



Oral and dental alterations and growth disruption following chemotherapy in long-term survivors of childhood malignancies

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Abstract

Purpose More attention has been focused on the long-term side effects of treatment protocols since impressive advances in childhood cancer treatment have resulted in a growing population of patients. The purpose of this study was to investigate the disturbances of dento-facial development in children who were long-term survivors of childhood malignancies.

Methods Fifty-three children (mean age, 10 years + 4 months) in long-term remission underwent oral/dental and radiographic examinations after completion of therapy. Crown and root malformations, gingival/periodontal status, enamel defects, discolorations, decayed and unerupted teeth, premature apexifications, agenesis, maximal interincisal opening and lateral movement of jaws, and soft tissue abnormalities were noted. Caries were evaluated by the decayed-missing-filled teeth (DMFT) index. Forty healthy children (mean age, 12 years + 4 months) belonging to the same age group and socioeconomic community were served as controls. All participants in the study were evaluated in terms of craniofacial development.

Results The data of the study showed that higher prevalence of root malformation, unerupted teeth, and enamel hypoplasia were detected as a consequence of childhood cancer and/or antineoplastic therapy. Although no differences of craniofacial growth and development were observed between groups ($P > 0.05$), plaque and gingival index scores were statistically higher in the study group ($P < 0.05$).

Conclusion A range of variations in dental structures is recognized as a side effect of childhood cancer therapy in long-term survivors of pediatric malignancies that may affect their quality of life.

Keywords Chemotherapy · Childhood · Cancer · Maxillofacial development

Introduction

According to the ninth revision of the International Classification of Diseases, childhood cancers are defined as malignant tumors diagnosed in children under the age of fifteen [1]. In recent years, as the prognosis of childhood cancer

has improved, more attention has been directed to the long-term side effects of various treatment protocols. These efforts focus on reducing treatment frequency and severity while still improving the cure rate. The disease and its treatment can seriously affect the child's quality of life going forward: A child affected by a malignant tumor is at greater risk for growth and developmental deficiencies.

Cancer and its therapy have been shown to cause profound systemic, craniofacial, and dental abnormalities. Oral sequelae and discomfort related to treatment carry long-term and potentially lethal consequences for many pediatric cancer patients [2]. The dental sequelae resulting from chemotherapy and radiation are irreversible [3]. The consequence of both treatment types can be salivary changes [2–4], oral infections, and orodental development alterations [2, 5, 6]. Treatment with these modalities during the early stages of tooth development can lead to dental agenesis or microdontia, and during later stages can disturb root development [7]. The varying

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ability of cytotoxic agents and radiotherapy to cause sub-lethal or lethal damage to tooth-forming cells contribute to the clinical outcome. Chemotherapeutic agents such as vinblastine and vincristine induce qualitative and quantitative changes in dental tissues, and they affect mature secretory odontoblasts and ameloblasts. Interference with odontoblast microtubules disrupts collagen fibril formation and dentin matrix secretion resulting in short, thin tapered roots [3, 8]. Anti-neoplastic agents inhibit odontogenesis and eruption [3, 8].

Radiation to the dental arches in doses as low as 0.72–1.22 Gy has been shown to cause mild developmental defects in both the root and enamel of teeth. Acute lymphoblastic leukemia (ALL) survivors who received 24 Gy of radiation were affected more severely than those who received 18 Gy [9]. The exposure to radiotherapy doses over 20 Gy contributed to a fourfold to tenfold increase in the risk of developing dental abnormalities [10].

The lack of specificity in both chemotherapeutic agents and radiotherapy in terms of differentiating neoplastic cells from metabolically active normal cells may result in dental and facial abnormalities. The extent of these abnormalities depends on many factors, including the type of chemotherapeutic agent used, the half-life of the agent, and the number of cells in susceptible phases of the cell cycle. Undifferentiated mesenchymal cells are affected less, and differentiated odontoblasts have been shown to produce dental tissues even during chemotherapy [11]. Although the immediate effects of chemotherapy and irradiation on soft tissues are well documented, less is known about the long-term effects on oral health and developing dental tissues [12, 13].

The aim of this study was to assess the oral health status and disturbances to dental and craniofacial development in children treated with chemotherapy who are long-term survivors of childhood malignancies.

