Population, Concept, Context) was used to formulate the review question and establish the inclusion criteria. For this review, the defined criteria were as follows: P) Oral and maxillofacial OS; C) Molecular alterations; C) Prognostic and diagnostic implication. Eligible for inclusion were observational studies (cohort studies, case-control studies, or cross-sectional studies), case reports, as well as systematic reviews published in English, Spanish, and Portuguese.

The exclusion criteria were as follows: 1) Studies that did not address molecular alterations of oral and maxillofacial OS; 2) Clinical trials, experimental studies, narrative reviews, protocols, brief communications, personal opinions, letters, book chapters, and conference abstracts; 3) Studies for which full-text articles were not available; 4) Studies published in languages other than English, Spanish, or Portuguese; 5) Insufficient clinicopathological data.

2.3 Information sources and search strategy

The search strategies were conducted on January 18, 2025, without restrictions on publication date, and were developed by combining appropriate keywords and index terms to find all relevant studies addressing the review question. Bibliographic databases, including MEDLINE (PubMed), Scopus, Web of Science, and EMBASE, were used to identify articles on this topic. A gray literature search, including Google Scholar and ProQuest Dissertation and Theses, was also carried out to identify unpublished references. Additionally, the reference lists of included studies were cross-checked. The search strategy is detailed in **Table S1**. The retrieved studies were imported into the reference manager Rayyan® (Ouzzani *et al*, 2016), where duplicate references were removed.

2.4 Selection of sources of evidence

The study selection process was performed in two phases by two independent reviewers (IVF and RALS). In the first phase, the titles and abstracts of the studies selected in Rayyan® (Ouzzani *et al*, 2016) were reviewed. Studies that met all inclusion criteria proceeded to the second phase, which involved a full-text review and confirmation of eligibility criteria. In case of disagreement or uncertainty between the two reviewers, the third reviewer (FVM) was consulted to resolve the issue through a consensus meeting.

2.5 Data charting process and data items

The data from the included studies were collected by one reviewer (IVF) and reviewed by a second reviewer (RALS). Disagreements were resolved by discussion and consensus among the authors. The extracted data was organized and processed in Microsoft Excel®. The main data extracted included: study and population characteristics, molecular alterations, and prognostic information.

2.6 Synthesis of results

A qualitative synthesis was performed by grouping the data from all included studies according to similar features to determine frequency data for each of the characteristics of interest and summarized the type of settings for the category of interest, describing settings, measures, and general outcomes.

3 RESULTS

3.1 Selection of sources of evidence

Of the 2,265 records identified through database searches, 1,488 remained after

duplicate removal. These records were then screened for eligibility using a two-phase selection process. In the first phase, titles and abstracts were reviewed, resulting in 95 studies selected for full-text analysis in the second phase. Following this assessment, 17 studies were included in the descriptive synthesis. Additionally, 3 studies were identified through other methods, including gray literature and manual reference checking of the selected studies, bringing the total to 20 studies (Garcia *et al*, 1998; Lopes *et al*, 2001; Patrikidou *et al*, 2002; Entz-Werle *et al*, 2003; Khayat and Johnston, 2004; Diniz *et al*, 2010; Akouchekian *et al*, 2016; LI *et al*, 2016; Guérin *et al*, 2016; Liu *et al*, 2017; Hirose *et al*, 2017; Ogi *et al*, 2020; Limbach *et al*, 2020; Haefliger *et al*, 2021; Yap *et al*, 2021; Yokoyama *et al*, 2023; Tahir *et al*, 2024; Khan *et al*, 2024; Zhu *et al*, 2024; Saucier *et al*, 2024) (**Figure S1**), The reasons for exclusion in the second phase 2 are detailed in **Table S2**.

3.2 Characteristics of sources of evidence

The detailed information of each study is available in **Table S3.** The studies were conducted in the following countries: the United States (5), Japan (3), France (3), Brazil (1), Australia (1), Canada (1), China (1), India (1), Iran (1), Spain (1), the United Kingdom (1), and Switzerland (1) **(Figure S2)**. Among them, 13 were case reports, 3 were cohort studies, and 4 were cross-sectional studies. All studies were published in English between 1990 and 2024, with the highest number of publications in 2024 (5 studies).

3.3 Clinical and demographic characteristics

A total of 68 patients diagnosed with OS in the maxillofacial region were analyzed. Among them, one patient developed a second primary tumor two years after the diagnosis of the first primary tumor (Saucier et al, 2024). The summarized data are presented in **Table 1**.

Out of the 55 patients with available sex information, the majority were male, representing 50.9% of the total. The age range spanned from 6 to 81 years, with a mean age of 39.3 ± 20.4 years and a median age of 38.5 years. Regarding tumor location, the mandible was the most frequently affected site, involving 46 patients (69.7%), followed by the maxilla, which was affected in 18 patients (27.3%). For tumor size, 30 cases provided this information, and the average largest diameter was 4.8 ± 2.4 cm, with a range from 1.5 cm to 11 cm.

3.4 Histopathological features and staging

In terms of histological subtype, data from 56 cases were available. Among these, the majority were classified as chondroblastic (28 cases, 50%), followed by osteoblastic (22 cases,

39.2%), and fibroblastic (18 cases, 32.1%). Some tumors were reported with more than one histological subtype per lesion, including 6 cases (10.7%) classified as both osteoblastic and chondroblastic, and 5 cases (8.9%) as osteoblastic, chondroblastic, and fibroblastic. Additionally, two cases (3.5%) were classified as telangiectatic (Tahir *et al*, 2024; Khan *et al*, 2024), one case (1.7%) as giant cell-rich (Hirose *et al*, 2017), and one case (1.7%) as parosteal (Lopes *et al*, 2001).

Among the 58 patients with available histological grade data, the majority of tumors (46 cases, 79.3%) were classified as high-grade. Lymphovascular invasion was documented in only one case (Tahir *et al*, 2024). Data on neural or perineural invasion were not reported, and information on necrosis was available for four cases, with three exhibiting necrosis (Liu et al, 2017; Haefliger et al, 2021; Khan et al, 2024). Additionally, data regarding the stage were provided for only one case, which was classified as stage IA (pT1 and pN0) (Tahir et al, 2024).

3.5 Risk factors and genetic predispositions

Regarding genetic factors, data from 32 patients were available. Among them, 15 patients (46.9%) were diagnosed with Li-Fraumeni syndrome (LFS) (Garcia *et al*, 1998; Patrikidou *et al*, 2002; Akouchekian *et al*, 2016; LI *et al*, 2016; Ogi *et al*, 2020; Haefliger *et al*, 2021; Saucier *et al*, 2024). Among these, eight patients had a documented history of additional cancers. Of these, five had a prior history of OS. The remaining three patients had the following medical histories: one with disorders of sex development, OS, and Bowen's disease; another with lobular breast carcinoma; and one with multiple malignancies, including neuroblastoma, rhabdomyosarcoma, phyllodes tumor, bronchioloalveolar carcinoma, invasive ductal breast carcinoma, papillary thyroid carcinoma, OS, gastric adenocarcinoma, and acute myeloid leukemia.

In terms of risk factors, data for 15 patients revealed that eight (53.3%) had a history of radiation exposure in the affected region (Garcia *et al*, 1998; Lopes *et al*, 2001; LI *et al*, 2016; Guérin *et al*, 2016; Yokoyama *et al*, 2023; Zhu *et al*, 2024). Among these 8 patients, 3 had tumors related to post-radiotherapy effects: 1 with cerebral astrocytoma, 1 with papillary thyroid carcinoma (latency period of 11 years), and 1 with squamous cell carcinoma (latency of 13 years, total dose of 60 Gy). Although not considered a risk factor for OS by the World Health Organization (WHO)(WHO, 2023), one patient (1.4%) had cemento-osseous dysplasia (Haefliger *et al*, 2021), and two (2.9%) had fibrous dysplasia (Yap *et al*, 2021; Zhu *et al*, 2024).

3.6 Molecular profiles

In the 68 tumors analyzed, a variety of molecular tests were employed to investigate genetic alterations, as detailed in **Table S3**. The *TP53* gene was the most frequently altered. Amplification was observed in 4 out of 32 cases, while missense mutations occurred in 23 cases, frameshift mutations in 2 cases, in-frame deletion in 1 case, and a splice variant in 1 case. Additionally, for 1 case, it was unclear whether the mutation was a missense or a frameshift mutation. *MDM2* amplification was found in 13 out of 30 cases, while *CDK4* amplification was observed in 7 out of 12 tested cases. *SAS* gene amplification was noted in 6 out of 9 cases, and *RASAL1* amplification was detected in 3 out of 14 tested cases. Additionally, three missense mutations in *GNAS* were identified: R201C, R201H, and A201C.

Reinforcing the molecular complexity of OS, various genetic alterations were observed, although less frequently. Among the amplifications, the genes *CCNE1, KEL, EZH2, XRCC2, PTEN, TERT, C17orf39*, and *KRAS* stand out. Missense and truncation mutations were identified in genes such as *MUC4, MUC6, MUC17, MUC20, HLA, ZNF221, ZNF417, ZNF517, ZNF595, ZNF774, ZNF831, CYP2A7, CYP27C1, GADD45B, MSH4, TDG, MCM4, RBBP8NL, PER3, CDK11B, CDC27, CCNE1, LTK (S183F), BRCA2 (S758C), ERBB3 (R1118Q), KMT2A (MLL) (G73E), KMT2C, APC, RAD50, PTEN, RB1, LTK (W707*), and *PBRM1*. Additionally, in-frame fusion was detected in *RAD50*, in-frame deletion in *RB1*, and a splicing site mutation in *RB1* (*539+1G>A)*. Homozygous deletions were identified in *CDKN2A/2B, PTEN*, and *RB1*, while a hotspot mutation in the promoter was found in *TERT*. Chromoplexy events led to subsequent amplifications on 5p, 8pter, 12, and 19p, as well as deletions on 5q, 6, 7, 10p, 13, and 22. In one of the cases analyzed, an aberrant transcript of the *WWOX* gene was identified, showing total or partial exon loss.

3.7 Treatment, tumor behavior, and follow-up

Out of the 30 patients with available treatment information, surgery was the most common treatment modality, performed in 27 patients (90%). Among them, 14 (51.9%) underwent surgery combined with chemotherapy, 11 (40.7%) had surgery alone, 1 (3.7%) received surgery with radiotherapy and chemotherapy, and 1 (3.7%) underwent surgery with radiotherapy. Additionally, 3 patients (10%) were treated with radiotherapy alone (1; 3.3%), chemotherapy alone (1; 3.3%), or a combination of both treatments (1; 3.3%).

Regarding surgical margins, data from 12 cases were available. In 11 cases (91.6%), the margins were negative, though two were close. One case (8.4%) showed a positive margin. Local recurrence, assessed in 27 cases, was observed in three patients (11.1%), while 24 patients (88.8%) remained recurrence-free. Distant metastases, evaluated in 25 cases, occurred in four

patients (16%), affecting the liver, lungs, bone marrow, and multiple bone sites. In one case, it was unclear whether the sternal spindle cell sarcoma was a primary tumor or a metastasis from maxillary OS. Follow-up data were available for 31 cases, with a mean duration of 23.66±24.18 months), ranging from 2 to 120 months. At the last follow-up, 23 patients (69.7%) were alive, while 8 (24.2%) had died.

3.8 Association between molecular alterations and prognosis

Of the 19 patients with *TP53* gene alteration, 11 had high-grade tumors. Of these, 3 experienced local recurrence, and 4 developed distant metastases. After a mean follow-up of 28.3±27.8 months, 12 out of 19 remained alive. Among the 7 patients with *MDM2* amplification, 4 had high-grade tumors. None showed local recurrence or metastases. With a mean follow-up of 15±9.9 months, 6 out of 7 were still alive.

In the group of 6 patients with *CDK4* gene amplification, 3 cases were classified as high-grade tumors. Similar to the previous group, no local recurrence or metastases were observed. After a mean follow-up of 15 ± 10.6 months, all patients remained alive. Lastly, among the six patients with SAS amplification, half had low-grade tumors. None of these patients developed local recurrence or metastases. With a mean follow-up of 16.8 ± 9.7 months, all patients were alive at the time of the analysis.

4 DISCUSSION

OS in the maxillofacial region presents significant differences from OS in long bones, both in clinical presentation and in biological behavior and prognosis. In the oral and maxillofacial region, OS primarily affects the mandible and maxilla, with common symptoms such as swelling, pain, dental mobility, and paresthesia (Hameed *et al*, 2020; Zhu *et al*, 2024). In this study, 97% of the cases involved these sites. Radiologically, maxillofacial OS is highly aggressive, characterized by destructive growth, periosteal reaction, and extension into soft tissues. Computed tomography is the imaging modality of choice for staging and surgical planning, while magnetic resonance imaging (MRI) is essential for assessing intraosseous extension and soft tissue involvement (**Figure 1A-C**) (Luo *et al*, 2020; Haefliger *et al*, 2022).

According to the current WHO classification (2023), OS in the gnathic region includes the following subtypes: conventional, small cell, telangiectatic, central low-grade, parosteal, periosteal, high-grade surface, giant cell-rich and radiation-induced. The conventional subtype is the most common and aggressive, while the periosteal subtype is of intermediate grade, and the central and parosteal subtypes are classified as low-grade. Conventional OS, characterized

as a high-grade intraosseous tumor, presents highly atypical cells, with the main diagnostic feature being the production of osteoid tumor. Its wide morphological variation allows subclassification into three main types, based on the predominant matrix formed: osteoblastic, chondroblastic, and fibroblastic (**Figure 1D-I**) (Cleven *et al*, 2020; Haefliger *et al*, 2022). Rarer subtypes, such as small cell and telangiectatic OS, are extremely uncommon in the gnathic region (Cleven *et al*, 2020). In our study, we observed one case of telangiectatic OS, one case rich in giant cells, and one case of parosteal OS. The giant cell-rich OS is a morphological subtype that should be remembered and differentiated from other giant cell-rich lesions affecting the jaws (WHO, 2023). The majority of the cases were chondroblastic (50%) and classified as high-grade (79.3%).

Although most cases of OS are sporadic, there are recognized risk factors and genetic predispositions associated with its development. Known predisposing factors include Paget's disease, a history of retinoblastoma, and prior radiation exposure (McHugh *et al*, 2006). Additionally, patients with LFS, who carry germline mutations in the *TP53* gene, have a higher incidence of OS (McHugh *et al*, 2006; de Álava, 2007). LFS is associated with a high rate of multiple tumors, especially metachronous ones (Saucier *et al*, 2024). In our study, 15 patients (46.9%) were diagnosed with LFS, and 8 of them had a history of additional cancers. All 15 cases were positive for the *TP53* mutation. Early diagnosis is crucial for implementing appropriate strategies and adjusting follow-up based on the risk of developing a second cancer. Without systematic germline *TP53* mutation testing, identifying LFS in OS patients can be challenging, especially when it is the first malignancy (Renaux-Petel *et al*, 2018; Saucier *et al*, 2024).

Radiation-associated maxillofacial OS is rare but represents the most common radiation-related sarcoma subtype in the head and neck region. The latency period following radiation is, on average, 11 years, ranging from 4 to 23 years (Arlen *et al*, 1972; McHugh *et al*, 2006). In our study, 8/15 (53.3%) patients had a history of radiation exposure in the region. Compared to primary maxillofacial OS, radiation-induced OS tends to be more aggressive, high-grade, and fibroblastic, with elevated p53 protein expression levels, as well as a less favorable prognosis (Takahama Junior *et al*, 2003; McHugh *et al*, 2006). *TP53* mutations, associated with p53 overexpression, play a crucial role in the pathogenesis of radiation-induced OS. Radiation-associated maxillofacial OS exhibits a higher frequency of mutations and p53 overexpression compared to primary tumors. However, most studies suggest that p53 expression has no significant prognostic value (Nakanishi *et al*, 1998; Lopes *et al*, 2001;

Takahama Junior *et al*, 2003). In our study, of the 8 cases of radiation-induced OS, 4 were classified as high-grade, and 3 were positive for *TP53*.

The differentiation between low-grade OS and benign fibro-osseous lesions of the maxillofacial region, such as fibrous dysplasia and ossifying fibromas, can be challenging, especially in the absence of comprehensive imaging or when biopsy material is limited (Cleven *et al*, 2020). Although the over-protein expression of MDM2 and CDK4 may be helpful in diagnosis, its specificity is limited and should be interpreted with caution (Dujardin *et al*, 2011). Molecular testing plays a crucial role in achieving a more accurate diagnosis. From a cytogenetic perspective, low-grade OS frequently presents recurrent alterations, such as ring chromosomes containing multiple copies of the 12q13-15 region, which harbors the *MDM2* and *CDK4* genes (Tabareau-Delalande and de Pinieux, 2016; Cleven *et al*, 2020). *MDM2* gene amplification has been observed in over 60% of low-grade OS, while it is absent in benign fibro-osseous lesions (Mejia-Guerrero *et al*, 2010). In our study, *MDM2* was positive in 13 cases, with 10 classified as high-grade, while *CDK4* alterations were identified in 7 cases, including 4 of high-grade.

