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ORIGINAL RESEARCH

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Prevalence and association of dental anomalies and tooth decay in Italian childhood cancer survivors

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Abstract

The aim of this cross-sectional study was to assess the prevalence and severity of dental anomalies according to age at cancer treatment and type of antineoplastic protocol using the Modified Dental Defect Index (MDDI) and to explore the association between MDDI scores and caries experience in Italian childhood cancer survivors (CCS). A total of 88 CCSs (age range 6–20 years) treated with chemotherapy and/or radiotherapy for malignant diseases and in remission from at least 2 years were consecutively recruited from March 2019 to July 2022. All participants were examined for dental caries and enamel defects in the permanent dentition according to the decayed-missing-filled teeth (DMFT) index and the Aine rating scale. Dental abnormalities were diagnosed using panoramic radiographs and graded for severity according to the MDDI. The MDDI values were categorized as normal (MDDI, 0), moderately abnormal ($1 \leq$ MDDI $<$ 16), and severely abnormal (MDDI $\geq$16). None of the enrolled children had normal MDDI score. MDDI and DMFT values were higher in CCSs submitted to cancer treatment before 5 years of age, while no statistically significant association was found with anticancer protocols. A significant positive correlation emerged between DMFT and MDDI values ($p < 0.001$). CCSs with moderately abnormal disturbances had statistically significant lower DMFT scores ($p < 0.001$) than those with severe dental abnormalities. These findings suggest that children in remission from malignant diseases with MDDI values $\geq$16 have poorer dental health and should be strictly monitored by dental specialists.

Keywords

Adverse effects; Cancer survivors; Caries; Dental; Modified dental defect index; Tooth abnormalities

1. Introduction

Considerable increase in survival rate and life expectancy of childhood cancer survivors (CCS) has been seen during the last decades, owing to the enhanced effectiveness of antineoplastic treatment protocols, typically multiple-agent chemotherapy (CT), radiotherapy (RT) or their combination [1]. However, these therapeutic modalities lack specificity, resulting in immediate or delayed side effects on non-target normal tissues [2].

Dental alterations in permanent dentition are quite common side effects in cancer therapy, involving up to 90% of CSSs [3, 4]. These anomalies are irreversible and may compromise function, esthetics and quality of life; nonetheless, investigators have reported suboptimal rates of regular dental care among CCSs [5]. The type and the extent to which dental anomalies develop depend on the type of malignant disease, on the dose, duration and frequency of the anticancer therapy, as well as on the developmental stage of the tooth during oncologic treatment [4, 6]. Children treated before the age of 5 seem to be at the highest risk for severe dental disturbances as most of their permanent teeth are in the early developmental stage [7, 8].

While high RT doses cause irreversible damage to odontogenic cells resulting in arrested crown and/or root formation, low doses induce immature odontoblasts to produce osteodentin, predisposing to enamel hypoplasia and root malformation [9]. CT exerts a toxic, selective action on any cell in active proliferation interfering with DNA synthesis and replication, and RNA transcription [10]. Tooth abnormalities, including reduced root size and/or enamel and dentin defects, are generally localized due to the short half-life of the cytotoxic agent [3, 4, 11], but it should not be neglected that disturbances of enamel and dentin mineralization along with impairment of salivary gland function frequently result in early caries development [12, 13].

Recently, a simplified index, the Modified Dental Defect Index (MDDI), has been introduced to allow measurement of both tooth/root alterations and enamel mineralization defects in permanent dentition of CCSs [14]. This makes data collection more meaningful and amenable for interpretation. To date,

there is one study from Korea using the MMDI, but it does not report any data on dental decay [14].

Therefore, the aims of the present cross-sectional study were to assess the prevalence and severity of dental anomalies according to age at cancer treatment and type of antineoplastic protocol using the MDDI index, and to explore the association between MDDI scores and caries experience in Italian CCSs. The hypothesis is that age at the time of cancer treatment and anticancer therapy are associated with the frequency of dental anomalies.

2. Materials and methods

2.1 Study design and participants

The children/adolescents included in this cross-sectional study were consecutively recruited at the Section of Pediatric Dentistry, University of Turin (Italy), from March 2019 to July 2022 through an ongoing program for the assessment of late dental side effects of anticancer treatment in CCSs. All patients had been treated for cancer at the Pediatric Onco-Hematology and Stem Cell Transplant Division of the Regina Margherita Children Hospital of Turin. Eligible for this observational study were all patients aged 6 years or more on the day of the dental examination, in remission from cancer disease for at least 2 years (according to the guidelines of the Children's Oncology Group for the assessment of late side effects of antineoplastic treatment), regardless of the type of malignancy, and treated with CT and/or RT. Exclusion criteria included any concurrent syndrome and/or any past or current orthodontic treatment.

