A case-control study of dental abnormalities and dental maturity in childhood cancer survivors

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Objective. The aim of this study was to evaluate dental abnormalities and dental maturity (DM) in the permanent dentition of childhood cancer survivors (CCSs) in comparison with that of healthy individuals.

Study Design. A retrospective, case-control study, with convenience sampling, evaluated 111 panoramic radiographs (PRs) of CCSs compared with 111 PRs of healthy individuals matched for age and gender. Dental anomalies (DAs) were associated with age of cancer diagnosis and type of antineoplastic treatment. DM was assessed by using the Demirjian method.

Results. A higher prevalence of microdontia, hypodontia, and dental root anomalies were present in CCSs compared with healthy individuals ($P < .05$). CCSs were the only individuals with 10 or greater DAs compared with healthy individuals. Microdontia was the only DA associated with age of cancer diagnosis less than 71 months ($P < .05$). Impacted teeth were associated with multimodal cancer treatment ($P < .001$). DM did not present a significant statistical difference between CCSs and healthy individuals ($P > .05$).

Conclusions. CCSs had a higher prevalence of DAs without DM alteration compared with healthy individuals. Age of cancer diagnosis and type of treatment can influence the prevalence of some dental abnormalities. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:498–507)

In the pediatric population, noncommunicable diseases, such as cancer, have been increasing in the last years. For that reason, cancer has become one of the principal causes of death in children and a priority on the global agenda for child health.[1] Approximately 300,000 new cases of cancer are estimated to occur in children age 0 to 19 years around the world.[2]

Among antineoplastic treatments (ATs) for children with cancer, chemotherapy (CHT) and radiotherapy (RT) currently allow for a 5-year survival rate of 80% among children.[3] Among the childhood cancer survivors (CCSs), approximately two-thirds have at least one late effect resulting from ATs.[4]

There are differences between pediatric patients with cancer and adult patients with cancer because in children, some body systems are still in development and maturation, which can be interrupted or altered by CHT and/or RT.[5] These different body systems, such as the neurosensorial, hormonal, cardiovascular, pulmonary, skeletal, and dental systems, can present some late effects of CHT and/or RT. It has been reported that late effects can be more evident between ages 5 and 25, years after completion of ATs.[4,6]

Among dental anomalies (DAs) as late effects of CHT and/or RT, some studies have reported DAs, such as hypodontia, microdontia, dental root anomalies (DRAs), taurodontism, root dilacerations, and supernumerary teeth.[7-9] However, the studies that used panoramic radiographs (PRs) for evaluating DAs only evaluated a small subset of DAs, but not the majority of DAs that can be evaluated by using PRs of CCSs. Some of those studies did not include a control group, and also, no clear differentiation was demonstrated between DAs in the deciduous and permanent dentition stages.[10] In addition, studies on how CHT and/or RT can affect dental maturity (DM) in CCSs is scarce.[11]

The objective of this study was to evaluate DAs and DM in the permanent dentition identified on the PRs of CCSs subjected to CHT and/or RT and to compare those radiographs with the PRs of healthy patients.

MATERIALS AND METHODS

This retrospective, case-control study with convenience sampling evaluated DAs and DM by using digital PRs. The present study was approved by the Ethics and Research National Committee and followed the guidelines of the Helsinki Declaration.

Statement of Clinical Relevance

This report of a case-control study provides information about the late effects of antineoplastic treatment on tooth development in childhood cancer survivors; this information may be used to develop dental care plans that improve the quality of life in this population.

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The study group (SG) was composed of the digital PRs of CCSs. These PRs were obtained before dental treatment and were stored in the database of an institute of childhood cancer between 2011 and 2016. The inclusion criteria consisted in PRs of CCSs without an association with syndromes, regardless of the ethnicity of the patient or the type of cancer; patient age was less than 192 months at the time of cancer diagnosis, and the patients underwent CHT and/or RT. In addition, the following information of CCSs was obtained from patient records: age, sex, oncologic diagnosis, date of diagnosis, type of treatment, date of end of the AT, and date of obtaining the radiograph.

The control group (CG) was composed of the digital PRs of healthy nonsyndromic individuals, matched by age and sex with those in the SG. These PRs were obtained from a database of a dentistry school.

The radiographic evaluation was performed by 2 previously calibrated examiners (Kappa intra- and interexaminer agreement >0.8).

Dental abnormalities evaluation

To evaluate the DAs, the classification of Alvares and Tavano[12] was used (Table I).

To evaluate DRAs, we used a novel classification based on the Miho classification.[13] We modified this classification by adding a first stage designated as "V0." This classification of DRAs presents 6 types of DRAs according to the root morphology and crown/root ratio. The classification was as follows: "V0" = presence of crown with almost total or total absence of dental root formation; "V1" = proportion of crown/root smaller than 1 with a V-shape apex; "V2" = proportion of crown/root larger than 1 with a V-shape apex; a "Y" crown/root ratio less than 1, with the end portion of the fine root giving a Y-appearance; a U1 crown/root ratio less than 1 with a U-shaped apex; and a U2 crown/root ratio greater than 1 with a U-shaped apex. DRAs were evaluated only if root formation had been completed (Figure 1).

Table I. Alvares and Tavano classification of dental anomalies, identified by using panoramic radiographs

Classification of dental anomalies	*Types of dental anomalies*
Hypoplastic	
Reduction in number or incomplete development of teeth, with structural, morphologic, and/or functional alterations	• Hypodontia • Microdontia
Hyperplastic	
Increase in number of teeth or increase of tissue components, with structural, morphologic and/or functional alterations	• Supernumerary tooth • Supernumerary root • Fusion • Concrescence • Gemination • Macrodontia • Taurodontism
Heterotopic	
Eruption and/or position of the teeth outside their usual place or by the displacement and development of dental tissues, with loss of normal relation between them.	• Dilaceration • Tooth torsion • Tooth transposition • Tooth transmigration • Invaginated tooth • Impacted tooth

Dental maturity evaluation

To evaluate DM, we used the Demirjian method,[14] whereby the final values established by the author of this method were converted into dental age (DAG). To compare the DAG with the chronologic age (CAG), we created a mathematical formula of reason, which consisted of the DAG converted into months divided by the CAG in months (DAG in months/CAG in months).

