Revisión Sistemática
https://doi.org/10.47990/z67n3841

Long-term Complications in Dental Development of Pediatric Patients After Oncologic Treatment: A Systematic Review

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Abstract: **Introduction and aim of the study:** Childhood cancer is a rare disease that affects children and adolescents under 19 years of age and is one of the leading causes of mortality worldwide. Increased survival has led to the emergence of sequelae resulting from cancer treatment. The objective of this review was to describe the complications in dental development in this group of individuals after receiving cancer treatment. **Methodology:** An electronic database search and manual review were conducted to identify relevant studies. Cohort, cross-sectional, and case-control studies published in the last 20 years in English, Spanish, and Portuguese were included. The search strategy combined MeSH terms and free text. According to the PICO strategy, articles were selected that evaluated patients aged 0–19 years with childhood cancer treated with chemotherapy, radiotherapy, surgery, hematopoietic cell transplantation, and combination therapies. The outcome evaluated was the presence of long-term manifestations in dental development after cancer treatment. **Results:** Out of 116 studies, 21 were selected. The methodological designs were equitable (33.3% each). Leukemia was the most common childhood cancer (40.3%). Most patients received chemotherapy alone (71.6%), and the main dental abnormalities were root malformations (26.1%), enamel hypoplasia (24.8%), microdontia (24.6%), and tooth agenesis (17.8%). **Conclusion:** Antineoplastic therapies in pediatric oncology patients are associated with dental abnormalities. Integrating the dentist into the interdisciplinary team is key to preventing, diagnosing, and treating these manifestations.

Key words: Childhood cancer, antineoplastic treatment, dental development.

Complicaciones a largo plazo en el desarrollo dentario de pacientes pediátricos posteriores al tratamiento oncológico: una revisión sistemática

Resumen: **Introducción y objetivos**: El cáncer infantil es una enfermedad poco frecuente que afecta a niñas, niños y adolescentes menores de 19 años, siendo una de las principales causas de mortalidad a nivel mundial. El aumento de la supervivencia ha conllevado al desarrollo de secuelas derivadas del tratamiento oncológico. El objetivo de esta revisión fue describir las complicaciones en el desarrollo dentario de este grupo de pacientes tras recibir tratamiento antineoplásico. **Metodología:** Se realizó una búsqueda en bases de datos electrónicas y una revisión manual para identificar estudios relevantes. Se incluyeron estudios de cohortes, transversales y de casos y controles publicados en los últimos 20 años en inglés, español y portugués. La estrategia de búsqueda combinó términos MeSH y texto libre. Siguiendo la estrategia PICO, se seleccionaron artículos que evaluaran pacientes de 0 a 19 años con cáncer infantil tratados con quimioterapia, radioterapia, cirugía, trasplante de células hematopoyéticas y terapias combinadas. El desenlace evaluado fue la presencia de manifestaciones a largo plazo en el desarrollo dentario tras el tratamiento oncológico. **Resultados:** De 116 estudios, se seleccionaron 21. Los diseños metodológicos fueron equitativos (33,3% cada uno). La leucemia fue el cáncer infantil más frecuente (40,3%). La mayoría de los pacientes recibió quimioterapia exclusiva (71,6%) y las principales alteraciones dentarias fueron malformaciones radiculares (26,1%), hipoplasia del esmalte (24,8%), microdoncia (24,6%) y agenesia dentaria (17,8%). **Conclusión:** Las terapias antineoplásicas en pacientes oncopediátricos se asocian con alteraciones dentarias. La integración del odontólogo en el equipo interdisciplinario es clave para prevenir, diagnosticar y tratar estas manifestaciones.

Palabras clave: Cáncer infantil, tratamiento antineoplásico, desarrollo dentario.

