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Research Article

Dental Anomalies after Chemotherapy in Childhood Cancer Survivors: A Cross Sectional Study

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Abstract

Background: Since cancer therapy regimens mostly involve combinations of chemotherapy, radiotherapy, bone marrow transplantation and/or surgery, determining the causality of the dental anomalies observed in cohorts of childhood cancer survivors has been a challenge. Fortunately, effects of radiotherapy and surgery are localized however, due to the lack of specificity of these agents, chemotherapy affects the entire body. Therefore, this study aims to describe the effect of chemotherapy on dental development.

Methods: A total of 144 cancer survivors were selected from Children Cancer Hospital Egypt 57357 using stratified random sampling. The selected subjects matched the following criteria: (1) cancer survivors who were at least 6 years old (2) children who first started receiving chemotherapy at 4 years old or younger. We excluded (1) children who received radiotherapy on head and/or neck (2) children who received bone marrow transplantation (3) children with any associated developmental anomalies. Eligible subjects were assessed radiographically for dental anomalies of the permanent dentition using Holtta's Defect Index (DeI).

Results: 70.14% of the subjects had at least one dental anomaly (DeI ≥ 1). The highest mean DeI was of bone tumors while the least mean was of soft tissue sarcoma. The most frequently detected anomaly was microdontia (56.9%). Microdontia occurred most commonly (71%) in Acute Myeloid Leukemia and Non-Hodgkin's Lymphoma, while root resorption and hypdontia affected mostly bone tumors (66.67%, 33.33%, respectively).

Conclusion: This study confirms that children who receive antineoplastic chemotherapy before the age of 4 years are at high risk of developing dental anomalies.

Keywords: *Tooth Abnormalities; Neoplasms; Drug therapy; Anadontia; Tooth Root; Tooth Crown; Cancer Survivors*

Introduction

Over the last 30 years, the major advances in cancer therapy have increased the survival rates of childhood cancers. Now, more than 80% of children with cancer can survive for 5 years or more. In the mid-1970s, the 5-year survival rate was only 58% [1].

As the prognosis of cancer improved and survival rates increased, more attention has been focused on the late effects of the cancer therapy. Almost two-thirds of childhood cancer survivors are expected to experience a late effect of the therapy [2-4].

There is strong evidence in the literature to support the association between cancer therapy and dental anomalies [5-9]. However, very few studies have investigated the effect of a specific type of antineoplastic treatment (i.e, chemotherapy, radiotherapy, surgery or bone marrow transplantation) on the dental development. And of these studies, some were limited by the inclusion of children of highly variable age at start of cancer treatment while others were limited by the low number of subjects in the exposure group [7,9-11].

Also, most of the studies assessed the effect of chemotherapy on the dental development of children with leukemia while there is little information on the effects of chemotherapy in other neoplasms [11-17]. Therefore, this cross sectional study (ClinicalTrials.gov

NCT03445026) was designed to examine the effect of chemotherapy on the dental development of children with various types of neoplasms.

Materials and Method

This study was approved by the Institutional Review Board of Children Cancer Hospital Egypt 57357 and the Ethics Committee of the Faculty of Dentistry Cairo University. All participants provided an informed consent. This article conforms to the STROBE guidelines.

Recruitment

The Children Cancer Hospital Egypt 57357 electronic database was used in recruitment. Inclusion criteria were as follows: (1) cancer survivors who are at least 6 years old (2) first started receiving chemotherapy when they were 4 years old or younger. Exclusion criteria included: (1) subjects who received radiotherapy on head and/or neck, (2) subjects who received bone marrow transplantation and (3) subjects with any associated developmental anomalies (eg, ectodermal dysplasia, cleft lip or palate and Down syndrome). The database provided a list of 937 potential eligible patients and their contact information.

