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Long-term dental development in children after treatment for malignant disease

Margareta Näsman, Carl-Magnus Forsberg and Göran Dahllöf
Department of Orthodontics and Pediatric Dentistry, Karolinska Institutet, Stockholm, Sweden

SUMMARY A radiographic dental examination was performed in 16 children conditioned with total body irradiation (TBI) and cyclophosphamide (CY) prior to bone marrow transplantation (BMT), and in 52 children treated with multiagent chemotherapy. For each child, three age- and sex-matched healthy controls were selected. Evaluation of disturbances in dental development and tooth size was based on planimetric measurements of mandibular teeth on panoramic radiographs. Short V-shaped roots were diagnosed in 94 per cent of the children treated with TBI/CY compared with 19 per cent in the chemotherapy group ($P < 0.001$). Children receiving TBI/CY also exhibited a pronounced reduction in tooth size compared with the controls. Reductions varied from 19 per cent in incisors to 39 per cent in the second molars. In the chemotherapy group the corresponding values were 7 and 15 per cent respectively. When comparing crown/root ratios, the indices for incisors, canines ($P < 0.05$) and molars ($P < 0.01$) in the BMT group were significantly higher than the corresponding values in the control group. This indicates that the reduction in root size was more pronounced than the reduction in crown size. The premolars in the BMT group exhibited a similar reduction in crown and root size. All developing teeth were affected by multiagent chemotherapy and radiation therapy. The most severe disturbances were found in children treated with TBI/CY at a young age.

Introduction

With the improving cure rate in childhood malignancies, attention is now focused on the long-term survivors of childhood cancer and their quality of life (Sullivan *et al.*, 1984; Meadows *et al.*, 1986). Children conditioned with total body irradiation (TBI) prior to bone marrow transplantation (BMT) exhibit decreased growth rates, with no signs of catch-up even with growth hormone therapy (Sanders, 1991). This is in contrast to the situation in children with acute lymphoblastic leukaemia treated with multiagent chemotherapy. In these cases an initial growth retardation during the first 6 months of treatment is followed by catch-up growth after completion of therapy (Lannering and Albertsson-Wikland, 1989).

In growing individuals the dental sequelae to chemotherapy and irradiation are irreversible. Dental defects attributed to chemotherapy include arrested root development and disturbances in enamel formation (Rosenberg *et al.*, 1987; Pajari *et al.*, 1988). The timing of tooth eruption, however, seems unaffected by chemotherapy (Dahllöf *et al.*, 1988a,b). The most severe and extensive disturbances have been reported in children treated with TBI before 6 years of age (Jaffe *et al.*, 1984; Dahllöf *et al.*, 1988a,b; Sonis *et al.*, 1990; Näsman *et al.*, 1994).

The aim of the present investigation was to study, compare and quantify disturbances in dental development in long-term survivors who had received different types of treatment for malignant diseases during childhood.

Subjects and methods

Patients

The BMT group comprised 16 children (seven boys and nine girls) treated for haematological malignancies at Huddinge Hospital before the age of 12 years (mean ± SD, 6.3 ± 3.5) and surviving for more than 3 years. The preoperative conditioning included 10 Gy of

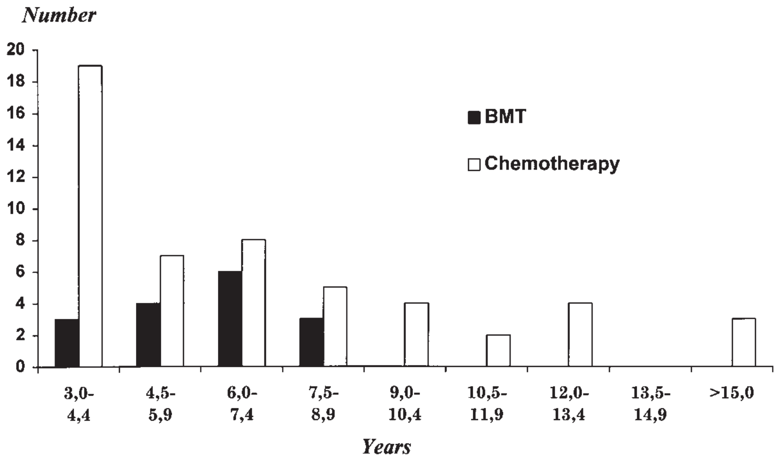

Figure 1 BMT group: number of years elapsed between bone marrow transplantation and radiographic registration for tooth size evaluation. Chemotherapy group: number of years elapsed between the start of chemotherapy and radiographic registration.

