Impact on quality of life due to therapy-related oral complications in pediatric cancer survivors: a scoping review

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Abstract

Objective: This study aimed to scope the academic literature on the effects of cancer treatment-related oral complications on the quality of life in pediatric cancer survivors. This study is built upon a similar review of literature from 2000 – 2011; the current study reviewed the literature for 10 years since that original review (2011-2021).

Methods: We used a scoping review methodology informed by Arksey and O'Malley's methodological framework, Levac et al. and the Joanna Briggs Institute (JBI). We included published literature from the five databases included in our systematic scoping review search. The inclusion criteria included articles focused on the impact of oral complications on the quality of life (QoL) of child cancer survivors (aged 0-18 years at the time of the cancer diagnosis), written in English or French, and published from 2011-2021. Exclusion criteria included articles involving mixed populations of adults and children, and with non-specific disease categories. A team of two reviewers independently charted the retrieved data. A total of 5304 articles were identified from the initial search. The final sample was reduced to 86 articles after meticulously evaluating abstracts and full-text articles. A data extraction tool was used to extract relevant information from the selected articles. The data extracted from the final sample were categorized and summarized descriptively and using tables, graphs, and pie charts.

Results: Among the reviewed publications, we identified 41 types of cancer, with leukemia being the most extensively studied. The results of both the current and original review show that chemotherapy was the predominant treatment modality leading to oral complications, oral mucositis was the most prevalent acute complication, and leukemia was the most studied neoplasm. Moreover, in both reviews, the majority of studies had quantitative designs, followed by qualitative studies, and one mixed-method study. In contrast to the original review, a substantial number of studies reported that children self-reported symptoms and completed assessment tools rather than relying solely on their parents and health care providers to provide this information. Furthermore, since the original review, the use of measures of QoL and oral health-related quality of life (OHRQoL) has increased, however they were used in a minority of studies.

Additionally, we found that tooth and root abnormalities were the most frequent late complication, often occurring with other chronic complications. Pain (in the mouth, teeth, jaw, and throat) had

the greatest impact on QoL in children. A few articles emphasized the importance of integrating dentists' and oral health education programs into pediatric oncology units.

Conclusion: This scoping review charts the literature on oral complications in pediatric cancer patients. Leukemia is still the most extensively reported neoplasm. Oral mucositis remains the most common and distressing oral complication associated with cancer therapy. Chemotherapy is the primary treatment associated with oral complications. The use of QoL and OHRQoL measures and inclusion of children's self-reported symptoms has increased in recent studies compared to the previous review, suggesting a growing recognition of the importance of patient-reported outcomes and subjective measures of OHRQoL in assessing oral complications in pediatric cancer patients. However, the use of qualitative methodologies has decreased. Future directions should aim to incorporate qualitative studies to capture the subjective experiences of cancer therapy in children to supplement the quantitative data to provide a deeper understanding of the multifaceted impact of oral complications on children's QoL.

Résumé

Objectif: Cette étude a pour but d'examiner la littérature académique sur les effets des complications bucco-dentaires liées au traitement du cancer sur la qualité de vie des enfants ayant survécu à un cancer. Cette étude s'appuie sur une analyse similaire de la recherche entre 2000 et 2011 ; l'étude actuelle a examiné la recherche pendant les 10 années qui ont suivi cette analyse originale (2011-2021).

Méthodes: Nous avons utilisé une méthodologie d'examen de la portée de l'étude en nous inspirant du cadre méthodologique d'Arksey et O'Malley, de Levac et al. et de l'institut Joanna Briggs (JBI). Nous avons inclus la recherche publiée dans cinq bases de données. Les critères d'inclusion comprenaient les articles axés sur l'impact des complications bucco-dentaires sur la qualité de vie des enfants survivants du cancer (âgés de 0 à 18 ans au moment du diagnostic du cancer), rédigés en anglais ou en français et publiés entre 2011 et 2021. Les critères d'exclusion comprennent les articles portant sur des populations mixtes d'adultes et d'enfants, ainsi que les articles portant sur des catégories de maladies non spécifiques. Une équipe de deux évaluateurs a consigné de manière indépendante les données extraites. Au total, 5304 articles ont été identifiés à partir de la recherche initiale. L'échantillon final a été réduit à 86 articles après une évaluation méticuleuse des résumés et des articles en texte intégral. Un outil d'extraction de données a été utilisé pour extraire les informations pertinentes des articles sélectionnés. Les données extraites de l'échantillon final ont été classées et résumées de manière descriptive et à l'aide de tableaux, de graphiques et de diagrammes circulaires.

Résultats: Parmi les publications examinées, nous avons identifié 41 types de cancer, la leucémie étant la plus étudiée. Les résultats de la présente étude et de l'étude originale montrent que la chimiothérapie est la principale modalité de traitement entraînant des complications bucco-dentaires, que la mucosite buccale est la complication aiguë la plus fréquente et que la leucémie est le néoplasme le plus étudié. De plus, dans les deux revues, la majorité des études étaient quantitatives, suivies d'études qualitatives et d'une étude à méthode mixte. Contrairement à l'examen initial, un nombre substantiel d'études ont rapporté que les enfants déclaraient eux-mêmes leurs symptômes et remplissaient des outils d'évaluation au lieu de s'en remettre uniquement à leurs parents et aux prestataires de soins de santé pour fournir ces informations. En outre, depuis l'examen initial, l'utilisation de mesures de la qualité de vie et de la qualité de vie liée

à la santé bucco-dentaire (QVLSB) a augmenté, mais ces mesures n'ont été utilisées que dans une minorité d'études.

De plus de cela, nous avons constaté que les anomalies des dents et des racines étaient la complication tardive la plus fréquente, se produisant souvent avec d'autres complications chroniques. La douleur (dans la bouche, les dents, la mâchoire et la gorge) a eu le plus grand impact sur la qualité de vie des enfants. Quelques articles ont souligné l'importance d'intégrer des programmes d'éducation des dentistes et de la santé bucco-dentaire dans les unités d'oncologie pédiatrique.

Conclusion: Cette examen de la portée résume La chimiothérapie est le principal traitement associé à des complications bucco-dentaires. L'utilisation de mesures de la qualité de vie et de la qualité de vie au travail et l'inclusion de symptômes déclarés par les enfants ont augmenté dans les études récentes par rapport à l'examen précédent, mais les rapports qualitatifs ont diminué. Ces résultats suggèrent une reconnaissance croissante de l'importance des résultats rapportés par les patients et des mesures subjectives de la QDVH dans l'évaluation des complications bucco-dentaires chez les enfants atteints de cancer. Toutefois, l'utilisation de méthodologies qualitatives a diminué. Les orientations futures devraient viser à incorporer des études qualitatives pour saisir les expériences subjectives de la thérapie anticancéreuse chez les enfants afin de compléter les données quantitatives pour fournir une compréhension plus profonde de l'impact à multiples facettes des complications bucco-dentaires sur la qualité de vie des enfants. La recherche sur les complications bucco-dentaires chez les patients pédiatriques atteints d'un cancer. La leucémie reste le néoplasme le plus fréquemment rapporté. La mucosite buccale reste la complication buccale la plus fréquente et la plus pénible associée au traitement du cancer.

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This project is a heartfelt tribute to my beloved sister, Aishwarya. I love you.

List of acronyms

1. ALL: Acute Lymphoblastic Leukemia
2. AML: Acute Myeloid Leukemia
3. AUQEI: Modified Autoquestionnaire Qualité de Vie Enfant Imagé
4. BASC-2: Behavior Assessment System for Children, Second Edition
5. BMT: Bone Marrow Transplantation
6. BL: Burkitt Lymphoma
7. BPFAS: Behavioral Pediatrics Feeding Assessment Scale
8. CCS questionnaire: Childhood Cancer Survivor Study questionnaire
9. ChIMES: Children's International Mucositis Evaluation Scale
10. CHQ-PF50: Child Health Questionnaire - Parent Form 50
11. CNS: Central Nervous System
12. COHIP: Child Oral Health Impact Profile
13. CT: Computed Tomography
14. CTC scale WHO: Common Toxicity Criteria scale by the World Health Organization
15. DDA: Dental developmental anomalies
16. EBP: Evidence-Based Practice
17. FACT-ECS: Functional Assessment of Cancer Therapy Esophageal Cancer Sub-scale
18. FLACC scale: Face, Legs, Activity, Cry, Consolability scale
19. GVHD: Graft-versus-Host Disease
20. HDI: Holtas Defect Index
21. HCP: Healthcare providers
22. HRQoL: Health-Related Quality of Life
23. HSCT: Hematopoietic Stem Cell Transplantation
24. HNC: Head and Neck Cancer
25. IMRT: Intensity-Modulated Radiation Therapy
26. JBI: Joanna Briggs Institute
27. JML: Juvenile Myelomonocytic Leukemia
28. LED: Light-Emitting Diode
29. LLLT: Low-Level Laser Therapy
30. MSAS: Memorial Symptom Assessment Scale
31. NHL: Non-Hodgkin's Lymphoma

32. NPC: Nasopharyngeal Carcinoma
33. OAG: Oral Assessment Guide
34. OHIP-14: Oral Health Impact Profile-14
35. OHRQoL: Oral Health-Related Quality of Life
36. OMDQ-MTS: Oral Mucositis Daily Questionnaire - mouth and throat soreness
37. OMQoL: Oral Mucositis Quality of Life scale
38. OM: Oral Mucositis
39. PBM: Photo Biomodulation Therapy
40. PBS: Pencil Beam Scanning
41. PedsQL: Pediatric Quality of Life Inventory
42. PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews
43. PT: Proton Therapy
44. QLQ-HN 35: Quality of Life Questionnaire-Head and Neck 35
45. RMS: Rhabdomyosarcoma
46. RT: Radiation Therapy
47. SR: Systematic Review
48. SSPedi: Symptom Screening in Pediatrics tool
49. TBI: Total Body Irradiation
50. TP: Proton Therapy
51. TRSC-C: Therapy-Related Symptoms Checklist for Children
52. TPN: Total Parenteral Nutrition
53. QoL: Quality of Life
54. VAS: Visual Analogue Scale
55. WBS pain scale: Wong-Baker Faces Pain Rating Scale
56. WHO: World Health Organization

Chapter 1: Introduction

According to the World Health Organization, in 2020 nearly 280 000 children and young adults around the world were diagnosed with cancer, and about 110 000 died from it (1) Fortunately, due to substantial developments in treatment and remedies, the number of mortalities continues to decrease. The survival rate has improved with the aid of several chemotherapeutic agents. In the United States, the overall 5-year survival rate for cancer is 85% for those under 15 years of age and 86% for 15-19 year olds. In Canada, the 5-year survival rate of cancer in 0–14-year-olds is 84% (902) and 85% for 15–19 year olds (3). The 5-year survival rate indicates "the percentage of people who will be alive 5 years after diagnosis. It does not include those who die from other diseases" .

The survival rate of cancer in pediatric patients depends on factors such as the type of cancer, cellular changes, assigned treatment, and the general health of the patient (4). The term pediatrics can be classified into the following categories: infancy (birth-2 years), childhood (2-12 years) and adolescence (12-21 years) (5) The most common pediatric malignancies are leukemia, brain tumor, lymphoma, Wilms' tumor, and neuroblastoma (1). Frequently used treatment modalities include surgery, chemotherapy, immunotherapy, radiation therapy, and stem cell transplant (6). Chemotherapy and radiation therapy function by destroying fast growing, rapidly dividing cancerous cells (6). However, these therapies cannot differentiate between healthy cells and cancerous cells. As a result, healthy cells in the body that are actively multiplying and dividing, such as hair follicles, bone marrow, and the lining of the digestive system, are adversely affected (7).

The oral cavity is the first part of the digestive system. There is a high turnover rate of cells in the oral mucosa which makes it susceptible to damage from cancer therapies, resulting in uncomfortable conditions – referred to in the dental literature as 'oral complications' or 'effects' – in the mouth (8). In this thesis, I will use the term oral complications to refer to these resultant conditions. For example, oral mucositis is a condition characterized by mucosal inflammation resulting in painful ulcerations, infections, and difficulty eating, drinking, or swallowing (8). Thus, while cancer therapy is crucial for battling the disease, the treatments can also influence the oral health and resultant QoL of cancer patients. These complications can be particularly difficult for children (9). For example, oral mucositis can negatively impact children's nutritional status, functionality, and treatment adherence (10). In addition, cancer therapies may

affect the development of a child's dental and facial structures during the period of growth; the risk is greater when treatment is administered before the age of three (10). Radiation exposure can lead to abnormal craniofacial structures and skeletal malocclusions in children (10).

Pediatric cancer patients may experience early and late oral complications due to cancer treatment. The early complications, also known as acute effects, are those that occur during or shortly after treatment is completed (9). These complications are also classified as 'short-term' based on the duration of the complication: they develop during treatment and usually resolve after the treatment (9). They include oral mucositis, gingivitis, dry mouth, taste changes, and oral infections such as candidiasis and herpes (9). In contrast, late complications (or 'long-term') occur after months or years, including in the period of remission (9). Some examples of late complications are dental developmental anomalies, dental caries, jaw malformations, and secondary malignancies (9). Altogether, these complications can be distressing for pediatric cancer patients leading to pain and discomfort, as well as affecting self-esteem (9). They can also negatively affect oral functions such as speaking, chewing, and swallowing (10) and have long term repercussions.

Author's academic background and professional experience

In India, I graduated with a bachelor's in dental surgery and worked as a general dentist at a hospital. My interest in community oral health emerged during my internship as part of my undergraduate degree. While volunteering, I provided free dental checkups to underprivileged individuals in field camps held in schools and remote locations. Although I enjoyed practicing clinical dentistry, I was intrigued by dental research, but I was unsure of how to proceed. This inspired me to apply for a master's degree in dental sciences at McGill University in the cluster of population oral health as a steppingstone towards my career in dental research.

As I was selecting a topic for my thesis, I asked my supervisor if I could choose a cancer-related subject. Since my sister passed away from cancer a few years ago, I wanted to work on a topic related to cancer and oral health, as I have expertise in this area. The study also had to be carefully planned in light of the global pandemic. Taking all these factors into consideration, my supervisor recommended that I update a previous project. In 2012, Noronha and Macdonald published a scoping review on the "Impact on quality of life due to therapy-related oral complications in pediatric cancer patients" (9). The findings from their review show that pediatric cancer patients experience the aforementioned early and late oral complications. These conditions impact their

oral health and ultimately their QoL. The complications affect the physical, functional, and psychosocial health of children who have undergone cancer therapy (9), which can continue to affect them months or years after treatment is completed.

Purpose of the study

The objective of this master's thesis was to update this previous review, summarizing current literature on developments in pediatric dentistry and oncology as a way to contribute to improving treatment and care for pediatric cancer survivors. Working with a team, including my supervisor and two other graduate students (Nona Kakhki and Olawale Dudubo), we hypothesized that in the 10 years since the original work, the literature would have grown substantially in the domain of cancer treatments as well as regarding attention to children's OHRQoL, a new concept that has been growing in dental research.

I led this review with the help of this team. The methodology used for this scoping review is informed by Arksey and O'Malley's methodological framework, Levac et al. and the Joanna Briggs Institute (11-13). Scoping reviews are a type of research synthesis that aim to map the literature on a specific subject or research domain and provide an opportunity to describe key concepts and gaps in the literature (14). I reviewed the published literature in the past ten years.

Building on the previous review, we added the concept of OHRQoL, "a multidimensional construct that includes a subjective evaluation of the individual's oral health, functional well-being, emotional well-being, expectations and satisfaction with care, and sense of self"(15). As mentioned above, OHRQoL was not incorporated into the original review; the authors were interested in "understanding the overall impact of treatment-related complications on a patient and not just the impact on health due to treatment" (9). Studies on OHRQoL among children with cancer were scarce at the time, as the concept of OHRQoL was underdeveloped (9). Therefore, this study also intended to assess the extent to which the literature has expanded in regard to OHRQoL in children and adolescents with cancer.

In addition, a new approach to child-focused research has started to engage children directly in research to better understand their experiences first-hand (9). Further, given that OHRQoL is a subjective measure, we were interested to explore if or how research on the impact of cancer treatment on children's QoL may have increasingly included children since the original review

(9). Our objective was to examine the literature subsequent to the previous review and examine if and how children's perspectives had been considered in understanding how cancer treatment affects their QoL. By comparing our findings with the results of the previous review, we aimed to identify any advancements in including children's perspectives in this field of research.

The following chapter provides an overview of current research on pediatric cancer, oral complications resulting from cancer treatment, QoL, and OHRQoL. In chapter 3, the rationale and overview of the scoping review methodology is explained. Following, chapter 4 includes the descriptive analysis of the data, and chapter 5 presents the Discussion and chapter 6 presents the Conclusion. This thesis concludes with the appendices, which include the PRISMA-ScR flow diagram, search strategy, the data analysis table with the data extracted from the literature examined in our study, as well as data tables, graphs, and charts.

Chapter 2: Literature review

This chapter defines and explains the core concepts used in this thesis project. It starts with a summary of the most common pediatric cancers, followed by frequently used treatment modalities. It also provides a synopsis of the oral complications due to cancer therapy. Finally, it reviews literature about the QoL and OHRQoL of pediatric cancer survivors, as well as the measures to assess these constructs in children and ends with the rationale for this thesis project.

2.1 Pediatric cancer survivors and oral health

Pediatric cancer survivors experience early and late dental complications resulting from cancer therapies (9). The term survivorship, when used in the context of cancer survivors, encompasses the overall physical and emotional well-being of the individual starting from the moment of diagnosis and continuing throughout their life (9). The period of survivorship involves the physical, psychological, social, and financial impacts of disease on the individual, throughout the treatment process and beyond (9). For children, chemotherapy can interfere with tooth development, and radiotherapy can affect dental structures by destroying the tooth bud or surrounding soft tissues and salivary gland dysfunction. Cancer therapy can also impact craniofacial development, and temporomandibular joint function (16). Moreover, radiation to the head and neck region and hematopoietic stem cell transplantation elevates the risk of secondary neoplasms in the oral cavity (16).

Children who receive cancer therapy before 3 years of age have a high incidence of dental anomalies and developmental dental defects as the affected teeth are in their initial formative stage and sensitive to the effects of cancer therapy (10). Furthermore, these children have greater prevalence of caries, gingival inflammation, and xerostomia in contrast with individuals that do not have a history of cancer (10). Due to these complications, pediatric cancer survivors experience poor oral and dental health (16). The oral and dental complications of cancer therapies can cause pain, speech impairments, eating, smiling, and personal dental care, which significantly impact the QoL of these patients (9).

In the past decade, the overall childhood cancer mortality rate has decreased; this is attributed to advancements in healthcare facilities and the development of novel therapeutic strategies and targeted drugs for pediatric cancer (17) As the number of pediatric cancer survivors increase, it is crucial for healthcare providers to be knowledgeable about the potential oral and dental treatment-

related complications to facilitate early detection and interventions that can optimize health and QoL (18). During the initial stages of cancer treatment, primary care providers should assess children's oral health to anticipate potential complications (18). It is also important to maintain oral hygiene for pediatric cancer patients throughout treatment and as well as survivorship (18). Often cancer survivors are not aware of the dental complications associated with cancer therapy; they may rely on health professionals for education. Effective communication between primary care providers, radiation oncologists, oncologists, and dentists is essential to ensure optimal care for these patients (18). Good oral and dental health is crucial for nutrition and QoL; however, many health care providers receive little training in this area (18). If dentists have access to the cancer treatment summary, they can assess the potential risks imparted by the therapies on oral and dental structures. The dentist and primary care provider can discuss these complications with the patient and their caregivers before providing care. Therefore, it is important to integrate dental care into cancer treatment protocols to improve the QoL of childhood cancer survivors.

2.2 Childhood cancers

Childhood cancers constitute a heterogeneous group of malignancies with varying occurrence patterns, aetiologies, treatments, survival rates, and early and late complications. (19) There are at least 12 major forms of pediatric cancer and more than 100 subtypes (20). Cancer can affect any part of a child's body. Leukemia and central nervous system tumors account for the majority of cancer diagnoses among children (20). There are several other types of childhood cancers that occur frequently, including neuroblastoma, soft tissue sarcoma, Wilms' tumor, non-Hodgkin's lymphoma, Hodgkin's lymphoma, retinoblastoma, osteosarcoma (21).

