Long-term effect of anticancer therapy on dentition of Italian children in remission from malignant disease: A cross-sectional study

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Abstract

Aim To investigate the effects of anticancer therapy on dental development and caries formation in Italian childhood cancer survivors compared to healthy controls.

Methods A total of 52 children treated with chemotherapy and/or radiotherapy when younger than 10 years and in remission from at least 2 years, and 52 healthy age- and gender-matched children were consecutively enrolled in this cross-sectional study. All participants were examined for dental caries and enamel defects according to the decayed-missing-filled teeth (dmft/DMFT) index and the Aine rating scale. Panoramic radiographs were taken to estimate dental age and to assess dental abnormalities using the Höltta Defect Index.

Results Compared to healthy controls, children in remission from malignant diseases showed increased prevalence of dental abnormalities and enamel defects in the permanent dentition, more teeth with active carious lesions and higher dental age ($p < 0.05$). The almost totality of dental agenesis and microdontia were detected in patients treated with stem cell transplantation when younger than 5 years of age, while no difference between radiotherapy and chemotherapy was observed.

Conclusion These children are at high risk for tooth developmental abnormalities and poor dental health and should be closely monitored by a specialist dentist.

KEYWORDS Anomalies; Adverse effects; Caries, dental; Malignancies.

Introduction

Oral and dental alterations occur as a consequence of a wide spectrum of inherited and acquired conditions and may severely influence the masticatory performance and well being of vulnerable children. Thus, preventive strategies and early dental treatment should target this high-risk population [Ferrazzano et al., 2019; Rodríguez Peinado et al., 2018; Sneha et al., 2022]. Within vulnerable children, the number of childhood cancer survivors (CCS) has been increasing over the past years thanks to more effective antineoplastic treatment regimens. As a consequence, more attention has been focused on the late oral effects of treatment protocols [Siegel et al., 2021]. Dental alterations are quite common side effects of cancer therapy and seriously affect the quality of life; nonetheless dental care remains a neglected area of paediatric cancer care [Seremidi et al., 2019].

Dental development is a complex process influenced by genetic signals and controlled by a network of activators and inhibitors [Bei, 2009]. Radiation therapy (RT) and chemotherapy (CT) can interfere with the physiological dental development [Goho, 1993]. RT causes lethal damage not only to neoplastic but also to normal cells by releasing X photons, gamma rays and beta particles, which can damage directly or indirectly DNA and amino acids [Bushberg, 1994]. Cell vulnerability is strictly related to the cell-cycle phase, with cells being most radiosensitive in the G2-M phase [Pawlik and Keyomarsi, 2004]. The impact of RT on dental development depends not only on the total radiation dose given to the patient, but also on the daily radiation fraction size [Kaste et al., 2009]. Therefore, while high radiation dose can lead to the complete destruction of dental follicles resulting in single or multiple missing teeth, low dose does not affect mature cells, but their more vulnerable precursors [Le Masney et al., 1990]. Immature odontoblasts change their shape from columnar to cuboidal and produce osteodentin in place of normal dentin. Due to its lower content in phosphorylated phosphoproteins, essential for the secretion of hydroxyapatite, osteodentin impairs the enamel mineralisation process predisposing to enamel hypoplasia and abnormal root development [Linde, 1989].

CT exerts a toxic, selective action on cell mitosis by interfering with DNA synthesis and replication, RNA transcription and cytoplasm transport mechanism [Goho, 1993]. The damage involves any cell in active proliferation, not only cancer cells. Altered root development and enamel and dentin defects are frequently documented [Çetiner et al., 2019; Gawade et al., 2014; Seremidi et al., 2019]. People treated with CT generally exhibit localised dental anomalies due to the short half-life of the cytotoxic agent [Glick, 1979]. As the chronology of tooth development is well known, it is easy to follow the timetable of dental disturbances [Burgueño Torres et al., 2015]. Primary incisors tend to erupt at six months of life, and primary dentition is completed at around three years of age. Permanent teeth start to form between the 20th week of embryonic life and the 10th month of life. Thus, children under 5 years of age

have most of the permanent teeth in the early developing stage, therefore they are the most severely damaged by these therapies [Kang et al., 2018].

Considering the sparse comprehensive reports in Italy [Bagattoni et al., 2014; Uderzo et al., 1997], the aims of this observational study were to investigate the long-term effects of cancer therapy on enamel mineralisation, dental development and caries formation in a population of Italian survivors of childhood malignancies, highlighting the relationship between age at cancer therapy and dental anomalies, and to compare the findings with those in healthy children.