To minimize potential bias, the PRs of the SG and the CG were randomized so that the groups were not identifiable. In addition, the examiners had access to all of the clinical information of both groups only after the radiographic assessment was completed.

A total of 222 PRs were evaluated, 111 in the SG and 111 in the CG. By following all of the inclusion criteria mentioned before, a total of 14 PRs of the SG were excluded from the data analysis for the following reasons: 10 PRs of CCSs belonged to individuals who did not have a history of CHT and/or RT as part of their AT; 3 PRs were of individuals who had undergone CHT for hemangioma; and 1 PR was of a patient with Job syndrome. In the CG, all 111 PRs were included. Thus, a total of 197 PRs were used for the analysis and data interpretation—that is, 97 PRs of the SG and 111 PRs of the CG. However, to increase accuracy in the methodology, some PRs of patients with a history of orthodontic treatment were excluded from evaluating some DAs. Additionally, PRs of patients with hypodontia or 1 or more missing teeth in the left lower permanent dentition (except the third molar) were excluded from DM assessment. All of the details are provided in Supplementary Table I.

Statistical analysis

The statistical software Statistica 12 was used to perform the data analysis. To choose the statistical test, the Shapiro-Wilk normality test was used. The Mann-Whitney U-test was used to compare the prevalence of DAs between the SG and the CG. To compare the number of DAs relative to the type of treatment, the Kruskal-Wallis test was used. To associate the most prevalent DAs in the SG with regard to age at diagnosis and the duration of treatment, as well as to

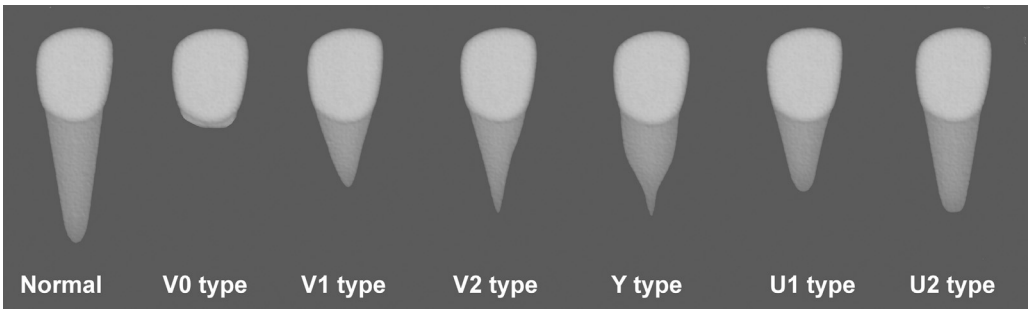

Fig. 1. Classification of dental root anomalies.

compare the DAG and the DAG and CAG between the SG and the CG, a *t* test and the Mann-Whitney U-test were performed. Finally, some data were analyzed by using descriptive statistics. All the tests were performed with a significance level of $P < .05$.

RESULTS

Among the 97 PRs of CCSs analyzed, 56 PRs (57.73%) were of females, and 41 (42.27%) were of males. The majority of CCSs (92; 94.85%) had undergone CHT, where the main chemotherapeutic agents used were vincristine (62.89%), doxorubicin (51.55%), methotrexate (57.67%), and cyclophosphamide (57.73%). A total of 30 (30.93%) CCSs had undergone RT as part of their AT; among them, 23 individuals were irradiated in the head and neck area, 5 individuals underwent total body irradiation, and 2 individuals were irradiated in other areas, such as the mediastinum and the abdomen. The last 2 PRs of these individuals were excluded from the analysis of the association between DAs and the type of treatment. The patients had received a minimum dose of 120 Gy and a maximum dose of 540 Gy (mean 330.4 Gy). Of these patients, there was no radiation dose information for 4. Other characteristics, such as distribution of the type of treatment and the type of neoplasms, are provided in Table II.

More DAs were identified in the PRs of CCSs in comparison with those of the CG ($P < .05$). Thus, DAs within the "hypoplastic" classification (microdontia and hypodontia) and the DRAs were the most prevalent DAs in the SG compared with those in the CG ($P < .05$) (Table III) and (Figures 2–5). All details of the characteristics of the CCSs with these prevalent DAs are described in Supplementary Table II. Analysis of the quantity of DAs per individual revealed that 10 or more DAs were present only on the PRs of CCSs and that this quantity was totally in contrast to the CG, where the majority had only 1 or no DA (Table IV). The distribution of DAs for the teeth affected is described in Table V.

In the SG, when the type of AT was associated with the presence of DA, impacted teeth were the only DA that showed this association ($P < .05$). From the 8 (100%) individuals with impacted teeth, 6 (75%) were undergoing CHT concomitant with RT and 2 (25%) individuals only CHT.

Analysis of the association among age at cancer diagnosis, duration of AT, and the most prevalent DAs on the PRs of CCSs (microdontia, hypodontia, and

Table II. Characteristics, distribution of type of treatment, and type of neoplasms of childhood cancer survivors

Study group characteristics	*Minimum (months)*	*Maximum (months)*	*Mean (months)*
Age at the time of taking radiographs	57	341	160.1
Age at cancer diagnosis	6	190	83.2
Time elapsed between the end of the AT and taking of radiographs	7	193	18.3
Type of treatment	n (%)		
Chemotherapy	67 (69.07)		
Radiotherapy	5 (5.15)		
Chemotherapy and radiotherapy	25 (25.78)		
Types of neoplasms	n (%)		
Acute lymphoid leukemia	39 (40.21)		
Rhabdomyosarcoma	6 (6.18)		
Wilms tumor	5 (5.15)		
Burkitt lymphoma	5 (5.15)		
Meduloblastoma	4 (4.12)		
Astrocytoma	4 (4.12)		
Hodgkin lymphoma	4 (4.12)		
Non-Hodgkin lymphoma	4 (4.12)		
Neuroblastoma	4 (4.12)		
Osteosarcoma	4 (4.12)		
Acute myeloid leukemia	3 (3.09)		
Hepatoblastoma	3 (3.09)		
Pineoblastoma	2 (2.06)		
Chronic myeloid leukemia	2 (2.06)		
Langerhans cell histiocytosis	2 (2.06)		
Lymphagiomatosis	1 (1.03)		
Anaplasic ependioma	1 (1.03)		
Craniopharyngioma	1 (1.03)		
Retinoblastoma	1 (1.03)		
Primitive neuroectodermal tumor, mediastinal	1 (1.03)		
Fibromatosis	1 (1.03)		

AT, antineoplastic treatment; *n,* number.