Complications resulting from cancer, or secondary to cancer treatment, can affect the mouth (22). For example, children with acute myeloid leukemia may present with gingival enlargement and ulcerations resulting from neutropenia or the infiltration of rapidly multiplying immature leukocytes (blast cells). Additionally, chemotherapy and radiotherapy can cause complications such as mucositis and xerostomia in children with acute myeloid leukemia, as these treatments target rapidly dividing cells (23). Oral and dental complications associated with pediatric cancer treatment can result in oral infections, delayed speech, nutritional deficiencies, sleep disturbances, or aesthetic concerns with a negative impact on the QoL of cancer survivors (18).

Types of pediatric cancer, their treatments, and their oral health effects.

The following are the five types of childhood cancer that frequently lead to oral complications in children, either as a result of the cancer itself or the treatment methods.

2.2.1. Leukemia

Leukemia develops due to uncontrolled proliferations of hematopoietic stem cells, which result in neoplastic cells that fail to differentiate and do not undergo programmed cell death (23). When precursor cells do not mature, they accumulate in the bone marrow, suppressing normal blood cell production (hematopoiesis), resulting in a lack of mature leukocytes, erythrocytes, and platelets. Acute leukemia manifests in a sudden and aggressive manner (23). Acute lymphoblastic leukemia is the most frequently diagnosed cancer in children, constituting 25% of all childhood cancer and accounts for 72% of all childhood leukemia cases (24, 25). The oral cavity is a vulnerable site to complications related to acute leukemia and chemotherapy. Oral complications such as gingival enlargement can develop due to the leukemia resulting from the infiltration of leukemic cells in the gingiva, whereas the effects of chemotherapy can make the oral cavity susceptible to infections and ulcers (26). In most cases, these complications are acute (mucositis, reduced salivation, opportunistic infections, bleeding), however in some instances they can be long-term and affect the dental and craniofacial health of the child (27).

A recent study investigating the OHRQoL of children with acute leukemia noted that the most commonly reported dental complications were calculus deposits, misaligned teeth, caries, sensitivity, and oral ulcerations (27). Children reported eating difficulties as the most frequently affected daily activity, while oral ulcers were the most common complaint (27). The findings of this study demonstrate that oral problems, in addition to general health problems, worsen the QoL of children with acute leukemia which is already compromised by the cancer and chemotherapy (27).

2.2.2 Central Nervous System tumors

Second to leukemia, pediatric brain and spinal cord tumors are the most common solid malignancy diagnosed in children. These central nervous system tumors have the highest mortality among pediatric cancers. There are various subtypes of central nervous system tumors such as teratomas, gliomas and medulloblastomas (28). Children with central nervous system tumors, especially in the brainstem region, often experience dysphagia (difficulty swallowing), which can cause aspiration of saliva, food, and fluids (29). Damage to the vagus nerve can result

in dysphonia (hoarse voice and change in voice pitch) (29). Female patients with tumors that cause hormonal imbalance may have vocal virilization and low frequency voices. These tumors can affect speech, language, swallowing, phonation and cause facial palsy or paralysis (29). The treatment of central nervous system tumors in children can involve a combination of surgical intervention, chemotherapy, targeted therapies, and cranial radiation therapy (30).

2.2.3 Burkitt Lymphoma

Burkitt lymphoma is an aggressive form of B-cell non-Hodgkin's lymphoma. There are three main variations of this cancer: the African (endemic) form (prevalent worldwide), the American (sporadic) form (prevalent in North America), and the immunodeficiency-associated form (31). The African Burkitt lymphoma form typically affects the facial bones and surrounding soft tissue, and is linked with Epstein-Barr virus (31). The prognosis of Burkitt lymphoma can be improved by early identification and treatment; however, a variety of symptoms can be present, which can lead to misdiagnosis and late treatment. Chemotherapy, radiotherapy, and surgery are among the treatment options for managing Burkitt's lymphoma in children (32). However, for oral Burkitt lymphoma, chemotherapy alone is often considered the primary treatment approach (32). If left untreated, the disease can be fatal (31). In terms of oral presentation, the mandible is the most commonly affected site, more specifically the posterior region of the jaw. Oral Burkitt lymphoma is characterized by swelling, pain, displaced dentition, facial asymmetry, tooth mobility and pain (33).

2.2.4 Neuroblastoma

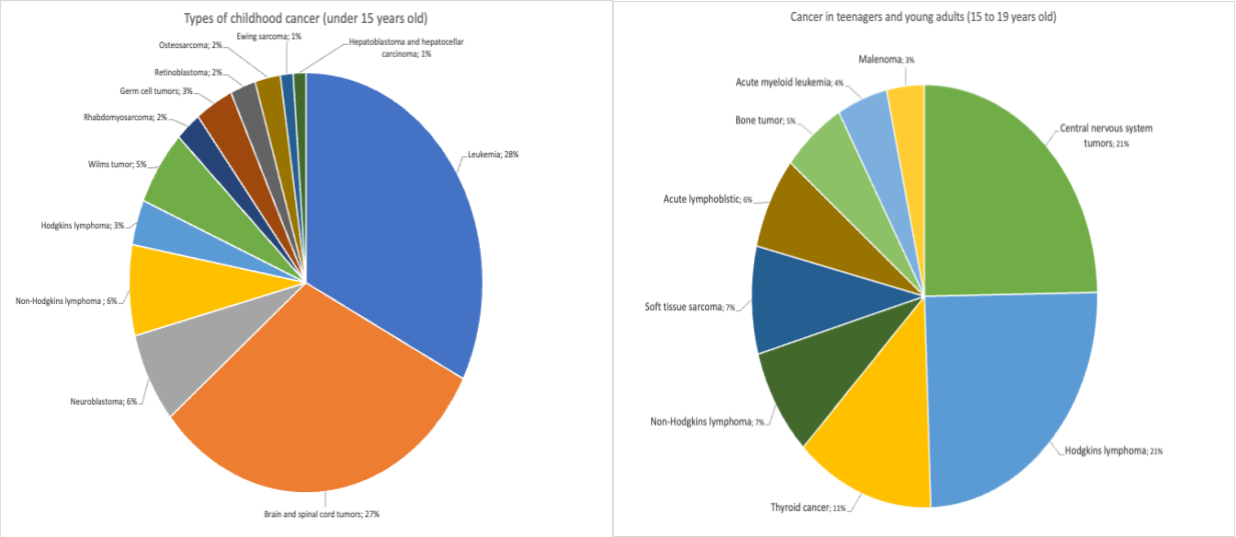
Neuroblastoma is a type of cancer that develops from neural crest stem cells in the embryo. It is considered the most common malignancy in infants whereas among children it is the most prevalent extracranial solid tumor (34). Children of all ages may experience a wide range of clinical outcomes, with potential for rapid remission in younger patients. However, there is a high risk of aggressive disease in older children (34). Treatment for neuroblastoma includes chemotherapy and radiation; these treatment modalities increase the risk of abnormal dental development in children which may adversely affect the child's QoL (35). A study investigated dental disturbances in children treated for neuroblastoma at an early age with chemotherapy and radiation therapy (35), finding that most children presented with dental developmental abnormalities, such as microdontia (small teeth), excessive caries, root stunting, hypodontia (missing teeth), and enamel hypoplasia (thin enamel) (35).

2.2.5 Rhabdomyosarcoma

Rhabdomyosarcoma is the predominant soft-tissue sarcoma observed in children and adolescents, frequently affecting the head and neck region. It is the third most prevalent extracranial solid tumor in the pediatric population, following Wilms' tumor and neuroblastoma (36). Rhabdomyosarcomas are characterized by their aggressive nature, high recurrence rate, and ability to metastasize through both blood and lymphatic pathways (36). Lesions affecting the posterior mandible, particularly the alveolar variant, are associated with a poor prognosis (36). Children who receive radiotherapy for head and neck rhabdomyosarcoma may experience long-term complications from the treatment (37). Radiotherapy significantly contributes to various dental complications in these patients, including microdontia, trismus, jaw hypoplasia, hypodontia, root stunting, xerostomia, and radiation caries (37).

The aforementioned childhood cancers are the most common types, each impacting the oral cavity directly or as a consequence of treatment. There are additional types of childhood cancers, as seen in Figure 1. It is important to note that while the data presented in the diagram is specific to the pediatric population in the United States, these cancer types affect children worldwide.

Figure 1: Types of childhood cancer, under 15 years and 15-19 years in the United States (6)



2.3 Treatment modalities

The treatment approaches employed for pediatric cancer are multiple; please see Table 1. The chosen treatment will be influenced by several factors, including the type of cancer, its location,

and the stage of the disease. In children with cancer, the treatment options may include a combination of surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, or hematopoietic stem cell transplantation (21). Chemotherapy includes a wide range of cytostatic drugs that are administered in various combinations and multimodal therapy approaches with the aim of eradicating tumor cells in individuals diagnosed with cancer (21). Radiation therapy uses high-energy radiation to target and destroy cancer cells and shrink tumors. It works by damaging the DNA inside cancer cells, which disrupts their ability to divide and grow (38). Targeted therapies specifically target and block the key biochemical pathways or abnormal proteins involved in tumor cell growth and survival (39). Immunotherapy aims to activate the body's immune system to trigger a sustained immune response that recognizes and destroys cancer cells (39). Targeted therapies and immunotherapy are particularly advantageous for childhood cancer patients due to their non-genotoxic mode of action and the ability to mitigate risks associated with severe late complications, including second primary malignancies (21). Moreover, immunotherapy utilizing monoclonal antibodies has become a valuable adjunct to chemotherapy, particularly in case of relapsed leukemia (40). Hematopoietic stem cell transplantation refers to the procedure of intravenous infusion of hematopoietic stem and progenitor cells to re-establish the production of blood cells in patients who have a compromised bone marrow or immune system (41).

The selection of treatment modalities should be carefully tailored to each individual case, taking into consideration the specific characteristics of the cancer and the child's overall health. The goal is to achieve the most optimal outcomes while minimizing potential long-term complications (42).

Table 1: Summary of the most common types of pediatric cancer and treatment modalities.

Note: This table was developed using information obtained from the website, www.cancer.net, which is funded by the American Society of Clinical Oncology. (6)

	Type of cancer	**Primary Treatment**	**Treatment for high risk or recurrent cancers**
1.	Leukemia	CT	BMT, RT
2.	CNS	SR, RT*, CT, TC	SR, RT*, CT, TC, BMT
3.	Neuroblastoma	SR, CT, RT	SR, CT, RT, CC, IM, BMT
4.	Lymphoma	CT, IM, TT	RT, BMT
5.	Wilms' tumor	SR, CT	SR, RT

6.	Rhabdomyosarcoma	SR, CT	SR, CT
7.	Germ Cell tumor	SR, CT	SR, CT, RT, BMT
8.	Retinoblastoma	SR, RT, CRT, LT	SR, RT, CRT, LT, CT, BMT
9.	Osteosarcoma	SR, CT, RT**	SR, CT
10.	Ewing sarcoma	CT, RT, SR	CT, RT, SR, BMT
11.	Liver cancer	SR, RT, CT	TT, IM

*RT is not advised in children below 3 years due to risk of cognitive complication

**RT is recommended if surgery is not possible

CT= Chemotherapy RT= Radiotherapy BMT= Bone Marrow Transplant SR=Surgery TC= Target Chemotherapy

CC=Combination Chemotherapy IM= Immunotherapy TT= Targeted Therapy

CRT= Cryotherapy LT= Laser therapy

2.4 Oral complications due to cancer therapy

Oral complications resulting from anticancer therapy are common among pediatric cancer patients; based on their onset they can be categorized as early (acute) or late (chronic).

2.4.1 Early (acute) oral complication

Early complications – also called 'acute' - refer to those that arise during therapy and subside within a month of treatment completion (43). Early complications include conditions such as oral mucositis, taste alterations, dysphagia, and opportunistic infections such as candidiasis (43).

a) Oral mucositis

According to cancer patients, oral mucositis has been reported as the most debilitating complication of treatment (44). Approximately 80% of children undergoing chemotherapy experience some degree of oral mucositis, although the incidence may vary depending on the type of cancer and treatment modality employed (44). For example, children with hematologic malignancies tend to have a higher incidence and more severe case of oral mucositis than those with solid tumors (44). The development of oral mucositis can be attributed to the effects of chemotherapy and radiation, which target rapidly dividing cells. As a result, the oral mucosa is susceptible to damage due to the high turnover rate of cells in this region. Mucosal inflammation

can lead to painful ulcerations, infections, and difficulties eating, drinking, and swallowing (8). These complications significantly impact the patient's nutrition, functional abilities, and adherence to cancer therapy (44).

b) Taste alterations

Taste alterations, also known as dysgeusia, is a taste disorder characterized by foul, salty, rancid or metallic taste in the mouth (45). It commonly begins at the onset of chemotherapy and may continue even after its completion, lasting for weeks or months (46) . Furthermore, taste alterations can sometimes occur prior to the initiation of therapy; this supports the notion that cancer itself can play a role in the occurrence of taste alterations (46). Taste alterations impact the enjoyment of food, which greatly contributes to an individual's QoL (47). Taste alterations have been linked to increased morbidity and mortality due to insufficient energy and nutrient intake, resulting in weight loss, malnutrition, a compromised immune response, and reduced adherence to chemotherapy in cancer patients (47). A recent study reported that taste changes observed in children undergoing cancer therapy have a negative impact on QoL; these changes were frequently described as "disappointing" or "frustrating" (48). In children, taste alterations can lead to changes in their eating behavior, including changes in food preferences and appetite (48). While some of these variations may be attributed to chemosensory alterations, children also reported certain medications or hospital food as contributors to their altered eating habits (48).

c) Dysphagia

Dysphagia refers to difficulty in swallowing. It can present as a short- or long-term complication of cancer therapy (49). Irradiation can cause the muscles and lining of the mouth, throat, and esophagus to become stiff, thereby impairing the normal swallowing process (50). Radiation therapy can also lead to the narrowing of the swallowing passage, a condition known as 'stricture' (51). Treatment with certain chemotherapeutic drugs, including vinblastine, dactinomycin, and methotrexate, can lead to injury to the esophageal mucosa. These drugs have been associated with the development of esophageal ulcerations and fibrosis, which can eventually lead to the formation of strictures in children (52). Cancer itself can lead to pre-treatment dysphagia. Malignancies in the head and neck region, particularly in the pharynx, tongue, and esophagus, can cause dysphagia. The presence of a tumor in the head and neck region can affect the motility of the structures involved in swallowing (49). Moreover, patients who experience disordered swallowing prior to treatment are at increased risk of developing dysphagia following treatment (53).

c) Opportunistic infections

Opportunistic infections can develop in immunocompromised individuals. Candidiasis is a prevalent opportunistic infection in cancer patients, secondary to decreased saliva production and alterations in saliva quality (43). In addition, the use of broad-spectrum antibiotics, corticosteroids, cytostatic substances, and invasive surgical procedures increases children's susceptibility to fungal infections (54). Moreover, chemotherapy drugs might predispose patients to candidiasis because they affect epithelial cells in the buccal mucosa, which may lead to fungal septicemia (54).

2.4.2 Late (chronic) oral complications

Late (chronic) complications arise after therapy completion and, in certain instances, may persist permanently (43). Examples of chronic complications include trismus, hyposalivations, xerostomia, radiation caries, dental developmental anomalies, osteoradionecrosis, and dysphagia. In addition, surgical intervention is often required to treat head and neck cancer, which can have enduring physical consequences impacting the patients' oral function and social life (43).

a) Trismus

Trismus refers to the inability to completely open the mouth (55). Radiotherapy can have detrimental effects on the muscles and bones, causing issues such as muscle fibrosis, hindered bone growth, and incomplete development, ultimately leading to jaw dysfunction. Trismus can also develop following surgical resection of the maxilla or mandible due to the postoperative healing process, fibrosis and contraction scars (55).

b) Hyposalivation and xerostomia

Childhood cancer survivors have an increased prevalence of salivary gland dysfunction; it can manifest as hyposalivation, which is a decrease in salivary secretion and/or xerostomia, which is the subjective sensation of a dry mouth (56). Salivary gland dysfunction is a significant late complication that may be underestimated and has a negative impact on overall health (56). Dry mouth is caused by the effects of chemotherapeutic agents that decrease salivary flow rates and alter saliva composition (57). Irradiation of the salivary glands causes damage to the salivary gland tissues; which can lead to significant reductions in salivary gland function and alterations in saliva composition (58). Saliva plays a crucial role in maintaining oral health by protecting the oral mucosa and teeth. Hyposalivation can lead to various complications including oral discomfort, pain, difficulty speaking, chewing, and swallowing, impaired taste

perception, poor nutrition, sleep disorders, and dental erosion (56). Xerostomia is associated with an increased risk of dental caries and an increased likelihood of oral mucosal infections in children (56).

c) Radiation caries

Post-radiotherapy head and neck cancer patients are more prone to dental caries because radiotherapy reduces saliva production and damages tooth structure (59). Radiation caries progress rapidly within a few months following radiation therapy (60). Due to the rapid division of presecretory odontoblasts (dentine forming cells) during tooth development in children, they are particularly susceptible to the adverse effects of alkylating agents or radiation. The impact on the dentin calcification process consequently disrupts the enamel mineralization, leading to enamel opacities and increased vulnerability to caries in children undergoing cancer therapy (61). Dental caries can result in pain and discomfort, and may have negative effects on the patient's QoL (59).

d) Dental developmental anomalies

Children receiving cancer treatment at the age of 6 or younger are reported to have a high prevalence of dental developmental anomalies (10, 62, 63). Dental developmental anomalies are often observed as a long-term consequence of childhood cancer therapy (64). The majority of anti-neoplastic drugs used in the treatment of childhood malignancies hinder cell growth or impact cells involved in odontogenesis (tooth development) (65). Some common dental developmental anomalies include alterations in tooth shape (microdontia, macrodontia, and taurodontia), hypodontia, enamel defects such as discolorations and hypoplasia, disorders in root formation (blunt root, tapering root, and delayed root development), retained teeth, altered eruption patterns, coronal hypocalcification, early closure of root apices, and tooth agenesis (congenital absence of teeth) (65). These anomalies can result in various complications, including anatomical, functional, and aesthetic concerns. Microdontia leads to aesthetic, functional, and occlusal issues, while hypodontia impacts the dental arch and disrupts tooth symmetry, aesthetics, and functionality (63). Furthermore, severe dental developmental anomalies may lead to malocclusion, affect facial development, and have an impact on QoL of childhood cancer survivors (64). Results from a recent study reported that children who received cancer therapy had a higher incidence of malformed teeth compared to children with no history of cancer (63, 66). In addition, the combined use of chemotherapy and radiotherapy in antineoplastic treatment seems to elevate the risk of

dental developmental anomalies (63). Furthermore, radiation targeting the patients' head and neck region was identified as a significant factor in increasing the risk of dental developmental anomalies in children (63).

e) Osteoradionecrosis

Patients who undergo radiotherapy in the head and neck have a long-term risk of developing osteoradionecrosis of the jaw, a condition characterized by the non-healing exposure of bone accompanied by tissue death (67). It typically originates from a breach in the oral mucosa and lasts for at least of 3 months in individuals who have previously undergone radiotherapy (68). The symptoms of osteoradionecrosis include trismus, oral pain, foul odor, and difficulties chewing. The oral mucosa above the bony lesion often exhibits an ulcerated, rolled border that may bleed when examined (36).

2.5 QoL and OHRQoL

The World Health Organization defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment" (69). As this definition illustrates, QoL is a subjective assessment of an individual's perception of their reality in relation to their goals "as viewed through the lens of their culture and values" (70).

The definition of QoL also emphasizes the connection between QoL and health factors (71). The concept of QoL recognizes that the state of health is multidimensional (71). One such dimension of health includes OHRQoL, which is a subset of Health-Related Quality of Life (HRQoL) (71). OHRQoL reflects an updated perspective on dental care with the primary objective of dental treatment being improving oral health (72). It is defined as "a multidimensional construct that reflects (among other things) people's comfort when eating, sleeping, and engaging in social interaction; their self-esteem; and their satisfaction with respect to their oral health" (73). OHRQoL serves to gauge the effectiveness of treatment outcomes from the patient's perspective, considering their perceptions of illness and the limitations experienced in their everyday activities (71). OHRQoL is influenced by several factors; these include functional factors, psychological factors, social factors, and subjective perceptions of pain and discomfort (72).

Why is QoL and OHRQoL of pediatric cancer survivors important?