Materials and methods

All patients included in the present cross-sectional study were consecutively selected among those referred to the Section of Paediatric Dentistry, University of Turin from the Paediatric Onco-Hematology and Stem Cell Transplant Division of the Regina Margherita Children Hospital of Turin for routine dental care between March 2019 and January 2020. The Institutional Ethics Committee of the "AOU Città della Salute e della Scienza", of Turin (Italy) approved the research protocol (No. 0038521) and written informed consent was obtained from participants or their parents or legal guardians. The study was performed according to the ethical principles of the Helsinki Declaration and reported according to the STROBE guidelines.

Participants and data collection

All children treated for malignancy before the age of 10 years and in remission from the disease for at least 2 years (time required for the assessment of alterations, as indicated in the guidelines of the Children's Oncology Group) were invited to participate. Exclusion criteria were any concurrent medical condition and/or any past or current orthodontic treatment. Healthy controls matched for age and gender to CCS subjects were identified from the dental hospital database and were recruited when attending for routine dental care.

Data on age, gender, socioeconomic background, malignant diagnosis, age at the time of cancer therapy, treatment regimen – CT and/or RT, Hematopoietic Stem Cell Transplantation (HSCT) or Bone Marrow Transplantation (BMT) –, and date of inclusion in the off-therapy list were collected using a questionnaire. With regard to dental history, data on previous trauma, orthodontic, endodontic, restorative or surgical treatments were also recorded.

A specialist in paediatric dentistry performed the dental examinations of both groups of children. Diagnosis of carious lesions was based on the criteria established by the World Health Organization. Each patient was given a score resulting from the sum of the decayed, missing (for extraction or trauma) and filled teeth in either primary (dmft index) or permanent dentition (DMFT index). Disturbances of enamel mineralisation were examined on incisal edges, buccal, palatal, cuspal and occlusal surfaces of permanent teeth and recorded using the Aine rating scale, where grade I defines qualitative defects (opacities and discolorations), grades II, III and IV represent quantitative defects (hypoplasia) of increasing severity [Aine et al., 1990].

Dental abnormalities were diagnosed on panoramic radiographs (OPG) using the Höltta Defect Index (DeI), representing the overall degree of tooth alterations in the permanent dentition [Höltta et al., 2002]. All children of both groups, except for 3 cases who did not have OPG, were evaluated according to reliable and repeatable criteria: number of tooth agenesis, microdontia and abnormalities in root/crown (R/C) ratio. Crown (C) heights and root (R) lengths were measured using the method described by Lind [1972]. Root length assessment included the longest root in multi-rooted teeth, and the longest buccal root in mandibular molars and premolars. Each tooth, excluding third molars, was categorised according to the criteria listed in Table 1. Finally, the DeI score was calculated as follows: (nD1 × 1) + (nD2 × 2) + (nD3 × 3) + (nD4 × 4) + (nD5 × 5) with n being the number of the affected teeth in each category.

Dental age was assessed using the Demirjian's method that converts the dental maturity score into the corresponding dental age according to a pre-defined conversion table [Demirjian, Goldstein, Tanner, 1973].

In order to evaluate the impact of cancer therapy on dental development and to compare data with those previously reported in the literature, CCS individuals were divided into different subgroups according to gender, age at time of cancer diagnosis (≤ 5 or > 5 years), and type of cancer therapy (CT and/or RT, HSCT).

Measurement reproducibility

Each OPG was examined blindly by the senior member of the Department of Paediatric Dentistry (reference examiner) and by the same clinician who recorded duplicate measures with an interval of three weeks between the first and the second examination. The intra- and inter-examiner agreement

Dental disturbances	Description
ND	Not Determined A. Developing tooth with no final outcome B. Missing tooth not categorised as aplastic because of the age of the patient C. Not clearly visible on radiograph
D0	R/C ratio > 1.6; no disturbance
D1	R/C ratio 1.2-1.6; mild alteration
D2	R/C ratio 0.9-1.1; severe alteration
D3	R/C ratio < 0.9; very severe disturbance or arrested tooth development
D4	Microdontia: tooth visually less than 50% of its expected size
D5	Aplasia, missing tooth

TABLE 1 Dental disturbances classification according to Höltta's Defect Index.

Diagnosis	Number of patients (%)
Acute Lymphoblastic Leukemia	29 (55.8%)
Acute Myeloblastic Leukemia	4 (7.7%)
Medulloblastoma	3 (5.8%)
Familiar Hemophagocitic Lymphohistiocitosis	3 (5.8%)
Lymphoma	2 (38%)
Juvenile Myelomonocytic Leukemia	2 (3.8%)
Wilms tumour	1 (1.9%)
Epatoblastoma	1 (1.9%)
Rhabdomyosarcoma	1 (1.9%)
Ewing-PNET Sarcoma	1 (1.9%)
Severe Aplastic Anaemia	1 (1.9%)
Xantoastocitoma	1 (1.9%)
Wide Cells Anaplastic Lymphoma	1(1.9%)
Histiocytosis	1(1.9%)

TABLE 2 The diagnosis of the cancer patients.