Methods

Study population

The study protocol was approved by the Medical and Health Research Ethics Committee of Gazi University. All eligible subjects were thoroughly informed of the nature, potential risks, and benefits of their participation in the study, and written informed consent was obtained from all participants and/or their guardians.

Fifty-three Caucasian children (41 male, 12 female, mean age, 10 years + 4 months) in long-term remission were studied from individuals referred to Gazi University, Faculty of Medicine, Department of Pediatric Oncology, Ankara, Turkey. Average time after the cessation of therapy was 1 to 5 years (mean, 2 years + 4 months). The diagnoses of the patients and their treatment protocols are described in Table 1.

Forty systemically healthy Caucasian children with a similar age and sex distribution (19 male, 21 female, mean age, 12 years + 4 months) were recruited from the patient pool of Gazi University, Faculty of Dentistry, Department of Pediatric Dentistry, Orthodontics and Periodontology, to serve as controls.

None of the patients had received maxillofacial radiation prior to evaluation. The patients' oral and dental examinations were performed after the cessation of therapy. After a verbal explanation of the dental procedures, informed consent from the patients and/or legal guardians was obtained prior to dental evaluation.

Oral examination

The oral and dental condition of both the test and control groups was evaluated by an experienced periodontist. Crown anomalies, eruption status of the permanent teeth, and any soft tissue abnormalities were evaluated and recorded in a clinical examination. A tooth was considered to be erupted if any part of the crown was visible in the oral cavity. After all the teeth were dried, the enamel defects and surface discolorations were recorded. Maximal mouth opening and lateral excursions of the jaw were also determined.

Periodontal conditions and oral hygiene of the patients were evaluated using the Gingival Index (GI) [14] and Plaque Index (PI) [15]. Teeth were evaluated in cases with permanent dentition central incisors, first premolars, and first molars and in cases of primary or mixed dentition succeeding deciduous teeth for the aforementioned teeth. If the designated tooth did not exist, the nearest deciduous or permanent tooth was substituted.

The teeth were also examined for dmft/DMFT (decayed-missing-filled teeth index, lowercase for deciduous and uppercase for permanent teeth) and dmfs/DMFS (decayed-missing-filled surfaces index, lowercase for deciduous and uppercase for permanent teeth) scores, which were calculated as previously described [16].

Children or accompanying legal guardians were questioned regarding previous dental treatments and tooth extractions.

Radiographic examination

Of the 53 children screened in test group, 22 patients declined to undergo maxillofacial radiographic measurements for evaluating craniofacial development, due to their health conditions. Thirty-one subjects in the test group voluntarily agreed to participate in this part of the study.

The 31 patients from the test group were divided into four subgroups according to chronological age: (i) group I; five patients (4 boys, 1 girl; aged 4 to 7 years); (ii) group II; nine patients (8 boys, 1 girl; aged 7 to 10 years); (iii) group III; eight patients (8 boys; aged 10 to 13 years); (iv) group 4; nine

Table 1 The diagnosis and treatment protocols of the patients

Diagnosis	Patients (N)	Treatment protocol (N)	
Hodgkin lymphoma	10	COPP	7
		ABVD	2
		COPP + ABVD	1
Non-Hodgkin lymphoma	36	BFM-90	27
		LSA2L2	4
		LMT-89	5
Neuroblastoma	2	Vincristine + ARA + C + cisplatin	1
		Vincristine + cyclophosphamide	1
Wilms tumor	1	Vincristine + ACT + D + adriamycine	1
Retinoblastoma	2	Vincristine + cyclophosphamide	1
		Vincristine + adriamycine + cyclophosphamide	1
Rhabdomyosarcoma	1	VAC	1
Nasopharynx carcinoma	1	Modified EVAC	1
Total	53		

patients (2 boys, 7 girls; aged 14 to 14+ years) (Table 2). The 26 control subjects were matched to three subgroups (excluding the first subgroup), according to age and sex, and displayed class I skeletal relationships, typical vertical and sagittal growth patterns.

Panoramic, lateral cephalometric, and hand-wrist radiographs were taken from test and control group patients. The chronological age distribution was conducted on standardized lateral cephalometric radiographs in the test group before (T_1) and after (T_2) cessation of therapy. The radiographic examination included assessment of crown/root malformations, unerupted teeth, premature apexifications, microdontia, and agenesis.