The GNAS gene mutation is present in 50 to 80% fibrous dysplasias, being a widely recognized marker of this condition. Although rare, it has also been found in low-grade OS (Romeo *et al*, 2012) and other fibro-osseous lesions (Tabareau-Delalande and de Pinieux, 2016). In our study, the GNAS gene mutation was identified in three high-grade OS cases (Yap *et al*, 2021; Zhu *et al*, 2024). (Zhu *et al*, 2024) reported two cases of high-grade OS, one of which had a history of fibrous dysplasia. Both cases presented concurrent mutations in the *TP53* and *APC* genes, suggesting a possible synergistic effect in the development of osteosarcoma. Similarly, (Yap *et al*, 2021) described a case of high-grade OS associated with fibrous dysplasia, proposing that *GNAS* and *TP53* mutations may play a role in the transformation of fibrous dysplasia into OS. These findings highlight the importance of interpreting molecular test results with caution and emphasize the need to integrate molecular data with clinical-pathological findings to improve diagnostic accuracy (Romeo *et al*, 2012).

A diagnostic dilemma also arises when differentiating chondrosarcoma from the chondroblastic variant of OS, especially because the management of each tumor is distinct (Haefliger *et al*, 2022). The chondroblastic variant, which is common in the mandible, can mimic chondrosarcoma, which is rare at this site. The presence of tumoral osteoid, characteristic of OS, is a pathognomonic marker that allows for the distinction between the chondroblastic OS and chondrosarcoma (Cleven *et al*, 2020). Furthermore, molecular tests may be useful to confirm the diagnosis, as 49-61% of chondrosarcomas harbor mutations in *IDH1/2*. Detection

of these mutations supports the diagnosis of chondrosarcoma. Consistent with the literature, in our study, no cases of OS presented mutations in *IDH1/2*. However, since not all chondrosarcomas have *IDH1/2* mutations, the wild-type form of the gene cannot be used to completely exclude a diagnosis of chondrosarcoma (Kerr et al, 2013).

Genetic data on OS of the gnathic bones is scarce, and it is still unclear whether these tumors share the same pathophysiology as extragnathic OS. To date, no comprehensive genomic analysis has been conducted specifically on gnathic bone OS (Zhu *et al*, 2024). In general, OS exhibits a highly complex genomic landscape, characterized by multiple chromosomal rearrangements and chromothripsis events, as well as aneuploid karyotypes and numerous structural and numerical aberrations, reflecting significant genomic instability (Behjati *et al*, 2017; Grünewald *et al*, 2020). High-grade OS have an even more complex genomic profile, with numerous aberrations, possibly resulting from cataclysmic events such as chromothripsis or chromoplexy (Kansara *et al*, 2014; Haefliger *et al*, 2022). Although the trigger for these disruptive chromosomal alterations is not yet fully understood, *TP53* inactivation appears to play a crucial role (Haefliger *et al*, 2022). Unlike low-grade OS, high-grade OS lacks a specific molecular signature, making their diagnosis and characterization even more challenging (Tabareau-Delalande and de Pinieux, 2016).

Gnathic bone OS has a more favorable prognosis compared to long bone OS, with higher survival rates and a lower frequency of metastases, which typically occur at more advanced stages of the disease (Zhu *et al*, 2024). However, local disease control remains challenging, often leading to treatment failures (Hameed *et al*, 2020). Surgical resection with clear margins is considered the standard treatment. The role of adjuvant therapy in oral and maxillofacial OS remains controversial, although studies suggest that chemotherapy may improve survival outcomes (Suzuki *et al*, 2023). In this study, positive surgical margins were found in 1/12 patients (8.4%), local recurrence occurred in 3/27 cases (11.1%), and distant metastases developed in 4/25 patients (16%). Surgery was the primary treatment modality, performed in 27/30 cases (90%), either with chemotherapy in 14/27 (51.9%) or alone in 11/27 (40.7%). After a mean follow-up of 23.6 months, 23/33 patients (69.7%) were alive. These findings align with the literature, which identifies positive resection margins as a strong predictor of poor prognosis and highlights the potential benefit of chemotherapy in improving survival for patients with high-grade tumors, local recurrence, or positive margins (Liang *et al*, 2019). Notably, radiation-induced OS presents a significantly worse prognosis, with higher morbidity and mortality rates compared to primary OS (McHugh *et al*, 2006).

The present study identified a large number of altered genes, highlighting the molecular complexity of OS and providing new perspectives for future studies. However, some limitations should be considered, such as the sample size, which may not fully capture the genetic heterogeneity of OS, and the absence of a clear correlation between genetic alterations and patient clinical outcomes. The genetic mapping of these lesions is crucial to identify prognostic correlations, guiding therapeutic decisions, and improving patient monitoring over time. Therefore, additional studies are needed to validate these findings, explore their clinical relevance, and investigate their application in personalized treatment strategies, especially in gnathic OS. This is justified by the fact that OS in the maxillofacial region presents significant differences compared to OS in long bones, both in clinical presentation and biological behavior and prognosis, with studies focusing on this specific region still being scarce.

5 CONCLUSION

Analysis of 68 cases of oral and maxillofacial revealed a predominance of aggressive and high-grade forms, with the mandible being the most affected site. Most cases exhibited histologic features typical of conventional OS, with a predominance of the chondroblastic and osteoblastic subtypes. The study also highlighted the influence of genetic factors, such as mutations in the *TP53* gene, and predisposing conditions. Prior radiation exposure was identified as a relevant factor in a significant proportion of patients, highlighting the role of prior treatments in the pathogenesis of oral and maxillofacial OS.

Molecular techniques have proven to be essential in the diagnostic approach, allowing for a more detailed analysis of genetic alterations, facilitating the differentiation of subtypes, and improving case management. The standard treatment primarily involves surgical resection. Despite a relatively high survival rate, local disease control and the risk of recurrence remain significant challenges, highlighting the need for new therapeutic approaches and follow-up strategies to optimize long-term prognosis. Further research is essential to deepen our understanding of the molecular complexity of oral and maxillofacial OS and to develop improved therapeutic options, ultimately leading to better outcomes.

AUTHOR CONTRIBUTIONS

Iara Vieira Ferreira: Conceptualization; investigation; writing – original draft; methodology; data curation; formal analysis. **Reydson Alcides de Lima Souza**: Conceptualization, investigation; writing – original draft; methodology; data curation; formal analysis. **Moisés Willian Aparecido Gonçalves:** Data curation; formal analysis; writing – original draft. **Luccas**

Lavareze: Data curation; formal analysis; writing – original draft. **Erika Said Abu Egal:** Writing – review and editing. **Albina Altemani:** Writing – review and editing. **Fernanda Viviane Mariano:** Conceptualization; supervision; writing – review and editing.

ACKNOWLEDGMENTS

The authors would like to gratefully acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES, Brasilia, Brazil, finance code 001) and the São Paulo Research Foundation (FAPESP, São Paulo, Brazil, grant number: 20/08431-4, 23/14770-4 and 22/11861-6) for the scholarships.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Iara Vieira Ferreira https://orcid.org/0000-0001-7443-7190

Reydson Alcides de Lima-Souza https://orcid.org/0000-0001-5045-6960

Moisés Willian Aparecido Gonçalves https://orcid.org/0000-0003-3712-5838

Luccas Lavareze https://orcid.org/0000-0003-3464-8879

Erika Abu Said Egal https://orcid.org/0000-0001-9429-6743

Albina Altemani https://orcid.org/0000-0002-9944-9734

Fernanda Viviane Mariano https://orcid.org/0000-0003-3694-5025

REFERENCES

Akouchekian M, Hemati S, Jafari D, Jalilian N, Dehghan Manshadi M (2016). Does PTEN gene mutation play any role in Li-Fraumeni syndrome. *Med J Islam Repub Iran* **30**: 378.

de Álava E (2007). Molecular pathology in sarcomas. *Clinical and Translational Oncology* **9**: 130–144. 10.1007/s12094-007-0027-2

Arlen M, Shan IC, Higinbotham N, Huvos AJ (1972). Osteogenic sarcoma of head and neck induced by radiation therapy. *N Y State J Med* **72**: 929–34.

Behjati S, Tarpey PS, Haase K, *et al* (2017). Recurrent mutation of IGF signalling genes and

distinct patterns of genomic rearrangement in osteosarcoma. *Nat Commun* **8**: 15936. 10.1038/ncomms15936

Cleven AHG, Schreuder WH, Groen E, Kroon HM, Baumhoer D (2020). Molecular findings in maxillofacial bone tumours and its diagnostic value. *Virchows Archiv* **476**: 159–174. 10.1007/s00428-019-02726-2

DeAngelis AF, Spinou C, Tsui A, *et al* (2012). Outcomes of Patients With Maxillofacial Osteosarcoma: A Review of 15 Cases. *Journal of Oral and Maxillofacial Surgery* **70**: 734–739. 10.1016/j.joms.2011.03.020

Demicco EG (2013). Sarcoma Diagnosis in the Age of Molecular Pathology. *Adv Anat Pathol* **20**: 264–274. 10.1097/PAP.0b013e31829c2c7b

Diniz M, Borges E, Pimenta F, *et al* (2010). Evidence of molecular alterations in the tumour suppressor gene WWOX in benign and malignant bone related lesions of the jaws. *Oncol Rep*. 10.3892/or.2010.1094

Dujardin F, Binh MBN, Bouvier C, *et al* (2011). MDM2 and CDK4 immunohistochemistry is a valuable tool in the differential diagnosis of low-grade osteosarcomas and other primary fibro-osseous lesions of the bone. *Modern Pathology* **24**: 624–637. 10.1038/modpathol.2010.229

Entz-Werle N, Schneider A, Kalifa C, *et al* (2003). Genetic alterations in primary osteosarcoma from 54 children and adolescents by targeted allelotyping. *Br J Cancer* **88**: 1925–1931. 10.1038/sj.bjc.6600968

Garcia AG, Barros F, Bouzas ML, Manuel Suarez Penaranda J (1998). Li-Fraumeni syndrome and osteosarcoma of the maxilla. *Journal of Oral and Maxillofacial Surgery* **56**: 1106–1109. 10.1016/s0278-2391(98)90267-1

Grünewald TG, Alonso M, Avnet S, *et al* (2020). Sarcoma treatment in the era of molecular medicine. *EMBO Mol Med* **12**. 10.15252/emmm.201911131

Guérin M, Thariat J, Ouali M, *et al* (2016). A new subtype of high-grade mandibular osteosarcoma with RASAL1/MDM2 amplification. *Hum Pathol* **50**: 70–78. 10.1016/j.humpath.2015.11.012

Haefliger S, Andrei V, Baumhoer D (2022). Update of Key Clinical, Histological and Molecular Features of Malignant Bone Tumours Arising in the Craniofacial Skeleton. *Front Oncol* **12**. 10.3389/fonc.2022.954717

Haefliger S, Harder D, Kovac M, Linkeschova K, Eufinger H, Baumhoer D (2021). Osteosarcoma of the Mandible in a Patient with Florid Cemento-Osseous Dysplasia and Li–Fraumeni Syndrome: A Rare Coincidence. *Head Neck Pathol* **15**: 704–708.

10.1007/s12105-020-01223-2

Hameed M, Horvai AE, Jordan RCK (2020). Soft Tissue Special Issue: Gnathic Fibro-Osseous Lesions and Osteosarcoma. *Head Neck Pathol* **14**: 70–82. 10.1007/s12105-019-01094-2

Hassanain O, Alaa M, Khalifa MK, Kamal N, Albagoury A, El Ghoneimy AM (2024). Genetic variants associated with osteosarcoma risk: a systematic review and meta-analysis. *Sci Rep* **14**: 3828. 10.1038/s41598-024-53802-w

Hirose K, Okura M, Sato S, *et al* (2017). Gnathic giant-cell-rich conventional osteosarcoma with *MDM2* and *CDK4* gene amplification. *Histopathology* **70**: 1171–1173. 10.1111/his.13141

Kämmerer PW, Shabazfar N, Vorkhshori Makoie N, Moergel M, Al-Nawas B (2012). Clinical, therapeutic and prognostic features of osteosarcoma of the jaws – Experience of 36 cases. *Journal of Cranio-Maxillofacial Surgery* **40**: 541–548. 10.1016/j.jcms.2011.10.001

Kansara M, Teng MW, Smyth MJ, Thomas DM (2014). Translational biology of osteosarcoma. *Nat Rev Cancer* **14**: 722–735. 10.1038/nrc3838

Kerr DA, Lopez HU, Deshpande V, *et al* (2013). Molecular Distinction of Chondrosarcoma From Chondroblastic Osteosarcoma Through IDH1/2 Mutations. *American Journal of Surgical Pathology* **37**: 787–795. 10.1097/PAS.0b013e31827ab703

Khadembaschi D, Jafri M, Praveen P, Parmar S, Breik O (2022). Does neoadjuvant chemotherapy provide a survival benefit in maxillofacial osteosarcoma: A systematic review and pooled analysis. *Oral Oncol* **135**: 106133. 10.1016/j.oraloncology.2022.106133

Khan E, Verma S, Sivakumar N, Sharma P, Chandra S, Gupta S (2024). Telengiectatic osteosarcoma of mandible with special emphasis on immunohistochemical and molecular characteristics: A case report with review of literature. *Oral Surg* **17**: 152–156. 10.1111/ors.12860

Khayat CM, Johnston DL (2004). Rhabdomyosarcoma, osteosarcoma, and adrenocortical carcinoma in a child with a germline p53 mutation. *Pediatr Blood Cancer* **43**: 683–686. 10.1002/pbc.20142

LI X, KANG J, PAN Q, *et al* (2016). Genetic analysis in a patient with nine primary malignant neoplasms: A rare case of Li-Fraumeni syndrome. *Oncol Rep* **35**: 1519–1528. 10.3892/or.2015.4501

Liang L, Zhang T, You Y, He Q, Fan Y, Liao G (2019). An individual patient data meta-analysis on the effect of chemotherapy on survival in patients with craniofacial osteosarcoma. *Head Neck* **41**: 2016–2023. 10.1002/hed.25668

Limbach AL, Lingen MW, McElherne J, *et al* (2020). The Utility of MDM2 and CDK4 Immunohistochemistry and MDM2 FISH in Craniofacial Osteosarcoma. *Head Neck Pathol* **14**: 889–898. 10.1007/s12105-020-01139-x

Liu J, Cranmer L, Larsen BT, Kuo PH, Kopp LM (2017). Recurrent Osteosarcoma Presenting as an Isolated Bone Marrow Relapse. *J Pediatr Hematol Oncol* **39**: 302–305. 10.1097/MPH.0000000000000719

Lopes MA, Nikitakis NG, Ord RA, Sauk J (2001). Amplification and protein expression of chromosome 12q13-15 genes in osteosarcomas of the jaws. *Oral Oncol* **37**: 566–571. 10.1016/s1368-8375(00)00130-5

Luk PP, Selinger CI, Cooper WA, *et al* (2019). Clinical Utility of In Situ Hybridization Assays in Head and Neck Neoplasms. *Head Neck Pathol* **13**: 397–414. 10.1007/s12105-018-0988-1

Luo Z, Chen W, Shen X, *et al* (2020). Head and neck osteosarcoma: CT and MR imaging features. *Dentomaxillofacial Radiology* **49**: 20190202. 10.1259/dmfr.20190202

Makary RF, Gopinath A, Markiewicz MR, Fernandes R (2017). Margin Analysis. *Oral Maxillofac Surg Clin North Am* **29**: 355–366. 10.1016/j.coms.2017.04.002

McHugh JB, Thomas DG, Herman JM, *et al* (2006). Primary versus radiation-associated craniofacial osteosarcoma. *Cancer* **107**: 554–562. 10.1002/cncr.22019

Mejia-Guerrero S, Quejada M, Gokgoz N, *et al* (2010). Characterization of the 12q15 *MDM2* and 12q13-14 *CDK4* amplicons and clinical correlations in osteosarcoma. *Genes Chromosomes Cancer* **49**: 518–525. 10.1002/gcc.20761

Moher D, Shamseer L, Clarke M, *et al* (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* **4**: 1. 10.1186/2046-4053-4-1

Nakanishi H, Tomita Y, Myoui A, *et al* (1998). Mutation of the p53 gene in postradiation sarcoma. *Lab Invest* **78**: 727–33.