Variables	D1	D2	D3	D4	D5
Patients (n= 104)					
CCS subjects (n=52)	3.57±4.26**	0.74±2.17**	0.19±0.50**	1.91±3.16**	0.94±1.75***
Controls (n=52)	0.85 ±2.16	0.00	0.00	0.00	0.29±0.71
CCS subjects (n=52)					
Gender					
Males (n=31)	3.89±4.73	0.74±1.77	0.22±0.58	1.30±2.35	0.63±1.71
Females (n=21)	3.15±3.62	0.75±2.67	0.15±0.37	2.75±3.92	1.35±1.76*
Age at cancer therapy					
≤ 5 years (n=37)	2.94±4.16	0.97±2.56	0.24±0.56	2.64±3.53**	1.30±1.98*
> 5 years (n=15)	5.07±4.27*	0.21±0.43	0.07±0.27	0.21±0.58	0.07±0.27
Cancer therapy					
CT (n=36)	2.56±3.07	0.34±1.12	0.13±0.42	1.53±2.58	0.81±1.49
CT + RT (n=16)	5.73±5.61*	1.60±3.40	0.33±0.62	2.73±4.13	1.20±2.24
Transplantation (n=19)	4.05±4.81	1.45±3.04*	0.36±0.66*	3.59±3.94***	1.82±2.24***
No transplantation (n=5)	3.16±3.77	0.12±0.33	0.04±0.20	0.44±0.87	0.16±0.37

*Note: Values with superscript asterisks show statistically significant difference between groups: *p <0.05; **p <0.01; ***p <0.001*
Abbreviation: D1= mild alteration; D2= severe alteration; D3= very severe alteration; D4= microdontia; D5= agenesis; CCS= childhood cancers survivors.

TABLE 3 Dental development defects according to the Defect Index in the study groups (mean ± standard deviation).

was excellent (Cohen's Kappa coefficient 0.89 and 0.85, respectively). Examiner calibration for caries status was conducted in 20 subjects with clinical conditions similar to the study subjects. The kappa scores for intra- and inter-examiner agreement were 0.93 and 0.88, respectively.

Statistical analysis

Difference in DeI scores between CCS children and healthy controls was set as the primary outcome of the study. According to a previous investigation [Bagattoni et al., 2014], a sample size of 52 individuals per group was calculated to detect a minimum difference of 10 in DeI values between the groups with an expected standard deviation of 18, an alpha error of 0.05 and a power of 0.80. Data were filled in Microsoft Excel. They were entered twice on separate occasions, then compared, and corrected for any discrepancy before data analysis began. Any inconsistency was highlighted and checked with the original data sheets. This was done blindly with regard to any results. The details were then added to the main data sheet according to the subject number. Data from the first assessment of OPG were used for the statistical analysis.

Values of quantitative variables were expressed as mean ± standard deviation, while values of categorical variables were presented as frequencies.

The Shapiro-Wilk test and Q-Q normality plots were applied to verify the normal distribution of quantitative variables. The statistical significance of differences between the study groups (males versus females, cases versus controls, treatment at/before versus after 5 years of age, transplantation versus no transplantation, CT versus CT + RT) was evaluated using the independent t-test (for variables with Gaussian distribution) and the Mann-Whitney U-test (for variables without a Gaussian distribution). Associations between qualitative variables were analysed with the chi-square test. The significance level was set at 5% ($p < 0.05$) and statistical analysis was carried using the Statistical Package for the Social Sciences (SPSS), version 24.0 software (SPSS Inc., Chicago, IL, USA).

Results

Fifty-two (31 males and 21 females) CCS subjects, aged from 4 to 22 years at the time of dental examination (mean age 10.6 ± 3.8 years), and 52 age- and gender-matched healthy controls (32 males and 20 females, mean age 11.5 ± 4.5 years) were included in this study.

As reported in Table 2, all CCS children had been diagnosed with different malignancies between the age of 0 month and 9 years (mean age 3.8 ± 2.6 years) and 37 of them (71.2%) were younger than 5 years at the time of cancer diagnosis.

