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SARCOMAS DE CABEÇA E PESCOÇO - PERFIL CLÍNICO DEMOGRÁFICO DE UMA POPULAÇÃO PEDIÁTRICA EM CENTRO DE REFERÊNCIA DO SUL DO BRASIL E REVISÃO SISTEMÁTICA DA LITERATURA

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Tese apresentada ao Programa de Pós-graduação em Odontologia da Universidade Federal do Rio Grande do Sul como requisito parcial à obtenção do título de Doutora em Odontologia, na área de Clínica Odontológica-Estomatologia.

Orientadora: Profª. Dra. Manoela Domingues Martins

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DEDICATÓRIA

As Mães e aos Filhos....

As Mães que me confiam seu bem mais precioso, seus filhos,

Acreditando que sempre vou dar o meu melhor.

Aos Filhos, meus pacientes,

confesso que a busca pelo conhecimento, me trouxe os títulos, de especialista,

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mas nenhum título consegue superar a profundidade, a confiança e o

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obrigada. O **TALMUD** (coleção de escritos sagrados dos judeus) gira em torno do “ensinar, instruir” ou também “aprender”. É um registro de discussões sobre leis, tradições, éticas e costumes, basicamente a filosofia judaica. Um dos grandes ensinamentos do TALMUD é que “*não se deve estudar sozinho, porque quem estuda sozinho corre o risco de errar e repetir esse erro ao longo dos anos”*.... Foi neste grupo que vivenciei esse ensinamento, o verdadeiro significado de estudarmos juntos.

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“A wife who loses a husband is called a widow. A husband who loses a wife is called a widower. A child who loses his parents is called an orphan. There is no word for a parent who loses a child. That’s how awful the loss is.”

“Uma esposa que perde o marido é chamada de viúva. Um marido que perde a esposa é chamado de viúvo. Uma criança que perde os pais é chamada de órfão. Não existe palavra para um pai que perde um filho, de tão terrível que essa perda é.”

An Orphan’s Tale by Jay Neugeboren

RESUMO

SPIGUEL, MONICA HERMANN. **SARCOMA DE CABEÇA E PESCOÇO - PERFIL CLÍNICO DEMOGRÁFICO DE UMA POPULAÇÃO PEDIÁTRICA EM CENTRO DE REFERÊNCIA DO SUL DO BRASIL E REVISÃO SISTEMÁTICA DA LITERATURA.** Tese (Pós-graduação em Odontologia com ênfase em Clínica Odontológica, Estomatologia) – Faculdade de Odontologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2023.

Sarcomas são um grupo específico e heterogêneo de neoplasias malignas que tem origem em células progenitoras mesenquimais. Em região de cabeça e pescoço os sarcomas são raros e representam 1% de todas as neoplasias malignas. Poucos estudos avaliam o perfil dos sarcomas nesta região e em crianças e adolescentes. Portanto, o objetivo do Artigo 1 do presente trabalho foi realizar uma revisão sistemática da literatura sobre sarcoma de Ewing (ES) de cabeça e pescoço com relação às características demográficas e clínicas dos pacientes, achados histopatológicos, imunohistoquímicos, moleculares, tratamento, acompanhamento e taxa de sobrevivência. Foi realizada uma busca eletrônica em quatro bancos de dados. Foram incluídos artigos que descreviam relatos de casos ou séries de casos. Os resultados foram avaliados pelo método de Kaplan-Meier juntamente com a regressão de Cox. A busca resultou em 186 estudos que descreviam 227 casos de ES. A idade média foi de 22,7 anos, e os homens foram ligeiramente mais afetados. Mais da metade dos casos foram diagnosticados até os 20 anos. O trato respiratório foi o local mais relatado, seguido pelos ossos maxilares. Clinicamente, foram descritos aumento de volume ou nódulos sintomáticos, com duração média de quatro meses. O manejo envolveu regimes de tratamento multimodal. Recorrência local, metástase linfonodal e à distância foram observadas em 10,7%, 12,6% e 20,3% dos casos, respectivamente. A análise estatística revelou que os pacientes mais velhos com metástase a distância tiveram uma taxa de sobrevida global menor ($p<0,05$). Este estudo forneceu uma visão geral do ES de cabeça e pescoço que pode auxiliar os patologistas, clínicos, estomatologistas, no diagnóstico e ampliar o conhecimento de cirurgiões e oncologistas sobre essa condição. **No Artigo 2,** o objetivo foi realizar um levantamento retrospectivo dos sarcomas na área de cabeça e pescoço em crianças e adolescentes (SCPCA) diagnosticados em um período de 22 anos

em um centro de referência do sul do Brasil, bem como avaliar suas características clínico demográficas, tratamento e fatores prognósticos. Os casos diagnosticados como SCP entre 2000 e 2022 foram coletados retrospectivamente. Os registros médicos foram examinados para extrair informações demográficas, clínicas, patológicas e de acompanhamento. Foram diagnosticados 268 casos de SCP sendo que 65 (24,2%) eram SCPCA. Desses 65 pacientes, 38 (58,5%) tiveram o diagnóstico de rabdomiossarcoma, 14 (21,5%) de sarcoma de Ewing, 06 (9,2%) de osteossarcoma, 04 (6,2%) fibrossarcoma, 02 (3,1%) condrossarcoma, 01 (1,5%) sarcoma sinovial. Quanto ao gênero, 37 (56,9%) eram feminino, a média de idade foi de 8,23 anos (±5,97), o principal sítio anatômico foi a região orbitária acometendo 11 pacientes (16,9%) seguida por 10 casos (15,5%) de múltiplos locais de envolvimento e 7 casos (10,8%) no cérebro. 90% dos pacientes apresentavam sintomatologia e 84,8% apresentavam aumento de volume relatando uma média de 3,25 meses de evolução. O tratamento de escolha foi principalmente multimodal envolvendo quimioterapia e radioterapia na maior parte dos casos. No acompanhamento foi observado que 87,5% não apresentaram metástase, 66,7% não tiveram recorrência e 82,9% estavam vivos. A probabilidade de sobrevivência em 7 meses foi de 94,1% e em 28 meses foi de 72,7%. O rabdomiossarcoma foi o único sarcoma que apresentou metástase e que demonstrou pior prognóstico quando afetou adolescente. Em conclusão, o SCPCA é raro e se apresenta como aumento de volume rápido associado à dor. A localização do tumor está relacionada ao subtipo do tumor. O RMS foi o tumor mais frequente, afeta mais a órbita e os adolescentes tiveram pior prognóstico do que as crianças. Mesmo raro, é importante que médicos e dentistas conheçam as principais características do SCPCA para promover o diagnóstico precoce e o tratamento ideal para esses pacientes, a fim de aumentar as taxas de sobrevida.

Palavras-chave: Sarcomas, Neoplasias Malignas, Cabeça e Pescoço, Pediatria

ABSTRACT

SPIGUEL, MONICA HERMANN. **HEAD AND NECK SARCOMA - CLINICODEMOGRAPHIC PROFILE OF A PEDIATRIC POPULATION IN A REFERENCE CENTER IN SOUTHERN BRAZIL AND SYSTEMATIC REVIEW OF THE LITERATURE.** Thesis (Post-graduation in Dentistry with emphasis in Clinical Dentistry, Stomatology) - School of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, 2023.

Sarcomas are a specific and heterogeneous group of malignant neoplasms that originate from mesenchymal progenitor cells. In the head and neck region, sarcomas are rare and represent 1% of all malignant neoplasms. Few studies evaluate the profile of sarcomas in this region and in children and adolescents. Therefore, the aim of Article 1 of the present study was to perform a systematic review of the literature on Ewing's sarcoma (ES) of the head and neck with regard to the demographic and clinical characteristics of patients, histopathological findings, treatment, follow-up and survival rate. An electronic search of four databases was performed. Articles describing case reports or case series were included. The results were assessed by the Kaplan-Meier method together with Cox regression. The search resulted in 186 studies describing 227 cases of ES. The mean age was 22.7 years, and males were slightly more affected. More than half of the cases were diagnosed by the age of 20 years. The respiratory tract was the most reported site, followed by the maxillary bones. Clinically, symptomatic swellings or nodules were described, with an average duration of four months. Management involved multimodal treatment regimens. Local recurrence, lymph node and distant metastasis were observed in 10.7%, 12.6% and 20.3% of cases, respectively. Statistical analysis revealed that older patients with distant metastasis had a lower overall survival rate ($p<0.05$). This study provided an overview of head and neck ES that may assist oral and maxillofacial pathologists in diagnosis and broaden the knowledge of surgeons and oncologists about this condition. In **Article 2**, the aim was to perform a retrospective survey of head and neck sarcomas (SCP) in children and adolescents diagnosed over a 22-year period in an important referral center for malignant tumors in southern Brazil, as well as to evaluate their demographic and clinicopathological characteristics, treatment and prognostic factors. Cases diagnosed as HNS between 2000 and 2022 were retrospectively collected.

Medical records were examined to extract demographic, clinical, pathological and follow-up information. A total of 268 cases of HNS were diagnosed, and 65 (24.2%) were in children and adolescents. Of these 65 cases, rhabdomyosarcoma affected 38 (58.5%) of them, Ewing's sarcoma affected 14 (21.5%), and osteosarcoma affected 6 (9.2%). The mean age was 8.23 years (5.97), with 37 (56.9%) of the participants being female. The region of the orbit was the primary anatomical site. 11 occasions (16.9%), followed by 10 cases (15.5%) with numerous sites of involvement, 7 cases (10.8%) in the brain. Clinically, 90% of the patients were symptomatic and 84.8% presented with volume increase reporting a mean of 3.25 months of evolution. The treatment of choice was multimodal involving chemotherapy and radiotherapy in most cases. At follow-up was observed that 87.5% had no metastasis, 66.7% had no recurrence and 82.9% were alive. The probability of survival at 7 months was 94.1% and at 28 months 72.7%. RMS was the only sarcoma that metastasized and showed worse prognosis when affecting adolescents. In conclusion, HNS in children and adolescents are rare lesions that promote rapid volume increase in face associated to symptomatology. Although of malignant characteristics, patients have been demonstrated to benefit from multimodal therapy and high survival rates are observed. In conclusion, HNS in children and adolescents are rare and presented as rapid swelling associated with pain. The location of tumor was related with tumor subtype. RMS was the most frequent tumor, affects more the orbit and adolescents had worse prognosis than youngers. Even rare, it is important that physicians and dentist know the main characteristics of the HNS to promote the early diagnose and the ideal treatment for these patients to increase the survival rates.

Keywords: Sarcoma, Head and Neck Neoplasms, Head and Neck Cancer, Pediatrics, Adolescent

SUMÁRIO

1. INTRODUÇÃO

A incidência de câncer vem crescendo a cada ano no mundo, se estima que no ano de 2020 surgiram 19,3 milhões de novos casos, com cerca de 9,9 milhões de óbitos (SUNG et al., 2021). Dentre todos os tipos de câncer, temos os sarcomas que constituem um grupo específico que tem origem em células progenitoras mesenquimais, sendo um grupo bastante diversificado, que corresponde a cerca de 1% de todos os tumores malignos. Nos EUA, os sarcomas possuem uma incidência de 16.250 casos ao ano, representando cerca de 1% dos casos de tumores malignos (BROWNSTEIN; DELANEY, 2020). Em cabeça e pescoço, os sarcomas representam 4-10% das neoplasias malignas (ALISHAHI et al., 2015).

A etiologia da maioria desses sarcomas permanece obscura. Dentre os fatores conhecidos estão os fatores genéticos, que se dividem em: defeitos simples de cariótipo e defeitos complexos de cariótipo (HUI J.Y.C.2016). Neurofibromatose do tipo I (condição de desordem genética) em alguns casos está associada ao desenvolvimento de rabdomiossarcoma, lipossarcoma e fibrossarcoma na população infantil. Ainda podemos citar desordens como síndrome de Gardner, tríade de Carney, hemocromatose hereditária e síndrome de Werner no desenvolvimento de outros sarcomas (POTTER; STURGIS, 2003). Dentre os fatores ambientais conhecidos podemos citar a radiação, onde o período de latência pode variar de 11 a 13 anos da irradiação até o diagnóstico o sarcoma pleomórfico indiferenciado (previamente chamado de fibrohistiocitoma maligno) é a neoplasia mais comum causada pela radiação (DE BREE et al., 2010).