TBI and high-dose cyclophosphamide (CY). To prevent or modify graft-versus-host disease (GVHD), methotrexate, cyclosporin or both combined were given (for details see Ringdén *et al.*, 1989). The mean time between BMT and dental examination was 5.7 years (range 3.0–8.6; Figure 1).

The chemotherapy group comprised 52 children (29 boys and 23 girls) treated at the Paediatric Cancer Unit at Karolinska Hospital. Their malignancies were diagnosed before 12 years of age (mean ± SD, 5.1 ± 3.3) and all had survived for more than 3 years. Twenty-eight children were treated for haematological malignancies: 19 for acute leukaemia, nine for malignant lymphoma. Twenty-four children were treated for solid tumours: six for Wilm's tumour, six for rhabdomyosarcoma, three for neuroblastoma, three for optic glioma, three for other CNS tumours and three for other tumours. Prophylactic cranial irradiation with 18–24 Gy was given to 13 patients. The mean time between diagnosis and dental examination was 6.6 years (range 3.0–17.5; Figure 1).

For each child, three age- and sex-matched healthy controls were selected. (Three controls for each patient were used to increase the power of the statistical tests.) The controls were selected from the patient files at the Department of Orthodontics. Only children with a moderate degree of malocclusion were selected.

Methods

A panoramic radiograph (PRG) of the teeth was taken of all children in connection with dental examination (patients) or orthodontic treatment planning (controls). All PRGs were coded and the subsequent measurements were performed without the investigator knowing to which group the PRG belonged. Disturbances in dental development were analysed using the method described by Dahllöf *et al.* (1988a). The disturbances were classified into five major groups: (i) arrested root development with short V-shaped roots; (ii) arrested root development and premature apical closure; (iii) enamel hypoplasia; (iv) microdontia; and (v) aplasia.

The evaluation of tooth size was based on planimetric measurements of mandibular teeth on the PRG. The radiographic procedure produces an enlarged image of the teeth. The enlargement factor is difficult to control as it varies in different areas of the picture and between individuals. It is reasonable to assume, however, that these variations are randomly distributed, and under such circumstances the enlargement error should not affect comparisons of mean values to any mentionable degree. In order to test the validity of this assumption, the tooth widths of lower left second incisors, first premolars and first molars were measured on the study models of 20 patients randomly selected from the files of the Orthodontic Department. These measurements were subsequently compared with the corresponding tooth widths obtained from the patients' panoramic radiographs. All measurements were made with a sliding caliper with and accuracy of 0.01 mm. On the basis of the recordings, a mean radiographic magnification factor for each type of tooth could be calculated. This factor was found to be 1.12 (SD 0.06, skewness –0.81, NS) for the incisors, 1.21 (SD 0.07, skewness –0.59, NS) for the premolars and 1.30 (SD 0.07, skewness 0.34, NS) for the molars. The probalility distributions of the magnification factors for the individual teeth were tested and found to be normal within all three groups of teeth. This result verifies the relevance of the assumption that the variation in radiographic magnification may be regarded as a random variable. Consequently, in the present determinations of crown and root areas, no attempt was made to correct the recorded values for radiographic enlargement. In one part of the study, however, the ratio between the crown and root areas was analysed. The formation of ratios eliminates the effect of the radiographic enlargement, and the values obtained could be used to check the relevance of the mean values achieved through direct measurement of the crown and root areas.

Measurements of areas

The recordings of the crown and root areas were made with a digitizer online with a microcomputer. A number of reference points on the outlines of the crown and root were digitized. The area encompassed by a line joining the reference points was then calculated by the computer, and the crown/root ratio was formed. The crown areas were defined by seven reference points. Definition of root areas required nine points for single-rooted teeth and seventeen points for double-rooted teeth (Figure 2).