Thirty-six (69.2%) of 52 CCS subjects were treated with CT and 16 (30.8%) with a combination of CT and RT. Twenty-four cancer children (46.2%) were submitted to a transplantation, 19 subjects to HSCT and 5 to BMT. No differences were detected between the groups in socioeconomic characteristics (p=0.557).

Dental developmental abnormalities

Disturbances in dental development were diagnosed examining 1,365 permanent teeth in the CCS group and 1,456 in the control group on OPGs. As reported in Table 3, there were statistically significant differences in number and frequency of root malformations, microdontia, and agenesis between CCS and control subjects ($p < 0.01$). Thirty-one patients from the CCS group (59.6%) and 6 healthy controls (11.5%) displayed mild (D1) and severe alterations (D2-D3) in root development and R/C ratio. Statistically significant higher number and frequency of R/C alterations were also detected in patients treated with CT and RT compared to those submitted to CT alone, in patients treated before 5 years of age and in transplant patients.

Microdontia (D4) was absent in healthy controls, while 90 (6.6%) teeth with microdontia were observed in 19 CCS subjects, and most of the affected teeth were first (27.8%) and second premolars (23.3%) and second molar (27.8%). The almost totality of teeth with microdontia (87/90) were detected in patients who had undergone cancer therapy before the age of 5 years (17/19 subjects) (p=p=0.012). Also transplant

Variables	AINE 1	AINE 2	AINE 3	AINE 4
Patients (n= 104)				
CCS subjects (n=52)	3.36±5.31***	0.64±1.48***	0.56±1.47***	0.27±0.86***
Controls (n=52)	0.19±0.71	0.04±0.29	0.00	0.00
CCS subjects (n=52)				
Gender				
Males (n=31)	2.58±3.16	0.88±1.73	0.77±1.86	0.38±1.10
Females (n=21)	4.42±7.27	0.32±1.00	0.26±0.56	0.11±0.31
Age at cancer therapy				
≤ 5 years (n=37)	3.03±5.80	0.47±1.36	0.67±1.71	0.33±1.03
> 5 years (n=15)	4.00±4.26	1.00±1.69	0.33±0.82	0.13±0.35
Cancer therapy				
CT (n=36)	2.50±3.19	0.50±1.36	0.43±1.55	0.30±1.02
CT + RT (n=16)	5.07±7.92	0.93±1.71	0.80±1.32	0.20±0.41
Transplantation (n=19)	4.10±6.70	0.67±1.59	0.48±1.03	0.29±0.90
No transplantation (n=5)	1.04±2.52	0.24±0.89	0.21±1.07	0.08±0.50

TABLE 4 Disturbances of enamel mineralisation according to the Aine classification in the study groups (mean ± standard deviation).

*Note: Values with superscript asterisks show statistically significant difference between groups: *p< 0.05; **p=0.01; ***p <0.001 Abbreviation: CCS= childhood cancers survivors.*

patients showed a higher percentage of microdontia (12.9%) compared to non-transplant patients (1.5%) (p <0.001).

The mean number of missing teeth (D5) per patient was higher in CCS subjects compared to controls. Forty-four teeth were identified in 16 patients compared to 10 teeth in 5 controls (p <0.001). Among survivors of paediatric cancers, agenesis was more frequent in the female group (p=0.04), in patients submitted to oncological treatment before the age of 5 years (p=0.01) or to transplantation (p <0.001). Agenesis affected a total of 44 teeth, 43 were detected in 15 patients who had undergone treatment before 5 years of age and 40 in 12 transplant patients. The second premolar (38%) and second molar (25%) were the teeth most frequently involved.

Consistent with previous data, the overall mean value of DeI was higher in cancer patients (19.7 ± 21.07) compared to controls (2.26 ± 4.01), in patients submitted to treatment before 5 years of age (25.97 ± 22.88) compared to those treated after 5 years of age (6.71 ± 6.15) and in transplant (31.73 ± 23.32) versus non-transplant patients (7.10 ± 5.9) (all p < 0.001).

Enamel defects

A total amount of 773 permanent teeth were examined in the CCS group and 920 in the control group. Enamel hypoplasia affected 28.1% (217/773) of the teeth in the CSS group (Aine grade I: 19.5%; grade II: 3.7%; grade III: 3.2%; grade IV: 1.5%), while no alteration was detected in the remaining 71.9% (556/773). As described in Table 4, cancer patients showed more enamel defects, irrespective of the degree, compared to controls (all p <0.001). No statistically significant association was found with gender, age at cancer therapy and type of treatment.

Dental age

The difference between the mean chronological age and the mean dental age in the CCS group (-0.72 ± 1.6 years) was larger than that observed in the control group (0.03 ± 0.8 years) and reached statistical significance (p=0.01).

