Acquiring a Comprehensive Awareness of the Current Insights on Pediatric Oral and Maxillofacial Malignancies

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Eur Dent Res Biomater J 2024;5:1–7.

Abstract

Orofacial tumors constitute a heterogeneous collection of pathological conditions characterized by distinct types of histology and clinical behaviors. Numerous accounts of craniofacial tumors in kids and young adults are being recorded globally. Within the pediatric population, leukemia, lymphoma, and nervous system tumors are the most common forms of pediatric cancer in developing nations; yet, when concentrating on specific anatomical regions, such as the head and neck, the incidence of malignant tumors is comparatively low. Additionally, the occurrence of oral and maxillofacial malignancy in pediatric populations is rare, varying from roughly 0.5 to 6%. The authors of this article conducted a comprehensive retrospective review of various cases and studies concerning oral and maxillofacial malignancies in the pediatric population, utilizing electronic databases, such as PubMed, Scopus, Web of Science, and Google Scholar to identify pertinent articles. We performed a narrative review on the current aspects and therapeutic procedures related to the four most prevalent oral and maxillofacial malignancies: Burkitt's lymphoma, mucoepidermoid carcinoma, rhabdomyosarcoma, and osteosarcoma.

Keywords
- orofacial malignancies
- children's
- therapeutic approaches
- pediatric
- tumors

Introduction

Childhood cancer is a significant public health issue, with a large number of occurrences worldwide (385,509 per year among individuals aged 0 to 19 years). These incidence rates have been on the rise throughout the 1980s, ranging from 124 to 140.6 cases per million person-years.[1] Leukemia, lymphoma, and central nervous system tumors continue to be the most common kinds of pediatric cancer in developing nations, with leukemia accounting for 18 to 41% of cases, lymphoma accounting for 13 to 24% of cases, and central nervous system tumors accounting for 7 to 17% of cases.[2] However, when specifically considering anatomical regions, such as the orofacial region and neck, the proportion of malignant tumors is rather small, accounting for about 5%. In pediatric populations, the occurrence of oral and maxillofacial cancer is rare, with a prevalence ranging from around 0.5

article published online
February 5, 2025

DOI https://doi.org/10.1055/s-0044-1800918.
ISSN 2791-7452.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

to 6%.[3] Pediatric oral and craniofacial cancer encompasses a diverse range of histological types, with an uncertain etiology. Identifying risk factors is crucial in this context.[4] While most oral and maxillofacial diseases in children are typically caused by inflammation or are benign in nature, it is important to acknowledge that extremely aggressive malignant tumors can sometimes be encountered in routine clinical settings.[5]

Society does not appreciate the news of an oral cancer diagnosis, especially when it occurs in a child or adolescent, which can make it even more surprising and challenging.[6] While oral cancer is less prevalent in youngsters than in older persons, new research indicates that roughly 1 in 285 children in the United States get diagnosed with the condition before the age of 20 years.[7] Oral cancer is often believed by many clinicians to be more serious in young patients and is linked to lower survival rates compared with adults.[8] Prior research has demonstrated that the predominant forms of pediatric oral and maxillofacial cancer include Burkitt's lymphoma (BL), mucoepidermoid carcinoma, rhabdomyosarcoma (RMS), and osteosarcoma.[9,10] Researchers and practitioners hold varying perspectives on the precise description of pediatric head and neck tumors.[11] Previous studies on these tumors were either restricted by standards that did not specifically pertain to the orofacial and neck region, or were predominantly centered around a certain racial group and a specific spot where the tumor occurred.[12]

It is crucial to eliminate any inconsistencies and variations in the investigation of pediatric head and neck tumors. Establishing a clear definition and accurate incidence rates for these cancers is of utmost importance. The objective of this research is to outline the most predominant types of oral and maxillofacial cancers in children and discuss their current understanding and therapeutic approaches.