Ogi H, Tanaka T, Yoshitake Y, Shinohara M, Nakayama H, Imamura T (2020). A rare mandibular osteosarcoma case of Li-Franmeni syndrome with a germline p53R273H mutation. *J Oral Maxillofac Surg Med Pathol* **32**: 132–135. 10.1016/j.ajoms.2019.05.004

Ottaviani G, Jaffe N (2009). The Epidemiology of Osteosarcoma. In: , pp. 3–13. 10.1007/978-1-4419-0284-9_1

Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016). Rayyan—a web and mobile app for systematic reviews. *Syst Rev* **5**: 210. 10.1186/s13643-016-0384-4

Page MJ, McKenzie JE, Bossuyt PM, *et al* (2021). The PRISMA 2020 statement: an updated

guideline for reporting systematic reviews. *BMJ*: n71. 10.1136/bmj.n71

Patrikidou A, Bennett J, Abou-Sleiman P, Delhanty JDA, Harris M (2002). A novel, de novo germline TP53 mutation in a rare presentation of the Li-Fraumeni syndrome in the maxilla. *Oral Oncol* **38**: 383–390. 10.1016/s1368-8375(01)00078-1

Renaux-Petel M, Charbonnier F, Théry J-C, *et al* (2018). Contribution of de novo and mosaic *TP53* mutations to Li-Fraumeni syndrome. *J Med Genet* **55**: 173–180. 10.1136/jmedgenet-2017-104976

Romeo S, Dei Tos AP, Hogendoorn PCW (2012). The clinical impact of molecular techniques on diagnostic pathology of soft tissue and bone tumours. *Diagn Histopathol* **18**: 81–85. 10.1016/j.mpdhp.2011.11.004

Saucier E, Bougeard G, Gomez-Mascard A, *et al* (2024). Li–Fraumeni-associated osteosarcomas: The French experience. *Pediatr Blood Cancer* **71**. 10.1002/pbc.31362

Spies JR (2013). *The open science framework: improving science by making it open and accessible.* University of Virginia.

Suzuki H, Takano G, Tsukushi S, *et al* (2023). Impact of age for overall survival in head and neck sarcoma. *Medicine* **102**: e32966. 10.1097/MD.0000000000032966

Tabareau-Delalande F, de Pinieux G (2016). Molecular Markers of Fibro-Osseous Lesions and Osteosarcomas of the Craniofacial Complex—Current Situation and Recent Advances. *Curr Oral Health Rep* **3**: 102–110. 10.1007/s40496-016-0086-y

Tahir M, Wei EX, Madelaire C, Yu AS, Herrera GA, Shackelford RE (2024). A Primary Telangiectatic Mandibular Osteosarcoma With Germ-Line Malignancy-Associated DNA Damage Repair Gene Polymorphisms: A Case Report. *Case Rep Oncol Med* **2024**. 10.1155/2024/2418888

Takahama Junior A, de Abreu Alves F, Lopes Pinto CA, Lopes Carvalho A, Kowalski LP, Lopes MA (2003). Clinicopathological and immunohistochemical analysis of twenty-five head and neck osteosarcomas. *Oral Oncol* **39**: 521–530. 10.1016/s1368-8375(03)00017-4

Tran N-A, Guenette JP, Jagannathan J (2020). Soft Tissue Special Issue: Imaging of Bone and Soft Tissue Sarcomas in the Head and Neck. *Head Neck Pathol* **14**: 132–143. 10.1007/s12105-019-01102-5

Tricco AC, Lillie E, Zarin W, *et al* (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* **169**: 467–473. 10.7326/M18-0850

Weber V, Stigler R, Lutz R, Kesting M, Weber M (2023). Systematic review of craniofacial osteosarcoma regarding different clinical, therapeutic and prognostic parameters. *Front Oncol* **13**. 10.3389/fonc.2023.1006622

WHO (2023). *Classification of Tumours Editorial Board. Head and neck tumours [Internet]*. 5th Edition. International Agency for Research on Cancer: Lyon (France).

Yap FHX, Amanuel B, Van Vliet C, Thomas M, Wong D (2021). Malignant transformation of fibrous dysplasia into osteosarcoma confirmed with TP53 somatic mutation and mutational analysis of GNAS gene. *Pathology* **53**: 652–654. 10.1016/j.pathol.2020.08.027

Yokoyama Y, Ueki Y, Ohshima S, *et al* (2023). Genomic analysis of radiation-induced osteosarcoma in the maxilla. *Oral Oncology Reports* **8**: 100107. 10.1016/j.oor.2023.100107

Zhu GG, Lu C, Petrovic I, *et al* (2024). DNA Mutational and Copy Number Variation Profiling of Primary Craniofacial Osteosarcomas by Next-Generation Sequencing. *Head Neck Pathol* **18**: 48. 10.1007/s12105-024-01634-5

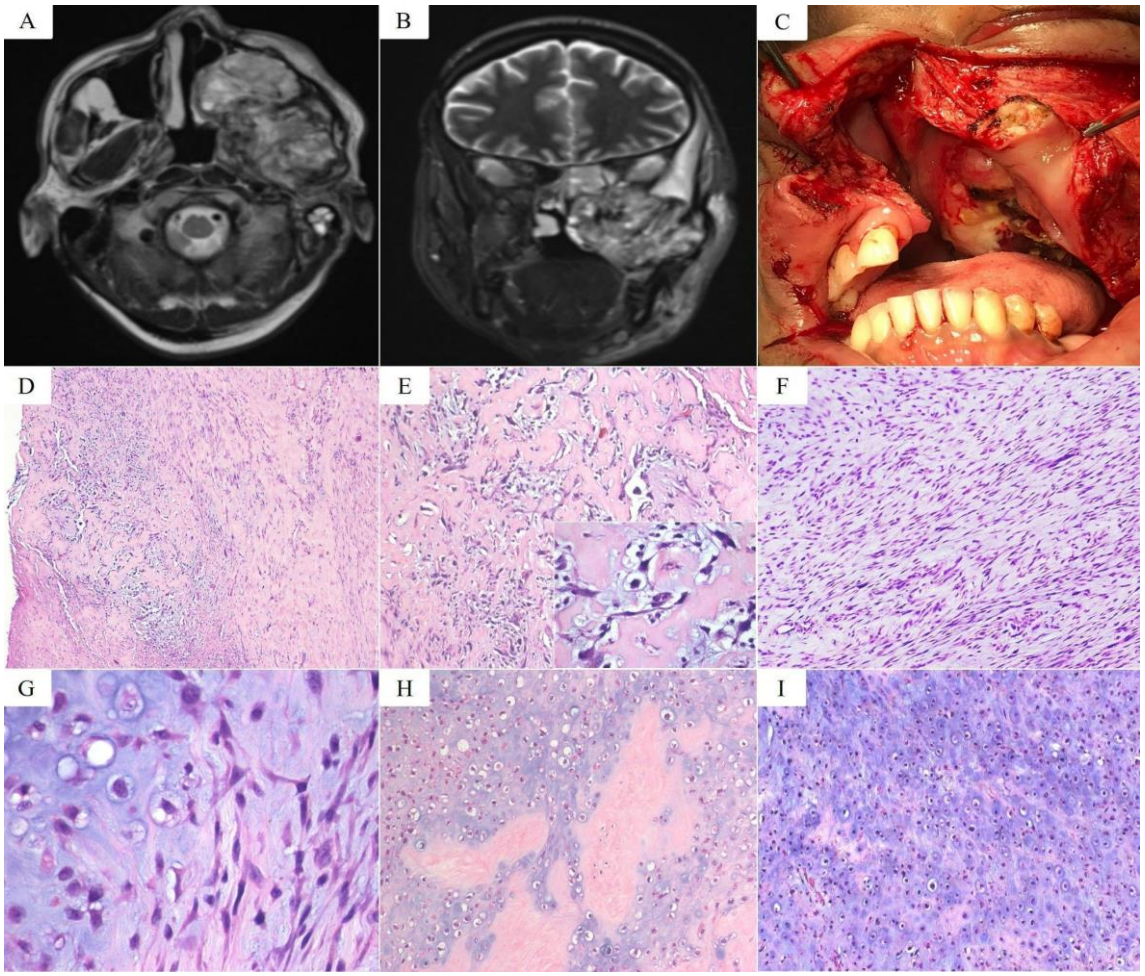
Table 1 Summary of 68 oral and maxillofacial osteosarcomas.

Clinicopathological variables	Value %
Sex (n=55)	
Male	28 (50.9%)
Female	27 (49.1%)
Age (years) (n=66)	
Mean	39.39±20.4
Median	38.5
Range	6-81
Tumor location (n=66)	
Mandible	46 (69.7%)
Maxilla	18 (27.3%)
Sphenoid	1 (1.5%)
Frontal sinus and infratemporal fossa	1 (1.5%)
Size (cm) (n=30)	
Mean	4.8±2.4

Median	4.35
Range	1.5-11
Histological subtype (n=56)	
Chondroblastic	28 (50%)
Osteoblastic	22 (39.2%)
Fibroblastic	18 (32.1%)
Telangiectatic	2 (3.5%)
Giant cell-rich	1 (1.7%)
Parosteal	1 (1.7%)
Grade (n=58)	
High	46 (79.3%)
Intermediate	5 (8.6%)
Low	7 (12.1%)
Genetic factor: Li-Fraumeni syndrome (n=32)	
No	17 (53.1%)
Yes	15 (46.9%)
Risk factor (n=15)	
No	7 (46.7%)
History of radiation exposure in the region	8 (53.3%)
Treatment (n=30)	
Surgery	27 (90%)
Chemotherapy	17 (56.6%)
Radiotherapy	4 (13.3%)
Margin status (n=12)	

Negative	11 (91.6%)
Positive	1 (8.4%)
Local recurrence (n=27)	
No	24 (88.8%)
Yes	3 (11.1%)
Metastasis (n=25)	
No	21 (84%)
Yes	4 (16%)
Status (n=33)	
Alive	23 (69.7%)
Died	8 (24.2%)
Lost follow-up	2 (6.1%)
Time of follow-up (months) (n=31)	
Mean	23.6±24.1
Median	16
Range	2-120

Figure 1 Imaging and Histopathological Features of Osteosarcoma. **(A)** Axial and **(B)** coronal MRI sections showing an expansive, infiltrative osteosarcoma adjacent to the remnant of the left maxillary sinus, extending into the buccal space and orbit. **(C)** Intraoperative view of the lesion. **(D, E)** Presence of immature bone, characteristic of osteosarcoma (H&E). **(F, G)** Fibroblastic-appearing neoplastic cells (H&E). **(H, I)** Abundant neoplastic chondroblastic matrix (H&E).



SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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

Database	(Search date: January 18th, 2025)	**Results**
PubMed	(Osteosarcoma[Mesh] OR Osteosarcomas OR "Osteogenic sarcoma" OR "osteosarcoma tumor" OR "osteosarcoma tumors" OR "Tumor, Osteosarcoma" OR "Tumors, Osteosarcoma" OR "Sarcoma, Osteogenic" OR "Osteogenic Sarcomas" OR "Sarcomas, Osteogenic" OR “bone tumours” OR “bone tumor" OR “Neoplasms, bone tissue"[Mesh]) **AND** ("Gene Expression"[Mesh] OR Mutation[Mesh] OR "Pathology, Molecular"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "molecular diagnostics" OR "molecular markers" OR "molecular alterations" OR "genetic alterations" OR "genomic analysis" OR "molecular profiling") **AND** (Mouth[Mesh] OR Jaw[Mesh] OR Maxillofacial OR "Head and Neck" OR "oral and maxillofacial" OR jaws OR mandible OR maxilla OR craniofacial OR oral OR “oral cavity” OR extraskeletal)	234
Scopus	TITLE-ABS-KEY (Osteosarcoma OR Osteosarcomas OR "Osteogenic sarcoma" OR "osteosarcoma tumor" OR "osteosarcoma tumors" OR "Tumor, Osteosarcoma" OR "Tumors, Osteosarcoma" OR "Sarcoma, Osteogenic" OR "Osteogenic Sarcomas" OR "Sarcomas, Osteogenic" OR “bone tumours” OR “bone tumor" OR “Neoplasms, bone tissue") **AND** TITLE-ABS-KEY ("Gene Expression" OR "Mutation" OR "Pathology, Molecular" OR "Chromosome Aberrations" OR "molecular diagnostics" OR "molecular markers" OR "molecular alterations" OR "genetic alterations" OR "genomic analysis" OR "molecular profiling") **AND** TITLE-ABS-KEY (Mouth OR Jaw	832

	OR Maxillofacial OR "Head and Neck" OR "oral and maxillofacial" OR jaws OR mandible OR maxilla OR craniofacial OR oral OR "oral cavity" OR extraskeletal)	
Embase	(Osteosarcoma OR Osteosarcomas OR 'Osteogenic sarcoma' OR 'osteosarcoma tumor' OR 'osteosarcoma tumors' OR 'Tumor, Osteosarcoma' OR 'Tumors, Osteosarcoma' OR 'Sarcoma, Osteogenic' OR 'Osteogenic Sarcomas' OR 'Sarcomas, Osteogenic' OR 'bone tumours' OR 'bone tumor' OR 'Neoplasms, bone tissue') **AND** ('Gene Expression' OR Mutation OR 'Pathology, Molecular' OR 'Chromosome Aberrations' OR 'molecular diagnostics' OR 'molecular markers' OR 'molecular alterations' OR 'genetic alterations' OR 'genomic analysis' OR 'molecular profiling') **AND** (Mouth OR Jaw OR Maxillofacial OR 'Head and Neck' OR 'oral and maxillofacial' OR jaws OR mandible OR maxilla OR craniofacial OR oral OR 'oral cavity' OR extraskeletal)	1082
Web of Science	TS=(Osteosarcoma OR Osteosarcomas OR "Osteogenic sarcoma" OR "osteosarcoma tumor" OR "osteosarcoma tumors" OR "Tumor, Osteosarcoma" OR "Tumors, Osteosarcoma" OR "Sarcoma, Osteogenic" OR "Osteogenic Sarcomas" OR "Sarcomas, Osteogenic" OR “bone tumours” OR “bone tumor" OR “Neoplasms, bone tissue") **AND** TS=("Gene Expression" OR "Mutation" OR "Pathology, Molecular" OR "Chromosome Aberrations" OR "molecular diagnostics" OR "molecular markers" OR "molecular alterations" OR "genetic alterations" OR "genomic analysis" OR "molecular profiling") **AND** TS=(Mouth OR Jaw OR Maxillofacial OR "Head and Neck" OR "oral and maxillofacial" OR jaws OR mandible OR maxilla OR craniofacial OR oral OR "oral cavity" OR extraskeletal)	108
Grey Literature		
Google Scholar	First 100 more relevant hits. No patents and no citations.	100

	(osteosarcoma OR “osteogenic sarcoma”) **AND** (“molecular diagnostic” OR “molecular markers” OR “molecular analysis”) **AND** ("head and neck" OR "oral and maxillofacial")	
ProQuest	TI,AB(osteosarcoma OR “osteogenic sarcoma”) **AND** TI,AB (“molecular diagnostic” OR “molecular markers” OR “molecular analysis”) **AND** TI,AB("head and neck" OR "oral and maxillofacial")	140
Total		**2496**

Figure S1 Flow diagram of literature search and selection process adapted from PRISMA.

