

Long term oral and dental effects in adolescents who were treated for cancer in childhood

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Abstract

Background: Survival following childhood cancer has increased considerably. We examined associations of specific types of cancer therapy with the presence of oral and dental abnormalities among childhood cancer survivors. **Procedure:** 131 children who were diagnosed with malignancies during childhood were referred to full oro-dental exams. Permanent teeth were examined clinically and radiographically to identify dental caries and anomalies in dental developmental: hypocalcification or hypoplasia, microdontia, root changes and absent tooth bud categorized hypodontia. **Results:** Dental developmental anomalies were observed in 56 (46%) of 121 children, in 309 teeth (9%). Hypocalcification or hypoplasia of enamel appeared in 21 (17%) patients. The mean decayed, missing and filled teeth (DMFT) score was 6.69 (SD 6.19). Altered root development appeared in 26 patients and hypodontia affected 13 (10%). Dental anomalies were observed in 36 (43%) individuals who received chemotherapy and not radiation, in 20 (52.63%) who received radiotherapy, and in 15 (60%) of those who received head & neck radiotherapy. Young age (under 6 years) was associated with a higher number of malformed teeth among patients who received only chemotherapy. Various chemotherapy agents associated similarly with dental anomalies and also with DMFT. **Conclusions:** Antineoplastic treatment that combines chemotherapy and radiotherapy appears to increase the risk of developing serious dental anomalies. Radiation to the head and neck area particularly increases the risk of dental developmental anomaly. No specific chemotherapy agent was found to be associated more than the others with dental side effects.

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Abbreviations key

BMT	Bone marrow transplantation
DMFT	Decayed, missing, and filled teeth
SD	Standard deviation
TBI	Total Body Irradiation

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INTRODUCTION

Current multimodality therapies have improved the survival of patients with childhood cancer. Consequently, research nowadays focuses on the long-term quality of life of these survivors¹⁻³, and on the increased risk for a variety of health problems resulting from their childhood cancer or its treatment. Some complications of childhood cancer only become apparent later in life⁴⁻⁶. Long-term systemic complications can affect children's general growth and development, and impair their reproductive, respiratory, cardiovascular, skeletal, nervous and endocrine systems^{2,7,8}. Some oral manifestations may present shortly after inception of cytotoxic and radiation treatment, and some may only become apparent years or even decades after treatment⁵. Acute oral effects include: mucositis, bleeding, taste alterations, secondary infections, salivary gland dysfunction, periodontal conditions and neurotoxicity^{2,9,10}. Late oral phenomena include: exacerbated dental caries, temporomandibular dysfunction, osteoradionecrosis, cranio-dental development, dental anomalies and oral graft versus host disease^{2,9-16}. Children are particularly vulnerable to the harmful effects of radiotherapy and chemotherapy. A new field in oncology, '*Survivorship care*', focuses on the identification, treatment and prevention of long-term side effects.

Morphogenesis and calcification of teeth begin in utero and continue for 14–15 years; the process is ongoing and complex¹⁷. Permanent incisors and first permanent molars begin to mineralize around the time of birth

but mineralization of permanent dentition is often not completed until the end of the second decade¹⁸⁻²⁰. Metabolic disturbances that arise during tooth formation may cause ameloblasts and odontoblasts to lay abnormal tissue that is eventually incorporated into the permanent tooth structure; the consequent disturbances become visible at tooth eruption. The continuation of severe or long-term upsets may damage root formation, thus leading to a shortened or tapered root. Root development plays a dominant role in the eruption; disturbance to a tooth root might impair tooth eruption and occlusion^{14,17}. The first sign of dental disturbances can be expected within one or two years of anticancer treatment¹⁴. Reported abnormalities include: hypodontia / agenesis (missing teeth), microdontia (the formation of small teeth), damage to root development (premature closure of the apex, tapering roots with apical constriction, root stunting, and V-shaped degenerated root), hypoplasia and hypocalcification (including damage to the enamel structure, resulting in incomplete calcification), over-retention of primary teeth, impaction, premature eruption, malocclusion, decreased temporomandibular joint mobility, trismus and facial deformities^{2,6,14,15,23,24,26,29-38}.

The purpose of the present study was to examine associations of specific types of cancer therapy with the presence of oral and dental abnormalities among childhood cancer survivors, treated at Hadassah Medical Center, Jerusalem, Israel.