Os sarcomas podem ser classificados de acordo com o seu tecido de origem, diferenciação celular e localização anatômica (ANDERSEN et al., 2019; O'NEILL; BILSKY; KRAUS, 2013; PACHECO et al., 2011; SCELSI et al., 2019; BROWNSTEIN; DELANEY, 2020; WHO - WORLD HEALTH ORGANIZATION 2020). De todos os sítios anatômicos na região de cabeça e pescoço 80% dos casos acometem tecidos moles, enquanto os de tecido ósseo, cartilagem e de outras origens representam cerca de 20% (PENG; WANG, 2013; STAVRAKAS et al., 2016), os sítios mais frequentes em cabeça e pescoço são cavidade nasal e seios paranasais (22%), ossos maxilares (15,1%), pescoço (14%), órbita (12,9%), escalpo (12,4%), e tecidos moles da face (10,8%) (TAJUDEEN; ST. JOHN, 2015). Na população infantil a ocorrência de sarcomas de cabeça e pescoço (SCP) é equilibrada entre os gêneros, ocorrendo mais frequentemente dos 5 aos 9 anos de idade (PENG; WANG, 2013).

O diagnóstico dos sarcomas é desafiador em função da pouca especificidade dos sintomas clínicos, achados imaginológicos e histológicos (SCELSI et al., 2019). As lesões podem não causar sintomas, sendo descobertas em estágios tardios quando provocam dor, que é presente em 7%, aumento de volume local e/ou assimetria facial em cerca de 59,9% dos casos. Outros sintomas relatados são: obstrução nasal (11%), hipoestesia (8%), alteração na visão (8%) e dor de cabeça (8%) (BENTZ et al., 2004; GORSKY; EPSTEIN, 2000; TAJUDEEN; ST. JOHN, 2015).

Exames de imagem como tomografia, ressonância magnética e PET-CT são importantes aliados no diagnóstico, localização do tumor e principalmente no estadiamento clínico da doença (BENTZ et al., 2004; HUI, 2016). Uma característica clínica particular de SCP é que grande parte dos tumores são N0

no momento do diagnóstico (PARK et al., 2015; SALCEDO-HERNÁNDEZ et al., 2014; SHUMAN et al., 2015). Salcedo-Hernándes et al, (2014) relatam uma taxa de 82,4 % em sua série de casos, taxa semelhante ao encontrado por Mucke et al, (2010) 85,1% e Smith et al, (2012) 83,0% (MÜCKE et al., 2010; SALCEDO HERNÁNDEZ et al., 2014; SMITH; OVERTON; LENTSCH, 2012). Em contrapartida, metástases a distância são mais comuns, Salcedo-Hernandez et al, (2014) reportaram uma taxa de 82,4%, em contrapartida, Bentz et al, (2004) apresentaram uma taxa de 33%. Pulmão e ossos são os sítios mais comumente afetados (BENTZ et al., 2004; SALCEDO-HERNÁNDEZ et al., 2014).

O diagnóstico dos sarcomas usualmente envolve a avaliação clínica e exames de imagem como mencionado acima, seguido de biópsia incisional e avaliação morfológica da peça (SBARAGLIA; DEI TOS, 2019). Os subtipos histológicos mais comuns em cabeça e pescoço na população pediátrica são: rabdomiossarcoma, fibrohistiocitoma maligno (atualmente denominado sarcoma pleomórfico indiferenciado), osteossarcoma e sarcoma de Ewing (PENG; WANG, 2013). A análise imuno-histoquímica é fundamental para determinar o subtipo da neoplasia, podendo ser empregado um amplo painel que vai depender das características morfológicas para classificar adequadamente o tumor (BENTZ et al., 2004; HUI, 2016; SBARAGLIA; DEI TOS, 2019; SCELSI et al., 2019). Além da análise morfológica e imuno-histoquímica, a hibridização *in situ* é utilizada para identificar alterações genéticas que estão associadas à algumas neoplasias oportunizando o diagnóstico definitivo, como por exemplo o gene *EWSR-1*, associado ao sarcoma de Ewing, bem como para determinar fatores prognósticos (DE BREE et al., 2010; WHO - WORLD HEALTH ORGANIZATION, 2020).

Por ser um grupo raro e muito diverso é difícil estabelecer protocolos de tratamento ideais (CUNHA et al., 2023). O tratamento de escolha leva em consideração o tipo e estadiamento do tumor. Para o SCP, esse estadiamento é baseado na classificação da *AJCC* TNM *8th Edition*, que consiste em: tumor primário (T), linfonodos regionais (N) e presença ou ausência de metástases a distância (KALAVREZOS; SINHA, 2020).

Embora potencialmente mutilador na maioria dos casos, o tratamento cirúrgico é o mais utilizado por proporcionar um controle clínico efetivo da doença enquanto quimioterapia e/ou radioterapia podem ser empregadas como tratamentos adjuvantes. Quimioterapia associada a radioterapia sem cirurgia, quimioterapia exclusiva e radioterapia exclusiva também são utilizados variando de acordo com o subtipo da doença, sítio anatômico e estadiamento, assim como resposta da mesma ao tratamento (BENTZ et al., 2004; SCELSI et al., 2019; STAVRAKAS et al., 2016). Segundo (CUNHA et al., 2023) a radioterapia quando combinada com a cirurgia não parece melhorar o prognóstico geral em EWS, CS e OS, mas a quimioterapia tem um papel maior a desempenhar nesses tumores agressivos.

A quimioterapia é reservada para os tumores não-rabdomiossarcoma, a primeira linha de tratamento inclui: ifosfamida com doxorrubicina, embora se utilize ciclos alternados de vincristina, doxorrubicina e ciclofosfamida com ifosfamida e etoposideo que são utilizados tradicionalmente para sarcomas de Ewing. Várias combinações são utilizadas em casos de recaída (ou recidiva, recorrência) ou casos refratários, incluindo altas doses de: ciclofosfamida e topotecano, irinotecano e temozolomida; outras combinações possíveis são: ciclofosfamida com vinorelbina, e gencitabina com docetaxel (RASHID et al., 2021).

A sobrevida dos pacientes com SCP depende de uma série de fatores como idade do paciente, tamanho do tumor, presença de metástase, grau de diferenciação, recorrência e tipo de tratamento. Nesse sentido, a literatura demonstra que a sobrevida em cinco anos é menor em paciente com tumores maiores que 10 centímetros, com metástase cervical, com G III de diferenciação recorrência local e pacientes na sexta década de vida (BENTZ et al., 2004; CHANG et al., 2014; PARK et al., 2015). Assim como a maioria das neoplasias que afetam a região, a ausência de metástase em linfonodos cervicais aumenta consideravelmente a sobrevida em cinco anos (VAN DAMME et al., 2010; ZAGARS et al., 2003). Van Damme et al, (2010) relata em seu estudo de coorte que o fator de prognóstico mais importante é a ressecção local da lesão com margens livres, proporcionando o controle local da doença e consequente maior sobrevida aos pacientes (VAN DAMME et al., 2010). A sobrevida geral dos pacientes é favorável, sendo reportadas taxas 49% a 81% (DE BREE et al., 2010; VAN DAMME et al., 2010; MATTAVELLI et al., 2013; TAJUDEEN; ST. JOHN, 2015). É descrito para a população pediátrica com SCP uma taxa de 71% em 10 anos (PENG; WANG, 2013).

Um estudo publicado recentemente estabelece uma associação entre terapia multimodal locorregional do câncer (cirurgia ou radioterapia, ou ambos) e aumento da intervenção cirúrgica tardia em sobreviventes de câncer infantil pediátrico. Este aumento é potencialmente devido a um aumento do número de sobreviventes com doença de alto risco que se submeteram a intensa terapia multimodal, incluindo radiação locorregional e cirurgia complexa em no caso de malignidades do SNC, neuroblastoma e sarcoma de tecidos moles, e o aumento da implementação de procedimentos de preservação de membros para terapia

primária em vez de amputação em sobreviventes de sarcomas ósseos como o osteossarcoma. Portanto, este estudo elucida que o aumento de novas intervenções cirúrgicas, o aumento de tratamento nas condições crônicas de saúde, o desenvolvimento de condições agudas, (uma fratura tardia ou falha protética em um sobrevivente submetidos a cirurgia conservadora), ou ressecção do tumor para recidiva tardia em um sobrevivente, vem de um aumento da sobrevida em função dos novos tratamentos quimioterápicos, o que apesar de positivo traz a necessidade de um novo entendimento quanto ao efeito tardio crônico do câncer pediátrico e portanto um cuidado maior no acompanhamento clínico desses pacientes. Portanto, a possibilidade de novasintervenções cirúrgicas tardias devem ser informadas aos pais e cuidadores de pacientes pediátricos com câncer. No câncer infantil os sobreviventes devem ter acompanhamento clínico de longo prazo (vitalício) para tratamento e prevenção de sequelas, aconselhamento genético, que possam antecipar e tratar precocemente o curso da doença (DIEFFENBACH et al., 2023).

A incidência de tumores malignos na população infanto juvenil é baixa, porém o câncer é a principal causa de morte por doença entre crianças e adolescentes de 1 a 19 anos (GATTA et al., 2005; KAATSCH, 2010; RABINOWICZ et al., 2013). No Brasil, segundo o Instituto Nacional do Câncer (INCA), estima-se que ocorram 8.460 novos casos de neoplasias malignas por ano nessa faixa etária. Os mais frequentes são leucemia, lesões de sistema nervoso central, linfomas e tumores sólidos, como neuroblastoma e sarcomas (CUNHA et al., 2023).

No estudo realizado por Cunha et al. (2023) foi observado que apesar da raridade das neoplasias malignas orais e maxilofaciais em crianças

os sarcomas são os mais prevalentes. Dentre eles os que mais ocorrem nessa faixa etária de tecidos moles são rabdomiossarcoma, sarcoma de Ewing e osteossarcoma.

Rabdomiossarcoma

O rabdomiossarcoma (RMS) é o sarcoma mais comum de tecidos moles em crianças, e representa 4,5% de todas as malignidades pediátricas. Embora a maioria dos RMS surjam esporadicamente, RMS pode se desenvolver como resultado de Síndrome de Li-Fraumeni (mutações da proteína tumoral p53), Síndrome de Beckwith-Wiedemann (defeitos 11p15), von Doença de Recklinghausen (mutações neurofibromatose tipo 1), síndrome cardiofaciocutânea (mutações B-Raf) e síndrome de Noonan [sarcoma de rato (RAS)/mutações da via de sinalização da proteína quinase ativada por mitógeno). Os RMS ocorrem predominantemente na primeira década de vida, e ocorre um pouco mais frequentemente em homens do que nas mulheres, mas não há tal diferença no RMS que origina-se na região da cabeça e pescoço (MORETTI et al., 2010; TURNER J.H.; RICHMON J.D. 2011). Aproximadamente 35% de todos os RMS se desenvolvem na região da cabeça e pescoço. Destes, aproximadamente 44% são localizados na região parameníngea (PM-RMS), que inclui a cavidade nasal, nasofaringe, seios paranasais, ouvido médio, fossa infratemporal e pterigopalatina, enquanto 25,6% dos casos na cabeça e pescoço ocorrem na região orbital (TURNER J.H.; RICHMON J.D. 2011). O RMS é um tumor quimio e radiossensível complexo que requer cuidados multidisciplinares. Por causa da raridade, todos os pacientes com RMS devem ser colocados em

Terapia baseada em protocolo. O protocolo determina o tempo de quimioterapia, radioterapia e cirurgia. Se excisão cirúrgica completa é necessária antes do início da quimioterapia ou após deve ser determinada por um cirurgião oncologista com experiência no tratamento de sarcomas. A necessidade de radioterapia adjuvante é baseada no local do tumor primário e a integridade da excisão cirúrgica (HAYES-JORDAN et al., 2009). No entanto, os efeitos tardios entre os sobreviventes são preocupantes.

