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

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July 2012

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Dental Sciences

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Abstract:

Objectives: To systematically review the research literature on the relationship between Quality of Life (QoL) and cancer therapy-related oral side-effects in a pediatric population. Methods: A scoping review was conducted using 16 databases (research and grey literature), websites, reference lists, and key journals. Inclusion criteria included studies pertaining to children 0-20 years, in English or French, published from 2000 to 2011. Exclusion criteria included mixed population of adults and children and non-discrete disease categories. Data was independently charted by two reviewers. Results: A total of 1270 articles were identified through the initial search. A rigorous review of abstracts and full text reduced the sample to 82 articles, all of which were categorized through a data extraction process. Data analysis resulted in the following findings: Leukemia studies were predominant. The most common side-effect was mucositis; however, side-effects mostly co-occurred. Twenty-one articles dealt directly with the effect on QoL, citing impacts such as changes in taste, eating, drinking, sleep habits, voice and weight loss. Twenty-five articles examined the long-term effect of treatment on pediatric dentition, showing that resultant caries and malformed teeth can affect eating and speech. Conclusions: Preventive oral care before, during and after cancer therapy can decrease the oral side-effects and improve the QoL of the pediatric patient; however, few studies to date advance recommendations for QoL improvement. This study underscores the need for a dental oncology program in pediatric hospitals.
Résumé:

Objectifs: Examiner systématiquement la littérature en recherche sur les liens entre la Qualité de vie (QV) et les effets secondaires des approches thérapeutiques pour traiter le cancer buccal chez une population pédiatrique. Méthodes: Un survol de la littérature été réalisé en utilisant 16 bases de données (recherche et littérature grise), des sites web, des listes de référence et des revues-clés. Critères d'inclusion : études portant sur une population âgée de 0 à 20 ans, publiées en anglais ou en français entre 2000 et 2011 inclusivement. Critères d'exclusion : études concernant une population mixte d'enfants et d'adultes et études d'enfants ayant plus d'un diagnostique. Les données ont été recueillies indépendamment par deux chercheurs; 1270 articles ont été repérés dans un premier survol. Un examen rigoureux des résumés et textes intégraux permit de réduire l'échantillon à 82 articles, par la suite classés à travers un processus d'extraction des données.

Résultats d'analyse: Les études sur la leucémie étaient prédominantes. Le plus commun des effets secondaires était la mucosité, mais la plupart des effets secondaires survenaient en cooccurrence. Vingt-et-un articles traitent directement des effets sur la qualité de vie, citant des impacts tels une modification du sens du goût, des changements dans les habitudes alimentaires (e.g. boire et manger) et dans celles du sommeil, des pertes de poids ainsi qu’une modification de la voix. Vingt-cinq articles examinaient l'effet à long terme des traitements sur la dentition pédiatrique et démontrent que la carie et les malformations dentaires qui en résultent peuvent affecter l'alimentation et la parole. Conclusions : Des soins préventifs oraux avant, pendant et après le traitement pour le cancer peuvent
 diminuer les effets secondaires oraux et améliorer la qualité de vie. Cette étude souligne la nécessité d'un programme d'oncologie dentaire dans les hôpitaux pédiatriques.
Acknowledgements:

To Dr. Mary Ellen Macdonald for all her help and supervision not only in the preparation of this thesis, but also for her constant guidance throughout my Master’s program. You were and always will be an amazing source of knowledge and inspiration.

To my committee members, Dr. Christophe Bedos and Dr. Michael Wiseman for their helpful feedback.

To Angella Lambrou and Lorie Kloda, liaison librarians and Akanksha Srivastava, Master’s student, McGill University for assistance with the search strategy and abstract selection.

To Linda Riffon and Martine Levesque for assistance with the French translation of the thesis abstract.

To the Program in Pediatric Palliative Care Research and the Pediatric Oncology Department at the Montreal Children’s Hospital and all my colleagues at the Oral Health and Society Research Unit, Faculty of Dentistry for their valuable feedback.

To my husband, Raj, and my son, Rahul, for encouraging me and for supporting me in numerous ways to help me realize my dream.
Chapter 1: Introduction

(Please note: The thesis follows a manuscript based format and therefore some information may be repeated).

Childhood cancer, though relatively rare, is still the second leading cause of death in children under the age of 14 in the United States. (1) Fortunately, aggressive cancer treatment has led to increased survival rates of over 82%. (2) However, these curative treatments often have serious side-effects, some of which affect the oral cavity of the patient. Oral side-effects of cancer therapy may occur during or soon after treatment and are classified as acute or early effects. Complications occurring months or years later, even when the child is in remission, are considered to be late effects.

Early effects of cancer treatment include oral mucositis, xerostomia (dry mouth), and oral infections (e.g., candidiasis and herpes virus infections) and taste disturbances. Xerostomia is not a disease but occurs as a result of reduced or no saliva. Complications from these side-effects, such as dental infections, can impede treatment. Dental infections can lead to widespread infections in the body, reducing the body’s ability to cope with cancer treatment. So, cancer treatment has to be interrupted until the dental infection can be resolved. Further, oral complications of cancer therapy may delay future tooth development in the child once in remission. Late effects of cancer treatment in pediatric cancer patients include abnormalities in dental development, caries and abnormalities in jaw development; a more serious consequence is the development of secondary
malignancies including tumors at the irradiated sites. (3) Both early and late effects can be painful for the child; moreover, they can affect speaking, eating and swallowing.

Patients with cancer are facing a life-threatening disease in addition to the consequences of its treatment. To date, dental care is a neglected area of pediatric cancer care. (4) Any area of symptom neglect will ultimately lead to a lower quality of life for the child. The treatment of a child with cancer must involve both curative and palliative care and management of any complications resulting from treatment. (5)

Oral health affects general health. The mouth is not a separate entity from the rest of the body. Maintaining good oral health ensures reduction in incidence of cavities and gum diseases. Changes in oral health affect eating, sleeping and voice quality. (6) Poor oral hygiene resulting in tooth loss impacts behavior and general health physically, functionally, socially, emotionally and psychologically. It impedes social interaction and communication and basic physical functions such as eating and chewing food. Caries, in children, can lead to tooth loss. Missing teeth and tooth decay are associated with pain, discomfort and problems with eating and sleeping. Thus, quality of life related to oral health and, therefore, to general health is affected. (7)

Dental development occurs throughout childhood until adolescence. The treatments for cancer, including pharmacological (e.g., chemotherapy), radiation and stem cell transplantation, as well as the underlying cancer can have both
short-term and long-term impacts on the developing dentition of a child with cancer. Further, the impact can be both physical and psychological, affecting the general well-being of the patient. These oral complications can affect treatment outcomes when they interfere with treatment timelines.

There is increasing literature on oral complications from cancer therapy in adult cancer patients. (8, 9) Numerous studies mention oral complications of cancer therapies in children (10-12), but the effects on the childhood cancer patient’s quality of life are understudied. This lack of research led us to conduct a scoping review to understand broadly the extent of research related to oral complications of cancer treatment and QoL. By understanding the ways in which QoL is affected by treatment, researchers can focus on treatments with better outcomes.

The main focus of this Master’s thesis is to explore the published and unpublished research literature relevant to the side-effects related to cancer treatment and QoL in children and to find out where the research gaps lie by conducting a scoping review. The gaps will help us build future research priorities in the fields of dentistry and pediatric oncology. In the next chapter, I will review the current literature related to childhood cancer, oral effects of cancer therapy and QoL. Following, in chapter 3, I give an overview of the method chosen for this study and the rationale behind this choice.

This scoping review will “map” the literature in the fields relevant to oral complications associated with cancer treatment in children. “Mapping” is a process of summarizing a range of evidence in order to convey the breadth and
depth of the field. (13) This is a first step in a larger research program dealing with pediatric palliative care and oral health led by my supervisor. Chapter 4 is a manuscript for publication and conclusion for this study is in chapter 5. Supplementary information related to the method and results are included in the appendices.
Chapter 2: Literature Review

This chapter gives an overview of the different childhood cancers, the treatment of these cancers and the relevant aspects of QoL and Health Related QoL (HRQoL). The background information in this chapter covers the current state of knowledge, sets up the basis for this study and explains the concepts involved.

2.1 Childhood Cancers

Cancer is the general name for a group of diseases in which abnormal cells in a body grow and produce more abnormal cells. During childhood, the period between birth and adolescence, a child can be affected by cancer. The main types of childhood cancers are leukemia, brain and central nervous system tumors, lymphomas, sarcomas, liver and kidney cancers and other rarer forms of childhood cancers.(14) Childhood cancers differ from adult cancers in type and treatment. Adult cancers are frequently linked to environmental and lifestyle factors. Childhood cancers occur, quite often, as a result of changes in cells even before birth.(15) In adults, common cancers are of the glands or tissues lining organs while in children they are more commonly blood-related. Childhood cancers are treated with more aggressive treatment regimens than are adult cancers since childhood cancers respond better to treatments such as chemotherapy. The result is that childhood cancers have a better 5-year survival rate than adult cancers do, but the side-effects may be greater. Long-term effects of cancer therapy are seen more often in children than in adults since children are at a developmental stage. The side-effects can also be greater because they are at this stage.(15)
**Leukemias** are cancers that arise in the bone marrow and tissues that produce blood cells. Acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) are the most common types of leukemia and also the most common types of childhood cancer. Thirty-three percent of childhood cancers in Canada are leukemia.\(^\text{(16)}\)

**Globally, brain and central nervous system tumors** are the second most common type of childhood cancer. Gliomas are the most common type of brain cancer occurring in the cells of the central nervous system (CNS). They are not a specific type of tumor; rather, glioma is the generic name for tumors that start in the CNS.\(^\text{(15)}\)

**Lymphomas** arise in the lymph tissue in the body’s immune system. Two major types are Hodgkin’s lymphoma and non-Hodgkin’s lymphoma.\(^\text{(14)}\)

**Sarcomas** are tumors occurring in bones and soft tissue, such as muscles. Osteosarcomas are common types of bone cancers. Rhabdomyosarcoma is a soft-tissue cancer found in the muscles of the head, neck, arms and legs.\(^\text{(14)}\)

**Liver cancers** are rare in children and teenagers. Hepatoblastoma is the most common type of liver cancer in children, but is rare compared to other solid tumors in children.\(^\text{(1)}\)

**Kidney cancers** are cancers that form in the tissue of the kidneys. Wilm’s tumor and clear-cell sarcoma can occur in one or both kidneys.

**Other rare childhood cancers** include retinoblastoma and germ cell tumors. Retinoblastoma is a cancer of the retina, a membrane at the back of the eye. Germ
cell tumors can arise in the testes, ovaries and at the bottom of the spine, as well as in the chest, abdomen and middle of the brain. (14)

Childhood cancers can be treated in a number of ways: through surgery, chemotherapy, radiation therapies, hematopoietic stem cell transplantation (HSCT) and immunotherapy. In this study, we have focused on chemotherapy, radiotherapy and HSCT because oral complications are associated with these therapies. (14) Childhood cancers are generally treated with a combination of therapies.