Statistical analyses

For error determination, the digitizing procedures were repeated after 2 weeks in 20 randomly selected cases. The error of the method (s_i) was calculated according to the formula:

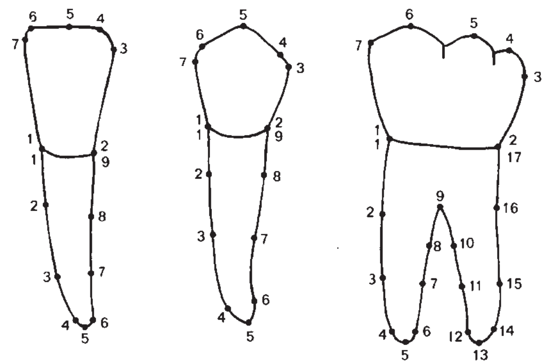

Figure 2 Reference points on panoramic radiographs used for calculations of tooth area. For incisors and canines there were seven reference points for the crown and nine for the root; for molars there were seven for the crown and 17 for the root.

$$s_i = \sqrt{(\Sigma(d^2/2N))}$$

where d is the difference between double determinations.

When comparing disturbances in dental development between the groups, the χ^2-test was used. The tooth sizes in the different groups were normally distributed. Consequently dimensional differences between the groups could be evaluated with Student's t-test.

Results

Error determination

With the exception of the incisors, the method errors for the crown/root ratios were very small (Table 1). The error variances constituted only 0.2–1.1 per cent of the biological variances. For the incisors the corresponding value was 10.6 per cent.

Disturbances in dental development

As can be seen in Table 2, children in the BMT group treated with TBI/CY exhibited disturbances in dental development significantly more often than children treated with combination chemotherapy. For example, short V-shaped roots were diagnosed in 15 of the 16 (94 per cent)

Table 1 Error determinations of digitized tooth area determinations*.

Teeth	Method errors s_i	Error variances s_i^2	Biological variances SD^2	$s_i^2/SD^2 \times 100$ (%)
Incisors	0.077	0.0059	0.056	10.6
Canines	0.021	0.0004	0.201	0.2
Premolars	0.025	0.0006	0.095	0.7
Molars	0.025	0.0006	0.057	1.1

* Method errors, biological variances and error variances in per cent of biological variances obtained after 20 double determinations of the crown/root area in four types of teeth.

Table 2 Number of patients exhibiting disturbances in dental development in relation to the total number of patients in each group.

Treatment	Age of start of treatment in years, $x \pm SD$	Type of disturbances[1]				
		I	II	III	IV	V
Total body irradiation/ cyclophosphamide	6.3 ± 3.5	15/16 (94%)	11/16 (69%)	7/16 (44%)	12/16 (75%)	9/16 (56%)
Chemotherapy	5.1 ± 3.3	10/52 (19%)	4/52 (8%)	7/52 (13%)	7/52 (13%)	11/52 (21%)
Significance[2]	NS	$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.001$	$P < 0.05$

[1] Classification of disturbances: (I) arrested root development with short V-shaped roots; (II) arrested root development with premature apical closure; (III) enamel hypoplasia; (IV) microdontia; and (V) aplasia.
[2] χ^2 test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

children treated with TBI/CY, compared with 10/52 (19 per cent) in the chemotherapy group ($P < 0.001$).

Reduction in tooth size

The total tooth size was reduced as a result of chemotherapy or radiation therapy (Table 3). Children receiving TBI/CY in the BMT group exhibited the most extensive reduction. Compared with the control group, reductions in tooth size varied from 19 per cent in the incisors to 39 per cent in the second molars. The corresponding values in the chemotherapy group were 7 and 15 per cent. The previous prophylactic cranial irradiation given to 13 patients in this group did not seem to affect the size of the examined mandibular teeth significantly.

Crown size in the BMT group was significantly more reduced compared with the control and chemotherapy groups. In the chemotherapy group no significant reduction was seen in crown area in the incisors, whereas a significant reduction was seen in canines ($P < 0.01$), premolars and molars ($P < 0.001$).