Dmft/DMFT indexes

As described in Table 5, CCS subjects showed significantly higher mean dmft score in comparison to controls (p=0.037), with the number of decayed primary teeth contributing most to the overall score (p=0.029). There was no significant change in caries experience related to gender, age at cancer therapy and type of treatment in the CCS group.

With regard to the prevalence of dental caries in the permanent dentition, CCS patients showed significantly higher DMFT scores compared to healthy controls (Table 6), in particular they presented a higher number of missing (p=0.040) and filled teeth (p=0.031). A significant difference was also found when comparing males and females in the CCS group, with lower mean DMTF values among females (p=0.045).

The mean DMFT scores were also higher among survivors treated when older than 5 years of age (p=0.030), mainly for decayed (p=0.022) and missing components (p <0.001).

Variables	dmft	d	m	f
Patients (n= 104)				
CCS subjects (n=52)	4.15±3.25*	2.52±2.86*	0.58±1.3	1.06±1,73
Controls (n=52)	2.59 ± 3.04	1.19 ± 2.06	0.22±0.55	1.28±2.19
CCS subjects (n=52)				
Gender				
Males (n=31)	3.83±3.56	2.63±3.84	0.54±1.32	0.67±1.17
Females (n=21)	6.07±5.27	4.07±5.20	0.40±1.06	1.60±2.23
Age at cancer therapy				
≤ 5 years (n=37)	4.87±4.82	3.39±4.75	0.26±0.82	1.23±1.82
> 5 years (n=15)	4.00±1.85	2.38±2.77	1.38±2.00	0.25±0.71
Cancer therapy				
Chemotherapy (n=36)	4.57±4.23	2.93±4.14	0.60±1.35	1.03±1.71
Chemotherapy and radiotherapy (n=16)	5.11±5.06	4.00±5.41	0.11±0.33	1.00±1,73
Transplantation (n=19)	4.00±3.73	2.53±3.17	0.26±0.56	1.21±2.10
No transplantation (n=5)	5.35±4.91	3.80±5.34	0.70±1.59	0.85±1.23

TABLE 5 Dental caries in primary teeth according to the dmft index in the study groups (mean ± standard deviation).

*Note: Values with superscript asterisks show statistically significant difference between groups: *p<0.05; **p <0.01; ***p <0.001 Abbreviation: dmft= decayed missing filled primary teeth; d=decayed primary teeth; m= missing primary teeth for extraction; f= filled primary teeth; CCS= childhood cancers survivors.*

Variables	DMFT	D	M	F
Patients (n= 104)				
CCS subjects (n=52)	1.70±2.21* * *	0.85±1.48	0.09±0.38*	0.85±1.54*
Controls (n=52)	1.09±1.79	0.49±1.27	0.00	0.60±1.21
CCS subjects (n=52)				
Gender				
Males (n=31)	3.46±3.89*	1.42±2.37	0.15±0.46	2.00±3.01
Females (n=21)	1.75±2.92	0.40±0.94	0.10±0.45	1.25±2.47
Age at cancer therapy				
≤ 5 years (n=37)	1.90±3.25	0.52±1.12	0.00	1.48±3.00
> 5 years (n=15)	4.40±3.72*	1.93±2.82*	0.40±0.74***	2.07±2.31
Cancer therapy				
Chemotherapy (n=36)	2.58±3.16	1.03±2.14	0.13±0.43	1.42±2.20
Chemotherapy and radiotherapy (n=16)	3.00±4.41	0.87±1.51	0.13±0.52	2.20±3.75
Transplantation (n=19)	1.52±3.30	0.29±0.72	0.10±0.44	1.29±2.99
No transplantation (n=5)	3.72±3.54***	1.56±2.42***	0.16±0.47	2.00±2.61

TABLE 6 Dental caries in permanent teeth according to the DMFT index in the study groups (mean ± standard deviation).

*Note: Values with superscript asterisks show statistically significant difference between groups: *p<0.05; **p <0.01; ***p <0.001*
Abbreviation: DMFT= decayed missing filled permanent teeth; D=decayed permanent teeth; M= missing permanent teeth for extraction; F= filled permanent teeth; CCS= childhood cancers survivors

Also non-transplant patients had significantly higher mean DMFT scores compared to transplant patients. Decayed teeth contributed the most to the DMFT score (p <0.001).