Burkitt's Lymphoma

BL is a cancer that arises from B-lymphocytes. This is a particularly aggressive kind of B-cell non-Hodgkin lymphoma that appears in three distinct clinical forms: the endemic form, the sporadic form, and the form linked with immunodeficiency.[13–15] While they share the same histological characteristics, there are variations in their epidemiology, clinical appearance, and genetic traits.[13] More than 50% of instances of the disease affect the jaw in its endemic form. It commonly appears as a painless growth on the face that extends to other areas outside of the lymph nodes.[14,16] From a clinical perspective, this condition primarily affects pediatric patients. The highest occurrence of this condition is observed between the ages of 3 and 8 years, with boys being affected approximately twice as often as females. The lesions primarily affect the maxilla, mandible, and abdomen. When it comes to oral presentation, the lower jaw is the most common site (►**Fig. 1A**). The rear region of the mandible experiences the greatest impact.[16] The primary observations in oral BL include swelling, discomfort, tooth displacements, and facial asymmetry. Additional symptoms include heightened tooth mobility and toothache resulting from infiltration in the pulp, particularly in growing teeth.[14] Paraesthesia, which refers to abnormal sensations such as tingling or numbness, frequently occurs in the inferior alveolar nerve or other sensory face nerves.[17] The radiographic findings in BL consist of radiolucent pictures showing bone deterioration (►**Fig. 1B**) with indistinct and uneven borders.[18,19] Histologically, a microscopic appearance like a "starry sky" pattern (►**Fig. 1C**), characterized by the presence of tiny, evenly distributed, uniform, immature, and undifferentiated lymphocytes interspersed with many macrophages having ample cytoplasm.

Current Treatment Regimens

The treatment is categorized according to the patient's age and stage of the disease. For pediatric children who have undergone complete surgical removal of the disease, it is advisable to administer two cycles of moderate-intensity chemotherapy. This chemotherapy regimen often includes cyclophosphamide, vincristine, prednisolone, and doxorubicin. For children with stages I and II illness, the overall survival rate exceeds 98%.[20] Children with residual or stage III disease should undergo at least four cycles of dose-intensive chemotherapy. This includes two rounds of cyclophosphamide, prednisolone, vincristine, doxorubicin, and high-dose methotrexate. Following that, the patient undergoes two sessions of cytarabine and high-dose methotrexate.

The National Comprehensive Cancer Network provides current recommendations, which involve the use of multiagent regimens with central nervous system prophylaxis. R-hyper-CVAD and CODOX-M/IVACA (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate, alternating with ifosfamide, etoposide, and cytarabine) are chemotherapy regimens. Regardless of whether rituximab is administered or not, the dosage remains the same. Rituximab is administered in conjunction with altered etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab (EPOCH) regimen.[21–23] Investigation is currently being conducted on newer anti-CD20 drugs, such as ofatumumab and obinutuzumab. Blinatumomab, a monoclonal antibody that targets CD19, and inotuzumab, a monoclonal antibody that targets CD22, are currently being studied. Novel pharmaceutical compounds that can impede the proliferation of BL B-cells by triggering programmed cell death are histone acetylase inhibitors (such as rapamycin, valproic acid, and tubacin) and mammalian target of rapamycin inhibitors (such as temsirolimus). Anti-programmed cell death protein 1 (PD1) drugs inhibit the ability of tumor cells to avoid detection by the immune system through the PD1 pathway. Investigations are now being conducted on therapies that suppress the myelocytomatosis oncogene.[24]

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is currently acknowledged as the predominant malignant tumor of the salivary glands in adults, constituting approximately 29 to 34% of all malignancies affecting the major as well as minor salivary glands.[25] The typical age of a patient is 47 years; however, it can range from 8 to 92 years.[26] This tumor predominantly affects the salivary gland, although it can also be present in the upper

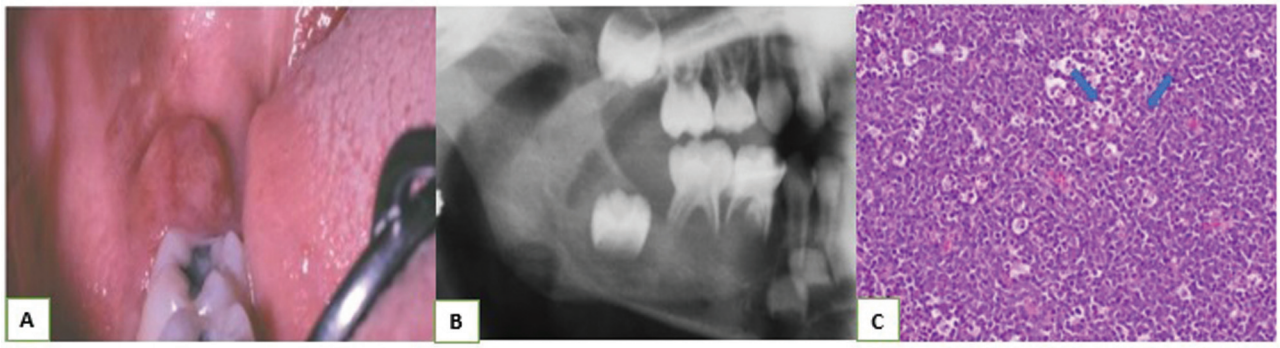

Fig. 1 (A) Clinical image of Burkitt's lymphoma involving the retromolar region. (B) Radiographic image in pediatric patient with evidence of bone destruction with tooth mobility. (C) Histopathological picture of Burkitt's lymphoma is characterized by sheets of uniform intermediate-sized cells with a "starry sky" appearance.