Medical advancements have led to a higher survival rate for paediatric oncology patients; however, the QoL of these children is still affected by cancer treatment, and efforts to enhance their QoL continue (74). The assessment of QoL concerning the oral health of pediatric cancer survivors is essential due to the significant impact of cancer therapies on patients' eating habits, social relationships, and interactions (74). Therapy-induced complications often lead to treatment interruptions to address opportunistic infections, thereby impairing medical therapy and prolonging hospitalization periods (74). Children's oral health has a significant impact on various aspects of their lives, including eating, smiling, speaking, and socializing. Dental conditions like dental caries can cause pain, which can affect a child's daily activities, such as missing school or experiencing difficulty eating (75). Additionally, facial appearance, which is closely tied to body image, self-esteem, and emotional well-being, plays a crucial role in social interactions for children (75). There are limited studies linking oral health with cancer patients' QoL (74). Moreover, the scarcity of research is even more pronounced when it comes to children and adolescents, as the available studies focus on the effects of cancer treatment on the oral cavity rather than its broader impact on QoL (74). Moreover, conventional approaches to measure oral health rely on clinical dental indices, which focus on the presence or absence of oral diseases (76). However, these methods do not provide information about the children's overall oral well-being, including their subjective experiences and functional aspects such as the ability to chew and enjoy food (76). In response to this limitation, measures of QoL have been developed to evaluate the holistic impact of oral health, encompassing both the physical and psychosocial aspects of well-being (76). Such QoL measures aim to capture an individual's perceptions and experiences related to their oral health, providing a more comprehensive assessment beyond clinical indicators alone (76). Therefore, it is critical to measure the oral impacts on children, as this information can assist researchers, clinicians, and policymakers in assessing the need for dental care, prioritizing treatment, and evaluating the outcomes of interventions (75).

There are several measures to evaluate OHRQoL in children. For example, the Child-Oral Impacts on Daily Performances (Child-OIDP) tool assesses the influence of oral conditions on various aspects of a child's daily life, including eating, speaking, oral hygiene practices, smiling, emotional well-being, relaxation, academic performance, and social interactions (77). A study using the Child-OIDP scale to evaluate the impact of OHRQoL on children with acute leukemia (27)

reported that the prevalence of dental problems that affect daily activities such as eating, speaking, oral hygiene practices, relaxation, sleep, smiling, studying, and social interactions was 52.5% over the past three months (27). The most affected activity was eating difficulty, reported by 45% of children (27). The study concluded that children aged 11 and above can self-assess their own general and oral health, and can recognize the impact it has on their daily lives (27).

The Child Oral Health Impact Profile (COHIP) is an OHRQoL measure for children and adolescents (78). COHIP was the first measure designed to incorporate both positive and negative impacts on health; this allowed it to measure not only the absence of oral conditions but also the positive aspects and improved well-being resulting from oral care (78). The COHIP has demonstrated good validity and reliability in children and adolescents aged 8-15 years (78). The questionnaire is available in two versions: a long version with 34 items and a short version with 19 items. The COHIP assesses OHRQoL across five domains i.e., Oral Health, Functional Well-Being, Social-Emotional Well-Being, School Environment, and Self-Image (78).

Conclusion and rationale

In summary, pediatric cancer survivors experience significant short- and long-term oral complications resulting from cancer therapies. These complications can have adverse effects on the QoL and OHRQoL of children, affecting their physical, psychological, and social well-being. Dental anomalies, developmental defects, and poor oral health are common among these survivors, emphasizing the need for early detection and intervention. As advancements in healthcare and targeted therapies have led to an increase in the number of pediatric cancer survivors, it becomes crucial for healthcare providers to be well-informed about these potential complications. Integrating dental care into oncology and providing education to patients and caregivers can contribute to improved oral and dental health to enhance the QoL for childhood cancer survivors. Additionally, identification of gaps in the current literature is vital for determining the specific areas that require improvement in order to provide optimal care for pediatric patients and enhance their QoL.

The findings of the original review presented the oral complications of cancer treatment and demonstrated the impact of early and late complications on the QoL of children up until 2011. This study aimed to update and expand on the findings of the original review. In addition, it aimed

to explore recent advancements in cancer treatments and the growing attention to children's OHRQoL in dental research.

The subsequent chapter outlines the methodology used in this study and describes the rationale for its selection.

Chapter 3: Methodology and methods

This chapter describes the methodology chosen for this study – scoping review - as well as an description of the scoping review process we followed.

3.1 Why a scoping review?

Developments in cancer research depend on the collaborative efforts of researchers, clinicians, patients, and other stakeholders. Medical decisions taken by health care providers are influenced by evidence-based research (79). Evidence-based practice can be defined as "applying or translating research findings in our daily patient care practices and clinical decision-making" (79). Evidence-based practice aims to integrate available evidence with clinical expertise. Thus, obsolete procedures can be eliminated, and healthcare professionals can choose scientifically validated methods of treatment that align with their patients' unique needs and preferences (79). Therefore, efficient and effective cancer treatment relies on research to gather evidence on the benefits and potential risks of various cancer therapies.

A scoping review is an exploratory research method that scopes the literature on a given topic (14). It identifies gaps in current research and highlights domains that require further investigation. A scoping review has been defined as "a type of research synthesis that aims to map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research"(14). A review of this nature aims to identify linkages rather than outcomes, while mapping emphasizes the characteristics involved (80). Therefore, the purpose of conducting a scoping review is to identify the available evidence on a subject, clarify key concepts in the literature, examine how research is conducted in a certain field, and identify and analyze knowledge gaps (81). Furthermore, as current approaches to searching in scoping reviews borrow from systematic review searching where appropriate, this allows for a highly comprehensive sample of the literature (82).

One of the advantages of a scoping review methodology is its versatility to accommodate a broad research question and a wide range of research objectives (83). Systematic reviews are typically designed to answer a specific question or series of questions based on a predefined set of delimiting factors specified in the protocol, whereas scoping reviews take a broader approach with

the aim of mapping literature and addressing broader research questions (83). In addition, unlike traditional systematic reviews, scoping reviews are not constrained by strict inclusion criteria. The scoping review methodology allows for an iterative approach to explore and identify relevant studies and map the literature (83, 84). Moreover, scoping reviews serve as valuable tools for mapping a body of literature, taking into consideration factors such as time, location, source, and origin (83). Given the aforementioned attributes of a scoping review, this methodology was ideal for our study as it aligned with our objectives.

The primary objective of our study was to explore the current literature pertaining to the impact of therapy-related oral complications on the QoL of childhood cancer survivors. We were interested in assessing the extent to which the literature has expanded in the realm of cancer treatments and resultant oral complications in children and adolescents since Noronha's original review. Furthermore, building on the gaps identified in the original review, our aim was to examine the existing literature regarding OHRQoL in children and adolescents with cancer; due to a lack of literature on this topic during the earlier review, this aspect was not included. We wanted to learn if there had been an increased focus on OHRQoL for pediatric cancer survivors. Finally, we were interested in analyzing the extent to which children's contributions were incorporated into the research, including their experiences and perspectives. QoL is a subjective concept; it is critical to examine whether the studies acknowledged and incorporated children's insights.

In conclusion, a scoping review methodology can aid in a thorough synthesis, mapping and summarizing of the existing literature. By applying this methodology, advancements in literature can be identified along with important gaps and research priorities for the future. This review can facilitate the development of interventions and policies in support of pediatric cancer survivors to improve their QoL.

3.2 Methodology

The protocol for this project has been a team effort. I would especially like to acknowledge Nona Kakhki, a PhD student, who took the lead in writing the protocol as she will apply the results of this review to her doctoral work. Therefore, she is the first author of the protocol. In addition, she contributed to the screening process by being a second reviewer and assisting with article selection. Her valuable input and efforts significantly contributed to our project's overall success.

My own contribution to this protocol involved reviewing various templates, such as scoping protocols in BMJ and JBI, to prepare the protocol outline. Additionally, I drafted the preliminary version of the protocol and collaborated with Nona on editing the final version.

Following is the version of the protocol that will be submitted to a journal shortly.

What are the impacts of oral complications from cancer therapy on the quality of life of children? A protocol to update a scoping review.

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Abstract

Introduction Cancer treatments can damage healthy tissues and organs, and leave harmful impacts on cancer survivors, especially on children and adolescents. The oral complications from cancer treatment can occur during or soon after treatment, or months – even years – later. Cancer treatments can also affect the child, psychologically and socially, by hindering their speech, eating, sleeping, and social interactions. These complications can have profound impacts on children's quality of life (QoL). Building on a previous review published in 2012, this scoping review aims to identify and map the current evidence base underpinning the oral health-related impacts of cancer treatment on the QoL of children with cancer.

Methodology and methods Our methodology is informed by Arksey and O'Malley's methodological framework, Levac et al. and the Joanna Briggs Institute (11-13). Five electronic databases will be systematically searched using a predefined search strategy. Two reviewers will independently screen the retrieved articles using Rayyan software and chart data from included articles. One of the team's senior research members will act as a third reviewer and make the final decision on disputed documents. We will include literature with a focus on oral health-related quality of life (OHRQoL) of children undergoing cancer treatments. Following the selection of

studies, data will be extracted, synthesized, and reported thematically and the relevant stakeholder's insight will be added to our results.

Ethics and dissemination No ethical approval is required as exclusively secondary data will be used. Results will be disseminated in cancer and oral health conferences, symposia, and a peer-reviewed journal. The information extracted from this review will also be the base for a qualitative study on the quality-of-life impacts of oral health effects of childhood cancer including children's perspectives.

Introduction

According to the World Health Organization, each year approximately 400,000 children and young adults are diagnosed with cancer globally (85). The most common types of childhood cancer are leukemia, lymphomas, brain cancer, and solid tumors, including neuroblastoma and Wilms' tumor (86). Whereas childhood cancer mortality used to be dire, today upwards of 80% can be cured with treatments such as pharmaceuticals, surgery, and radiotherapy (85). Notwithstanding the vast improvement in mortality rates, cancer treatments can leave devastating impacts on cancer survivors, damaging healthy tissues and causing systemic complications. These complications can be especially devastating for young people who experience high rates of radiotherapy- and chemotherapy-induced complications (87). A common location for these complications is the oral cavity, including the soft and hard tissues in the mouth, from the lips anteriorly to faucial pillars posteriorly (88, 89).

Treatment-related oral complications can occur during or soon after treatment, or months – even years – later. They are classified as early (acute) complications and late (chronic) complications. (90) Early oral complications include oral mucositis, xerostomia (dry mouth), oral infections (e.g., candidiasis and herpes virus infections), and taste disturbances. Late complications include dental decay, and abnormalities in dental and jaw development. Combined treatments such as combination of chemotherapy with radiation increase the risk of dental problems such as dental caries, taste disturbances, and missing teeth or roots (89). These conditions influence the physical, functional, and psychosocial health of children who have undergone cancer therapy, and can continue to affect them months or years after the treatment is completed (87).

Evidence has highlighted the profound impact that oral health can have on a child's QoL (9, 91-93). Specific to childhood cancer, a scoping review by Noronha and Macdonald on the oral

complications of cancer treatment demonstrated the devastating impact of such complications on the QoL children (9). Children in the reviewed studies experienced both early and late oral complications as follows:

- Mucositis was the most common early complication in this review, affecting almost 100% of children undergoing chemotherapy (8). In addition to pain, mucositis has psychological and social impacts; for example, speech issues associated with oral mucositis can reduce a child's engagement in social interaction (94).

- Xerostomia is a result of damage to the salivary gland which changes the consistency and amount of saliva in the mouth. It can be an early complication when caused by chemotherapy and can have a long-term complication when caused by radiotherapy to the head and neck. Decreased salivary flow and increased viscosity can cause difficulty with chewing, swallowing, speech, and also affect the function of taste buds resulting in taste alteration, causing a dislike for some foods and appetite loss. This taste alteration can result in nausea, vomiting, pain, and discomfort (89).

- After mucositis and xerostomia, taste disturbance after chemotherapy were found to be the next most common complication (9). These children were more sensitive to bitterness, and had taste recognition errors, which affected their appetite. This appetite change can lead to malnutrition and impair QoL by affecting appetite, body weight, and psychological well-being (95).

- According to this review, more than 80% of children treated for cancer had at least one longer-term dental anomaly (e.g., root shortening, smaller teeth, enlarged pulp chambers). These malformations arise during remission and can hinder eating, speech, and social interactions, and can require additional complex clinical interventions (9).

Since this scoping review, the oral health-specific measure, OHRQoL, has become more commonly used in studies on the effects of oral diseases and oral complications on patients' oral symptoms. This multidimensional construct focuses on how an individual's oral health affects their comfort, abilities and well-being (e.g., eating, sleeping, social interactions, self-esteem). (96) The increased use of OHRQoL follows the growing recognition of oral health as an essential component of systemic health and general wellbeing (97, 98). As oral health is strongly age-

dependent, and therefore OHRQoL in children is different from adults, this measure has been adapted for child populations (99).

Further, according to this prior review, there was a dearth of qualitative research into the experiences of children about how oral complications of cancer therapy impacts their QoL (9). This result is not surprising; in a 2007 review of pediatric oncology studies, 85% of studies on childhood cancer did not solicit patient-reported outcomes, instead relying on parent reports and health care professionals reports (100). While having the parents' and HCPs' perspective is clearly important, it has become evident that children's perspectives are not always consistent with adults. As a result, a new approach to child-focused research has started to engage children directly in research to better understand their experiences first-hand (101). This movement is consistent with article 12 of The United Nations Convention on the Rights of the Child which stipulates that children's experiences must be rendered through their own voices and that they have a right to express their own views in matters that affect them (102). While dental research has started to follow this trend (103), it is not known if or how research on the impact of cancer treatment on children's QoL has followed suit since Noronha and Macdonald's review up to 2011.

Therefore, the aim of this scoping review is to scope the literature published since 2011 for the impacts on QoL due to therapy-related oral complications on childhood cancer survivors and the children's contribution in producing this knowledge. Below is the procedure we will follow to conduct this scoping review.

Methodology

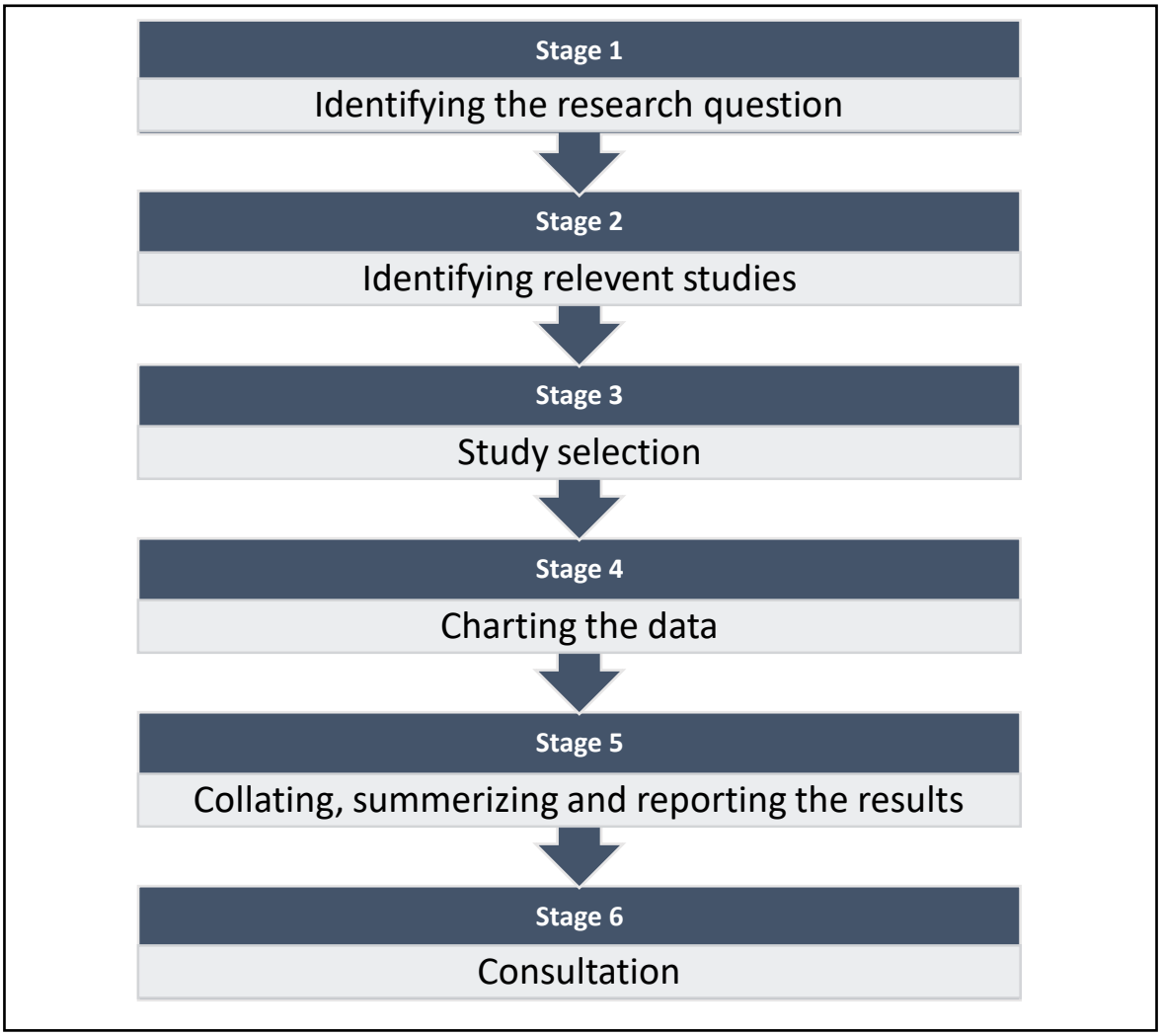
A scoping review is an exploratory research method that scopes the literature on a given topic and identifies gaps in the current research and highlight areas that require further inquiry (104). The purpose of conducting a scoping review is to identify the types of available evidence in a given field, clarify key concepts in the literature, examine how research is conducted on a certain topic or field, and identify and analyze knowledge gaps (104).

This protocol will follow the Joanna Briggs Institute Reviewer's Manual to assure transparency, accuracy, and completeness (13). We will also follow Arksey and O'Malley's methodological framework, which consists of six stages for conducting a scoping review: 1. Identifying the research question; 2. Identifying relevant studies; 3. Selecting studies; 4. Charting the data; 5.

Collating, summarizing, and reporting of results; and 6. Consulting with relevant stakeholders (11). (Figure 2)

All members of the research team developed, reviewed, and agreed with this protocol; we intend to complete the review by Fall 2023.

Figure 2: Arksey and O'Malley's Methodological Framework



1. Identifying the research question

Building on the work of Noronha and Macdonald mentioned above, the main objective of this review is to map and synthesize the knowledge on the impact of oral complications from cancer therapy on the QoL of children surviving cancer starting in 2011. Our primary research questions is:

What are the impacts of oral complications from cancer therapy on the quality of life of childhood cancer survivors?

And our secondary research questions will be: How are children involved in producing knowledge related to the effects of cancer treatment on their oral health-related quality of life?

2. Identifying relevant studies

The identification of relevant literature will consist of articles accessed through five electronic databases: MEDLINE/PubMed, Scopus, Embase, Web of Science, and PsychInfo. A librarian (MM) has created the search strategy; he will lead citation management and assist with search documentation. The initial search strategy has been piloted to verify breadth, comprehensiveness, and feasibility. This search strategy will be adapted and applied to each database. We will review the reference lists of included studies to identify relevant studies that were not identified in the initial search.

Table 2: Search Strategy

1. exp Antineoplastic Agents/
2. exp Radiotherapy/
3. exp Hematopoietic Stem Cell Transplantation/
4. exp Bone Marrow Transplantation/
5. (antineoplastic or chemotherap* or radiotherap* or ((h?ematopoietic or bone marrow) adj3 (SCT or transplant*))).tw,kw.
6. or/1-5
7. Oral Health/ or exp Dentistry/ or Halitosis/ or exp Stomatognathic Diseases/ or DMF Index/ or Periodontal Index/
8. (dentist* or endodont* or orthodonti* or periodont* or prosthodont* or apicoectom* or gingivectom* or gingivoplast* or glossectom* or "mandibular advancement" or alveolectom* or alveoloplast* or vestibuloplast* or "root canal" or (oral adj1 (care or health or hygiene or surgical or surgery or mucositis)) or oropharyng* or temporomandibular or TMJ or jaw or jaws or mandibular or maxillofacial or mandible* or maxilla* or "alveolar ridge" or dental or orthognathic or tooth or teeth or occlusion or malocclusion or mal-occlusion or odontolog* or tongue* or glossal or buccal or palatal or palate or palates or labial or lip or lips or gingiva* or gingiviti* or saliva* or DMF).tw,kw.