The study complied with the Declaration of Helsinki Ethical Principles and was documented according to the STROBE statement.

2.2 Data collection and diagnosis of dental decays and abnormalities

The following data were obtained retrospectively from patients' medical records: age, sex, oncologic diagnosis, date of diagnosis, age at the time of cancer therapy, type and duration of antineoplastic treatment, and date of inclusion in the off-therapy list.

One calibrated specialist in pediatric dentistry performed the intra-oral examination. All surfaces of the permanent teeth were clinically assessed for the presence of dental decay/restoration according to the criteria established by the World Health Organization (WHO). Then, each patient received a score resulting from the sum of the decayed, missing and filled teeth (DMFT index) [15]. To evaluate the disturbances of enamel mineralization on the permanent dentition the Aine rating scale was applied [16]. It classifies enamel qualitative defects (opacities and discolorations) as grade I, and enamel quantitative defects (hypoplasia) as grades II, III and IV according to the level of increasing severity [16].

Dental abnormalities (tooth agenesis, supernumerary tooth, microdontia, macrodontia, alteration in root development and in root/crown ratio) were diagnosed on ortopantomography (OPG). All OPGs were assessed under the same conditions by two calibrated clinicians (Kappa scores for intra- and inter-examiner agreement >0.9), acting independently and blindly with regards to patient's personal information, age, type of malignancy, and treatment protocol. Any observed discrepancy was discussed till agreement was achieved. Crown height and root length were assessed according to the method described by Lind [17]. For multi-rooted teeth, the longest root in mandibular molars and the longest buccal root in maxillary molars were measured. Root shortage was recognized when the root/crown length ratio was lower than 1.6 in teeth with completed root development [18]. A tooth was considered microdontic when its size was half or less than that of a comparable homologue or of a tooth of the same class [19], and hypodontia was defined when a tooth germ was missing.

Dental disturbances were scored using the MDDI developed by Kang *et al.* [14]. It is a modified version of the defect index and dental disturbances classification and severity rating scale proposed by Sonis *et al.* [20] and Holtta *et al.* [18]. MDDI combines dental development disturbances in terms of microdontia, alterations in crown calcification, crown/root length and tooth agenesis, thus representing the overall degree of tooth alterations in the permanent dentition. The total MDDI was calculated by adding the score assigned to each permanent tooth. Finally, it was categorized in each patient as normal (MDDI, 0), moderately abnormal ($1 \leq$ MDDI < 16), and severely abnormal (MDDI ≥ 16). The cut-off score (MDDI, 16) was set to the median value for CCS with an abnormal MDDI score (≥ 1) as proposed by Kang *et al.* [14].

2.3 Statistical methods

Statistical analysis was performed using IBM SPSS, version 27.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA). In order to evaluate the impact of cancer therapy on dental development, CCS were divided into different subgroups according to age at time of cancer diagnosis, therapy performed and MDDI categories.

Values of quantitative variables were expressed as mean $\pm$ standard deviation (SD), while values of categorical variables were presented as absolute and relative frequencies. The Shapiro-Wilk test was used to verify the Gaussian distribution of quantitative variables. The statistical significance of differences between the study groups (treatment at/before versus after 5 years of age, CT versus RT versus CT + RT, moderately versus severely abnormal MDDI) was evaluated using the independent *t*-test or Mann-Whitney U-test and the analysis of the variance or the Kruskall-Wallis test, as appropriate. The associations between qualitative variables were analysed with the χ^2 test or the Fisher exact test when expected counts were lower than 5. The correlation between MMDI and DMFT values was evaluated using the Spearman's correlation coefficient.

A multiple logistic regression model was built to identify factors associated with severely abnormal MDDI (dependent variable). Purposeful selection of statistically (p-value ≤ 0.2 in the univariate analyses) and clinically relevant independent variables was conducted. The association was reported using the adjusted odds ratio (OR) and 95% confidence interval (CI). $p < 0.05$ was considered statistically significant.

3. Results

3.1 Patient characteristics

Eighty-eight Caucasian CCSs (58.0% males) with a mean age of 11.4 ± 4.2 years at the time of dental examination were included in the study. All participants had been diagnosed with different malignancies (Table 1) under 10 years of age (mean age 5.1 ± 3.1 years) and 49 of them (55.7%) were younger than 5 years at the time of cancer treatment.