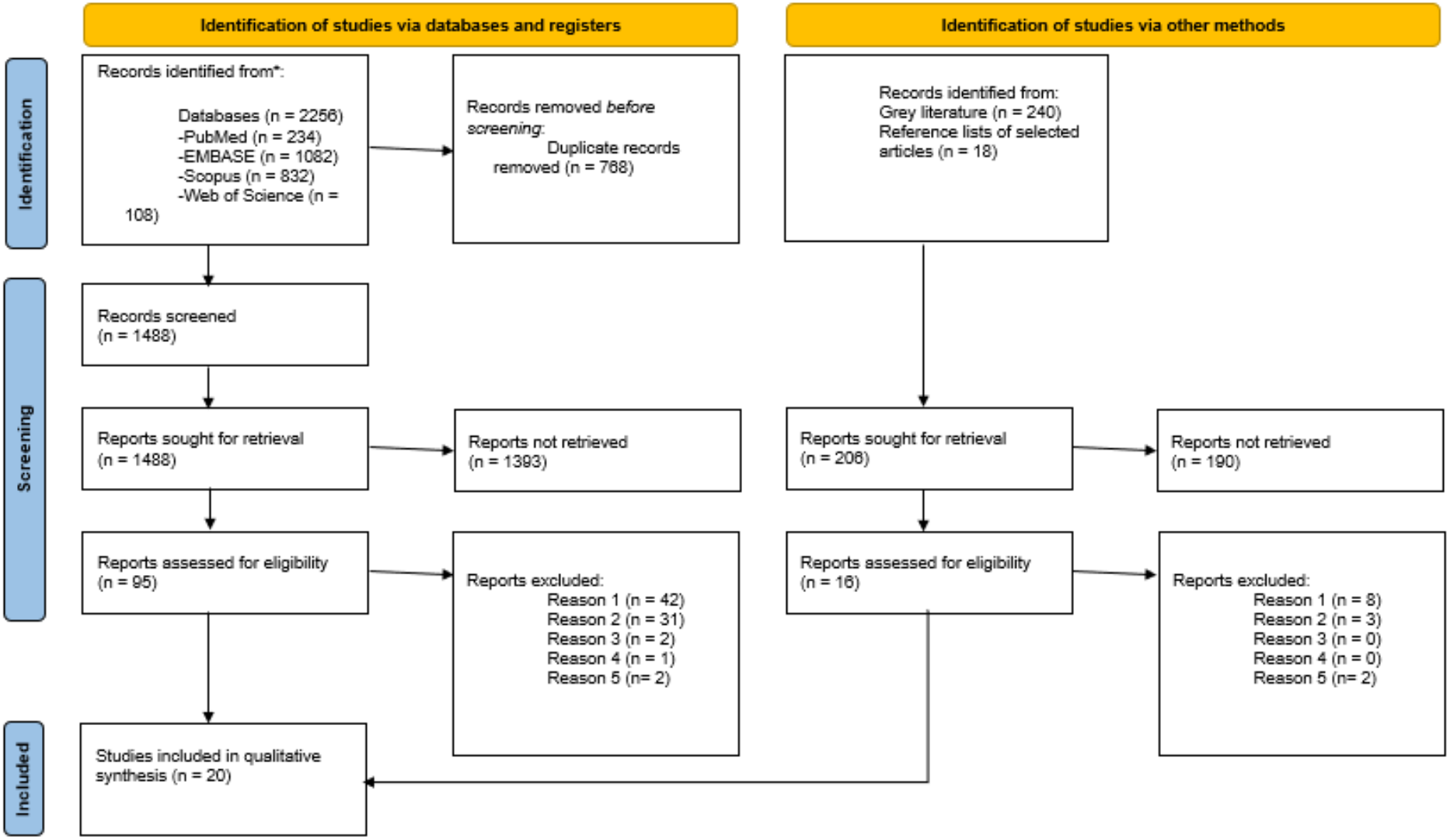


Table S2 Excluded articles in Phase 2 and the respective reasons for their exclusion (n=91).

	References	Reasons for exclusion
1.	Grünewald TG, Alonso M, Avnet S, Banito A, Burdach S, Cidre-Aranaz F, Di Pompo G, Distel M, Dorado-Garcia H, Garcia-Castro J, González-González L, Grigoriadis AE, Kasan M, Koelsche C, Krumbholz M, Lecanda F, Lemma S, Longo DL, Madrigal-Esquivel C, Morales-Molina Á, Musa J, Ohmura S, Ory B, Pereira-Silva M, Perut F, Rodriguez R, Seeling C, Al Shaaili N, Shaabani S, Shiavone K, Sinha S, Tomazou EM, Trautmann M, Vela M, Versleijen-Jonkers YM, Visgauss J, Zalacain M, Schober SJ, Lissat A, English WR, Baldini N, Heymann D. Sarcoma treatment in the era of molecular medicine. EMBO Mol Med. 2020 Nov 6;12(11):e11131. doi: 10.15252/emmm.201911131. Epub 2020 Oct 13. PMID: 33047515; PMCID: PMC7645378.	2
2.	Cleven AHG, Schreuder WH, Groen E, Kroon HM, Baumhoer D. Molecular findings in maxillofacial bone tumours and its diagnostic value. Virchows Arch. 2020 Jan;476(1):159-174. doi: 10.1007/s00428-019-02726-2. Epub 2019 Dec 14. PMID: 31838586; PMCID: PMC6968989.	2
3.	Haefliger S, Andrei V, Baumhoer D. Update of Key Clinical, Histological and Molecular Features of Malignant Bone Tumours Arising in the Craniofacial Skeleton. Front Oncol. 2022 Jul 7;12:954717. doi: 10.3389/fonc.2022.954717. PMID: 35875137; PMCID: PMC9301068.	2
4.	Xu B. Proceedings of the North American Society of Head and Neck Pathology, Los Angeles, CA, March 20, 2022. Emerging Bone and Soft Tissue Neoplasms in the Head and Neck Region. Head Neck Pathol. 2022 Mar;16(1):158-167. doi: 10.1007/s12105-022-01418-9. Epub 2022 Mar 21. PMID: 35307771; PMCID: PMC9019004.	1
5.	Kumar P, Surya V, Urs AB, Augustine J, Mohanty S, Gupta S. Sarcomas of the Oral and Maxillofacial Region: Analysis of 26 Cases with	1

	Emphasis on Diagnostic Challenges. Pathol Oncol Res. 2019 Apr;25(2):593-601. doi: 10.1007/s12253-018-0510-9. Epub 2018 Oct 31. PMID: 30382526.	
6.	Berner K, Bjerkehagen B, Bruland ØS, Berner A. Extraskeletal osteosarcoma in Norway, between 1975 and 2009, and a brief review of the literature. Anticancer Res. 2015 Apr;35(4):2129-40. PMID: 25862869.	1
7.	Machado I, Llombart-Bosch A, Charville GW, Navarro S, Domínguez Franjo MP, Bridge JA, Linos K. Sarcomas with EWSR1::Non-ETS Fusion (EWSR1::NFATC2 and EWSR1::PATZ1). Surg Pathol Clin. 2024 Mar;17(1):31-55. doi: 10.1016/j.path.2023.07.001. Epub 2023 Aug 7. PMID: 38278606.	1
8.	Fisch, A. S., St. John, M. A., & Sajed, D. P. (2023). Molecular Pathology of Head and Neck Tumors. In *Molecular Surgical Pathology* (pp. 493-516). Cham: Springer International Publishing.	2
9.	Tabareau-Delalande, F., de Pinieux, G. Marcadores moleculares de lesões fibro-ósseas e osteossarcomas do complexo craniofacial — situação atual e avanços recentes. *Curr Oral Health Rep* 3 , 102–110 (2016). https://doi.org/10.1007/s40496-016-0086-y	2
10.	Romeo, S., Dei Tos, A. P., & Hogendoorn, P. C. (2012). The clinical impact of molecular techniques on diagnostic pathology of soft tissue and bone tumours. *Diagnostic Histopathology*, *18*(2), 81-85.	2
11.	Judson I. Targeted therapies in soft tissue sarcomas. Ann Oncol. 2010 Oct;21 Suppl 7:vii277-80. doi: 10.1093/annonc/mdq288. PMID: 20943628.	1
12.	van den Berg, H. (2006). Biology and therapy of solid tumors in childhood. *Update on Cancer Therapeutics*, *1*(3), 367-383.	2
13.	Patnaik S, Nayak BK, Das BR. Rearrangement in the coding and 5' region of p53 gene in human oral tumors. IUBMB Life. 1999 Sep;48(3):305-9. doi: 10.1080/713803524. PMID: 10690643.	1
14.	Woo VL, Pharar J, Herschaft EE, Hughes CC, Akerson HA, Danforth RA. Facial asymmetry associated with a mixed radiolucent-radiopaque change of the maxillofacial bones. J Am Dent Assoc. 2014	1

Mar;145(3):274-9. doi: 10.14219/jada.2013.42. PMID: 24583893.	
15. Hameed M, Horvai AE, Jordan RCK. Soft Tissue Special Issue: Gnathic Fibro-Osseous Lesions and Osteosarcoma. Head Neck Pathol. 2020 Mar;14(1):70-82. doi: 10.1007/s12105-019-01094-2. Epub 2020 Jan 16. PMID: 31950477; PMCID: PMC7021863.	2
16. Bertin, H., Guilho, R., Brion, R., Amiaud, J., Battaglia, S., Moreau, A., ... & Rédini, F. (2019). Jaw osteosarcoma models in mice: first description. *Journal of Translational Medicine*, *17*, 1-8.	2
17. de Alava, E. (2007). Molecular pathology in sarcomas. *Clinical and Translational Oncology*, *9*, 130-144.	2
18. Gonin-Laurent N, Hadj-Hamou NS, Vogt N, Houdayer C, Gauthiers-Villars M, Dehainault C, Sastre-Garau X, Chevillard S, Malfoy B. RB1 and TP53 pathways in radiation-induced sarcomas. Oncogene. 2007 Sep 6;26(41):6106-12. doi: 10.1038/sj.onc.1210404. Epub 2007 Mar 19. PMID: 17369843.	1
19. Tang N, Deng W, Wu Y, Deng Z, Wu X, Xiong J, Zhao Q. Decoding the role of SLC25A5 in osteosarcoma drug resistance and CD8+ T cell exhaustion: The therapeutic potential of phyllanthin. Phytomedicine. 2025 Jan;136:156291. doi: 10.1016/j.phymed.2024.156291. Epub 2024 Dec 8. PMID: 39752785.	2
20. Liu, W., Shi, T., Zheng, D. *et al.* Identificação do fator inflamatório-1 do aloenxerto suprimindo a progressão e indicando bom prognóstico do osteossarcoma. *BMC Musculoskelet Disord* 25 , 233 (2024). https://doi.org/10.1186/s12891-024-07363-8	2
21. Yao Y, Zhang Q, Li Z, Zhang H. MDM2: current research status and prospects of tumor treatment. Cancer Cell Int. 2024 May 13;24(1):170. doi: 10.1186/s12935-024-03356-8. PMID: 38741108; PMCID: PMC11092046.	2
22. Macy ME, Mody R, Reid JM, Piao J, Saguilig L, Alonzo TA, Berg SL, Fox E, Weigel BJ, Hawkins DS, Mooney MM, Williams PM, Patton DR, Coffey BD, Roy-Chowdhuri S, Takebe N, Tricoli JV, Janeway KA, Seibel NL, Parsons DW. Palbociclib in Solid Tumor Patients With Genomic Alterations in the cyclinD-cdk4/6-INK4a-Rb Pathway:	2

	Results From National Cancer Institute-Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice Trial Arm I (APEC1621I). JCO Precis Oncol. 2024 Sep;8:e2400418. doi: 10.1200/PO-24-00418. PMID: 39298716; PMCID: PMC11488755.	
23.	Fan J, Liao J, Huang Y. Combined bioinformatics and machine learning methodologies reveal prognosis-related ceRNA network and propose ABCA8, CAT, and CXCL12 as independent protective factors against osteosarcoma. Adv Clin Exp Med. 2024 Aug;33(8):857-868. doi: 10.17219/acem/172663. PMID: 38315381.	1
24.	Nie J, He C, Shu Z, Liu N, Zhong Y, Long X, Liu J, Yang F, Liu Z, Huang P. Identification and experimental validation of Stearoyl-CoA desaturase is a new drug therapeutic target for osteosarcoma. Eur J Pharmacol. 2024 Jan 15;963:176249. doi: 10.1016/j.ejphar.2023.176249. Epub 2023 Dec 7. PMID: 38070637.	2
25.	Gu Y, Song Y, Pan Y, Liu J. The essential roles of m^6A modification in osteogenesis and common bone diseases. Genes Dis. 2023 Mar 28;11(1):335-345. doi: 10.1016/j.gendis.2023.01.032. PMID: 37588215; PMCID: PMC10425797.	2
26.	Li A, Hancock JC, Quezado M, Ahn S, Briceno N, Celiku O, Ranjan S, Aboud O, Colwell N, Kim SA, Nduom E, Kuhn S, Park DM, Vera E, Aldape K, Armstrong TS, Gilbert MR. TGF-β and BMP signaling are associated with the transformation of glioblastoma to gliosarcoma and then osteosarcoma. Neurooncol Adv. 2023 Dec 19;6(1):vdad164. doi: 10.1093/noajnl/vdad164. PMID: 38292240; PMCID: PMC10825841.	2
27.	Wang, J., Zheng, L., Chen, W. *et al.* O direcionamento de RBM39 suprime o crescimento tumoral e sensibiliza as células do osteossarcoma à cisplatina. *Oncogene* (2024). https://doi.org/10.1038/s41388-024-03242-7	2
28.	Pepper, T., Carey, B., Alibhai, M., Fry, A., & Sandison, A. (2023). 24. Sarcomas presenting as epithelial neoplasia in the head and neck-a case series. *British Journal of Oral and Maxillofacial Surgery*, *61*(10), e9-e10.	2

29. Filippini DM, Carosi F, Querzoli G, Fermi M, Ricciotti I, Molteni G, Presutti L, Foschini MP, Locati LD. Rare Head and Neck Cancers and Pathological Diagnosis Challenges: A Comprehensive Literature Review. Diagnostics (Basel). 2024 Oct 23;14(21):2365. doi: 10.3390/diagnostics14212365. PMID: 39518333; PMCID: PMC11544949.	2
30. Sombutthaweesri T, Wu S, Chamusri N, Settakorn J, Pruksakorn D, Chaiyawat P, Sastraruji T, Krisanaprakornkit S, Supanchart C. Relationship Between O-GlcNAcase Expression and Prognosis of Patients With Osteosarcoma. Appl Immunohistochem Mol Morphol. 2022 Jan 1;30(1):e1-e10. doi: 10.1097/PAI.0000000000000970. PMID: 34469899.	1
31. Sonaglio V, de Carvalho AC, Toledo SR, Salinas-Souza C, Carvalho AL, Petrilli AS, de Camargo B, Vettore AL. Aberrant DNA methylation of ESR1 and p14ARF genes could be useful as prognostic indicators in osteosarcoma. Onco Targets Ther. 2013 Jun 17;6:713-23. doi: 10.2147/OTT.S44918. PMID: 23836983; PMCID: PMC3699305.	1
32. Weber V, Stigler R, Lutz R, Kesting M, Weber M. Systematic review of craniofacial osteosarcoma regarding different clinical, therapeutic and prognostic parameters. Front Oncol. 2023 Mar 24;13:1006622. doi: 10.3389/fonc.2023.1006622. PMID: 37035145; PMCID: PMC10080080.	1
33. Yan GN, Lv YF, Guo QN. Advances in osteosarcoma stem cell research and opportunities for novel therapeutic targets. Cancer Lett. 2016 Jan 28;370(2):268-74. doi: 10.1016/j.canlet.2015.11.003. Epub 2015 Nov 10. PMID: 26571463.	2
34. Pakos EE, Kyzas PA, Ioannidis JP. Prognostic significance of TP53 tumor suppressor gene expression and mutations in human osteosarcoma: a meta-analysis. Clin Cancer Res. 2004 Sep 15;10(18 Pt 1):6208-14. doi: 10.1158/1078-0432.CCR-04-0246. PMID: 15448009.	1
35. Amer HW, Algadi HH, Hamza SA. Mandibular small cell osteosarcoma: a case report and review of literature. J Egypt Natl Canc Inst. 2023 Sep 18;35(1):30. doi: 10.1186/s43046-023-00191-2. PMID:	1

37718329.	
36. Li Z, Dou P, Liu T, He S. Application of Long Noncoding RNAs in Osteosarcoma: Biomarkers and Therapeutic Targets. Cell Physiol Biochem. 2017;42(4):1407-1419. doi: 10.1159/000479205. Epub 2017 Jul 17. PMID: 28715796.	2
37. Varachev V, Shekhtman A, Guskov D, Rogozhin D, Zasedatelev A, Nasedkina T. Diagnostics of *IDH1/2* Mutations in Intracranial Chondroid Tumors: Comparison of Molecular Genetic Methods and Immunohistochemistry. Diagnostics (Basel). 2024 Jan 16;14(2):200. doi: 10.3390/diagnostics14020200. PMID: 38248076; PMCID: PMC10814347.	2
38. Wu CC, Beird HC, Andrew Livingston J, Advani S, Mitra A, Cao S, Reuben A, Ingram D, Wang WL, Ju Z, Hong Leung C, Lin H, Zheng Y, Roszik J, Wang W, Patel S, Benjamin RS, Somaiah N, Conley AP, Mills GB, Hwu P, Gorlick R, Lazar A, Daw NC, Lewis V, Futreal PA. Immuno-genomic landscape of osteosarcoma. Nat Commun. 2020 Feb 21;11(1):1008. doi: 10.1038/s41467-020-14646-w. PMID: 32081846; PMCID: PMC7035358.	1
39. Yu XW, Wu TY, Yi X, Ren WP, Zhou ZB, Sun YQ, Zhang CQ. Prognostic significance of VEGF expression in osteosarcoma: a meta-analysis. Tumour Biol. 2014 Jan;35(1):155-60. doi: 10.1007/s13277-013-1019-1. Epub 2013 Aug 2. PMID: 23907576.	1
40. Jiang L, Tao C, He A. Prognostic significance of p53 expression in malignant bone tumors: a meta-analysis. Tumour Biol. 2013 Apr;34(2):1037-43. doi: 10.1007/s13277-012-0643-5. Epub 2013 Jan 23. PMID: 23341181.	1
41. Fukunaga M. Low-grade central osteosarcoma of the skull. Pathol Res Pract. 2005;201(2):131-5. doi: 10.1016/j.prp.2004.12.001. PMID: 15901134.	1
42. Deshpande, A. M. (2003). *Characterization of a novel tumor suppressor gene involved in osteosarcoma tumorigenesis*. University of Connecticut.	1