**Table 1: Childhood cancers and treatments causing oral complications**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>CT, RT, HSCT</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>CT, RT, HSCT</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>CT, RT, HSCT</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>CT, RT</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>CT, RT</td>
</tr>
<tr>
<td>Brain and CNS tumors</td>
<td>CT, RT, HSCT</td>
</tr>
<tr>
<td>Other childhood cancers</td>
<td>CT, RT</td>
</tr>
</tbody>
</table>

CT- chemotherapy, RT- radiotherapy, HSCT – hematopoietic stem cell transplantation

**2.2 Early oral complications that can arise from cancer treatment:**

**Oral mucositis** is an acute inflammation or ulceration of the oral mucous membranes. Oral mucositis can occur as a consequence of radiation treatment.
near the mouth, after total body irradiation and after high-dose chemotherapy. Oral mucositis is one of the most debilitating complications of cancer treatment; it can induce intense pain and affects almost 100% of patients undergoing chemotherapy. (17) Oral mucositis is the most common oral complication of cancer treatment and is the most severe. The resulting pain and ulcerative lesions can cause compromised nutritional intake. (18) Supportive guidelines for adults have been established for treatment of mucositis. (19) These guidelines are evidence-based and have been produced by several organizations, including The Cochrane Collaboration (20), the National Comprehensive Cancer Network, Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (19) and the European Society of Medical Oncology. In children and teenagers with cancer, evidence-based guidelines have been established by the Children’s Cancer and Leukemia Group/Cancer and Leukemia Nurses Forum’s Mouth Care Group. (21)

Xerostomia is the subjective feeling of a dry mouth. It is characterized by low or almost no saliva. (22) It can be an early side-effect when caused by chemotherapy and can have a long-term effect when caused by radiotherapy to the head and neck. Xerostomia is a result of damage to the salivary gland which changes the consistency and amount of saliva in the mouth. The salivary change that occurs results in increased acidity in salivary pH creating more opportunity for development of dental caries and infections. (23) The occurrence of xerostomia can also lead to a change in taste sensations.
**Taste Disturbance:** Dysgeusia is an alteration in taste and is associated with ageusia, which is the complete lack of taste, and hypogeusia, which is a decrease in taste sensitivity. Dysgeusia is a common complaint of patients undergoing chemotherapy and radiotherapy.(24) Taste changes can occur from chemotherapy or radiotherapy or as a result of mouth sores due to oral mucositis and xerostomia.

**Oral Hemorrhage:** Chemotherapy may induce thrombocytopenia or an abnormally low number of platelets which can cause an oral hemorrhage.(24)

**Oral infections** such as candidiasis and other viral, bacterial or fungal infections can lead to periodontitis, which in turn leads to ulceration and oral hemorrhage. Periodontitis is inflammation of the bones and ligaments that support the teeth occurring when gum infections are left untreated or treatment is delayed.(25) Oral infections may be caused by xerostomia or may be due to damage from chemotherapy or radiotherapy.(26)

### 2.3 Late effects of cancer therapy

**Dental developmental abnormalities:** The tooth is made up of a crown and root. A healthy tooth has a space inside it called the pulp space which is filled with soft tissues. . (27) Root stunting is the term to describe shortening of the roots of the teeth. Other developmental abnormalities include microdontia and hypodontia. Microdontia is a condition of abnormally small teeth. Hypodontia refers to partial absence of teeth.(28, 29)

Kaste and colleagues found that root stunting, microdontia, hypodontia, enlarged pulp chambers, over-retention of primary teeth and dental caries are of high incidence in children who have been treated for cancer.(30, 31) In another study
by Minicucci and colleagues, children treated for leukemia were found to have
similar dental abnormalities. (32) These dental abnormalities are late effects of
cancer therapy and can occur in children even several years later, when the child
is in remission. (33)

**Dental caries:** Children undergoing cancer therapy are at a high risk of
developing dental caries. (34) Dental caries is otherwise known as tooth decay and
is characterized by pits on the tooth surface. (35) Damage to the salivary glands by
radiotherapy and chemotherapy results in reduced salivary flow, which causes
changes in the mouth’s environment and increases the chances of developing
caries. (36)

**Trismus,** a side-effect of radiation therapy, is the inability to open the jaw wide. It
affects speech, eating and the possibility of clinical examination of the radiation
site. It is a common symptom in patients with nasopharyngeal carcinoma. (37)

Oral graft-versus-host disease (GVHD) occurs subsequent to allogenic
hematopoietic stem cell transplantation (HSCT). Allogenic transplantation is a
mode of treatment when a patient receives bone marrow cells from a donor.
HSCT is one of the most severe cancer therapies and is subsequent to
chemotherapy. Oral GVHD manifests itself in the mouth as oral lesions. (38)

The frequency and intensity of oral side effects depends on the age of the child,
the intensity of treatment, the stage of tooth development and the location of the
cancer. As survival rates increase, and since oral health can impact general health,
it is important to understand the effect on quality of life of the cancer treatment-
related complications.
2.4 Quality of life:

There are several concepts related to QoL and several meanings attached to it. The WHO definition of QoL is “QoL is a broad multi-dimensional concept that includes subjective evaluations of positive and negative aspects of life.” (39) QoL can be affected in several ways, namely, physically, functionally, psychologically, socially and emotionally. A more comprehensive definition especially related to children with cancer was formulated at the American Cancer Society Workshop on Quality of Life in Children's Cancer: Implications for Practice and Research. The workshop participants met specifically to discuss issues dealing with QoL for children with cancer. They concluded: “Quality of life in paediatric oncology is multidimensional. It includes, but is not limited to, the social, physical and emotional functioning of the child and adolescent, and when indicated, his/her family, and it must be sensitive to the changes that occur throughout development.” (40)

The main characteristic of QoL is that it is multi-dimensional and is seen as a dynamic construct. (41) In pediatric assessment of QoL, sensitivity to different age groups should be taken into account. Children are always changing and developing, so an age-sensitive instrument will take into account whether or not a child is functioning at the level of his or her peers. (42)

Why measure QoL?

QoL studies are conducted to identify specific problems in psychosocial functioning of the patient and to investigate the secondary effect of disease
treatment regimens on symptoms. In adult oncology literature, QoL studies provide comparison of alternate therapies, evaluation of prognostic factors, aid in identifying late effects of cancer therapy and aid in policy decision-making by providing the true cost of treatments. Different studies conceptualize QoL in different ways. QoL may be assessed by the patient subjectively, by caregivers or objectively by clinicians. Hence there is little consistency obtained in results between studies. Haes and colleagues conducted a literature review of the “QoL of cancer patients” and found much inconsistency. A patient is the best judge of his or her QoL. On the other hand, patients tend to report their QoL as being better than it actually may be to avoid being troublesome to caregivers.

QoL Scales for Children:

The interest in measuring children’s QoL increased in the 1980s. This interest developed when the focus of treatment of disease changed from curing an illness to include curative treatment with supportive care. QoL assessment is important in life-limiting illnesses as well as acute illnesses since palliation of symptoms can occur even if cure of the disease is not possible. Due to improved survival rates, it is important to evaluate QoL over different periods of time and to understand the long-term effects of disease and treatment. QoL assessment is important in pediatrics to understand the child’s perspective and for clinicians to make treatment decisions and evaluate interventions. One of the earliest studies assessing QoL in children was by Ditesheim and Templeton. In this study, the patient’s age was an important factor in determining QoL. Childhood is a time of
change and treatment strategies can have a different impact at different stages of the child’s development. Additionally, depending on the illness and the stage in a person’s life, a person’s evaluation of his or her QoL may vary over a period of time.

QoL scales were developed for adults, and these adult scales were adapted for children in the case of some diseases, such as cancer. Adult scales tend to be longer than scales for QoL assessment in children. Adaptations need to be made in the language used too. Items related to ‘work’ or ‘shopping’ are not child appropriate, and hence a more child-centered scale had to be developed.(48) For any disease, in this case cancer, there should be a generic QoL scale and a disease-specific one adapted to the pediatric population. Generic scales allow comparisons across populations and across diseases. A disease-specific scale is sensitive to the impact of the treatment or that particular disease on the QoL of the patient. (40) The PedsQL is one such pediatric QoL scale with a cancer specific component. The Child Oral Health Quality of Life Questionnaire has been used in studies on QoL due to dental diseases. Wogelius and colleagues used this scale in their study on survivors of childhood cancer. They reported that cancer treatment was not associated with decreased OHRQoL. Their study indicated that the only possible explanations for this finding were that cancer survivors had a better pain threshold and/or that they did not know what was normal in terms of oral function.

Formal assessment of QoL has been developed through studies conducted in the field of pediatric oncology. Initially, simple parent or clinician reported outcomes
were used for assessment.(48) These proxy reported outcomes are still used today in pediatric QoL assessment and are useful in the cases of very young children or children too ill to take part in a study. Eighty-five percent of outcomes are proxy reported in childhood cancer studies.(49)

While proxy reporting measures are used in QoL assessment, important differences must be considered. What an adult may consider as a “good” QoL is different from what a child would consider it to be. Parents may not be able to judge the effect of QoL in social relationships in adolescents. Weyant et al. (2007), for instance, found there are discrepancies in parent and adolescent ratings of oral health: parents rated the teen’s oral health on the basis of psychosocial factors while the adolescent rated it on symptoms.

**Health Related Quality of Life (HRQoL)**

As discussed above, there are different definitions of the term “Quality of Life.” In order to narrow the focus, the concept of health related quality of life (HRQoL) was developed. According to the Center for Disease Control and Prevention (CDC), HRQoL is a broad multidimensional concept that usually includes self-reported measures of physical and mental health.(50) HRQoL measures the impact of disease on an individual’s health and functional status. It considers those aspects of QoL which are directly linked to a person’s health, namely: physical, emotional and social. Multi-dimensional health status scales measure other salient aspects of HRQoL such as the function and how the patient feels.
about himself. This kind of self-assessment by a child is not possible in the case of very young children.

Clinically, measurement of QoL and HRQoL aids treatment-making decisions and palliative care by clinicians. There are several generic instruments to measure QoL and HRQoL, such as the Medical Outcomes Study 36 item Short Form Health Survey, and disease specific instruments like the FACT-Head and Neck scale.(51) None of these instruments are applicable to the pediatric population, however.

A study by Kav and colleagues on patients who had undergone HSCT assessed QoL after treatment, and the patients rated their HRQoL as good or excellent. Presence of disease does not necessarily imply a bad QoL.(52)

2.5 Late oral effects of cancer therapy on QoL

The severity of the dental disturbance due to cancer therapy is age and treatment dependent. If children have radiation treatment before the age of 5, they exhibit greater dental effects of treatment.(53) Dental caries, though, seems to increase at age 12 when the children were treated between the ages of 5 and 6.(36)

Several studies have looked at the prevalence of treatment-related oral complications but not their impact on QoL.(54) Subsequent to the 1989 National Institute of Health (NIH) Development Consensus Conference on the oral complications of cancer therapies(55), several extensive systematic reviews were conducted by the Multinational Association of Supportive Care in Cancer which assessed the prevalence of the oral complications in mixed
populations of adults and children. These reviews also recognized the lack of literature in a pediatric population on our study’s topic. Studies frequently assess the prevalence of these complications and not the impact on QoL. Extensive studies on oral mucositis have led to the formulation of treatment guidelines for this specific complication. One organization to carry out such studies is the Cochrane Collaboration, which has conducted systematic reviews on interventions to treat oral mucositis. (20)

In the literature, there is a dearth of studies measuring OHRQoL in children with cancer. The Oral Health Related QoL (OHRQoL) reports are self-reports capturing the functional, social and psychological impact of disease. (57) Traditional measurements of oral health were related only to physical status by measuring the number of decayed, missing and filled teeth. It is increasingly important to measure the impact of oral disease on QoL. (58) Studies on oral health and OHRQoL are relatively recent.