Table III. Comparison of dental anomalies between groups

Dental anomaly	*SG n (%)*	*SG No. of anomalies*	*CG n (%)*	*CG No. of anomalies*	*Mann Whitney U-test (P value)*
Supernumerary tooth	3 (3.09)	3	6 (5.41)	10	.932
Supernumerary root	8 (8.25)	17	8 (7.21)	16	.660
Fusion	0 (0.00)	0	0 (0.00)	0	1.0
Concrescence	0 (0.00)	0	0 (0.00)	0	1.0
Gemination	0 (0.00)	0	1 (090)	1	.368
Macrodontia	2 (2.06)	3	0 (0.00)	0	.121
Taurodontism	11 (11.34)	34	13 (11.71)	38	.989
Without anomalies	73 (75.26)	0	83 (74.77)	0	
Total	**97 (100.00)**	**57**	**111 (100.00)**	**65**	
Hypoplastic*					
Microdontia	18 (18.56)	35	1 (0.90)	6	<.001
Hypodontia	11 (11.34)	17	4 (3.60)	9	.026
Without anomalies	68 (70.10)	0	106 (95.50)	0	
Total	**97 (100.00)**	**52**	**111 (100.00)**	**17**	
Heterotopic*					
Dilaceration	40 (41.24)	88	45 (40.54)	90	.534
Invaginatus	7 (7.22)	23	8 (7.21)	20	.869
Without anomalies	50 (51.55)	0	58 (52.25)	0	
Total	**97 (100.00)**	**111**	**111 (100.00)**	**110**	
Tooth torsion	20 (24.10)	37	17 (20.73)	27	.552
Tooth transposition	0 (0.00)	0	0 (0.00)	0	1
Tooth transmigration	0 (0.00)	1	1 (1.22)	0	.322
Impacted tooth	8 (9.64)	17	3 (3.66)	4	.120
Without anomalies	55 (66.27)	0	61 (73.39)	0	
Total	**83 (100.00)**	**55**	**82 (100.00)**	**31**	
Root dental anomalies*					
With anomalies	9 (10.84)	51	2 (2.44)	3	.017
Without anomalies	74 (89.16)	0	80 (97.56)	0	
Total	**83 (100.00)**	**51**	**82 (100.00)**	**3**	

*Name of the group of the dental anomalies.
CG, control group; *SG,* study group.

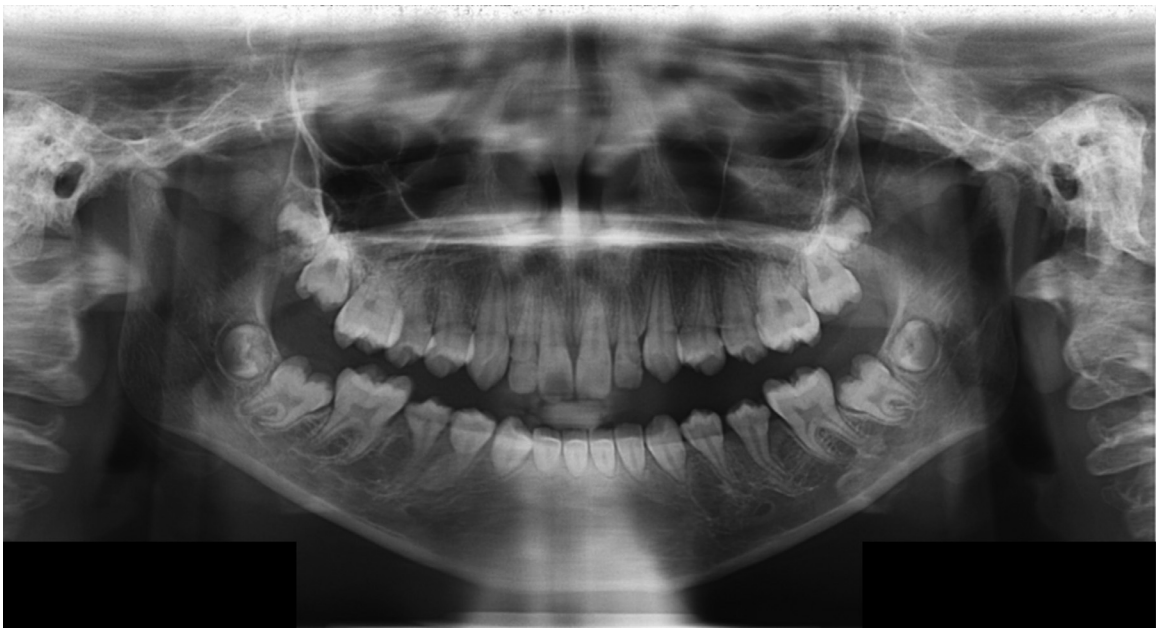

Fig. 2. Panoramic radiograph of an 11-year-old child who had been diagnosed with primitive pineoblastoma at age 43 months and submitted to chemotherapy and radiotherapy for 7 months, revealing dental root anomalies as described in the adapted Miho classification. The lower central incisors and lower right lateral incisor (V0), lower left lateral incisor (V1), lower canines, lower right first premolar (U1), lower first molars, second right lower premolar, and first lower left premolar (V2).