The cephalometric reference landmarks and reference planes used in this study are shown in Fig. 1. One cranial (cranial base flexure angle [NSBa]), three sagittal (sella-nasion-point A [SNA], sella-nasion-point B [SNB], A point-nasion-B point [ANB] angle), and three vertical (ML/SN, NL/SN, ML/NL angles) (SN: sella-nasion line, NL: nasal line, ML: mandibular line) cephalometric variables were measured.

Statistics

The statistical analysis of the results was performed using the Statistical Package for Social Sciences (SPSS v.17.0; SPSS Inc., Chicago, USA). The results are represented as the $\bar{X} \pm S_x$ (\bar{X} : mean and S_x : standard error of mean) for quantitative variables and number (percent) for qualitative variables. The Student *t* test was used if the assumptions of normal distribution were provided, and the Mann-Whitney *U* test, if not, if there was any difference between the categories of the qualitative variable with two categories for the quantitative variable. The chi-square and Fisher exact tests were used for the

relationship between two qualitative variables. A *P* value < 0.05 was considered statistically significant.

Results

Dental disturbance and oral health parameters

Enamel discoloration was found in 56.6% ($n = 30$) (255 teeth) and 22% ($n = 9$) (72 teeth) of patients in the test and control groups, respectively. The both patient and tooth level differences between the two groups were statistically significant, respectively ($P < 0.001$, $P < 0.048$). Enamel hypoplasia was observed in 58.2% of the patients ($n = 32$) (147 teeth) in the study group, and 42.5% ($n = 17$) (62 teeth) in the control group; this difference was insignificant at patient level ($P = 0.131$), but it was significant at tooth level ($P < 0.004$) (Table 3).

In the test group, root malformations were observed in 40.7% of the patients (49 teeth) and this ratio was 17.1% in control patients. Of the 49, most of the affected teeth were lower central and lateral incisors displaying V-shaped roots; others were molars and premolars. The difference in root malformations between groups was statistically significant at only patient level ($P < 0.013$) (Table 3). Two children (3 teeth) were diagnosed with microdontia in the test group, while no microdontia teeth were observed in the control group (Table 3). No statistically groupwise comparisons were made due to the fact that microdontia could not be diagnosed in control patients.

Thirteen children with 49 unerupted teeth (25 incisors, 14 premolars, 8 first molars, 2 second molars) were observed in the test group, and seven children with 24 teeth (4 incisors, 18 premolars, 2 second molars) were observed in the control

Table 2 Chronological age and maturation stages of the patients in test group

Group	Patient	Chronological age	Maturation stage
I	61	4.11	Prior to PP ₂ =
	26	5	Prior to PP ₂ =
	9	5.8	Prior to PP ₂ =
	10	6.4	Prior to PP ₂ =
	11	6.9	Prior to PP ₂ =
	5 patients		
II	14	7.6	Prior to PP ₂ =
	7	8	Prior to PP ₂ =
	1	8.4	Prior to PP ₂ =
	13	8.8	Prior to PP ₂ =
	21	9.1	Prior to PP ₂ =
	68	9.1	PP ₂ =
	58	9.4	PP ₂ =
	62	9.6	MP ₃ =
	57	9.7	PP ₂ =
III	9 patients		
	8	10	Prior to PP ₂ =
	56	10	MP ₃ =
	24	10.2	PP ₂ =
	69	11.1	MP ₃ cap
	70	11.2	PP ₂ =
	65	13	MP ₃ =
	4	13.6	MP ₃ =
	67	13.8	MP ₃ cap
IV	8 patients		
	63	14.5	Ru
	66	14.9	MP ₃ =
	16	15.11	Ru
	29	15.11	Ru
	54	15.5	Ru
	60	15.7	Ru
	23	16.9	Ru
	59	17.4	Ru
9 patients	2	18.7	Ru

Pre-peak stage: PP₂, proximal phalanx of the second finger, the epiphysis as wide as the diaphysis; MP₃, medial phalanx of the third finger, the epiphysis as wide as the diaphysis

Peak stage: MP₃cap, medial phalanx of the third finger, the diaphysis is covered by the cap-shaped epiphysis

Post-peak or completion of growth: Ru, complete union of epiphysis and diaphysis of the radius

group (Table 3). The difference between groups was found statistically insignificant in both patient ($P=0.407$) and tooth levels ($P=0.279$).