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Complicações a longo prazo no desenvolvimento dentário de pacientes pediátricos após o tratamento oncológico: Uma revisão sistemática

Resumo: **Introdução e objetivos:** O câncer infantil é uma doença rara que afeta crianças e adolescentes com menos de 19 anos, sendo uma das principais causas de mortalidade no mundo. O aumento na taxa de sobrevivência tem levado ao surgimento de sequelas decorrentes do tratamento oncológico. O objetivo desta revisão foi descrever as complicações no desenvolvimento dentário deste grupo após o tratamento antineoplásico. **Metodologia:** Foi realizada uma busca em bases de dados eletrônicas e uma revisão manual para identificar estudos relevantes. Foram incluídos estudos de coorte, transversais e de caso-controle publicados nos últimos 20 anos em inglês, espanhol e português. A estratégia de busca combinou termos MeSH e palavras livres. Seguindo a estratégia PICO, foram selecionados artigos que avaliaram pacientes de 0 a 19 anos com câncer infantil tratados com quimioterapia, radioterapia, cirurgia, transplante de células hematopoiéticas e terapias combinadas. O desfecho avaliado foi a presença de manifestações a longo prazo no desenvolvimento dentário após o tratamento oncológico. **Resultados:** De 116 estudos, foram selecionados 21. Os desenhos metodológicos estavam distribuídos igualmente (33,3% cada). A leucemia foi o câncer infantil mais frequente (40,3%). A maioria dos pacientes recebeu quimioterapia exclusiva (71,6%) e as principais alterações dentárias foram malformações radiculares (26,1%), hipoplasia do esmalte (24,8%), microdontia (24,6%) e agenesia dentária (17,8%). **Conclusão:** As terapias antineoplásicas em pacientes oncopediátricos estão associadas a alterações dentárias. A integração do cirurgião-dentista na equipe interdisciplinar é fundamental para prevenir, diagnosticar e tratar essas manifestações.

Palavras-chave: Câncer infantil, tratamento antineoplásico, desenvolvimento dentário.

Introduction

Childhood cancer (CC) is a heterogeneous group of rare neoplasms affecting children and adolescents aged 0–19 years. Globally, it ranks among the main causes of mortality in this population, with approximately 280,000 new cases and 110,000 deaths reported in 2020[1,2]. In Chile, the incidence between 2017 and 2019 was 142.3 cases per million in individuals under 15 years, with a total of 1,580 new diagnoses[3]. The most common types include leukemias, central nervous system (CNS) neoplasms, lymphomas, and solid tumors, the latter classified according to the affected organ[2,3].

Childhood cancer is potentially curable when diagnosed and treated promptly. The main therapeutic approaches include chemotherapy (CT), radiotherapy (RT), and surgery, used individually or in combination depending on the cancer type, stage, and patient's age [4]. However, these treatments cause systemic toxicity and adverse effects, which may appear immediately or later[5]. In dentistry, long-term sequelae depend on the patient's age and the type of therapy received[6,7]. CT affects ameloblasts and odontoblasts due to their high replication rate, while RT, through ionizing radiation, damages cellular DNA, affecting tooth development and eruption[8,9]. The most frequent dental complications include agenesis, microdontia, enamel hypoplasia, and root malformations[6], with anatomical, functional, and esthetic consequences[7] that may impact self-esteem, social interaction, and academic or occupational performance[10,11].

Currently, survival rates for CC have significantly improved thanks to advances in diagnosis and treatment, reaching

approximately 78% five-year survival in Chile[12,3]. This progress poses the challenge of ensuring a good long-term quality of life for survivors and their families, promoting social integration and autonomy[13]. The aim of this study is to characterize these alterations and their impact on oral and maxillofacial health, enabling clinicians to anticipate interventions that optimize patient outcomes.

Methodology

This systematic review included studies published between 2004 and 2024. Variable selection followed the PICO framework, considering as participants children and adolescents aged 0 to 19 years diagnosed with CC who received antineoplastic treatment. The interventions analyzed included various treatment modalities such as chemotherapy, radiotherapy, surgery, hematopoietic cell transplantation, or combination therapies. The outcome evaluated was the presence of long-term dental developmental alterations following oncologic treatment.

The study search was conducted according to PRISMA 2020 guidelines across PubMed (MEDLINE), Web of Science, and SciELO databases until March 14, 2024. A combined strategy of MeSH terms and free-text keywords using Boolean operators “AND” and “OR” was applied, with terms including "Child," "Adolescent," "Antineoplastic Agents," "Radiotherapy," "Tooth Abnormalities," "Dental Enamel Hypoplasia," and "Abnormal Root Development."