Aproximadamente metade dos sobreviventes dos sarcomas infantis têm pelo menos um desfecho adverso importante em seu estado de saúde, ilustrando a necessidade de desenvolver produtos menos tóxicos dos tratamentos que ainda são eficazes (STEVENS et al., 2005; PUNYKO et al., 2005). Devido a complexidade anatômica da região, ressecções com margens oncológicas livres e amplas são praticamente impossíveis na região de cabeça e pescoço. Portanto, a ressecção radical pode não ser o tratamento inicial de escolha. De acordo com as diretrizes do International Soft Tissue Sarcoma Database Consortium a quimiorradiação baseada em VAC continua sendo a modalidade preferida de tratamento inicial para PM-RMS, com cirurgia limitada à biópsia inicial para estabelecer o diagnóstico (CASEY et al. 2022). Se a ressecção cirúrgica for considerada, menores tumores (<5 cm, aqueles sem envolvimento dural) parecem ser mais passíveis de ressecção em relação a tumores maiores (DAYA et al.,2000). Esses tumores são geralmente ressecados através de uma abordagem transfacial ou crânio-orbitozigomática, o que pode necessitar de técnicas de reconstrução complexas após a ressecção do tumor. (KOBAYASHI et al. 2018). De acordo com Moretti et al, 2010, o tratamento multimodal é o mais preconizado. No seu levantamento com 24 casos, todos os pacientes realizaram quimioterapia (QT), 62,5% deles

também realizaram radioterapia (RT) e 16,67% foram submetidos à cirurgia. Destes, 8 (33,3%) morreram, 6 (25%) foram encontrados livres de neoplasia e 2 (8,3%) tiveram recidiva tumoral.

Sarcomas de Ewing

Os tumores da Família de Ewing (TFSE) compreendem o sarcoma de Ewing, o tumor de Ewing extra-osseo, e o tumor neuroectodérmico primitivo periférico. São tumores que atingem tanto tecidos ósseos quanto tecidos moles. Um estudo de revisão sistemática sobre sarcoma de Ewing em cabeça e pescoço realizado por Spiguel et al (2023) mostrou que a localização mais frequente foi o trato respiratório, seguido dos maxilares e dos ossos do crânio. O sexo masculino foi ligeiramente mais atingido, e 60% dos casos ocorreu nas primeiras duas décadas de vida. Clinicamente, 78,2% das lesões manifestaram-se como edema ou nódulos. Dos 210 dos casos que forneceram informações sobre os sintomas dos pacientes, assimetria/edema foi relatado em 59% dos indivíduos, seguido de dor em 21,4%, congestão nasal em 17,6% diplopia/perda da acuidade visual em 16,6% e cefaléia em 11,9%.

Devido à raridade da doença, a maioria dos estudos de sarcoma de Ewing no cabeça e pescoço são retrospectivos. Mesmo na região da cabeça e pescoço, a ressecção completa deve sempre ser tentada; no entanto, ressecção completa é difícil de conseguir nas regiões de cabeça e pescoço sem defeitos cosméticos ou funcionais significativos, e a radiação é quase sempre necessária A quimiorradiação baseada em agentes alquilantes pode ser uma alternativa razoável à cirurgia para tratar tumores que requerem um

um grau inaceitável de morbidade pós-ressecção (DAW et al, 2000, GRADONI et al 2010).

Osteossarcoma

Os osteossarcomas representam aproximadamente ≤1% de todos os casos de câncer da cabeça e pescoço. A grande maioria ocorre na mandíbula e maxilar (MENDENHALL et al., 2011). Osteossarcomas de cabeça e pescoço apresentam e se comportam de maneira diferente dos osteossarcomas de ossos longos mais comuns. Portanto, é controverso tratar com base em evidências de diferentes regiões (KHADEMBASCHI et al., 2022). Ao contrário à boa resposta histológica à quimioterapia esperada em 50% dos pacientes com osteossarcomas de extremidades, a proporção de boas respostas histológicas foi muito inferior, relatada em 35% (GRANOWSKI-LECORNU et al., 2011) e 0% dos pacientes com osteossarcomas de cabeça e pescoço (HUH et al.,2012), muito em função da dificuldade de abordagem cirúrgica. Em vários estudos retrospectivos nenhum benefício significativo na pela quimioterapia neoadjuvante (THARIAT et al., 2013). Esses achados sugerem que a eficácia da quimioterapia neoadjuvante nos osteossarcomas de cabeça e pescoço é inferior ao de osteossarcomas de ossos longos (KHADEMBASCHI et al. 2022). Kobayashi et al, 2023 analisaram 18 artigos de 264 artigos publicados entre 1940 e 2019 que eram estudos retrospectivos de cinco ou mais casos, e apenas três artigos relataram impacto positivo da quimioterapia neoadjuvante na sobrevida. A partir destes artigos, 222 pacientes foram comparados por aqueles que fizeram cirurgia com aqueles que fizeram quimioterapia neoadjuvante e cirurgia, e não houve diferença estatística na sobrevida

doença-específica (P = 0,26). Além disso, mesmo quando restrito a pacientes com nível intermediário ou histologia de alto grau, o uso de quimioterapia neoadjuvante não fez diferença na sobrevida(P = 0,37). No entanto, a maioria dos dados analisados eram de estudos retrospectivos com tamanho de amostra relativamente pequeno. Dado a raridade desta doença e a dificuldade na realização ensaios controlados, é imperativo acumular evidências por meio de estudos observacionais multicêntricos

Cunha et al (2023) investigaram também a capacidade de diagnóstico destas lesões pelos cirurgiões-dentistas e observaram que a hipótese diagnóstica sobre a natureza da lesão foi correta em apenas 41% dos casos, o que indica falta de preparo dos cirurgiões-dentistas para o tema, e a necessidade de reforçar a importância dos levantamentos epidemiológicos sobre neoplasias malignas para determinar a prevalência de lesões e características clínico-demográficas da população afetada. O conhecimento de neoplasias que acometem crianças e adolescentes pode ajudar os profissionais pediátricos a identificar essas lesões, auxiliando em um processo diagnóstico mais rápido e correto.

2 OBJETIVOS

2.1 Artigo 1

2.1.1 Objetivo geral

Realizar uma revisão sistemática da literatura de estudos de casos clínicos de sarcoma de Ewing de cabeça e pescoço.

2.1.2 Objetivos específicos

Correlacionar os dados clínico demográficos com achados histopatológicos, tratamento, acompanhamento e taxa de sobrevida.

2.2 Artigo 2

2.2.1 Objetivo geral:

Realizar um levantamento retrospectivo dos sarcomas na região de cabeça e pescoço em crianças e adolescentes diagnosticados em um período de 22 anos em um importante centro de referência do sul do Brasil, bem como avaliar suas características demográficas e clínico-patológicas, tratamento e fatores prognósticos.

2.2.2 Objetivos específicos:

Avaliar a prevalência dos sarcomas em crianças e adolescentes dentro dos casos de sarcomas diagnosticados em região de cabeça e pescoço no período do estudo.

Avaliar as características clínico demográficas, tratamento e de acompanhamento dos sarcomas de cabeça e pescoço em crianças e adolescentes.

Avaliar a associação das variáveis clínico demográficas com o prognóstico dos sarcomas de cabeça e pescoço em crianças e adolescentes (desfecho e tempo de sobrevida).

3.1 ARTIGOS CIENTÍFICOS

Artigo 1. O presente artigo científico foi publicado no periódico Oral Diseases, 2023. Fator de impacto 4.068 e Qualis Capes A1

Ewing's sarcoma of the head and neck: a systematic review

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Abstract

Objective: The aim of the present study was to conduct a systematic review of head and neck Ewing sarcoma (ES) concerning patients' demographic and clinical features, histopathological findings, treatment, follow-up, and survival rate. **Material and methods**: An electronic search was undertaken in four databases. Articles describing case reports or case series were included. Outcomes were evaluated by the Kaplan–Meier method along with Cox regression.

Results: The search yielded 186 studies describing 227 ES cases. The mean age was 22.7 years, and males were slightly more affected. Interestingly, more than half the cases were diagnosed up to 20 years. The respiratory tract was the most reported site, followed by the jawbones. Clinically, symptomatic swelling or nodules were described, with a mean duration of four months. Management involved multimodal treatment regimens. Local recurrence, lymph node and distant metastasis were observed in 10.7%, 12.6%, and 20.3% of cases, respectively. Statistical analysis revealed that older patients with distant metastasis had a lower overall survival rate ($p<.05$).

Conclusion: This study provides an overall view of head and neck ES that can assist oral and maxillofacial pathologists with the diagnosis and extend the knowledge of surgeons and oncologists about this condition.

Keywords: Sarcoma, Ewing Sarcoma, Head and Neck Neoplasms, Head and Neck Cancer, Pediatrics

1 Introduction

Ewing's sarcoma (ES) is a small round-cell tumor typically arising in the bones, and only rarely affecting soft tissues (Fletcher, Bridge, Hogendoorn, & Mertens, 2013). It was originally described in 1921 by James Ewing in the radius of a 14-year-old girl as an endothelioma (Ewing, 1972). Clinical presentation is usually dominated by a bone mass with local pain. Cases are mainly diagnosed in the second decade of life, and occurrences are rare in individuals over the age of 30 years and under the age of five years (Gaspar et al., 2015; Gargallo et al., 2020). Globally, the incidence of ES is approximately 1.5 cases per million children, adolescents, and young adults (Grünewald et al., 2018).

Over the past decade, it has become clear that ES derives from a primitive neuroectodermal cell with variable differentiation (Kilpatrick, Reith & Rubin, 2018). The tumor is characterized in most cases by recurrent balanced translocations between the *EWSR1* gene on chromosome 22 and genes belonging to the ETS family of transcription factors (Pappo & Dirksen, 2018). In fact, ES is genetically well characterized. Its main driver is the reciprocal translocation between the *EWSR1* and *FLI1* genes (*EWSR1*:*FLI1*). ES with extensive neuroectodermal differentiation was formerly called primitive neuroectodermal tumor (PNET). Both share the same histochemical staining profile and recent studies have revealed that the pathognomonic translocations involving the FET family of genes (usually *EWSR1)* on chromosome 22 and a member of the ETS family of transcription factors, which is most commonly the *FLI1* gene on chromosome 11, are implicated in more than 95% of ES, PNET and Askin's tumor (Grevener et al., 2016). Therefore, these lesions are now regarded as a single entity, dubbed the Ewing sarcoma family of tumors. Several molecular techniques for the detection of FET/ETS fusions are widely used to confirm the diagnosis.

Primary ES arising in the head and neck region is extremely rare, comprising 1-9% of all cases of the disease (Whaleyet al. 2010; Tudor-Green, Fonseca, Gomez, & Brennan, 2017; Tudor Green, Gomez, & Brennan, 2017; Yanzon et al. 2021). To the best of our knowledge, no systematic review summarizing data about this condition has been conducted in the literature thus

far. In this sense, the aim of the present study was to review the cases of ES in the head and neck region in order to better understand this entity concerning its clinicodemographic aspects, histopathological profile, treatment, follow-up, and survival rate.

2 Material and Methods

2.1 Information sources and search strategies

Electronic searches without publication date restriction were undertaken in September 2020 (and update in February 2022) in the following databases: PubMed (National Library of Medicine), Web of Science (Thomson Reuters), Scopus (Elsevier), and Embase (Elsevier). The search strategy is detailed in **Supplementary Table 1**. Hand searches were also conducted by cross-checking the reference lists of the included articles in order to identify publications that might have been missed during the searches in the electronic databases. Duplicates were removed upon identification.

2.2 Eligibility criteria

Our study was based on the acronym PEOS, where P (participants) referred to people with ES of the head and neck, E (exposition) indicated to ES, O (outcomes) alluded to clinicopathological findings, and S (study type) referred to case reports and case series.

Inclusion criteria were articles describing case reports or case series of ES with enough clinical, radiological, and histopathological information to confirm the diagnosis. Moreover, to confirm the histogenesis of the tumor we included cases that were positive for at least one ES immunohistochemical marker (i.e., CD99, FLI1, NKX2.2) and/or one molecular translocation described for this tumor.

Exclusion criteria were: letters to the editor, conference abstracts, and review articles. Moreover, a language other than English, and non-head and neck cases were excluded. *2.3 Study selection*

Titles/abstracts of all references retrieved through the electronic searches were read independently by four review authors (B.S., J.T., L.S.K., and M.H.S.) If the title/abstract met the

eligibility criteria, the article was included. The full text of the articles with titles/abstracts providing insufficient information for a clear decision was obtained. The references that met the eligibility criteria were included after the full text assessment. Disagreements between the authors were solved upon discussion with an experienced oral and maxillofacial pathologist (M.D.M.).