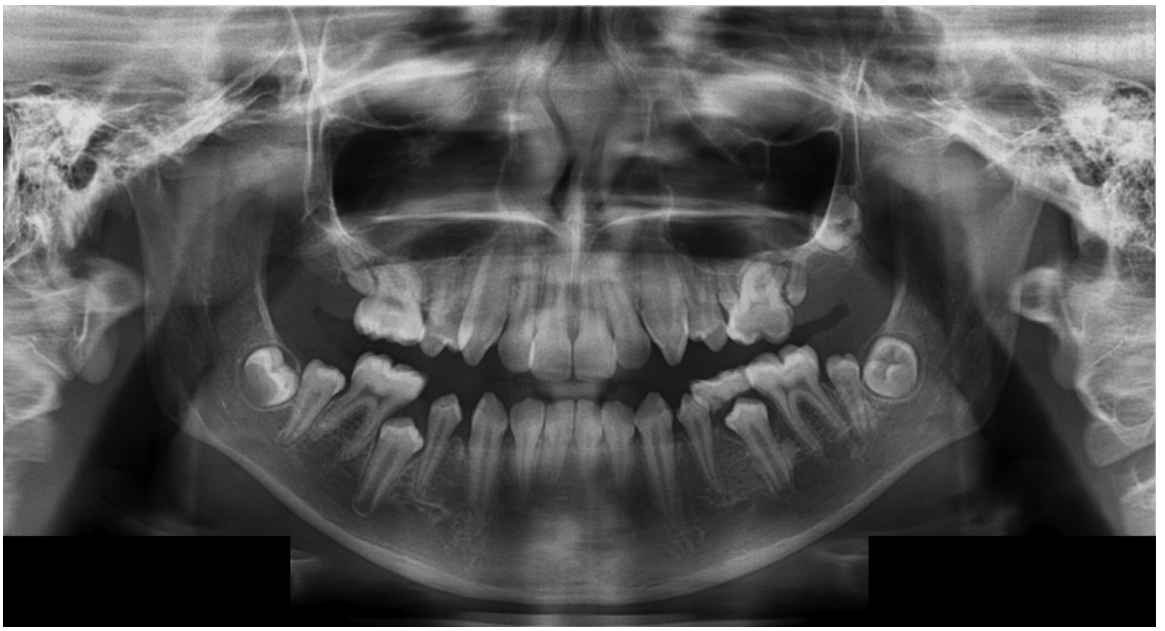

Fig. 3. Panoramic radiograph of a 13-year-old individual who had been diagnosed with a primitive neuroectodermal tumor at age 22 months and submitted to chemotherapy for 4 months, revealing microdontia of the second upper premolars and the second upper and lower molars.

DRA), microdontia was the only DA associated with age at cancer diagnosis ($P < .05$) and duration of AT did not present significant statistical difference ($P > .05$) (Table VI).

In DM evaluation, when we compared the DAG and the CAG of the SG and the CG, there was no significant statistical difference ($P > .05$) (Table VII).

DISCUSSION

AT in children with cancer occurs when they are still physically and emotionally in development and maturation.[5] The permanent dentition begins its development with the calcification of the first molar between ages 1 and 4 years,[15] and it ends with the complete mineralization of the third molar at age 18 years.[16] In

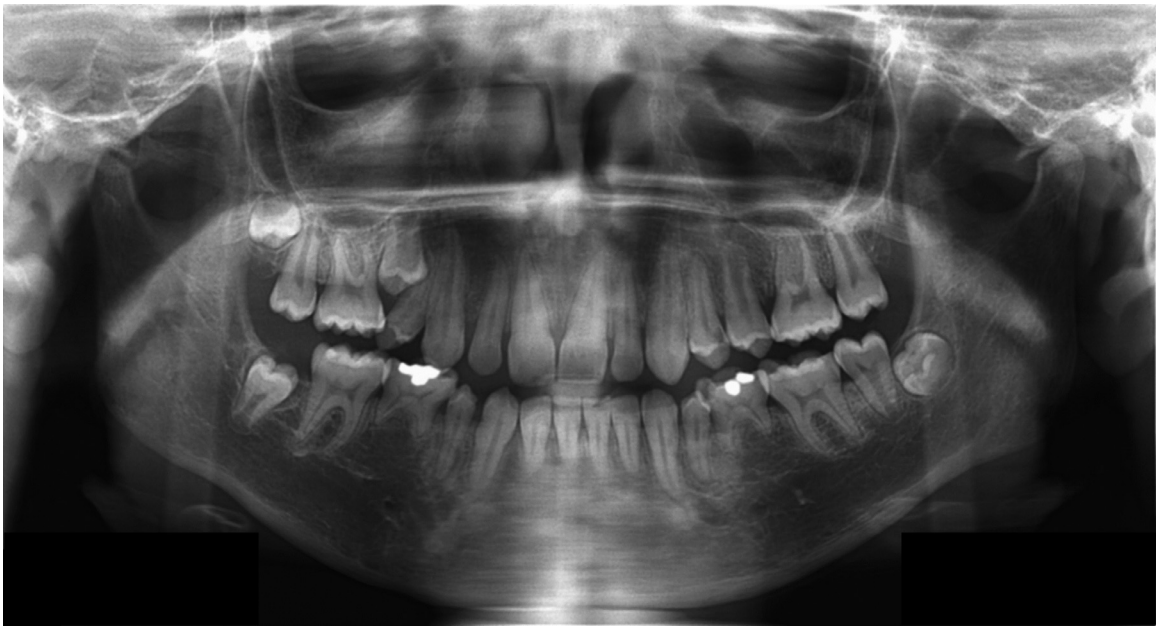

Fig. 4. Panoramic radiograph of a 15-year-old individual who had been diagnosed with rhabdomyosarcoma at age 28 months and submitted to chemotherapy for 15 months, revealing hypodontia of the second lower premolars, and microdontia of the first lower premolars.