9. 7 or 8
10. "Quality of Life"/ or exp rehabilitation/ or exp eating/ or exp human activities/ or (rh or px).fs.
11. (quality of life or well-being or long-term or (daily adj1 (life or living)) or rehabilitat* or depress* or pain or immunosuppress* or "disease management" or "Child Oral Health Impact Profile" or C-DAS or CFSS-DS or COHRQoL or COHIP or CPQ or ECOHIS or FIS or OASIS or OHQoL or OHRQoL or QOL or P-CPQ or POQL or (("Early Childhood Oral Health Impact" or "Oral Aesthetic Subjective Impact" or "Corah Dental Anxiety" or "Family Impact") adj1 Scale) or "Children's Fear Survey Schedule" or (("Child" or "Parental-Caregiver") adj1 "Perceptions Questionnaire")).tw,kw.
12. 10 or 11
13. 6 and 9 and 12
14. limit 13 to "all child (0 to 18 years)"
15. exp Child/ or exp Pediatrics/
16. (infan* or toddler* or minors or boy? or boyhood or girl? or child* or schoolchild* or school child* or adolescen* or juvenil* or youth* or teen* or under*age* or p?ediatric*).tw,kf.
17. 15 or 16
18. 13 and 17
19. 14 or 18
20. limit 19 to (english or french)

3. Selecting studies

In this stage, all retained studies will be merged into a single Endnote library with duplicated articles removed. The merged Endnote library will be imported into Rayyan software (Qatar Computing Research Institute, QCRI) for screening. The study screening and selection process will be conducted by two members of the research team (AS and NA). The two reviewers will be calibrated: they will independently assess titles and abstracts of the first 50 studies according to the inclusion and exclusion criteria, after which inter-rater reliability will be measured using Cohen's k coefficient. The calculated coefficient will act as an indicator of whether reviewers understand and apply the inclusion criteria consistently. If there is low agreement (<0.40), the

reviewers will consult, and, if needed, adjust or reword the eligibility criteria. This process will be repeated until inter-rater agreement reaches substantial levels (>0.40).

Screening and selecting studies will then consist of 2 phases during which the reviewers will assess study inclusion against a set of predefined eligibility criteria outlined in Table 3.

Table 3: Inclusion and Exclusion Criteria

Inclusion criteria	
Population	✓ Data specific to children, 0-18yrs ✓ Studies with adults who had cancer during childhood (0-18yrs)
Intervention	✓ All types of cancer treatment interventions ✓ Any type of childhood cancer ✓ Data specific to oral health complications from cancer treatment
Outcome	✓ The outcome consists of any information related to QoL and ORHQoL
Study type	✓ Any primary study type ✓ Publications between 2011 and 2021. ✓ English or French publications.
Exclusion criteria	
	✓ Studies involving a mixed sample of adults and children ✓ Studies in which the disease category was not well defined or defined as mixed diseases (e.g., studies that the child has both a cancer and a non-cancer disorder)

The first study selection phase includes the title and abstract screening of all identified documents. A third reviewer (OD) will assist in the selection process if the two primary reviewers cannot reach a consensus. Titles and abstracts that appear to meet the eligibility criteria will be retained. The second study selection phase consists of full-text review of studies that have been classified as potentially eligible during phase one. Each reviewer will review the full text of the selected articles and put their comments about the reason of including or excluding the study in Rayyan to be seen by other reviewers. Any disagreements concerning the eligibility of the articles will be solved

through discussion between the reviewers with the appointment of a third reviewer if required. This stage will include an iterative process, incorporating searching of the literature, refinement of search strategies, and selection of articles.

4. Charting the data

Arksey and O'Malley's methodological framework suggests charting the data according to central research themes. Thus, we will develop a data extraction tool in line with the review's' objectives and corresponding research questions. We anticipate the data extracted will include author, publication year, location of study, study design, age of children, type of cancer, type of treatment, type of oral complications, OHRQoL measurement tools and assessment strategies, the type of children's involvement in the study, and findings related to the effect of cancer treatment on the oral health-related QoL of the children.

To ensure that all relevant data are extracted, the tool used for data extraction will be reviewed by the two reviewers prior to implementation. Differences in the suggested information included will be discussed between reviewers (if necessary, with a third reviewer) in a meeting to reach agreement. Furthermore, to ensure the tool's utility, consistency with the research questions and purpose and, the agreement level between reviewers, it will be piloted on 10 articles by both reviewers and any needed modifications will be implemented.

In the charting phase, reviewers will compare their extracted data. Inconsistencies and disagreements will be discussed, reconsulting the respective documents and if necessary, requesting support by a senior researcher of the team. Further, the tool will be iteratively updated if necessary, during the study's full extraction process, with any modifications detailed in the full scoping review report. Finally, throughout the process, there will be weekly team meetings during which ambiguities, concerns or other issues will be discussed.

5. Collating, summarizing, and reporting findings

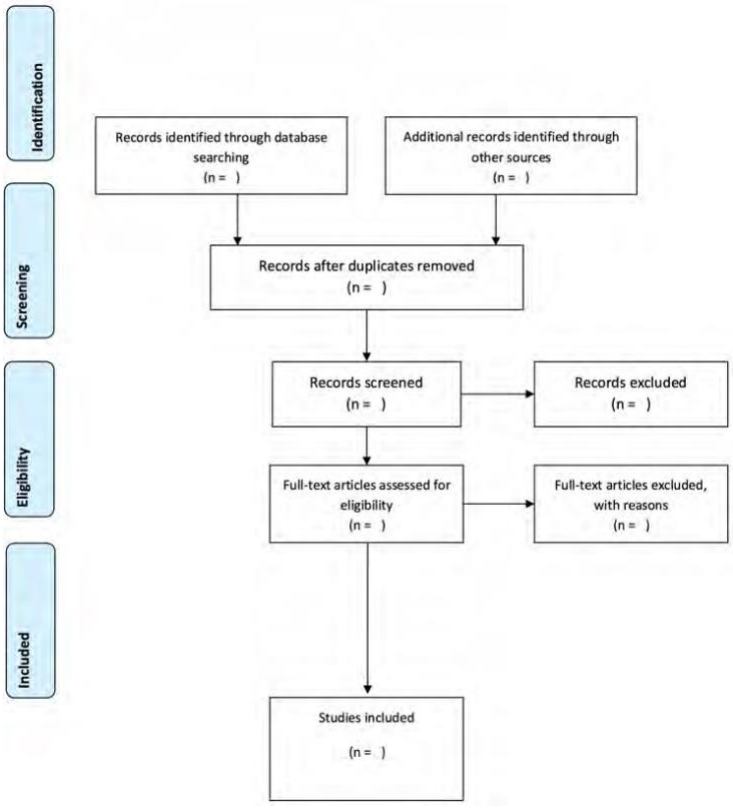
The primary goal of a scoping review is to present a comprehensive summary of current evidence and significant findings across various domains. (12) Therefore, the chosen analytical approach will be descriptive and narrative, aligning with the study objectives. We will follow the three steps outlined by Levac et al. (12) for this stage:

First, we will report the data using a descriptive numerical summary and thematic analysis to describe the characteristics of the included studies. We will use a PRISMA-ScR flow diagram, a version of PRISMA updated to include the literature found in databases to represent the process of identification, inclusion, and retention of articles fulfilling all eligibility criteria (Figure 3). (105) This diagram will aid replicability and transparency. The extent, scope and nature of retained literature will be summarized descriptively using ranges and counts, presented in graphs, charts, or tables according to our charting categories. This step will provide an overview of existing evidence and research activity trends, as well as highlight potential research gaps.(11)

Second, we will report the results specifically regarding the impact of cancer therapy on the OHRQoL of children and their involvement in producing this knowledge in studies. We will use graphs, charts, or tables where useful and provide an accompanying narrative summary to highlight how the results are linked to the objectives and research questions of this study.

Finally, we will identify the knowledge gaps and the broader implications for future research, policy and practice.

Figure 3: PRISMA-ScR flowchart (105)



6. Consultation with relevant stakeholders

While stakeholder consultation is considered optional in Arksey and O'Malley's framework (11) we believe it will provide additional valuable insights into our findings and opportunities for knowledge transfer in the field of pediatric oncology and pediatric dentistry. Thus, we will proceed by convening health care professionals (e.g., oral health professionals; oncological professionals) working for children surviving cancer, parents of these children and preferably the children themselves. By consulting and sharing the scoping study findings with these stakeholders and adding the experience of these groups we can gain insights that can lead to improved study outcomes.

Ethics:

For the initial review, ethical approval will not be required as there are no human participants involved. We will seek ethical approval specifically for the Stakeholder consultation; details will be determined after preliminary analysis is completed.

Conclusion:

In this scoping review, we aim to explore the impact of oral complications resulting from cancer treatment on the QoL of children who are going through or have survived cancer. Our goal is to gain a better understanding of how these complications affect their well-being and QoL. Thus this review will update a previous literature review, providing comprehensive information on the impacts of cancer treatment on the oral health related QoL of children undergoing cancer treatments by identifying, synthesizing, and summarizing the reported literature in the past ten years (9). Our preliminary review suggests that in the past ten years, the literature has grown substantially regarding children's OHRQoL. Moreover, as QoL is a subjective concept, we hypothesize we will find more children's direct involvement in reporting consequences related to their OHRQoL. We also anticipate our review will show areas that have been under-researched and may require further investigation and evaluation.

While the primary focus of treatment remains on combating cancer, mitigating the complication of treatment can contribute to enhancing the QoL of pediatric cancer survivors. Recognizing the influence of cancer treatment-related oral complications on QoL can assist healthcare professionals

in providing more holistic care and addressing the challenges faced by both patients and their families.

The results of this review will be shared through cancer and oral health conferences and symposia to disseminate the knowledge. Additionally, the findings will be published and shared with relevant stakeholders. The information extracted from this review will serve as a foundation for a qualitative study, focusing on the impacts of oral health effects of childhood cancer on QoL, with a specific emphasis on gathering perspectives from children themselves.

Funding:

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Methodological developments post protocol implementation

A medical librarian created a systematic scoping search strategy for Medline (Ovid), which is provided as Appendix B. The strategy comprised a combination of Medical Subject Headings, title/abstract key words, truncations, and Boolean operators. The search combined the concepts of cancer treatment, oral health, quality of life and was limited to the age group of children and adolescents through a fourth concept. It was subsequently translated by the librarian for Embase (via Ovid), PsycINFO (via Ovid), Scopus and Web of Science (106). All databases were searched from 1 January 2021 to 21 June 2021, and the reference lists of included articles were also manually screened to search for other relevant studies.
The scoping review methodology employs an iterative approach (11-13, 84), and we applied this method in our study in the following sections:

- The librarian's initial search strategy was reviewed and discussed with all team members to incorporate additional terms, if needed. The search process followed an iterative approach, if new terms were discovered, they were integrated into the search strategy and subsequently applied to other databases. For example, the librarian encountered the term "ChIMES" (Children's International Mucositis Evaluation Scale) during the initial search which was later integrated in the final search strategy due to its relevance to our project.
- The data extraction tool initially adhered to the same categories as those in the original scoping review. The two reviewers (AS and NA) conducted a pilot data extraction

process on 10 articles selected from the final set of articles. However, as we progressed with the data extraction process, we encountered valuable information. Therefore, we augmented the data extraction tool with additional categories that had not been part of the prior review. Subsequently, we refined the data extraction tool based on the insights gained during this pilot phase. Notably, three new categories—measurement tools, treatment outcomes and their impact on quality of life, and the involvement of patients in the study—were introduced.

- While the primary objective of this thesis did not center on adult survivors of childhood cancer, we decided to include articles related to this population. Our rationale for this inclusion stemmed from exploring the long-term effects of cancer therapy in this group. We aimed to review the research articles and refine our scope as we progressed in our study. Despite finding a few relevant studies regarding this population we did not make changes to the search strategy as it was not the primary focus of our study. We deemed it crucial to incorporate this information to ensure the inclusion of long-term oral complications and their effects on the QoL of cancer survivors. We believe that the insights derived from these articles could guide future research endeavors.

Chapter 4: Results: Collating, summarizing, and reporting

This chapter presents the results of our scoping review. Our final sample of articles comprised of 86 articles (please see Appendix A for PRISMA-ScR). In this chapter, I examined the key domains, trends, and insights derived from the reviewed literature. The extracted data is summarized and reported in the form of descriptive paragraphs, charts, and tables, with commentary providing valuable insights into pediatric cancer survivors' OHRQoL in the past decade between 2011-2021.

4.1 Type of cancers

We identified a total of 41 types of pediatric cancer in the reviewed articles. Among these 41 types of cancer, there were four subtypes of leukemia, four subtypes of central nervous system tumors, and three subtypes of lymphoma. Among the included articles, leukemia was the most extensively studied cancer, with 22 of the 86 articles focusing exclusively on acute leukemia and one additional study focusing specifically on chronic leukemia. Acute lymphoblastic leukemia was the most investigated leukemia subtype. Further, 3 articles focused exclusively on central nervous system tumors. Moreover,15 articles were exclusively centred tumors of the head and neck region. Among the 8 publications centred on rhabdomyosarcoma, nasopharyngeal carcinoma, was addressed in 4 articles and 3 articles on salivary gland tumors. In the remaining 45 articles included multiples types of childhood cancers (e.g., lymphomas, central nervous system tumors, neuroblastoma) which were studied along with the above-mentioned malignancies (See Appendix C Table 1).

4.2 Cancer treatment

Among the 86 articles reviewed, only 7 articles (107-113) did not involve chemotherapy as a cancer treatment modality (See Appendix C Table 6). The remaining 79 articles either exclusively used chemotherapy as the primary treatment approach or combined it with other treatments such as radiation therapy, surgery, or hematopoietic stem cell transplantation. Therefore, based on the collective evidence from the reviewed literature, chemotherapy emerged as the predominant type of cancer treatment leading to oral complications.

Specifically, oral mucositis was associated with chemotherapy either exclusively or in combination with other treatment approaches. Fifteen articles (114-128) focused exclusively on oral mucositis in relation to chemotherapy treatment. Additionally, 7 other articles explored OM

alongside co-occurring complications such as ulcers (129, 130), sialorrhea (131, 132). and oral infections (130, 133-135), specifically associated with chemotherapy. A total of 17 articles (136-152) included both chemotherapy and radiation therapy as cancer treatments. Chemotherapy and radiation therapy were most commonly used for treating rhabdomyosarcoma (137, 142, 147, 149) and central nervous system tumors (136, 145, 146, 151). Further, chemotherapy and radiation therapy were associated with dental developmental anomalies. Only two articles (111, 112) focused primarily on radiation therapy as the treatment modality, with the study populations experiencing long-term oral and dental complications jaw hypoplasia, hypodontia, microdontia, and malocclusion.

4.3 Oral complications

Oral mucositis was reported as the most prevalent complication as well as the most prevalent acute oral complication across the reviewed articles, with 22 publications exclusively focusing on it (See Appendix C Table 6). In contrast, tooth and root abnormalities were identified as the most frequent late complication observed in 13 articles. Oral infections were the second most frequently reported acute complication reported in 6 articles. Most late oral complications (See Appendix C Table 7) were reported along with other chronic complications; for example, tooth and/or root abnormalities and jaw hypoplasia were reported together in 8 articles (112, 142, 147, 149, 153-156). Tooth and/or root abnormalities and dental caries were found in 9 articles (138, 139, 147, 157-162). Xerostomia was reported in 13 articles including 7 of which also reported dental caries and xerostomia(128, 136, 146, 151, 162-164). Trismus was observed in nine articles, including two articles that identified trismus along with dental caries and xerostomia (136, 146) and two articles that reported trismus along with jaw hypoplasia and tooth and root abnormalities (147, 153). One of these articles also mentioned the presence of dental caries (147). A few articles reported distinct oral complications resulting from cancer therapy such as facial nerve deficit (110), palatal perforation (165), facial paralysis, and facial twitching (166).

4.4 Age of participants

The age range of participants in the selected articles varied from a 0 to 18 years old. Our review also included adult survivors of childhood cancer (See Appendix C Table 7 & 9). Out of the total sample of 86 articles, 20 articles (107, 111, 117-119, 121, 126, 129, 133-135, 148, 150, 166-172) included participants below 6 years of age. Among these 20 articles, a subset of only 4 articles (107, 167, 168, 170) specifically involved infants as study participants. Further, publications

involved adult survivors of childhood cancer, with 10 articles specifically focusing on this population (139, 142, 143, 148, 149, 153, 161, 162, 173, 174). Notably, the age of participants in the adult survivor group reached as high as 46 years old (162), reflecting the long-term impact of childhood cancer treatment on individuals well into adulthood.

4.5 QoL

QoL is a multi-dimensional concept, with OHRQoL being one of its subsets. Our data extraction process focused on evaluating the impact of oral health on various dimensions of QoL**,** including oral functioning, psychological well-being, social well-being, and pain and discomfort. All articles in the final sample touched on QoL dimensions, regardless of their primary research focus. While not all articles explicitly focused on the QoL or OHRQoL of the study participants, all 86 articles reported short or long-term oral complications resulting from cancer therapies (See Appendix C Table 6), including physical, psychological, and social implications of treatment-related oral complications and therefore were relevant to QoL.

A variety of impacts were observed in our analysis; these included oral pain, difficulty swallowing, eating, speaking, sleeping, and enjoying food, as well as distress, compromised nutrition, impaired speech, altered taste, psychosocial impairments, dental and craniofacial development anomalies, poor self-esteem, and poor oral hygiene. Further, pain was the most frequently reported QoL impact, present in 40 articles (See Appendix C Table 6); pain was reported in various areas such as the oral cavity, jaw, throat, and teeth. This prevalence emphasizes that the discomfort associated with pain has notable effects on various aspects of QoL, particularly oral function, and psychological well-being.

4.6 QoL and OHRQoL measures

A small minority of studies included a specific QoL (2 articles) or OHRQoL measure (9 articles). The only measure that focused on QoL was PedsQL™ 3.0 (Pediatric Quality of Life Inventory TM) module (124, 152) which is a tool used to evaluate the overall QoL in the pediatric population. While this measure is not specific to oral health, the results were connected to oral health. For example, the findings of one study (124) indicated that cognitive difficulties and smiling with embarrassment were two factors linked to impaired QoL. Although these measures may not specifically evaluate oral health, they can still be useful in evaluating the impact of other factors on overall well-being, including oral health.

Nine articles did include oral health measures. Among those that did, the Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire (OMDQ) was the most frequently employed questionnaire; however, it only appeared in 3 articles (125, 131, 175). The OMQoL (Oral Mucositis Quality of Life) questionnaire was used in 2 articles (131, 132). The OHIP-14 (Oral Health Impact Profile-14) (120, 176) and ChIMES (Children's International Mucositis Evaluation Scale) (116, 177) questionnaires were applied in 2 articles each. In addition, studies involving OHRQoL measures aimed to identify the specific oral health factors that affect QoL. For instance, one study (131) using OMQoL scores revealed that difficulties swallowing and sleeping had the most significant influence on OHRQoL. These factors were strongly associated with lower QoL and higher distress levels.

4.7 Treatment of oral complication

Out of the selected articles, 53 publications reported on the treatment of oral complications (See Appendix C Table 8). In particular, 7 of these articles highlighted the positive effects of treatment on the psychological (138, 140, 146, 151) and social (112, 165, 178) aspects of cancer survivors. In regard to oral mucositis, the treatment methods identified did not cure oral mucositis; instead these treatments reduced the severity of oral mucositis and alleviated its symptoms. Various treatment modalities reported for oral mucositis included low-level laser therapy, analgesics such as morphine and ketamine for pain management, increased water intake, Vitamin E, and pycnogenol, palifermin, and photobiomodulation therapy. Additionally, some articles explored the potential benefits of natural derivatives, such as chamomile mouthwash and curcumin mouthwash. In one article (179) it was suggested that electronic video games may prove beneficial when combined with morphine for the treatment of oral mucositis, indicating a reduction in morphine consumption and the alleviation of oral mucositis symptoms in children. Despite using less morphine, pain was reduced significantly. This was due to an increased parasympathetic vagal tone (the body's natural relaxation response). Therefore, even with lower medication levels, the body's own mechanisms help alleviate pain effectively. It suggests that physiological responses, such as the modulation of parasympathetic vagal tone, can contribute to pain relief, even with lower medication consumption.