43. Wang L, Liu Y, Yu G. Avasimibe inhibits tumor growth by targeting FoxM1-AKR1C1 in osteosarcoma. Onco Targets Ther. 2019 Jan 24;12:815-823. doi: 10.2147/OTT.S165647. PMID: 30774369; PMCID: PMC6353227.	1
44. Miyashita, H., Yoshida, K., Kameyama, K., Yazawa, M., Nakagawa, T., & Kawana, H. (2017). A case of dedifferentiated parosteal osteosarcoma in the maxilla. *International Journal of Oral and Maxillofacial Surgery*, *46*, 291.	1
45. Fu D, Lu C, Qu X, Li P, Chen K, Shan L, Zhu X. LncRNA TTN-AS1 regulates osteosarcoma cell apoptosis and drug resistance via the miR-134-5p/MBTD1 axis. Aging (Albany NY). 2019 Oct 10;11(19):8374-8385. doi: 10.18632/aging.102325. Epub 2019 Oct 10. PMID: 31600142; PMCID: PMC6814585.	1
46. Zhou, D., Wang, W., Yan, S., Ye, S., Wu, Y., Ding, Y., ... & Zhang, S. (2020). Comprehensive profiling of MDM2/TP53 genomic aberration in Chinese patients with diverse malignancies.	2
47. Rattanakuntee, S., Chaiyawat, P., Pruksakorn, D., Kritsanaprakornkit, S., Makeudom, A., & Supanchart, C. (2020). Associations between Expression Levels of O-GlcNAc Transferase (OGT) and Chemo-Response in Osteosarcoma. *Journal of the Medical Association of Thailand*, *103*(2).	3
48. Ege B, Yumrutas O, Ege M, Pehlivan M, Bozgeyik I. Pharmacological properties and therapeutic potential of saffron (Crocus sativus L.) in osteosarcoma. J Pharm Pharmacol. 2020 Jan;72(1):56-67. doi: 10.1111/jphp.13179. Epub 2019 Oct 23. PMID: 31645086.	1
49. Chopra, S. (2020, March). SATB2 Positivity Not Specific for Osteoblastic Differentiation and Caution Needed in Making Diagnoses of Osteosarcoma in the Absence of Histological or Radiological Evidence of Osteoid. In *LABORATORY INVESTIGATION* (Vol. 100, No. SUPPL 1, pp. 39-39). 75 VARICK ST, 9TH FLR, NEW YORK, NY 10013-1917 USA: NATURE PUBLISHING GROUP.	2
50. Liu JY, Zhu BR, Wang YD, Sun X. The efficacy and safety of Apatinib mesylate in the treatment of metastatic osteosarcoma patients who	1

progressed after standard therapy and the VEGFR2 gene polymorphism analysis. Int J Clin Oncol. 2020 Jun;25(6):1195-1205. doi: 10.1007/s10147-020-01644-7. Epub 2020 Mar 25. PMID: 32215805.	
51. Liu JF, Lee CW, Lin CY, Chao CC, Chang TM, Han CK, Huang YL, Fong YC, Tang CH. CXCL13/CXCR5 Interaction Facilitates VCAM-1-Dependent Migration in Human Osteosarcoma. Int J Mol Sci. 2020 Aug 24;21(17):6095. doi: 10.3390/ijms21176095. PMID: 32847038; PMCID: PMC7504668.	1
52. Liu JF, Chen PC, Chang TM, Hou CH. Thrombospondin-2 stimulates MMP-9 production and promotes osteosarcoma metastasis via the PLC, PKC, c-Src and NF-κB activation. J Cell Mol Med. 2020 Nov;24(21):12826-12839. doi: 10.1111/jcmm.15874. Epub 2020 Oct 6. PMID: 33021341; PMCID: PMC7686970.	1
53. Chen D, Wan B, Cheng Y, Luo Y, Bai X, Guo J, Li G, Jin T, Nie J, Liu W, Wang R. Carboxypeptidase E is a prognostic biomarker co-expressed with osteoblastic genes in osteosarcoma. PeerJ. 2023 Aug 30;11:e15814. doi: 10.7717/peerj.15814. PMID: 37663298; PMCID: PMC10474831.	1
54. Zhang Z, Zhang J, Duan Y, Li X, Pan J, Wang G, Shen B. Identification of B cell marker genes based on single-cell sequencing to establish a prognostic model and identify immune infiltration in osteosarcoma. Front Immunol. 2022 Dec 7;13:1026701. doi: 10.3389/fimmu.2022.1026701. PMID: 36569871; PMCID: PMC9774034.	2
55. Arman K, Saadat KASM, Igci YZ, Bozgeyik E, Ikeda MA, Cakmak EA, Arslan A. Long noncoding RNA ERICD interacts with ARID3A via E2F1 and regulates migration and proliferation of osteosarcoma cells. Cell Biol Int. 2020 Nov;44(11):2263-2274. doi: 10.1002/cbin.11434. Epub 2020 Aug 10. PMID: 32749762.	2
56. Arman K, Saadat KASM, Igci YZ, Bozgeyik E, Ikeda MA, Cakmak EA, Arslan A. Long noncoding RNA ERICD interacts with ARID3A via E2F1 and regulates migration and proliferation of osteosarcoma cells.	1

Cell Biol Int. 2020 Nov;44(11):2263-2274. doi: 10.1002/cbin.11434. Epub 2020 Aug 10. PMID: 32749762.	
57. Yi GZ, Zhu TC, Que TS, Li ZY, Huang GL. Individualized combination therapies based on whole-exome sequencing displayed significant clinical benefits in a glioblastoma patient with secondary osteosarcoma: case report and genetic characterization. BMC Neurol. 2022 Oct 21;22(1):390. doi: 10.1186/s12883-022-02920-x. PMID: 36271359; PMCID: PMC9587562.	1
58. Jiang Y, Wang J, Sun M, Zuo D, Wang H, Shen J, Jiang W, Mu H, Ma X, Yin F, Lin J, Wang C, Yu S, Jiang L, Lv G, Liu F, Xue L, Tian K, Wang G, Zhou Z, Lv Y, Wang Z, Zhang T, Xu J, Yang L, Zhao K, Sun W, Tang Y, Cai Z, Wang S, Hua Y. Multi-omics analysis identifies osteosarcoma subtypes with distinct prognosis indicating stratified treatment. Nat Commun. 2022 Nov 23;13(1):7207. doi: 10.1038/s41467-022-34689-5. PMID: 36418292; PMCID: PMC9684515.	1
59. Zheng W, Li S, Huang J, Dong Y, Zhang H, Zheng J. Down-Regulation of Ubiquitin-Specific Peptidase 9X Inhibited Proliferation, Migration and Invasion of Osteosarcoma via ERK1/2 and PI3K/Akt Signaling Pathways. Biol Pharm Bull. 2022;45(9):1283-1290. doi: 10.1248/bpb.b22-00198. PMID: 36047196.	1
60. Hong J, Li Q, Wang X, Li J, Ding W, Hu H, He L. Development and validation of apoptosis-related signature and molecular subtype to improve prognosis prediction in osteosarcoma patients. J Clin Lab Anal. 2022 Jul;36(7):e24501. doi: 10.1002/jcla.24501. Epub 2022 May 16. PMID: 35576501; PMCID: PMC9280000.	1
61. Mai W, Kong L, Yu H, Bao J, Song C, Qu G. Glycogen synthase kinase 3β promotes osteosarcoma invasion and migration via regulating PTEN and phosphorylation of focal adhesion kinase. Biosci Rep. 2021 Jul 30;41(7):BSR20193514. doi: 10.1042/BSR20193514. PMID: 33969873; PMCID: PMC8314432.	1
62. Luo T, Zhou X, Jiang E, Wang L, Ji Y, Shang Z. Osteosarcoma Cell-Derived Small Extracellular Vesicles Enhance Osteoclastogenesis and	2

	Bone Resorption Through Transferring MicroRNA-19a-3p. Front Oncol. 2021 Mar 25;11:618662. doi: 10.3389/fonc.2021.618662. PMID: 33842319; PMCID: PMC8029976.	
63.	Conley AP, Trent J, Zhang W. Recent progress in the genomics of soft tissue sarcomas. Curr Opin Oncol. 2008 Jul;20(4):395-9. doi: 10.1097/CCO.0b013e328302edc0. PMID: 18525334.	1
64.	Ordóñez JL, Osuna D, García-Domínguez DJ, Amaral AT, Otero-Motta AP, Mackintosh C, Sevillano MV, Barbado MV, Hernández T, de Alava E. The clinical relevance of molecular genetics in soft tissue sarcomas. Adv Anat Pathol. 2010 May;17(3):162-81. doi: 10.1097/PAP.0b013e3181d98cbf. PMID: 20418671.	1
65.	VAYEGO, S. A., DE CONTI, O. J., & SILVA, A. E. Aspectos genético-moleculares dos tumores ósseos.	2
66.	Donner, L. R. (1994). Cytogenetics of tumors of soft tissue and bone: implication for pathology. *Cancer genetics and cytogenetics*, *78*(2), 115-126.	2
67.	Dai Z, Liu Z, Yang R, Cao W, Ji T. EVI2B Is a Prognostic Biomarker and Is Correlated with Monocyte and Macrophage Infiltration in Osteosarcoma Based on an Integrative Analysis. Biomolecules. 2023 Feb 8;13(2):327. doi: 10.3390/biom13020327. PMID: 36830696; PMCID: PMC9953216.	1
68.	de Álava, E. Molecular pathology in sarcomas. *Clin Transl Oncol* **9**, 130–144 (2007). https://doi.org/10.1007/s12094-007-0027-2	2
69.	Deutsch EC, Seyer LA, Perlman SL, Yu J, Lynch DR. Clinical monitoring in a patient with Friedreich ataxia and osteogenic sarcoma. J Child Neurol. 2012 Sep;27(9):1159-63. doi: 10.1177/0883073812448460. Epub 2012 Jun 29. PMID: 22752483; PMCID: PMC3674811.	2
70.	Salaün, H., Le Nail, L. R., Simon, C., Narciso, B., De Pinieux, G., Vegas, H., & Vinceneux, A. (2022). Unexpected severe hepatic and skin toxicities during high dose methotrexate course for osteosarcoma. *Journal of Oncology Pharmacy Practice*, *28*(6), 1458-1464.	1

71. Persha HE, Kato S, De P, Adashek JJ, Sicklick JK, Subbiah V, Kurzrock R. Osteosarcoma with cell-cycle and fibroblast growth factor genomic alterations: case report of Molecular Tumor Board combination strategy resulting in long-term exceptional response. J Hematol Oncol. 2022 Aug 28;15(1):119. doi: 10.1186/s13045-022-01344-x. PMID: 36031605; PMCID: PMC9420268.	1
72. de Maeyer VM, Kestelyn PA, Shah AD, Van Den Broecke CM, Denys HG, Decock CE. Extraskeletal osteosarcoma of the orbit: A clinicopathologic case report and review of literature. Indian J Ophthalmol. 2016 Sep;64(9):687-689. doi: 10.4103/0301-4738.97555. PMID: 27853024; PMCID: PMC5151166.	1
73. Lopes-Brás R, Lopez-Presa D, Esperança-Martins M, Melo-Alvim C, Gallego L, Costa L, Fernandes I. Genomic Profiling of Sarcomas: A Promising Weapon in the Therapeutic Arsenal. Int J Mol Sci. 2022 Nov 17;23(22):14227. doi: 10.3390/ijms232214227. PMID: 36430703; PMCID: PMC9693140.	2
74. Wu P, Wu D, Zhao L, Huang L, Shen G, Huang J, Chai Y. Prognostic role of STAT3 in solid tumors: a systematic review and meta-analysis. Oncotarget. 2016 Apr 12;7(15):19863-83. doi: 10.18632/oncotarget.7887. PMID: 26959884; PMCID: PMC4991424.	1
75. Pan L, Meng L, Liang F, Cao L. miR-188 suppresses tumor progression by targeting SOX4 in pediatric osteosarcoma. Mol Med Rep. 2018 Jul;18(1):441-446. doi: 10.3892/mmr.2018.8997. Epub 2018 May 9. PMID: 29749512.	1
76. Bertin H, Gomez-Brouchet A, Rédini F. Osteosarcoma of the jaws: An overview of the pathophysiological mechanisms. Crit Rev Oncol Hematol. 2020 Dec;156:103126. doi: 10.1016/j.critrevonc.2020.103126. Epub 2020 Oct 10. PMID: 33113487.	2
77. Zhu, G., Lu, C., Nafa, K., Klein, M., Hwang, S., Wang, L., & Hameed, M. (2019, March). Comprehensive genomic profiling of the primary craniofacial osteosarcomas. In *LABORATORY INVESTIGATION* (Vol.	1

	99). 75 VARICK ST, 9TH FLR, NEW YORK, NY 10013-1917 USA: NATURE PUBLISHING GROUP.	
78.	Junior AT, de Abreu Alves F, Pinto CA, Carvalho AL, Kowalski LP, Lopes MA. Clinicopathological and immunohistochemical analysis of twenty-five head and neck osteosarcomas. Oral Oncol. 2003 Jul;39(5):521-30. doi: 10.1016/s1368-8375(03)00017-4. PMID: 12747978.	1
79.	Si, Xh., Liu, Z. Expression of cyclin D1 and CDK4 in osteosarcoma of the jaws. *Chin. J. Cancer Res.* **13**, 140–143 (2001). https://doi.org/10.1007/s11670-001-0033-9	1
80.	Chen WL, Feng HJ, Li HG. Expression and significance of hypoxemia-inducible factor-1alpha in osteosarcoma of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Aug;106(2):254-7. doi: 10.1016/j.tripleo.2008.01.029. Epub 2008 Jun 13. PMID: 18554951.	1
81.	Asioli S, Righi A, Rucci P, Tarsitano A, Marchetti C, Bacchini P, Balbi T, Bertoni F, Foschini MP. p16 protein expression and correlation with clinical and pathological features in osteosarcoma of the jaws: Experience of 37 cases. Head Neck. 2017 Sep;39(9):1825-1831. doi: 10.1002/hed.24835. Epub 2017 May 31. PMID: 28560748.	1
82.	Zelinka, J., Blahák, J., Daněk, Z., & Bulik, O. (2018). Chondroblastic osteosarcoma of maxilla, a patient with Li-Fraumeni syndrome. *Česká a Slovenská Neurologie a Neurochirurgie*, *81*.	3
83.	Wang L, Wu Q, Sun K. [Image analysis of cell nuclear morphology and DNA content in osteosarcoma of the jaws]. Zhonghua Kou Qiang Yi Xue Za Zhi. 1997 Mar;32(2):78-80. Chinese. PMID: 10677953.	4
84.	Jensen MR, Stoltze U, Hansen TVO, Bak M, Sehested A, Rechnitzer C, Mathiasen R, Scheie D, Larsen KB, Olsen TE, Muhic A, Skjøth-Rasmussen J, Rossing M, Schmiegelow K, Wadt K. 9p21.3 Microdeletion involving *CDKN2A/2B* in a young patient with multiple primary cancers and review of the literature. Cold Spring Harb Mol Case Stud. 2022 Jun 22;8(4):a006164. doi: 10.1101/mcs.a006164. PMID: 35422439; PMCID: PMC9235845.	1

85. Wen B, Chen J, Ding T, Mao Z, Jin R, Wang Y, Shi M, Zhao L, Yang A, Qin X, Chen X. Development and experimental validation of hypoxia-related gene signatures for osteosarcoma diagnosis and prognosis based on WGCNA and machine learning. Sci Rep. 2024 Aug 12;14(1):18734. doi: 10.1038/s41598-024-69638-3. PMID: 39134603; PMCID: PMC11319349.	1
86. McHugh, J. B., Thomas, D. G., Herman, J. M., Ray, M. E., Baker, L. H., Adsay, N. V., ... & Lucas, D. R. (2006). Primary versus radiation-associated craniofacial osteosarcoma: biologic and clinicopathologic comparisons. *Cancer*, *107*(3), 554-562.	5
87. Ji, J., Quindipan, C., Parham, D., Shen, L., Ruble, D., Bootwalla, M., ... & Mascarenhas, L. (2017). Inherited germline ATRX mutation in two brothers with ATR-X syndrome and osteosarcoma. *American journal of medical genetics Part A*, *173*(5), 1390-1395.	1
88. Kim, Y. D., Hwang, D. S., Kim, C. H., Shin, S. H., Kim, U. K., Kim, J. R., & Chung, I. K. (2007). Impact of Methylation of the Gene $ p16^{INK4a} $ on Prognosis of Head and Neck Osteosarcoma. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*, *33*(1), 46-54.	5
89. Jang, H. S., Cho, J. O., Yoon, C. Y., Kim, H. J., & Park, J. C. (2001). Demonstration of Epstein–Barr virus in odontogenic and nonodontogenic tumors by the polymerase chain reaction (PCR). *Journal of oral pathology & medicine*, *30*(10), 603-610.	5
90. Ginat, D., Schulte, J., Gooi, Z., & Cipriani, N. (2018). High-grade conventional osteosarcoma of the mandible associated with P53 germline mutation. *Journal of Craniofacial Surgery*, *29*(3), 738-740.	1
91. Wang, H., Rodgers, W. H., Chmell, M. J., Svitek, C., & Schwartz, H. S. (1995). Osteosarcoma oncogene expression detected by in situ hybridization. *Journal of orthopaedic research*, *13*(5), 671-678.	5

1. Studies that did not address molecular alterations in oral and maxillofacial osteosarcoma;

2. Clinical trials, experimental studies, narrative reviews, protocols, brief communications, personal opinions, letters, book chapters, and conference abstracts;
3. Studies without full-text availability;
4. Studies published in languages other than English, Spanish, or Portuguese;
5. Insufficient clinicopathological data.