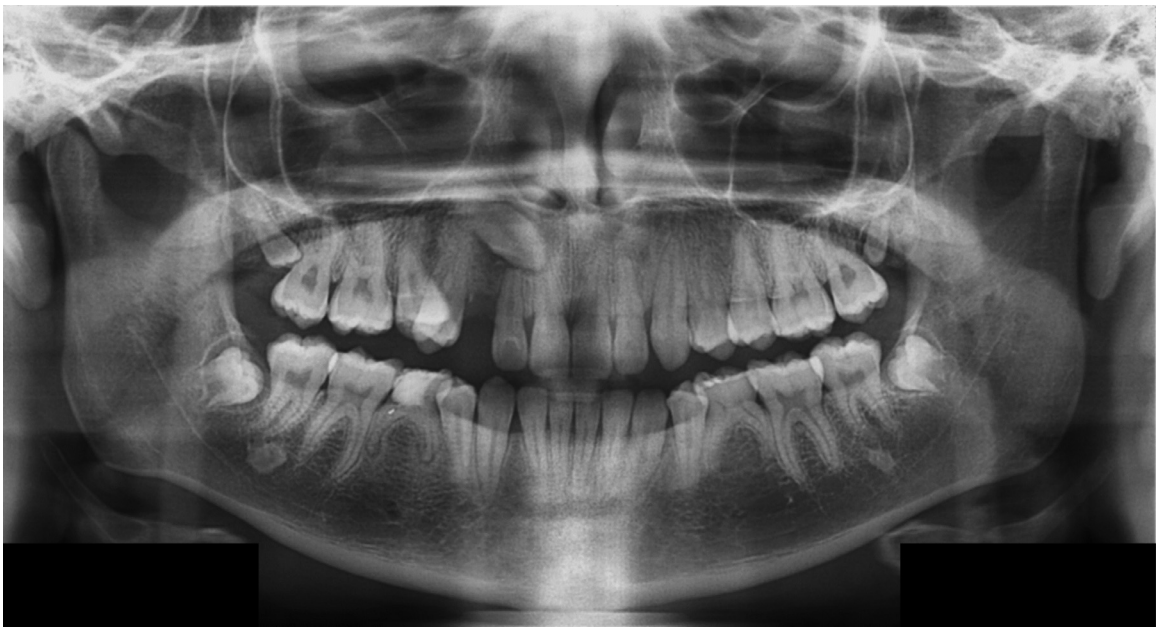

Fig. 5. Panoramic radiograph of a 17-year-old individual who had been diagnosed with non-Hodgkin lymphoma at age 28 months and submitted to chemotherapy for 7 months, revealing hypodontia of the second lower premolars, microdontia of the first lower premolars and third upper molars, and an impacted canine.

Table IV. Number of dental anomalies per individual in groups

No. of anomalies	*SG n (%)*	*Mean*	*SD*	*CG n (%)*	*Mean*	*SD*
0–1	41 (42.27)	0.3902	0.5864	61 (54.95)	0.4153	0.5559
2–5	35 (36.08)	3.3142	1.1316	41 (36.94)	3.0714	1.0908
6–9	12 (12.37)	7.2000	0.9189	9 (8.11)	7.0001	1.2472
>10	9 (9.28)	5.1000	6.8361	0 (0.00)		
Total	**97 (100.00)**			**111 (100.00)**		

CG, control group; *SD,* standard deviation; *SG,* study group.

the present study, in all the CCSs, the permanent dentition was still in the development stage when they underwent CHT and/or RT. The majority of the CCSs (88; 90.72%) were less than 163 months of age, and the remaining CCSs (9; 9.28%) were between 168 and 190 months of age.

Some studies that reported DAs, such as microdontia, hypodontia, and DRAs, used the Dahllöf method[17] and the Hölttä defect index[18]; both these methods were developed to analyze these specific DAs. In addition to these DAs, other studies have reported that CCSs may also present taurodontism, supernumerary teeth, and root dilacerations.[7,9,19] Our study evaluated DAs by using a methodology that allowed for the evaluation of 16 different types of DAs, which included not only the DAs already reported in the literature but also other DAs that had not been reported before. This was useful to show that DAs in CCSs can be present not only because of the influence of ATs but also because other factors, such as hereditary or genetic factors, that increase the final quantity of DA in each individual. Our study revealed that CCSs had a high quantity of DAs (≥10) in contrast to the majority of healthy individuals who have low quantity of DAs (≤1).

In this study, when the DAs in CCSs and healthy individuals were compared, the most prevalent DAs in CCSs were microdontia, hypodontia (hypoplastic DA), and DRAs. These results are consistent with the findings of some studies that reported these 3 DAs as being the most common in CCSs in comparison with healthy individuals.[8,20,21] This can be explained by the association between the actions of CHT and RT in the cell proliferation of odontogenesis and/or rhizogenesis. In contrast to other studies that reported taurodontism, supernumerary teeth, and root dilacerations as the late effects of ATs,[7,9,22] our study revealed similar prevalence and distribution of these DAs in both the SG and the CG.

CHT (systemic action) and RT (local action) can cause the disruption of or a decrease in cell proliferation during odontogenesis and/or rhizogenesis,[23] and when some of the stages in dental formation suffer

Table V. The dental anomalies distribution according to type of tooth

	Sup. tooth SG/CG	*Sup. root SG/CG*	*Fusion SG/CG*	*Gemination SG/CG*	*Concrescence SG/CG*	*Macrodontia SG/CG*	*Taurodontism SG/CG*
Central incisor	0/0	0/0	0/0	0/0	0/	0/0	0/0
Lateral incisor	1/3	0/0	0/0	0/1	0/0	0/0	0/0
Canine	0/1	0/0	0/0	0/0	0/0	0/0	0/0
First premolar	0/4	5/5	0/0	0/0	0/0	1/0	0/0
Second premolar	0/2	11/10	0/0	0/0	0/0	0/0	0/0
First molar	0/0	2/1	0/0	0/0	0/0	0/0	16/14
Second molar	2/0	0/0	0/0	0/0	0/0	2/0	18/24