For our project, our review was conducted using the concept of QoL and not OHRQoL or HRQoL since we wanted to understand the overall impact of treatment related complications on a patient and not just the impact on health due to treatment. QoL is a broad construct encompassing the patient’s values and providing information apart from clinical status. For a scoping review, the search strategy has to be as exhaustive as possible. In many medical databases such as PubMed, QoL is a medical subject heading and HRQoL studies are included under the term QoL. Thus we used the term “QoL” basing our choice on the inclusiveness of a scoping review search.
Currently, childhood cancer affects approximately 850 children in Canada between the ages of 0-14 every year. Better treatment options have led to improved survival rates; however, the consequences of aggressive cancer treatment include short and long-term effects on various systems of the body including the oral cavity. These short and long-term complications affect the QoL of the patient. Preventive and follow-up care improves the QoL of the patient especially in cases of increased survival. While QoL is an important concept, it has not yet been systematically applied to oral health.

Despite studies on effects of childhood cancer treatment, there is a lack of knowledge related directly to the impact on QoL due to cancer treatment-related oral complications. Hence, we conducted a scoping review, a newer method of knowledge synthesis, focusing on the oral health effects of cancer treatment in children and their impact on QoL in order to systematically identify the gaps in the current literature and thereby aid in the careful planning of future research on this topic.

The research question guiding our scoping review was: In pediatric oncology patients undergoing chemotherapy, radiotherapy or HSCT, how do oral complications of cancer therapy impact Quality of Life (QoL)? In answering this question, we had one main objective which was to understand the relation between QoL and the oral side-effects secondary to treatment therapy in pediatric cancer patients.
Chapter 3: Rationale and Overview of Methods

The following chapter explains the rationale for the method used in this scoping review and provides background information on scoping reviews. More detail of our study follows in Chapter 4, our manuscript.

The emphasis on evidence-based practice has increased the need for comprehensive reviews to aid clinicians in decision making. Evidence-based clinical practice is an approach to decision-making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits that patient best. (59) Evidence-based practice is an integration of clinical expertise, the best evidence through a systematic search and the patient’s values and expectations. (60) The Cochrane Collaboration, an international body of health care practitioners, policy and methodology experts was established to develop systematic reviews, the best evidence available for clinical decision making. (61) A systematic review is a structured review of all primary research literature, using a relatively focused research question and with quality appraisal of the selected studies. It is structured in the sense that it follows pre-planned methods with explicit, reproducible criteria for study selection. The research question needs to be well-structured and clinically relevant. It typically uses the PICO format.

The Cochrane Oral Health Group is an international collaboration conducting, maintaining and disseminating systematic reviews of randomized controlled trials
in oral health. Oral health includes the prevention, treatment and rehabilitation of oral, dental and craniofacial diseases and disorders. (62)

3.1 Scoping Reviews

While systematic reviews are important for assessing the quality of research evidence, in some clinical areas there is not enough research to justify a systematic review. As far as we know, in the area of oral health and QoL of pediatric cancer patients, the research literature has yet to be summarized and translated to an important end-user, the clinician. When the extent of research activity in an area is unknown, it is feasible to utilize a scoping review. While systematic reviews related to the topic of oral complications due to cancer therapy have been published (8, 20, 63), these reviews have not been included in our review since we included only primary research. Further, they do not focus on our topic “impact on QoL.” They would still be potentially useful for developing further research in this area.

Scoping reviews also follow a similar structured format but use a broader question and do not have quality appraisal of included studies as a step in the process. (13) Scoping reviews are useful to plan a primary study. They are not appropriate for answering clinical questions. (64)

Our study’s goal was exploratory in nature: to review the literature in depth, for which purpose we included all types of childhood cancers and different treatment modalities without restrictions on study design. Thus, we chose the scoping review methodology.
Scoping reviews may be undertaken for four main reasons: 1. to examine the nature, range and extent of research activity, 2. to determine the value of undertaking a full systematic review, 3. to summarize and disseminate research findings and 4. to identify gaps in the existing literature. (13)

Our review was undertaken to summarize and disseminate findings and to identify gaps in the literature. Our findings could lead to an improvement in patient care.

This review was conducted to answer a broad question using all study designs. Arksey & O’Malley (2005) suggest a methodological framework for conducting such a review and describe the stages as follows:

Stage 1: Identifying the research question

Stage 2: Identifying relevant studies

Stage 3: Study selection

Stage 4: Charting the data

Stage 5: Collating, summarizing and reporting the results.

Each of these steps is described in detail in the manuscript in Chapter 4. Details of the search strategy, the studies found and reporting of the studies are included in the Appendices.

Working with two McGill University liaison librarians, our search strategy was developed, piloted and refined. (See Appendices, C and D) Our initial search yielded 1158 records. An additional scan of reference lists, electronic search of journals and grey literature searches yielded another ninety-five records. Nine
hundred and thirty-six (936) records were screened by two reviewers after duplicates had been removed using EndNote reference management software. These records were initially screened using only title and abstract based on our inclusion and exclusion criteria (described in chapter 4), resulting in 137 articles. The full-texts of the 137 articles were screened and another fifty-five were excluded. Articles were excluded if they did not pertain to oral complications that arose due to cancer treatment or based on the other exclusion criteria. Three studies were “sibling” reports in the sense that they were multiple reports of the same study. They were linked together for the final sample. The final sample of studies was eighty-two. (See Appendix E)

Grey literature is defined by the Grey Literature International Steering Committee as “Information produced on all levels of government, academics, business and industry in electronic and print formats not controlled by commercial publishing i.e. where publishing is not the primary activity of the producing body.” It includes policy documents, government reports, theses and dissertations, conference abstracts and bibliographies. Grey literature databases were selected with the assistance of a liaison librarian. Grey literature may not be peer-reviewed but is included in the scoping review search to encompass as comprehensive a search as possible.(65)

Scoping review methodology is often iterative.(13) For example, when we began this study, our initial inclusion criterion was the age group 0-18 years. We then amended our search strategy to include the ages until 20 years since we found relevant studies that included this age group.(66)
The search strategy was broad and included all types of childhood cancers using a treatment of chemotherapy, radiotherapy or HSCT without a focus on any particular study design. The search was developed with the assistance of a liaison librarian with expertise in dentistry and pediatric oncology. The process of the scoping review was documented at every stage to ensure that it is reproducible.

Reporting of the study was done using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The aim of the PRISMA statement is to ensure transparent reporting of systematic reviews and meta-analyses. We adapted the PRISMA flow diagram for the reporting of our scoping review. The flow diagram maps out the number of studies identified, included and excluded. (67, 68)
Chapter 4: Manuscript

This manuscript will be submitted to a scientific journal for publication. The findings were presented as a poster in June 2012 at the Multinational Association of Supportive Care in Cancer symposium (New York, NY). The conference presentation has been published in the journal Supportive Care in Cancer.

**Oral Complications of Childhood Cancer Therapies and Their Effect on Quality of Life: a Scoping Review**

Noronha C, Macdonald M.E

**Purpose:** To systematically review the research literature on oral side-effects of childhood cancer treatment and Quality of Life (QoL).

**Method:** A scoping review was conducted using 16 databases (research and grey literature), websites, reference lists, and key journals. Inclusion criteria included primary research studies pertaining to children 0-20 years undergoing or who have undergone cancer treatment, in English or French and published from 2000 to 2011. Exclusion criteria included studies containing a mixed population of adults and children and non-discrete disease categories. Data was charted independently by two reviewers.

**Results:** A total of 1270 articles were identified through the systematic search. A rigorous review of abstracts and full-text articles reduced the sample to 82 articles, all of which were categorized through a data extraction process. Data
analysis revealed that leukemia studies were predominant; the most common side-effect was mucositis; however, side-effects mostly co-occurred. Twenty-one articles dealt directly with the effect on QoL, citing impacts such as pain, changes in taste, eating, drinking, sleep habits, voice, and weight loss. Twenty-five articles examined the long-term effects of treatment on pediatric dentition showing that resultant caries and malformed teeth can affect eating and speech.

**Conclusions:** Preventive oral care before, during and after cancer therapy can decrease the oral side-effects and improve the QoL of the pediatric cancer patient. Few studies to date have advanced recommendations for QoL improvement. This study underscores the need for a dental oncology program in pediatric hospitals.

**Keywords:** scoping review, cancer therapy, tooth diseases, pediatric, Quality of life

**Introduction:**

Childhood cancer is the second leading cause of death in Canadians aged 1-14. Aggressive cancer treatment in children has led to increased survival rates of over 82 %.(69) Unfortunately, cancer treatment regimens consisting of chemotherapy, radiotherapy and hematopoietic stem cell transplantation (HSCT) all lead to unwanted side-effects. Some of these side-effects are manifested in the oral cavity of the pediatric cancer patient. They can be characterized as early and late effects. Early effects may occur during treatment, while late effects may manifest themselves when the patient is in remission several years later. The early oral complications of cancer therapy include mucositis, taste disturbance, oral
hemorrhage, xerostomia and salivary gland dysfunction. (10) These early complications may be short-term in nature and may resolve soon after treatment ends. The late effects are dental caries, dental developmental abnormalities, trismus and oral graft-versus-host disease. (70) Xerostomia may occur as a late effect too when there is damage to the salivary glands.

Oral complications of cancer therapy can interrupt the treatment of the cancer, and this can lead to longer hospitalization. In the case of children treated before the age of 5, it is important to manage the dental care of the patient because of the developing dentition and the risk for increased caries and tooth development anomalies. (71, 72)

The purpose of this scoping review is to explore the published and unpublished literature on the relation between oral side-effects and quality of life (QoL) secondary to treatment in pediatric cancer patients.

In the adult literature, systematic reviews have noted the dearth of oral health studies in the field of pediatric oncology. (63) Hence, our second objective was to summarize the literature and, additionally, to find out where the research gaps lie in terms of the impact that these complications have on the QoL of the patient. This review will add to the current evidence and knowledge on the impact of these complications and assist in the understanding of the role of a dentist on a pediatric oncology team.

**Oral side-effects of cancer treatment:**
For purposes of our research, we use the definition of QoL given by the World Health Organization: “QoL is a broad multidimensional concept that includes subjective evaluations of positive and negative aspects of life.” It is defined as “the patient’s appraisal and satisfaction with their current level of functioning compared to what is perceived to be possible or ideal.” (73) The World Health Organization (WHO) measures QoL in several domains such as the physical, psychological and social. QoL measurement instruments evaluate the functioning of the patient and the effect of disease on their emotional well-being. We have not used the term “Oral Health Related QoL” since this is a relatively recent concept and there is a scarcity of information in the literature on this aspect in children with cancer.

The physical aspect of QoL encompasses domains such as pain, sleep and rest. Functional status refers to the physical status or the health status of the QoL construct. The psychological aspects of QoL are concerned with domains such as body image, feelings, thinking and learning. Personal relationships, emotional well-being and social support are connected with the social aspects of QoL. (74)

To date, systematic reviews on oral complications due to cancer therapy have focused only on adult populations or on a mixed population of adults and children. (75) The World Health Organization (WHO) defines chronic diseases as those diseases that last a long time with a slow progress. Cancer has thus been classified by the WHO as a chronic disease. Quality of life assessment in chronically ill children is a relatively new concept, and thus we decided to focus
not just on the outcome “quality of life.” We included in our review keywords that would implicitly refer to quality of life such as “activities of daily living.”

Method: Given that there is a lack of literature on QoL and treatment-related oral complications in pediatric cancer patients, we wanted to search broadly. We undertook a scoping review since it allows an in-depth search. Scoping reviews are a type of structured exploratory research review. They are similar to systematic reviews except that systematic reviews have more focused research questions and include quality appraisal of the studies. (13) Quality appraisals are typically not a step in the scoping review method. Though we mention steps, the review process is iterative.