Premature closures of the apices of teeth were observed in seven teeth from four children belonging to the test

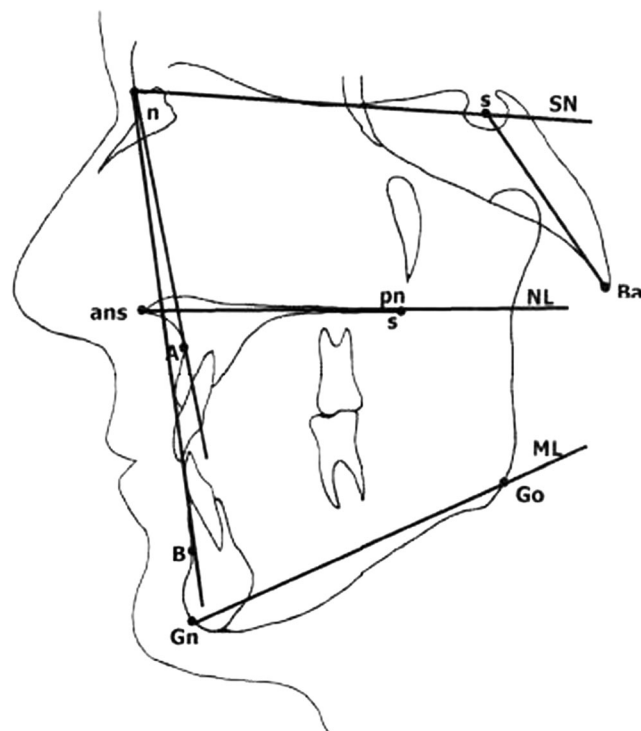


Fig. 1 The cephalometric reference landmarks and reference planes used in the study. The cephalometric points and lines. A subspinale, ans anterior nasal spina, B supramentale, Ba basion, Go gonion, gn gnathion, SN sella-nasion line, NL nasal line, ML mandibular line

group. P value could not be calculated statistically at both patient and tooth levels due to none of teeth exhibited premature closures of the apices in control group. There was a trend toward premature apexification in the test group (Table 3).

In the test group, 21 children exhibited agenesis of seven incisors, two premolars, and 56 wisdom teeth including third molars. In the control group, two premolars, two incisors, and 18 wisdom teeth were observed in 11 patients. The difference between the groups in terms of agenesis was found statistically significant at patient level ($P<0.003$) and insignificant at tooth level ($P=0.800$). When the third molar was excluded, there were six children diagnosed with agenesis in the treatment group, compared to only three patients in the control group. The insignificant statistical outcome was found when wisdom teeth were excluded at both patient ($P=0.125$) and tooth levels ($P=0.279$) (Table 3). Limited mouth opening and lateral movements were not observed in either group (Table 3).

The values of oral health parameters are detailed in Table 3. The GI and PI scores were found to be significantly higher in the test group than in the control group. In contrast, the mean and scores of dmft/DMFT and dmfs/DMFS were not statistically significant between the groups (Table 3). None of the patients in the test and control groups presented with soft tissue abnormalities.