Observational descriptive and analytical studies (case-control and cohort) were included if they analyzed panoramic radiographs and/or oral clinical examinations, describing dental abnormalities such as agenesis, hypodontia, microdontia, enamel hypoplasia, and root malformations. Only full-text articles in English, Portuguese, or Spanish were included. Exclusion criteria comprised theses, systematic reviews, in vitro or animal studies, and those lacking post-treatment dental data or unclear oncologic diagnoses. Studies without details on treatment modality were also excluded.

References were exported to Rayyan®, where two reviewers independently screened titles and abstracts from 116 studies according to inclusion and exclusion criteria. A third reviewer resolved conflicts. Subsequently, full-text review excluded duplicates, non-eligible languages, and inaccessible papers, resulting in 21 studies for final analysis. Data were extracted and tabulated in Microsoft Excel®, organized into four tables summarizing study characteristics, patient demographics, treatment type, and reported dental alterations. Descriptive statistical analysis was applied to summarize findings.

Results

A total of 116 articles were identified, with 76 retrieved from PubMed and 40 from Web of Science. No relevant studies were found in SciELO. After screening and exclusion, 21 studies were included in the final analysis. Europe accounted for 81% of publications (n=17), followed by Asia and the Americas (n=2 each). Türkiye contributed the highest

number of studies (23.8%). The designs were evenly distributed among cross-sectional, case-control, and cohort studies (33.3% each). The detailed study characteristics are summarized in (Figure 1).

Article Description

Regarding the geographical distribution of publications, Europe concentrates the largest proportion, representing 81% (n=17) of the total, followed by Asia and America, with 9.5% (n=2) each. Türkiye is the country with the highest number of publications, contributing 23.8% (n=5) of the analyzed articles. Regarding the methodological design of the selected studies, an equal distribution was observed among cross-sectional, case-control, and cohort studies, with seven articles in each category, representing 33.3% of the total. A detailed characterization of the studies is presented in (Table 1).

Description/characterization of the patients

The age range of the analyzed patients varied between 0 and 10 years at the time of diagnosis and the start of antineoplastic treatment, while some were up to 21 years old at the time of clinical and/or radiographic examination.

Regarding oncological diagnoses, in 16 of the

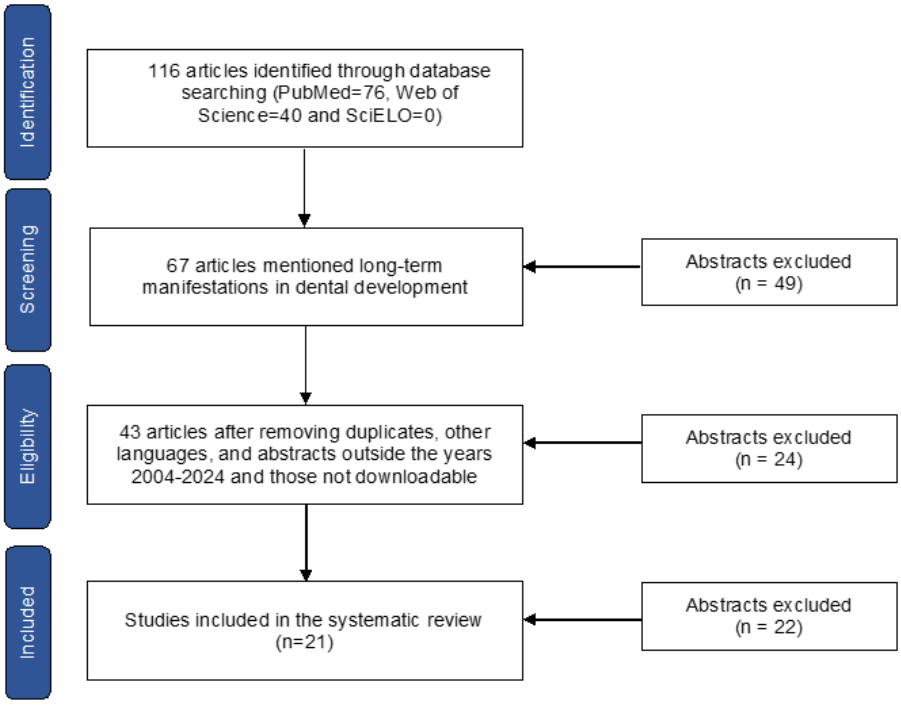

Figure 1. *Flow diagram of the phases of the study selection process, according to PRISMA guidelines.*

Table 1. *Characterization of the included studies* [36-50].