4.8 Involvement of children

Among the articles, 53 articles provided information regarding children's involvement in the research (See Appendix C Table 9). Out of these articles, 5 publications displayed 'research on' children since they were examined by the health care provider (107, 108, 127) researcher (111) and the evaluator (128). Since the majority of the publications included minors, consent was sought from the caregivers of the participants; in only 4 of these articles (125, 142, 161, 169) was children's assent explicitly documented.

Further, we reviewed the literature to identify if and how children's perspective was taken into consideration; this was done by examining if participants self-reported symptoms, completed questionnaires or interviews independently, or with the assistance of their caregiver, and if they were involved in the treatment process. Notably, 20 articles indicated that participants themselves reported their symptoms and completed the assessment tools. In 5 additional studies (125, 131, 141, 152, 180) the caregiver, health care provider, or both assisted the participant to report; in these 5 studies the age of the youngest participant was 5 years (152) and 6 years (125, 131, 141, 180). In addition, one article (181) mentioned that participants and caregivers both were involved in deciding the treatment and mutually approved it. Further, another article (151) mentioned that both caregiver and participant reported the medical history.

4.9 Incorporating oral health care in pediatric oncology

Two of the articles (118, 177) specifically highlighted the importance of integrating dentists and dental education programs into pediatric oncology units. The first article (118) emphasized the significance of incorporating oral health education, particularly concerning dental hygiene practices, into the daily regimen of children undergoing oncological treatment; it also included the importance of collaboration among dentists to establish oral health protocols, and the importance of conducting thorough patient assessments before and during cancer treatment (118).The second article (177) focused on the implementation of preventive dental care by educating patients and caregivers about oral mucositis. The findings from this study demonstrate that offering oral health care education is an effective strategy for reducing the severity of oral mucositis in pediatric oncology patients (177).

4.10 Study design

The majority of the retained articles (48 studies) used a quantitative design. In addition, there were 31 case reports, 3 case series (157, 167, 171) and 2 clinical reports (145, 156). Only 1 study had a qualitative design (169, 172), and 1 was a mixed-method study (74). (See Appendix D, Figure 4).

4.11 Year of publication

During the early years of our sample (2011 and 2012), 9 articles were conducted each year, respectively. Following, there was a slight decline in the number of publications in 2013 and 2014 (7 articles per year); 2015 had the least number of publications (4 articles) among all 10 years. However, in 2016 there was an overall increase in the number of articles, peaking at 15 publications in the year. Subsequently, the number of publications remained relatively stable (See Appendix D, Figure 5).

4.12 Language and location

The inclusion criteria included English and French; however, all of the retrieved articles were published in English. The location of the final sample of publications was determined according to where the study was conducted or where the diagnosis and treatment of the oral complication took place (in the case of case reports and series); based on this, 71 articles mentioned the location. Brazil and Turkey conducted the most publications (8 each), followed by Italy and China (7 each), and India and Iran (5 publications each). Other countries, such as Canada, USA and Japan had 4 articles each country (See Appendix D, Figure 6).

4.13 Comparison between the original review and our study

One of the objectives of this project was to update the original scoping review and build upon the previous review conducted between 2000 and 2011. Our focus extended from 2011 to 2021, aiming to assess the growth and evolution of the literature in the past decade since the initial review. By comparing our study to the previous one, we sought to identify both similarities and differences in our research findings. Leukemia emerged as the most prevalent cancer type in both reviews. However, in the context of head and neck cancers, the original review only included 2 articles reporting nasopharyngeal carcinoma, while our study encompassed 18 articles specifically addressing various head and neck cancer such as rhabdomyosarcoma, nasopharyngeal carcinoma, salivary gland tumors, and central nervous system tumors. Both reviews identified chemotherapy

as the predominant cancer treatment leading to oral complications in pediatric cancer patients. However, in our review, we found 15 articles exclusively focused on chemotherapy-induced oral mucositis. In terms of long-term oral complications, both reviews yielded similar findings, but our review additionally reported some distinct complications due to cancer treatment such as facial nerve deficit (110), palatal perforation (165), facial paralysis, and facial twitching (166). The age range of participants in both studies was 0-18 years. However, the authors of the original review expanded the age range to include studies up to 20 years of age, as they identified relevant literature within this broad range. In contrast, our review aimed to include adult survivors of childhood cancer and identified 10 relevant articles in this domain.

In terms of the impact on QoL, both reviews observed adverse effects that affected participants' functional, physical, psychological, and social well-being. The original review included 21 articles on QoL impacts, while our review identified 86 publications on this topic. Furthermore, the original review did not explore specific measures of QoL or OHRQoL. In contrast, our review encompassed 11 studies that utilized QoL measures (2 articles) and OHRQoL measures (9 articles). Treatment of oral complications was reported in 25 articles in the original review. Our study identified 53 articles reporting on this aspect, particularly emphasizing preventive treatments for oral mucositis. In terms of symptom reporting, the previous review indicated that caregivers were mostly commonly involved in reporting symptoms, whereas our findings revealed that participants themselves self-reported symptoms or completed surveys, questionnaires, or interviews in 22 studies. Finally, both reviews predominantly included studies with a quantitative study design in their final selection.

The comparative table (See Table 4) provides an overview of the key points of convergence and divergence between our study and the previous review. By comparing and contrasting these similarities and differences, we aimed to gain insights into the progress and advancements in pediatric oncology and treatment over the past decade, highlighting areas of consensus and areas where new knowledge has emerged.

Table 4: Comparison between the findings of the original and current scoping review.

Domains	**Original Review**	**Current Review**
Final sample	82 articles	86 articles

Type of cancers	Leukemia was most common; NPC most common in head and neck	Leukemia was most common, RMS most common in head and neck
Cancer treatment causing oral complication	Chemotherapy	Chemotherapy
Oral Complications	OM (most common)	OM (most common)
Age of participants	0-20 years	0-18 years + adult survivors of childhood cancer
QoL impact	Reported by 21 articles	Reported by 86 articles
QoL and OHRQoL measures	Not evaluated	PedsQoL, OMDQ, OMQoL, OHIP-14, ChiMES
Treatment of oral complications	Reported by 25 articles	Reported by 53 articles
Involvement of children in the study	Parent reported symptom was common; participants only reported in 3 articles	Patient reported symptom was common; participants reported in 20 articles
Study design of included articles	78 Quantitative, 3 qualitative, 1 mixed design	48 Quantitative, 31 case reports, 3 case series, 2 clinical reports, 1 qualitative, 1 mixed design
Location	Brazil was most common (11 publications)	Brazil and Turkey were most common (8 publications each)

Conclusion

In conclusion, our review demonstrates the diverse effects on pediatric cancer patients' QoL during cancer treatment and beyond. These complications have wide-ranging consequences, affecting children's physical, functional, psychological, and social well-being. The literature on adult survivors of childhood cancer also highlights the long-term impact of cancer treatment on QoL and oral health. Our review indicates that preventive treatments for distressing complications may alleviate symptoms (e.g., pain associated with OM), which may improve the QoL for the individual (e.g., reducing the need for parental nutrition).

Despite the growing use of QoL and OHRQoL measures in pediatric oncology research, they still constitute a minority of studies. These measures should be further incorporated into future studies to provide insight into the impact of cancer treatment on children's well-being and oral health. Moreover, integrating these measures alongside qualitative research methods can help understand children's subjective experiences during cancer therapy. By delving deeper into children's own perspectives, emotions, and challenges, researchers may gain a more nuanced and specific understanding of how these oral complications affect their overall QoL. Combining these approaches can lead to targeted and supportive interventions, thereby improving the overall well-being and survivorship experience of pediatric cancer patients.

Chapter 5: Discussion

The results of this scoping review indicate that over the past decade, since the completion of the original review by Noronha (9) important advancements have been made in the research regarding the oral complications experienced by pediatric cancer patients following cancer therapy. For example, there has been a rise in the development and use of OHRQoL measures to assess the impact on QoL due to treatment-related oral complications in children with cancer, and increase in children's own involvement in assessments, and our findings also indicate growth in international research dedicated to exploring oral health challenges faced by children. It is critical to educate patients and their families about both early and late oral complications associated with cancer treatment. Regular dental examinations before, during, and after treatment are crucial for early diagnosis and intervention. By proactively addressing oral health issues, healthcare professionals can mitigate the impact of these complications and improve pediatric cancer patients' overall QoL. In this chapter I discuss the results of this review, address the similarities and differences between the current and original review (9), identify gaps in the existing literature, and propose relevant directions for future research.

QoL and oral-health impact

In contrast to the previous review which identified 21 articles out of 82 (9), our study identified a larger number of articles (86 articles) that touched on the effects of oral complications resulting from cancer treatment on children's QoL. This substantial increase in the number of articles reflects an important growth in the literature on this subject. Moreover, this expanded body of research highlights the growing recognition of the importance of assessing and understanding the QoL implications of oral complications in cancer patients.

Pain surfaced as the predominant factor influencing both children's QoL and oral health, manifesting in various areas such as the oral cavity, teeth, throat, and jaw. OM can cause painful ulcers, infections, and challenges eating, drinking, and swallowing (182). These complications have a significant impact on the patient's nutritional intake, functional abilities, and adherence to cancer treatment (183). Moreover, conditions like dental caries can induce pain, which can hinder a child's daily routines, such as attending school or experiencing difficulties while eating (75).

Types of cancer

In the studies included in this review, acute leukemia emerged as the most frequently studied childhood cancer; this finding concurs with the fact that it is the most prevalent form of cancer in this population (184, 185). In contrast, rhabdomyosarcoma was the most extensively researched solid tumor in the head and neck (HNC) region, despite it being only the third most common solid tumor in that area among children (36). Rhabdomyosarcoma is characterized by its high aggressiveness and metastasis propensity (36); that may explain why it was more common in our sample. The original review (9) identified only 2 publications related to HNC tumors, while our study revealed 15 articles. Despite the fact that central nervous system (CNS) tumors account for the majority of solid tumors among children, we encountered limited literature pertaining to CNS tumors; yet, long-term survivors of pediatric brain tumors are susceptible to late dental complications, including trismus and dental developmental anomalies like microdontia and hypodontia (186).

Type of cancer treatment

Chemotherapy was the most commonly utilized cancer treatment modality in this population; it was also the most common treatment leading to oral complications, especially mucositis. Chemotherapy's targeted action on cells rapidly dividing in the oral mucosa and teeth contributes to these complications (182). Additionally, both CT and RT were associated with dental developmental anomalies (DDA), which is consistent with the fact that the combined use of chemotherapy and radiotherapy during treatment elevates the risk of DDA like microdontia, hypodontia and jaw hypoplasia (63).

OM was found to be the most commonly studied oral complication in the children with cancer in both reviews. OM has been reported as the most debilitating complication of treatment (183). It has been observed that approximately 80% of children undergoing chemotherapy experience some degree of OM.

Among long-term complications, we found some distinct complications compared to the findings of the previous review (9). These included facial nerve deficit, facial paralysis and twitching. Further, we found literature that exclusively dealt with HNC tumors, particularly salivary gland tumors, which are in close proximity to the facial nerve. Facial nerve paralysis can impact the dental health, oral hygiene, and OHRQoL of affected individuals; this results from food particles which remain on teeth surfaces which cannot be removed through the natural self-

cleaning mechanisms of the oral cavity (187). Due to this, it may result in the formation of dental plaque, increasing the risk of dental, periodontal, and other health conditions (187).

Age of participants

In contrast to the previous review (9), our study explored the long-term oral health outcomes and QoL implications for individuals who have survived childhood cancer and transitioned into adulthood. The original review (9) focused on participants ranging from 0 to 20 years of age since their primary objective was to investigate how oral complications impact QoL in pediatric cancer survivors. Therefore, they did not include older adults.

We found 10 articles that reported the long-term therapy related complications, including microdontia, hypodontia, malocclusion, which can impact oral function, aesthetics (63) and have an impact on QoL of childhood cancer survivors (64). In addition, it should be noted that the highest age among the study participants was 46 (188); this indicates the long-lasting effects of cancer treatment on oral health and the need for continued monitoring and support for survivors well into adulthood.

QoL and OHRQoL measures

The previous review (9) did not include QoL or OHRQoL measures in their results. We found a eleven studies that incorporated these measures into their research. While the QoL measures used in the studies encompassed a wide range of factors in their questionnaires, it is important to note that they do not specifically focus on oral health. These measures aim to assess the overall QoL and well-being of individuals, considering various aspects such as physical health, psychological well-being, social relationships, and functional abilities. However, they may not capture the specific impacts and challenges related to oral health conditions or oral discomfort.

Therefore, for a more targeted assessment of OHRQoL, specific measures such as the OMDQ, OMQoL, OHIP-14, and ChiMES are more useful. These measures have questions specifically directed towards oral discomfort, function, and the impact of oral health conditions on daily life. Thus, they provide valuable information about the specific aspects of oral health that impact patients' QoL, allowing for a comprehensive evaluation of children's subjective experiences and their functional limitations related to oral health conditions. In addition, all four of the above-mentioned OHRQoL measures have been adapted and validated for different age groups, to ensure

that the questions and response options are appropriate and understandable for individuals in specific age ranges.

Importantly, OMDQ, OMQoL and ChiMES focus only on OM. Therefore, the future of this field should focus on refining and developing measures that encompass a broad range of cancer therapy related acute oral complications (e.g., taste changes, oral infections). Moreover, it is also important to address the impact of long-term oral complications associated with cancer therapy by using OHRQoL measures. By expanding our scope of assessment to include the various aspects it may be possible to tailor interventions based on individual experiences of how these complications affect children.

Treatment of oral complication

The treatment of oral complications resulting from cancer treatment was addressed in 25 articles out of the 82 articlesI identified in the previous review (9); our review identified a substantially larger number of articles (53 articles out of 86). The increase in literature focusing on oral complications in pediatric cancer patients reflects the expanding range of treatment methods, interventions, and management strategies available in this field. It is noteworthy that a significant portion of the recommended treatments were preventive and palliative measures targeting OM, which aligns with the fact that OM is one of the most distressing complications of cancer treatment. Moreover, our literature also highlighted the exploration of natural remedies (e.g. chamomile mouthwash and curcumin mouthwash) that could complement conventional treatments for OM.

Study design

In both reviews, the majority of the studies had a quantitative design; there were fewer qualitative and mixed methods studies (we found 1 qualitative study and one mixed method study). The original review had 3 qualitative studies whereas our study only identified 1 qualitative study in the final sample. In addition, our review included 31 case reports, 3 case series (157, 167, 171) and 2 clinical reports (145, 156).

The case reports provided detailed and in-depth descriptions of individual cases, with a few reporting unique complications and treatment approaches. Moreover, the case series studies gave information about the oral complications and treatment outcomes associated with cancer treatment in children. Quantitative methods (e.g., randomised control trial and cohort studies) provided

objective data and statistical analysis; these methods enabled the quantification of outcomes, such as the effectiveness of oral complications treatments and identifying factors impacting the oral health of children due to cancer treatment.

The qualitative study included in our review (172) analyzed interview data based on a grounded theory approach to learn about children's subjective experiences. This study reported that children took different actions to address taste changes, including sucking on candy, brushing their teeth, and modifying their food choices. Moreover, it was seen that "the experience of changes in taste was common yet highly variable in its presentation and resultant changes in food preferences" (172). Thus, qualitative research enables the exploration of individual experiences and perspectives.

It has become well established that qualitative studies can provide an extensive understanding of QoL that cannot be captured by clinical trials or other quantitative designs (189). Moreover, as suggested in the introduction, growing literature is demonstrating the importance of involving children in health research, since research on children has traditionally viewed them as objects rather than active participants (190). This perspective has been influenced by cultural beliefs that portray children as lacking competence and being passive recipients of care (190). Thus, in light of our findings in which we only found one qualitative study seeking children's own perspectives, future research in this area needs to understand the importance of including children's voices in research related to their oral health and QoL, and qualitative research is the best methodological approach to do so. Integrating both objective measurements and subjective experiences will ultimately lead to the development of informed and patient-centered approaches to treatment and care (191).

Involvement of children in the studies

In the original review (9), the predominant source of symptom reporting was caregivers, with limited involvement of the children themselves (only in 3 articles). Our study revealed a notable shift, as 20 articles reviewed in our study presented that children self-reported symptoms through questionnaires, surveys, or interviews. A reason for this increase can be attributed to the fact that we found literature that incorporated QoL and OHRQoL measures; these measures typically involve participants self-reporting their symptoms. This emerging trend not only reflects the increasing recognition of children's perspectives, but also underscores

the importance of capturing their own experiences when assessing the impact of oral complications on their well-being.

For example, a cross sectional study (74) included in our review employed a questionnaire administered as an interview to gather information from children to gain valuable insights into their experiences; it was observed that when children with cancer had mouth sores, they expressed feelings of unhappiness.(74). In addition, their findings indicated that oral pain and discomfort hindered the children's ability to eat properly and maintain good oral hygiene practices. Specifically, when asked about toothache, children responded negatively (74), indicating the impact of this condition on their QoL. It was observed that children with a history of cancer had lower QoLindicators associated with these oral health issues (74). The children's first-hand responses provided their perspective on oral pain, discomfort, functional impairment, and emotional distress, all showing their compromised QoL resulting from cancer treatment (74). Thus, it is important that symptoms are reported directly by children (whenever possible) and not only their caregivers.

Incorporating oral health care in pediatric oncology

A few articles (177, 192) touched on inclusion of dentists and preventive dental care in pediatric oncology. Rimulo (192) stressed the importance of integrating oral health education, especially regarding dental hygiene practices, into the daily routine of patients in oncological treatment; it is crucial for dentists to collaborate on developing an oral health protocol and conducting patient assessments before and during cancer treatment. Rimulo also argued that the inclusion of a dentist as part of the oncological team is essential and the establishment of guidelines should be supported by clinical evidence to promote and prioritize the maintenance of oral health (192).

In line with this, a collaborative effort between the department of pediatric dentistry and pediatric residents at New York University resulted in the development of the "Chemo Without Cavities" program (193), showcasing the impact of an educational initiative on oral health care for pediatric cancer patients. Pediatric cancer patients received an oral examination and fluoride varnish as a preventive measure against cavities resulting from cancer treatment. Non-dental healthcare providers were trained by dental professionals to enhance their knowledge of oral health care of children with cancer (193). The success of the program emphasizes the importance of raising awareness, educating patients and their families,

and advocating for interprofessional collaboration in pediatric oncology care (193). The authors encourage the adoption of this program in other pediatric oncology centers and the integration of an interprofessional framework in pediatric oncology departments (193).

The second study (177) implemented preventive dental care by educating patients and caregivers about oral mucositis. The findings demonstrate that offering oral health care education is an effective strategy for reducing the severity of oral mucositis in pediatric oncology patients (177). Hence, proactive dental care yields positive results in the prevention and management of oral mucositis. A similar study (194) conducted in Brazil introduced a protocol that involved referring pediatric cancer patients to dentists prior to initiating cancer treatment (194). In addition, the patients received regular evaluations by dentists and researchers, and prompt treatment was provided for severe oral mucositis (194). According to the findings, enhanced surveillance of oral complications decreased the duration of severe oral mucositis and fewer interruptions to chemotherapy in pediatric patients (194).

Strengths and Limitations

There are several strengths to this scoping review.

1) The objectives of our review were to build on the gaps identified in the previous review (1). Our review highlighted the trends observed in the literature over the past decade regarding the QoL implications of oral complications of cancer treatment in pediatric cancer survivors. We compared our findings with the original review. Therefore, together we have summarized the developments and limitations in this field over the past 20 years.

2) We included literature pertaining to QoL and OHRQoL and their specific measures, thereby demonstrating an important trend in this field

3) The review incorporated literature on adult survivors of childhood cancer to ensure long-term dental complications were not overlooked. By taking into account research on both pediatric and adult populations, this review offers insight into the short and long-term oral complications in cancer survivors, bridging the gap between pediatric and adult care and highlighting the challenges faced by survivors as they transition into adulthood.