2.4 Data collection

The same four authors extracted all data from the included studies. For each study, the following data were extracted: (1) author's name, year, and country of publication; (2) patient's age and sex; (3) anatomical site; (4) clinical appearance of the lesion; (5) symptomatology; (6) time to diagnosis, reported by the patient - in months; (7) imaginological features – according to type of exam; (8) size of the lesion; (9) histopathological characteristics; (10) immunohistochemical expression; (12) molecular results; (13) treatment; (14) regional or distant metastasis; (15) recurrence – during the follow-up; and (16) survival status – alive or death.

2.5 Critical appraisal

The quality of the included articles was assessed using The Joanna Briggs Institute (University of Adelaide) tools for case reports or case series (Gagnier et al. 2013). Two authors (L.S.K. and M.H.S.) analyzed the studies according to the following parameters: a clear description of the patient's demographic characteristics, medical history, current clinical condition, a clear description of the propaedeutics, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report (i.e., clinical and/or radiographic documentation with representative images). For each parameter, the included article could be awarded a "yes", "no", "unclear", or "not applicable" comment. A third author (M.D.M.) solved the disagreements.

2.6 Data analysis

All the extracted data were tabulated on Microsoft Office Excel 2019 (Microsoft® software, Redmond, WA, USA) and analyzed descriptively. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Mac, version 27.0 (IBM

Corporation), and Kaplan-Meier survival curves were constructed based on the information collected. The survival curves were compared using the Log-rank test. Cox Regression Univariable tests were also performed to determine the Hazard Ratio (HR) alongside its 95% confidence interval. A p-value <0.05 was considered statistically significant.

2.7 Other information

This systematic review of case reports and case series of ES was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Page et al., 2021). A protocol was drafted, and registration was carried out at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42021232082.

3 Results

3.1 Study selection

The electronic quest screened a total of 1,684 references. After removing 794 duplicates, inclusion and exclusion criteria were applied and 108 studies were selected. Next, 78 studies were added manually after a hand search. A total of 186 articles for a total of 227 ES cases published between 1980 and 2021 were included. A flowchart shows the results of the search process in detail (**Supplementary Figure 1**).

3.2 Critical appraisal

The critical appraisal of the studies is presented in **Supplementary Table 2 and Supplementary Table 3**. The risk of bias was categorized as High when the study reached up to a 49% “yes” score, Moderate when the study reached a 50% to 69% “yes” score, and Low when the study reached more than a 70% “yes” score. One-hundred-and-seventy-three (93.0%) studies showed a low risk of bias, 12 (6.4%) showed a moderate risk and only 1 (0.5%) showed a high risk of bias.

3.3 Data analysis

Table 1 summarizes the data of the ES cases and **Supplementary Table 4** shows all the information in detail. The 186 articles were published in 36 different countries on four continents, as follows: Asia (n=96), America (n=52), Europe (n=35), and Oceania (n=3). Of the informed cases, males (n=129/56.8%) were more affected with a mean age at diagnosis of 22.7 (±18.5) years, ranging from birth to 77 years. A total of 138 (60.8%) cases were diagnosed up to 20 years of age (**Table 1**).

3.3.1 Anatomical location, clinical presentation, symptoms, and duration Regarding the anatomical site, the respiratory tract was the most affected site (n=59/25.9%), followed by the jawbones (n=44/19.3%) and the cranial bones (n=42/18.5%). **Figure 1** illustrates the distribution of ES according to the head and neck sites. The clinical characteristics of the published cases are summarized in **Table 1**. Clinically, the lesions manifested as swelling or nodules in most cases (n=140/78.2%), with hard/firm (n=37/74.0%) consistency and a smooth surface (n=10/47.6%). In total, 210 of the cases gave information regarding patients' symptoms. Asymmetry/edema was reported in 124 (59.0%) individuals, followed by pain in 45 (21.4%), nasal congestion in 37 (17.6%), diplopia/loss of visual acuity in 35 (16.6%), and headache in 25 (11.9%).

The mean time of evolution was 115.6 (±170.6) days, ranging from 2 to 1460 days. Tumor dimensions were reported in 151 cases and the largest diameter described for each lesion was considered. Size ranged from 0.8 cm to 15.3 cm, with an average size of 5.1 cm (±2.44) (**Table 1**).

3.3.2 Imaginological features

The total number of exams requested was 289, with imaging exams mentioned in 204 cases. Computed tomography (n=149/73.0%) was performed more frequently, followed by magnetic resonance (n=94/46.0%) and radiography (n=19/9.3%). Ultrasound (n=13/6.3%), videolaparoscopy (n=8/3.9%), positron emission tomography (PET) scan (n=5/2.4%) and bone scintigraphy (n=1/0.5%) were also reported.

The radiological features were reported in 74 imaging exams; 15 (20.3%) cases presented as radiolucent/hypodense images, 14 (18.9%) as radiopaque/hyperdense images, and 45 (60.8%) as mixed images. The lesion was considered well-defined in 18 of 32 reports that provided this information. Bone and adjacent structure involvement was reported in more than 70% of informed cases.

3.3.3 Histopathological features

In general, most of the authors included in this systematic review described the general histological findings under low magnification a proliferation of neoplastic cells in a sheet-like growth pattern or forming nests separated by connective tissue. Other growth patterns described included cords and lobules. Higher magnification analysis revealed that the individual cells had a uniform small and round morphology, with scant eosinophilic or pale cytoplasm. A few authors mentioned about indistinct membranes. The nuclei were generally described as hyperchromatic with prominent nucleolus. Some authors reported neuroectodermal differentiation findings such as pseudorosettes and true neural rosettes. The term "rosette" is used as these structures present a radial arrangement of cells like that of rose petals. Pseudorosettes present this radial arrangement associated with a dense feltwork of interwoven cytoplasmic processes in the center, while in true neural rosettes the cells surround a central lumen containing small cytoplasmic extensions. Besides these specific ES-related findings, authors described other general microscopic features such as presence of mitosis and necrosis. **Table 2** summarize the histopathological features.

3.3.4 Immunohistochemistry and Molecular Analysis

Of the 227 head and neck ES cases included in this systematic review, 220 (96.9%) had been submitted to immunohistochemical studies for diagnostic purposes. **Supplementary Table 5** displays the antibodies most frequently used according to their positive or negative immune expression, without considering the pattern, intensity, or localization of immune staining. The immunomarkers most frequently used were CD99 (209 cases/100%), and neuron-specific enolase (NSE) (52 cases/73.2%).

Molecular tests were performed in 97 cases (42.7%) (**Supplementary Table 6**). Polymerase chain reaction (PCR) and fluorescence *in situ* hybridization (FISH) were the molecular tools most used. The most frequent results observed were the presence of EWSR1 gene rearrangement detected by FISH (62 positive cases) and EWS-FLI1 fusion detected by PCR (30 positive cases).

3.3.5 Treatment, metastasis, follow-up, recurrence, and status

Treatment was described in 212 cases. Surgery with chemotherapy and radiotherapy (n=78/36.7%) was the most common treatment performed, followed by chemotherapy and radiotherapy (n=55/25.9%) and surgery with chemotherapy (n=37/17.4%) (**Table 3**). Most chemotherapy schemes appeared to derive from the EURO – EWING protocol: vincristine, actinomycin D, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Other drugs were reported but at low frequency, such as cisplatin, carboplatin, paclitaxel, dactinomycin, bleomycin, busulfan, and melphalan. The radiotherapy doses most frequently employed ranged from 36 to 60 Gy.

Local recurrence was identified in 16 (10.7%) of 150 patients. Lymph node and distant metastasis occurred in 14 cases (12.6%) and 30 cases (20.3%), respectively. The most common metastatic sites were lungs (8 cases, 26.6%), brain (5 cases, 16.6%), and mediastinum (5 cases, 16.6%).

Mean follow-up was 27.5 (± 35.2) months. Of the 227 cases described, 159 reported survival status, and 81.1% (n=129) of the patients were alive. Based on Kaplan-Meier analysis, the estimated cumulative proportions of 2-year and 5-year survival were 0.83 (standard error 0.03) and 0.71 (standard error 0.05), respectively. The overall survival curve (**Figure 2A**) revealed that all ES-associated deaths reported in the studies reviewed occurred within the first 3 years after diagnosis. After that period all studies reported that patients were alive at follow-up.

3.8 Survival and Prognostic Factor Analysis

Kaplan-Meier curves are presented in **Figure 2** and Cox regression analysis for disease specific survival is presented in **Supplementary Table 7**. Diagnosis within the 51-80-year range

(HR, 2.77, 95% CI 1.05 – 7.32, p=0.03) and the presence of distant metastasis (HR, 8.74, 95% CI 3.35 – 22.77, p<0.01) were significantly associated with shorter survival during follow-up. None of the other factors investigated were significantly associated with survival rates; however, a tendency to a poor prognosis was noted for cases with nodal metastasis and recurrence, as can be seen in the survival curves (**Figure 2**).

4 Discussion

ES is a high-grade primitive small round cell sarcoma with variable neuroectodermal differentiation (El-Naggar, Chan, Grandis, Takata, & Slootweg, 2017). Based on the rarity of ES cases diagnosed in the head and neck, few studies assessing its characteristics are available. In the present systematic review, we summarize 227cases (described in 186 articles) of ES in the head and neck region published between 1980 to 2021. This study brings relevant information about the demographic and clinical features of ES of the head and neck region, as well as the histopathological profile, treatment, follow-up, and survival rate.

It was observed from this literature review that head and neck ES is slightly more common in males, with a male female ratio of 1.3:1. This corroborates with previous case series of head and neck ES, that reports men being more affected compared to women (Grevener, et al. 2016; Torabi et al., 2020. An important finding of this systematic review concerns the age at diagnosis. Sarcomas in the head and neck region are commonly diagnosed in middle-aged adults (Yanzon et al. 2021; Moreira et al. 2020). Alishahi, Kargahi, & Homayouni et al. (2015), for example, observed in their retrospective study that individuals with sarcomas had a mean age of 41 years. The present study identified that head and neck ES mean age at diagnosis was 22.7 years old, which is significantly younger compared to other head and neck sarcomas. As a matter of fact, 60% of the cases in the present survey occurred in children and younger subjects, corroborating with the findings by Torabi and colleagues (2019) – which observed that 50.3% of head and neck ES cases occurred in patients under 18 years of age (Torabi et al. 2020). Little is known about the earlier incidence of ES. Some studies hypothesize a genetic contribution to ES susceptibility Gargallo et al., 2020; Martinelli et al., 2022). However, we believe that more research from a

genetic perspective is therefore required. Knowing the general epidemiological profile of patients is important for clinicians that will be responsible for making the diagnosis. In this sense, awareness of pediatricians and pediatric dentists is a key aspect in regards to ES.

Head and neck ES affected different sites, which were classified / gathered into 16 sites by the authors. Among these, the respiratory tract represented the most affected site, followed by jawbones and cranial bones. Clinical ES manifestations and symptoms directly correlate with the affected site. Clinical signs described included hard/firm swelling or nodules and asymmetry/edema. Symptoms included pain, visual acuity, nasal congestion, and headache. Interestingly, the literature demonstrated that head and neck sarcomas affecting soft tissues are usually painless lesions, whereas pain is the most common symptom in sarcomas that affect the bones (Aljabab, Nason, Kazi, & Pathak, 2011). After clinical examination, imaginological exams are usually recommended to characterize the neoplasia and to understand its relationship with neighboring structures (Olson, Van Abel, Wehrs, Garcia, & Moore, 2018). According to Scelsi et al. (2019), head and neck sarcomas have heterogeneous presentations, often posing a diagnostic challenge to radiographic interpretation. Unfortunately, 23 of 227 cases did not report imaginological exams. When requested, several types of exams are often used. In the present study, 204 cases reported requests for exams, the most frequently used being computed tomography (CT) (73%), followed by MRI and radiography. The imaginological appearance of ES depends on the affected site and is not pathognomonic of ES. Several other lesions mainly of neoplastic origin, such as lymphoma, rhabdomyosarcoma, and synovial sarcoma are a challenge for the differential diagnosis with ES (Huh et al. 2015; Yaprak, Toru, Ozbudak, & Derin, 2019).. In this sense, the investigation of the characteristics of the lesions on imaging exams and their relation to adjacent structures is vital for an adequate evaluation of the case and for planning the biopsy procedure and treatment.