	Dilaceration SG/CG	*Invaginatus SG/CG*	*Tooth torsion SG/CG*	*Transposition SG/CG*	*Transmigration SG/CG*	*Impacted tooth SG/CG*
Central incisor	1/0	12/11	0/0	0/0	0/0	0/0
Lateral incisor	14/10	11/9	9/6	0/0	0/0	0/0
Canine	6/5	0/0	21/17	0/0	0/0	3/2
First premolar	12/14	0/0	5/0	0/0	0/0	2/0
Second premolar	16/18	0/0	2/2	0/0	0/0	2/1
First molar	16/17	0/0	0/2	0/0	0/0	3/0
Second molar	23/26	0/0	0/0	0/0	0/0	7/1

	Hypodontia SG/CG	*Microdontia SG/CG*	*Root anomaly SG/CG*
Central incisor	1/0	2/0	8/0
Lateral incisor	2/1	4/0	5/0
Canine	0/0	0/0	6/0
First premolar	1/3	2/0	8/1
Second premolar	13/5	5/0	11/2
First molar	0/0	0/0	7/0
Second molar	0/0	14/1	6/0
Third molar	0/0	8/0	0/0

CG, control group; I, incisive; *SG,* study group; *Sup.,* supernumerary.

alterations, some DAs of size, shape, number or structure may develop.[24]

Disturbances in the morphodifferentiation stage of odontogenesis can provoke microdontia, where a few cells are arranged to sketch the size of the tooth with an altered morphologic pattern.[25] In our study, in CCSs, the second molars and the second premolars were the teeth most affected by microdontia, similar to other studies.[9,26] In healthy individuals, microdontia is more prevalent in the upper lateral incisor and the third molar.[27]

Hypodontia occurs when there is lack of initiation or there is interruption of the proliferative stage of odontogenesis. A higher prevalence of hypodontia can be found in the third molars, followed by the second premolars and the upper lateral incisors.[28] In our study population, hypodontia mainly affected the second premolars in both the SG and the CG, as reported by another study.[26] Despite the fact that hypodontia has been reported as being more prevalent in CCSs compared with healthy individuals,[9,29,30] no study has detailed which teeth were affected and whether hypodontia could affect one or multiple teeth in an individual. We considered it important to highlight that of the 11 CCSs with hypodontia, 7 presented only one case of hypodontia.

DRAs were those DAs that appeared more exclusively as a late effect of CHT and/or RT in CCSs compared with healthy individuals.[20,31] The most vulnerable proliferative cells are found in the epithelium of the Hertwig sheath, which is responsible for root formation and can be affected by CHT and/or RT.[32] The odontoblasts are responsible for maintaining the morphogenesis and structure of the Hertwig sheath, where the β-catenin odontoblastic molecule acts as an essential regulator of morphogenesis and root development.[33] A study in rats revealed that after the administration of a chemotherapeutic agent, dental root development was disrupted, causing cellular damage in odontoblasts and the Hertwig sheath. As a result, the early closure of the apex by impairing the mitotic activity in this region provoked short roots of teeth in the SG compared with the CG.[34] In our study, DRAs affected all types of teeth except the third molar. Among them, the most frequent type of root anomaly was the U1 classification (n = 17), followed

by V0 (n = 16), V2 (n = 8), U2 (n = 8), and V1 (n = 2). In the CG, there were only 2 DRAs: one in the first premolar, U2 (n = 1), and the other in the second premolar, V2 (n = 1).

To better understand the possible factors associated with the most prevalent DAs in CCSs, we compared DAs on the basis of age at diagnosis of cancer. We found that microdontia was the only DA that showed an association because 27 of the 35 microdontia occurred in individuals before age 71 months. In the literature, studies about the influence of age at diagnosis are variable. It was reported that CCSs diagnosed before age 60 months had a higher number of cases of microdontia, hypodontia, and DRAs.[19,21,30] However, other studies have mentioned that the number of cases of microdontia and hypodontia increased when the cancer diagnosis occurred earlier than age 60 months and that DRAs increased when age at diagnosis was greater than 60 months.[22,26] Likewise, when we analyzed the association between DAs and duration of ATs, there was no difference between the groups. Treatment time duration does not seem to influence the occurrence of DAs,[9,35] probably because the type and dose of CHT and/or RT are more influential than duration of treatment.[9,19]

An individual receiving CHT concomitantly with RT in the head and neck area may experience a higher number of DAs compared with those individuals who had CHT and RT separately.[10] In our study, from the 16 types of DAs in CCSs that were compared with regard to the type of AT, impacted teeth were the only DA that showed an association with the type of treatment. There are few studies in the literature evaluating the occurrence of impacted teeth in CCSs. Dental eruption begins once the dental crown has formed, and the coordinated events between the reabsorption and bone remodeling of the alveolar bone actively interact among the cells that make up the follicle of the dental germ.[36] The osteoblast activity may be affected not only by CHT[37] but also by RT,[38] and this can affect the cells of the follicle of the dental germ, causing cellular disorganisation.[39] These factors may prevent normal tooth eruption.

Our study revealed that high quantities of dental abnormalities per individual (≥10) were present only in CCSs (100%) compared with the CG. This can be explained because DAs can develop in CCSs not only after ATs but also before ATs. Therefore, if the presence of DAs can impact quality of life negatively in individuals without history of cancer,[40] it suggest that the negative impact could be higher in CCSs. There are no studies on the influence of DAs on quality of life and masticatory efficiency in CCSs and on the nutrition of these individuals; therefore, we suggest that studies on these topics need to be performed.

Finally, to evaluate DM, we used the Demirjian method,[14] which has been shown to be a feasible method to study patients with cancer with the use of PRs.[41] Our results suggested that CHT and/or RT did not influence DM. These results are similar to the findings of some studies[42,43] that reported that DM can be determined by genetic and/or ethnic factors.[43] In contrast, another study mentioned that DM was advanced in CCSs in comparison with controls; nonetheless, that study emphasized that the sample size was small and that DM could be influenced by several factors. For that reason, it is difficult to determine the degree of influence of ATs on DM.[11] Although our sample is larger, we consider that it is still a small sample to confirm our results.