Based on a previous study by Pedersen., *et al* 2012, a total sample size of 144 cases were needed to provide a two-sided 95% confidence interval for a single proportion using the large sample normal approximation and was extended 5% from the observed proportion for an expected proportion of 0.105. Sample size estimation was performed by Epi Info statistical package.

The 144 cancer survivors were selected using stratified random sampling and were contacted to attend to the dental department of Children Cancer Hospital Egypt 57357. The survey was conducted in two phases –eligibility screening followed by a panoramic radiograph examination. The screening consisted of a series of questions on the participant's dental history and family history of dental anomalies. Dental Panoramic radiographs were taken using ORTHOPHOS XG5 (Dentsply Sirona, Germany) and were evaluated using Holtta's Defect Index (DeI) to assess dental anomalies. All permanent teeth, excluding third molars, were assessed in successive quadrants and each tooth was given a number using the criteria in table 1.

ND	Not determined: (a) Developing teeth with an unclear final outcome (b) Teeth not reliably seen on radiograph
D0	R/C ratio >1.6; no disturbance
D1	R/C ratio 1.2-1.6; mild disturbance
D2	R/C ratio 0.9-1.1; severe disturbance
D3	R/C ratio <0.9; very severe disturbance or arrested root development
D4	Microdontia
D5	Hypodontia

Table 1: *Holtta's Criteria of Radiological Evaluation for Permanent Dentition.*

The defect index score (DeI) was finally calculated using the following equation: (nD1 x 1) + (nD2 X 2) + (nD3 X 3) + (nD4 X 4) + (nD5 x 5), where n is the number of teeth affected in each category [5].

Crown/root ratios were measured using the "SIDEXIS neXt Generation" software (Dentsply Sirona, Germany) as previously described by Holtta., *et al.*

Statistical analysis

Statistical analysis was performed with SPSS 20®, Graph Pad Prism® and Microsoft Excel 2016. At first, descriptive study was performed using cross-tabulation. Then, one way analysis of variance (ANOVA) test was performed followed by Tukey`s post hoc test for multiple comparisons to detect the level of significance between all tumors for each index and between all indices for each tumor type. The significant level was set at $P \leq 0.05$ [9,18].

Results

The mean age of the study sample was 10.22 (± 2.81) years old at examination and 2.56 (± 1.02) years at start of chemotherapy. Most of our study sample received chemotherapy for Acute Lymphoblastic Leukemia (38.2%) as shown in table 2. Regarding gender distribution, most of our sample were males (56.3% of 144).

	Count	%
Acute Lymphoblastic Leukemia	55	38.2%
Acute Myeloid Leukemia	7	4.9%
Bone tumors	3	2.1%
Brain tumors	2	1.4%
Germ Cell Tumor	6	4.2%
Hepatoblastoma	4	2.8%
Hodgkin's Lymphoma	2	1.4%
Langerhan's Cell Histiocytosis	7	4.9%
Neuroblastoma	19	13.2%
Non-Hodgkin's Lymphoma	17	11.8%
Renal tumors	14	9.7%
Retinoblastoma	4	2.8%
Soft tissue sarcoma	4	2.8%
Total	144	100%

Table 2: *Disease distribution of the study population.*

Of the total study sample, 70.14% of the 144 subjects had a Holtta Defect Index (DeI) score of 1 or more. The mean DeI for the study population was 9.3 (± 10.13). The tumor type with the highest mean DeI was bone tumor (19.67 ± 18.61), followed by acute lymphoblastic leukemia (12 ± 11.32) while the least mean values were with soft tissue sarcoma (2 ± 4), followed by langerhan's cell histiocytosis (3.28±4.35). Microdontia (56.9%) was the most frequently detected anomaly followed by root resorption (19.44 %) and hypodontia (9.72%). Microdontia occurred most commonly (71%) in subjects receiving chemotherapy for Acute Myeloid Leukemia and Non-Hodgkin's Lymphoma, while root resorption and hypdontia affected mostly children with bone tumors (66.67%, 33.33%, respectively). The distribution of the dental anomalies according to tumor types is described in table 3.