Scoping Review Methodology: We followed the Arksey & O’Malley (13) methodological framework for conducting such a review, and the steps we employed were:

Stage 1: Identifying the research question. The research question was identified after a review of the literature and through conversations with the McGill Faculty of Dentistry (Montreal) and clinicians at a tertiary care children’s hospital.

Review Question: In pediatric oncology patients undergoing chemotherapy, radiotherapy or HSCT, how do oral complications of cancer therapy impact Quality of Life?

Stage 2: Identifying relevant studies. A search strategy was developed with a McGill University librarian. MeSH terms relating to cancer treatment, oral manifestations of cancer treatment in pediatric oncology and QOL were combined
(See Table 1), and a pilot search was run on MEDLINE and then modified for the other databases. (See Appendix B.)

<table>
<thead>
<tr>
<th>neoplasms</th>
<th>mouth disease</th>
<th>activities of daily living</th>
</tr>
</thead>
<tbody>
<tr>
<td>antineoplastic agents</td>
<td>tooth disease</td>
<td>eating</td>
</tr>
<tr>
<td>radiotherapy</td>
<td>Stomatitis</td>
<td>speaking</td>
</tr>
<tr>
<td>hematopoietic stem cell</td>
<td>Xerostomia</td>
<td>QoL</td>
</tr>
<tr>
<td>transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td>mouth care</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Keywords combined in our search strategy**

The following databases were searched: MEDLINE, EMBASE, CINAHL, Global Health, AMED and Cochrane Library, DARE, Proquest Dissertations and Theses, PsycInfo.

Unpublished studies were identified through the following databases: ISI Web of Science (includes Conference Proceedings and Journal Citation Reports), Scopus, Open Grey, NYAM, WorldCat and through websites of organizations such as the International Association for Dental Research, International Society of Pediatric Oncology and Multinational Association of Supportive Care in Cancer. Reference lists from relevant studies were also scanned.

**Inclusion criteria:**
- Completed primary research from 2000-2011 in English or French pertaining to children who have undergone chemotherapy, radiotherapy or HSCT and who exhibit any type of early or late oral effect of cancer therapy.

- All types of childhood cancers

- Age group 0-20 years

**Exclusion criteria:**

- Any studies that used a mixed population of adults and children

- Studies in which the disease category was not discrete (i.e. included non-cancerous diseases)

**Stage 3: Study selection.** Studies were selected using the inclusion and exclusion criteria. Selected studies were transmitted to EndNote reference management software and duplicates were removed. Two reviewers independently screened the selected studies, using the title and abstract. If there was a disagreement in study selection, it was solved by consensus or by discussion with an additional team member. The data extractors had unique skills: one had stronger methodological knowledge while the other had stronger substantive knowledge. A total of 1270 articles were identified through the search.

Studies with insufficient information in the abstract were retained for full-text searching. Full-text articles were excluded based upon our exclusion criteria if the study was of a mixed population, mixed disease, included oral complications unrelated to cancer therapy or the sample was older than 20 years. Wherever full
text was not available, a copy was requested from the author. If all methods of contacting the author were exhausted and we had no further information, the study was excluded.

**Stage 4: Charting the data** Data charting is a process involving the extraction of information from individual selected studies. (13) Twenty percent of the abstracts were charted by two reviewers to refine the process of charting and for accuracy. Categories of data extraction included the type of cancer, age range, sample size, type of treatment, type of oral complication, treatment of the complication, study design, year, authors, first author’s discipline, journal title, journal discipline methods used, study location.

**Stage 5: Collating, summarizing and reporting the results:** Results were descriptively summarized and are reported below using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The PRISMA guidelines ensure transparent reporting of systematic reviews and meta-analyses. (68)

**Results:**

Our final sample of studies was 82. (Please see Appendix A for how this sample was determined.)

**Types of Cancers:** The studies were mainly based on leukemia. There were 19 studies exclusively on the leukemic population (2, 32, 76-87) and 50 studies on leukemia in combination with other childhood cancers. Chemotherapy, radiotherapy, bone marrow transplantation or combination therapies are all used
for leukemia treatment, and all of them cause oral and dental complications. There were only two studies in the area of head and neck cancer, and both were on nasopharyngeal carcinoma (NPC). (88, 89)

**Cancer treatment:** Among the studies included, the type of cancer treatment leading to oral complications was predominantly chemotherapy (10, 34, 76, 78, 90-94), followed by 18 studies evaluating the effects of bone marrow transplantation and its effects on oral health. There were two studies specifically dealing with radiotherapy in which the study population showed long-term oral effects. The cancers in these cases were leukemia, lymphoma, tumors and rhabdomyosarcoma. (36, 95)

**Oral Complications:** Oral mucositis was the main complication that occurred during treatment. Several oral complications can co-occur, such as mouth sores, bleeding and oral infections. Long-term defects included dental developmental delays and dental caries, occurring most often when the patient was below the age of 3 at the time of treatment. (71, 72, 94, 96)

Twenty-five articles (Table 2) report on the long-term effect of cancer treatment on the dental development of the child. These articles describe findings of delayed root development (71, 88, 89, 96, 97) stunted tooth development (32, 72, 81, 94, 98-100) caries and jaw abnormalities. (88, 89, 101) Some of these studies overlap with those in Table 1 which help show the long-term effects on QoL when impaired dental development affect eating and speech.
Age: There were varying age ranges within a minimum of zero years and a maximum of 18 years. There were a few studies which included patients above the age of 18 years. On the basis of these relevant studies, we modified our initial inclusion criteria to include studies with patients below the age of 20 years. (66, 88, 89, 91, 102)

QoL: QoL is a multi-dimensional concept; therefore, we focused our extraction on physical, functional and social, psychological and emotional impacts. Twenty-one articles dealt with the impact that treatment-related oral complications can have on QoL. The types of impacts described were oral pain, taste changes, voice changes, emotional changes and changes in sleeping habits, difficulties in swallowing, eating and drinking, and weight loss (Table 1).

Table 2: Summary of included studies showing an impact on QoL

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Cancer</th>
<th>Treatment</th>
<th>Complications</th>
<th>QoL impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeh, C.H.(76)</td>
<td>all types</td>
<td>CT</td>
<td>mouth sores, dry mouth</td>
<td>Difficulty swallowing, taste change</td>
</tr>
<tr>
<td>Williams, P.D.(90)</td>
<td>leukemia, osteosarcoma, lymphoma, testicular cancer, rhabdomyosarcoma, or optic glioma</td>
<td>CT</td>
<td>sore mouth</td>
<td>Taste changes, eating</td>
</tr>
<tr>
<td>Voskuilen, I.(97)</td>
<td>leukemias and other blood cancers</td>
<td>CT/HSCT</td>
<td>reduced saliva</td>
<td>Dry mouth, short roots (long-term)</td>
</tr>
<tr>
<td>Skolin, I.(92)</td>
<td>leukemia, solid</td>
<td>CT</td>
<td>mouth blisters</td>
<td>Oral pain, taste disturbance</td>
</tr>
<tr>
<td>Authors</td>
<td>Tumor Types</td>
<td>Treatment</td>
<td>Side Effects</td>
<td>Other Symptoms</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Shen, C.</td>
<td>Tumor, lymphoma</td>
<td>CT/RT</td>
<td>hypo salivation</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Rodgers, C.</td>
<td>Nasopharyngeal carcinoma</td>
<td>CT/RT/HSCT</td>
<td>dry mouth</td>
<td>Taste changes</td>
</tr>
<tr>
<td>Hedström, M.</td>
<td>Leukemia, lymphoma, osteosarcoma, Ewing’s sarcoma, other solid tumors</td>
<td>CT</td>
<td>mouth ulcers</td>
<td>Mouth pain, altered taste</td>
</tr>
<tr>
<td>Fadda, G.</td>
<td>Cancers</td>
<td>CT/HSCT</td>
<td>mucositis</td>
<td>Weight loss</td>
</tr>
<tr>
<td>El Housseiny</td>
<td>Leukemia, lymphoma, neuroblastoma, others</td>
<td>CT</td>
<td>mucositis</td>
<td>Oral pain, dry mouth</td>
</tr>
<tr>
<td>Daoud, J.</td>
<td>Nasopharyngeal carcinoma (NPC)</td>
<td>CT/RT</td>
<td>mucositis, trismus, xerostomia</td>
<td>Dry mouth, oral pain</td>
</tr>
<tr>
<td>Cheng, K.K.</td>
<td>Solid tumors, hematological malignancies</td>
<td>CT</td>
<td>mucositis</td>
<td>Difficulties in swallowing, drinking, eating, sleeping and speaking</td>
</tr>
<tr>
<td>Cheng, K.K.</td>
<td>Leukemia, lymphoma, osteosarcoma, others</td>
<td>CT</td>
<td>mucositis</td>
<td>Pain, eating, emotional tension, distress, weight loss, nutrition, social problem</td>
</tr>
<tr>
<td>Cheng, K.K.</td>
<td>Solid tumors, hematological malignancies</td>
<td>CT</td>
<td>mucositis</td>
<td>Mouth pain</td>
</tr>
<tr>
<td>Chen, C.F.</td>
<td>Leukemia, lymphoma</td>
<td>CT</td>
<td>ulcerated mucosa</td>
<td>Deeper or raspy voice, dry lips</td>
</tr>
<tr>
<td>Bakish, J.</td>
<td>Medulloblastoma or</td>
<td>CT/RT</td>
<td>mucositis</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Authors</td>
<td>Diagnosis/Condition</td>
<td>Treatment</td>
<td>Side Effect</td>
<td>Oral Symptom</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Hegde, A.M. (86)</td>
<td>supratentorial primitive neuroectodermal tumors</td>
<td>CT/RT</td>
<td>low saliva</td>
<td>Dry mouth, jaw pain</td>
</tr>
<tr>
<td>Paulino, A.C. (95)</td>
<td>acute lymphoblastic leukemia</td>
<td>RT</td>
<td>microdontia, trismus, hypoplasia, hypodontia, root stunting, xerostomia, caries</td>
<td>Dry mouth, dental developmental defects</td>
</tr>
<tr>
<td>Green, R. (111)</td>
<td>sarcoma, leukemia, lymphoma, primitive neuroectodermal tumor</td>
<td>CT</td>
<td>mucositis</td>
<td>Mouth pain, compromised nutritional intake</td>
</tr>
<tr>
<td>Sepulveda (112)</td>
<td>leukemia, lymphoma, retinoblastoma, medulloblastoma and rhabdomyosarcoma</td>
<td>CT</td>
<td>mucositis, ulcers</td>
<td>Oral pain</td>
</tr>
<tr>
<td>Kokkonen, J. (113)</td>
<td>leukemia, lymphoma, nephroblastoma, rhabdomyosarcoma</td>
<td>CT</td>
<td>mouth wounds</td>
<td>Mouth pain</td>
</tr>
<tr>
<td>Cheng, K.K.F. (114)</td>
<td>leukemia, bone cancer, others</td>
<td>CT</td>
<td>mucositis, ulcerative lesions</td>
<td>Oral pain</td>
</tr>
</tbody>
</table>

Legend: CT chemotherapy, RT radiotherapy, HSCT hematopoietic stem cell transplantation
Table 3: Studies showing long-term effects on dental development