Notwithstanding these strengths, this scoping review has certain limitations. Firstly, there is a language bias as only studies published in French and English were included, potentially excluding

valuable contributions from other languages. As a result, our findings may have a greater relevance for English and French speaking countries. Secondly, the review solely focused on published literature, excluding gray literature sources such as conference papers and unpublished studies, which may lead to publication bias and an incomplete representation of the available evidence.

Future directions

Based on the gaps identified in the literature, future directions should include the following:

1. Incorporating qualitative studies to capture the subjective experiences of cancer therapy in children to supplement the quantitative data; this will provide a deeper understanding of the multifaceted impact of oral complications on children's QoL.

2. In addition, more longitudinal studies are needed to evaluate the OHRQoL implications for individuals who survived childhood cancer and transitioned into adulthood.

3. Since the original review there has been growth in the literature regarding the use of OHRQoL measures in pediatric oncology. However, there is still limited literature that includes these specific OHRQoL and QoL measures to evaluate the impact on pediatric cancer survivors' well-being and oral health. Moreover, most of the OHRQoL measures were used for OM. Therefore, future research should focus on refining and using these measures to evaluate the impact of other acute and chronic treatment related oral complications.

By focusing on these future directions, we can aim to improve the awareness, prevention, and management of oral complications in pediatric oncology, ultimately enhancing the oral health and QoL of children affected by cancer treatment.

Additionally, as part of future directions, our team's next step is to develop a stakeholder consultation as the final stage of this scoping review, building on the results of this thesis. This consultation will involve working with children and youth who have had cancer, their parents, and clinicians to solicit feedback on, and future directions in relation to this subject.

Overall, this scoping review provides a comprehensive summary of the short and long-term oral side-effects of cancer treatment in pediatric cancer survivors. The findings of this review emphasize the need for more qualitative and mixed research, longitudinal studies of adult survivors of childhood cancer, use of specific OHRQoL measures, incorporating dental care in

pediatric oncology and oral health education programs to improve the awareness, prevention, and management of oral complications in pediatric oncology, ultimately enhancing the oral health and QoL of children affected by cancer treatment.

Chapter 6: Conclusion

In conclusion, this scoping review summarizes the literature over the past decade on oral complications experienced by pediatric cancer patients due to cancer treatment, picking up where the original review left off and comparing the results. According to our findings, leukemia is still the most extensively studied neoplasm, and oral mucositis remains the most common and distressing oral complication associated with cancer therapy, despite advances in preventative and palliative treatments. Additionally, chemotherapy is the most common treatment modality associated with oral complications, particularly mucositis, and the combined use of chemotherapy and radiotherapy was associated with an increased risk of dental developmental anomalies. Oral pain was the most common factor adversely affecting children's QoL, indicating the significant impact of pain on their oral function and psychological well-being.

The use of QoL and OHRQoL measures has increased, enabling a detailed assessment of children's subjective experiences, self-reported symptoms and functional limitations. However, there is still a dearth of literature using these OHRQoL measures in children with cancer, which is important to capture the specific impacts and challenges related to oral health conditions in this population. The majority of the studies had a quantitative design; there is a need for more qualitative research to include the subjective experiences of the impact of oral complications on children's QoL.

Future research in pediatric oncology should focus on understanding the multifaceted impact of oral complications on children's QoL by incorporating both qualitative and quantitative data. Moreover, longitudinal studies tracking individuals from childhood cancer survivorship into adulthood can evaluate the impact of cancer treatment on their OHRQoL. In addition, OHRQoL and QoL measures should be used to assess the impact on pediatric cancer survivors' well-being and oral health. Furthermore, the majority of OHRQoL measures have been applied primarily to oral mucositis; this highlights the need to concentrate on enhancing and applying these measures to acute and chronic treatment-related oral complications beyond oral mucositis.

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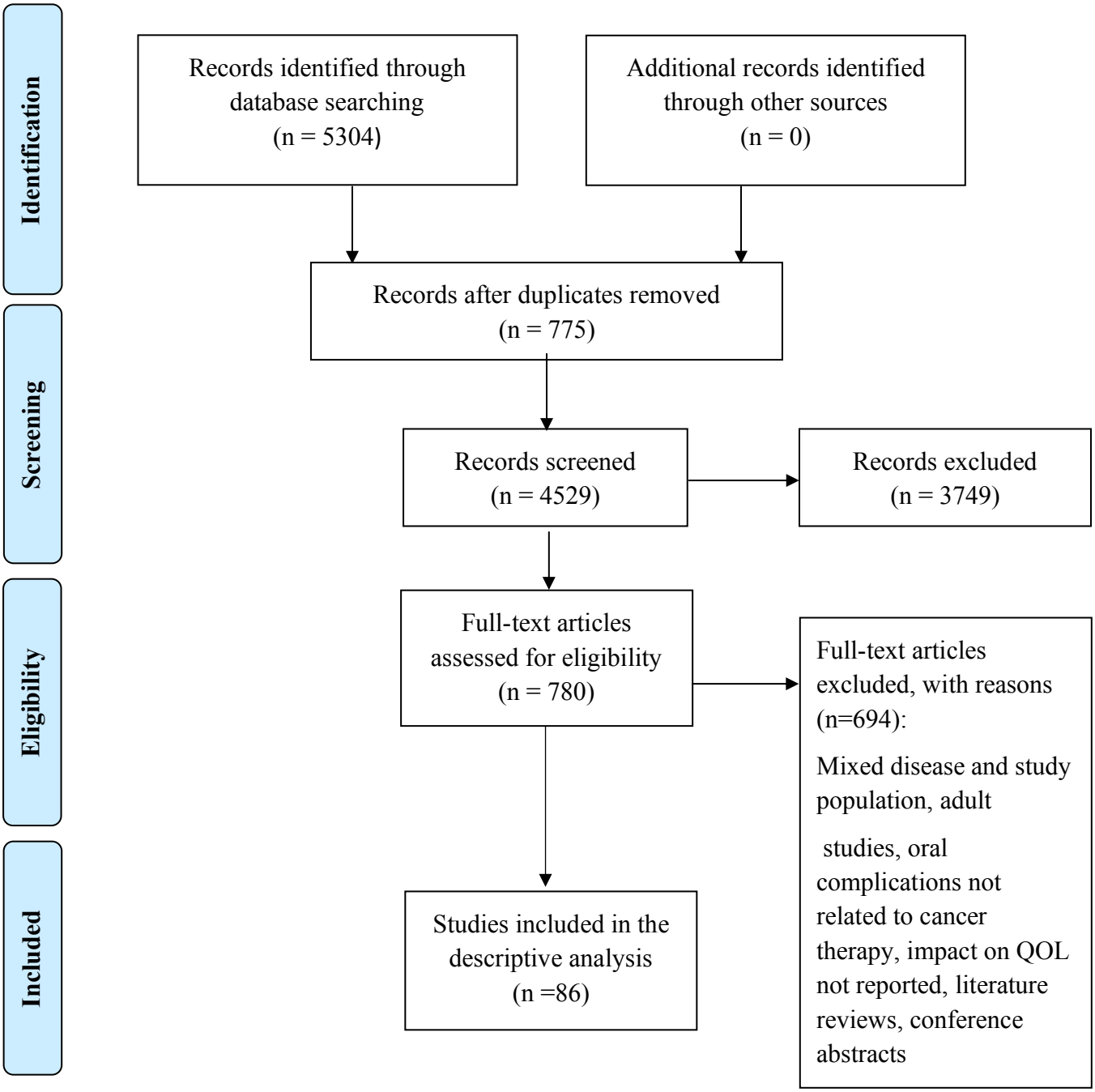
Appendix A: PRISMA-ScR

Following the established protocol, we adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (105) guidelines to summarize and present the number of studies identified, included, and excluded from our review.



Appendix B: Cohen's kappa

Inter-rater reliability between two reviewers was measured using Cohen's kappa coefficient (195). Cohen's kappa is a way to predict agreement between reviewers considering the chance agreement due to guessing that is always a possibility (195).

The Kappa statistic varies from 0 to 1, where the value indicates the following:

- 0 = agreement equivalent to chance.
- 0.1 – 0.20 = slight agreement.
- 0.21 – 0.40 = fair agreement.
- 0.41 – 0.60 = moderate agreement.
- 0.61 – 0.80 = substantial agreement.
- 0.81 – 0.99 = near perfect agreement
- 1 = perfect agreement

We measured the Cohen's kappa statistics in the first 50 abstracts of studies imported into Rayan software. The two reviewers included or excluded studies according to the inclusion and exclusion criteria. Cohen's kappa coefficient (k) was calculated according to the below formula (195):

$$k = (P_o - p_e) / (1 - p_e)$$

The value of Cohen's kappa coefficient in our study was 0.79, which indicates substantial agreement between reviewers.

For calculating Cohen's kappa coefficient, the number of included and excluded studies was counted (Table 5) and the relative observed agreement among reviewers (P_0) and the hypothetical probability of chance agreement (P_e) was calculated according to the below formulas:

P_o = number in agreement/total

$$P_o = (11 + 35) / 50 = 0.92$$

P_e = The total probability of the reviews both including studies randomly and both excluding studies randomly

The probability that the raters would randomly both include studies.

The first reviewer included 15/50 of the studies, or 30% (0.3).

The second reviewer included 11/50 of the studies, or 22% (0.22).

The total probability of the reviews both including studies randomly is:

0.3 * 0.22 = 0.066

The probability that the raters would randomly both exclude studies.

The first reviewer excluded 35/50 of the studies, or 70% (0.7).

The second reviewer excluded 39/50 of the studies, or 78% (0.78).

The total probability of the reviews both excluding studies randomly is:

0.7 * 0.78 = 0.546

$P_e = 0.066 + 0.546 = 0.612$

Cohen's kappa coefficient (K) was then calculated:

$k = (P_o - p_e) / (1 - p_e) = (0.92\text{-}0.612) / (1\text{-}0.612) = 0.793$

Table 5: The number of included and excluded studies by the two reviewers

		First Reviewer		
Second Reviewer		**Yes**	**No**	
	Yes	**11**	**0**	**11**
	No	**4**	**35**	**39**
		15	**35**	**50**

Appendix C: Data extraction tools

Table 6: Impact of cancer treatment on QoL and oral health

First Author	Type of Cancer	Treatment	Complication	Oral Health and QoL Impact
Cauwels, R. G. (114)	Leukemia, lymphoma, neuroblastoma, osteosarcoma, Ewing sarcoma, germ cell tumor	CT	Oral mucositis	Oral pain, difficulty swallowing and speaking, compromised nutrition
Najafi, S.H. (143)	Hodgkin's lymphoma	CT, RT	Root resorption, stunted roots, mobile teeth, gingivitis, root malformations	Difficulty eating and maintaining oral hygiene, poor oral health, dental developmental anomalies
Rimulo, A.L (118)	Acute myeloid leukemia	CT	Oral mucositis	Oral pain
Vagliano, L. (107)	Central nervous system tumors	HSCT	Oral mucositis	Oral pain, compromised nutrition
Bertoglio, J.C. (167)	Hematological malignancies, solid tumors	CT	Oral mucositis , oral bleeding, ulcers, bacterial and fungal infections	Severe oral pain, difficulty eating, drinking, speaking, odynophagia
Shigeru, S.M. (159)	Acute lymphoid leukemia	CT, HSCT, TBI	Stunted roots, dental caries, microdontia, retained teeth, altered teeth development	Dental developmental anomalies

Manji, A. (159)	Acute myeloid leukemia, relapsed acute lymphoid leukemia, advanced lymphoma, solid tumors, brain tumor	CT, HSCT	Oral mucositis	Oral pain, difficulty swallowing, drinking, and talking
Nielsen, B. N. (117)	Type of cancer not mentioned	CT	Oral mucositis	Oral pain, Odynophagia and pain while brushing teeth
Padmanabhan, M.Y. (163)	Maxillofacial Burkitt lymphoma	CT	Oral mucositis , dental caries, xerostomia	Difficulty chewing and swallowing, dry mouth
Pedersen, L.B. (196)	Leukaemia, lymphomas, reticuloendothelial neoplasms, renal and hepatic neoplasms, sympathetic nervous system tumours, retinoblastomas, CNS tumor, bone and soft tissues sarcoma, germ cell tumor	CT	Microdontia, hypodontia	Dental developmental anomalies
Pels, E. (135)	Acute lymphoid leukemia	CT	Oral mucositis , fungal infection	Oral pain, nutritional support
Bektaş-Kayhan, K.K (136)	Nasopharyngeal carcinoma	CT, RT	Xerostomia, dental caries, trismus	Difficulty swallowing speaking, sleeping
Elad, S. (115)	Burkitt lymphoma, Ewing sarcoma, osteosarcoma,	CT	Oral mucositis	Oral pain

	undifferentiated sarcoma			
Inati, A. (134)	Acute lymphoid leukemia	CT	Oral mucositis, necrotic and hemorrhagic lesions in mouth, dental caries	Unable to eat, drink and sleep
Khurana, H. (116)	Acute lymphoid leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma	CT	Oral mucositis	Odynophagia, compromised nutrition, distress
Nemeth, O. (160)	Type of cancer not mentioned	CT	Tooth agenesis, microdontia, macrodontia, retained teeth, root malformation, dental caries, hypodontia	Dental developmental anomalies, adaptive eating strategies, poor oral health
Nishimura, S. (144)	Acute myeloid leukemia, acute lymphoid leukemia, non-Hodgkin's lymphoma, adrenal cortical carcinoma, medulloblastoma, neuroblastoma, primitive neuroectodermal tumour, undifferentiated sarcoma of bone, Wilms' tumour, hepatoblastoma	CT, TBI	Tooth agenesis, microdontia, stunted roots	Dental developmental anomalies
Tummawanit, S. (156)	Retinoblastoma	CT, RT, surgery	Jaw hypoplasia, microdontia, hypodontia, skeletal malocclusion	Dental and orofacial developmental anomalies, cosmetic deformity, distress

Czyzewski, K. (108)	Lymphoma, neuroblastoma or other solid tumors	HSCT	Oral mucositis	Oral pain, unable to eat and swallow
Lauritano, D. (109)	Acute lymphoid leukemia	HSCT	Oral mucositis	Oral pain, nutritional support
Saha, A. (161)	Central nervous system tumors	CT, RT, surgery, HSCT	Microdontia, hypodontia, root malformation, dental caries, gingivitis	Dental developmental anomalies, impaired speech, altered taste, psychosocial impairment
Yavuz, A. (146)	Nasopharyngeal carcinoma	CT, RT	Xerostomia, dental caries, thermosenstivity, gingivitis, trismus, altered teeth development	Difficulty chewing and speaking, dry mouth psychosocial distress, cosmetic deformity
Grant, S. R. (110)	Salivary gland tumor	RT, surgery	Oral mucositis, facial nerve deficit, trismus, craniofacial growth abnormalities	Oral pain, odynophagia difficulty swallowing, adaptive eating strategies, nutritional support, weight loss, dental developmental anomalies
Man, Q.W. (140)	Lymphoma	CT, RT	Osteoradionecrosis, facial asymmetry	Cosmetic deformity, impaired oral function

Santos-Silva, A.R. (164)	Chronic myeloid leukemia	CT, HSCT	Chronic GVHD, gingival atrophy, lichenoid hyperkeratosis, ulcers, xerostomia, dental caries, discolored teeth	Difficulty eating, swallowing, taste changes
Amadori, F. (119)	Leukemia, lymphoma solid tumours	CT	Oral mucositis	Oral pain
Bardellini, E. (120)	Acute lymphoid leukemia	CT	Oral mucositis	Oral pain, poor QoL
Bardellini, E. (121)	Acute lymphoid leukemia	CT	Oral mucositis	Oral pain, difficulty eating, swallowing and speaking
Hafiz, A. (137)	Rhabdomyosarcoma (RMS)	CT, RT	Dental caries, root agenesis, mid-face hypoplasia	Dental and craniofacial developmental anomalies
Lucchese, A. (122)	Acute lymphoid leukemia	CT	Oral mucositis	Oral pain, unable to eat, drink, swallow, or speak
Marangoni-Lopes, L. (141)	Hodgkin's lymphoma	CT, RT	Xerostomia	Oral pain, burning sensation, difficulty swallowing, speaking, eating, trismus, opening mouth, poor QoL
Owosho, A.A. (155)	Head and neck RMS	CT, IMRT	Facial asymmetry, jaw hypoplasia,	Dental and craniofacial

			tooth agenesis, hypodontia, root agenesis, stunting, malformation, enamel hypoplasia, xerostomia, trismus	developmental anomalies
Ozdere, E. (145)	Nasopharyngeal carcinoma	CT, RT	Trismus, dental caries	Jaw pain
Wilberg, P. (162)	Acute lymphoid leukemia	CT	Dental caries, enamel hypoplasia, microdontia, hypodontia, xerostomia	Dental developmental anomalies
Bardellini, E. (130)	Burkitt lymphoma	CT	Oral mucositis, ulcers, bacterial infection	Oral pain, difficulty in chewing and swallowing
Gandhi, K. (133)	Hodgkins lymphoma, Non-Hodgkin's lymphoma, acute lymphoid leukemia, acute myeloid leukemia, RMS, osteosarcoma, stem cell glioma, glioblastoma, astrocytoma, carcinoma lung, neuroblastoma, Ewing sarcoma, anaplastic astrocytoma, carcinoma in situ, hepatoblastoma	CT	Oral mucositis, head and neck lymphadenopathy, cracked lip, ulcers, herpes simplex infection temporomandibular joint pain, oral petechiae, ecchymosis, gingivitis, fungal infection (candidiasis) xerostomia	Oral pain, dry mouth, difficulty in swallowing and speaking
Chouksey, G.C. (165)	Acute lymphoid leukemia	CT	Palatal perforation	Difficulty in eating, swallowing, and nasal

				regurgitation, impaired speech
Garrocho-Range, J.A. (171)	Acute lymphoid leukemia	CT	Oral mucositis , cracked lips, coated tongue, angular cheilitis	Oral pain, poor oral hygiene
Horri, A. (178)	Acute myeloid leukemia	CT	Necrotic fungal infection, facial asymmetry	Difficulty in eating and speaking, cosmetic deformity, asymmetrical smile, social isolation, lack of self-confidence, psychosocial impact, missing school
Lupi, S.M. (139)	Acute myeloid leukemia	CT, RT	Hypodontia, mobile teeth, root hypoplasia and malformation, dental caries	Toothache, dental developmental anomalies
Wu, W.J. (111)	Salivary gland tumor	RT	Jaw hypoplasia	Dental developmental anomalies
Çetiner, D. (197)	Hodgkin's lymphoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, RMS, neuroblastoma, Wilms' tumor, retinoblastoma	CT	Root malformation, retained teeth, enamel hypoplasia and discoloration, premature apexification, microdontia, tooth agenesis	Dental developmental anomalies
Hernandez, M. (181)	Acute myeloid leukemia	CT, HSCT	Enamel defects, microdontia, stunted root,	Dental developmental anomalies,

			hypodontia, malocclusion	cosmetic deformity, difficulty chewing, root abnormalities, failure to perform orthodontic treatment due to dental anomalies
King, E. (138)	Neuroblastoma and head and neck RMS	CT, RT	Teeth agenesis, hypoplasia, microdontia, root malformation, delayed eruption, malocclusions, dental caries, periodontitis	Cosmetic deformity, self-conscious about appearance, dental developmental anomalies
Loves, R. (172)	Leukemia, lymphoma, solid tumor, brain tumor, other types	CT, RT, surgery, HSCT	Oral mucositis , fungal infection (thrush), dysgeusia	Tastes changes, adaptive eating strategies, brushing teeth frequently due to bad taste
Martin, P. (112)	Bilateral retinoblastoma	RT	Hypodontia, microdontia, jaw hypoplasia, malocclusion	Cosmetic deformity, psychosocial impact, impaired oral function, discomfort, dental developmental anomalies
Mattos, V.D. (142)	RMS	CT, RT	Facial symmetry, jaw hypoplasia, root agenesis, stunted root, anodontia, root malformation microdontia, delayed eruption, small pulp	Dental and craniofacial developmental anomalies

			chambers, premature apexification	
Michalak, I. (154)	RMS, Burkitt's lymphoma	CT, RT, surgery	Root agenesis, missing tooth bud, delayed root formation, jaw hypoplasia, facial hypoplasia, demineralised enamel, resorption of jawbone	Dental and craniofacial developmental anomalies difficulty biting and chewing, impaired speech, cosmetic deformity, poor oral health
Noirrit-Esclassan, E. (150)	Leukemia, CNS tumor, lymphoma, bone tumor, non-bone sarcoma	CT, RT	Oral mucositis	Oral pain, unable to eat
Bendoraitiene, E.A. (113)	Central nervous system tumors	RT, surgery	Dental caries, poor oral hygiene, gingivitis	Cosmetic deformity, adaptive eating strategies, poor oral health
Hoogeveen, R.C. (148)	head and neck RMS	CT, RT	Facial asymmetry, jaw dysplasia, stunted roots, root agenesis, microdontia, root malformations, hypoplastic enamel, tooth agenesis	Dental developmental anomalies
Liu, Y. (198)	Acute myeloid leukemia	CT, HSCT	chronic GVHD, secondary malignancy	Oral pain
Shum, M. (176)	RMS, central nervous system tumor, leukemia, lymphoma, kidney tumor, retinoblastoma, other sarcoma's and cancer	CT, RT, surgery, HSCT	Tooth agenesis, microdontia, root abnormalities	Dental developmental anomalies, poor QoL