The histopathological exam associated with immunohistochemistry and molecular studies is vital for the final diagnosis. The present data demonstrated the main characteristics of ES that have been previously reported in the literature. ES is composed of a distinctively monomorphic round cell population, showing vesicular nuclei with finely dispersed chromatin,

and scant cytoplasm (Sbaraglia, Righi, Gambarotti, & Dei Tos, 2020). Pseudorosettes (Homer Wright rosettes) and true neural rosettes (Flexner-Wintersteiner rosettes) were demonstrated in some cases included in this systematic review. Muralidhar, Vasugi, & Sundaram (2021) published a retrospective study of 58 ES cases in which small numbers of Homer-Wright pseudorosettes were observed, whereas true neural rosettes were not mentioned by the authors. Similarly, just one out of 50 cases published by Jahanseir et al. (2019) showed rosettes. When Murugan, Rao, Tamboli, Czerniak, & Guo (2018) looked at 23 cases of ES of the kidney, they detected Homer Wright's rosette development in many of them. Mitosis and necrosis were two other components commonly mentioned in the studies included in this systematic review. A wide range of mitotic figures and necrosis in more than half the cases have been described (Murugan, Rao, Tamboli, Czerniak, & Guo, 2018; Jahanseir et al., 2020).

The differential microscopy diagnosis of ES is difficult, and immunohistochemistry may be necessary. Small round cell tumors comprise heterogeneous neoplasms composed of relatively small, round to oval, closely packed undifferentiated cells such as osteomyelitis, rhabdomyosarcoma, poorly differentiated synovial sarcoma, neuroblastoma, and lymphoma (Potratz, Dirksen, Jürgens, & Craft, 2012). However, it is important to highlight that ES is a representative small round cell tumor that expresses CD99 in the membrane, which differentiates it from other small round cell tumors with similar microscopic and/or immunohistochemical features (Bahrami, Truong, & Ro, 2008). In agreement with this, the immunohistochemical findings of the current study showed 100% of cases expressing the adhesion receptor CD99. Nevertheless, CD99 expression is not specific for ES and occurs in a large group of normal tissues and tumor types, including other round cell sarcomas, lymphoblastic lymphoma, and leukemia (Grünewald et al., 2018; Rekhi, Vogel, Basak, Desai, S.B., & Jambhekar, 2014). Primary cutaneous ES was investigated in a systematic review conducted by Delaplace et al. (2012). Immunohistochemical findings revealed that strong membrane staining for CD99, and the negativity of other immunostaining methods established the diagnosis in the cases of 25 of the 26 studies included. For better differentiation, immunohistochemical detection of *FLI1* is more specific for ES than CD99. When the cases have unusual clinical and histopathological features,

the diagnosis of ES can be confirmed only by molecular study. In the present review we identified molecular tests in 97 cases, and the most frequent results were the presence of *EWSR1* gene rearrangement determined by FISH and *EWS-FLI1* fusion determined by PCR. Although molecular tests are ideal, many studies were conducted prior to their availability. The literature points out that molecular and cytogenetic techniques were not usually performed before 2000. Moreover, due to their high costs, these techniques are not available to all ES patients in several services (Delaplace et al., 2012).

The standard management of ES consists of a multimodal treatment regimen including surgical resection and/or local radiotherapy, as well as intensive multi-agent chemotherapy (Pappo, & Dirksen, 2018, Delaplace et al., 2012). The most commonly used chemotherapy schemes identified in the present systematic review seemed to derive from the EURO-EWING protocol. Some prognostic factors have been associated with successful treatment. Jagodzińska Mucha et al. (2021) analyzed 569 patients with ES and showed that the results of treatment were significantly better in children up to 10 years of age. We observed that individuals aged more than 51 years had a poor prognosis than young patients. Moreover, tumor size, primary site, N stage and M stage are independent risk factors affecting the overall survival and cancer-specific survival of ES patients (Zhan et al. 2021).

It is generally accepted that head and neck sarcomas show distinct biological behavior compared to sarcomas at other anatomical sites. These tumors are typically smaller and less often associated with distant metastasis than sarcomas arising at other anatomical sites (Yanzon et al., 2021). The literature shows that metastasis is the most powerful adverse prognostic factor in ES (Delaplace et al., 2012), as confirmed in the current paper. Nodal and distant metastases were associated with a poor prognosis, as well as the recurrence rate. The current systematic review revealed that 81.1% of the patients were alive within a mean time of 27.5 months. Yanzon et al. (2021) reported that the disease-free survival rates for head and neck sarcomas were 86%, 72%, and 58% at 1, 2, and 5 years, respectively. We showed similar findings for head and neck ES, with a 2-year and 7-year survival rate of 83% and 71%, respectively. Moreover, our results reveled that individual above 51 years were also associated with a poor survival rate. In the article

conducted by Zhan et al. (2021) using the SEER program database, patients with ES over 60 years had lower overall survival and cancer-specific survival than those of patients aged 18–59 years and < 17 years. According to some studies, the worse prognosis that comes with getting older is caused by a larger propensity for metastasis, the necessity for a more careful chemotherapy scheme, and the more common presence of systemic comorbidities in the aged population (Lee, Hoang, Ziogas, Zell, 2010; Grevener et al., 2016; Zhan et al., 2021).

Our systematic review has some limitations that should be highlighted. Despite the fact that only 13 (6.9%) of the scientific articles underwent a critical review that revealed a high to moderate risk of bias, several crucial data are still missing, including survival status, occurrence, and follow-up. It is important to point out that our search only included articles written in the English language. Even with this language limitation, we believe that most of the documented cases are part of our sample.

5 Conclusion

In summary, head and neck ES represents an uncommon tumor, mainly affecting pediatric male individuals. The histopathological diagnosis is challenging, requiring the use of immunohistochemical markers and/or molecular tests. The findings presented in this systematic review demonstrated that more advanced age and the presence of distant metastasis were associated with shorter survival times. Therefore, this study provides useful knowledge that could help dentists, surgeons, oncologists, otorhinolaryngologists as well as oral and maxillofacial pathologists with the diagnosis and management of ES.

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Table 1. Summarized data of the ES cases in the present systematic review.

Variable	N (%)
Sex (n=227)	
Male	129 (56.8%)
Female	98 (43.2%)
Age (n=227)	
0-10	59 (26.0%)
11-20	79 (34.8%)
21-30	34 (14.9%)
31-40	18 (7.9%)
41-50	11 (4.8%)
51-60	8 (3.5%)
61-70	13 (5.7%)
71+	5 (2.2%)
Anatomical location (n=227)*	
Respiratory tract	59 (25.9%)
Jawbones	44 (19.3%)
Cranial bones	42 (18.5%)
Orbit/Eye	22 (9.7%)
Central nervous system	19 (8.4%)
Neck (subcutaneous, pharyngeal spaces)	19 (8.4%)
Thyroid	12 (5.2%)
Salivary glands	10 (4.4%)
Oral cavity (other than jaws)	8 (3.5%)
Zygoma	6 (2.6%)
Skin and scalp	5 (2.2%)
Masseter muscle	4 (1.7%)
Temporal region (soft tissue)	3 (1.3%)
External ear canal	1 (0.5%)
Peripheral nerves	1 (0.5%)
Esophagus	1 (0.5%)
Type of lesion (n=179)	
Swelling	140 (78.2%)
Nodule	31 (17.3%)
Necrosis	5 (2.7%)
Ulcer	3 (1.6%)
Consistency (n=50)	
Firm/Hard	37 (74.0%)
Soft	8 (16.0%)
Rubbery/elastic	5 (10.0%)

Surface (n=21)	
Smooth	10 (47.6%)
Friable	5 (23.8%)
Polypoid	6 (28.5%)
Symptoms (n=210)*	
Asymmetry/edema	124 (59.0%)
Painful	45 (21.4%)
Nasal congestion	37 (17.6%)
Diplopia/loss of visual acuity	35 (16.6%)
Headache	25 (11.9%)
Nausea/vomiting	11 (5.2%)
Paresthesia/hyperesthesia	11 (5.2%)
Facial paralysis or fatigue	9 (4.2%)
Dysphagia	7 (3.3%)
Hearing loss or impairment	7 (3.3%)
Dysarthria/dysphasia	6 (2.8%)
Hypo/anosmia	6 (2.8%)
Fever	5 (2.3%)
Incoordination/dysbasia/ataxia	4 (1.9%)
Breathing problems	4 (1.9%)
Otalgia	4 (1.9%)
Lethargy/listlessness	3 (1.4%)
Other types of head and neck paralysis	3 (1.4%)
Body/limbs fatigue or paralysis	2 (0.9%)
Local warmth sensation	1 (0.4%)
Duration of the lesion, in days (n=131)	
Mean (SD)	115.6 (±170.6)
Range	2 - 1460
Lesion size in centimeters(n=151)	
Mean (SD)	5.1 (±2.44)
Range	0.8 – 15.3
Imaginological exams (n=204)*	
Computed tomography	149 (73.0%)
Magnetic Resonance	94 (46.0%)
Radiography	19 (9.3%)
Ultrasound	13 (6.3%)
Videolaparoscopy	8 (3.9%)
Positron Emission Tomography (PET) scan	5 (2.4%)
Scintigraphy	1 (0.5%)
Metastasis (n=148)	
No	118 (79.7%)
Yes	30 (20.3%)

Lung	8 (26.6%)
Brain	5 (16.6%)
Mediastinum	5 (16.6%)
Bone	3 (10.0%)
Articulation	1 (3.32%)
Not specified	8 (26.6%)
Recurrence (n=150)	
No	134 (89.3%)
Yes	16 (10.7%)
Follow – up in months (n=175)	
Mean (SD)	27.5 (±35.2)
Median	24
Range	0 - 360
Status (n=159)	
Alive	129 (81.1%)
Dead	30 (18.9%)

* In some cases, more than one symptom was identified. In this sense, we consider 210 cases as 100% of symptom data

Table 2. Histopathological features of head and neck Ewing sarcoma

Characteristics	Presence (n)
Appearance/Growth/Pattern	
Sheets	37
Nests	27
Cords	11
Lobules	12
Diffuse	9
Solid	14
Trabecular	3
Peritheliomatous	2
Nodular	2
Clusters	1
Alveolar	1
Zellballen pattern	1
Cribriform	1
Cell morphology	
Round	159
Blue	35
Oval	6
Epithelioid	4
Spindle	1
Cell size	
Small	149
Medium	7
Large	2
Nucleus morphology	
Round	62
Oval	32
Hyperchromatic	28
Vesicular	11
Irregular	4
Regular/Uniform	4
Pleomorphic	3
Nucleus size	
Small	11
Large	4
Nucleoli	
Prominent	12
Inconspicuous	17

Cytoplasm	
Scant	75
Eosinophilic	9
Vacuolated/Clear	17
Indistinct	5
Pale	1
Mitosis	
Yes	63
No	2
Pseudorosettes (Homer-Wright rosettes)	
Yes	11
No	11
True neural rosettes (Flexner-Wintersteiner rosettes)	
Yes	17
No	11
Necrosis	
Yes	43
No	6

Table 3. Treatment description of all 212 cases included.