Discussion

CT and RT are aggressive cancer treatments affecting the whole body and are even more detrimental to growing patients. We assessed dental development and caries status in 52 paediatric patients in long-term remission from childhood malignancies and compared them to healthy children matched according to age and gender. In line with other published data [Steiner et al., 2018; Gawade et al., 2014; Kaste et al., 2009], the present study showed that CCS children who received CT, alone or in combination with RT, had a statistically higher prevalence of root development abnormalities compared to healthy controls (56% vs 11.5%). Similar results were found when considering microdontia, affecting 36.5% of the cancer survivors and none of the healthy patients, and tooth agenesis, affecting 30.8% of the oncological patients compared to 9.6% of the controls [Stolze et al., 2021]. It is worth noting that, in agreement with previous studies [Quispe et al., 2019; Van der Pasvan Voskuilen et al., 2009], the severity and extension of dental abnormalities were strongly influenced by younger age at cancer therapy, as most permanent teeth are in the development stage below 5 years of age, and by transplant treatment, because of more aggressive antineoplastic protocols. The most affected teeth were first and second premolars and second molars. These findings further confirm the detrimental effect of RT and CT on cells in the earliest stages of odontogenesis and/or rhizogenesis (proliferation and duplication) with consequent change in enamel and dentin structure [Linde, 1989; Kaste et al., 1994]. In the CCS group, females were more frequently diagnosed with tooth agenesis than males (4.8% vs 2.1%).

All permanent teeth can be affected by root growth impairment in terms of R/C ratio alterations and/or early closure of the apex. We compared the chronological age to the dental age estimated using the Demirijan technique, which has been shown to be a feasible method to study CCS subjects using OPGs [Flores et al., 2015]. We found that oncological patients had a more advanced dental age (almost 1 year more) than age-matched healthy controls, confirming the irreversible deleterious effects of cancer treatment on permanent teeth [Bagattoni et al., 2014; Çetiner et al., 2018; Pajari, 1995]. It is known that the changes that occur over time in dental tissues are indicative of the biological development of each individual [Pereira et al., 2019]. Thus, the shortening of dental roots and the premature apexification might explain the dental maturity observed in the CCS group.

The prevalence of enamel defects was statistically higher in cancer patients compared to controls, as already described in literature [Avsar et al., 2007]. According to previous studies the most frequently detected lesions were white/yellow opacities, in patients treated with CT or a combination of CT and RT [Kaste et al., 1998; 2009]. This results from the impact of cytotoxic agents on ameloblasts in the first stages of dental development. Recent studies demonstrated that vinblastine, vincristine and cyclophosphamide, which were commonly administered to the patients, could affect their secretory function, membrane permeability and microtubule calcium transport mechanisms leading to hypomineralised enamel defects [Goho, 1993; Oguz et al., 2004].

Consistent with previous data [Avsar et al., 2007; Bica et al., 2017; Purdell-Lewis et al., 1998], the present study reported a higher prevalence of carious lesions in both primary and permanent dentition of long-term survivors of childhood cancer compared to healthy age- and gender-matched controls. This could be attributed to the frequent xerostomia and vomiting induced by CT and RT favouring the development of intraoral cariogenic microflora. In addition, such patients, because of the high incidence of painful mucositis and dysgeusia, usually prefer the intake of sugar and soft foods that are easier to swallow but more cariogenic. They also cannot perform effective oral hygiene procedures because of the risk of bleeding in the stages of aplasia.

It is interesting to underline how patients who had received therapy after 5 years of age exhibited higher DMFT scores (in particular D and M values) compared to children treated early in age, further suggesting a direct impact of CT and RT on permanent teeth erupting during cancer treatment.

Patients receiving both CT and RT had DMFT scores quite similar to those found in children treated with CT alone. This observation is confirmed by the study by Avsar et al. [2007] and can rely on the temporary hyposalivation induced by RT (under 26 Gys). Further studies are needed to evaluate the effect of RT on both the quality and quantity of saliva in growing patients.

In the present study non-transplant patients had a higher DMFT index compared to transplant subjects and this might be attributed to the strict dental check-ups scheduled before

and after transplantation in order to prevent infections and treatment failures. On the contrary, non-transplant patients frequently arrive to a first dental visit too late, during the course or upon the completion of cancer therapy, because of the need of a timely dental treatment.

With regard to gender as a risk factor for tooth decay, the average DMFT value in males was higher than in females and this is probably due to a lower compliance in oral hygiene procedures.It should be considered that the treatment regimen, dose level, and duration might be all implicated in the occurrence of dental malformations. In the present study differences between CT and CT combined with RT were not statistically significant, but we did not evaluate the impact of different antineoplastic protocols on dental development. However, this is a common limitation of the studies available in the literature. In addition, the study sample was a convenience sample because of the easy access to the cancer patients in this centre. This implies limitation in the generalisability for the whole population of children in remission from malignancies. Further multi-centre studies with larger number of CCS and control subjects and longer follow-up periods should be performed.