Attinà, G. (129)	Central nervous system tumor, sarcoma, lymphoma, others solid tumors	CT	Oral mucositis, ulcers	Oral pain, difficulty eating, nutritional support, poor QoL
Guimarães, J.R. (126)	Acute myeloid leukemia, acute lymphoid leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, solid malignant tumors	CT	Oral mucositis	Oral pain
Miranda-Silva, W. (170)	Acute myeloid leukemia, acute lymphoid leukemia, juvenile myeloid leukemia, other cancer	CT, TBI, HSCT	Oral mucositis, sialorrhea, xerostomia	Odynophagia, nutritional support
Brink, M. V. (180)	Acute myeloid leukemia, acute lymphoid leukemia, RMS lymphoma, medulloblastoma, bone tumor	CT	Dysgeusia, hypogeusia	Taste changes, appetite loss, eating disorders
Scarpelli, A.C. (151)	Nasopharyngeal carcinoma	CT, RT	Discolored teeth, dental caries, xerostomia, dry lips	Toothache, psychosocial impact, impaired aesthetics
Caran, E.M. (173)	Hemangiopericytoma	CT, RT, surgery	Facial asymmetry, trismus, tooth loss, malocclusion	Impaired oral function and aesthetics, social isolation, psychological impact, poor QoL, dental developmental anomalies
Ip, W.Y. (132)	Haematological malignancies, solid tumors	CT	Oral mucositis, sialorrhea	Oral and throat pain, difficulty swallowing,

				eating, sleeping and speaking
Fernandes,K.S. (157)	Acute myeloid leukemia, malignant osteopetrosis	CT, TBI, HSCT	GVHD, stunted roots, root agenesis, taurodontism, delayed eruption, oral soft tissue alterations, enamel hypoplasia, dental caries	Dental developmental anomalies
Cheng, K.K.F. (125)	Hematological malignancies, solid tumors	CT	Oral mucositis	Difficulty swallowing, drinking, eating, speaking and sleeping
Cheng, K.K.F. (131)	Hematological malignancies, solid tumors	CT	Oral mucositis, sialorrhea, alterations in saliva consistency	Severe oral pain, difficulty speaking, drinking, sleeping, psychological distress
Korfage, A. (153)	Nasopharyngeal carcinoma, RMS	CT, RT, surgery	Microdontia, root malformation, mid-face hypoplasia, trismus, jaw hypoplasia, hypodontia, microstomia, malformed teeth	Impaired oral function and aesthetics, dental developmental anomalies
Loves, R. (169)	Central nervous system tumor, leukaemia, lymphoma, solid tumour, other	CT, RT, surgery, HSCT	Oral mucositis, dysgeusia	Loss of appetite, unable to enjoy food, adaptive eating strategies, increased hydration, frequently brushing teeth due to bad taste

Bektaş-Kayhan, K. (147)	RMS	CT, RT	Jaw hypoplasia, trismus, hyposalivation, incomplete dentition, dental caries, stunted root, blunt roots, retained tooth	Poor oral health, dental developmental anomalies, impaired oral function and aesthetics
Cockerill, C. (166)	Salivary gland tumor	CT, RT, surgery	Facial twitching, xerostomia, facial paralysis, gustatory sweating (Frey's syndrome), secondary malignancy, jaw hypoplasia, sialorrhea	Facial paralysis, numbness and pain, dental developmental anomalies, impaired speech, difficulty eating, impaired oral function, nutritional support, phycological impact (depression), self-conscious about appearance
Dev, K. (199)	Ewing sarcoma	CT, RT, surgery	Secondary malignancy	Oral pain
Kamasaki, Y. (200)	Acute lymphoid leukemia	CT, HSCT	Cellulitis, trismus	Poor oral health, severe oral pain, impaired aesthetic due to healing scar
Leiser, D. (168)	RMS	CT, pencil beam scanning (PBS), proton therapy (PT)	Impaired dental growth, facial hypoplasia	Cosmetic deformity, dental developmental anomalies
Shahriari, M. (201)	Acute lymphoid leukemia	CT, HSCT	Mucosal hypertrophy, leukemia cutis	Burning sensation, oral pain

			(relapse of leukemia due to infiltration in oral mucosa and skin)	
Carneiro, T. V. (124)	Central nervous system tumors, leukemia, lymphoma, other solid tumors	CT, RT, surgery	Dental caries, oral lesions	Smiling with embarrassment, toothache
Kostak, M. A. (177)	Acute lymphoid leukemia	CT	Oral mucositis	Oral pain
Popescu, B. (202)	Well-differentiated squamous cell carcinoma and Ewing sarcoma	CT, RT, surgery	Tongue resection	Impaired oral function and aesthetic, healing scars, altered voice, impaired speech, social isolation, difficulty speaking
Soares, A. D. S. (128)	Leukemia	CT	Oral mucositis	Oral pain
Wang, Y. (203)	Acute lymphoid leukemia	CT	Dental caries, gingivitis, xerostomia	Poor oral health, loss of appetite, adaptive eating strategies
White, M.C. (204)	Acute lymphoid leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, primitive neuroectodermal tumor, other	CT, HSCT	Oral mucositis	Oral pain
Williams, P.D. (152)	Acute myeloid leukemia, solid tumors, nervous system tumors, Other	CT, RT	Oropharyngeal symptoms, dysphagia	Jaw pain, difficulty swallowing, soreness in mouth and throat

Misir, A. F. (149)	RMS	CT, RT	Enamel hypoplasia, malocclusion, facial asymmetry, stunted and tapered roots, root agenesis, jaw hypoplasia, teeth agenesis	Dental developmental anomalies
Carneiro, T. V. (74)	Type of cancer not mentioned	Specific type not mentioned	Oral mucositis, dental caries	Oral pain, toothache, discomfort, feeling sad, difficulty eating and maintaining oral hygiene due to pain, poor QoL
Pourdeghatkar, F. (127)	Acute myeloid leukemia	CT	Oral mucositis	Oral pain, adaptive eating strategies
Arpaci, T. (205)	Central nervous system tumor, leukemia, solid tumor, lymphoma, others	CT, RT, surgery, HSCT	Oral mucositis, dysgeusia	Poor nutrition, taste changes, oral pain
Bostanabad, M. A. (123)	Acute myeloid leukemia, acute lymphoid leukemia, central nervous system tumor, lymphoma, neuroblastoma, Wilms' tumor, connective tissue sarcoma	CT	Oral mucositis	Oral pain
Alonso-Prieto, M. (179)	Acute myeloid leukemia, acute lymphoid leukemia	CT, HSCT	Oral mucositis	Oral pain

Hong, H.C. (174)	CNS tumor, leukemia, lymphoma, solid tumor, other	CT, RT, surgery, HSCT	Xerostomia, mouth sores	Taste changes, oral pain, difficulty swallowing and sleeping, lack of concentration and energy, feeling sad, depressed, anxious
Kameoka, R. (166)	Acute myeloid leukemia	CT, HSCT	Dental caries, stunted and tapered roots, tooth agenesis, anomalies in permanent dentition	Poor oral health, dental developmental anomalies

Table 7: Long-term effects of cancer treatment on oral health

First Author	Age of Participants	Type of Cancer	Treatment	Long-term Effect
Najafi, S.H. (143)	26 years	Hodgkin's lymphoma	CT, RT	Root resorption, stunted roots, mobile teeth, gingivitis, root malformations
Shigeru, S.M (159)	9 years	Acute lymphoblastic leukemia	CT, HSCT, TBI	Stunted roots, dental caries, microdontia, retained teeth, altered teeth development
Padmanabhan, M.Y. (163)	8 years	Maxillofacial Burkitt lymphoma	CT	Dental caries, xerostomia
Pedersen, L.B. (196)	12-18 years	Leukaemia, lymphomas, reticuloendothelial neoplasms, renal and hepatic neoplasms, sympathetic nervous system tumours, retinoblastomas, central nervous system and intracranial and intraspinal neoplasms, bone and soft tissues sarcoma, gonadal neoplasms	CT	Microdontia, hypodontia
Bektaş-Kayhan, K.K. (136)	13, 14 & 15 years	Nasopharyngeal carcinoma	CT, RT	Xerostomia, dental caries, trismus
Nemeth, O. (160)	12.2 ± 0.5 years	Type of cancer not mentioned	CT	Tooth agenesis, microdontia, macrodontia, retained teeth, root malformation,

				dental caries, hypodontia
Nishimura, S. (144)	Average age of 17.7 years	Acute myeloid leukemia, acute lymphoid leukemia, Non-Hodgkin's lymphoma, adrenal cortical carcinoma, medulloblastoma, neuroblastoma, primitive neuroectodermal tumour, undifferentiated sarcoma of bone, Wilms' tumour, hepatoblastoma	CT, TBI	Tooth agenesis, microdontia, stunted roots
Tummawanit, S. (156)	16 years	Retinoblastoma	Surgery, CT, RT	Jaw hypoplasia, microdontia, hypodontia, skeletal malocclusion
Saha, A. (161)	11.4–22.5 years	Central nervous system tumors	Surgical, RT, CT, HSCT	Microdontia, hypodontia, root malformation, dental caries, gingivitis
Yavuz, A. (146)	17 years	Nasopharyngeal carcinoma	CT, RT	Xerostomia, dental caries, thermosenstivity, gingivitis, trismus, altered teeth development
Grant, S. R. (110)	6-18 years	Salivary gland tumor	RT, surgery	Facial nerve deficit, trismus, craniofacial growth abnormalities
Man, Q.W. (140)	18 years	Lymphoma	CT, RT	Osteoradionecrosis, facial asymmetry

Santos-Silva, A.R. (164)	14 years	Chronic myeloid leukemia	CT, HSCT	Chronic GVHD, gingival atrophy, lichenoid hyperkeratosis, ulcers, xerostomia, dental caries, discolored teeth
Hafiz, A. (137)	12 years	Rhabdomyosarcoma (RMS)	CT, RT	Dental caries, root agenesis, mid-face hypoplasia
Marangoni-Lopes, L. (141)	6–16 years	Hodgkin's lymphoma	CT, RT	Xerostomia
Owosho, A.A. (155)	7–16 years	Head and neck rhabdomyosarcoma	CT, IMRT	Facial asymmetry, jaw hypoplasia, tooth agenesis, hypodontia, root agenesis, stunting, malformation, enamel hypoplasia, xerostomia, trismus
Ozdere, E. (145)	13 years	Nasopharyngeal carcinoma	RT, CT	Trismus, dental caries
Wilberg, P. (162)	19–46 years	Acute lymphoid leukemia	CT	Dental caries, enamel hypoplasia, microdontia, hypodontia, xerostomia
Horri, A. (178)	8 years	Acute myeloid leukemia	CT	Facial asymmetry
Lupi, S.M. (139)	25 years	Acute myeloid leukemia	CT, RT	Hypodontia, mobile teeth, root hypoplasia and malformation, dental caries

Wu, W.J. (111)	2-18 years	Salivary gland tumor	RT	Jaw hypoplasia
Çetiner, D. (197)	Mean age 10 years + 4 months in cases 12 years + 4 month in controls	Hodgkin's lymphoma, Non-Hodgkin's lymphoma, nasopharyngeal carcinoma, RMS, neuroblastoma, Wilms' tumor, retinoblastoma,	CT	Root malformation, retained teeth, enamel hypoplasia and discoloration, premature apexification, microdontia, tooth agenesis
Hernandez, M. (181)	7 years	Acute myeloid leukemia	CT, HSCT	Enamel defects, microdontia, stunted root, hypodontia, malocclusion
King, E. (138)	18 years and 15 years	Neuroblastoma and head and neck RMS	CT, RT	Teeth agenesis, hypoplasia, microdontia, root malformation, delayed eruption, malocclusions, dental caries, periodontitis
Loves, R. (172)	4-18 years	Leukemia, lymphoma, solid tumor, brain tumor, other types	CT,RT, surgery, HSCT	Dysgeusia
Martin, P. (112)	18 years	Bilateral retinoblastoma	RT	Hypodontia, microdontia, jaw hypoplasia, malocclusion
Mattos, V.D. (142)	Between 0-5 years and >20	RMS	CT, RT	Facial symmetry, jaw hypoplasia, root agenesis, stunted root, anodontia, root malformation microdontia, delayed eruption, small pulp chambers,

				premature apexification
Michalak, I. (154)	8 years and 5 years	RMS, burkitt's lymphoma	Surgery, CT, RT	Root agenesis, missing tooth bud, delayed root formation, jaw hypoplasia, facial hypoplasia, demineralised enamel, resorption of jawbone
Bendoraitiene, E.A. (113)	11 years	Central nervous system tumor	Surgery, RT	Dental caries, poor oral hygiene, gingivitis
Hoogeveen, R.C. (148)	25, 23, 21, 10, years and 5 yrs and 11 months	Head and neck RMS	CT, RT	Facial asymmetry, jaw dysplasia, stunted roots, root agenesis, microdontia, root malformations, hypoplastic enamel, tooth agenesis
Liu, Y. (198)	16 years	Acute myeloid leukemia	HSCT, CT	Chronic GVHD, secondary malignancy
Shum, M. (176)	14–16 years	RMS, central nervous system tumor, leukemia, lymphoma, kidney tumor, retinoblastoma, other sarcoma's and cancer	Surgery, CT, RT, HSCT	Tooth agenesis, microdontia, root abnormalities
Miranda-Silva, W. (170)	0-17 years	Acute myeloid leukemia, acute lymphoid leukemia, juvenile myeloid leukemia, other cancer	CT, TBI, HSCT	Xerostomia

Scarpelli, A.C. (151)	14 years	Nasopharyngeal carcinoma	RT, CT	Discolored teeth, dental caries, xerostomia, dry lips
Caran, E.M. (173)	22 years	Hemangiopericytoma	Surgery, CT, RT	Facial asymmetry, trismus, tooth loss, misaligned teeth
Fernandes,K.S. (157)	6, 8, 13 years	Acute myeloid leukemia, malignant osteopetrosis	CT, TBI, HSCT	GVHD, stunted roots, root agenesis, taurodontism, delayed eruption, oral soft tissue alterations, enamel hypoplasia, dental caries
Korfage, A. (153)	24 and 25 years	Nasopharyngeal carcinoma, RMS	Surgery, CT, RT	Microdontia, root malformation, mid-face hypoplasia, trismus, jaw hypoplasia, hypodontia, microstomia, malformed teeth
Bektaş-Kayhan, K. (147)	18 years	RMS	CT, RT	Jaw hypoplasia, trismus, hyposalivation, incomplete dentition, dental caries, stunted root, blunt roots, retained tooth
Cockerill, C. (166)	3 to 18 years	Salivary gland tumor	Surgery, RT, CT	Facial twitching, xerostomia, facial paralysis, gustatory sweating (Frey's syndrome), secondary malignancy, jaw hypoplasia, sialorrhea

Dev, K. (199)	16 years	Ewing sarcoma	Surgery, RT, CT	Secondary malignancy
Leiser, D. (168)	0.8-15.5 years	RMS	CT, pencil beam scanning (PBS), proton therapy (PT)	Impaired dental growth, facial hypoplasia
Shahriari, M. (201)	8 years	Acute lymphoid leukemia	CT, HSCT	Mucosal hypertrophy, leukemia cutis (relapse of leukemia due to infiltration in oral mucosa and skin)
Carneiro, T. V. (124)	5-18 years	CNS tumors, leukemia, lymphoma, other solid tumors	CT, RT, surgery	Dental caries, oral lesions
Wang, Y. (203)	<18 years	Acute lymphoid leukemia	CT	Dental caries, gingivitis, xerostomia
Williams, P.D. (152)	5 to 17 years	Acute myeloid leukemia, solid tumors, nervous system tumors, Other	CT, RT	Oropharyngeal symptoms, dysphagia
Misir, A. F. (149)	22 years	RMS	CT, RT	Enamel hypoplasia, malocclusion, facial asymmetry, stunted and tapered roots, root agenesis, jaw hypoplasia, teeth agenesis
Carneiro, T. V. (74)	6-15 years	Type of cancer not mentioned	Specific type not mentioned	Dental caries

Hong, H.C. (174)	19-39 years	Central nervous system tumor, leukaemia, lymphoma, solid tumor, other	CT, RT, surgery, HSCT	Xerostomia, mouth sores
Kameoka, R. (158)	5 yrs 3months	Acute myeloid leukemia	CT, HSCT	Dental caries, stunted and tapered roots, tooth agenesis, anomalies in permanent dentition

Table 8: The treatment of the oral complications and outcome on QoL

Author	Oral Complication	Treatment for Complication(s)	Treatment Outcome and Impact on QoL (If mentioned)
Cauwels, R. G. (114)	Oral mucositis	Low-Level Laser Therapy (LLLT)	Alleviates symptoms, improved oral functional
Najafi, S.H. (143)	Root resorption, stunted roots, mobile teeth, gingivitis, root malformations	Extraction and prosthetic rehabilitation of missing teeth	
Rimulo, A.L. (118)	Oral mucositis	Light emitting diode (LED) therapy	Alleviates symptoms
Bertoglio, J.C. (167)	Oral mucositis, oral bleeding, ulcers, bacterial and fungal infections	SAMITAL® oral suspension	Alleviates symptoms, improved oral functional, improved QoL
Shigeru, S.M. (159)	Stunted roots, dental caries, microdontia, retained teeth, altered teeth development	Dental fillings, extraction	Patient doing well on follow up; no symptoms reported since treatment
Nielsen, B. N. (117)	Oral mucositis	Topical morphine	Alleviates symptoms
Padmanabhan, M.Y. (163)	Oral mucositis, dental caries, xerostomia	Water intake, analgesics, sugar-free gums, prophylactic casein phosphopeptide for caries	Alleviates symptoms, improved oral functional
Pels, E. (135)	Oral mucositis, fungal infection	Mix of polyantibiotic and antifungal therapy	Alleviates symptoms
Bektaş-Kayhan, K.K. (136)	Xerostomia, dental caries, trismus	Mouth moisturizing gel, mouthwash containing	Dental problems relapsed in 2 patients

		lysozyme, lactoferrin, lactoperoxidase for xerostomia topical neutral fluoride gel and dental fillings physical therapy and hot pack to treat trismus	due to incompliance to treatment; the 3rd patient (15 years old) complied with the treatment and trismus improved
Elad, S. (115)	Oral mucositis	Chlorhexidine 0.2% mouthwash with curcumin mouthwash	Alleviates symptoms, mouthwash was safe and well-tolerated
Inati, A. (134)	Oral mucositis, necrotic and hemorrhagic lesions in mouth, dental caries	Total Parenteral Nutrition (TPN), topical mycostatin, 0.12% chlorhexidine mouthwash, gentle tooth brushing, water intake	Improved oral functional, complete remission
Khurana, H. (116)	Oral mucositis	Vitamin E and pycnogenol (pine bark extract)	Alleviates symptoms
Tummawanit, S. (156)	Jaw hypoplasia, microdontia, hypodontia, skeletal malocclusion	Extraction, overdenture prosthesis for missing teeth, orthodontic treatment, fluoride paste, preventive dental care	Improved function and aesthetics
Czyzewski, K. (108)	Oral mucositis	Keratinocyte growth factor (palifermin)	Alleviates symptoms, well-tolerated
Lauritano, D. (109)	Oral mucositis	Palifermin	Alleviates symptoms, reduced duration of parenteral nutrition
Yavuz, A. (146)	Xerostomia, dental caries, thermosenstivity, gingivitis, trismus, altered teeth development	Sugar-free gums, water intake, endodontic treatment followed by full mouth metal ceramic veneers	Improved oral function and aesthetics, satisfied with appearance

