Long Term Dental Effects in Adolescents Who were Treated for Cancer in Childhood

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Research Article

Keywords: children, cancer survivors, developmental anomalies, hypocalcification, microdontia, hypodontia, chemotherapy, radiotherapy, dental caries.

DOI: https://doi.org/10.21203/rs.3.rs-707204/v1

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Abstract

Objectives: Survival following childhood cancer has increased considerably. We examined associations of cancer therapy with the presence of Dental Developmental Anomalies (DDA) among childhood cancer survivors.

Procedure: 131 children who were diagnosed with malignancies during childhood were included. Permanent teeth were examined clinically and radiographically to identify DDA: hypocalcification or hypoplasia, microdontia, root changes and hypodontia.

Results: observed in 56 (46%) of 121 children, in 309 teeth (9%). Hypocalcification or hypoplasia of enamel appeared in 21 (17%) patients. 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.

Conclusions: Antineoplastic treatment that combines chemotherapy and radiotherapy appears to increase the risk of developing DDA. Radiation to the head and neck area particularly increases the risk of DDA. No specific chemotherapy agent was found to be associated more than the others with dental side effects.

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 survivors\textsuperscript{1,2}, 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 life\textsuperscript{3,4}. Long-term systemic complications can affect children’s general growth and development, and impair their reproductive, respiratory, cardiovascular, skeletal, nervous and endocrine systems\textsuperscript{5,6}. Some oral manifestations may present shortly after inception of cytotoxic and radiation treatment, and some may only become apparent years or even decades after treatment\textsuperscript{3}. Acute oral effects include: mucositis, bleeding, taste alterations, secondary infections, salivary gland dysfunction, periodontal conditions and neurotoxicity\textsuperscript{5,6}. Late oral phenomena include: exacerbated dental caries, temporomandibular dysfunction, osteoradionecrosis, cranio-dental development, dental anomalies and oral graft versus host disease\textsuperscript{7,6-10}. 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 complex. 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 decade\textsuperscript{10,11}. 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\textsuperscript{9}. The first sign of dental disturbances can be expected within one or two years of anticancer treatment\textsuperscript{3}. Reported abnormalities include: hypodontia / agenesis (missing teeth), microdontia (the formation of small teeth), 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\textsuperscript{10–20}.

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 criteria. 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). All the methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from the parents or legal guardians of all the participants.

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 1
Patient characteristics

| Variable                              | # of patients (%) |
|---------------------------------------|-------------------|
| Gender                                |                   |
| Male                                  | 76 (63%)          |
| Female                                | 45 (37%)          |
| Ethnicity                             |                   |
| Arab                                  | 75 (62%)          |
| Jewish                                | 45 (37%)          |
| Other                                 | 1 (1%)            |
| Diagnosis Category (1)                |                   |
| Acute lymphocytic leukemia (ALL)      | 27 (22%)          |
| Acute myelocytic leukemia (AML)       | 10 (8%)           |
| Non-Hodgkin lymphoma (NHL)            | 9 (7%)            |
| Hodgkin lymphoma (HL)                 | 7 (6%)            |
| Sarcoma                               | 17 (14%)          |
| Neuroblastoma                         | 14 (12%)          |
| Other solid tumors                    | 4 (3%)            |
| Hematological condition               | 31 (26%)          |
| Other                                 | 2 (2%)            |
| Diagnosis Category (2)                |                   |
| Leukemia and lymphoma                 | 53 (45%)          |
| Solid tumor                           | 35 (29%)          |
| Hematological                         | 31 (26%)          |
| Treatment                             |                   |
| Chemotherapy only                     | 83 (69%)          |
| Any radiotherapy (chemotherapy and radiation therapy or radiation therapy only) | 38 (31%) |
| Radiotherapy                          |                   |
| None                                  | 83 (69%)          |
| Total body irradiation (TBI)          | 14 (12%)          |
| Head/neck                             | 15 (13%)          |
| Other                                 | 9 (7%)            |
| Surgical treatment                    |                   |
| No                                    | 102 (84%)         |
| Yes                                   | 19 (16%)          |
| Bone Mineral Transplantation          |                   |
| No                                    | 85 (70%)          |
| Yes                                   | 36 (30%)          |