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age at Tx (yrs)</th>
<th>Cancer</th>
<th>Tx</th>
<th>Long-term effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedersen, L.B. (94)</td>
<td>&lt;8-18</td>
<td>all cancers</td>
<td>CT</td>
<td>Microdontia, hypodontia</td>
</tr>
<tr>
<td>Oğuz, A. (98)</td>
<td>3.2-15</td>
<td>non-Hodgkin's lymphoma</td>
<td>CT</td>
<td>Microdontia, root malformation</td>
</tr>
<tr>
<td>Minicucci (32)</td>
<td>1-12</td>
<td>acute lymphoid leukemia</td>
<td>CT</td>
<td>Microdontia, agenesis, shortened root</td>
</tr>
<tr>
<td>Marec-Berard, P. (99)</td>
<td>3-12.7</td>
<td>nephroblastoma</td>
<td>CT</td>
<td>Microdontia, hypodontia, taurodontia</td>
</tr>
<tr>
<td>Maciel, J.C.C. (81)</td>
<td>&lt;12</td>
<td>acute lymphoblastic leukemia</td>
<td>CT</td>
<td>Tooth malformation</td>
</tr>
<tr>
<td>Cubukcu, C. (115)</td>
<td>0-12</td>
<td>solid tumors, lymphomas</td>
<td>CT/RT</td>
<td>Microdontia, tooth agenesis</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Oral Effects</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Holtta(72)</td>
<td>0-15</td>
<td>Neuroblastoma</td>
<td>CT/HSCT/RT</td>
<td>Short roots, arrested root development, microdontia and tooth aplasia, missing permanent teeth, severe root defect, microdontia</td>
</tr>
<tr>
<td>Voskuilen(97)</td>
<td>5.1-17.8</td>
<td>Blood cancers</td>
<td>CT/TBI/HSCT</td>
<td>Missing teeth, short roots, early root closure, xerostomia</td>
</tr>
<tr>
<td>Shen(88)</td>
<td>8-20</td>
<td>Nasopharyngeal carcinoma (NPC)</td>
<td>CT/RT</td>
<td>Caries, xerostomia</td>
</tr>
<tr>
<td>Daoud(89)</td>
<td>8-20</td>
<td>NPC</td>
<td>CT/RT</td>
<td>Xerostomia, trismus, dental damage</td>
</tr>
<tr>
<td>Hegde(86)</td>
<td>4-10</td>
<td>Acute lymphoblastic leukemia</td>
<td>CT/RT</td>
<td>Caries, low saliva, TMJ tenderness, gingival disease</td>
</tr>
<tr>
<td>Wogelius(36)</td>
<td>7-15</td>
<td>Leukemia, lymphoma CNS and non-CNS tumors</td>
<td>CT/RT</td>
<td>Dental caries</td>
</tr>
<tr>
<td>Author</td>
<td>Age Range</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Additional Findings</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Avşar, A. (34)</td>
<td>2.9-13.1</td>
<td>lymphomas, tumors, rhabdomyosarcoma</td>
<td>CT</td>
<td>caries, bacteria, opacities, arrested root development</td>
</tr>
<tr>
<td>Dyer (116)</td>
<td>Not mentioned</td>
<td>acute lymphocytic leukemia</td>
<td>CT/RT</td>
<td>Tooth developmental delays</td>
</tr>
<tr>
<td>Martin (80)</td>
<td>0.1-11</td>
<td>acute lymphoblastic leukemia</td>
<td>CT/RT</td>
<td>Altered dental age</td>
</tr>
<tr>
<td>Hutton (117)</td>
<td>0-17</td>
<td>solid tumors, lymphoma</td>
<td>CT/HSCT</td>
<td>Caries, microdontia, opacities</td>
</tr>
<tr>
<td>Hobbie (118)</td>
<td>9.5-14.5</td>
<td>neuroblastoma</td>
<td>CT/HSCT</td>
<td>root stunting, microdontia, missing teeth</td>
</tr>
<tr>
<td>Clarke (119)</td>
<td>8-18</td>
<td>leukemia</td>
<td>HSCT</td>
<td>Dental defects</td>
</tr>
<tr>
<td>Estillo (66)</td>
<td>20 and below</td>
<td>H &amp; N rhabdomyosarcoma</td>
<td>Multimodal RT</td>
<td>Enamel defects, bony hypoplasia/facial asymmetry, trismus, velopharyngeal incompetence, tooth/root agenesis, and disturbance in</td>
</tr>
<tr>
<td>Paulino (95)</td>
<td>2.2-11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Age</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Complications</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>-----------------------</td>
<td>-----------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Doğan</td>
<td>6.6-9</td>
<td>leukemia/lymphoma</td>
<td>CT</td>
<td>malocclusion, caries, missing teeth, plaque, calculus</td>
</tr>
<tr>
<td>Pajari</td>
<td>1.3-15.7</td>
<td>leukemia, solid tumor</td>
<td>CT/RT</td>
<td>caries</td>
</tr>
<tr>
<td>Cubukcu</td>
<td>No age</td>
<td>leukemia</td>
<td>CT</td>
<td>White spot lesions</td>
</tr>
<tr>
<td>Chen</td>
<td>2-17</td>
<td>leukemia, lymphoma</td>
<td>CT</td>
<td>Dry lips, oral debris</td>
</tr>
<tr>
<td>Wong</td>
<td>Below 19</td>
<td>cancers</td>
<td>CT</td>
<td>caries</td>
</tr>
</tbody>
</table>

**Treatment of the Oral complications:** Only 25 articles studied the treatment of these oral complications. Few studies recommended a follow-up of the cancer patient, though two studies recommended complete preventive oral exams and dental follow-up care for pediatric cancer patients(97, 121). The main treatment for oral mucositis, as can be seen in the table below, was mouthwashes. Laser treatment has also been effective in oral mucositis treatment. Treatments such as administration of Vitamin A and chewing gum have not been effective in treating the oral complication.
Table 4: Studies showing the treatment of the oral complications

<table>
<thead>
<tr>
<th>Author</th>
<th>Oral complication</th>
<th>Treatment</th>
<th>Tx outcomes(if mentioned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voskuilen(97)</td>
<td>caries, dental developmental delays</td>
<td>preventive care</td>
<td></td>
</tr>
<tr>
<td>Halperson(121)</td>
<td>caries</td>
<td>preventive care</td>
<td></td>
</tr>
<tr>
<td>Williams(90)</td>
<td>sore mouth</td>
<td>mouth rinse, complementary medicine</td>
<td></td>
</tr>
<tr>
<td>Pereira-Pinto(79)</td>
<td>mucosal erythema, edema and ulcers</td>
<td>0.12% chlorhexidine gluconate reduces incidence</td>
<td></td>
</tr>
<tr>
<td>Özkaya(122)</td>
<td>OM</td>
<td>mouthwash alleviates OM</td>
<td></td>
</tr>
<tr>
<td>Tang (123)</td>
<td>OM</td>
<td>hexetidine mouthwash</td>
<td></td>
</tr>
<tr>
<td>Fadda(1)</td>
<td>OM</td>
<td>mouthwash, standard care</td>
<td></td>
</tr>
<tr>
<td>Melo de Brito(124)</td>
<td>OM</td>
<td>mouth rinse</td>
<td></td>
</tr>
<tr>
<td>Cheng(125)</td>
<td>OM</td>
<td>mouth rinse, tooth brushing</td>
<td></td>
</tr>
<tr>
<td>Cheng(114)</td>
<td>OM</td>
<td>mouthwash</td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Condition</td>
<td>Treatment</td>
<td>Effect</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>Cheng(50)</td>
<td>Mouth pain, ulcerative lesions and wounds</td>
<td>tooth brushing, 0.2% chlorhexidine mouth rinse and 0.9% saline rinse</td>
<td>reduction in symptoms</td>
</tr>
<tr>
<td>Avşar(34)</td>
<td>Caries, bacterial infection</td>
<td>mouthwash, brushing</td>
<td></td>
</tr>
<tr>
<td>Green(111)</td>
<td>OM</td>
<td>mouthwash, narcotics</td>
<td></td>
</tr>
<tr>
<td>Lazic(126)</td>
<td>OM</td>
<td>mouthwash</td>
<td>Alleviates</td>
</tr>
<tr>
<td>Soares(79, 127)</td>
<td>OM</td>
<td>0.12% chlorhexidine gluconate mouthwash</td>
<td>Alleviates symptoms</td>
</tr>
<tr>
<td>Whelan(127)</td>
<td>OM</td>
<td>light emitting diode therapy</td>
<td></td>
</tr>
<tr>
<td>Moraes(128)</td>
<td>OM</td>
<td>extra-oral laser therapy</td>
<td>Alleviates symptoms</td>
</tr>
<tr>
<td>Cruz(129)</td>
<td>OM</td>
<td>laser application</td>
<td></td>
</tr>
<tr>
<td>Kuhn(130)</td>
<td>OM</td>
<td>low-intensity laser therapy</td>
<td>alleviates</td>
</tr>
<tr>
<td>Gandemer(131)</td>
<td>OM</td>
<td>chewing gum</td>
<td>No difference</td>
</tr>
<tr>
<td>Kokkonen(113)</td>
<td>Mouth pain and wounds</td>
<td>vitamin A</td>
<td>No protective effect</td>
</tr>
<tr>
<td>Rodgers(103)</td>
<td>OM, dry mouth, taste changes</td>
<td>water intake, brushing teeth and tongue, personal eating strategies</td>
<td>Personal strategies helped</td>
</tr>
</tbody>
</table>
Uderzo(132) | OM | intravenous glutamine enriched solution | Does not aid OM
---|---|---|---
Sixou(93) | Oral bacteria | antibiotic therapy |
Vaidya(91) | OM | antibiotic therapy |

Legend: OM = oral mucositis

**Patient-reported outcomes:**

Parent or caregiver reporting of symptoms is most common in general pediatric area research (49, 86), and patient-reported outcomes were seen in only 3 studies (76, 103, 108).

**Study Design:** The majority of the studies (78 studies) included in this review were quantitative in design, with only 3 qualitative (103, 108, 111) and 1 mixed method study (92).

**Year:** Research in the area of oral complications due to childhood cancer therapy increased in the years 2006 and 2007 and has since been steady, with a large increase in 2011 with 22 studies.

**Record Type:** Journal articles (64 studies) and conference abstracts (16 abstracts) were the main studies included in our search. The conference abstracts were mainly from the International Association of Dental Research (IADR) and International Society of Paediatric Oncology (SIOP) conferences (1, 77, 97, 102,
The remaining records were a thesis and one study from an online database, clinicaltrials.gov.

**Journal and author information:** The relevant studies were published mainly in oncology and dentistry journals, with 37 and 20 studies respectively, the first authors being from dentistry, oncology and pediatrics. Though there were 12 first authors from the nursing field, there were only 3 studies published in nursing journals (90, 104, 114). One investigator, Dr. KKF Cheng from Singapore had authored multiple articles.(50, 107, 108, 114, 125, 140)


Studies published in the dentistry journals (2, 10, 36, 77, 78, 80, 84, 85, 93, 94, 98, 105, 107, 112, 117, 122, 133-135, 140, 146)

**Study Location:** Of the 82 articles, the majority of articles were from Brazil (11 studies-(2, 32, 79, 81, 84, 124, 128-130, 147, 148) the USA (10 studies(66, 80, 82, 90, 95, 103, 111, 116, 118, 127), France (8 studies(1, 93, 99, 105, 131, 139, 149, 150) and 7 each from Hong Kong(50, 102, 107, 108, 114, 123, 125) and Turkey(34, 62, 83, 85, 98, 115, 122). There were two studies from Canada(110, 144)There was only one from Australia(151).