The reduction in total tooth size was mainly due to severe disturbances in root development, which were particularly pronounced in the BMT group (Table 4). The mean reduction ranged from 24 per cent in the incisors to 46 per cent in the second molars in the BMT group, compared with 13 per cent in incisors and 18 per cent in second molars in the chemotherapy group.

When comparing crown/root ratios (Table 5) in the BMT and control groups, the indices for incisors, canines ($P < 0.05$) and molars ($P < 0.01$) in the BMT group were significantly higher.

Regression lines were calculated for crown/root ratios to age at TBI or initiation of chemotherapy, and a significant correlation was found in the BMT group for all teeth examined ($P < 0.05$), while no correlation was found in the chemotherapy group (Figure 3A–D).

Table 3 Mean areas (mm^2) of mandibular teeth obtained from panoramic radiographs in the two patient groups and one control group: comparison of mean values.

Tooth	(A) BMT group (n = 16)[1]		(B) Chemotherapy group (n = 52)[2]		(C) Control group (n = 156)[3]		Significance[4], per cent reduction				
	x	SD	x	SD	x	SD	A–B	B–C	%	A–C	%
Central incisor	79.0	18.2	91.1	19.5	97.8	18.4	*	*	7	***	19
Lateral incisor	84.2	21.4	104.3	19.8	116.3	20.6	***	**	10	***	28
Canine	120.9	41.0	159.2	32.4	182.2	47.1	***	**	13	***	34
First premolar	100.3	30.6	128.5	21.8	148.6	38.4	***	**	13	***	32
Second premolar	105.2	36.1	133.9	31.5	155.6	42.0	**	**	14	***	32
First molar	201.4	48.8	239.8	40.7	284.4	49.6	**	***	16	***	29
Second molar	164.4	48.1	228.2	46.8	268.1	53.1	***	*	15	***	39

[1] Due to aplasia or incomplete root development, $n = 12$ for second premolars and $n = 13$ for second molars.
[2] Due to aplasia or incomplete root development, $n = 39$ for second premolars and $n = 47$ for second molars.
[3] Due to aplasia or incomplete root development, $n = 129$ for second premolars and $n = 100$ for second molars.
[4] Student's t-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 4 Mean root areas (mm^2) of mandibular teeth obtained from panoramic radiographs in two patient groups and one control group: comparison of mean values.

Tooth	(A) BMT group (n = 16)[1]		(B) Chemotherapy group (n = 52)[2]		(C) Control group (n = 156)[3]		Significance[4], per cent reduction				
	x	SD	x	SD	x	SD	A–B	B–C	%	A–C	%
Central incisor	39.6	14.6	45.0	11.8	52.0	10.1	NS	**	13	***	24
Lateral incisor	40.0	17.4	52.8	12.7	63.1	13.9	**	***	16	***	37
Canine	63.0	30.3	89.5	25.8	104.4	39.4	**	*	14	***	40
First premolar	47.5	21.3	62.9	17.7	74.9	30.4	**	*	16	***	37
Second premolar	48.9	24.9	64.2	22.2	78.6	35.4	*	*	18	***	38
First molar	99.3	43.7	124.4	30.1	151.5	37.1	*	***	18	***	34
Second molar	72.8	36.2	112.1	29.5	135.9	41.6	***	**	18	***	46

[1] Due to aplasia or incomplete root development, $n = 12$ for second premolars and $n = 13$ for second molars.
[2] Due to aplasia or incomplete root development, $n = 39$ for second premolars and $n = 47$ for second molars.
[3] Due to aplasia or incomplete root development, $n = 129$ for second premolars and $n = 100$ for second molars.
[4] Student's t-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 5 Ratios for crown/root areas in two patient groups and one control group. Comparisons of mean values.