aerodigestive system, tracheobronchial tree and lacrimal sac, thyroid, and liver.[27] The parotid gland is the most frequent location for substantial salivary gland involvement. Less frequently, the minor salivary glands, mandible, and maxilla (►**Fig. 2A**) are affected.[28] Mucoepidermoid carcinoma is uncommon in children compared with adults, yet it is responsible for 50% of salivary gland cancers in kids and adolescents. Mucoepidermoid carcinoma is the most prevalent malignant tumor in the salivary glands of children, followed by acinic cell and adenoid cystic carcinoma.[29,30] Histologically, it is characterized by mucous, intermediate, and epidermoid cells, exhibiting columnar, clear cell, or oncocytoid traits (►**Fig. 2B**). A retrospective survey conducted across multiple organizations discovered 103 kids under the age of 18 years who had mucoepidermoid carcinoma, which was the most prevalent histology observed in 71 of these patients. The investigators did not provide information on whether patients had received prior treatments; however, they did state that out of 103 individuals, 12 had a previous diagnosis of lymphoma. The overall 10-yearsrelapse-free survival percentage for the entire group was 91%.[31] An analysis of the Investigation, Statistics, and End Outcomes Program database revealed a total of 284 individuals under the age of 20 years who had developed tumors in their parotid gland. The survival ratio reached 96% at 5 years, 95% at 10 years, and 83% at 20 years. The death rates among adolescents were more (7.1%) compared with children under the age of 15 years.[32]

Current Treatment Regimens

The European Cooperative Study Group for Paediatric Rare Tumours, as part of the PARTNER project (Paediatric Rare Tumours Network - European Registry), has just released a set of consensus recommendations outlining the recommended approaches for diagnosing and treating salivary gland tumors in children.[33]

Surgery: Whenever feasible, the preferred treatment for salivary gland tumors is complete surgical resection, with the potential inclusion of radiation therapy for tumors that are high grade or exhibit invasive features such as lymph node metastasis, positive operative margins, extracapsular expansion, or perineural extension.[34,35]

Radiation therapy: A retrospective study conducted a comparison between proton treatment and conventional radiation therapy, revealing that proton therapy exhibited a more favorable acute toxic effect and dosimetric profile.[36] A different study conducted a retrospective analysis where 24 children diagnosed with mucoepidermoid carcinoma and exhibiting high-risk indicators were treated using brachytherapy involving iodine I 125 seeds. Seeds were inserted within a period of 4 weeks following surgical removal. After a period of

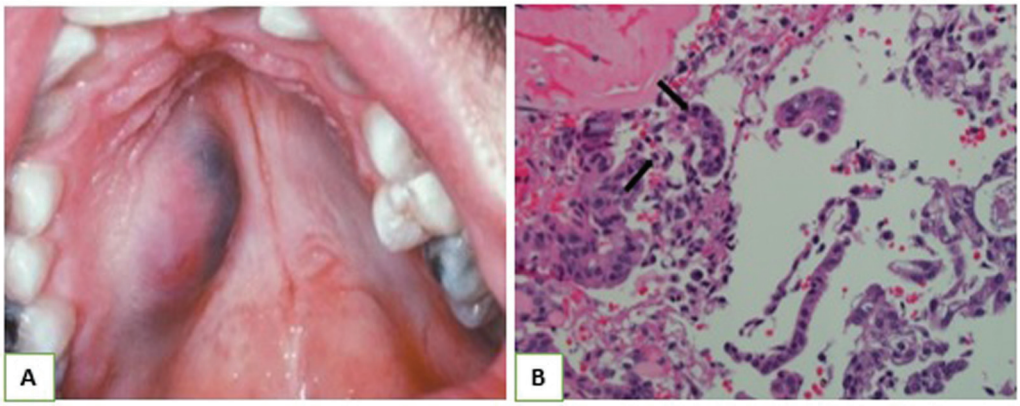

Fig. 2 (A) Clinical picture of mucoepidermoid carcinoma involving posterior lateral hard palate. (B) Histopathological image exhibiting an abundance of a chondroid matrix interspersed among neoplastic cells.