Table 3 Scores of the dental disturbance and oral health parameters in the study

	Test group (<i>n</i> = 53)		Control group (<i>n</i> = 40)	
	Patient	Teeth	Patient	Teeth
Enamel discoloration ^a	56.6% (<i>n</i> = 30)	35.4% (<i>n</i> = 255)	22.0% (<i>n</i> = 9)	28.6% (<i>n</i> = 72)
Enamel hypoplasia ^a	58.2% (<i>n</i> = 32)	19.5% (<i>n</i> = 147)	42.5% (<i>n</i> = 17)	13.1% (<i>n</i> = 62)
Crown/root malformation ^a	40.7% (<i>n</i> = 22)	9.5% (<i>n</i> = 49)	17.1% (<i>n</i> = 7)	5.7% (<i>n</i> = 11)
Unerupted teeth ^a	24.1% (<i>n</i> = 13)	15.7% (<i>n</i> = 49)	17.1% (<i>n</i> = 7)	12.2% (<i>n</i> = 24)
Premature apexification	7.0% (<i>n</i> = 4)	7.1% (<i>n</i> = 7)	–	–
Microdontia	4.0% (<i>n</i> = 2)	6.2% (<i>n</i> = 3)	–	–
Agenesis (including the 3rd molars) ^a	39.6% (<i>n</i> = 21)	3.7% (<i>n</i> = 25)	15.9% (<i>n</i> = 11)	3.4% (<i>n</i> = 12)
Agenesis (excluding the 3rd molars) ^b	10.9% (<i>n</i> = 6)	6.0% (<i>n</i> = 10)	4.0% (<i>n</i> = 3)	4.8% (<i>n</i> = 4)
Maximal mouth opening	nr		nr	
Lateral jaw movement	nr		nr	
Soft tissue anomalies	–		–	
GI ^c	<i>X</i> + Sx, 1.07 ± 0.49; range, 0.00–3.00		<i>X</i> + Sx, 0.80 ± 0.59; range, 0.10–2.40	
	95% CI for the differences between groups 0.01–0.49			
PI ^c	<i>X</i> + Sx, 1.47 ± 0.61; range, 0.00–3.00		<i>X</i> + Sx, 0.84 ± 0.51; range, 0.10–2.30	
	95% CI for the differences between groups 0.31–0.76			
dmft/DMFT ^c	<i>X</i> + Sx, 6.62 ± 4.53; range, 0–22		<i>X</i> + Sx, 7.00 ± 2.21; range, 0–14	
	95% CI for the differences between groups 0.26–3.07			
dmfs/DMFS ^c	<i>X</i> + Sx, 9.26 ± 9.68; range, 0–35		<i>X</i> + Sx, 7.70 ± 4.93; range, 0–24	
	95% CI for the differences between groups 1.04–5.97			

GI Gingival index, PI Plaque index, dmft/DMFT decayed-missing-filled teeth index, dmfs/DMFS decayed-missing-filled surfaces index, *X* mean, Sx standard mean of error, nr no restriction within normal limits

^a *P* < 0.05, chi-square test

^b *P* < 0.05, Fisher's exact test

^c *P* < 0.05, Student's *t* test

Craniofacial growth parameters

Thirty-one subjects in the treatment group who had voluntarily agreed to participate in the study for maxillofacial radiographic measurements were evaluated in terms of craniofacial development. The 26 control subjects were matched according to age and sex. The age distribution of the patients who participated in the study is shown in Table 4. The difference between the test and control groups was found to be statistically insignificant (*P* = 0.196) (Table 4). Growth of patients during observation period was higher in group III as compared with others (Table 4).

The average values of parameters measured from the lateral cephalometric radiographs are shown in Table 5. No statistically significant differences were found among the study groups (*P* = 0.248).

Discussion

Chemotherapy is an aggressive and systemic treatment that affects the whole organism and is particularly detrimental to

still-growing organisms. Dental and craniofacial development, gingival, and caries status of 53 long-term survivors of childhood malignancies treated with chemotherapy were evaluated in this study.

The results indicate that long-term survivors of the pediatric malignancies exhibit a range of dental disturbances. Because none of the patients showed any abnormality in jaw function, it can be inferred that chemotherapy does not interfere with temporomandibular joint (TMJ) structures. Oral mucositis is the most frequent and severe complication of chemotherapy in children [17] and is a devastating complication following radiotherapy treatment in patients with head and neck cancers [18]. It can lead to a decline in clinical condition and quality of life through extreme pain, which may result in an inability to tolerate food or fluids and, in turn, can cause dehydration, malnutrition, and possible electrolyte imbalances [19, 20]. In addition, oral mucositis can inhibit a patient's ability to talk, which can contribute to depression [20].

The author investigated whether the chance of pediatric cancer patients experiencing oral mucositis during treatment has increased significantly with the increased use of high-dose and multiple chemotherapy agents in treating childhood

Table 4 Chronological age distribution and duration of observation period

Groups	T_1	T_2		$T_2 - T_1$
	$\bar{X} \pm Sx$	$\bar{X} \pm Sx$		$\bar{X} \pm Sx$
Test group I ($n = 5$)	4.82 ± 0.38	5.64 ± 0.50		0.82 ± 0.44
Test group II ($n = 9$); control group II ($n = 9$)	6.18 ± 0.31	8.86 ± 0.24	NS	2.68 ± 0.28
		8.86 ± 0.30		
Test group III ($n = 8$); control group III ($n = 8$)	7.51 ± 0.95	11.61 ± 0.57	NS	4.30 ± 0.59
		12.53 ± 0.79		
Test group IV ($n = 9$); control group IV ($n = 9$)	12.74 ± 0.50	15.98 ± 0.46	NS	3.24 ± 0.50
		15.49 ± 0.32		