Table VI. Prevalent dental anomalies in childhood cancer survivors associated with age at diagnosis and duration of treatment

Number of dental anomalies and age at cancer diagnosis						
		Diagnosis ≤71 months		*Diagnosis ≥71 months*		
Dental anomaly	*No. of DAs*	*Mean*	*SD*	*Media*	*SD*	*P value*
Microdontia	35	2.454	1.508	1.142	0.378	**.041***
Hypodontia	17	1.428	0.534	1.251	0.501	.706†
Root anomalies	51	9.001	8.185	1.251	0.501	.104*
Number of dental anomalies and duration of cancer treatment						
		Treatment >1 year		*Treatment <1 year*		
Dental anomaly	*No. of DAs*	*Mean*	*SD*	*Mean*	*SD*	*P value*
Microdontia	35	1.751	1.164	2.101	1.524	.599*
Hypodontia	17	1.333	0.516	1.801	1.304	.438*
Root anomalies	51	4.751	7.126	6.501	7.778	.766*

*t test;
†Mann-Whitney U-test.
SD, standard deviation.

Table VII. Comparison of dental age and chronologic age between groups

Dental age						
Group	*n*	*Median*	*Minimum*	*Maximum*	*SD*	*P value*
SG	88	146	33	259	58.323	.378*
CG	81	168	36	259	57.63	
Dental age and chronologic age						
Group	*n*	*Median*	*Minimum*	*Maximum*	*SD*	*P value*
SG	88	0.946	0.258	1.356	0.206	.092*
CG	81	0.978	0.537	6.317	0.647	

*Mann-Whitney U-test.
CG, control group; *SD,* standard deviation; *SG,* study group.

Studies on the late effects of CHT and/or RT on DM are scarce, and this hinders further understanding of this subject. The development of the permanent dentition takes several years,[15,24] and it is considered a complex process because many factors are involved, and these factors are still the subject of current research.[44,45]

This study included different types of cancer because the focus was to analyze the effects of CHT and/or RT on dental development to show the major diversity of DAs in CCSs. This factor became a limitation in offering distinct information on oncohematologic and solid neoplasms because each type of cancer can have specific features in its treatment, and the results would probably be different if the cancers were studied separately. Finally, without information on the doses of chemotherapeutic agents, a deep analysis of the impact of this factor in the development of DAs in CCSs could not be performed.

CONCLUSIONS

CCSs treated with CHT and/or RT in this study of the PRs of CCSs revealed a higher prevalence of microdontia, hypodontia, and DRAs compared with healthy individuals. Among those DAs, microdontia was associated with initiation of ATs before age 71 months. In CCSs who undergo multimodal treatment with CHT and RT, there may be an increase in the prevalence of impacted teeth. However, despite the higher prevalence of DAs in CCSs, DM in these individuals was not influenced by CHT and/or RT. Therefore, our results suggest that all CCSs who undergo CHT and/or RT need dental follow-ups as a preventive strategy; this approach can offer better dental management of this population to support the multidisplinary team that strives to offer a better quality of life for CCSs.

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SUPPLEMENTARY TABLE I

Number of panoramic radiographs excluded of analyses according to the influence of orthodontic treatment on evaluation of dental anomalies and dental maturity

DA influenced by the orthodontic treatment	*Total of PR excluded*	*Total of PR evaluated*
Dental root anomalies Impacted tooth Tooth Transmigration Tooth torsion Tooth transposition	Total=43 SG=14 CG=29	83 SG 82 CG
PR excluded for DM analyses	***Total of PR excluded***	***Total of PR evaluated***
Absence or hypodontia of one or more teeth of the left lower permanent teeth.	Total=39 SG=9 CG=30	88 SG 81 CG
DA that are not influenced by the orthodontic treatment	***Total of PR Evaluated***	***Total of PR excluded***
All DA of the hyperplastic and, hypoplastic group. Two DA of the heterotopic group such as root dilaceration and invaginated tooth.	0	97 SG 111 CG

DA, Dental anomalies; PR, panoramic radiograph; DM, dental maturity; SG, study group; CG, control group.

SUPPLEMENTARY TABLE II

Features of each individual with hypodontia

Patient	*N*DA*	*Gender*	*Type of cancer*	*Age of diagnostic (months)*	*CHT*	*Type of CHT*	*RT*	*Area of RT*	*Dose of RT(cGy)*	*Time of treatment (months)*
1	2	M	Rhabdomyosarcoma	28	Yes	Vincristine / Actinomycin D / Cyclophosphamide / Ifosfamide / Carboplatin / Etoposide	No			15
2	1	F	ALL	54	Yes	Vincristine / Cytarabine / Metrotexate / Etoposide / Ifosfamide / Cyclophosphamide / Asparaginase -L / Doxorubicin / Daunorubicin	No			28
3	1	F	Rhabdomyosarcoma	30	Yes	Actinomicina / Vincristina / Ciclofosfamida	Yes	Abdomen		11
4	4	F	ALL	54	Yes	Metrotexate / Mercaptopurine	No			11
5	1	M	ALL	54	Yes	Methotrexate / Mercaptopurine / Cytarabine / Ifosfamide / Etoposide / Cyclophosphamide / Doxorubicin / Vincristine / Asparginase-C	No			36
6	1	F	Burkitt lynphoma	70	Yes	Cyclophosphamide, Oncovin (Vincristine) / Prednisone / Adriamycin / Doxorubicin / Methotrexate / Cytarabine	No			4
7	1	F	Osteosarcoma	154	Yes	Methotrexate / Cyclophosphamide / Cisplatin / Doxorubicin	No			17
8	2	F	AML	WI*	Yes	WI*	WI*			23
9	2	M	Hodgkin lynphoma	97	Yes	Doxorubicin / Bleomycin / Vimblastine / Cyclophosphamide / Procarbazine / Vincristine	Yes	Mediastinum	7	108

(*continued*)