Treatment (Protocol)	**n (%)**
Surgery, chemotherapy, radiotherapy	78 (36.7%)
Chemotherapy, radiotherapy	55 (25.9%)
Surgery, chemotherapy	37 (17.4%)
Chemotherapy	15 (7.0%)
Surgery	14 (6.6%)
Surgery, radiotherapy	6 (2.8%)
Radiotherapy	3 (1.4%)
Chemotherapy, Surgery, END**	1 (0.5%)
Surgery, chemotherapy, radiotherapy, END**	1 (0.5%)
Chemotherapy, SCT***	1 (0.5%)
Chemotherapy, radiotherapy, SCT***	1 (0.5%)

ND*: Neck dissection, END**: Elective neck dissection, SCT***: Stem cell transplantation

Figure legends

Figure 1. Top 10 anatomical distribution of head and neck Ewing sarcoma

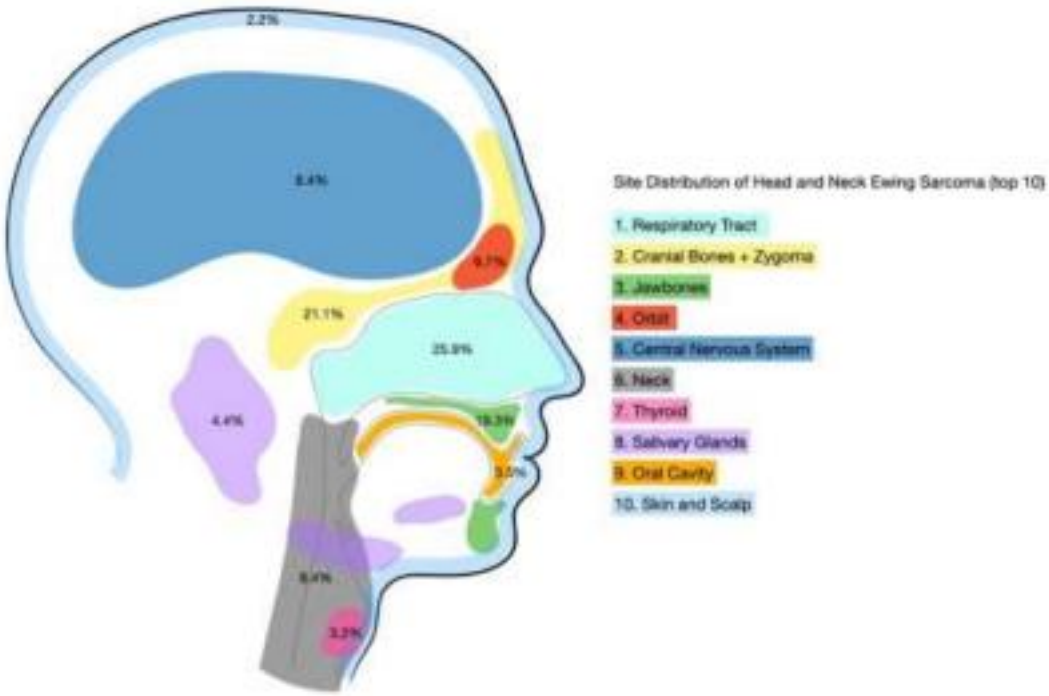
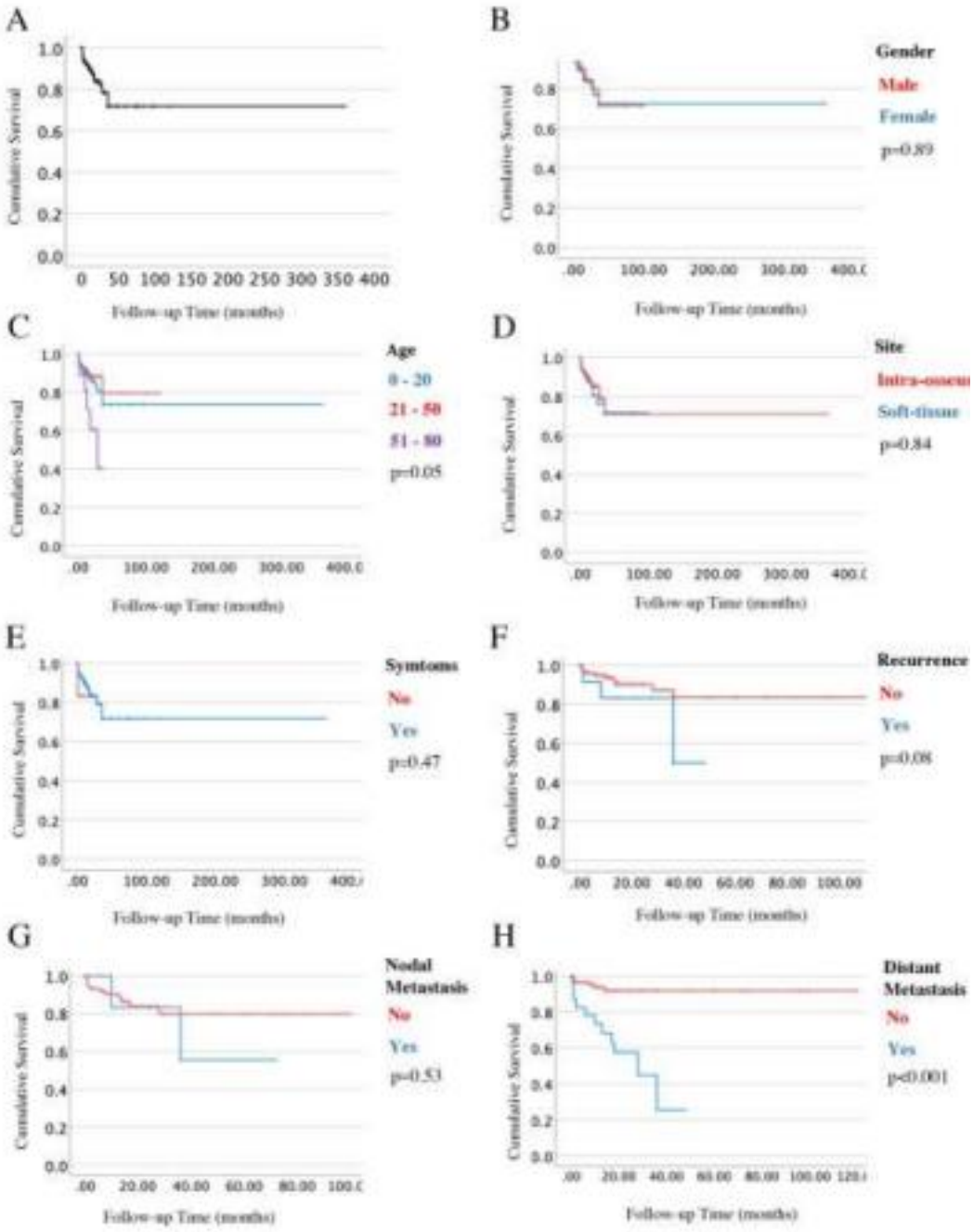


Figure 2. Independent variables associated with cumulative survival



3.2 Artigo 2

Este artigo será enviado para a Revista Head & Neck, Impact fator:2.9, Qualis A1.

Head and neck sarcomas in children and adolescents: a retrospective study of 65 cases at a reference cancer center in southern Brazil

The aim of the present study was to perform a retrospective survey of head and neck sarcomas (HNS) in children and adolescents diagnosed over a 22-year period in a referral center in southern Brazil, as well as evaluate their clinical demographic characteristics, treatment, and prognostic factors. Cases diagnosed as HNS between 2000 and 2022 were retrospectively collected. Medical records were examined to extract demographic, clinical, pathologic, and follow-up information. A total of 268 cases of HNS were diagnosed, and 65 (24.2%) were in children and adolescents. Of these 65 patients, 38 (58.5%) were diagnosed with rhabdomyosarcoma (RMS), 14 (21.5%) with Ewing's sarcoma (ES), 06 (9.2%) with osteosarcoma (OS), 04 (6.2%) with fibrosarcoma, 02 (3.1%) with condrossarcoma, and 01 (1,5%) with synovial sarcoma. Regarding gender, 37 (56.9%) were female, and the mean age was 8.23 years (±5.97). The main anatomical site was the orbital region 11 patients (16.9%) followed by multiple sites 10 cases (15.5%) of involvement and brain 7 cases (10.8%). Clinically, 90% of the patients were symptomatic, and 84.8% presented with a volume increase, reporting a mean of 3.25 months of evolution. The treatment of choice was multimodal, involving chemotherapy and radiotherapy in most cases. At follow-up it was observed that 87.5% had no metastasis, 66.7% had no recurrence, and 82.9% were alive. The probability of survival at 07 months was 94.1% and at 28 months was 72.7%. RMS was the only sarcoma that metastasized and showed a worse prognosis when affecting adolescents. In conclusion, HNS in children and adolescents are rare lesions that promote rapid facial swelling associated with local symptoms and pain. Despite the malignant characteristics, patients have demonstrated that they benefit from multimodal therapy, and high survival rates have been observed. In conclusion, HNS in children and adolescents are rare and presents as rapid swelling associated with

pain. Tumor location was related to tumor subtype. RMS was the most frequent tumor, affected the orbit more, and adolescents had worse prognosis than youngsters. Although rare, it is important that physicians and dentists know the HNS main characteristics to promote early diagnosis and the ideal treatment to increase the survival rates.

Introduction

The incidence of cancer is growing every year in the world, it is estimated that in the year 2020 there were 19.3 million new cases, with about 9.9 million deaths (SUNG et al., 2021). Among all types of cancer, sarcomas are a specific entity being a diverse group that display a wide spectrum of clinical behavior, corresponding to about 1% of all malignant tumors. In the USA, sarcomas have an incidence of 16,250 cases per year, representing about 0.92% of cases of malignant tumors (BROWNSTEIN; DELANEY, 2020). In the head and neck, they represent 4-10% of malignant neoplasms (ALISHAHI; KARGAHI; HOMAYOUNI, 2015). In the pediatric and adolescent population, cancer is considered a rare event (GATTA et al., 2005; KAATSCH, 2010; RABINOWICZ et al., 2013). Despite its rarity, cancer is the leading cause of death from disease among children and adolescents aged 1 to 19 years. In Brazil, according to the National Cancer Institute (INCA), it is estimated that 8,460 new cases of malignant neoplasms occur per year in this age group. The most frequent are leukemia, central nervous system tumor, lymphomas and solid tumors, such as neuroblastoma and sarcomas (CUNHA et al., 2023).

The diagnosis of sarcomas in the head and neck area is challenging due to the low specificity of clinical symptoms, imaging, and histological findings (SCELSI et al., 2019). Lesions may not show symptoms, being discovered in late stages when they cause pain, which is present in 7%, local swelling and/or facial asymmetry in about 59.9% of cases, and other symptoms, nasal obstruction (11%), numbness (8%), change in vision (8%) and headache (8%) (BENTZ et al., 2004; GORSKY; EPSTEIN, 2000; TAJUDEEN; ST. JOHN, 2015). However,

studies showed that early diagnosis can lead to more effective treatment in 80% of children and adolescents with a good quality of life after treatment. Because sarcomas in the head and neck area in children and adolescents are uncommon, they present many of the obstacles associated with rare tumors such as delayed and inaccurate diagnosis, limited clinical knowledge, and low research interest. In addition, recent surveys with a representative sample of these tumors in southern Brazil are scarce. Therefore, the current study sought to conduct a retrospective survey of sarcomas in the head and neck area in children and adolescents diagnosed over a 22-year period at a major reference center for malignant tumors treatment in southern Brazil, as well as assess their demographic and clinico-pathologic characteristics, treatment, and prognostic factors.

Material and Methods

This retrospective cross–sectional observational study was approved by the Ethics Committee on Human Research of Complexo Hospitalar Santa Casa de Misericordia de Porto Alegre (CAEE:57087622.8.0000.5335)

Study Population

All patients with a clinical and histopathological diagnosis of sarcoma of the head and neck between January 2000 and December 2022 at Santa Rita Hospital - Irmandade da Santa Casa de Misericordia de Porto Alegre were identified. After identification, the WHO's definition of childhood was used to set a cutoff age of 20 years, which was then divided into the first and second decades of life. At the Pathology Department, search criteria have been set based on the type of sarcoma (as classified by the 4th edition of the World

Health Organization Classification of Head and Neck Tumors) and topography. Age, gender, date of diagnosis, anatomical sites, clinical presentation, symptomatology, histopathological diagnosis, size, regional metastasis, distant metastasis, primary tumor treatment, recurrence (yes or no), and clinical outcome were all extracted manually from the medical records.

Statistical analysis

Statistical analysis was performed with the MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). A descriptive analysis of the demographic and clinical characteristics of the sample was run. The Kaplan-Meier test was used to calculate the survival probability. The chi-square test was used to evaluate the association between prognosis and symptoms as well as between age (first decade and second decade) and prognosis. Statistical significance was set at $p < 0.05$.

Results

The demographic and clinical characteristics of the sample are displayed in Table 1. Among the 268 sarcomas in the head and neck region identified, 65 (24.2%) occurred in children and adolescents. Of these 65 cases, rhabdomyosarcoma represented 38 (58.5%) of them, Ewing's sarcoma affected 14 (21.5%) patients, osteosarcoma occurred in 06 (9.2%), 04 (6.2%) with fibrosarcoma, 02 (3.1%) with chondrosarcoma, and 01 (1,5%) with synovial sarcoma. The mean age was 8.23 years (5.97), with 37 (56.9%) of the participants being female. The orbital region was the primary anatomical site with 11 cases (16.9%), followed by 10 cases (15.5%) with numerous sites of involvement, 7 cases (10.8%) in the brain, 6 cases (9.2%) intraoral, 6 cases

(9.2%) jaws, 6 cases (9.2%) nasal cavity, and 5 cases (7.6%) in the parotid gland.