The other 36 studies focused on the oral complications due to treatment but not explicitly on the impact on QoL. We retained these studies since it gave us an
understanding of the oral health issues faced by childhood cancer patients and created literature repository to enable further research.

**Discussion:**

The results of this scoping review indicate that there is a growing body of international research on the oral complications faced by pediatric cancer patients subsequent to cancer therapy. To our knowledge, this is the first scoping review demonstrating the impact that treatment-related oral complications can have on the QoL of a child with cancer. The oral complications of cancer therapy can interrupt cancer treatment and affect treatment outcomes and the quality of life of the patient. (33, 78) Many of the oral complications co-occur and affect eating, speech and swallowing. The general topic of oral complications was evidenced in these articles even if the specific focus of our study, the impact on QoL, was not mentioned. Our decision to include these articles was based on the implicit factor that a side-effect of treatment could impact a patient’s health thus creating a literature repository for the development of future research. Our study thereby presents researchers with the depth and breadth of research activity in this field.

In the studies covered in this review, leukemia was the childhood cancer that was studied most often. This finding concurs with the fact that leukemia is the most common type of childhood cancer. (14)

While all 82 studies reported on the oral complications, few had recommendations for the treatment of these complications. Longitudinal studies and clinical trials of early oral effects are needed to demonstrate the impact of these complications and
recommendations of treatment. Our results are contrary to that of Wogelius and colleagues who concluded that there is no association between OHRQoL and cancer treatment. This study used the Child Perceptions Questionnaire to compare OHRQoL in childhood cancer survivors and those who did not have cancer. Recall could be a factor in answering the questionnaire as children who had recently completed their cancer treatment might have answered differently from those who had completed treatment several years earlier. (152) The researchers suggest further longitudinal studies to understand these results and conclude that time from the end of treatment could be a factor in evaluating OHRQoL. Another suggestion is that these cancer survivors may not have been aware of what is “normal” in relation to oral health and therefore have rated their OHRQoL as being good. (152)

In the WHO definition of QoL (153), QoL is affected by the person’s physical health, psychological state, level of independence, social relationships and his or her relationship to salient features of his or her environment.

The physical domain includes pain, sleep and rest. The functional status of a person is his/her ability to perform daily activities to meet basic needs and to maintain one’s health. Since the physical aspects of QoL affect the functional aspects of a person, we have combined these aspects in discussing the results. The physical pain that a patient may feel in the oral cavity and radiation injuries to the salivary glands may affect eating and contribute to changes in taste. This pain makes it very difficult for the person to eat, drink or swallow. These changes in turn affect the nutritional status of the child. Lowered levels of nutrition can lead
to slower recovery. Pain is a common factor throughout these studies, but pain does not relate only to oral complications in the cancer. It can be due to the cancer itself, due to the treatment or due to the side-effects of treatment. (154) Thus, if pain is controlled, it can lead to a better QoL. We can infer that a complication like mucositis does affect QoL since it causes oral pain, which in turn impedes eating (108) Oral mucositis, with the resulting pain, leads to a cyclical process wherein lack of nutritional intake leads to dehydration, increasing the risk for xerostomia and dental caries.(22)

Dental abnormalities such as caries and malformed teeth arising in remission can impact the overall QoL of the child since they can hinder eating, speech and social interactions. Children’s dentition is constantly developing until adolescence, and a child treated at a very young age may be cured of the cancer but can develop dental abnormalities many years later even during remission. This late effect may be seen in remission. Long-term effects on dental development may also require orthodontic treatment. Studies reporting dental abnormalities in childhood cancer survivors varied in their follow-up method. Some studies reported follow-up based on the number of years after treatment and some reported it based on the age of the patient.

Activities of daily living such as eating and personal mouth care are affected by cancer therapy. Eating is affected when taste changes and mouth sores occur. Caregiver and patient education is important to understand the kinds of food that a child with cancer facing difficulty in eating can manage in order to have adequate nutrition. If the patient is assisted in choosing foods that are manageable given his
or her oral condition, this can improve nutrition. Cheng et al (2009) found that maintaining personal mouth care was felt to be an issue for children with cancer and that the pediatric patient felt pressure to maintain oral hygiene. Children considered mouth care a forced activity by parents and were uncomfortable because of the pain involved. The unpleasant taste of mouthwashes also was an issue. There are inconsistencies in mouth care in hospitals from the perspective of nursing staff due to lack of guidelines and education. (75) Nurses often lack adequate knowledge about mouth care. Increased education on mouth care and coordination with the hospital dentist would assist nurses in giving adequate mouth care. (155) Implementation of oral care guidelines can help nurses and patients to maintain standards of oral hygiene.

The psychological, emotional and social domains overlap and cannot be separated and evaluated independently of each other. They are inter-related and impact QoL. Cheng (2009) evaluated the effect of oral mucositis on pediatric cancer patients qualitatively and found it to have a psychological and social impact. Speech issues associated with oral mucositis can contribute to the adolescent patient’s reluctance to engage in social interaction. The major psychological and social impacts on QoL can be seen in Cheng’s study. Similarly, Green and colleagues have documented the impact on various dimensions of QoL through patient interviews. (107, 108). The following verbatim remark speaks to the importance of the issue of oral complications such as mucositis: “When people talked to me, I couldn’t answer them, and they’d think that I was ignoring them. I had an oral ulcer and I couldn’t speak. I wanted to talk but I couldn’t. People
didn’t know that. My friends found it strange that I became so introverted (informant 2—child”). (108) Patients in Green’s study described mouth soreness as “hard and painful to eat” but developed their own strategies to combat mouth problems. (111) Understanding the QoL of life issues resulting from treatment can help pediatric oncologists identify further avenues of care in conjunction with a specialist. Most of the studies included in our review focus on mucositis. It would be useful to increase our knowledge on the effects of the other oral complications, such as oral graft-versus-host disease, xerostomia and trismus. Currently, guidelines have been developed to assess and treat oral mucositis by some organizations, such as the National Comprehensive Cancer Network and the Multinational Association of Supportive Care in Cancer. Evidence-based guidelines for the management of the other oral complications of cancer therapy would assist clinical staff in caring for the patient and improve his or her QoL.

Treatment and follow-up care of pediatric cancer patients requires a multi-disciplinary approach. (14) The intensity of the oral complications depends on the site of the cancer, the intensity of the treatment, the age of the child, the status of oral and dental health and the level of dental care before, during, and after therapy. Adequate and timely oral care of pediatric cancer patients minimizes the risk of oral complications during cancer therapy. Work by Glenny and colleagues underscores the importance of dental care during cancer treatment (156), reporting that only 36% of cancer centers in the U.K. sent pediatric cancer patients for oral checkups before the cancer treatment. (157) Therapy-related oral complications may not get entirely addressed; however, they can be minimized and preventive
oral care can aid in focusing attention on cancer treatment. The oral cavity is a part of the body and needs to be treated in conjunction with the rest of the body to minimize effects on general health.

In our sample, there was a lack of longitudinal studies to evaluate how treatment affects a child’s oral health in the long term. In the literature, there are many more studies on the oral complications experienced by the adult population, especially in the case of xerostomia. A systematic review led by the Oral Care Study group of the MASCC found a dearth of studies in the pediatric population related to xerostomia for example. (75) There is relatively little focus on the impact of these oral complications on QoL of the pediatric cancer patient, especially using qualitative methods. Using qualitative methods can provide an insight into the psychosocial issues faced by the cancer patient which may not easily be drawn from clinical trials.

Proxy ratings of QoL may be used in a child too ill to give his/her evaluation of QoL. Assessing QoL and the late effects of cancer treatment is also important from a financial perspective. Late effects of treatment can involve corrective orthodontic procedures and regular follow-up care. This could entail a relatively large financial burden for families of survivors.

Further work is needed in comparing and evaluating the different types of cancer treatments against the side-effects in order to aid in clinical treatment decisions. This could be done through randomized clinical trials (RCTs). (158)
Our scoping review had certain limitations. We were able to include only studies in English and French because of our own linguistic limitations; therefore, our results may be more relevant to countries in North America and Europe. There was no quality appraisal of the selected studies since quality assessment is not a part of the scoping review methodology. Since we are not assessing quality, this study may not aid evidence-based medicine and dentistry.

The strength of our study is that it is the first scoping review to study in depth the literature on the oral side-effects of cancer treatment in pediatric oncology. This review provides a literature repository for future research in dental oncology since we have charted both the research and gray literature on the topic of QoL and cancer-treatment-related oral complications.

Our review was undertaken to summarize and disseminate findings, including any identified gaps in the literature. The gaps in the literature that were identified were related to oral complications, treatments of these complications and qualitative studies as follows: Future studies should include clinical research on complications apart from oral mucositis, on intervention to treat of the oral complications and qualitative interviews with parents and children who have undergone cancer therapy, specifically on the psychosocial aspects of cancer treatment as related to oral side-effects.

**Conclusion:**

An increase in survival rates of childhood cancer necessitates the integration of a preventive oral care protocol in pediatric oncology treatment to reduce oral late
effects of cancer treatment. It is clear that oral complications of cancer therapy have an effect on the QoL of the pediatric cancer patient. This study demonstrates the need for an inter-professional collaboration of the fields of dentistry and pediatric oncology and the need for the inclusion of a dentist on the pediatric oncology team to provide preventive oral care. Children’s dentition is constantly developing until adolescence and neglected oral care during treatment can have an effect on the child in remission. Recent studies have begun to focus on the long-term oral effects in cancer survivors. Understanding that QoL is affected by cancer-treatment-related oral complications may help clinicians give better care to patients. The treatment focus must be on the cancer; moreover mitigating the side-effects of the treatment can lead to an improvement in the cancer patient’s QoL.

**Acknowledgements:** We thank Angella Lambrou and Lorie Kloda, liaison librarians at the McGill University Life Sciences Library (Montreal) for assistance in the literature search, and Akanksha Srivastava, graduate student, McGill University Faculty of Dentistry for assistance in abstract selection. We also thank the Division of Oral Health and Society in the McGill Faculty of Dentistry, and the Pediatric Oncology Department and Program in Pediatric Palliative Care Research and the Montreal Children’s Hospital for their feedback throughout this study.

Crystal Noronha designed the research protocol, conducted the literature search, data mapping, and analysis and prepared a first draft of the manuscript. Mary Ellen Macdonald assisted with the design, data analysis and interpretation and
with drafting the manuscript. The authors have read and approved the final manuscript.

Appendix A: PRISMA diagram

Appendix B: MEDLINE search strategy

The appendices of the manuscript have not been duplicated and appear solely at the end of the thesis.

Conflicts of interest

The authors declare that they have no potential conflicts of interests.


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More cancer patients are surviving. Thus there is a need to think about their side-effects. QoL in pediatric cancer patients is affected by cancer treatment-related oral complications. Treatment-related oral complications impact the patient physically, functionally, socially, emotionally and psychologically. QoL may be assessed by the patient themselves subjectively or more objectively by the clinician or caregiver; even if a person is perceived by the caregiver to be in poor health, he or she may still consider themselves as having a good QoL. This may be due to the fact that they are habituated to the different disease processes that they are experiencing during that period of time. QoL may be linked to health and state of disease. When assessing QoL related to oral health, the person and not just the mouth has to be considered. To reiterate, oral health is a window to general health and the mouth is not separate from the rest of the body.