Table S3 Demographic, clinicopathological, and molecular characteristics of the 20 studies (68 cases) of oral and maxillofacial osteosarcoma included in the scoping review.

Author (year)	Country	Type of Study	N	Age (years)	Sex	Risk factors	Genetic factors	Other history	Location	Size (cm)	Histology	Grade	T	N	M	Stage	Molecular test	*TP53*	*MDM2*	*CDK4*	*GNAS*	*SAS*	OTHERS	Treatment	Surgical margins	LR	Metastases	Follow-up (months)	Status
Entz-Werle et al. (2003)	France	Cohort	1	9	NI	NI	NI	NI	MD	NI	NI	H	NI	NI	NI	NI	PCR	Normal status	NI	NI	NI	NI	RB1, D9S171 (9p21), D5S346 (5q21):Allelic imbalance (heterozygous); D5S492 (5q21): homozygous	Surgery+CT	NI	NI	NI	7	DOD
Tahir et al. (2024)	USA	Case report	1	81	F	NI	NI	High incidence of cancer in her paternal relatives	MD	5.0x4.0	TG	I	pT1	pN0	NI	IA	NGS	Missense and/or frame shift mutation	NI	NI	NI	NI	Missense and frameshift mutations: MUC4, MUC6, MUC17, MUC20, HLA, ZNF221, ZNF417, ZNF517, ZNF595, ZNF774, ZNF831, CYP2A7, CYP27C1, GADD45B, MSH4, TDG, MCM4, RBBP8NL, PER3, CDK11B, CDC27, and CCNE1	Surgery	NI	NI	NI	NI	NI
Liu et al. (2017)	USA	Case report	1	17	F	NI	NI	NI	MD	NI	NI	NI	NI	NI	NI	NI	FISH	Amp	NI	NI	NI	NI	Primary tumor: PTEN loss, TP53 R342, C17orf39 amplification and RB1 splice site 539+1G>A, Recurrent tumor: TP53 R342 mutation and a KRAS amplification	Surgery+CT+RT	Pos	No	Yes (bone marrow)	58	DOD
Ogi et al. (2020)	Japan	Case report	1	17	M	NI	LFS	History of cancer in his paternal relatives	MD	8.5x5.3x7.4	CD	H	NI	NI	NI	NI	PCR	Amp	NI	NI	NI	NI	NI	NI	NI	NI	NI	120	NED
Patrikidou et al. (2002)	UK	Case report	1	26	F	NI	LFS	Hermaphroditism at age 1, osteosarcoma of the maxilla at age 26, and Bowen's disease at age 31. History of cancer in her paternal relatives	MX	NI	NI	NI	NI	NI	NI	NI	PCR	Amp	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	Alive
Diniz et al. (2011)	Brazil	Cross-sectional	2	48	F	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	qPCR; RT-PCR	NI	NI	NI	NI	NI	(1) WWOX: aberrant transcripts	NI	NI	NI	NI	NI	NI

				34	F	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI		NI	NI	NI	NI	NI	with total or partial loss of exon length	NI	NI	NI	NI	NI	NI
Zhu et al. (2024)	USA	Cohort	15	19	M	NI	NI	No	MD	11	OB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array	(11) TP53: missense mutations (n = 8), frameshift truncation (n = 1), in-frame deletion (n = 1), and splice variant (n = 1).	NI	NI	Missense mutation R201C and R201H in two cases	NI	Other recurrently altered genes occurred at lower frequencies (2–3 cases /14), including CDKN2A/2B homozygous deletion, TERT amplification or hotspot mutation in the promoter, PBRM1 frameshift truncations, KMT2C missense mutations, APC missense mutations, PTEN homozygous deletion, frameshift truncation and missense mutation, RB1 homozygous deletion, missense mutation and in-frame deletion, and RAD50 missense mutation and in-frame fusion. RB1, TGFB1, and CBL were other mutated genes that occurred only in one case.	NI	NI	NI	NI	NI	NI
				58	M	Post-radiation	NI	No	MX	4.2	OB CD	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				67	M	Post-radiation	NI	No	MD	6.5	OB CD FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				54	F	NI	NI	No	MX	1.5	OB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				54	M	Post-radiation	NI	No	MD	3.5	OB CD FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				22	F	NI	NI	No	MD	6.5	OB CD	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				52	M	NI	NI	No	Frontal sinus and infratemporal fossa	7.0	OB CD FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				37	F	NI	NI	No	MD	5.3	OB CD FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				74	F	NI	NI	No	MX	6.5	FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				52	M	Fibrous dysplasia	NI	No	MX	4.0	OB CD FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				24	M	NI	NI	No	MD	8.0	FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				43	M	NI	NI	No	MX	4.5	CD	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				25	M	NI	NI	No	MD	5.5	CD	H	NI	NI	NI	NI	NGS: SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				67	M	NI	NI	No	MD	5.3	FB	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
				29	F	NI	NI	No	Sphenoid	2.9	OB CD	H	NI	NI	NI	NI	NGS: MSK-IMPACT, SNP Array		NI	NI		NI		NI	NI	NI	NI	NI	NI
Saucier et al. (2024)	France	Cohort	10	9	NI	NI	LFS	No	MD	NI	CD	I	NI	NI	NI	NI	NGS	Missense c.814G>A	NI	NI	NI	NI	NI	Surgery+CT	NI	No	No	23	Alive
				31.7	NI	NI	LFS	19.5y: 1st Osteosarcoma (limb). This is 2nd tumor, not metastasis	MD	NI	CD	I	NI	NI	NI	NI	NGS	Missense c.842A>T	NI	NI	NI	NI	NI	Surgery	NI	Yes	No	51	Alive
				6.5	NI	NI	LFS	No	MD	NI	OB CD	H	NI	NI	NI	NI	NGS	Missense c.742C>T	NI	NI	NI	NI	NI	Surgery+CT	NI	Yes	No	9	Dead
				8.3	NI	NI	LFS	6.5y: 1st Osteosarcoma (jaw). This is the 2nd tumor, not metastasis	MD	NI	OB	H	NI	NI	NI	NI	NGS	Missense c.742C>T	NI	NI	NI	NI	NI	Surgery+CT	NI	No	No	9	DOD

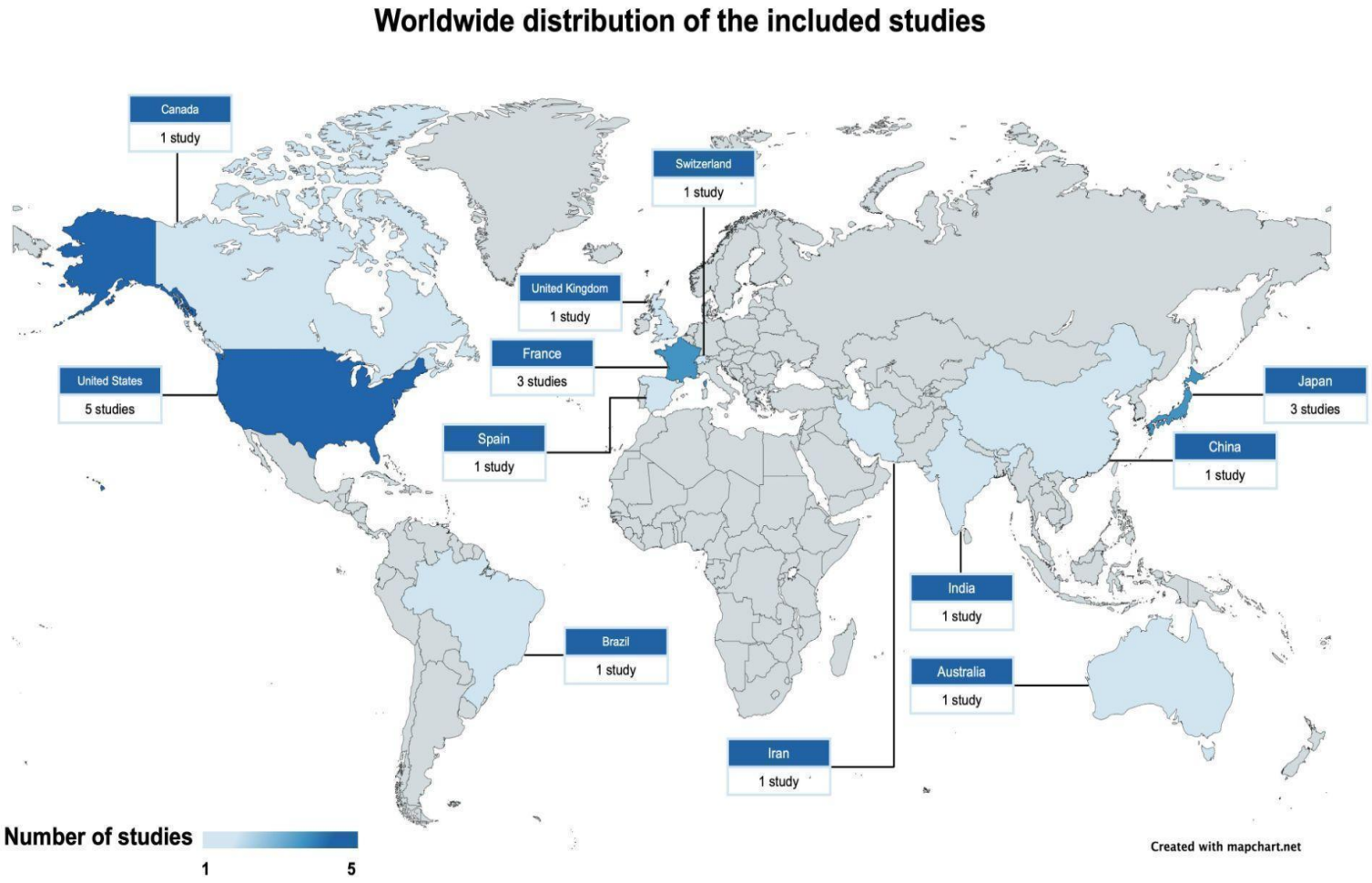
				12.8	NI	NI	LFS	No	MD	NI	OB CD	H	NI	NI	NI	NI	NGS	Missense c.518T>C	NI	NI	NI	NI	NI	Surgery+CT	NI	No	No	16	Alive
				19.2	NI	NI	LFS	11.9y: 1st Osteosarcoma (limb). This is the 2nd tumor, not metastasis	MD	NI	CD	H	NI	NI	NI	NI	NGS	Missense c.844C>T	NI	NI	NI	NI	NI	Surgery+CT	NI	No	No	24	Alive
				15.7	NI	NI	LFS	No	MD	NI	CD	H	NI	NI	NI	NI	NGS	Missense c.717C>G	NI	NI	NI	NI	NI	Surgery+CT	NI	No	No	16	DOD
				20.9	NI	NI	LFS	16.7y: 1st Osteosarcoma (limb). This is 2nd tumor, not metastasis	MD	NI	CD	H	NI	NI	NI	NI	NGS	Missence c.652_654del	NI	NI	NI	NI	NI	NI	NI	No	NI	29	Alive
				19	NI	NI	LFS	7y: 1st Osteosarcoma (axial). This is 2nd tumor, not metastasis	MD	NI	NI	H	NI	NI	NI	NI	NGS	Missence c.833C>G	NI	NI	NI	NI	NI	Surgery+CT	NI	No	No	24	Alive
				19	NI	NI	LFS	No	MD	NI	OB CD	H	NI	NI	NI	NI	NGS	Missence c.818G>A	NI	NI	NI	NI	NI	Surgery	NI	Yes	No	24	Alive
Garcia et al. (1990)	Spain	case report	1	40	F	Post-radiation: Acerebral astrocytoma	LFS	Lobular carcinoma of the breast with lymphatic involvement	MX	NI	NI	NI	NI	NI	NI	NI	Single-strand conformation polymorphism analysis	G-+-A substitution at base 743 (codon 248, exon 7) of thep53 gene.	NI	NI	NI	NI	NI	Surgery	NI	No	Yes (multiple osseous locations)	2	DOD
Akouchekian et al. (2016)	Iran	Case report	1	43	M	No	LFS	History of cancer in his paternal relatives	MD	NI	NI	NI	NI	NI	NI	NI	PCR, DNA Sequencing, Multiplex ligation-dependent probe amplification (MLPA)	Amp	NI	NI	NI	NI	PTEN amplification	NI	NI	NI	NI	NI	NI
Li et al. (2016)	China	Case report	1	41	F	Post-radiation	LFS	7y: Neuroblastoma and rhabdomyosarcoma (upper lip); 28y: Cystosarcoma phyllode (breast); 29y: Bronchioalveolar cell carcinoma (bronchio); 39y: Infitranting ductal carcinoma (breast) and thyroi papillary carcinoma (thyroid); 41y: Osteosarcoma (maxila) and gastric adenocarcinoma (stomach); 43y: osteosarcoma (sternum); 45y: Acute myeloid leukemia (blood)	MX	NI	NI	NI	NI	NI	NI	NI	NGS: whole-genome sequencing (WGS) and whole-exome sequencing (WES)	Two missense mutations (rs1042522 and rs28934576) in TP53	NI	NI	NI	NI	NI	Surgery+CT	NI	NI	Not confirm that the sternal spindle cell sarcoma was a primary or a metastasis from the maxillary osteosarcoma.	45	DOC
Lopes et al. (2001)	Brazil	Cross-sectional	9	32	F	(1) Post-radiation:papillary thyroid carcinoma Latency:11 years Total dose: NI	No	No	MX	1x1	CD	L	NI	NI	NI	NI	PCR	NI	Neg	Amp	NI	Neg	NI	Surgery	Neg	No	No	11	Alive
				36	F		No	No	MX	5x4	Parosteal	L	NI	NI	NI	NI		NI	Neg	Neg	NI	Amp	NI	Surgery	Neg	No	No	12	Alive
				20	F		No	No	MD	2.5x1.7	CD	H	NI	NI	NI	NI		NI	Amp	Amp	NI	Amp	NI	Surgery+CT	Neg	No	No	33	Alive
				63	M		No	No	MX	1.5x1	CD	I	NI	NI	NI	NI		NI	Amp	Amp	NI	Amp	NI	Surgery	Neg	No	No	19	Alive