METHODS

Patients

The study population consisted of patients who had been diagnosed with malignancies during their childhood at the Department of Pediatric Hematology–Oncology, Hadassah Hebrew-University Medical Center, Jerusalem, Israel, and who underwent annual general examinations at the survivorship care clinic during 2017 -2019. All the participants were referred to the Department of Pediatric Dentistry for a full oro-dental examination. Eligibility criteria required that children were under age 18 years at the time of anticancer treatment and at least 7 years old on the day of their dental examinations. Of the 131 survivors evaluated, 121 met the inclusion criteria. The demographic data recorded included the age at diagnosis, the age at the dental examination, gender and ethnic origin. Medical history information comprised: primary diagnosis, other medical conditions, the type of therapy or therapies applied (chemotherapy, radiotherapy, surgical excision, bone marrow transplantation (BMT)), systemic late complications, the chemotherapy agents used, the dates of chemotherapy sessions and complications after chemotherapy.

Using a dental mirror and explorer, permanent teeth were examined for dental caries and dental developmental anomalies under the artificial light of the dental unit. The radiographic dental examination included a set of 2 bitewings and a panoramic x-ray if indicated. The DMFT index scoring system was used to permit the calculation of caries: Decayed (D), Missing (M), Filled (F) per teeth (T) according to World Health Organization criteria⁴⁰. The presence of dental developmental anomalies was classified into five major groups: no disturbance identified; hypocalcification or hypoplasia, which indicated developmental anomaly of enamel mineralization; microdontia, which indicated a change in tooth size; root changes; and absent tooth bud categorized as hypodontia.

Ethical Considerations

The study protocol was approved by the Institutional Human Subjects Ethics Committee of Hadassah Medical Organization, Jerusalem, Israel (0004-16-HMO).

Statistics

The data were analyzed using statistical software (Stata version 12.1, StataCorp). Descriptive statistics, including numbers and percentages of patients were tabulated for demographic and clinical characteristics. Chi-squared and Fisher's exact tests were utilized to test associations between the categorical variables and treatment groups. The t-test was utilized to examine associations between the continuous variables (DMFT) and treatment groups. The data were stratified by three age groups (< 6, >6 and < 12 years, and >12 years) and by gender. For this analysis, a p-value less than 0.05 was considered statistically significant.

RESULTS

Table 1 presents demographic characteristics of the children, the types of cancer and types of treatment. The underlying diseases were leukemia\ lymphoma in 53 (45%) patients, solid tumors in 35 (29%) and hematological conditions leading to BMT in 31 (29%). Most children (83, 69%) had received chemotherapy without radiotherapy. Thirty-eight patients received radiation therapy only or in combination with chemotherapy. Of these, 14 (12%) had received total body irradiation (TBI) and 15 (12.5%) radiation to the head and/or neck area. The remaining 9 patients had received radiotherapy to other areas. Thirty percent of the cohort had undergone BMT.

Table 2 presents the numbers of children and the numbers of teeth with each dental anomaly. In total, 56 (46%) patients had at least one dental developmental anomaly, in 309 teeth (9%). Hypocalcification or hypoplasia of enamel presented in 21 (17%) patients (Figure 1A); and the same number of microdontic teeth presented (Figure 1B). Altered root development presented in 26 (21%) patients (Figure 1C₁) and hypodontia in 13 (11%) (Figure 1C₂). Table 3 presents dental anomalies according to anticancer treatment modalities. Malformed teeth were detected in 36/83 (43%) patients who had received only chemotherapy, 20/38 (53%) of those who had received radiation, 15/36 (42%) of those who underwent BMT, and 9/15 (60%) of those who had received head & neck radiotherapy group. The age at initiation of oncology treatment ranged from 0 to 18 years. The proportion of children with malformed teeth was higher among those who initiated treatment at age 6 years or younger (31/55, 56%) than among those who initiated treatment between ages 6 and 12 years (19/43, 44%) (Table 4). In addition, all the types of dental developmental anomalies were more frequent in children who initiated anticancer treatment at age 6 years and younger (Table 4) .