observation lasting 7.2 years, the rates of both disease-free survival and overall survival were 100%. There were no instances of serious problems related to radiation reported.[37]

Targeted therapy: Every patient with recurring neurotrophic tyrosine receptor kinase (NTRK) fusion–positive MASC who received entrectinib or larotrectinib treatment showed favorable objective responses.[38,39] In one of the studies, out of the 11 teenager or adult individuals with TRK fusion–positive salivary gland tumors, 10 had either partial or complete responses after being treated with larotrectinib.[39]

Rhabdomyosarcoma

RMS is a malignant tumor that develops in soft tissues. It is composed of cells that originate from the early stage of connective tissue development and has a strong inclination to undergo muscle formation.[40] RMS is the prevailing kind of soft tissue sarcoma found in children, occurring at a rate of 4.5 incidences per 1 million children per year.[41] The occurrence of RMS varies depending on age, ethnicity, and histology. The prevalence of RMS in certain Asian populations, including Japanese, Indian, and Chinese, appears to be comparatively lower than that of Europe and the United States.[42] The head and neck region is the most frequent site of occurrence, accounting for 35% of cases. The genitourinary tract is the second most common location, representing 23% of cases. Other sites include the retroperitoneum and the extremities, each accounting for 17% of cases.[43] The orbit, paranasal sinuses, and neck are frequently afflicted regions in the head and neck region. RMS is an uncommon occurrence in the oral cavity, making up just 10 to 12% of all instances involving the head and neck (►**Fig. 3A**). The tongue is the most commonly affected site in cases of RMS in the oral cavity, followed by the palate and buccal mucosa. In extremely rare instances, it may also affect the gingiva.[43,44]

Other soft tissue tumors, such as hemangioma, fibroma, rhabdomyoma, and lymphangioma, should be investigated in the differential diagnosis.[45] Computed tomography (CT) and magnetic resonance imaging with contrast are required to assess the main location of the tumor and its adjacent structures. These assist in formulating a differential diagnosis for the tumor. To initially diagnose RMSs, it is necessary to completely remove the tumor with negative margins. Alternatively, an incisional biopsy should be performed when the resection might impact the function. The conclusive diagnosis relies on histological evidence of myogenesis, tadpole or strap cells, and individual tumor cells (►**Fig. 3B**), with or without cross-striation.[46]

Current Treatment Regimens

The conventional approach to treating RMS involves the administration of chemotherapeutic (vincristine, actinomycin D, and cyclophosphamide/ifosfamide), radiation treatment, and surgical removal of the tumor. While the majority of patients with localized RMS can achieve a cure, the prognosis of those with metastasis or recurring RMS is unfavorable.[47,48] Multiple fundamental and applied investigations have been conducted on different therapeutic approaches, encompassing altered or innovative chemotherapy regimens, molecularly targeted pharmacotherapy, immunotherapy, and novel treatment methods for RMS.[49] Doxorubicin has been extensively utilized in the management of soft tissue tumors. Nevertheless, its contribution to the management of RMS is still a subject of debate.[50] Furthermore, some studies have shown that the inclusion of topotecan or irinotecan in the chemotherapeutic treatment did not provide any advantages in the management of RMS.[51] A recent analysis indicated that the use of low-dose maintained chemotherapy following conventional chemotherapy resulted in enhanced outcomes for individuals with RMS. The patients who received maintenance chemotherapy had a disease-free survival rate of 78% over a 5-year period, while the patients who did not get maintenance chemotherapy had a rate of 70%.[49] Due to the limited number of clinical studies specifically focused on RMS, it is frequently challenging to evaluate the effectiveness and safety of novel treatments for RMS. Nevertheless, multiple clinical trials investigating the effectiveness of molecular targeted medicines and immunotherapy have demonstrated positive outcomes among individuals suffering RMS.[49,51]