Forty-one CCSs (46.6%) were treated with CT, 13 (14.8%) with RT and 34 (38.6%) with a combination of both. RT was mostly used in older patients (mean age 8.4 ± 4.4 years), while CT was predominantly administered in younger children (mean age 3.8 ± 2.8 years) ($p < 0.001$). No differences were observed in the socioeconomic status of their parents/caregivers.

TABLE 1. Distribution of cancer type among patients.

Diagnosis	Number of patients (%)
Acute Lymphoblastic Leukemia	47 (53.4)
Acute Myeloblastic Leukemia	9 (10.2)
Medulloblastoma	8 (9.1)
Rhabdomyosarcoma	4 (4.5)
Wide Cells Anaplastic Lymphoma	3 (3.4)
Juvenile Myelomonocytic Leukemia	3 (3.4)
Hemophagocytic Lymphohistiocytosis	3 (3.4)
Others	11 (12.6)

Values are presented as number (percentage). Others indicate hepatoblastoma, Wilms tumor, lymphoma, histiocytosis, xantoastocitoma, aplastic anemia and astrocytoma.

3.2 Dental development disturbances

The OPGs of all patients showed at least one abnormality (Table 2); abnormal root development (72.0%) was the most prevalent, followed by microdontia (28.4%) and tooth agenesis (28.4%). Agenesis affected a total of 67 teeth, excluding third molars, with first (19.4%) and second premolars (53.7%) being the most often missed. Microdontia involved 104 teeth; most of them were first (24.4%) and/or second premolars (25.9%) and second molars (27.9%). Only two supernumerary teeth were observed in two children submitted to antineoplastic treatment when younger than 5 years, one to CT and the other one to a combination of CT and RT.

Tooth agenesis and microdontia were more frequently detected in children treated before 5 years of age (65.3% versus 7.7%, $p < 0.001$), whereas alterations in root development were more often observed in the older group (92.3% versus 63.3%, $p = 0.001$).

There was also a statistically significant association between the type of antineoplastic treatment and the tooth development disturbances. In the CT group 42.9% of patients exhibited microdontia as compared to 8.3% and 16.7% in the RT and CT + RT groups, respectively ($p = 0.012$). Abnormal root development occurred more often in children treated with RT alone or in combination with CT, with 92.3% and 85.3% of them, respectively, showing at least one alteration in root development compared to 63.4% of children treated with CT alone ($p = 0.038$). No statistically significant differences were observed for the frequency of tooth agenesis among groups.

3.3 Enamel defects

Two patients were excluded since they had no fully erupted permanent teeth at the dental visit. A total amount of 1675 permanent teeth were examined; 362 of them (21.6%) were affected by enamel hypoplasia (Aine grade I: 12.1%; grade II: 4.2%; grade III: 4.2%; grade IV: 1.2%). As described in Table 3, no statistically significant association was found with the age at cancer diagnosis and type of antineoplastic protocols.

3.4 MDDI and DMFT

None of the enrolled children had normal MDDI score. As expected, 44 out of 88 children examined showed moderately severe disturbances ($1 \leq \text{MDDI} < 16$) and 44 severe damages (MDDI ≥ 16) to the permanent teeth.

Table 4 summarizes MMDI and DMFT values according to the age at cancer therapy and the type of anticancer treatment. In the group submitted to cancer treatment before the age of 5 years, the MDDI value was 24.9 ± 19.4 and it decreased to 16.0 ± 10.6 in children treated after reaching the age of 5. The MDDI score was statistically significantly higher in the younger group ($p = 0.046$).

With regard to the treatment regimen, no statistically significant differences were observed among groups ($p = 0.658$). The mean value of MDDI was 19.9 ± 16.2 in the CT group and increased to 22.7 ± 17.5 in the group treated with the combination of CT and RT and to 20.2 ± 16.8 in the group treated only with RT.

Patients younger than 5 at the time of cancer therapy showed lower mean DMFT scores than those treated after 5 years of age (3.0 ± 2.6 versus 4.1 ± 3.3). No statistically significant differences were observed among different anticancer protocols.

A statistically significant positive correlation was found between DMFT and MDDI values (rho = 0.457, $p < 0.001$). When DMTF scores were stratified according to the MDDI categories, the group with moderately abnormal disturbances ($1 \leq \text{MDDI} < 16$) had a mean DMFT of 2.5 ± 2.4 and the group with severely abnormal disturbances (MDDI ≥ 16) showed a mean DMFT of 4.7 ± 3.2 with a statistically significant difference ($p < 0.001$).