Conclusion

Late effects of cancer therapies can involve different organs, including dental tissues, with a wide spectrum of side effects and a major or minor morbidity. Children receiving oncological therapies, compared to healthy controls, showed higher prevalence of abnormalities in dental development (ranging from microdontia to short and fragile roots up to tooth agenesis), enamel defects and caries. Treatment before 5 years of age or by stem cell transplantation was associated with the highest number of teeth with microdontia or agenesis.

Dental effects may compromise function, esthetics, and quality-of-life. Thus, a first dental visit should always be carried out before starting the cancer treatment to early detect and treat carious lesions and to educate parents/caregivers in supporting children to perform correct home oral hygiene manoeuvres and to maintain a non-cariogenic diet. During and after anticancer therapy it is important to schedule a strict follow-up programme including preventive dental treatments (fissure sealants, fluoride applications, oral healthcare regimens) and x-ray examination (OPG and intraoral x-ray) to identify dental development abnormalities and caries.

Paediatric dentists, as members of the multidisciplinary team treating such patients, should be conscious about their dental needs. It is extremely important for these patients to maintain healthy periodontal conditions, because bone loss around a tooth with short roots can compromise its long-term prognosis. For the same reason, clinicians should be very cautious in performing any orthodontic treatment because of mechanical stress on such fragile teeth. The long-term maintenance of good dental and oral health will improve the quality of life of these growing patients because the effects on dentition of anticancer treatment are permanent.

Conflict of interest

The authors declare the absence of any potential conflict of interests and that they have no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