Author, year	Country	Study type	Sample size	Diagnosis	Antineoplastic treatments
Pedersen et al., 2012	Denmark	Case–control	150	NH/TS/TSNC	CT
Kılınç et al., 2019	Türkiye	Case–control	93	Le/Ly/TR/TH/TSNC/TO/TG	CT/CS
Çetiner et al., 2019	Türkiye	Case–control	53	Ly/TR/R/N/STB	CT
Halperson et al., 2022	Israel	Cross-sectional	121	Le/Ly/N/O	CT/RT/S/T
Quispe et al., 2019	Brazil	Case–control	111	Le/Ly/TR/TH/R/TSNC/N/STB/TO/O	CT/RT/CS
Hölttä et al., 2005	Finland	Cohort	55	Le/Ly/TR/N/TG/STB/O	T
Hutton et al., 2010	United Kingdom	Cohort	120	Ly/TR/N/STB/O	CT
Stolze et al., 2021	Netherlands	Cross-sectional	154	NH/TS/TCE	CT/RT/CS/T
Ruyssinck et al., 2019	Belgium	Cohort	42	Le/Ly/TR/N/TG/O	T
Cubukcu et al., 2012	Türkiye	Case–control	37	Ly/TR/TH/R/TSNC/N/TG/STB	CT/CS
Owosho et al., 2016	United States	Cohort	13	R	CS
Rabassa-Blanco et al., 2024	Spain	Cohort	109	NH/TS/TSNC	CT/CS/T
Lauritano et al., 2012	Italy	Cohort	52	Le	CT
Tanaka et al., 2017	Japan	Cross-sectional	56	Le/Ly/TR/TH/R/N/TG	CT/RT/CS/T
Marec-Berard et al., 2005	France	Cohort	27	TR	CT
Wilberg et al., 2016	Norway	Cross-sectional	111	Le	CT
Avşar et al., 2007	Türkiye	Case–control	96	Ly/STB/TO	CT
Oğuz et al., 2004	Türkiye	Case–control	36	Ly	CT
Jodłowska et al., 2022	Poland	Cross-sectional	37	NH/TS	CT
Bica et al., 2017	Romania	Cross-sectional	36	Le	CT
Kyriaki et al., 2023	Greece	Cross-sectional	70	NH/TS/TSNC	CT/CS

21 studies the International Classification of Childhood Cancer, Third Edition (ICCC-3), was used. The most prevalent types of neoplasms were leukemias (40.3%), followed by lymphomas (22.7%), other unspecified malignant neoplasms (11.7%), kidney tumors (10.7%), neuroblastomas (8.5%), malignant bone tumors (1.5%), soft tissue sarcomas (1.1%), CNS neoplasms (1%), liver tumors (0.8%), retinoblastoma (0.7%), and germ cell tumors (0.7%).

In the remaining five studies, diagnoses were classified according to other criteria. In these, a higher prevalence of hematological neoplasms (55.2%) was observed, followed by solid tumors (28.5%), CNS tumors (15%), and brain tumors (1.4%).

Table 2. *Relationship between dental development manifestations and antineoplastic treatment.*

Manifestations	Chemotherapy (n)	Radiotherapy (n)	Combined therapy (n)	Surgery (n)	Transplant (n)
Root malformations	231	11	27	0	7
Enamel hypoplasia	300	0	42	0	3
Microdontia	254	5	35	0	6
Agenesis	154	4	17	0	3
Total	939	30	121	0	19

The total number of patients included in the reviewed articles was 1,579. Of these, 71.6% (n=1,194) received chemotherapy alone, followed by transplant (12.8%, n=214), combined therapy (10.8%, n=181), radiotherapy (3.7%, n=61), and resective surgery (1.1%, n=19).

Complications in dental development

In the study group (n = 1,579), root malformations were the most prevalent dental alteration in pediatric oncology patients, at 26.1% (n = 412), followed by enamel hypoplasia (24.8%), microdontia (24.6%), and dental agenesis (17.8%). In contrast, 80 patients (5%) showed no abnormalities in dental development. In the control group (n=637), the majority of individuals (78.5%) had no dental alterations. However, enamel hypoplasia was identified in 8%, followed by root malformations (6%), dental agenesis (6.2%), and microdontia (1.3%).