	D1	D2	D3	D4	D5	DeI (M±SD)
	Count (%)					
Acute Lymphoblastic Leukemia	35%[a]	9%[a]	0%[a]	62%[a]	3.64%[a]	12 ± 11.32 a
Acute Myeloid Leukemia	14%[b]	0%[a]	0%[a]	71%[a]	0.00%[a]	8.28 ± 7.34 a
Bone tumors	67%[c]	33%[a]	33%[b]	67%[a]	33.33%[a]	19.67 ± 18.61 a
Brain tumors	50%[c]	0%[a]	0%[a]	50%[a]	0.00%[a]	5.5 ± 3.53 a
Germ Cell Tumor	0%[b]	0%[a]	0%[a]	50%[a]	0.00%[a]	4.67 ± 6.4 a
Hepatoblastoma	25%[b]	0%[a]	0%[a]	25%[a]	25.00%[a]	5 ± 6.88 a
Hodgkin's Lymphoma	0%[b]	0%[a]	0%[a]	50%[a]	0.00%[a]	6 ± 8.49 a
Langerhan's Cell Histiocytosis	0%[b]	0%[a]	0%[a]	14%[a]	28.57%[a]	3.28 ± 4.35 a
Neuroblastoma	5%[b]	0%[a]	0%[a]	58%[a]	21.05%[a]	10.26 ± 10.21 a
Non-Hodgkin's Lymphoma	0%[b]	0%[a]	0%[a]	71%[a]	11.76%[a]	9.12 ± 9.49 a
Renal tumors	0%[b]	0%[a]	0%[a]	57%[a]	7.14%[a]	7.07 ± 9.17 a
Retinoblastoma	25%[b]	0%[a]	0%[a]	50%[a]	25.00%[a]	4.5 ± 6.14 a
Soft tissue sarcoma	0%[b]	0%[a]	0%[a]	33%[a]	0.00%[a]	2 ± 4 a
P-value	0.022**	0.804*	0.00**	0.317*	0.219*	0.2665*

Table 3*: Distribution and comparative analysis of each Holtta Defect Index score according to tumor type.*
*M; Mean, SD; Standard Deviation, P; Probability Level Values with same superscript letter in the same column were insignificant different Values with different superscript letter in the same column were significant different *insignificant different.*

There was no statistical significant difference between tumor types for D2, D4, D5 and DeI. However, there was a statistical significant difference between tumor types for D1 and D3, as shown in table 2.

Also, there was a statistical significant difference between the defect indices for Acute Lymphoblastic Leukemia**,** Acute Myeloid Leukemia, Germ Cell Tumor, Neuroblastoma, Non-Hodgkin's Lymphoma and Renal tumors, as shown in table 4.

	D1	D2	D3	D4	D5	P-value
	Count (%)					
Acute Lymphoblastic Leukemia	35%[a]	9%[b]	0%[b]	62%[c]	3.64%[b]	<0.0001**
Acute Myeloid Leukemia	14%[a]	0%[b]	0%[b]	71%[c]	0%[b]	0.046**
Bone tumors	67%[a]	33%[a]	33%[a]	67%[a]	33.33%[a]	0.33*
Brain tumors	50%[a]	0%[a]	0%[a]	50%[a]	0%[a]	0.589*
Germ Cell Tumor	0%[a]	0%[a]	0%[a]	50%[b]	0%[a]	0.03**
Hepatoblastoma	25%[a]	0%[a]	0%[a]	25%[a]	25.00%[a]	0.615*
Hodgkin's Lymphoma	0%[a]	0%[a]	0%[a]	50%[a]	0%[a]	0.486*
Langerhan's Cell Histiocytosis	0%[a]	0%[a]	0%[a]	14%[a]	28.57%[a]	0.331*
Neuroblastoma	5%[a]	0%[a]	0%[a]	58%[b]	21.05%[c]	<0.0001**
Non-Hodgkin's Lymphoma	0%[a]	0%[a]	0%[a]	71%[b]	11.76%[c]	<0.0001**
Renal tumors	0%[a]	0%[a]	0%[a]	57%[b]	7.14%[c]	0.000185**
Retinoblastoma	25%[a]	0%[a]	0%[a]	50%[a]	25.00%[a]	0.306*
Soft tissue sarcoma	0%[a]	0%[a]	0%[a]	33%[a]	0.00%[a]	0.263*