T_1 before cessation of therapy value, T_2 after cessation of therapy value, $T_2 - T_1$ difference, \bar{X} mean, Sx standard mean of error, NS $P > 0.05$ (Student's t test)

cancer [17]. The treatment regimen, chemotherapy with or without radiotherapy, dosage, duration and sequence, type of malignancy, age, neutrophil count, and level of oral care are all implicated in the incidence of mucositis [18, 19]. The severity of mucositis is largely related to the agent used. Methotrexate, fluorouracil, doxorubicin, paclitaxel, capecitabine, and etoposide are particularly stomatotoxic [20, 21]. In the present study, the period between the cessation of chemotherapy and the referral for dental examination was long enough for soft tissue complications like mucositis to subside.

Studies related to childhood oncology suggest that for the 2 weeks following cranial or cervical chemotherapy, patients should adhere to oral hygiene introductions [10, 11, 17, 18]. Children and adolescents appear to have a greater incidence of chemotherapy-induced inflammatory changes, which might be explained by a more rapid epithelial mitotic rate. Patients with good dental health who maintain scrupulous oral hygiene during cancer treatment tend to have fewer episodes than patients with poor oral health. An increased risk of dental abnormalities may reflect decreased access to dental care and

potentially decreased use of preventive care [10]. Statistically significant differences were found both for PI and GI in this study. All of the children in both groups were in mixed dentition. However, cancer chemotherapy damages and breaks the epithelial barrier of the oral mucosa and allows infection by the resident oral flora. Hutton et al. reported that neuroblastoma and rhabdomyosarcoma patients who receive high-dose chemotherapy with stem cell rescue require greater dental input with more emphasis on prevention techniques such as fissure sealants, oral healthcare regimes, and long-term dental follow-up to address the likely occurrence dental anomalies [22].

Although the effects of radiotherapy on dental caries are clear enough, some conflicting results have been reported for chemotherapy [23]. Chemotherapy-induced xerostomia promotes a more acidic pH, creating an environment that is conducive to dental caries. Salivary flow is reduced in adults by chemotherapeutic agents such as cyclophosphamide, cisplatin, and methotrexate [24, 25]. Chemotherapy appears to cause less acute damage alone than when in combination with

Table 5 Descriptive statistics of the skeletal morphology in the groups and the statistical evaluation of intra-group differences

	NSBa $\bar{X} \pm Sx$	ML/SN $\bar{X} \pm Sx$	NL/SN $\bar{X} \pm Sx$	NL/ML $\bar{X} \pm Sx$	SNA $\bar{X} \pm Sx$	SNB $\bar{X} \pm Sx$	ANB $\bar{X} \pm Sx$
Test group I ($n = 5$)	130.08 ± 2.71	36.68 ± 1.28	11.23 ± 1.19	35.44 ± 0.91	77.95 ± 1.40	74.63 ± 1.39	3.32 ± 0.97
Test group II ($n = 9$)	131.40 ± 1.52	36.95 ± 1.55	10.96 ± 1.20	25.98 ± 1.71	77.65 ± 0.96	74.54 ± 1.37	3.10 ± 0.74
Control group II ($n = 9$)	133.07 ± 1.48	37.39 ± 2.28	8.21 ± 1.40	29.18 ± 1.50	79.14 ± 0.83	76.37 ± 1.28	2.78 ± 0.85
	NS	NS	NS	NS	NS	NS	NS
Test group III ($n = 8$)	130.64 ± 2.70	36.40 ± 1.56	9.62 ± 0.81	26.79 ± 1.70	78.75 ± 0.98	75.59 ± 0.94	3.17 ± 0.49
Control group III ($n = 8$)	133.68 ± 2.98	33.89 ± 1.27	10.64 ± 0.85	23.26 ± 1.20	78.06 ± 2.08	75.64 ± 1.36	2.43 ± 0.97
	NS	NS	NS	NS	NS	NS	NS
Test group IV ($n = 9$)	130.93 ± 1.76	33.51 ± 1.72	8.12 ± 1.30	25.39 ± 1.70	79.87 ± 0.92	77.74 ± 1.08	2.13 ± 0.73
Control group IV ($n = 9$)	133.76 ± 2.25	33.55 ± 1.18	11.00 ± 0.97	22.56 ± 0.88	79.66 ± 1.57	78.16 ± 1.55	1.49 ± 0.74
	NS	NS	NS	NS	NS	NS	NS