Tooth	(A) BMT group (n = 16)[1]		(B) Chemotherapy group (n = 52)[2]		(C) Control group (n = 156)[3]		Significance[4], per cent reduction		
	x	SD	x	SD	x	SD	A–B	B–C	A–C
Central incisor	1.12	0.45	1.08	0.40	0.93	0.38	NS	*	*
Lateral incisor	1.32	0.69	1.02	0.34	0.88	0.33	*	*	*
Canine	1.10	0.51	0.85	0.35	0.90	0.54	*	NS	*
First premolar	1.27	0.46	1.14	0.49	1.19	0.65	NS	NS	NS
Second premolar	1.42	0.78	1.21	0.45	1.27	0.77	NS	NS	NS
First molar	1.21	0.49	0.97	0.24	0.94	0.37	**	NS	**
Second molar	1.42	0.47	1.01	0.29	1.07	0.37	***	NS	**

[1] Due to aplasia or incomplete root development, n = 12 for second premolars and n = 13 for second molars.
[2] Due to aplasia or incomplete root development, n = 39 for second premolars and n = 47 for second molars.
[3] Due to aplasia or incomplete root development, n = 129 for second premolars and n = 100 for second molars.
[4] Student's t-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Discussion

The results of this study indicate that all teeth are affected by antineoplastic therapy initiated in children below 12 years of age. The use of multiagent chemotherapy, often combined with radiation therapy, makes it difficult to attribute defects in odontogenesis to any single agent or therapy in these cases. The present results, however, provide an opportunity to distinguish between disturbances caused by chemotherapeutic agents on the one hand and total body irradiation in combination with chemotherapy on the other.

BMT group

Children treated with TBI/CY exhibited significantly more disturbances in dental development than children treated with multiagent chemotherapy. The most common abberation was arrested root development and short V-shaped roots, which was found in 94 per cent of the children treated with TBI/CY. In a study of 20 children treated for soft tissue sarcomas of the head and neck, it was found that any developing tooth in a treated field receiving a radiation dose of 4 Gy showed some developmental abnormality (Fromm *et al.*, 1986). Sonis *et al.* (1990) studied 97 children who were diagnosed with acute lymphoblastic leukaemia before 10 years of age, and treated with chemotherapy alone or in combination with cranial irradiation. It was shown that the most severe developmental dental derangement occurred in patients who were younger than 5 years of age at the time of cranial irradiation. This was probably due to the relatively high position of the maxillary permanent posterior tooth germs in young children, which would place those teeth in the direct field of irradiation. Therefore, the most pronounced effect was seen in the maxillary posterior teeth.

As regards tooth dimensions in the BMT group, the present results demonstrate a general reduction in size which was most obvious in the second molars (39 per cent, Table 3).

A separate evaluation of the root areas showed that the size reduction in the BMT group for this variable was even more pronounced. These findings were confirmed by the crown/root ratios, which were greater in general in the BMT group than in the control group, a fact which indicates that the treatment given in the patient