It is important to measure QoL especially in the adolescent age group since treatment effects may not just be physical but have a strong functional, emotional, psychological and social impact. (40) The teen years represent development of independence and if QoL is impaired due to disease or treatment the patient may have to depend on a parent or caregiver for certain functional tasks as well as social support. QoL assessment in the health field has increased in importance due to increased participation by patients and families in their own treatment. (159) Curative treatment is not the sole option in managing a patient’s illness.

**Importance of the study:**
This study is the first scoping study to review the research and grey literature in depth in this field of pediatric oncology and dental complications of cancer therapy. The results of this thesis emphasize the necessity of developing a comprehensive program of dental care within a pediatric oncology setting.

**Clinical application:**

To date, there is no accepted integrated model of preventative dental care in pediatric cancer treatment. Preventative oral care can minimize oral side-effects of treatment. Inter-professional collaboration with a specialist pediatric dental team at cancer treatment centers will contribute to improvement of QoL for this population.

**Future directions:** Further studies can involve clinical trials evaluating treatments of the oral complications to develop evidence-based recommendations. There is also a lack of clinical studies on the extent of dental diseases and dental developmental delays in the pediatric cancer population. Other areas that could be scientifically developed include the pediatric psychosocial aspects of cancer treatment. There is scope for pediatric dental oncology programs to be developed as in the case for the adult cancer patient.
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Appendix A: PRISMA

Records identified through database searching (n = 1158)

Records after duplicates removed (n = 939)

Records screened (n = 936)

Records excluded (n = 816)

Full-text articles assessed for eligibility (n = 120 + 17)

Full-text articles excluded (n = 55)

Studies included in descriptive summary (n = 82)
Appendix B: Search Strategy

Medline

1. exp Antineoplastic Agents/
2. exp Radiotherapy/
3. exp Hematopoietic Stem Cell Transplantation/
4. 1 or 2 or 3
5. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
6. "Quality of Life"/ or exp rehabilitation/ or exp eating/ or exp human activities/ or rh.fs. or px.fs.
7. 4 and 5 and 6
8. limit 7 to ("all child (0 to 18 years)" and (english or french))
9. exp Antineoplastic Agents/ae, ct, po, re, to [Adverse Effects, Contraindications, Poisoning, Radiation Effects, Toxicity]
10. exp Radiotherapy/ae, ct [Adverse Effects, Contraindications]
11. exp Hematopoietic Stem Cell Transplantation/ae, ct [Adverse Effects, Contraindications]
12. 9 or 10 or 11
13. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
14. exp cohort studies/
15. 12 and 13 and 14
16. limit 15 to ("all child (0 to 18 years)" and (english or french))
17. 8 or 16

PsycInfo
1. exp Neoplasms/co [Complications]

2. exp Antineoplastic Agents/ae, ct, po, re, to [Adverse Effects, Contraindications, Poisoning, Radiation Effects, Toxicity]

3. exp Radiotherapy/ae, ct [Adverse Effects, Contraindications]

4. exp Hematopoietic Stem Cell Transplantation/ae, ct [Adverse Effects, Contraindications]

5. 1 or 2 or 3 or 4

6. Oral Health/

7. 5 and 6

8. limit 7 to (yr="2000 -Current" and "all child (0 to 18 years)" and (english or french))

9. halitosis/

10. exp Stomatognathic Diseases/

11. dmf index/ or periodontal index/

12. 9 or 10 or 11

13. 5 and 12

14. limit 13 to (yr="2000 -Current" and "all child (0 to 18 years)" and (english or french))

15. exp *Neoplasms/co or exp *Antineoplastic Agents/ae, ct, po, re, to or exp *Radiotherapy/ae, ct or exp *Hematopoietic Stem Cell Transplantation/ae, ct

16. 14 and 15

17. "Quality of Life"/

18. exp Human Activities/

19. exp Rehabilitation/

20. 17 or 18 or 19

21. 14 and 20

22. exp tooth diseases/

23. 5 and 22

24. exp *Neoplasms/ or exp *Antineoplastic Agents/ae, ct, po, re, to or exp *Radiotherapy/ae, ct or exp *Hematopoietic Stem Cell Transplantation/ae, ct
25. 12 and 24
26. 20 and 25
27. 12 and 17 and 24
28. limit 27 to (yr="2000-Current" and "all child (0 to 18 years)" and (english or french))
29. exp mouth diseases/et or exp tooth diseases/et
30. 5 and 29
31. 20 and 30
32. 21 or 28 or 31
33. exp Neoplasms/dt, pc, rt, th [Drug Therapy, Prevention & Control, Radiotherapy, Therapy]
34. exp Antineoplastic Agents/ae, re [Adverse Effects, Radiation Effects]
35. exp Drug Therapy/ae [Adverse Effects]
36. exp Radiotherapy, Intensity-Modulated/ or exp Radiotherapy, Adjuvant/ or exp Radiotherapy Dosage/ or exp Radiotherapy/ or exp Radiotherapy, Conformal/ or Radiotherapy, High-Energy/
37. exp Hematopoietic Stem Cell Transplantation/ae [Adverse Effects]
38. exp Stomatitis/ci, dt, rt [Chemically Induced, Drug Therapy, Radiotherapy]
39. exp Xerostomia/ci, dt, rt [Chemically Induced, Drug Therapy, Radiotherapy]
40. exp Candidiasis, Oral/ or Candidiasis/
41. exp Gingivitis, Necrotizing Ulcerative/ or exp Gingivitis/
42. exp Stomatognathic Diseases/dt, rt [Drug Therapy, Radiotherapy]
43. exp Dental Caries/ci, dt, rt [Chemically Induced, Drug Therapy, Radiotherapy]
44. exp Trismus/ci, dt, rt [Chemically Induced, Drug Therapy, Radiotherapy]
45. exp Oral Health/
46. 33 or 34 or 35 or 36 or 37 or 45
47. 38 or 39 or 40 or 41 or 42 or 43 or 44
48. exp "Quality of Life"/px [Psychology]
49. 46 and 47 and 48
50. limit 49 to (english language and yr="2000" and "all child (0 to 18 years)" and (english or french))
51. 46 and 47
52. limit 51 to (english language and yr="2000" and "all child (0 to 18 years)" and (english or french))

AMED

1. exp Antineoplastic Agents/
2. exp Radiotherapy/
3. exp Hematopoietic Stem Cell Transplantation/
4. 1 or 2 or 3
5. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
6. "Quality of Life"/ or exp rehabilitation/ or exp eating/ or exp human activities/ or rh.fs. or px.fs.
7. 4 and 5 and 6
8. limit 7 to ("all child (0 to 18 years)" and (english or french))
9. exp Antineoplastic Agents/ae, ct, po, re, to [Adverse Effects, Contraindications, Poisoning, Radiation Effects, Toxicity]
10. exp Radiotherapy/ae, ct [Adverse Effects, Contraindications]
11. exp Hematopoietic Stem Cell Transplantation/ae, ct [Adverse Effects, Contraindications]
12. 9 or 10 or 11
13. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
14. exp cohort studies/
15. 12 and 13 and 14
16. limit 15 to ("all child (0 to 18 years)" and (english or french))
17. 8 or 16
18. limit 17 to yr="2011"
19. limit 18 to "all child (0 to 18 years)"
20. exp Antineoplastic Agents/
21. exp Radiotherapy/
22. exp Hematopoietic Stem Cell Transplantation/
23. 20 or 21 or 22
24. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
25. "Quality of Life"/ or exp rehabilitation/ or exp eating/ or exp human activities/ or rh.fs. or px.fs.
26. 23 and 24 and 25
27. limit 26 to ("all child (0 to 18 years)" and (english or french))
28. exp Antineoplastic Agents/ae, ct, po, re, to [Adverse Effects, Contraindications, Poisoning, Radiation Effects, Toxicity]
29. exp Radiotherapy/ae, ct [Adverse Effects, Contraindications]
30. exp Hematopoietic Stem Cell Transplantation/ae, ct [Adverse Effects, Contraindications]
31. 28 or 29 or 30
32. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
33. exp cohort studies/
34. 31 and 32 and 33
35. limit 34 to ("all child (0 to 18 years)" and (english or french))
36. 27 or 35
37. limit 36 to (yr="2011" and "all child (0 to 18 years)")
38. (("oral health" or "stomathognathic diseases" or "mouth mucosa" or mouth or "dental health" or "tooth diseases") and (chemotherapy or radiotherapy or "hematopoietic stem cell disease" or neoplasms or "antineoplastic")).af.
39. limit 38 to ((english or french) and yr="2000 -Current")
40. limit 39 to (yr="2011" and "all child (0 to 18 years)")
41. limit 40 to (english or french)
42. from 41 keep 12
EMBASE

1. exp Antineoplastic Agents/
2. exp Radiotherapy/
3. exp Hematopoietic Stem Cell Transplantation/
4. 1 or 2 or 3
5. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or
dmf index/ or periodontal index/
6. "Quality of Life"/ or exp rehabilitation/ or exp eating/ or exp human activities/
or rh.fs. or px.fs.
7. 4 and 5 and 6
8. limit 7 to ("all child (0 to 18 years)" and (english or french))
9. exp Antineoplastic Agents/ae, ct, po, re, to [Adverse Effects, Contraindications, Poisoning, Radiation Effects, Toxicity]
10. exp Radiotherapy/ae, ct [Adverse Effects, Contraindications]
11. exp Hematopoietic Stem Cell Transplantation/ae, ct [Adverse Effects, Contraindications]
12. 9 or 10 or 11
13. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or
dmf index/ or periodontal index/
14. exp cohort studies/
15. 12 and 13 and 14
16. limit 15 to ("all child (0 to 18 years)" and (english or french))
17. 8 or 16

Global Health

1. exp Antineoplastic Agents/
2. exp Radiotherapy/
3. exp Hematopoietic Stem Cell Transplantation/
4. 1 or 2 or 3
5. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
6. "Quality of Life"/ or exp rehabilitation/ or exp eating/ or exp human activities/ or rh.fs. or px.fs.
7. 4 and 5 and 6
8. limit 7 to ("all child (0 to 18 years)" and (english or french))
9. exp Antineoplastic Agents/ae, ct, po, re, to [Adverse Effects, Contraindications, Poisoning, Radiation Effects, Toxicity]
10. exp Radiotherapy/ae, ct [Adverse Effects, Contraindications]
11. exp Hematopoietic Stem Cell Transplantation/ae, ct [Adverse Effects, Contraindications]
12. 9 or 10 or 11
13. Oral Health/ or exp dentistry/ or halitosis/ or exp Stomatognathic Diseases/ or dmf index/ or periodontal index/
14. exp cohort studies/
15. 12 and 13 and 14
16. limit 15 to ("all child (0 to 18 years)" and (english or french))
17. 8 or 16

CINAHL

Limiters - Language: English, French; Published Date from: 20000101-20111031; Age Groups: Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years

S4 and S9 and S10 Search modes - Boolean/Phrase
S13  
("cohort studies") and (S4 and S9 and S10)

S12  
("cohort studies") and (S5 and S9 and S10)

S11  
"cohort studies"

S10  
"quality of life" OR eating OR "human activities"

S9  
"dental health" OR "oral health" OR "stomatognathic diseases"

S8  
""dental health" OR "oral health" OR "stomatognathic diseases"

S7  
( ((MH "Antineoplastic Agents/AE/RE") OR radiotherapy OR Hematopoietic Stem Cell Transplantation) and (S2 or S3 or S4) ) AND "oral health"

S6  
( ((MH "Antineoplastic Agents/AE/RE") OR radiotherapy OR Hematopoietic Stem Cell Transplantation) and (S2 or S3 or S4) ) AND "oral health"