NSBa cranial base flexure angle, SNA sella-nasion-point A, SNB sella-nasion-point B, ANB A point-nasion-B point, SN sella-nasion line, NL nasal line, ML mandibular line, \bar{X} mean, Sx standard mean of error, NS $P > 0.05$ (Student's t test)

cranial irradiation or total body irradiation [26, 27]. However, some investigators found no significant differences in xerostomia or hyposalivation between total body irradiation (TBI)-exposed or non-exposed patients [28]. It has also been suggested that the administration of anticholinergic antiemetics during the early phases of chemotherapy may reduce salivary flow. Autopsies on adult recipients of doxorubicin and cyclophosphamide revealed histopathologic changes such as ductal dilatation, cyst formation, acinar degeneration, and infiltration in inflammatory cells in salivary gland tissue [29].

A higher incidence of caries in children receiving antineoplastic therapy has also been reported. The disease itself and/or the therapy have both been implicated as the cause [23]. Patients with DMFS and DMFT scores higher than the controls are prone to dental caries [12, 23]. According to some researchers, the caloric intake of these children is important during medical treatment. Because it is often difficult for them to achieve an adequate level of nutrition, these patients are fed high-calorie diets, which, by their nature, are likely to be cariogenic [12, 23]. Also, they are more likely to receive sweets given as rewards for their medical procedures, thus contributing to a cariogenic diet [22]. However, in the present study, no positive correlation was found between dental caries and chemotherapy. Patients were advised to restrict foods that may be traumatic to the oral mucosa in the case of chemotherapy mucositis, and 0.2% chlorhexidine gluconate (CHX) mouth rinses were also prescribed in this group of patients. The results of the present study may be the result of continued use of CHX mouth rinses and dietary restrictions in chemotherapy patients.

Microdontia and agenesis are common features in patients receiving antineoplastic therapy during the development stage of teeth [30, 31]. According to Pedersen et al., both first and second premolars and second permanent molars were affected, whereas no first permanent molars were affected, and the most frequently affected teeth were second premolars [29]. Sevinir et al. examined the late adverse effects of anticancer therapy on developing permanent teeth by using the Disability Equality Index (DEI) [32]. In their study, all patients treated for childhood malignancy with chemotherapy and a chemotherapy-with-radiotherapy combination had disturbances in dental development as compared to healthy controls. The nature and extent of the alterations included a wide range of changes, from clinically significant findings to severe consequences compromising the occlusal function and psychosocial well-being of some children [32].

Some investigators found a significant relationship between age at chemotherapy practice (< 3.5 years) and the presence of microdont teeth [22]. Van der Pas-van Voskuilen et al. suggested that an age of less than 3 years at the start of treatment for malignancy is a risk factor for agenesis. Age remained a significant risk factor after adjustment for gender and TBI [28]. However, the data indicated that children who

were aged < 5 years when they were exposed to alkylating agents, particularly those who received high cumulative doses, were at high risk for developing dental abnormalities [10]. In our study, microdontia was not observed in the control group, but was observed in three teeth in two patients in the test group. Agenesis was observed in both the test and control groups. The affected teeth were wisdom teeth, incisors, and premolars. Since agenesis of wisdom teeth is not infrequent, statistical evaluation was also performed in the absence of wisdom teeth, and both were found to be statistically significant at patient level and insignificant at tooth level. In the present study, we did not evaluate the abnormal enlarged pulp cavities.

Using methods from Demirjian et al. [33] for dental age assessment, Vasconcelos et al. [34] investigated the dental age of children with ALL who were submitted to chemotherapy with and without radiation therapy. In their study, when comparing dental and chronological age of patients with ALL to patients in the control group, they found that the average dental age in patients with ALL was statistically higher than their average chronological age. When they compared the dental age and chronological age of patients submitted to different methods of treatment (chemotherapy with or without concomitant use of radiation therapy), no significant relationship was found [34].