Man, Q.W. (140)	Osteoradionecrosis, facial asymmetry	Surgical reconstruction, prosthodontic rehabilitation	Satisfied with appearance
Santos-Silva, A.R. (164)	Chronic GVHD, gingival atrophy, lichenoid hyperkeratosis, ulcers, xerostomia, dental caries, discolored teeth	Cyclosporine A, chlorhexidine rinse (0.12%, alcohol-free), dental fillings	Failed dental fillings
Amadori, F. (119)	Oral mucositis	LLLT	Alleviates symptoms
Bardellini, E. (120)	Oral mucositis	Fluoride toothpaste with salivary enzymes, essential oils, proteins, and colostrum extract (Bioxtra)	No difference
Bardellini, E. (121)	Oral mucositis	Solution of verbascoside, polyvinylpyrrolidone and sodium hyaluronate (Mucosyte)	Alleviates symptoms
Hafiz, A. (137)	Dental caries, root agenesis, mid-face hypoplasia	Endodontic treatment followed by prosthodontic rehabilitation	
Lucchese, A. (122)	Oral mucositis	Palifermin	Alleviates symptoms
Ozdere, E. (145)	Trismus, dental caries	Custom-made mouth-opening device therapy, finger stretching exercises, periodontal and endodontic treatment	Trismus improved
Bardellini, E. (130)	Oral mucositis, ulcers, bacterial infection	Polyantibiotic therapy (Amikacin and Ceftazidime)	Alleviates symptoms, no dental complaints

Chouksey, G.C. (165)	Palatal perforation	Palatal obturator	Improved oral function, favorable social impact, comfortable speaking and using the appliance
Horri, A. (178)	Necrotic fungal infection, facial asymmetry	Antifungal therapy, prosthetic rehabilitation	Favorable social impact, comfortable speaking and smiling, performing well in academics
Lupi, S.M. (139)	Hypodontia, mobile teeth, root hypoplasia and malformation, dental caries	Extraction followed by implant supported crowns	Patient doing well on follow up; no symptoms reported since treatment
Hernandez, M. (181)	Enamel defects, microdontia, stunted root, hypodontia, malocclusion	Dental fillings	
King, E. (138)	Teeth agenesis, hypoplasia, microdontia, root malformation, delayed eruption, malocclusions, dental caries, periodontitis	Teeth whitening, direct composite veneers, multidisciplinary dental care including endodontic and prosthodontic rehabilitation	Satisfied with appearance, oral function did not improve
Martin, P. (112)	Hypodontia, microdontia, jaw hypoplasia, malocclusion	Multidisciplinary approach including surgical, orthodontic and implant supported prosthodontic rehabilitation, speech therapy	Favorable socio-psychological impact, improved oral function
Michalak, I. (154)	Root agenesis, missing tooth bud, delayed root formation, jaw hypoplasia, facial hypoplasia,	Orthodontic treatment, prosthetic rehabilitation	Improved mandibular abduction in first patient Poor stability of appliance in second

	demineralised enamel, resorption of jawbone		patient due to growth (growth of what?)
Noirrit-Esclassan, E. (150)	Oral mucositis	Preventive dental care, analgesics and photobiomodulation (PBM) therapy	Alleviates symptoms, well-tolerated,
Bendoraitiene, E.A. (113)	Dental caries, poor oral hygiene, gingivitis	Preventive dental care, dental fillings	No dental complaints, improved oral hygiene habits, persistent irregular diet
Liu, Y. (198)	Chronic GVHD, secondary malignancy	Surgical excision	No recurrence
Attinà, G. (129)	Oral mucositis, ulcers	Pethidine, fentanyl, and oral rinses, clonazepam (1 drop/10 kg/day) to prevent the risk of seizures associated with pethidine	Alleviates symptoms and improved oral function in mild cases insufficient to improve symptoms, oral function and parenteral nutrition in severe cases
Miranda-Silva, W. (170)	Oral mucositis, sialorrhea, xerostomia	Prophylactic dental treatment and PBM therapy	
Scarpelli, A.C. (151)	Discolored teeth, dental caries, xerostomia, dry lips	Teeth whitening gel followed by micro-abrasion, dental filling	Improved aesthetics, satisfied with appearance
Caran, E.M. (173)	Facial asymmetry, trismus, tooth loss, misaligned teeth	Jaw reconstruction	Improved oral function and hygiene
Fernandes,K.S. (157)	GVHD, stunted roots, root agenesis, taurodontism, delayed	Dental filling, periodontal treatment	

	eruption, oral soft tissue alterations, enamel hypoplasia, dental caries	(root planning), topical fluoride therapy	
Korfage, A. (153)	Microdontia, root malformation, mid-face hypoplasia, trismus, jaw hypoplasia, hypodontia, microstomia, malformed teeth	Surgical reconstruction, prosthetic rehabilitation	Improved oral function and aesthetics
Bektaş-Kayhan, K. (147)	jaw hypoplasia, trismus, hyposalivation, incomplete dentition, dental caries, stunted root, blunt roots, retained tooth	Prosthetic rehabilitation with implant assisted fixed prosthesis	Patient doing well on follow up; no symptoms reported since treatment, satisfactory oral hygiene, satisfied (who was satisfied?) with the oral function and the aesthetics
Dev, K. (199)	Secondary malignancy	Radiotherapy, palliative chemotherapy	Successful treatment
Kamasaki, Y. (200)	cellulitis, trismus	Antibiotic therapy followed by periodontal treatment	Successful treatment, not satisfied with aesthetics
Shahriari, M. (201)	mucosal hypertrophy, leukemia cutis (relapse of leukemia due to infiltration in oral mucosa and skin)	Chemotherapy	Alleviated oral lesions
Kostak, M. A. (177)	Oral mucositis	Preventive dental care	Alleviates symptoms
Soares, A. D. S. (128)	Oral mucositis	LLLT, andiroba oil	Alleviates symptoms

White, M.C. (204)	Oral mucositis	Ketamine adjunct to morphine	Alleviates symptoms, reduced use of morphine, less side effects of medication
Misir, A. F. (149)	Enamel hypoplasia, malocclusion, facial asymmetry, stunted and tapered roots, root agenesis, jaw hypoplasia, teeth agenesis	Extraction	
Pourdeghatkar, F. (127)	Oral mucositis	Chamomile mouth wash (15 drops in 10cc water)	Alleviates symptoms
Bostanabad, M. A. (123)	Oral mucositis	Satureja hortensis extract gel of 1% (ingredients: carvacrol, thymol, beta-pinene, paracemenu, lemothen, camphene, minerals, and vitamins)	Alleviates symptoms
Alonso-Prieto, M. (179)	Oral mucositis	Electronic Video Games (EVG) along with self-administered morphine pump	Alleviates symptoms, reduced use of morphine after playing EVG
Kameoka, R. (158)	Dental caries, stunted and tapered roots, tooth agenesis, anomalies in permanent dentition	Extraction, endodontic treatment, preventive dental care	Patient doing well on follow up; no oral symptoms or complaints reported since treatment, successful treatment

Table 9: The measures used and if and how children were included in the data generation.

First Author	Age at Involvement in the Study	Measurement Tools	Involvement of Patients in the Study
Cauwels, R. G. (114)	9.4 years (mean age)	Visual Analog Scale (VAS) for pain The World Health Organization (WHO) mucositis scale A questionnaire concerning oral functions, nutrition, speech and deglutition, to assess the grade of mucositis	Participants answered the questionnaire
Rimulo, A.L. (118)	5 years	WHO mucositis scale VAS for pain	Participants self-reported the symptoms
Vagliano, L. (107)	0-18 years	WHO mucositis scale	Healthcare provider (HCP's) examined the participant
Manji, A. (175)	≥12 and <18 years	OMDQ WHO mucositis scale VAS for pain Functional Assessment of Cancer Therapy Esophageal Cancer Sub-scale (FACT-ECS).	Participants self-reported the symptoms
Nielsen, B. N. (117)	2-17 years	VAS modified with six faces for pain Face Leg Activity Cry Consolability (FLACC) scale WHO mucositis scale	Participants self-reported the symptoms

Elad, S. (115)	13-16 years	WHO mucositis scale The Oral Mucositis Assessment Scale (OMAS) Visual Analog pain scale (patient reporting scale of 0-10)	Participant self-reported the symptoms caregivers gave consent
Khurana, H. (116)	6-15 years	WHO mucositis scale OMAS Children's International Mucositis Evaluation Scale (ChIMES)	Participant self-reported the symptoms caregiver gave consent
Nishimura, S. (144)	average age of 17.7 years		Participants and/or caregiver gave consent
Czyzewski, K. (108)	(median, 10.4 vs. 13.2 years	WHO mucositis scale	HCP examined the participant
Lauritano, D. (109)	7-16 years	WHO mucositis scale	Caregiver gave consent
Saha, A. (161)	11.4–22.5 years	Behavior Assessment System for Children, 2nd Edition (BASC-2) Children's Health Questionnaire, Parent Form (CHQ-PF50) Childhood Cancer Survivor Study (CCSS) questionnaire	Participants (minors) provided assent; caregiver gave consent and completed the questionnaire Adult survivors provided consent and completed the questionnaire
Yavuz, A. (146)	17 years		Caregiver gave consent

Amadori, F. (119)	3-18 years	VAS for pain WHO mucositis scale	Participants self-reported the symptoms Participants and their caregiver gave consent
Bardellini, E. (120)	6-14 years	Short form of Oral Health Impact Profile (OHIP-14) questionnaires Common Toxicity Criteria (CTC) scale of the WHO	Participants answered the survey Participants and their caregiver gave consent
Bardellini, E. (121)	5-18 years	VAS for pain CTC scale	Participants and their caregivers gave consent
Hafiz, A. (137)	12 years		Participant gave consent
Lucchese, A. (122)	7-16 years	WHO mucositis scale OMDQ	Caregiver gave consent Participants answered the questionnaire
Marangoni-Lopes, L. (141)	6–16-year-old	Quality of Life – Head and Neck module 35 questionnaire (QLQ-HN 35)	Caregiver gave consent Participants completed the questionnaire along with their caregiver
Wilberg, P. (162)	19–46 years	Oral health was reported using a five-point, categorical scale	Participants gave consent completed the questionnaire and self-reported the symptoms

		then dichotomized as good or poor	
Bardellini, E. (130)	16 years	WHO mucositis scale	Caregiver gave consent
Gandhi, K. (133)	2 -14 years	WHO mucositis scale	Caregiver and HCP gave consent
Garrocho-Range, J.A. (171)	3-12 years	WHO mucositis scale	Caregiver gave consent
Wu, W.J. (111)	2-18 years		Researcher examined the participant
Çetiner, D. (197)	Mean age 10 years + 4 months in cases 12 years + 4 month in controls		Participants and/or their caregiver gave consent
Hernandez, M. (181)	7 years		Participants and their caregiver mutually approved the treatment plan
Loves, R. (172)	4-18 years	Single semi-structured interview Symptom Screening in Pediatrics Tool (SSPedi) (age 8–18) mini-SSPedi (age 4–7)	Participants and their caregiver gave consent Participant self-reported the symptoms
Martin, P. (112)	18 years		Participants and their caregiver were

			motivated to obtain dental treatment
Mattos, V.D. (142)	>5-10 to >20 years		Participants and/or their caregiver gave consent Participants (minor) provided assent form
Noirrit-Esclassan, E. (150)	3-18 years	WHO mucositis scale HEDEN mucositis scale VAS for pain	Participants and their caregiver gave consent
Bendoraitiene, E.A. (113)	11 years		Caregiver gave consent
Shum, M. (176)	14–16 years	Holtta's Defect Index (HDI) Oral Health Impact Profile-14 (OHIP-14)	Participants answered the survey Participants above 16 years of age solely gave consent Both participants (below 16) and their caregivers gave consent
Attinà, G. (129)	4–18 years	WHO mucositis scale Wong–Baker FACES Pain Rating Scale (WBS)	Caregiver gave consent
Guimarães, J.R. (126)	1-18 years	Modified Oral Assessment Guide (OAG)	
Brink, M. V. (180)	6–18 years	Behavioral Pediatrics Feeding Assessment Scale (BPFAS)	Consent was obtained from Caregiver and participants ≥ 12 years

		Likert scale (1 “very bad” to 5 “very good”) for assessment for smell, taste and appetite	Participants assessed and reported the symptoms Caregivers reported the BPFAS
Scarpelli, A.C. (151)	14 years		Participant and the caregiver both reported the medical history and examination
Ip, W.Y.(132)	6-18 years	Chinese version of the State Anxiety Scale for Children (CSAS-C) Oropharyngeal Mucositis Quality of Life Scale (OMQoL)	Caregiver gave consent
Cheng, K.K.F. (125)	6–18 years	Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire (OMDQ MTS) Short form of the Chinese version of the State Anxiety Scale for Children (CSAS-C)	Participants provided assent and their caregiver gave consent Participants completed the questionnaire with the assistance of caregivers
Cheng, K.K.F. (131)	6-18 years	Chinese version of the Oral Mucositis Daily Questionnaire (OMDQ) Oral Mucositis-specific Quality of Life Measure (OMQoL)	Participants self-reported symptoms and completed the questionnaire with the assistance of caregivers, if needed

Loves, R. (169)	4–18 years	Structured interview Symptom Screening in Pediatrics Tool (SSPedi) (age 8–18) mini-SSPedi (age 4–7)	Participants provided assent and their caregivers gave consent Participant self-reported the symptoms
Cockerill, C. (166)	3 to 18 years	Phone interview and Patients were also contacted by phone for a follow up survey	Participants provided consent (206)
Leiser, D. (168)	0.8-15.5 years	PedQoL Questionnaire: The proxy-rating version (PedQoL proxy) self-rating version for children older than 4 years (PedQoL self)	Caregivers completed the questionnaire for the participants
Carneiro, T. V. (124)	5-18 years	Pediatric Quality of Life Inventory (PedsQL™ 3.0 module)	Participants above the age of 12 years answered directly Caregivers of participants below the age of 12 answered for them
Kostak, M. A. (177)	8-18 years	WHO mucositis scale ChIMES	Participant self-reported the symptoms
Soares, A. D. S. (128)	4-12 years	WHO mucositis scale Wong-Baker visual analog scale for pain	Evaluator examined the participant
Wang, Y. (203)	No more than 18 years		Researchers examined the participant

			Participants completed the questionnaire Caregiver gave consent
White, M.C. (204)	3-14 years	NCI-CTC scales for OM Wong and Baker Faces with a 0–10 numerical rating scale VAS for pain FLACC scale	Participant self-reported the symptoms; if the participant could not report the HCP used an observational tool (FLACC)
Williams, P.D. (152)	5 to 17 years old	Therapy-Related Symptom Checklist Children (TRSC-C) PedsQL™ 3.0 module	Participants self-reported symptoms; the caregivers and HCP could assist the participants to complete the checklist, if needed
Carneiro, T. V. (74)	6-15 years	Modified Autoquestionnaire Qualité de Vie Enfant Imagé (AUQEI)	Caregiver gave consent Participants answered the questionnaire in an interview
Pourdeghatkar, F. (127)	6-15 years	WHO mucositis scale	Caregiver gave consent HCP examined the participant
Arpaci, T. (205)	3–18 years		Caregivers perspective was reported
Bostanabad, M. A. (123)	3-14 years	Oucher pain scale	Participants answered the questionnaire in an interview with the assistance of the HCP Participant self-reported the symptoms
Alonso-Prieto, M. (179)	4 and 17 years	WHO mucositis scale	Participant self-reported the symptoms

		Numerical Rating Scale (score 0-10) to measure pain intensity	
Hong, H.C. (174)	19-39 years	Memorial Symptom Assessment Scale (MSAS)	Participants completed the surveys
Kameoka, R. (158)	5 yrs 3months		Caregiver gave consent

Appendix D: Graphs and Pie Charts

Figure 4: Study Design of the Included Articles

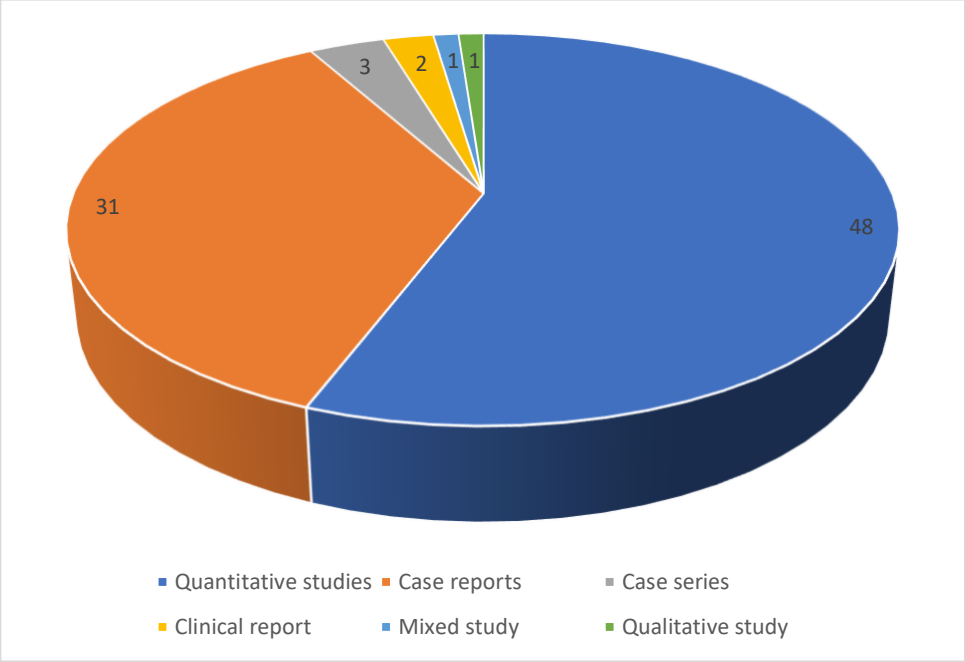


Figure 5: Yearly distribution of publications over the past 10 years

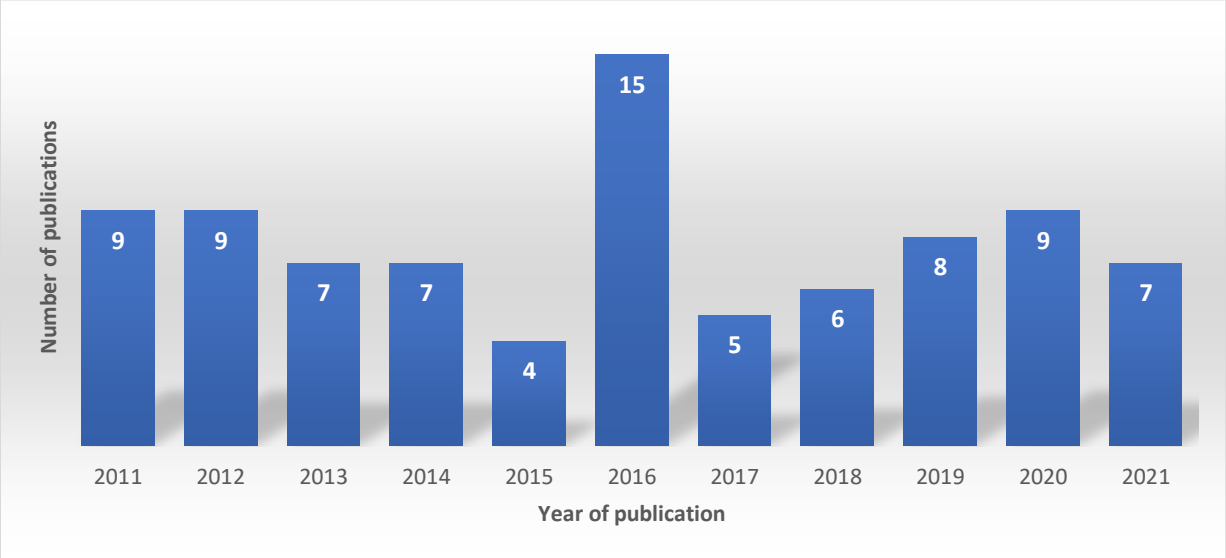


Figure 6: Global distribution of included publications