According to the multiple logistic regression analysis (Table 5), age less than 5 years at treatment odds ratio (OR) 4.46, 95% confidence interval (CI): 1.40, 14.23; $p = 0.012$) and age at the time of dental examination (OR 1.18, 95% CI: 1.02, 1.36; $p = 0.024$) were significantly associated with the likelihood of exhibiting severe dental abnormalities and enamel defects in the permanent dentition (MDDI ≥ 16); on the other hand, no association was observed with the antineoplastic treatment regimens.

TABLE 2. Prevalence of dental development disturbances in the study groups.

Groups	D1	D2	D3	Microdontia	Tooth Agenesis
All (n = 88)	56 (63.6)	37 (42.0)	16 (18.2)	25 (28.4)	25 (28.4)
Age at cancer treatment					
<5 yr (n = 49)	23 (46.9)***	12 (24.5)***	4 (8.2)*	23 (46.9)***	23 (46.9)***
≥5 yr (n = 39)	33 (84.6)	25 (64.1)	12 (30.8)	2 (5.1)	2 (5.1)
Type of cancer therapy					
CT (n = 41)	22 (53.7)	9 (22.0)***	2 (4.9)**	18 (43.9)**	14 (34.1)
CT + RT (n = 34)	23 (67.6)	20 (58.8)	10 (29.4)	6 (17.6)	9 (26.5)
RT (n = 13)	11 (84.6)	8 (61.5)	4 (30.8)	1 (7.7)	2 (15.4)

*Values are presented as number (percentage), superscript asterisk shows statistically significant difference between groups: *p < 0.05; **p ≤ 0.01; ***p ≤ 0.001. D1, root/crown ratio from 1.6 to 1.2 indicating mild disturbance in tooth development; D2, root/crown ratio from 1.1 to 0.9 indicating severe disturbance in root development; D3, root/crown ratio <0.9 indicating very severe disturbance in root development. CT: chemotherapy; RT: radiotherapy.*

TABLE 3. Prevalence of enamel mineralization defects according to the Aine classification in the study groups.

Groups	Aine I	Aine II	Aine III	Aine IV
All (n = 86)	47 (54.7)	24 (27.9)	32 (37.2)	10 (11.6)
Age at cancer treatment				
<5 yr (n = 47)	26 (55.3)	10 (21.3)	20 (42.6)	7 (14.9)
≥5 yr (n = 39)	21 (53.8)	14 (35.9)	12 (30.8)	3 (7.7)
Type of cancer therapy				
CT (n = 40)	25 (62.5)	7 (17.5)	12 (30.0)	5 (12.5)
CT + RT (n = 33)	18 (54.5)	13 (39.4)	17 (51.5)	5 (15.2)
RT (n = 13)	4 (30.8)	4 (30.8)	3 (23.1)	0 (0.0)

Values are presented as number (percentage). CT: chemotherapy; RT: radiotherapy.

TABLE 4. Modified dental defect index (MDDI) and decayed missing filled teeth index (DMFT) according to the study groups.

Groups	MDDI	DMFT	D	M	F
All (n = 88)	21.0 ± 16.6	3.5 ± 3.0	1.6 ± 2.0	0.2 ± 0.7	1.8 ± 2.1
Age at cancer treatment					
<5 yr (n = 49)	24.9 ± 19.4*	3.0 ± 2.6	1.1 ± 1.3	0.0 ± 0.0**	1.9 ± 2.3
≥5 yr (n = 39)	16.0 ± 10.6	4.1 ± 3.3	2.1 ± 2.4	0.4 ± 1.0	1.7 ± 1.9
Type of cancer therapy					
CT (n = 41)	19.9 ± 16.2	3.3 ± 2.7	1.6 ± 2.3	0.1 ± 0.4	1.6 ± 1.6
CT + RT (n = 34)	22.7 ±17.5	3.9 ± 3.3	1.6 ± 1.8	0.3 ± 0.8	2.1 ± 2.7
RT (n = 13)	20.2 ±16.8	3.4 ± 3.5	1.5 ± 1.7	0.3 ± 1.1	1.5 ± 2.1

*Values are presented as mean ± standard deviation, superscript asterisk shows statistically significant difference between groups: *p < 0.05; **p ≤ 0.01. M, missing; D, decayed; F, filled teeth. CT: chemotherapy; RT: radiotherapy.*

TABLE 5. Multiple logistic regression analysis of potential risk indicators for severely abnormal modified dental defect index (MDDI).