The severity of the long-term disturbances in craniofacial development is dependent on the age of the subject at diagnosis and whether chemotherapy is combined with radiotherapy. Regarding craniofacial development, combination chemotherapy has no effect as compared to healthy controls [5]. Because of the broad age distribution in the present study, it was essential to sub-classify the study groups to evaluate craniofacial growth. The comparison of mean values showed that the craniofacial growth parameters of the study group were similar to expected values.

Dahllöf et al. [30] investigated the possible adverse effects of orthodontic treatment in long-term survivors after bone marrow transplantation (BMT). They found that facial growth is affected by TBI and observed a decrease in alveolar height linked to severely disturbed root development. The age at the initiation of orthodontic treatment in this study varied between 8 and 15 years. Sheller and Williams [35] advised that orthodontic treatment should be postponed until at least 2 years after BMT. By this time, the risk for relapse of the malignancy has diminished and the patient is no longer on immunosuppressive therapy. The growth rate and the need for growth hormone treatment have also been evaluated. Root resorption is a common side effect of orthodontic therapy [36] and would be particularly detrimental in these patients [37].

V-shaped roots and premature apical closure have been reported in the literature [10, 30]. In the present study, short and V-shaped roots were observed particularly in lower incisors in the test group that also displayed premature

apexification, which was statistically significant. Tooth development begins at 4 months in intrauterine life and continues into early adolescence when permanent crowns and roots are fully formed [1]. The author established in animal models that chemotherapeutic agents like vincristine and cyclophosphamide delay or disrupt odontogenesis, as manifested by an increased number of incremental lines and the deranged production of the dentinal matrix after administration of these drugs in animal models [8]. Children of the test group who received chemotherapy during the development stage of their teeth in the early years of their lives exhibited disturbances related to the adverse effects of antineoplastic therapy on dental development. In the present study, there was a trend that children receiving chemotherapy earlier in their lives had dental malformations like premature apexification, which is in agreement with many previous studies [11, 30, 38, 39].

Animal studies revealed that eruption and odontogenesis may be inhibited by antineoplastic drugs [40]. It has been thought that chemotherapy might interfere with tooth eruption since most of the unerupted teeth were the incisors and first molars that precede permanent teeth.

According to Hsieh et al., Holtta's Defect Index (HDI) scores increased with greater doses of cyclophosphamide, and participants receiving 7500 mg/m² or more had significantly higher HDI scores than patients not receiving this drug. They investigated that other chemotherapeutic agents, including doxorubicin, actinomycin-D, vinblastine, and vincristine, were not associated with HDI scores [41]. In the present study, differences between the test and control groups were statistically insignificant. Enamel hypoplasias and discolorations are the most frequently encountered dental complications from antineoplastic agents [30, 31, 39, 42]. In this study, enamel hypoplasias and discolorations were frequently observed and are related to the adverse effects of chemotherapy or the staining effects of the antineoplastic agents. This is likely the result of chemotherapeutic agents such as vincristine, vinblastine, and cyclophosphamide that were commonly administered to the patients and which affect the disruption of the ameloblast microtubule calcium transport mechanism, leading to hypomineralized enamel defects [3–6, 43, 44].

Conclusions

The present study showed that antineoplastic therapy or childhood cancer resulted in a higher prevalence of various malformations in teeth, but no difference in craniofacial growth and development was observed. Children treated in the early years of their lives had the most severe dental defects, suggesting that immature teeth are at greater risk for developmental disturbances than fully developed teeth. However, further studies with larger number of test and control subjects and longer follow-up periods should be performed. Also,

evaluations with respect to diagnosis and treatment protocols are crucial for a comprehensive understanding of the effects of antineoplastic chemotherapy on orodental tissues and craniofacial growth and development. Dental development may be affected by illness, and/or chemotherapy at any point prior to complete maturation of the teeth. Meticulous clinical and radiographic surveillance may facilitate the detection of abnormalities. Early diagnosis, treatment, and individual prevention programs based on the mechanical control of plaque are essential to minimize the oral repercussions of oncological treatment and to improve dental health.

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Compliance with ethical standards

The study protocol was approved by the Medical and Health Research Ethics Committee of Gazi University. Written informed consent was obtained from all participants and/or their guardians.

Conflict of interest The authors declare that they have no conflict of interest.

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