Table 4: *Comparative Analysis between Defect Indices for Each Tumor.*

*%; Percentage, P; Probability Level Values with same superscript letter in the same row were insignificant different Values with different superscript letter in the same row were significant different *insignificant different **significant different.*

Discussion

The present study confirmed that chemotherapy can on its own affect dental development, thereby resulting in dental anomalies. We found dental anomalies, including microdontia, hypodontia and root resorption, in more than half of the survivors who received multiagent chemotherapy when 4 years of age or younger. Because dental development is very active during this period, the high frequency of dental anomalies was not surprising.

We enrolled subjects who were 4 years old or younger when they first started receiving chemotherapy because previous studies have found that the association between chemotherapy and dental abnormalities was influenced by younger age at chemotherapy [10, 12, 19].

Eligible subjects were cancer survivors who were at least 6 years old to ensure that the permanent tooth germs have reached a certain level of calcification where it can be evident on the radiograph. Inclusion of too young individuals might make insufficiently calcified tooth buds be mistakenly diagnosed as missing teeth [20-22].

Holtta's defect index was used in our assessment of the radiographs because it has an excellent intra- and inter-examiner reliability which has indicated that the method is repeatable [5,7,9]; also, the use of this validated index allows our results to be compared with other studies.

This study excluded any consideration of third molars because the tooth germ formation and calcification starts at the ages of 3 - 4 years and 7 - 10 years respectively, and further the number of disturbances in the development of these teeth was highly observed in the general population [23].

According to our study, 70.14% of the children who received chemotherapy had disturbances in dental development. In a study done in 2012 on 509 healthy Egyptian orthodontic patients, only 32.6% of the patients had dental anomalies other than agenesis of third molars [24]. In another study conducted in the outpatient clinic of the Faculty of dentistry, Cairo University on a 1000 healthy Egyptian children, the frequency of dental anomalies found was 11.2% [25]. This finding is in accordance with earlier studies [7- 9,26] who also reported a higher prevalence of dental anomalies in cohorts of children receiving cancer therapy when compared to healthy controls.

The mean DeI for all the tumors included in the study was in accordance with the results revealed by Sevinir., *et al.* 2012 (10.8 ± 11.2) who examined 37 childhood cancer survivors treated under the age of 10 years with multimodal chemotherapy and/or head and neck radiotherapy for solid tumors and lymphomas and Krasuska-Sławińska., *et al.* 2016 (12.48 ± 13.16) who examined 60 patients who underwent chemotherapy for various tumors. Sevinir., *et al*. 2012 and Krasuska-Sławińska., figure 2016 also examined healthy controls and revealed a mean DeI of 1.9 ± 2.7 and 2.24 ± 3.84, respectively. The mean DeI of 24 healthy Egyptian children (age 11.46 ± 1.72) was examined by El Noury., *et al.* 2016 and was revealed 3.42 ± 3.09.

The total frequency of hypodontia in our study population excluding third molars was found to be 9.72% (14 of 144). In healthy Egyptian children, the prevalence of hypodontia excluding third molars was amounted to 2-4% [24,25].

The finding of a higher frequency of hypodontia in children exposed to chemotherapy in supports findings from several previous studies. Oğuz., *et al.* 2004 found that 44% of the 36 children treated with chemotherapy for Non Hodgkins Lymphoma had hypodontia while the percentage was 25% of the 36 healthy controls. Also, Sevinir., *et al.* 2012 found that 18% of the 27 children receiving chemotherapy only had hypodontia while none of the healthy control subjects included in the study had this condition. Sevinir., *et al.* 2012 then compared the results to a survey that revealed that the prevalence of hypodontia in healthy Turkish children was 2.6%.