Clinical manifestation was reported in 33 cases, and in 84.8% of them swelling was described. Regarding symptoms only in 20 medical records this information was available. Pain was referred in 90% of the cases. The mean size of the lesion was 2.47 cm, and the evolution time was around 3.25 months. The treatment of choice was surgery + CT +RT in 28.7% of the patients, CT + RT in 24.5%, and surgery alone in 22.4%. Most patients presented no metastasis (87.5%), no recurrence (66.7%), and were alive (82.9%) (Table 1). The survival probability at 7 months was 94.1%. In the 28-month assessment, the survival probability was 72.7% (Table 2). No association between prognosis and symptoms (Supp Table 1 and Supp Table 2), as well as between age and prognosis (Supp Table 3) was observed ($p > 0.05$).

Table 1: Overall demographic and clinico-pathologic characteristics of the sarcomas of head and neck in children and adolescents included in the study (n=65).

Variables	N (%)
Diagnosis (n=65)	
Rhabdomyosarcoma	38 (58.5)
Ewing	14 (21.5)
Osteossarcoma	06 (9.2)
Fibrosarcoma	04 (6.2)
Condrosarcoma	02 (3.1)
Sinovial sarcoma	01 (1.5)
Gender (n=65)	N (%)
Female	37 (56.9)
Male	28 (43.1)
Age (years) – Mean (SD); Median (Min-Max)	8.23 (5.97); 8.0 (0 – 20)
Anatomical site (n=65)	N (%)
Orbital region	11 (16.9)
Multiple sites	10 (15.5)
Brain	07 (10.8)
Intraoral	06 (9.2)
Jaws	06 (9.2)
Nose	06 (9.2)
Parotid gland	05 (7.6)
Skull	03 (4.6)
Face	03 (4.6)
Cervical	02 (3.1)
Ear region	02 (3.1)
Esfenoid	02 (3.1)
Temporal region	01 (1.5)
Scalp	01 (1.5)
Lesion size (cm) – Mean (SD); Median (Min-Max)	2.47 (1.93); 1.9 (0.5 – 9.5)
Lesion time (months) – Mean (SD); Median (Min-Max)	3.25 (3.69); 2.5 (0 – 12)
Pain (n=20)	
Yes	18 (90.0)
No	02 (10.0)
Clinical signs (n=33)	
Swelling	28 (84,8)
Eye disorders	05 (15.1)
Nasal Obstruction	02 (6.0)
Treatment (n=49)	
Surgery + Chemotherapy + Radiotherapy	14 (28.7)
Chemotherapy + Radiotherapy	12 (24.5)
Surgery	11 (22.4)
Surgery + Chemotherapy	07 (14.3)
Chemotherapy	03 (6.1)
Radiotherapy	01 (2.0)
Surgery + Radiotherapy	01 (2.0)
Metastasis (n=16)	
No	14 (87.5)
Yes	02 (12.5)
Recurrence (n=27)	N (%)
No	18 (66.7)
Yes	09 (33.3)
Status (n=35)	N (%)
Alive	29 (82.9)
Dead	06 (17.1)

Table 2: Survival analysis for children and adolescents with sarcoma

Time (months)	Number of cases	Status of the individual		Cumulative events	Remaining cases	Survival probability
		Alive	Dead			
1	2	1	1	1	33	97.1%
4	1	1	0	1	32	-
7	1	0	1	2	31	94.1%
9	1	0	1	3	30	91.1%
10	3	2	1	4	27	88.0%
12	1	0	1	5	26	84.8%
13-27	19	19	0	5	7	-
28	1	0	1	6	6	72.7%
29-243	6	6	0	6	0	-

Supp Table 1: Association between recurrence and symptoms

	Recurrence		*p* value*
	No – N (%)	Yes – N (%)	
Symptoms			
No	01 (14.3)	00 (00.0)	1.000
Yes	06 (85.7)	03 (100.0)	

*Fisher test

Supp Table 2: Association between life status and symptoms

	Status		*p* value*
	Alive – N (%)	Dead – N (%)	
Symptoms			
No	02 (20.0)	00 (000.0)	1.000
Yes	08 (80.0)	03 (100.0)	

*Fisher test

Supp Table 3: Association between age and prognosis

	Age		*p* value*
	Children – N (%)	Adolescents – N (%)	
Metastasis			
No	09 (81.8)	05 (100.0)	1.000
Yes	02 (18.2)	00 (000.0)	
Recurrence			
No	11 (57.9)	07 (87.5)	0.201
Yes	08 (42.1)	01 (12.5)	
Status			
Alive	19 (86.4)	10 (76.9)	0.648
Dead	03 (13.6)	03 (23.1)	

*Fisher test

Rhabdomyosarcoma

There were 38 patients with the diagnosis of RMS, representing 58.5% of the sample, 25 of these were female (65.8%) and 13 of them were male (34.2%). The average age was 7.76 years, with a 5.65 standard deviation. The symptoms duration referred by patients had an average of four and a half months. The most common site was the orbital region represented by 10 (26.4%), followed by multiple sites 07 (18.4%), the nasal cavity 06 (15.8%), and the salivary glands in 05 cases (13.2%). According to where the tumor was located, different clinical signs and physical findings were present throughout the diagnosis and illness progression. The access of metastasis information was obtained only in 16 of the total sample of 65 patients included in the study, and two cases described metastatic disease and both of them were RMS (Table 3).

Concerning the many forms of multimodal treatments, CT associated with RT was the most used (Table 3). In terms of follow-up, from the medical records in which metastasis, recurrence and status were informed, 22.2% individuals developed metastasis, 31.2% presented locoregional recurrence and 18.2% died of the disease (Table 4). There was no correlation among symptoms, recurrence, and life status (Supp Table 4 and Supp Table 5). There is an association between decades of life of rhabdomyosarcoma diagnosis with status of life. Adolescents presented a worse prognosis (Table 5).

Table 3: Demographic and clinical characteristics of the sample with rhabdomyosarcoma.

Variables	**N (%)**
Gender (n=38)	25 (65.8)
Female	13 (34.2)
Male	
Age (years) – Mean (SD); Median (Min-Max)	7.76 (5.65); 8.0 (0 – 20)
Anatomical site (n=38)	
Orbital region	10 (26.4)
Multiple sites	07 (18.4)
Nose	06 (15.8)
Parotid Gland	04 (10.6)
Intraoral	03 (7.9)
Skull	02 (5.3)
Face	02 (5.3)
Jaws	01 (2.6)
Cervical	01 (2.6)
Brain	01 (2.6)
Ear region	01 (2.6)
Lesion size (cm) – Mean (SD); Median (Min-Max)	2.15 (1.67); 1.7 (0.5 – 7.5)
Lesion time (months) – Mean (SD); Median (Min-Max)	4.25 (5.31); 2.5 (0 – 12)
Symptoms (n=10)	
No	01 (10.0)
Yes	09 (90.0)
Treatment (n=29)	
Chemotherapy + Radiotherapy	10 (34.6)
Surgery + Chemotherapy + Radiotherapy	09 (31.1)
Surgery + Chemotherapy	03 (10.3)
Surgery	03 (10.3)
Chemotherapy	03 (10.3)
Radiotherapy	01 (3.4)
Metastasis (n=9)	
No	07 (77.8)
Yes	02 (22.2)
Recurrence (n=16)	
No	11 (68.8)
Yes	05 (31.2)
Status (n=22)	
Alive	18 (81.8)
Dead	04 (18.2)

Table 4: Survival analysis for children and adolescents with rhabdomyosarcoma.

Time (months)	Number of cases	Status of the individual		Cumulative events	Remaining cases	Survival probability
		Alive	Dead			
1	1	0	1	1	21	95.5%
4	1	1	0	1	20	-
7	1	0	1	2	19	90.7%
10	2	1	1	3	17	85.9%
12	1	0	1	4	16	80.9%
13 - 220	16	16	0	4	0	-

Supp Table 4: Association between recurrence and symptoms among cases of rhabdomyosarcoma

	Recurrence		*p* value*
	No – N (%)	Yes – N (%)	
Symptoms			
No	01 (20.0)	00 (000.0)	1.000
Yes	04 (80.0)	02 (100.0)	

*Fisher test

Supp Table 5: Association between life status and symptoms among cases of rhabdomyosarcoma

	Status		*p* value*
	Alive – N (%)	Dead – N (%)	
Symptoms			
No	01 (16.7)	00 (000.0)	1.000
Yes	05 (83.3)	03 (100.0)	

*Fisher test

Table 5: Association between age and prognosis among cases of rhabdomyosarcoma

	Age		*p* value*
	Children – N (%)	Adolescents – N (%)	
Metastasis			
No	04 (66.7)	03 (100.0)	0.500
Yes	02 (33.3)	00 (000.0)	
Recurrence			
No	07 (63.6)	04 (80.0)	1.000
Yes	04 (36.4)	01 (20.0)	
Status			
Alive	14 (93.3)	04 (57.1)	0.007
Dead	01 (06.7)	03 (42.9)	

*Fisher test

Ewing Sarcoma

ES represented 21.5% (n=14) of the sample with equal gender distribution. Most cases affected the brain (43.2%) in patients in the first decade of life. Surgery associated with CT-RT was used in 36.4% of the patients. There was no connection among symptoms, recurrence, and life status (Table 6), and no association between age and prognosis among cases with ES. Few medical records informed follow-up status. From these, none described metastasis, 50% showed locoregional recurrence and in 25% death caused by the tumor was reported (Table 6). The survival rate was 87.5% in 28 months falling to 58.3% thereafter.

Table 6: Demographic and clinical characteristics of the sample of cases with Ewing sarcoma.

Variables	**N (%)**
Sex (n=14)	
Male	07 (50.0)
Female	07 (50.0)
Age (years) – Mean (SD); Median (Min-Max)	5.43 (4.84); 4.5 (0 – 15)
Anatomical site (n=14)	
Brain	06 (43.2)
Esfenoid	02 (14.2)
Jaws	01 (7.1)
Parotid gland	01 (7.1)
Skull	01 (7.1)
Face	01 (7.1)
Orbital region	01 (7.1)
Ear region	01 (7.1)
Lesion size (cm) – Mean (SD); Median (Min-Max)	1.79 (1.27); 1.25 (0.6 – 4.0)
Lesion time (months) – Mean (SD); Median (Min-Max)	2.00 (1.41); 2.0 (1 – 3)
Symptoms (n=4)	
No	01 (25.0)
Yes	03 (75.0)
Treatment (n=11)	
Surgery + Chemotherapy + Radiotherapy	04 (36.4)
Surgery + Chemotherapy	03 (27.2)
Chemotherapy + Radiotherapy	02 (18.2)
Surgery + Radiotherapy	01 (9.1)
Surgery	01 (9.1)
Metastasis (n=5)	
No	05 (100.0)
Yes	00 (00.0)
Recurrence (n=8)	
No	04 (50.0)
Yes	04 (50.0)
Status (n=8)	
Alive	06 (75.0)
Dead	02 (25.0)

Discussion

Cancer is considered as the leading cause of death in children and adolescents (INCA, ARBOLEDA et al., 2022). Among the myriad of malignant tumor subtypes and locations in this population, HNS are considered extremelly rare (MIRIAM et al., 2019). Based on that, professionals face many challenges associated with rare tumors, such as delayed and inaccurate diagnosis, limited clinical knowledge, and low research interest. Throughout this study, we provide new data from HNS in children and adolescents in a large cohort of a Southern Brazil pediatric population, allowing us to compare the main demographic, clinical, treatment, and prognosis features of our patients with the global trend in a more reliable way.

Epidemiologic studies conducted in different parts of the world report differences in the incidence, frequency of different subtypes and some clinic demographic aspects of HNS in children and adolescents (PACHECO et al., 2011; SALCEDO-HERNANDEZ et al., 2014; MIRIAM et al., 2016; ATARBASHI MOGHADAM et al., 2019; ARBOLEDA et al., 2022; RAM et al., 2022; CUNHA et al., 2023). Interestingly, some studies found different percentages of pediatric HNS compared to the adult population, ranging from 9.6% (ATARBASHI MOGHADAM et al., 2019), 17.0% (SALCEDO-HERNANDEZ et al., 2014), 30.6% (PACHECO et al., 2011) and 64.6% (RAM et a., 2022). In the present study, we found that from 268 cases of HNS diagnosed in a tertiary cancer health center, 24.2% affected children and adolescents similar to the 28.9% found by Moreira et al (2020).