Variables	Severely abnormal MDDI *vs.* Moderately abnormal MDDI		
	Odds Ratio	95% CI	*p*-value
Age at cancer treatment			
<5 yr	4.46	1.40–14.23	0.012
≥5 yr	1.00		
Age at dental examination	1.18	1.02–1.36	0.024
Anticancer treatment			
CT	0.37	0.09–1.55	0.173
CT + RT	0.88	0.22–3.52	0.186
RT	1.00		

CT: chemotherapy; RT: radiotherapy; CT + RT: their combination; 95% CI: 95% confidence interval.

4. Discussion

The present cross-sectional study confirmed the high frequency of developmental disorders observed in the permanent dentition of CCSs, with all OPGs showing at least one dental anomaly. Younger age at anticancer treatment (<5 years) was found to be the most important factors associated with dental abnormalities. This finding agrees with data previously reported in the literature [21] suggesting that, although dental development can be affected at any time before complete tooth maturation, the severity of dental disorders are strictly related to the tooth developmental stage and, therefore, to the child's age at the time of malignancy diagnosis and treatment. Consistently, microdontia and tooth agenesis were more frequently found in patients treated when younger than 5 years, as all pathogenic noxae occurring during this period affect teeth at a very early developmental stage [22]. High rate of alterations in the crown/root ratio was detected in CCSs treated after 5 years of age, after the beginning of root formation. Abnormal root development was the most common disturbance, whose severity was related to the duration of the therapy and to the time in which it was completed.

With regard to the role of the antineoplastic treatment, only few studies are available in the literature about the influence of CT on tooth development, without any concurrent RT. Holtta *et al.* [19] reported that 100% of children treated with CT showed at least one dental anomaly compared to 25% and 12.9% of healthy controls, respectively.

As CT protocols usually include a combination of two or more drugs, there is a lack of information on their individual impact on odontogenesis. Multi-agent CT, including cyclophosphamide, doxorubicin and vincristine, exert a negative impact on tooth formation in a dose-dependent pattern, related to increase in doses, treatment duration and severity of early complications such as mucositis and vomiting [23]. In animal models, alkylating agents, particularly cyclophosphamide, impair dentinogenesis as they are able to bind DNA in the S phase of mitosis, inducing early cell apoptosis, with devastating impact on the survival of primitive mesenchymal cells and pulp preodontoblasts [9, 10]. Consistently, we observed higher prevalence of microdontic teeth, mainly first and second premolars, in children submitted to CT. It is worth noting that CT was the treatment most often performed in younger children, underlying the vulnerability of developing dentition due to the proliferative activity of dental stem cells.

RT is capable of destroying cancer cells, but it also affects healthy tissue. For many organs in the head and neck region, radiation dosage constraints have been established to minimize late effects, whereas for the teeth forming tissues, there are no clear data about the dose thresholds affecting dental development [24]. Nonetheless, the present study showed that root formation was severely compromised in CCSs treated with RT. Previous studies reported that doses of 10 Gy and 30 Gy could damage mature ameloblasts and arrest dental development, respectively [25]. A recent systematic review by Milgrom *et al.* [26] emphasized the prominent role of radiation dose (>20 Gy) and age at cancer treatment in the occurrence of dental abnormalities among pediatric patients receiving head and neck RT. According to these findings, Kaste *et al.* [10] reported that exposure to radiation doses greater than 20 Gy increased by four- to ten-fold the risk of developing dental disturbances.

Many childhood cancers are treated with a combination of CT and RT to create synergic and additive effects. While this procedure reduces the toxicity of a single agent on odontoblasts and ameloblasts, it increases the number of agents able to affect them, making it more difficult to relate specific dental defects to a single agent or therapeutic protocol [9]. Although radiation exposure and alkylating agent therapy were independent risk factors for dental abnormalities, Kaste *et al.* [10] demonstrated a statistically significant additive effect only for microdontia. These findings support the results of the current study, in which the association of radio-chemotherapy treatment lead to a statistically significant increase in the prevalence of microdontia and alterations in the crown/root ratio.

For the first time the MDDI index was applied in a Caucasian population to quantify the extension and severity of dental anomalies in the permanent dentition of CCSs using a single numerical value, including both crown/root alterations and enamel anomalies [14]. As expected, the age the patients underwent cancer therapy was the main factor associated with MDDI scores, while the type of cancer protocols administered did not [23]. Guagnano *et al.* [8] showed a high prevalence of enamel defects, in addition to dental anomalies, in the permanent dentition of patients in remission from malignant pathologies.