				40	F		No	No	MD	3x1.5	CD	I	NI	NI	NI	NI		NI	Neg	Neg	NI	Neg	NI	Surgery	Neg	No	No	60	Alive
				46	M		No	No	MX	4x2	OB	H	NI	NI	NI	NI		NI	Amp	Amp	NI	Amp	NI	Surgery+RT	Close	No	No	21	Alive
				50	F		No	No	MD	1.6x1.5	CD	L	NI	NI	NI	NI		NI	Amp	Neg	NI	Amp	NI	Surgery	Neg	No	No	10	Alive
				51	M		No	No	MX	2.4x2	CD	L	NI	NI	NI	NI		NI	Amp	Amp	NI	Amp	NI	Surgery	Close	No	No	6	Alive
				64	F		No	No	MD	4.5x3	OB	H	NI	NI	NI	NI		NI	Amp	Amp	NI	Neg	NI	Surgery	Neg	No	No	5	Alive
Limbach et al. (2020)	USA	Cross-sectional	4	62	M	No	No	Prior colon cancer status post resection	MD	NI	OB	H	NI	NI	NI	NI	FISH	NI	Amp	NI	NI	NI	NI	CT+RT	NI	NI	NI	11	DOC
				34	M	No	No	No	MD	NI	OB	L	NI	NI	NI	NI		NI	Neg	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU
				41	F	No	No	No	MX	NI	FB	L	NI	NI	NI	NI		NI	Failed	NI	NI	NI	NI	RT	NI	No	NI	5	Alive
				NI	M	No	No	No	MX	NI	CD	L	NI	NI	NI	NI		NI	Neg	NI	NI	NI	NI	NI	NI	NI	NI	NI	LFU
Hirose et al. (2017)	Japan	Case report	1	64	M	No	No	No	MX	3.3x2.2	Giant cell–rich	H	NI	NI	NI	NI	FISH	NI	Amp	Amp	NI	NI	NI	NI	NI	NI	NI	NI	NI
Haefliger et al. 2021)	Switzerland	Case report	1	30	F	Cemento-osseous dysplasia	LFS	Bilateral breast cancer	MD	NI	OB	H	NI	NI	NI	NI	NGS and Microarray for copy number analysis and loss of heterozygosity	p.V173G TP53	NI	NI	Neg	NI	Chromoplexy with subsequent amplifications of 5p, 8pter, 12, and 19p as well as deletions of 5q, 6, 7, 10p, 13, and 22	Surgery+CT	Neg	No	No	36	NED
Yap et al. (2021)	Australia	Case report	1	21	M	Fibrous dysplasia	No	No	MX	3.1x2.4x2.2	NI	H	NI	NI	NI	NI	NGS and FISH	Separate point mutation in TP53 at codon 281 (Asp281Asn)	Neg	Neg	Missense mutation Arg201Cys	NI	NI	Surgery+CT	NI	No	No	10	NED
Yokoyama et al. (2023)	Japan	Case report	1	61	M	Post-radiation: squamous cell carcinoma Latency: 13 years Total dose: 60Gy	No	No	MX	NI	NI	NI	NI	NI	NI	NI	NGS	TP53 K321fs*15 mutation were detected	NI	NI	NI	NI	Amp: CCNE1, KEL, EZH2, XRCC2 Missense mutation: LTK S183F, BRCA2 S758C, ERBB3 R1118Q, KMT2A (MLL) G73E Truncation mutation: LTK W707*	Surgery+CT	NI	No	Yes (Multiple lung)	8	AWD
Khan et al. (2024)	India	Case report	1	17	F	No	No	No	MD	8x10x4	TG	NI	NI	NI	NI	NI	FISH	NI	Neg	Neg	NI	NI	NI	Surgery+CT	Neg	No	No	8	NED
Guérin et al. (2016)	France	Cross-sectional	14	61	M	NI	NI	NI	MD	NI	CD	H	NI	NI	NI	NI	PCR	NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				32	M	NI	NI	NI	MD	NI	CD	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				80	F	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Amp	NI	Neg	NI	RASAL1: Amp	NI	NI	NI	NI	NI	NI
				55	M	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Amp	NI	Neg	NI	RASAL1: Amp	NI	NI	NI	NI	NI	NI

				NI	NI	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				80	F	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Amp	NI	Neg	NI	RASAL1: Amp	NI	NI	NI	NI	NI	NI
				21	F	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				31	F	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				61	F	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Amp	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				49	M	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Amp	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				26	M	NI	NI	NI	MD	NI	FB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				46	M	NI	NI	NI	MD	NI	OB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				68	F	NI	NI	NI	MD	NI	OB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
				60	M	Post-radiation	NI	NI	MD	NI	OB	H	NI	NI	NI	NI		NI	Neg	NI	Neg	NI	RASAL1: Neg	NI	NI	NI	NI	NI	NI
Khayat et al. (2004)	Canada	Case report	1	7	NI	NI	NI	Rhabdomyosarcoma of scapula and adrenocortical carcinoma	MD	2x3	NI	NI	NI	NI	NI	NI	NGS	Testing for p53 mutation by DNA sequence analysis yielded a positive result of a CGT > CAT mutation at codon 273 (Arg > His)	NI	NI	NI	NI	NI	CT	NI	No	Yes (Liver)	7	DOD

LR (Local recurrence); H (High); I (Intermediate); L (Low); MD (Mandible); MX (Maxilla); LFS (Li-Fraumeni syndrome); Neg (Negative); Pos (Positive); LVI (Lymphovascular invasion); NPI (Neural/perineural invasion); FB (Fibroblastic); CD (Chondroblastic); OB (Osteoblastic); TG (Telangiectatic); Ampl (Amplification); NI (Not-Informed)

Figure S2 World map illustrating the distribution of the included studies.



3 DISCUSSÃO

Os sarcomas da região oral e maxilofacial podem se originar de qualquer tecido não epitelial nessas áreas (Wreesmann et al., 2022). Neste estudo, a maioria dos casos (70,4%) envolveu os ossos dessa região. A localização anatômica mostrou-se estatisticamente significativa em relação a sobrevida específica da doença, com sarcomas que acometem a região nasal e os seios maxilares apresentando um pior prognóstico em 5 anos (43,6%). Entre os subtipos histológicos, a revisão sistemática demonstrou que o osteossarcoma foi o mais prevalente, condizente com um recente estudo brasileiro (de Carvalho et al., 2020).

A radiação ionizante, especialmente a radioterapia externa na região da cabeça e pescoço, é um fator de risco bem estabelecido para o desenvolvimento de sarcomas, promovendo danos ao DNA e desregulação do ciclo celular (Coca-Pelaz et al., 2021; Zhu et al., 2016). Em nosso estudo, dos 89 casos de sarcomas de cabeça e pescoço induzidos por radiação, 65 foram osteossarcomas (73%), 16 sarcomas pleomórficos indiferenciados (18%), 7 fibrosarcomas (7,9%) e 1 sarcoma de células fusiformes (1,1%). Esses achados corroboram a literatura que aponta que as variantes histológicas mais prevalentes nesses casos incluem o sarcoma pleomórfico indiferenciado, osteossarcoma, condrossarcoma e fibrossarcoma, todos associados a um prognóstico desfavorável (Thiagarajan, 2014).

O diagnóstico do sarcoma induzido por radiação na cabeça e pescoço segue critérios bem estabelecidos, incluindo o surgimento do tumor em uma área previamente irradiada, a distinção histológica entre o tumor primário e o secundário, a ausência do tumor secundário durante o tratamento com radioterapia e um período de latência após o tratamento (Cahan et al., 1948; Murray et al., 1999). Estes tumores têm um prognóstico desfavorável devido a múltiplos fatores, como imunossupressão local, alterações genéticas induzidas pela radioterapia, dificuldades no tratamento de tecidos previamente irradiados e atrasos diagnósticos decorrentes de alterações anatômicas e histológicas (Patel, 2000; Wreesmann et al., 2022). Na nossa revisão sistemática, os sarcomas induzidos por radiação apresentaram o pior prognóstico, com uma taxa de sobrevida global de 5 anos de 20,4%. Dentre os subtipos histológicos, o osteossarcoma se destaca como o mais prevalente (Kumari et al., 2022; Zhu et al., 2016).

Em relação ao osteossarcoma induzido por radiação (OSIR), o carcinoma nasofaríngeo foi o tumor primário mais comum (59,3%), com a nasofaringe sendo a localização primária mais frequente (64,7%). Nossa revisão sistemática corrobora essa associação, identificando o carcinoma nasofaríngeo como o tumor primário mais frequentemente relacionado ao desenvolvimento de OSIR. A radioterapia, tratamento padrão para o carcinoma nasofaríngeo, geralmente envolve estruturas ósseas como a base do crânio, maxila, mandíbula e osso

pterigoide, áreas suscetíveis ao desenvolvimento de OSIR como uma complicação tardia (Wei et al., 2012). O período médio de latência observado foi de 11,7 anos (variação: 3–36 anos), achado semelhante ao descrito na literatura, que reporta uma média de 8 anos (variação: 3–34 anos) (Liao et al., 2016).

Ao analisar o perfil molecular dos osteossarcomas da região oral e maxilofacial, diversas alterações genéticas foram identificadas, com destaque para o gene *TP53*, que foi o mais frequentemente alterado. Em nosso estudo, 15 de 32 pacientes (46,9%) foram diagnosticados com a síndrome de Li-Fraumeni, e todos apresentaram mutações no *TP53*. Essa síndrome, causada por mutações no gene *TP53*, está associada a um aumento significativo no risco de sarcomas de tecidos moles e ósseos, que representam cerca de um quarto dos tumores diagnosticados em indivíduos afetados (Makary et al., 2017; Malkin et al., 1990; Sturgis and Potter, 2003; Zahm and Fraumeni, 1997).

Entre os fatores de risco avaliados, identificamos 8 casos de osteossarcoma induzido por radiação, dos quais 3 apresentaram mutações no *TP53*. Esses tumores exibem uma maior frequência de mutações e superexpressão da proteína p53 em comparação com osteossarcomas primários. Embora a maioria dos estudos indiquem que a expressão de p53, isoladamente, não tem valor prognóstico significativo (Lopes et al., 2001; Nakanishi et al., 1998; Takahama Junior et al., 2003), uma meta-análise demonstrou que mutações no *TP53* estão associadas a uma pior sobrevida em pacientes com osteossarcoma, sugerindo seu potencial como marcador prognóstico (Chen et al., 2016). Além disso, o *TP53* tem sido considerado um alvo terapêutico promissor, impulsionando o desenvolvimento de novas abordagens terapêuticas (Tang et al., 2019).

O osteossarcoma de baixo grau frequentemente apresenta amplificação da região 12q13-15, que abriga os genes *MDM2* e *CDK4* (Cleven et al., 2020; Tabareau-Delalande and de Pinieux, 2016). Estudos mostram que *MDM2* está amplificado em mais de 60% desses tumores, mas ausente em lesões benignas, sendo um marcador útil no diagnóstico diferencial (Mejia-Guerrero et al., 2010). No entanto, em nossa amostra, MDM2 foi positivo em 13 casos, incluindo 10 de alto grau, indicando que sua expressão não é restrita a tumores de baixo grau. Além disso, *CDK4* apresentou alterações em 7 casos, sendo 4 de alto grau. Esse gene codifica uma quinase essencial para a transição G1/S do ciclo celular, promovendo a proliferação tumoral. Sua presença em osteossarcoma de alto grau pode estar associada à maior proliferação e progressão da doença (Zhou et al., 2018).

Diferentemente dos osteossarcomas de baixo grau ou desdiferenciados, os osteossarcomas de alto grau não possuem uma assinatura molecular específica, o que torna seu

diagnóstico e caracterização mais desafiadores (Tabareau-Delalande and de Pinieux, 2016). Embora os mecanismos responsáveis por essas alterações cromossômicas disruptivas ainda não sejam completamente compreendidos, a inativação do *TP53* parece desempenhar um papel crucial nesse processo (Haefliger et al., 2022).

O tratamento dos sarcomas orais e maxilofaciais varia conforme o subtipo histológico do tumor (Grünewald et al., 2020). A abordagem terapêutica padrão envolve a ressecção cirúrgica do tumor primário, frequentemente associada à quimioterapia neoadjuvante e/ou adjuvante e radioterapia. A recorrência local progressiva é a principal causa de mortalidade, geralmente precedendo a disseminação sistêmica. Fatores prognósticos adversos incluem margens cirúrgicas comprometidas, tamanho tumoral, grau histológico, estágio da doença, envolvimento linfonodal e histórico de radioterapia (Makary et al., 2017).

Nossa revisão sistemática demonstrou que pacientes com tumores em estágios avançados (T3/T4) apresentam um risco de mortalidade 6,2 vezes maior em comparação àqueles com tumores em estágios iniciais (T1/T2). Da mesma forma, indivíduos diagnosticados em estágio clínico III/IV apresentam um risco 9,3 vezes superior ao daqueles em estágio I/II. Margens cirúrgicas livres de neoplasia reduzem o risco de mortalidade específica da doença em 73%. Além disso, a presença de recidiva local eleva o risco de morte em 5,5 vezes, enquanto a ocorrência de metástases à distância aumenta esse risco em 1,7 vezes. Esses achados reforçam a importância do diagnóstico precoce e da ressecção completa do tumor para melhorar o prognóstico dos pacientes.

Estratégias terapêuticas baseadas na imunoterapia, como anticorpos monoclonais, conjugados anticorpo-fármaco e células T receptoras de antígeno quimérico (CAR-T), estão em desenvolvimento clínico ativo, direcionadas a proteínas de superfície superexpressas nesses tumores. Com os avanços na compreensão biológica, modelos pré-clínicos mais robustos e novas abordagens terapêuticas, espera-se um progresso significativo no tratamento e prognóstico do osteossarcoma em um futuro próximo (Gill and Gorlick, 2021; Li et al., 2023).

4 CONCLUSÃO

Os achados deste estudo oferecem uma contribuição significativa para a compreensão das características clinicopatológicas dos sarcomas orais e maxilofaciais, evidenciando o impacto de fatores como idade, subtipo histológico, classificação T, estágio clínico, margens cirúrgicas, recorrência local e metástases à distância na sobrevida dos pacientes. Entre esses tumores, o osteossarcoma se destaca, particularmente pela sua associação com a exposição à radiação. O longo período de latência e o prognóstico reservado do OSIR sublinham a importância de um acompanhamento rigoroso dos pacientes que passaram por radioterapia. O estudo também ampliou o entendimento sobre a complexidade molecular do osteossarcoma oral e maxilofacial, abrindo novas perspectivas para aprimorar o diagnóstico e as estratégias de manejo clínico, com o objetivo de melhorar os desfechos e a qualidade de vida dos pacientes. A escassez de pesquisas focadas nessa região anatômica ressalta a relevância deste estudo, uma vez que os sarcomas maxilofaciais apresentam características distintas dos sarcomas de ossos longos.

REFERÊNCIAS[1]

Alishahi B, Kargahi N, Homayouni S. Epidemiological Evaluation of Head and Neck Sarcomas in Iran (the Study of 105 Cases Over 13 Years). Iran J Cancer Prev 2015b;8. https://doi.org/10.17795/ijcp-3432.

Barosa J, Ribeiro J, Afonso L, Fernandes J, Monteiro E. Head and neck sarcoma: Analysis of 29 cases. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:83–6. https://doi.org/10.1016/j.anorl.2012.11.007.

Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma in irradiated bone. Report of eleven cases. Cancer 1948;1:3–29. https://doi.org/10.1002/1097-0142(194805)1:1<3::AID-CNCR2820010103>3.0.CO;2-7.

de Carvalho WRS, de Souza LL, Pontes FSC, Uchôa DCC, Corrêa DL, de Cáceres CVBL, et al. A multicenter study of oral sarcomas in Brazil. Oral Dis 2020;26:43–52. https://doi.org/10.1111/odi.13211.

Chen Z, Guo J, Zhang K, Guo Y. TP53 Mutations and Survival in Osteosarcoma Patients: A Meta-Analysis of Published Data. Dis Markers 2016;2016:1–5. https://doi.org/10.1155/2016/4639575.

Cleven AHG, Schreuder WH, Groen E, Kroon HM, Baumhoer D. Molecular findings in maxillofacial bone tumours and its diagnostic value. Virchows Archiv 2020;476:159–74. https://doi.org/10.1007/s00428-019-02726-2.

Coca-Pelaz A, Mäkitie AA, Strojan P, Corry J, Eisbruch A, Beitler JJ, et al. Radiation-Induced Sarcomas of the Head and Neck: A Systematic Review. Adv Ther 2021;38:90–108. https://doi.org/10.1007/s12325-020-01556-y.

Demicco EG. Sarcoma Diagnosis in the Age of Molecular Pathology. Adv Anat Pathol 2013;20:264–74. https://doi.org/10.1097/PAP.0b013e31829c2c7b.