The frequency of hypodontia in our study was in accordance with Pedersen., *et al.* 2012 who found that (9.3%) of the children who received chemotherapy below 8 years at start of treatment had hypodontia of at least one tooth. Lopes., *et al.* 2006 however reported a lower frequency of hypodontia (6%) in the 137 children treated for various tumors with chemotherapy alone or in combination with radiotherapy whereas Krasuska-Sławińska., *et al.* 2016 found a higher frequency of hypodontia (27%) after chemotherapy than that presented in our study.

Our recording of microdontia was higher than previous studies. Lopes et al. 2006 found that microdontia occured in only 7% of 137 childhood cancer survivor who were submitted for chemotherapy alone or in combination with radiotherapy of the head and neck whilst Pedersen., *et al.* 2012 reported 19% of the 150 childhood cancer survivors. Krasuska-Slawinska., *et al.* 2016 reported microdontia in 22% of the 60 children who completed their chemotherapeutic treatment for various neoplasms. Still, however, our finding of a higher frequency of microdontia in cohorts of childhood cancer survivors when compared to healthy Egyptian controls [17] is in accordance to the previous studies.

The frequency of root resorption in our study was lower than that recorded by both Krasuska-Slawinska., *et al.* 2016 (60%) and Sevinir., *et al.* 2012 (86.4%).

As we compared this study's results with previous studies, it is possible to notice the many differences between the rates of dental abnormalities reported by other studies; this is probably due to the different assessment methodologies, different studied populations and the different number of tumor types included in the studies' population. Also some studies included children who were submitted for chemotherapy in combination with radiotherapy of the head and neck.

The insignificant statistical difference between tumor types for D2 (severe R/C disturbance), D4 (microdontia), D5 (hypodontia) and DeI may be due to the smaller number of subjects in some tumor types. On the other hand, the significant statistical difference that was

found between tumor types for D1 (mild R/C disturbance) and D3 (arrested root development) could be due to the association of gene mutations governing root resorption with certain tumor types. Several studies [27-29] have correlated the degree and severity of root resorption with variations in the Interleukin 1 beta gene, a cytokine which has been implicated as a factor in cancer risk [30] and tumor progression [31].

Also, the significant statistical difference found between the defect indices for Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Germ Cell Tumor, Neuroblastoma, Non-Hodgkin's Lymphoma and Renal tumors may be due to the fact that genes involved in dental development also have roles in other organs of the body. Several studies have associated mutations in genes governing tooth development with cancer [32-35]. RUNX (Runt related transcription factor) 1, 2, and 3, are genes involved in odontogenesis and have been the most targeted genes in acute myeloid leukemia and acute lymphoblastic leukemia. Furthermore, RUNX2 is amplified in various cancers including osteosarcoma and may play a role in breast and prostate cancer [36]. Mutations in AXIN2 (axis inhibition protein 2) causing hypodontia were also associated with colorectal cancer [33] and ovarian cancer [37].

Conclusion

Finally, the current observations suggest that chemotherapy disrupts the dental development and that children receiving chemotherapy are at a higher risk of developing dental anomalies. We recommend that studies would attempt to investigate the exact chemotherapeutic agent responsible for each dental anomaly. Additional studies that can evaluate the effect of genetics on dental anomalies are also needed since it may improve the precision to identify survivors at risk for dental late effects.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Author Contributions

G. A. Tahoun contributed to conception, design, data acquisition, analysis and interpretation, drafted and critically revised the manuscript. S. A. Mahmoud contributed to design and critically revised the manuscript. L. M. Shalaby contributed to interpretation and critically revised the manuscript. A. E. Abd El-Latif contributed to design and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

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