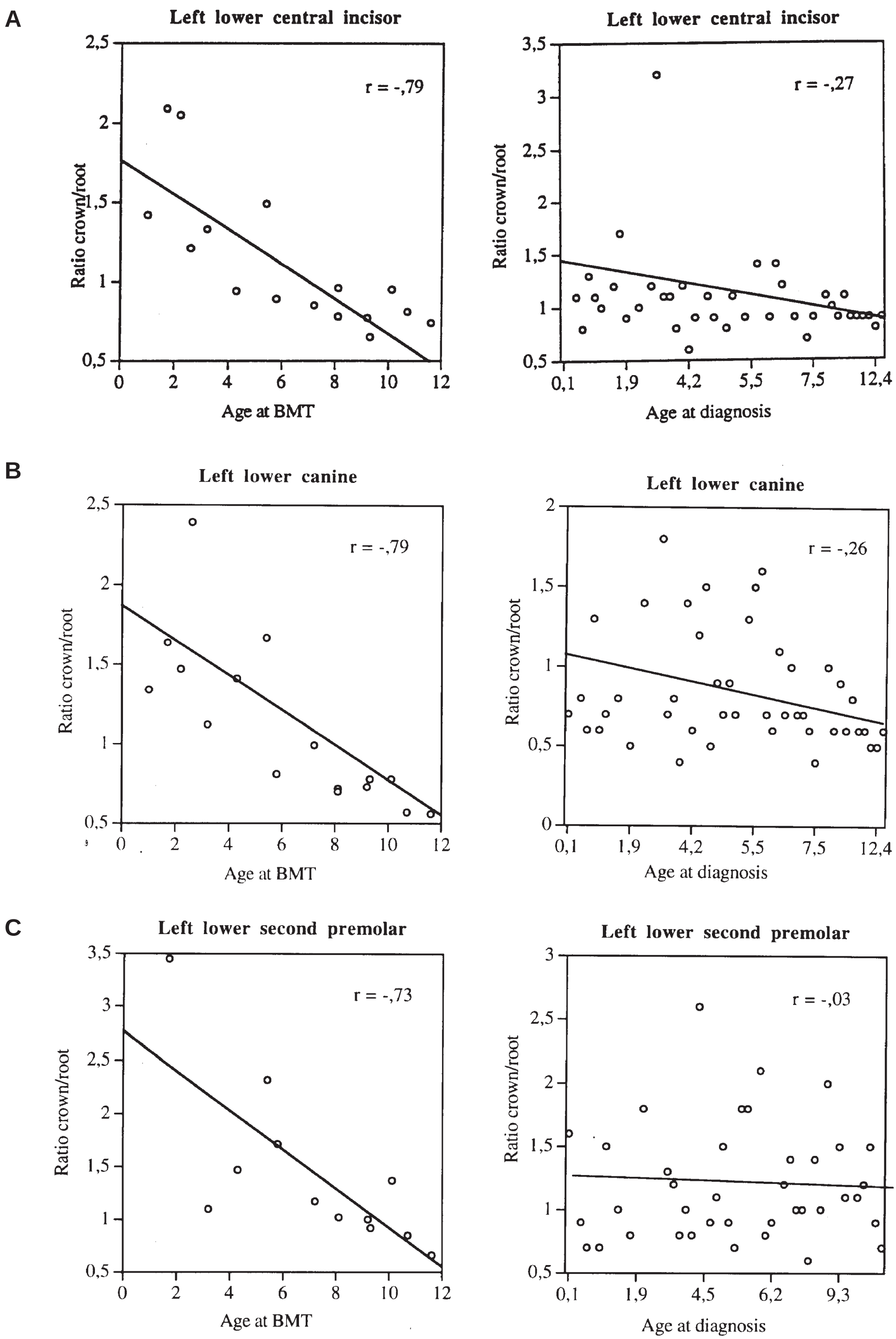
A
Left lower central incisor
r = -,79
Ratio crown/root
Age at BMT
Left lower central incisor
r = -,27
Ratio crown/root
Age at diagnosis
B
Left lower canine
r = -,79
Ratio crown/root
Age at BMT
Left lower canine
r = -,26
Ratio crown/root
Age at diagnosis
C
Left lower second premolar
r = -,73
Ratio crown/root
Age at BMT
Left lower second premolar
r = -,03
Ratio crown/root
Age at diagnosis

Figure 3 (A–C).