Continued

Patient	*N*DA*	*Gender*	*Type of cancer*	*Age of diagnostic (months)*	*CHT*	*Type of CHT*	*RT*	*Area of RT*	*Dose of RT(cGy)*	*Time of treatment (months)*
10	1	M	Meduloblastoma	WI*	Yes	Melphalan / Busulfan / Etoposide / Carboplatin / Metrotexate / Cyclophosphamide / Cisplatin / Lomustine / Vincristine	Yes	Cranium	WI*	WI*
11	1	M	Rhabdomyosarcoma	55	Yes	Dactinomycin / Etoposide / Irinotecan / Cyclophosphamide / Doxorubicin / Vincristine / Ifosfamide	Yes	Right nasal cavity	5.040	15

DA, dental anomalies; CHT, chemotherapy; RT, radiotherapy; WI*, without information

Features of each individual with hypodontia

Patient	*N*DA*	*Gender*	*Type of cancer*	*Age of diagnostic (months)*	*CHT*	*Type of CHT*	*RT*	*Area of RT*	*Dose of RT (cGy)*	*Time of treatment (months)*
1	1	F	Meduloblastoma	63	YES	Metrotexate / Cytarabine / Vincristine / Cyclophosphamide / Mercaptopurine / Doxorubicin	YES	Cranium	1.200	23
2	2	M	ALL	98	YES	Methotrexate / Vincristine / Cyclophosphamide / Etoposide / Daunorubicin / Asparginase-L / Cytarabine / Mercaptopurine	YES	Cranium	1.800	45
3	6	M	Pineoblastoma	22	YES	Vincristine / Cyclophosphamide / Ifosfamide / Etoposide	NO			4
4	4	M	Rhabdomyosarcoma	28	YES	Vancristina / Actinomycin D / Cyclophosphamide / Ifosfamide / Carboplatin / Etoposide	NO			15
5	1	M	ALL	97	YES	Mercaptopurine / Cytarabine / Metrotexate / Vincristine	NO			24
6	3	F	Rhabdomyosarcoma	30	YES	Actinomycin / Vincristine / Cyclophosphamide	YES	Abdomen		11
7	2	F	ALL	54	YES	Metrotexate / Mercaptopurine	NO			11
8	2	M	Astrocytoma	34	NO	NO	YES	Cranium	5.400	7
9	3	M	ALL	23	YES	Cytarabine / Methotrexate / Vincristine / Mercaptopurine / Doxorubicin / Cyclophosphamide / Daunorubicin	NO			17
10	1	M	Hodking lymphoma	105	YES	Cyclophosphamide / Doxorubicin / Vincristine / Carboplatin / Etoposide / Ifosfamide	NO			27
11	1	F	Burkitt lymphoma	66	YES	Melphalan / Carmustine / Carboplatin / Etoposide / Cytarabine / Metrotexate / Doxorubicin / Cyclophosphamide / Vincristine	NO			11
12	1	F	Burkitt lymphoma	70	YES	Cyclophosphamide, Oncovin (Vincristine) / Prednisone / Adriamycin / Doxorubicin / Methotrexate / Cytarabine	NO			4
13	2	F	Hepatoblastoma	8	YES	Cisplatin	WI*			11

(*continued*)

Continued

Patient	*N*DA*	*Gender*	*Type of cancer*	*Age of diagnostic (months)*	*CHT*	*Type of CHT*	*RT*	*Area of RT*	*Dose of RT (cGy)*	*Time of treatment (months)*
14	1	F	Willms tumor	62	YES	Carboplatin / Etoposide / Ifosfamide / Melphalan / Carboplatin / Cyclophosphamide / Dactinomycin / Doxorubicin / Vincristine	WI*			35
15	1	F	Craniopharyngoma	WI*	YES	WI*	NO			4
16	1	F	ALL	72	YES	WI*	WI*			WI*
17	2	M	Hodking lymphoma	98	YES	Doxorubicin / Bleomycin / Vimblastine / Cyclophosphamide / Procarbazine / Vincristine	YES	Mediastinum		7
18	1	M	Meduloblastoma	WI*	YES	Melphalan / Busulfan / Etoposide / Carboplatin / Metrotexate / Cyclophosphamide / Cisplatin / Lomustine / Vincristine	YES	Cranium		WI*

Features of each individual with dental root anomalies

Patient	*N*DA*	*Gender*	*Type of cancer*	*Age of diagnostic (months)*	*CHT*	*Type of CHT*	*RT*	*Area of RT*	*Dose of RT (cGy)*	*Time of treatment (months)*
1	4	M	Rhabdomyosarcoma	28	YES	Vancristine/ Actinomycin D / Cyclophosphamide / Ifosfamide / Carboplatin / Etoposide	YES	WI*		15
2	22	M	Rhabdomyosarcoma	52	YES	Vincristine / Actinomycin / Cyclophosphamide	YES	Neck (cervical)	450	12
3	5	F	ALL	40	YES	Metrotexate / Cytarabine / Mercaptopurine / Vincristine	NO			12
4	12	F	Pineoloblastoma	40	YES	Melphalan / Busulfan / Methotrexate / Cyclophosphamide / Etoposide / Cisplatin / Vincristine	YES	SNC	####	7
5	2	M	AML	168	YES	Methotrexate / Cytarabine / Melphalan / Asparaginase -L / Mitoxantrone / Bussulfan / Daunorubicin / Etoposide	WI*			13
6	2	F	Non-hodking lynhoma	66	YES	Melphalan / Carmustine / Carboplatin / Etoposide / Cytarabine / Metrotexate / Doxorubicin / Cyclophosphamide / Vincristine	NO			11
7	1	F	ALL	190	YES	Metrotexate / Cyclophosphamide / Etoposide / Mercaptopurine / Cytarabine / Asparaginase-L / Daunorubicin / Vincristine / Cytarabine	NO			47
8	1	F	Non-hodking lynhoma	106	YES	Cyclophosphamide / Vincristine / Prednisone / Doxorubicin / Metrotexate / Cytarabine	NO			3
9	1	M	Meduloblastoma	WI*	YES	Melphalan / Busulfan / Etoposide / Carboplatin / Metrotexate / Cyclophosphamide / Cisplatin / Lomustine / Vincristine	Sim	Cranium	WI*	WI*

DA, dental anomalies; CHT, chemotherapy; RT, radiotherapy; WI*, without information