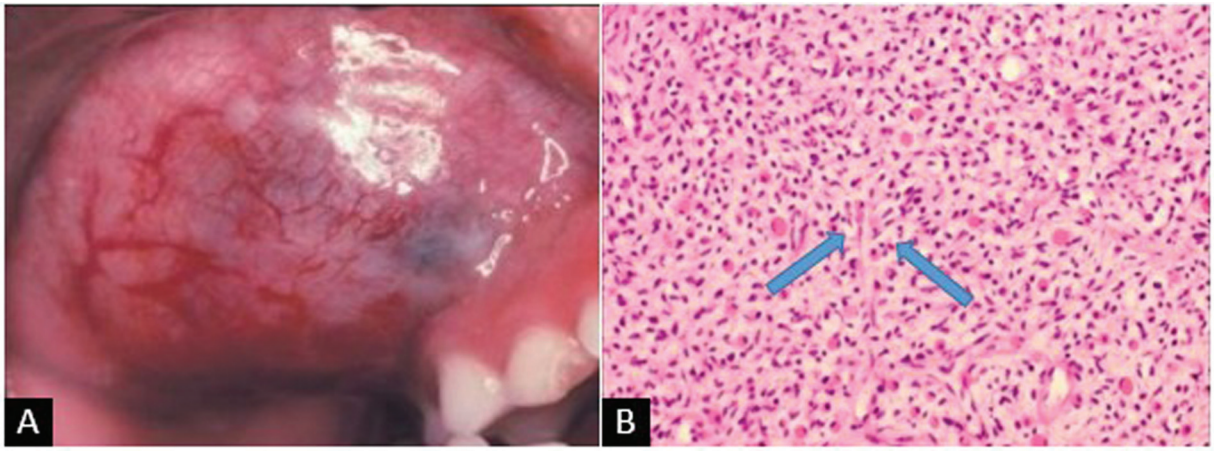

Fig. 3 (A) Clinical picture of rhabdomyosarcoma involving the right maxilla in a young child. (B) Histopathological image showing cells exhibits little myogenesis, comprising elongated myoblasts, undifferentiated mesenchymal cells, and poorly differentiated myofibers.

Osteosarcoma

When discussing sarcomas in the head and neck area, osteosarcoma, Ewing's sarcoma, and chondrosarcoma being the most prominent subtypes, with osteosarcoma being the most common.[52] Osteosarcomas are the predominant malignant tumors that originate in the bone and can manifest in many locations throughout the body, but they are most frequently observed in the long bones, particularly in the vicinity of the knee.[52] Osteosarcomas involving head and neck are rare and typically occur in individuals between their 30s and 40s, which is around 10 years later than the most prevalent occurrence of tumors in long bones and usually, these tumors develop as secondary growths following radiation or chemotherapeutic treatment for a preexisting tumor.[53,54] Primary osteosarcoma of head and neck region is a rare condition in pediatric patients. There are just a few case reports and short research series available in the literature.[55–58] According to the literature, the average age at which pediatric bone sarcoma of the head and neck are diagnosed is between 9 and 11 years, with the highest number of cases occurring between the ages of 10 and 19 years.[59] In the head and neck region, the mandible is typically the most frequently affected site. In the mandibular area, it commonly affects the mandibular body and ramus, while in the maxilla, it affects the upper alveolar ridge, hard palate, or maxillary sinus floor.[60] The primary manifestations of osteosarcoma, when affecting the mandible and maxilla, include pain, swelling, and ulceration. Pain is usually caused by the compression of nearby nerves or the impingement of the periosteum.[61]

Osteosarcoma exhibits radiological indications that lack specificity. The panoramic radiograph may display either an osteolytic or osteosclerotic look. Both appearances can exist simultaneously. Cervicofacial CT is utilized to evaluate the dimensions, boundaries, calcifications, periosteal response, density, and local invasion of the cancer. The presence of a "grass fire" or "sunburst" appearance is frequently observed (►**Fig. 4A**), although it is not a certain indicator of a specific condition.[62] Bone scintigraphy is capable of identifying multifocal osteosarcoma or metastasis. Nevertheless, biopsy remains the sole method to definitively confirm the diagnosis.[61,62] Osteosarcoma is characterized by three histological types based on cell differentiation: chondroblastic (►**Fig. 4B**), which is predominantly characterized by chondroid variations in 48% of cases; osteoblastic, which is characterized by the presence of an abundance of the osteoid tissue element in 29% of cases; and fibroblastic, which is characterized by the predominance of fibrous tissues in 23% of cases.[63]