Additionally, 15 studies described the relationship between dental development alterations and antineoplastic treatment. The distribution of these manifestations according to the treatment received is detailed in (Table 2).

Discussion

CI, with its high morbidity and mortality, continues to be a significant public health challenge due to its increasing prevalence worldwide. In Chile, this trend is similar, with a rise in CI rates according to measurements from 2007-2011, 2012-2016, and 2017-2019, recording 480.8, 516.8, and 526.7 annual cases, respectively[3]. In this review, most of the studies analyzed were conducted in Türkiye, which could reflect the increase in CI incidence in that country, rising from 17.3 per 100,000 inhabitants in 2020[14] to 18.3 in 2022[15,16]. Regarding diagnoses,

the 16 studies that used the ICCC-3 classification agree that leukemias (40.3%) and lymphomas (22.7%) are the most frequent, which aligns with WHO data[12]. In Chile, the pattern is similar, with leukemias being the most prevalent CI, followed by central nervous system (CNS) neoplasms and lymphomas[3].

Regarding dentomaxillofacial complications resulting from antineoplastic treatment, although this review did not allow grouping the sample by age ranges, the literature indicates that patients under 4 years old have a higher risk of dental anomalies. An increase in the rate of agenesis and microdontia has been reported in this age group[17]. Other studies indicate that receiving treatment before the age of 3 increases the risk of agenesis, while the likelihood of microdontia increases if chemotherapy (CT) is administered before 3.5 years of age[18,19]. The teeth most affected by agenesis and microdontia are the premolars and the second permanent molars[20], as their formation begins between 18 months and 3 years[21]. In contrast, in children without cancer, the tooth with the highest prevalence of microdontia is the permanent upper lateral incisor[22].

Exposure to cytotoxic agents during antineoplastic treatment can disrupt the formation and mineralization of enamel and dentin, causing dental development alterations such as enamel hypoplasia, microdontia, agenesis, and root malformations[8]. These findings are consistent with the results of this review, where 95% of the children in the study group presented dental anomalies: 26.1% root malformations, 24.8% enamel hypoplasia, 24.6% microdontia, and 17.8% agenesis. In 15 articles, chemotherapy was the treatment with the greatest impact on dental alterations, reporting 300 cases of enamel hypoplasia, 254 of microdontia, 231 of root malformations, and 154 of agenesis. The severity of these alterations depends on various factors, such as the patient's age, the dose, and the type of drug used, with methotrexate, cisplatin, and cyclophosphamide being most associated with complications[23-26].

On the other hand, the effects of radiotherapy (RT) were reported in 11 patients with root malformations, 10 with enamel hypoplasia, 5 with microdontia, and 4 with agenesis. Its severity varies depending on the dose, the patient's age, and the stage of dental development. Owosho et al. indicate that ameloblasts can be damaged with a dose of 10 Gy and that dental development stops at 30 Gy[27]. In addition, doses above 20 Gy in the head and neck increase the risk of dental alterations by 4 to 10 times[28].

Although most of the included studies considered only patients treated with chemotherapy (since it is the most common treatment due to the high prevalence of hematological neoplasms in childhood), the evidence indicates that radiotherapy has a greater impact on oral health when applied to the head and neck, directly affecting oral tissues. This is particularly relevant in CNS tumors[29], which represent the second most prevalent diagnosis in Chile.

Dental alterations have a significant impact on the quality of life and orofacial health of children and adolescents, not only in aesthetic terms, which can generate insecurities[30,31], but also in chewing function, with digestive and nutritional repercussions. In addition, they can affect speech, increase the risk of cavities, and compromise occlusion and craniofacial development[32-35]. Early detection of these alterations is fundamental for the intervention of the dental team, contributing to improving the quality of life of these patients.

Conclusion

Antineoplastic therapies in children and adolescents with cancer significantly increase the risk of developmental dental anomalies. Given their impact on oral and maxillofacial health, the integration of dentists into interdisciplinary oncology teams is essential before, during, and after treatment to ensure early diagnosis, prevention, and comprehensive management.

Abbreviations

CC: Childhood cancer

CNS: Central nervous system

CT: Chemotherapy

RT: Radiotherapy

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Recibido 14/04/25
Aceptado 01/11/25
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