Table 5 describes dental developmental anomalies according to eight groups of chemotherapy agents, classified according to their mechanisms of action. Most of the patients (N=46, 38%) had received a combination of three agents. The maximum combination treatment was composed of six agents. Eighty-eight patients had received alkylating agents. The number of malformed teeth and the types of malformation did not differ significantly according to chemotherapy agent. The mean DMFT in all 121 children was 6.69 (standard deviation [SD] 6.19) (Figure 1D). The 'D' component was the highest, 4.4 (SD 4.38); next was 'M', 0.51 (SD 2.40), and then 'F', 1.84 (SD 3.17). Mean DMFT values differed according to treatment: 5.93, 8.37, 6.85 and 7.93 for children who were treated with chemotherapy only, radiation of any type, BMT and head/neck radiation, respectively (Table 3). Compared to patients who had received only chemotherapy, among those who had received any radiation, the DMFT was higher (P-value=0.0219), as was the total number of malformed teeth (P-value=0.0508). Statistically significant differences were not found in the mean DMFT according to chemotherapy agents (Table 5). For most of the parameters examined, statistically significant differences were not found between males and females (Table 6). Two statistically significant differences regarding gender were observed: tooth malformation microdontia was more common among females (P-value=0.037) and decayed teeth were more common among males (P-value=0.025).

DISCUSSION

In our cohort of children who had received anticancer therapies, 46% had at least one malformed tooth; and 13% had more than five malformed teeth. Defects in enamel development and alterations in tooth size were equally distributed among the patients (17%). Future dental aberrations may be predicted to some extent by understanding them within the context of the developmental stage of tooth mineralization in which they occurred³⁸. In the current study, 62 teeth of 21 patients (17%) displayed some form of hypocalcification and hypoplasia. Several studies indicated higher rates of this dental alteration than observed in our cohort^{14,15,22, 42}. Twenty-one patients (17.4%) in the current study displayed microdontia in contrast to 0.8%-1.7%³⁸ in healthy populations. Microdontia causes esthetic, functional and occlusal complications, which require professional dental treatment later in life. Alterations of tooth root was the most frequent malformation found in the current study (21%) compared to 86.4% and even 100% in the literature^{34,48}. This compares with a range of 1.3%-5.6% in healthy populations³⁴. As tooth development is a relatively slow process, up to two years may be necessary before anomalies become evident on radiographs. Intensive, repetitive chemotherapy at the time of initial hard tissue formation may cause tooth agenesis^{27,38}, which is

the most severe impairment in dental development. Agenesis affects dental arches, and impairs tooth symmetry, esthetics and function. Hypodontia was seen in 11% of our patients, which compares with 2.8%-10% in healthy populations⁴⁹.

Associations of various anticancer therapies with the development of dental anomalies

Thirty-one percent of our patients who were treated with chemotherapy also received radiation. More than half the patients (53%) who received radiation displayed malformed teeth, a higher percent than among those who received only chemotherapy (43%). This difference concurs with a previous study⁴⁸. It is generally agreed that odontogenic cells in the pre-formative and differentiation phases are more radiosensitive than cells in the secretory or mature stage. If exposure to irradiation occurs before calcification, the tooth bud may be destroyed. Radiation at a later stage of development may arrest further growth and result in irregularities in enamel and dentin, together with shortened roots^{25,35,47}. Chemotherapy appears to cause less acute damage as a monotherapy, than when combined with cranial irradiation or total body irradiation²⁴. Notably, among our 15 patients who had received head or neck radiation, the prevalence of dental anomalies was higher than among patients who had received chemotherapy alone, or total body irradiation. This finding concurs with other studies^{6,26}.

Associations of chemotherapy agents with developing dental anomalies

Many pediatric cancers are treated with a combination of multi-agent chemotherapy to create synergistic and additive effects. In the current study, 46 patients (38%) had received a combination of three chemotherapy agents; the maximum combination treatment comprised six agents. Multiple agents make it difficult to attribute specific defects in odontogenesis to any single agent or therapy^{22,30}, and the odontogenic toxicities induced by individual chemotherapy agents remain obscure³¹. Individual differences may also present between patients; the same treatment may result in a variable number of teeth affected and in differences in severity of lesions between individuals²⁵. The cohort size of the current study was small for evaluating the effects of individual chemotherapeutic agents on dental developmental defects. We suggest that more studies will investigate associations of chemotherapy agents, according to their mechanisms of action, with dental anomalies.