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 (Fig. 1A); and the same number of microdontic teeth presented (Fig. 1B). Altered root development presented in 26 (21%) patients (Fig. 1C1) and hypodontia in 13 (11%) (Fig. 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,
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 2
The number of children who presented with each dental developmental anomaly, and the number of teeth involved

| Type of malformation                      | #children | #teeth       |
|------------------------------------------|-----------|--------------|
| N = 121                                   | N = 3388  |              |
| None                                     | 65 (54%)  | 3079 (91%)   |
| Hypocalcification or hypoplasia           | 21 (17%)  | 62           |
| Microdontia                              | 21 (17%)  | 57           |
| Root changes                             | 26 (21%)  | 160          |
| Hypodontia                               | 13 (11%)  | 30           |
| Any malformation                         | 56 (46%)  | 309 (9%)     |

### Table 3
Dental anomalies according to anticancer treatment modalities

| Chemotherapy only | Any radiation | BMT | Head/Neck Radiation |
|-------------------|---------------|-----|---------------------|
| N = 83            | N = 38        | N = 36 | N = 15              |
| Categorical Variables | #(%)) | #(%)) | #(%)) | #(%)) |
| Any malformed teeth | 36 (43%) | 20 (53%) | 15 (42%) | 9 (60%) |

The number of malformed teeth

|          | Chemotherapy only | Any radiation | BMT | Head/Neck Radiation |
|----------|-------------------|---------------|-----|---------------------|
| 0        | 47 (57%)          | 18 (47%)      | 21 (58%) | 6 (40%) |
| 1        | 7 (8%)            | 5 (13%)       | 4 (11%) | 2 (13%) |
| 2        | 7 (8%)            | 3 (8%)        | 0     | 2 (13%) |
| 3        | 8 (10%)           | 2 (5%)        | 5 (14%) | 1 (7%)  |
| 4        | 8 (10%)           | 0             | 3 (8%) | 0       |
| ≥ 5      | 6 (7%)            | 10 (26%)      | 3 (8%) | 4 (27%) |

The type of malformation (≥ 1 tooth with malformation)

| Type of malformation | Chemotherapy only | Any radiation | BMT | Head/Neck Radiation |
|----------------------|-------------------|---------------|-----|---------------------|
|                      | N = 83            | N = 38        | N = 36 | N = 15 |
| Hypocalcification or Hypoplasia | 11 (13%) | 10 (26.32%) | 5 (13.89%) | 5 (33.33%) |
| Microdontia          | 16 (19%)          | 5 (13%)       | 7 (19%) | 3 (20%) |
| Root changes         | 15 (18%)          | 11 (29%)      | 5 (14%) | 4 (27%) |
| Hypodontia           | 9 (11%)           | 4 (11%)       | 4 (11%) | 2 (13%) |
| DMFT                 | 5.93 (5.73)       | 8.37 (6.88)   | 6.67 (6.85) | 7.93 (5.46) |

BMT, bone mineral transplantation; DMFT, decayed, missing, and filled teeth
Table 4
Dental anomalies in children who received anticancer therapies, according to the age of initiation of treatment

| Type of Malformation                                      | ≤ 6 years N = 55 | > 6 ≤ 12 years N = 43 | P-Value | *Chi-squared test utilized |
|----------------------------------------------------------|------------------|-----------------------|---------|---------------------------|
| Total number of children with any malformation           | 31 (56%)         | 19 (44%)              | 0.231   |                           |
| Hypocalcification or hypoplasia N (%)                    | 8 (15%)          | 10 (23%)              | 0.269   |                           |
| Microdontia N (%)                                        | 18 (33%)         | 3 (7%)                | 0.002*  |                           |
| Root changes N (%)                                       | 15 (27%)         | 9 (21%)               | 0.469   |                           |
| Hypodontia N (%)                                         | 11 (20%)         | 1 (2%)                | 0.007*  |                           |
| Total number of malformed teeth                          | 4.15 (6.85)      | 1.67 (3.82)           | 0.013*  |                           |
| Mean (SD)                                                |                  |                       |         |                           |
| DMFT (SD)                                                | 6.07 (6.49)      | 6.02 (4.70)           | 0.483**** |                     |

DMFT, decayed, missing, and filled teeth; SD, standard deviation

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. Ninety-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) (Fig. 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. 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).
Associations of chemotherapy agents with developing dental anomalies

Patients who had received chemotherapy alone, or total body irradiation. This finding concurs with other studies. Damage from chemotherapy seems to be greater when the treatment is combined with cranial irradiation or total body irradiation, rather than administered as monotherapy. 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 study. Thirty-one percent of our patients who received chemotherapy were treated with radiation in addition. 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 study. This finding concurs with other studies.