In this cohort, HNS demonstrated a slight predilection for females with a

mean age of 8.23 years. De Bree et al., (2010) also found a higher frequency in females however, most studies observed is a slightly male preference without statistically significant difference (BRADY et al., 2017; RAM et al., 2021; ARBOLEDA et al., 2022; SUZUKI et al., 2023; CUNHA et al., 2023). Regarding the age group, our results are similar to studies that were performed only in pediatric patients that also found the mean age in the first decade of life (MIRIAM et al., 2019; ARBOLEDA et al., 2022; CUNHA et al., 2023).

Six different histopathological diagnoses of sarcoma were identified in our study. RMS represented the most frequent lesion, corresponding with more than half of the cases (58.5%), followed by ES with 21.5% and OS (9.2%). In fact, the literature appointed that these three lesions are the main sarcoma diagnosis in individuals under 20 years old (BRADY et al., 2017; RAM et al., 2021; ARBOLEDA et al., 2022; SUZUKI et al., 2023; CUNHA W-A et al., 2023; SPIGUEL et al. 2023). Regarding tumor location, in the present study, the orbit was the most common location, followed by multiple sites and brain. Anatomical sites are directly related to the main histological subtypes (ARBOLEDA et al., 2022; KOBAYASHI et al., 2023). Of the 11 cases of sarcomas in the orbit, 10 cases were RMS. Of 7 cases in the brain, 6 cases were ES. The high incidence of multiple sites is due to the proximity and interconnection of the anatomic sites in the head and neck. So, it is common for lesions to first appear in one location before spreading to other locations as they progress, making it challenging to define the primary anatomical site of the tumor at the time of diagnosis and so defining multiple locations (KOBAYASHI et al., 2023)

Sarcomas exhibit a wide range of clinical characteristics, ranging from slow growth to aggressive local and regional growth with systemic metastasis (RAM et al., 2021; ARBOLEDA et al., 2022). Usually manifests as painless mass in 80%

of the cases, pain is more related to bone sarcomas (LIUZZI et al, 2017; BRADY et al., 2017; RAM et al., 2021). Overall, our results agree with the previous studies because we observed that in 84.8% of our patients had swelling, the lesion presented 2.47cm in their mean size with an average of 3.25 months of evolution (LIUZZI et al, 2017; BRADY et al., 2017; RAM et al 2021). Only in 20 medical records was obtained information about symptomatology. From them in 18 cases (90%) pain was referred. This result should be interpreted with caution. This raises an important question as to whether the symptomatology was questioned by the professional but not recorded when asymptomatic or whether this investigation was not actually carried out. This is a limitation of retrospective studies in which absence of information could not be interpreted as no symptoms

but as missing data interfering in the percentage of the final data.

Treatment of HNS is dependent on histological type, location, stage of disease, tumor size and age of patient (MOREIRA et al., 2020; RAM et al 2021). Th treatment of choice was a multimodal combined surgery and/or CT and/or RT in 70% of the patients. Due to their proximity to vital structures, HNS offer surgical challenges and, depending on their location, may be managed with greater or lesser difficulty. Lesions located in the soft tissues of the neck or on the scalp tend to be more easily treated by surgery, but tumors located in the paranasal sinuses tend to be in the vicinity of the brain, which makes treatment more complex; this translates into a greater likelihood of positive margins after surgery (LIUZZI et al., 2017). Therefore, if the surgical procedure cannot be radical or the risk of mutilation and loss of function is very high, CT associated or not to RT will usually be the first option. Functional and cosmetic results of the procedure must also be taken into consideration in that case (KOBAYASHI et al., 2023).

Most patients presented no metastasis (87.5%), no recurrence (66.7%) and were alive (82.9%). No association of prognosis and age was reported when all the types of HNS were analyzed together. However, some interesting findings were observed when RMS was examined alone. In this tumor, adolescents presented a worse prognosis than children. The age of patients with HNS was considered an important predictor of survival (SUZUKI et al., 2023). In addition, the only two cases of metastasis described in the study were from RMS. The survival probability was high at 7 months with 94.1% and 72.7% after 28 months. Despite some older studies describing that HNS have a poor prognosis (TRAN et al.,1992; DUDHAT et al., 2000), more recent studies have appointed better results, better survival rates, similar to what we detected in our sample (PACHECO et al., 2011; PENG, WANG, 2013; MIRIAM et al., 2016; ARBOLEDA et al., 2022; RAM et al., 2022; CUNHA W-A et al., 2023). The excellent prognosis could be related to the treatment protocol used and maybe based on the fact that the lesions were mostly located in orbit and brain and probably detected in an early stage with low mean size of the lesion. In this sense, Kobayashi et al (2023) reported that excellent prognosis for patients with orbital RMS have been demonstrated in several studies from cooperative oncologic groups.

Despite the relevant information presented in our study, some limitations should be discussed. The main one was regarding the lack of description about symptoms and follow-up information in some cases. This should be justified by the retrospective nature of the study and the fact that we collected information from the last 22 years which included handwritten medical records.

Conclusion

The present study demonstrated that HNS in children and adolescents are rare in Southern Brazil. The most common subtypes were RMS, EW and OS that occurred preferentially in the first decade of life. The main clinical characteristics were rapid swelling associated with pain. The tumor subtype and location were statistically related. In general, HNS presented high survival rates. RMS was the most frequent tumor affecting the orbit and adolescents had worse prognosis than younger ones. Although rare, it is important that physicians and dentists know the HNS main characteristics to promote early diagnosis and the ideal treatment for pediatric patients.

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CONSIDERAÇÕES FINAIS

Através da revisão sistemática da literatura, foi possível traçar um perfil dos aspectos clínico-demográficos, perfil histopatológico, tratamento, seguimento e taxa de sobrevida do sarcoma de Ewing. Em resumo, o SE de cabeça e pescoço representa um tumor incomum, acometendo principalmente indivíduos pediátricos do sexo masculino. O diagnóstico histopatológico é desafiador, exigindo o uso de marcadores imuno-histoquímicos e/ou testes moleculares. Os achados apresentados nesta revisão sistemática demonstraram que a idade mais avançada e a presença de metástase à distância estiveram associadas a menor tempo de sobrevida. Apesar da raridade o sarcoma é uma realidade no paciente infantil, portanto este estudo fornece conhecimento útil que pode ajudar dentistas, cirurgiões, oncologistas, otorrinolaringologistas, bem como patologistas que atuam com esse público, e acreditamos que a conscientização de profissionais que trabalhem com este grupo especifico é de extrema importância para que um diagnóstico precoce possa ser realizado.

Ao longo da revisão, observamos que havia a necessidade de se investigar outros sarcomas que possam atingir a população pediátrica no nosso estado e, portanto, realizamos este estudo num centro de referência no sul do País. Por meio deste estudo pudemos observar que os sarcomas de cabeça e pescoço em crianças e adolescentes são raros no Sul do Brasil, os subtipos mais comuns são RMS, EW e OS e ocorreram preferencialmente na primeira década de vida. As principais características clínicas foram edema rápido associado à dor. A localização do tumor foi estatisticamente relacionada com o subtipo do tumor. Em geral, os sarcomas estudados apresentaram altas taxas de sobrevida. O RMS foi o tumor que mais acometeu a órbita e os adolescentes tiveram pior

pior prognóstico do que os mais jovens. Assim como outros estudos longitudinais, observamos que alguns dados importantes são perdidos pela dificuldade de termos um padrão na coleta dos dados na chegada destes pacientes pois a gravidade da situação, o rápido crescimento das lesões, os fatores emocionais/sociais envolvidos, e a necessidade de uma rápida atuação deste tipo de doença faz com que haja uma atenção maior para um pronto atendimento, limitando a coleta de dados. Como conclusão final, mesmo raro, é importante que médicos e dentistas conheçam as principais características de apresentação dos sarcomas pediátricos de cabeça e pescoço para promover o diagnóstico precoce e o tratamento ideal para os pacientes.

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ANEXO 1

Ficha Levantamento de Dados- Sarcomas de Cabeça e pescoço nº:_____
Dados gerais/demográficos:
Nº Prontuário:_____ Nº AP biópsia _____
Nº AP peça (tumor primário) _____ Nº AP peça (recidiva) _____
Nº AP peça (esvaziamento cervical) _____ Nº AP (outros) _____
Nome do paciente:_____
Data de nascimento:_____ **Sexo:** 1 ( ) masculino 2 ( ) feminino
Cor: 1 ( ) branca 2 ( ) preta 3 ( ) amarela 4 ( ) outra
Ocupação: _____ **Residência:** 1 ( ) urbana 2 ( ) rural

Histórico médico:
Histórico de câncer prévio: 1 ( ) sim 2 ( ) não. Se sim, qual: _____
Diabetes: 1 ( ) sim 2 ( ) não
HIV: 1 ( ) sim 2 ( ) não
Hipertensão: 1 ( ) sim 2 ( ) não
Hepatite C:1 ( ) sim 2 ( ) não
Outras doenças relevantes: _____

Hábitos:
Fumo: 1 ( ) sim 2 ( ) não 3 ( ) ex-fumante. Se ex-fumante, há quanto tempo: ____ meses
Tipo: 1 ( ) cigarro 2 ( )charuto 3 ( ) cachimbo 4 ( ) palheiro 5 ( ) outros: _____
Quantidade: _____ cigarros por dia
Periodo de uso: ____ meses
Álcool: 1 ( ) sim 2 ( ) não 3 ( ) ex-alcolista. Se ex-alcolista, há quanto tempo: ____ meses
Tipo: 1( ) cerveja 2 ( ) vodka 3 ( ) whisky 4 ( ) cachaça 4 ( ) outros:_____
Quantidade: _____ ml por dia
Periodo de uso: ____ meses
Outros hábitos relevantes: _____

Dados da Lesão:
Diagnóstico histopatológico:_____
Data de diagnóstico: _____
Sitio:_____
Aspecto clínico: 1 ( )nódulo 2 ( ) nódulo com úlcera 3 ( ) outro:_____
Dor: 1 ( ) sim 2 ( ) não
Parestesia associada: 1 ( ) sim 2 ( ) não
Tamanho: _____mm
Tamanho: 1 ( ) Tx 2 ( ) T0 3 ( ) “in situ” 4 ( ) T1 5 ( ) T2 6 ( ) T3 7 ( ) T4
Metástase regional: 1 ( ) NX 2 ( ) N0 3 ( ) N1 4 ( ) N2 5 ( ) N2a 6 ( ) N2b 7 ( ) N2c 8 ( ) N3
Metástase à distância: 1 ( ) MX 2 ( ) M0 3 ( ) M1
TNM: 1 ( )Estádio 0 2 ( )Estádio I 3 ( )Estádio II 4 ( )Estádio III 5 ( )Estádio IVa 6 ( )Estádio IVb 7 ( )Estádio IVc

Tratamento (tumor primário): 1 ( ) cirurgia isolada 2 ( ) radioterapia isolada 3 ( ) quimioterapia isolada 4 ( ) cirurgia + radioterapia 5 ( ) cirurgia + quimioterapia 6 ( ) radioterapia + quimioterapia 7 ( ) cirurgia, radio e quimioterapia.
Qual(is) quimioterápico(s) utilizados e doses:_____
Qual a dose de radioterapia total e campo (número de sessões):_____
Esvaziamento cervical: 1 ( ) sim 2 ( ) não
Tratamento (recidiva): 1 ( ) cirurgia isolada 2 ( ) radioterapia isolada 3 ( ) quimioterapia isolada 4 ( ) cirurgia + radioterapia 5 ( ) cirurgia + quimioterapia 6 ( ) radioterapia + quimioterapia 7 ( ) cirurgia, radio e quimioterapia
Se tiver o tipo de cirurgia (ex. parotidectomia parcial ou total)
_____
Recidiva: 1 ( ) sim 2 ( ) não. Se sim, qual a data da recidiva:_____
Desfecho: 1 ( ) vivo 2 ( ) falecido por outra causa 3 ( ) falecido pelo tumor
Se vivo, data última consulta:_____
Se morto, data de óbito: _____
Outros dados encontrados:
_____
_____
_____
_____
_____
_____
_____