Current Treatment Regimens

It is crucial to acknowledge that pediatric sarcomas in the head and neck area do not fit neatly into any specific surgical specialty, unlike in adults. Conventional methods such as maxillectomy or hemimaxillectomy can cause serious health problems for children as they develop. In these cases, using free microsurgical tissue transplant may be more challenging from a technical standpoint and the long-term outcomes may be less predictable due to growth. Removal of the upper or lower teeth can have significant negative effects on nutrition. Extensive scarring on the face can have a severe influence on quality of life from a psychological perspective.[64] The management of osteosarcoma necessitates a comprehensive and interdisciplinary strategy. The standard approach usually involves administering neoadjuvant and adjuvant therapy after surgical removal of the tumor.[63] Although chemotherapy treatments are associated with improved survival rates, the primary therapeutic approach is full surgical removal. The main factor that primarily increases survival rates following surgical resection is achieving negative margins. However, other major factors include staging, size of the tumor, presence of metastases, occurrence of local recurrence, and the proportion of tumor cells eliminated during neoadjuvant chemotherapy.[63,64] Virtual planning and computer-aided design/computer-aided manufacturing cutting guides and personalized plates are still being utilized in many craniomaxillofacial procedures, such as intricate panfacial trauma, surgery to reshape the cranial vault, orthognathic surgery, and reconstructive surgery for oncologic head and neck cases.[65] The

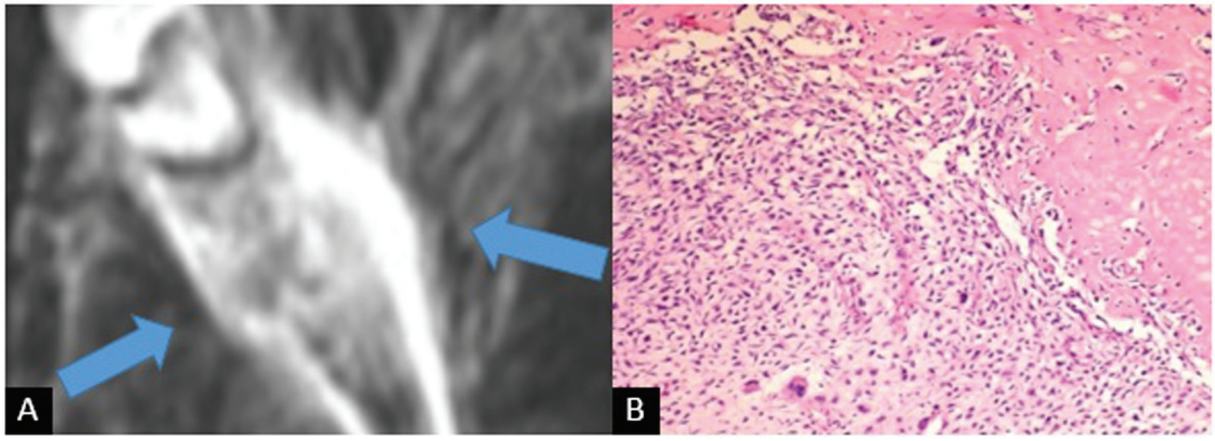

Fig. 4 (A) Computed tomography scan of osteosarcoma involving mandible with cortical destruction along with focal sunburst appearance. (B) Characteristic histological features of chondroblastic osteosarcoma, marked by a preponderance of chondroid matrix interspersed among neoplastic cells.

advantages of these techniques are numerous, including enhanced prediction in cranial surgery, decreased preliminary preparation time in craniofacial surgery, and precise composite tissue repair in oncologic surgery. The use of customized technologies can save operative time and potentially lower costs by minimizing the need for later changes, thanks to the improved correctness of the original outcome.[65] Mixed reality is another supplementary technology that is being used more and more in craniomaxillofacial surgeries for purposes such as training, educating patients and their families, and preparing surgeons.[66] This technique leads to a decrease in the duration of the operation, a decrease in the occurrence of problems, and an improvement in the overall esthetic results. Mixed reality refers to the capability of accurately determining the distance between the mass and important anatomical features, such as the base of the skull and major blood arteries. Moreover, the technique has the potential to provide preoperative simulation of which parts of the tumor can be removed by specific approaches.[65,66]

A more comprehensive inventory of oncoplastic procedures in the craniomaxillofacial region would be particularly advantageous, as we continue to identify the prevalence of specific subtypes of pediatric sarcoma or other surgically treatable tumors.

Limitations

Pediatric oral and maxillofacial malignancies encompass a diverse range of histopathological types, with their etiology remaining largely unidentified, thereby necessitating the identification of risk factors. This study discusses the four most prevalent oral carcinomas in children. However, it is important to acknowledge the existence of other oral and maxillofacial malignancies that may also be encountered in clinical practice, which should be addressed as necessary.

Conclusion

This study indicates that, despite the rarity of pediatric oral and maxillofacial cancers, enhancing awareness of risk factor reduction and advancements in early identification and care will decrease mortality, increase survival rates, and minimize impairment.

Conflict of Interest
None declared.

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