References

› Aine L, Maki M, Collin P, Keyrilainen O. Dental enamel defects in celiac disease. J Oral Pathol Med 1990;19(6):241–245.
› Avsar A, Elli M, Darka O, Pinarli GI. Long term effects of chemotherapy on caries formation, dental development and salivary factors in childhood cancer survivors. Oral Surg Oral Med Oral Pathol Oral Radiolol Endod 2007;104(6):781–789.
› Bagattoni S, D'alessandro G, Prete A, Piana G, Pession A. Oral health and dental late adverse effect in children in remission from malignant disease. A pilot case-control study in Italian children. Eur J Paediatr Dent 2014;15(1):45–50.
› Bei M. Molecular genetics of tooth development. Curr Opin Genet Dev 2009;19(5):504–510.
› Bica C, Ion V, Mártha K, Esian D, Chinceşan M, Monea, M. The evaluation of caries severity index and dental hypoplasia in children with acute lymphoblastic leukaemia. Results from a Romanian Medical Centre. J Interdiscip Med 2017;2(S1):31–35.
› Burgueño Torres L, Mourelle Martínez MR, de Nova García JM. A study on the chronology and sequence of eruption of primary teeth in Spanish children. Eur J Paediatr Dent 2015;16(4):301–304.
› Bushberg J. The essential physics of medical imaging. Baltimore, William and Wilkins, 1994.
› Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, version 4.0, 2014. https://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf
› Çetiner D, Çetiner S, Uraz A, Alpaslan GH, Alpaslan C, Toygar Memikoğlu TU, Karadeniz C. Oral and dental alterations and growth disruption following chemotherapy in long-term survivors of childhood malignancies. Support Care Cancer 2018;17(5):1891-1899.
› Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol 1973;45(2):211–227.
› Ferrazzano GF, Cantile T, Sangianantoni G, Ingenito A, Rengo S, Alcidi B, Spagnuolo G. Oral health status and Unmet Restorative Treatment Needs (UTN) in disadvantaged migrant and not migrant children in Italy. Eur J Paediatr Dent 2019;20(1):10–14. .
› Flores AP, Monti CF, Brunotto M. Dental and chronological age in children under oncological treatment. J Forensic Sci 2015;60(2):453-456.
› Gawade PL, Hudson MH, Kaste SC, Neglia GP, Constine MD, Robinson LL, Ness KK. Paediatr Blood Cancer 2014;61(3):407–416.
› Glick PL. Patterns of enamel maturation. J Dent Res 1979;58(B):883–892.
› Goho C. Chemoradiation therapy: effect on dental development. Paediatr Dent 1993;15(1):6–12.
› Holtta P, Alauusa S, Saarinen-Pihkala UM, Wolf J, Nystrom M, Hovi L. Long term adverse effects on dentition in children with poor risk neuroblastoma treated with high dose chemotherapy and autologous stem cell transplantation with or without total body irradiation. Bone Marrow Transplant 2002;29(2):121–127.
› Kang CM, Hahn SM, Kim HS, Lyu CJ, Lee JH, Lee J, Han JW. Clinical risk factors influencing dental developmental disturbances in childhood cancer survivors. Cancer Res Treat 2018;50(3):926–935.
› Kaste SC, Goodman P, Leisenring W, Stovall M, Hayashi RJ, Yeazel M, Beiraghi S, Hudson MM, Sklar CA, Robison LL, Baker KS. Impact of radiation and chemotherapy on risk of dental abnormalities: a report from the childhood cancer survivors study. Cancer 2009;115(24):5817–5827.
› Kaste SC, Hopkins KP, Bowman LC, Santana VM. Dental abnormalities in children treated for neuroblastoma. Med Paediatr Oncol 1998;30(1):22–27.
› Kaste SC, Hopkins KP, Jenkins JJ 3rd. Abnormal odontogenesis in children treated with radiation and chemotherapy: imaging findings. AJR Am J Roentgenol 1994;162(6):1407–1411.
› Le Masney NJ, Holland T, O'Brien C, O'Mullane DM. The effects of anti malignancy therapy as seen in the oral cavity of children and young adults: a review. J Ir Dent Assoc 1990;36:47–52.
› Lind V. Short root anomaly. Scand J Dent Res 1972;80(2):85–93.
› Linde A. Dentine matrix proteins: composition and possible functions in calcification. Anat Rec 1989;224(2):154–166.
› Oguz A, Vetiner S, Karadeniz C, Alpasla C, Pinarli G. Long term effect of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. Eur J Oral Sci 2004;112:8–11. https//doi.org/ 10.1111/j.0909-8836.2004.00094.x
› Pajari, U. Developmental defects of teeth in survivors of childhood ALL are related to the therapy and age at diagnosis. Med Paediatric Oncol 1995;24(5):310–314.
› Pawlik TM, Keyomarsi K. Role of cell cycle in mediating sensitivity to radiotherapy. Int J Radiation Oncology Biol Phys 2004;59(4):928–942.
› Pereira CP, Russell LM, de Pádua FM, Alves da Silva RH, Vargas de Sousa Santos RF. Dental age estimation based on development dental atlas assessment in a child/adolescent population with systemic diseases. Acta Stomatol Croat 2019;53(4):307–317.
› Purdell-Lewis DJ, Stalman MS, Leeuw JA, Humphrey GB, Kalsbeek H. Long term results of chemotherapy on developing dentition: caries risk and developmental aspects. Community Dent Oral Epidemiol 1998;16(2):68-71.
› Quispe RA, Rodrigues ACC, Buaes AMG, Capelozza ALA, Rubira CMF, da Silva Santos PS. A case-control study of dental abnormalities and dental maturity in childhood cancer survivors. Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128(5):498–507.
› Rodríguez Peinado N, Mourelle Martínez MR, Diéguez Pérez M, De Nova García MJ. A study of the dental treatment needs of special patients: cerebral paralysis and Down syndrome. Eur J Paediatr Dent 2018;19(3):233-238.
› Seremidi K, Kloukos P, Polychronopoulou A, Polychronopoulou A, Kattamis A, Kavvadia K. Late effects of chemo and radiation treatment on dental structures of childhood cancer survivors. A systematic review and meta-analysis. Head Neck 2019;41(9):3422–3433.
› Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics. CA Cancer J Clin 2021;71(1):7–33.
› Sneha K, Praveen P, Anantharaj A. An assessment of the effectiveness of oral health education on oral health-related knowledge and attitudes of caregivers of children with hearing impairment. Eur J Paediatr Dent 2022;23(1):10–14.
› Stolze J, Vlaanderen KCE, Holtbach FCED, Teepen JC, Kremer LCM, Loonen JJ, van Dulmen-den Broeder E, Heuvel-Eibrink MMVD, Pal HJHV, Versluys B, van der Heiden-van der Loo M, Louwerens M, Raber-Durlacher JE, Bresters D, Brand HS. Long-term effects of childhood cancer treatment on dentition and oral health: a dentist survey study from the DCCSS LATER 2 Study. Cancers (Basel) 2021;13:5264.
› Uderzo C, Fraschini D, Balduzzi A, Galimberti S, Arrigo C, Biagi E, Pignanelli M, Nicolini B, Rovelli A. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. Bone Marrow Transplant 1997;20(10):865–859.
› Van der Pas-van Voskuilen IGM, Veerkamp JS, Raber-Durlacher JE, Bresters D, van Wijk AJ, Barasch A, McNeal, S, Gortzak RA. Long-term adverse effects of hematopoietic stem cell transplantation on dental development in children. Support Care Cancer 2009;17(9):1169–1175.