**Table 5**

| Chemical Agent |
|----------------|
| N = 25 ATG    |
| N = 98 Alkylating Agent |
| N = 53 DNA Crosslinking Agents |
| N = 43 Antimetabolite 2 Inhibitors |
| N = 67 Topoisomerase Inhibitors |
| N = 36 Hormonal Agents |
| N = 67 Tubulin Inhibitors |
| N = 41 Miscellaneous |

| Drugs                                      | Any malformed teeth #(%): | Hypocalcification or Hypoplasia # (%): | Microdontia #(%): | Root change (%): | Hypodontia #(%): | DMFT Mean (SD): | Total number of malformed teeth Mean (SD): |
|--------------------------------------------|---------------------------|--------------------------------------|------------------|-----------------|-----------------|----------------|------------------------------------------|
| Anti-thymocyte globulin                    | 11 (44%)                  | 3 (12%)                              | 4 (16%)          | 4 (16%)         | 4 (16%)         | 6.12 (6.37)   | 2.4 (5.73)                                  |
| Busulfan                                  | 44 (45%)                  | 16 (16%)                             | 17 (17%)         | 21 (21%)        | 11 (11%)        | 6.31 (6.23)   | 2.55 (5.43)                                  |
| Melphalan                                 | 23 (53%)                  | 11 (26%)                             | 8 (19%)          | 9 (21%)         | 11 (11%)        | 7 (5.99)      | 3.42 (6.96)                                  |
| Treosulfan                                | 25 (47%)                  | 8 (15%)                              | 11 (21%)         | 11 (21%)        | 6 (14%)         | 6.53 (6.88)   | 2.17 (4.09)                                  |
| Cyclophosphamide                          | 32 (48%)                  | 12 (18%)                             | 14 (21%)         | 16 (24%)        | 3 (6%)          | 5.85 (5.69)   | 2.37 (4.50)                                  |
| Dacarbazine                               | 19 (53%)                  | 5 (14%)                              | 9 (25%)          | 11 (31%)        | 7 (10%)         | 6.94 (6.01)   | 2.31 (3.21)                                  |
| Temozolomide                              | 32 (47.76%)               | 13 (19.40%)                          | 14 (20.90%)      | 17 (25.37%)     | 2 (6%)          | 6.99 (6.27)   | 2.99 (5.58)                                  |
| Thiotepa                                  | 19 (46.34%)               | 5 (12.20%)                           | 8 (19.51%)       | 10 (24.39%)     | 2 (4.88%)       | 6.54 (6.87)   | 2.61 (5.09)                                  |

**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 occurred. 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. Twenty-one patients (17.4%) in the current study displayed microdontia in contrast to 0.8%-1.7% in healthy populations. 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.

**Associations of various anticancer therapies with the development of dental anomalies**

Thirty-one percent of our patients who received chemotherapy were treated with radiation in addition. 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 study. Acute damage from chemotherapy seems to be greater when the treatment is combined with cranial irradiation or total body irradiation, rather than administered as a monotherapy. 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.
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, and the odontogenic toxicities induced by individual chemotherapy agents remain obscure. 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 individuals. 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. This is because in this age interval, root formation is at an initial stage for all permanent teeth except the second and third molars. 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 tooth. 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. 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, due to the proliferation of dental stem cells during this period.

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 Israel. 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 antineoplastic therapy. 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 Fig. 1D), have a rapid onset and progression. 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 teeth.

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.

**Abbreviations**

| Abbreviation | Definition                     |
|--------------|--------------------------------|
| BMT          | Bone marrow transplantation    |
| DDA          | Dental Development Anomalies  |
| DMFT         | Decayed, missing, and filled teeth |
| SD           | Standard deviation             |
| TBI          | Total Body Irradiation         |

**Declarations**

**Conflict of interest statement**

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.
Acknowledgments

The authors thank the Department of Pediatric Dentistry, the Hebrew University – Hadassah School of Dental Medicine and the Department of Pediatric Hematology - Oncology Hadassah Hebrew University Medical Center, Jerusalem, Israel. The funding agencies have no role in the submitted work.

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**Figures**

**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, reveling: 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.