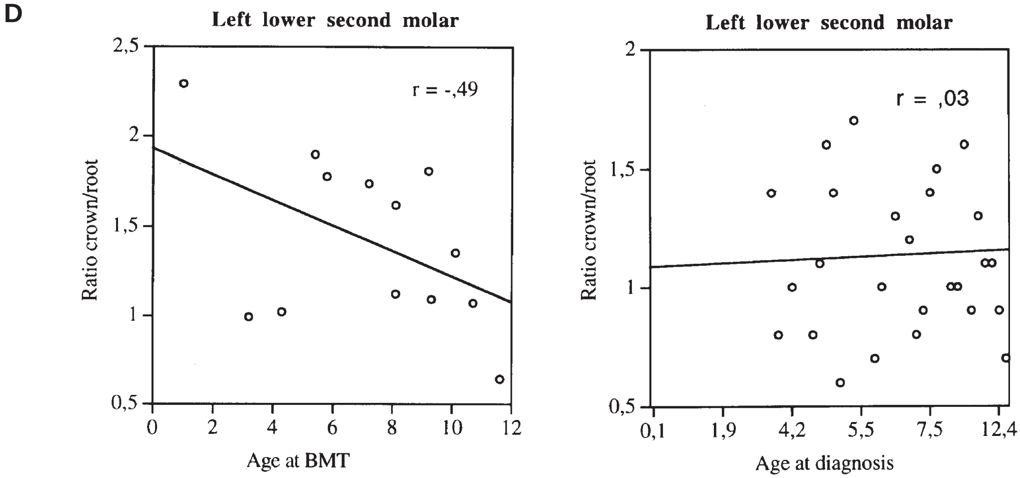

Figure 3 Regression lines. (A) Left figure = BMT group, right figure = chemotherapy group. Crown/root ratio to age at BMT or diagnosis for lower left central incisor. (B) Left figure = BMT group, right figure = chemotherapy group. Crown/root ratio to age at BMT or diagnosis for lower left canine. (C) Left figure = BMT group, right figure = chemotherapy group. Crown/root ratio to age at BMT or diagnosis for lower left second premolar. (D) Left figure = BMT group, right figure = chemotherapy group. Crown/root ratio to age at BMT or diagnosis for lower left second molar.

group had a particularly damaging effect on root development.

The importance of age at BMT as a factor influencing the crown/root ratios is illustrated by the regression lines in Figure 3A–D: the younger the patient at BMT, the more detrimental the effects on root development. Previous results have also shown that the most severe disturbances in dental development occur in patients who are below 6 years of age at BMT (Dahllöf *et al.*, 1988a). In the chemotherapy group no association between age at start of treatment and size of crown/root ratio was found (Figure 3A–D).

The negative effects on tooth development found in the BMT group may be explained by the fact that developing dental structures are particularly sensitive to radiation. High-dose radiation therapy causes damage to the odontoblasts and ameloblasts in susceptible phases of the cell cycle and, in contrast to chemotherapeutic agents, also to nonproliferating dental cells. Odontoblasts are most susceptible to radiation before the initiation of dentine matrix formation. The presecretory odontoblasts proliferate rapidly and have an increased mitotic activity (Koppang, 1973a,b).

Chemotherapy group

Ten children out of 52 (19 per cent) treated with combination chemotherapy exhibited short V-shaped roots. This is in agreement with the results of Rosenberg *et al.* (1987), who found that five patients out of 17 (29 per cent) had marked shortening of premolar dental roots. However, whereas Rosenberg *et al.* (1987) reported this effect only in premolars, the present results demonstrate reduced root size in all teeth.

Pajari *et al.* (1988) used planimetry to measure tooth areas in children treated with chemotherapy. The results of this study show that the mean root areas of all teeth, except the canines, were reduced in the children with cancer as compared with the control children. The mean crown areas were not affected. This is in contrast to the present result, which demonstrated crown size reduction in all teeth except incisors. The fact that the incisors did not exhibit reduction increown size may be explained by the comparatively early completion of mineralization of the crowns of these teeth (before 4 years of age). The chemotherapy was initiated in most children after 4 years of age and therefore affected root development to a greater extent.

Animal studies have shown that chemotherapeutic agents induce both qualitative and quantitative changes in both the enamel and dentine of the crown (Koppang, 1973a,b; Stene, 1979). However, the extent of these changes depends on factors such as 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 less affected, and differentiated odontoblasts probably have the ability to produce dental tissues even during chemotherapy. This may explain why the crown/root ratio in most types of teeth in the chemotherapy group did not differ significantly from the crown/root ratios in the control group.

In conclusion, the results of this study show that all developing teeth are irreversibly affected by multiagent chemotherapy and radiation therapy. The results also indicate that irradiation produces more severe effects than chemotherapeutic agents.The most severe disturbances were found in children treated with TBI at a young age. Taking these facts into consideration, particular care in the supervision of dental development is recommended after successful treatment of paediatric malignant disease.

Address for correspondence

Dr Margareta Näsman
Department of Orthodontics and
Pediatric Dentistry
Karolinska Institutet, PO Box 4064
S-141 04 Huddinge
Sweden

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