When comparing caries experience according to MDDI values, it was not surprising to find that, as MDDI increased, DMFT score became higher: indeed, according to what reported in literature, we found a statistically significant association between age at diagnosis and prevalence of tooth decays in pediatric cancer survivors. Wilberg *et al.* [27] observed a higher number of carious lesions in the permanent dentition of CCSs aged 5 or older at the time of cancer diagnosis when compared to patients diagnosed earlier. Conversely, patients treated before the age of 5 exhibited more severe dental

defects, being immature teeth at higher risk for developmental anomalies [28].

Interestingly, we did not detect any difference in the caries experience according to the type of treatment performed, and both CT and RT resulted in an increased susceptibility to dental decay [28]. Individuals with prolonged exposure to chemotherapeutic agents during childhood are at higher risk of caries, due to secondary salivary dysfunction leading to bacterial plaque accumulation [28]. Although CT alone is already associated with a 3-fold increase in caries occurrence, it is often administered in combination with other treatments, exacerbating such risk in the pediatric population [11]. Hyposalivation, a common side effect of RT, causes changes in the spectrum of bacteria colonizing the oral cavity, favoring the growth of caries-related microorganisms [28]. Furthermore, oral solutions are commonly preferred to capsules or tablets for drug delivery in pediatric patients, but they often have a sugar base, a further risk factor for caries development [22].

In agreement with Kang *et al.* [14], we calculated the median value of MDDI to identify the threshold to discriminate CCSs with moderate and severe dental disturbances; in the present sample the score was 16, while in the Korean population it was 14 [14]. This might demonstrate a different prevalence and severity of the dental late effects of the antineoplastic treatment in the Korean and Italian populations, probably due to differences in the burden of various types of malignancies and in the treatment protocols applied. Interestingly, CSSs with MDDI score $\geq$16 had higher prevalence of carious lesions. This suggests that they require more stringent prevention programs due to their poor dental health.

Proper daily oral hygiene, fluoride applications, use of sealants, and regular dental checkups are essential to control caries development [29, 30]. Early identification of caries is essential to prevent complications. Healthcare professionals should perform a thorough oral exam at each visit and ensure regular follow-ups by the dentist. All these patients are highly recommended to visit a dentist at least every 6 months [31, 32]. In agreement with the American Academy of Pediatric Dentistry, we suggest that CCSs with MDDI score $\geq$16 should be recalled every 3 months [31]. Considering that children undergoing antineoplastic treatment under the age of 5 are more likely of exhibit dental defects, they also need more frequent recalls.

This study acknowledges some limitations that should be considered when interpreting the results. Due to the limited sample size it was not possible to evaluate the associations between dental anomalies and different malignancies and antineoplastic treatment protocols. Furthermore, we enrolled a convenience sample of CCSs attending a specialized centre in North Italy and this may limit the generalizability of the present results. Finally, the study lacks a control group even if differences between CCSs and healthy controls have been largely and consistently documented in the literature [3, 4, 8].

5. Conclusions

In the present study, children in remission from malignant diseases with an MDDI $\geq$16 show a high number of dental anomalies, which makes them more prone to dental problems in the future (caries, malocclusion, periodontal disease). Thus, they should be strictly monitored in order to intercept and early treat any dental and oral pathology strictly related to the side effects of the antineoplastic treatment.

Although dental alterations are unavoidable side effects of the antineoplastic therapy, their detrimental impact on oral health should be avoided in CCSs. Indeed, identifying healthcare needs in such children could contribute to promote specific dental treatment guidelines and to improve their psychosocial wellbeing and their oral-health related quality of life.

ABBREVIATIONS

CCS, childhood cancer survivors; CI, confidence interval; CT, chemotherapy; DMFT, decayed-missing-filled teeth index; MDDI, modified dental defect index; OPG, orthopantomography (panoramic radiograph); OR, odds ratio; RT, radiotherapy; WHO, World Health Organization.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

PD—designed the research study. NB—performed the research. FR—analyzed the data. PD, NB and FR—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Ethics Committee of the "AOU Città della Salute e della Scienza", of Turin (Italy) (No. 0038521). All parents/legal guardians of each participant consented to participate in this study, participation was voluntary.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Patrizia Defabianis is serving as one of the Editorial Board members of this journal. We declare that Patrizia Defabianis had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LCM.

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