Associations of age and gender with developing dental anomalies

Malformed teeth of all the types examined presented more frequently among children who received anticancer treatment at age 6 years or younger than among older children. Young age also remained a significant factor for the total number of malformed teeth among patients who received chemotherapy only (P-value=0.001). Several publications suggest that children diagnosed with cancer between ages 3 and 5.5 years exhibited the most severe developmental dental anomalies^{19,25,27,34,38}. This is because in this age interval, root formation is at an initial stage for all permanent teeth except the second and third molars²⁵. Treatment administered during the first 3.5 years of life was more likely to affect the dental lamina and crown formation, and to result in a small tooth¹⁸. Anticancer therapy administered after age 5 years may still disturb root growth, especially in late developing premolars and permanent second molars. However, by this age, the roots in the early developing teeth have already reached a moderate length, which improves the final result.³⁴ In several studies, the most extensive dental developmental anomalies (agenesis, microdontia and root anomalies) were reported in children who were treated before ages 5–6 years^{2,6,15,25,26,38,42}, due to the proliferation of dental stem cells during this period^{2,3,31,44}.

Only minor differences were found between boys and girls in the current study. Two significant differences regarding gender were noticed: microdontia was higher amongst females (P-value=0.037) and decayed teeth were more prevalent amongst males (P-value=0.025).

Dental Caries- DMFT

The mean DMFT score for the study group was 6.69. This score is much higher than 1.66, which was reported for healthy 12-year-old children in Israel⁴⁵. In the present study, the 'DT' component was the

highest. Our findings concur with other reports of higher incidence of caries in children who received anti-neoplastic therapy^{27,31,37,46}. For our patients who received radiotherapy, the DMFT was even higher, 8.37; this compared to a score of 5.93 among children who received only chemotherapy. Aggressive and extensive caries, commonly known as radiation caries (such as seen in figure 1D), have a rapid onset and progression³⁵. Radiation caries are not caused directly by irradiation but result from the sequelae of xerostomia and a cariogenic shift in microflora. Ultimately, the carious process causes increased friability and the breakdown of teeth²³.

Our study has several limitations that should be considered when interpreting the results. First, differences between the patients in age, time lapsed from diagnosis and from treatment, and the presentation of other chronic health conditions could create bias in the results. Second, family history, hygiene patterns, and socioeconomic status play crucial roles in dental health, and can affect many variables and especially DMFT score.

In conclusion, treatment of childhood cancer is a success story of modern medicine, in which effective treatments have been identified for previously untreatable diseases. The growing population of child survivors of cancer, as well as young adult survivors, will require considerable attention from the medical and dental community in the decades to come. The work of pediatric dentists and oncologists is not done when cancer cells are gone, for the subsequent years may present challenges that may be recognized only in a later context. Radiation and chemotherapy are independent risk factors for adverse oral-dental sequelae among childhood cancer survivors. Mitigating the effects should be a goal when possible; and if not possible, the effects should be understood so that future treatment can account for such. The results of this study may help direct physicians to identify childhood cancer survivors at high risk of having tooth developmental anomalies. This highlights the importance of dental care for children who received oncology treatment at a young age (0-6 years), particularly if combined with radiotherapy, and especially in the head or the neck region. Data from our study and previous ones support restrictions of high caloric food and sweets by children with cancer. Dentists should play a significant role in the team that manages childhood cancer and long-term follow-up.

Conflict of interest: The authors have nothing to declare.

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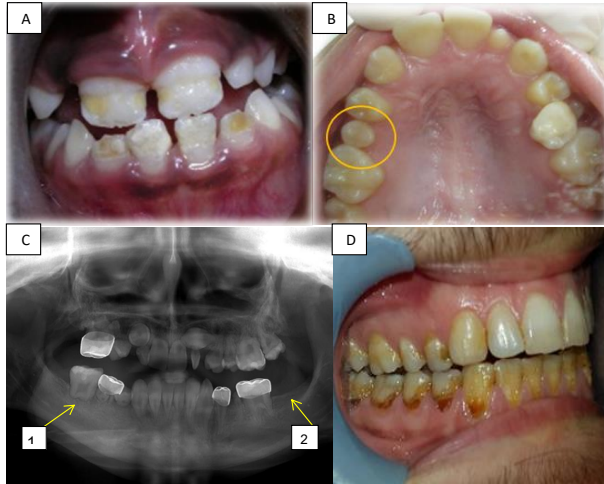


Figure 1: Long term dental effects. A. Hypoplasia in front upper and lower teeth in a girl age 9 yr. old treated for ALL at age 3.5 years old. B. Microdontia. Second upper right premolar. C. Panoramic radiograph of a 12-year-old boy diagnosed with Burkitt's lymphoma at 4 years of age, revealing: C₁. Altered root development at the first lower right molar, C₂. Hypodontia of the second lower left molar. D. Radiation caries in 21-year-old boy.