Giannini L, Incandela F, Fiore M, Gronchi A, Stacchiotti S, Sangalli C, et al. Radiation-Induced Sarcoma of the Head and Neck: A Review of the Literature. Front Oncol 2018;8.

[1]*De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors - Vancouver Group. Abreviatura dos periódicos em conformidade com o PubMed.

https://doi.org/10.3389/fonc.2018.00449.

Gill J, Gorlick R. Advancing therapy for osteosarcoma. Nat Rev Clin Oncol 2021;18:609–24. https://doi.org/10.1038/s41571-021-00519-8.

Grünewald TG, Alonso M, Avnet S, Banito A, Burdach S, Cidre-Aranaz F, et al. Sarcoma treatment in the era of molecular medicine. EMBO Mol Med 2020;12. https://doi.org/10.15252/emmm.201911131.

Haefliger S, Andrei V, Baumhoer D. Update of Key Clinical, Histological and Molecular Features of Malignant Bone Tumours Arising in the Craniofacial Skeleton. Front Oncol 2022;12. https://doi.org/10.3389/fonc.2022.954717.

Hassanain O, Alaa M, Khalifa MK, Kamal N, Albagoury A, El Ghoneimy AM. Genetic variants associated with osteosarcoma risk: a systematic review and meta-analysis. Sci Rep 2024;14:3828. https://doi.org/10.1038/s41598-024-53802-w.

Hui JYC. Epidemiology and Etiology of Sarcomas. Surgical Clinics of North America 2016;96:901–14. https://doi.org/10.1016/j.suc.2016.05.005.

Kalavrezos N, Sinha D. Head and neck sarcomas in adulthood: current trends and evolving management concepts. British Journal of Oral and Maxillofacial Surgery 2020;58:890–7. https://doi.org/10.1016/j.bjoms.2020.05.015.

Kämmerer PW, Shabazfar N, Vorkhshori Makoie N, Moergel M, Al-Nawas B. Clinical, therapeutic and prognostic features of osteosarcoma of the jaws – Experience of 36 cases. Journal of Cranio-Maxillofacial Surgery 2012;40:541–8. https://doi.org/10.1016/j.jcms.2011.10.001.

Kansara M, Teng MW, Smyth MJ, Thomas DM. Translational biology of osteosarcoma. Nat Rev Cancer 2014;14:722–35. https://doi.org/10.1038/nrc3838.

Khadembaschi D, Jafri M, Praveen P, Parmar S, Breik O. Does neoadjuvant chemotherapy provide a survival benefit in maxillofacial osteosarcoma: A systematic review and pooled analysis. Oral Oncol 2022;135:106133. https://doi.org/10.1016/j.oraloncology.2022.106133.

Kotecha S, Williams M, White HB, Graystone J, Gibbons M, Cosker T. Head and neck

sarcoma: three-year data from a tertiary referral centre. The Annals of The Royal College of Surgeons of England 2021;103:762–7. https://doi.org/10.1308/rcsann.2021.0119.

Kumari N, Majumdar KS, Usmani SA, Agarwal SP. Radiation-induced synchronous mandibular osteosarcoma and papillary thyroid carcinoma. J Cancer Res Ther 2022;18:305–7. https://doi.org/10.4103/jcrt.JCRT_366_20.

Li S, Zhang H, Liu J, Shang G. Targeted therapy for osteosarcoma: a review. J Cancer Res Clin Oncol 2023;149:6785–97. https://doi.org/10.1007/s00432-023-04614-4.

Liao L-Q, Yan H-H, Mai J-H, Liu W-W, Li H, Guo Z-M, et al. Radiation-induced osteosarcoma of the maxilla and mandible after radiotherapy for nasopharyngeal carcinoma. Chin J Cancer 2016;35:89. https://doi.org/10.1186/s40880-016-0153-8.

Liao Y, Hsu C, Leu C, Lai S, Huang Y, Hsieh M, et al. Radiation-induced sarcoma of head and neck: Clinical characteristics and molecular signatures. Head Neck 2023;45:638–46. https://doi.org/10.1002/hed.27279.

Lopes MA, Nikitakis NG, Ord RA, Sauk J. Amplification and protein expression of chromosome 12q13-15 genes in osteosarcomas of the jaws. Oral Oncol 2001;37:566–71. https://doi.org/10.1016/S1368-8375(00)00130-5.

Luk PP, Selinger CI, Cooper WA, Mahar A, Palme CE, O'Toole SA, et al. Clinical Utility of In Situ Hybridization Assays in Head and Neck Neoplasms. Head Neck Pathol 2019;13:397–414. https://doi.org/10.1007/s12105-018-0988-1.

Luo Z, Chen W, Shen X, Qin G, Yuan J, Hu B, et al. Head and neck osteosarcoma: CT and MR imaging features. Dentomaxillofacial Radiology 2020;49:20190202. https://doi.org/10.1259/dmfr.20190202.

Makary RF, Gopinath A, Markiewicz MR, Fernandes R. Margin Analysis. Oral Maxillofac Surg Clin North Am 2017;29:355–66. https://doi.org/10.1016/j.coms.2017.04.002.

Malkin D, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH, et al. Germ Line p53 Mutations in a Familial Syndrome of Breast Cancer, Sarcomas, and Other Neoplasms. Science (1979) 1990;250:1233–8. https://doi.org/10.1126/science.1978757.

Mannelli G, Bassani S, Cosi G, Fermi M, Gazzini L, Liberale C, et al. Global frequency and

distribution of head and neck sarcomas in adulthood: a systematic review. European Archives of Oto-Rhino-Laryngology 2024;281:2553–67. https://doi.org/10.1007/s00405-024-08477-4.

Mejia-Guerrero S, Quejada M, Gokgoz N, Gill M, Parkes RK, Wunder JS, et al. Characterization of the 12q15 *MDM2* and 12q13-14 *CDK4* amplicons and clinical correlations in osteosarcoma. Genes Chromosomes Cancer 2010;49:518–25. https://doi.org/10.1002/gcc.20761.

Murray EM, Werner D, Greeff EA, Taylor DA. Postradiation sarcomas: 20 cases and a literature review. International Journal of Radiation Oncology*Biology*Physics 1999;45:951–61. https://doi.org/10.1016/S0360-3016(99)00279-5.

Nakanishi H, Tomita Y, Myoui A, Yoshikawa H, Sakai K, Kato Y, et al. Mutation of the p53 gene in postradiation sarcoma. Lab Invest 1998;78:727–33.

Ottaviani G, Jaffe N. The Epidemiology of Osteosarcoma, 2009, p. 3–13. https://doi.org/10.1007/978-1-4419-0284-9_1.

Patel SR. Radiation-induced sarcoma. Curr Treat Options Oncol 2000;1:258–61. https://doi.org/10.1007/s11864-000-0037-6.

Sturgis EM, Potter BO. Sarcomas of the head and neck region. Curr Opin Oncol 2003;15:239–52. https://doi.org/10.1097/00001622-200305000-00011.

Tabareau-Delalande F, de Pinieux G. Molecular Markers of Fibro-Osseous Lesions and Osteosarcomas of the Craniofacial Complex—Current Situation and Recent Advances. Curr Oral Health Rep 2016;3:102–10. https://doi.org/10.1007/s40496-016-0086-y.

Takahama Junior A, de Abreu Alves F, Lopes Pinto CA, Lopes Carvalho A, Kowalski LP, Lopes MA. Clinicopathological and immunohistochemical analysis of twenty-five head and neck osteosarcomas. Oral Oncol 2003;39:521–30. https://doi.org/10.1016/S1368-8375(03)00017-4.

Tang F, Min L, Seebacher NA, Li X, Zhou Y, Hornicek FJ, et al. Targeting mutant TP53 as a potential therapeutic strategy for the treatment of osteosarcoma. Journal of Orthopaedic Research 2019;37:789–98. https://doi.org/10.1002/jor.24227.

Thiagarajan A. Radiation-induced sarcomas of the head and neck. World J Clin Oncol 2014;5:973. https://doi.org/10.5306/wjco.v5.i5.973.

Tran LM, Mark R, Meier R, Calcaterra TC, Parker RG. Sarcomas of the head and neck. Prognostic factors and treatment strategies. Cancer 1992;70:169–77. https://doi.org/10.1002/1097-0142(19920701)70:1<169::AID-CNCR2820700127>3.0.CO;2-F.

Tran N-A, Guenette JP, Jagannathan J. Soft Tissue Special Issue: Imaging of Bone and Soft Tissue Sarcomas in the Head and Neck. Head Neck Pathol 2020;14:132–43. https://doi.org/10.1007/s12105-019-01102-5.

Weber V, Stigler R, Lutz R, Kesting M, Weber M. Systematic review of craniofacial osteosarcoma regarding different clinical, therapeutic and prognostic parameters. Front Oncol 2023;13. https://doi.org/10.3389/fonc.2023.1006622.

Wei Z, Xie Y, Xu J, Luo Y, Chen F, Yang Y, et al. Radiation-induced sarcoma of head and neck: 50 years of experience at a single institution in an endemic area of nasopharyngeal carcinoma in China. Medical Oncology 2012;29:670–6. https://doi.org/10.1007/s12032-011-9828-9.

Williams L, Tmanova L, Mydlarz WK, Page B, Richmon JD, Quon H, et al. Radiation-Associated Sarcoma of the Neck: Case Series and Systematic Review. Annals of Otology, Rhinology & Laryngology 2018;127:735–40. https://doi.org/10.1177/0003489418789966.

Wreesmann VB, Oomen KP, Brennan PA. Angiosarcomas of the head and neck: Impact of large data analysis on clinical management. Journal of Oral Pathology & Medicine 2022;51:904–10. https://doi.org/10.1111/jop.13354.

Zahm SH, Fraumeni JF. The epidemiology of soft tissue sarcoma. Semin Oncol 1997;24:504–14.

Zhou Y, Shen JK, Yu Z, Hornicek FJ, Kan Q, Duan Z. Expression and therapeutic implications of cyclin-dependent kinase 4 (CDK4) in osteosarcoma. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2018;1864:1573–82. https://doi.org/10.1016/j.bbadis.2018.02.004.

Zhu W, Hu F, Zhao T, Wang C, Tao Q. Clinical Characteristics of Radiation-Induced Sarcoma of the Head and Neck: Review of 15 Cases and 323 Cases in the Literature. Journal of Oral and Maxillofacial Surgery 2016;74:283–91. https://doi.org/10.1016/j.joms.2015.07.013.

ANEXOS

Anexo 1. Comprovante de submissão – Artigo 1

Oral Diseases
Review Article

Clinicopathologic Analysis of Sarcomas in the Oral and Maxillofacial Region: A Systematic Review

Submission Status	Under Review
Manuscript ID	ODI-02-25--15454
Submitted On	5 February 2025 by Iara Vieira Ferreira
Submission Started	5 February 2025 by Iara Vieira Ferreira

This submission is under consideration and cannot be edited. Further information will be emailed to you by the journal editorial office.

Submission overview →

Anexo 2. Comprovante de publicação – Artigo 2

Oral Oncology 162 (2025) 107216

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

Radiation-induced osteosarcoma in the head and neck region: Case report and literature review

ABSTRACT

Radiation-induced sarcoma (RIS) is a rare but highly aggressive complication of radiotherapy, especially in the head and neck region (RIS-HN). This report describes a case of radiation-induced osteosarcoma (RIOS) in a 32-year-old woman with a history of craniopharyngioma treated with surgery and radiotherapy 13 years prior. The patient exhibited symptoms including epistaxis, diplopia, and ptosis of the right eyelid. Imaging revealed a large, inoperable tumor in the area that had received prior radiotherapy. A biopsy confirmed the diagnosis of osteosarcoma, and the patient initiated palliative chemotherapy. Unfortunately, the treatment was unsuccessful, and the patient passed away. A review of 148 RIOS cases published in the last 25 years in the literature shows that the maxilla and mandible are the most affected sites (68.86 %), with an average latency of 11.79 years. The most common primary tumor was nasopharyngeal carcinoma, treated with an average radiation dose of 61.69 Gy. The prognosis remains poor, with 72.3 % of patients dying within an average of 23 months of follow-up. This study highlights the clinical and pathological characteristics of RIOS, the importance of long-term monitoring of irradiated patients to detect and treat these tumors early, with the aim of improving patient outcomes.

Introduction

Radiotherapy is an essential treatment for head and neck cancer, with recent advancements leading to significant improvements in patient survival and quality of life [1–3]. However, this increase in survival rates has been accompanied by a rise in the incidence of secondary neoplasms, including radiation-induced sarcoma (RIS), a rare and highly lethal complication, particularly when located in the head and neck region (RIS-HN) [2–4]. The diagnosis of RIS-HN is based on well-defined criteria, including the emergence of the tumor in a previously irradiated area, histological distinction between the primary and secondary tumors, absence of the secondary tumor during radiotherapy, and a latency period after radiotherapy [5,6]. The most prevalent histological variants include malignant fibrous histiocytoma, osteosarcoma, chondrosarcoma, and fibrosarcoma, all of which are associated with a poor prognosis [3,7].

This article reports a case of RIS-HN, along with a literature review of radiation-induced osteosarcoma (RIOS) in this region.

Case report

A 32-year-old female patient from Itatiba, Brazil, presented to the clinic with a 20-day history of epistaxis, purulent nasal discharge, and severe frontal headache. Over the past seven days, she developed diplopia, right eye ptosis, and episodes of nausea and vomiting. The patient had a history of craniopharyngioma, diagnosed 13 years prior, treated via transsphenoidal craniotomy. The pathological examination at that time revealed a residual tumor in the dorsum sellae, adhered to the cavernous sinus. Following surgical resection, the patient underwent adjuvant radiotherapy, receiving 55.80 Gy in 31 fractions of 1.80 Gy each, delivered through three fields (right temporal, left temporal, and frontal) using 9 MV energy on an Al-Netuno device. Since then, the patient has been under clinical follow-up due to panhypopituitarism secondary to surgery, with continuous hormone replacement therapy. However, the emergence of new symptoms necessitated further investigation. Magnetic resonance imaging revealed an extensive lesion in the previously irradiated region, invading the clivus, cavernous sinus, maxillary sinus, and nasal cavity. A biopsy of the lesion in the nasopharynx was performed via an endoscopic nasal approach. Microscopic examination revealed a predominantly spindle-cell malignant neoplasm composed of atypical cells, including multinucleated cells, with numerous mitoses, both typical and atypical. The presence of high cellularity and the production of osteoid material by the neoplastic cells were observed, establishing the diagnosis of osteosarcoma (Fig. 1). Given the unresectable nature of the neoplasm, the patient was referred for palliative treatment with cisplatin and doxorubicin-based chemotherapy. Despite the implementation of these therapeutic measures, the clinical course was unfavorable, and the patient died of the disease after 16 months of follow-up.

Discussion

The etiopathogenesis of most sarcomas remains poorly understood, but genetic and environmental factors, including genetic alterations, radiation exposure, and infections, have been implicated in their development [8,9]. Ionizing radiation, particularly through external beam radiation in the head and neck, is a recognized risk factor, causing DNA damage and cell cycle dysregulation [10,11]. RIS-HN has a worse prognosis due to factors such as local immunosuppression, genetic alterations in tumor cells from radiotherapy, difficulties in treating irradiated areas, and diagnostic delays from anatomical and histological changes [9,12]. Among histological subtypes, osteosarcoma is the most prevalent [10,40]. This rare, aggressive neoplasm typically arises at least five years after radiation exposure [19,36]. The study presents a case of RIOS in a female patient, emphasizing diagnostic challenges and poor prognosis associated with this condition.

A comprehensive review on radiation-induced osteosarcoma revealed 148 cases published in PubMed over the past 25 years (Table 1)

https://doi.org/10.1016/j.oraloncology.2025.107216
Received 4 February 2025; Accepted 6 February 2025
Available online 12 February 2025

Anexo 3. Relatório de verificação de originalidade e prevenção de plágio

Iara Vieira Ferreira

ASPECTOS CLINOPATOLÓGICOS E MOLECULARES DOS SARCOMAS DA REGIÃO ORAL E MAXILOFACIAL

17% Similaridade geral

O total combinado de todas as correspondências, incluindo fontes sobrepostas, para cad...

Grupos de correspondência

126 Nem mencionado nem citado 12%
Correspondências sem citação ou aspas no texto

57 Citações ausentes 5%
Correspondências que ainda são muito semelhantes ao material original

0 Citação ausente 0%
Correspondências com aspas, mas sem citação no texto

0 Citado e mencionado 0%
Correspondências com citação presente no texto, mas sem aspas

Principais fontes

12% Fontes da Internet

13% Publicações

9% Trabalhos enviados (documentos de aluno)