S5  
((MH "Antineoplastic Agents/AE/RE") OR radiotherapy OR Hematopoietic Stem Cell Transplantation) and (S2 or S3 or S4)
Web of Science

TS= (chemotherap* or cancer or "drug therap*" or radiotherap* or hematopoietic or “radiation therap AND TS= ("quality of life")) AND (oral or mucos* or caries or gingiv* or mouth or periodont*or xerostomia or “oral candidiasis” or oral hemorr*)

(MH "Antineoplastic Agents/AE/RE") OR radiotherapy OR Hematopoietic Stem Cell Transplantation

(MH "Antineoplastic Agents/AE/RE") OR radiotherapy

(MH "Antineoplastic Agents/AE/RE")

(EV "Oral Care of the Hospitalized Patient")
Appendix C: Exclusions

not due to treatment/oral =10
mixed disease=9
mixed age group=12
not primary study=12
language not English or French=3
unable to get full text even after contacting author=5
case report=1
duplicate=3
Appendix D: Title and Abstract Screening Tool - 1st level of selection

Screen for title, abstract and keywords

INCLUDE IF:

Study pertains to Cancer/neoplasm treatment (chemotherapy, radiotherapy or hematopoietic stem cell transplantation)

AND

Pertains to any oral complication due to treatment viz, oral mucositis, stomatitis, mouth ulcers, oral candidiasis, oral infections, trismus, tooth complications, microdontia, salivary gland dysfunctions, oral late effects

AND

Pediatric or Child or Adolescent

EXCLUDE IF:

Prior to 2000 and not English/French

Mixed population: Adult and child/adolescent

Mixed disease category

Related to oral health but not due to cancer treatment

Animal studies/ systematic reviews
<table>
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<th>First Author</th>
<th>Title</th>
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<th>Late</th>
<th>impacting QoL</th>
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<td>Yeh C H (2009)</td>
<td>Assessment of Symptoms Reported by 10-to 18-Year-Old Cancer Patients in Taiwan</td>
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<td>taste change, mouth sores, dry mouth</td>
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<td>Williams P (2006)</td>
<td>Symptom monitoring and dependent care during cancer treatment in children</td>
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<td>sore mouth, taste change</td>
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<td>Changes of cariogenic microflora in children receiving chemotherapy</td>
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<td>Voskuilen I</td>
<td>Long-term adverse effects of hematopoietic stem cell transplantation on dental development in children</td>
<td>CT/HSCT/TBI</td>
<td>Late xerostomia, gingivitis, caries, agenesis, short roots, and early root closure.</td>
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<td>Vaidya S J</td>
<td>Autologous bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission - long-term follow-up</td>
<td>CT,BMT,TBI</td>
<td>Oral mucositis</td>
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<td>Uderzo C</td>
<td>Glutamine-enriched nutrition does not reduce mucosal morbidity or complications after stem-cell transplantation for childhood malignancies: a prospective randomized study</td>
<td>BMT</td>
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<td>Altered food intake and taste perception in children with cancer after start of chemotherapy: perspectives of children, parents and nurses</td>
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<td>Late taste disturbance, mouth blisters, pain, mucositis, oral pain, taste change</td>
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<td>Sixou J. L.</td>
<td>Capnocytophaga in the dental plaque of immunocompromised children with cancer</td>
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<td>Effects of methylenetetrahydrofolate reductase and reduced folate carrier 1 polymorphisms on high-dose methotrexate-induced toxicities in children with acute lymphoblastic leukemia or lymphoma</td>
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<td>Early mucositis, xerostomia, caries, dry mouth</td>
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<td>Pereira Pinto L (2006)</td>
<td>Prevention of oral lesions in children with acute lymphoblastic leukemia</td>
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<td>Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia</td>
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<td>MUCOSAL PATHOLOGY OF THE UPPER GASTROINTESTINAL TRACT ASSOCIATED WITH INTENSIVE CHEMOTHERAPY IN CHILDREN: Vitamin A Supplements Do Not Prevent Lesions</td>
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<td>Hoolta P</td>
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<td>Hobbie WL</td>
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<td>Distressing and positive experiences and important aspects of care for adolescents treated for cancer. Adolescent and nurse perceptions</td>
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<td>Gravina H G</td>
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<td>Gandemer V</td>
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<tr>
<td>Peretz B (2006)</td>
<td>Salivary Microorganisms and Oral Status in Children Undergoing Oncology Treatment</td>
<td>CT, RT</td>
<td>Early bacterial infection, caries</td>
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<td>Doğan C (2001)</td>
<td>Oral health status in children with acute lymphoblastic leukemia and lymphoma</td>
<td>CT</td>
<td>Late mucositis malocclusion, decayed, missing/filled plaque, calculus</td>
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<tr>
<td>de Oliveira Lula E. C (2007)</td>
<td>Chemotherapy-induced oral complications in leukemic patients</td>
<td>CT</td>
<td>impacting mucosal paleness, infections, bleeding, lesions</td>
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<tr>
<td>De Koning B. A. E. (2007)</td>
<td>Protection against chemotherapy induced mucositis by TGF-β2 in childhood cancer patients: Results from a randomized cross-over study</td>
<td>CT</td>
<td>impacting mucositis</td>
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<td>Clarke S. A (2011)</td>
<td>Clinical outcomes and health-related quality of life (HRQOL) following haemopoietic stem cell transplantation (HSCT) for pediatric leukemia</td>
<td>HSCT</td>
<td>dental effect</td>
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<td>Cheng K K F (2011)</td>
<td>Incidence and risk factors of oral mucositis in pediatric and adolescent patients undergoing chemotherapy</td>
<td>CT</td>
<td>Early</td>
<td>mucositis</td>
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<td>swallowing, drinking, eating, speaking</td>
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<tr>
<td>K. K. F. Cheng; A. M. Chang; M. P. Yuen</td>
<td>Prevention of oral mucositis in pediatric patients treated with chemotherapy: a randomized crossover trial comparing two protocols of oral care</td>
<td>CT</td>
<td>Early</td>
<td>mucositis, oral ulcers</td>
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<tr>
<td>Cheng K K F (2009)</td>
<td>Oral mucositis: a phenomenological study of pediatric patients' and their parents' perspectives and experiences</td>
<td>CT</td>
<td>Early: mucositis, mouth pain, Late: eating, emotional tension, distress, wt loss, nutrition, pressure on mouth care, education and compassion needs, pain when speaking, friends think they are ignoring</td>
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<td>Chen C F (2004)</td>
<td>Assessment of Chemotherapy-Induced Oral Complications in Children With Cancer</td>
<td>CT</td>
<td>Early: ulcerated mucous membranes, dry lips, oral debris. Late: Dry lips, oral debris, deeper or raspy voice</td>
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<td>Cubukcu C E (2011)</td>
<td>Disturbed dental development of permanent teeth in children with solid tumors and lymphomas</td>
<td>CT/RT</td>
<td>Late: agenesis, microodontia</td>
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<td>Avşar A (2007)</td>
<td>Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors</td>
<td>CT</td>
<td>Caries, bacteria, opacities, arrested root devt</td>
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<td>Anacak Y (2007)</td>
<td>Daily subcutaneous amifostine administration during irradiation of pediatric head and neck cancers</td>
<td>CT,RT</td>
<td>Early: mild mucositis, saliva thickening</td>
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<td>Rebecca G (2010)</td>
<td>Eating experiences of children and adolescents with chemotherapy-related nausea and mucositis</td>
<td>CT</td>
<td>mucositis, oral pain, mouth soreness</td>
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<td>Pajari U</td>
<td>The risk of dental caries in childhood cancer is not high if the teeth are caries-free at diagnosis</td>
<td>CT,RT</td>
<td>Early caries, infections</td>
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<td>Castellanos E</td>
<td>OUTCOME OF CHILDREN WITH HODGKIN LYMPHOMA LESS THAN 5 YEARS OF AGE TREATED WITH A RISK ADAPTED, RESPONSE - BASED REGIMEN APPROACH: REPORT FROM THE AHOPCA GROUP HL 2004</td>
<td>CT/RT</td>
<td>mucositis</td>
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<td>Maradiégue E</td>
<td>Efficacy of increasing doses of methotrexate from 1000 to 1500 mg/m2 in preventing testicular relapse in children with acute lymphoblastic</td>
<td>CT</td>
<td>mucositis</td>
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<td></td>
<td><strong>LEUKEMIA</strong></td>
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<td>Kovacs G</td>
<td>PHARMACOKINETIC OF HIGH DOSE METHOTREXATE (HD-MTX) TREATMENTS IN CHILDHOOD LEUKEMIA</td>
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<td>Late mucositis</td>
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<td>Lazic J</td>
<td>INCIDENCE OF ORAL MUCOSITIS AND EFFICIENT THERAPY WITH SUPERSATURATED CALCIUM AND PHOSPHATE SOLUTION IN PEDIATRIC CANCER PATIENTS</td>
<td>CT</td>
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<td>Caussa L (2011)</td>
<td>USING IMRT AND RADIOSURGERY FOR THE TREATMENT OF CANCER IN CHILDREN AND ADOLESCENTS: ASSESSMENT OF EARLY TOXICITY</td>
<td>RT</td>
<td>Mucositis, xerostomia</td>
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<td>Re´guerre Y (2011)</td>
<td>BURDEN OF LOCAL THERAPY IN SURVIVORS OF HIGH RISK NONMETASTATIC RHABDOMYOSARCOMA AND RELATED DIAGNOSES</td>
<td>CT/RT</td>
<td>mucositis (greater in 6 drug arm)</td>
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<td>Wogelius P (2011)</td>
<td>Oral health-related quality of life among survivors of childhood cancer</td>
<td>CT/RT</td>
<td>oral problems</td>
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<td>Soares A F (2011)</td>
<td>Frequency of oral mucositis and microbiological analysis in children with acute lymphoblastic leukemia treated with 0.12% chlorhexidine gluconate</td>
<td>CT</td>
<td>mucositis, bacteria</td>
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<td>Cabanas R (2011)</td>
<td>Safety and efficacy results of the children and adolescents CNS tumors Nimotuzumab B expanded program</td>
<td>CT/RT mucositis</td>
<td>Early Late impacting QoL</td>
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<td>Dufour C (2011)</td>
<td>Feasibility and efficacy of tandem high dose chemotherapy for children with high-risk medulloblastoma</td>
<td>CT/RT/HSC mucositis</td>
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Graphs and Pie Charts

Figure 1: Prevalence of Oral Complications

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<thead>
<tr>
<th>Oral Complication</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Oral Mucositis</td>
<td>47%</td>
</tr>
<tr>
<td>Root/tooth abnormalities</td>
<td>21%</td>
</tr>
<tr>
<td>Caries</td>
<td>9%</td>
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<tr>
<td>Dry mouth, Dry lips</td>
<td>7%</td>
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<tr>
<td>Oral infections</td>
<td>7%</td>
</tr>
<tr>
<td>Bleeding gums</td>
<td>3%</td>
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<tr>
<td>Taste Changes</td>
<td>3%</td>
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<tr>
<td>Jaw problem</td>
<td>3%</td>
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</table>
Figure 2: Distribution of Pediatric Cancers

Distribution of Cancers Studied (n=82)

Leukemias
Leukemias & other cancers
Lymphomas
Cranial/spinal tumors
Sarcomas
Neuroblastoma
23%
64%
5%
1%
5%
2%

Figure 3: Number of studies by year of publication
Figure 4: Studies by Continents

North Americas

Asia
Europe

Africa
South America

**Figure 5: Number of studies by discipline**
Figure 6: Distribution of sources