eLRD in Clinical and Laboratorial Research in Dentistry | Oral Pathology

A systematic review of the long-term effects of dental development disturbances after hematopoietic stem-cell transplantation in pediatric patients

• **Alexandre Viana Frascino** Department of Oral Surgery, Faculdades Metropolitanas Unidas, São Paulo, SP, Brazil • **Fábio Luiz Coracin** Department of Health III, Nove de Julho University, São Paulo, SP, Brazil • **Paulo Sérgio da Silva Santos** Department of Stomatology, Bauru School of Dentistry, University of São Paulo, Bauru, SP, Brazil

ABSTRACT | The purpose of this systematic review was to evaluate published data and to update our current knowledge about the impact on dental development of childhood hematopoietic stem-cell transplantation (HSCT), as well as the late effects of preparative regimens, for the treatment of onco-hematological malignancies. A systematic literature research was conducted to assess articles published since January 1980 until the present day that fitted the predetermined inclusion/exclusion criteria. Data compilation was divided into qualitative and quantitative dental development disturbances. Demographic records were also gathered. First and second premolars and second molars were significantly more affected in HSCT children. There was a positive correlation between age at the time of anticancer therapy administration and qualitative and quantitative dental development disturbances. The association of total body or head and neck radiation mieloablative treatments was shown to enhance the magnitude of dental development disturbances. Dental development disturbances due to childhood HSCT are commonly seen in long-term survivors. The knowledge of these alterations may help improve dental care and elevate the quality of life of these patients. Further studies are needed to understand the long-term effects of dental development disturbances in this group of patients.

DESCRIPTORS | Bone Marrow Transplantation; Hematopoietic Stem Cell Transplantation; Child; Drug Therapy; Radiotherapy.

RESUMO | **Revisão sistemática dos efeitos tardios de distúrbios de desenvolvimento dentário em pacientes submetidos a transplante de células-tronco hematopoiéticas durante a infância** • O objetivo desta pesquisa foi revisar sistematicamente as publicações referentes aos efeitos tardios decorrentes das alterações do desenvolvimento dentário em pacientes submetidos ao transplante de células-tronco hematopoiéticas durante a infância. A pesquisa sistemática da literatura avaliou os artigos publicados desde janeiro de 1980 até a presente data que se enquadraram nos critérios de inclusão/exclusão pré-determinados. A compilação dos dados foi dividida em distúrbios de desenvolvimento dentário qualitativos e quantitativos. Além disso, os registros demográficos foram contabilizados. Os primeiros e segundos pré-molares e os segundos molares foram os dentes significativamente mais afetados nas crianças submetidas ao transplante de células-tronco hematopoiéticas. Houve uma correlação positiva entre a idade em que as terapias antineoplásicas foram administradas e os distúrbios de desenvolvimento dentário qualitativos e quantitativos. A associação do tratamento mieloablativo por meio de radioterapia total ou em região de cabeça e pescoço apresentou correlação positiva com os distúrbios de desenvolvimento dentário. Essas alterações podem ser comumente vistas em pacientes que conseguem sobreviver ao transplante de células-tronco hematopoiéticas durante a infância. O conhecimento dessas alterações pode ajudar a melhorar o atendimento odontológico e elevar a qualidade de vida desses pacientes. Mais estudos são necessários para entender os efeitos de longo prazo dos distúrbios de desenvolvimento dentário para esse grupo de pacientes.

DESCRITORES | Transplante de Médula Óssea; Transplante de Células-Tronco Hematopoéticas; Criança; Quimioterapia; Radioterapia.

CORRESPONDING AUTHOR | • **Alexandre Viana Frascino** Department of Oral Surgery, Faculdades Metropolitanas Unidas, • **Rua Três de Maio, 61, ap. 61** São Paulo, SP, Brazil • **CEP 04044-020**
E-mail: alexandre.frascino@usp.br

• **Received** Sep 03, 2014 •**Accepted** Nov 14, 2014

INTRODUCTION

The treatment of childhood onco-hematological malignancies through hematopoietic stem-cell transplantation (HSCT) combined with surgery, multi-agent chemotherapy (CT) and/or radiotherapy (RT) has been successfully employed in more than 30,000 patients per year worldwide with successful results.[1,2] Currently, a 5-year survival rate for the most common hematologic neoplasia—acute lymphoblastic leukemia—has exceeded 80%. In some groups, this rate may achieve 95%.[3,4]

However, at least more than two-thirds of these children may present several long-term complications due to HSCT and its preparative regimen.[5,6] It is estimated that between 62% and 95% of the children surviving bone-marrow transplantation (BMT) will experience a late effect resulting from treatment and 27%–40% present serious consequences with elevated risk of death.[7] The most commonly reported systemic complications involve the endocrine system, heart, lung, kidneys, bones and neurological structures, and may present as osteopenia, growth deficiency, changes in anatomical proportions, hypogonadism, premature menopause/andropause and disorders in the development of secondary sexual characteristics.[8-10]

Dental development disturbances from HSCT have also been described and may involve tooth agenesis, microdontia, shortened roots, changes in tooth proportions (namely in the crown/root ratio), root stunting and V-shaped apex.[11-15] Chemotherapy-induced tooth formation anomalies have been reported to emerge mostly in the first and second premolars, and the second molar.[15-17] These complications have been mostly associated with patients' younger age at the time of transplantation but great controversy remains about:

1. the real impact of radiation therapies,
2. the extent of dental development disturbances and
3. patients' quality of life impairment due to these complications.[18]

However, in spite of these relevant publications, a conclusive data compilation is still lacking about dentofacial development disturbances in long-term survivors of childhood HSCT. In this paper we present a systematic review of all articles published in English about the dentofacial abnormalities observed in onco-hematologic children submitted to HSCT. The results include summarized demographic data about the patients, and the most commonly observed dental development disturbances findings in these long-term survivals.

METHODOLOGY

Search strategies and criteria for selecting studies

We performed a systematic review of published manuscripts that discussed the dental development disturbances and their subsequent late effects among survivors of HSCT for the treatment of childhood onco-hematological cancer, using the *Pubmed* and *Google Scholar* search engines. The following keyword combinations were employed in this review:

- hematopoietic stem cell transplantation;
- dental abnormalities;
- children;
- tooth development;
- bone marrow transplantation;
- dental development.

All of the article abstracts derived from this search were thoroughly reviewed for relevance. The inclusion criteria encompassed all of the full-articles published in the English language regarding the long-term dental follow-up of childhood-HSCT patients. The exclusion criteria comprised papers that failed to thoroughly present a comprehensive

description of the chemo- and/or radiotherapy involved; studies describing a follow-up period of less than 2 years; case reports or case-series; studies on adult-HSCT; and studies on HSCT for the treatment of solid tumors or congenital diseases.

Data collection

Two authors independently evaluated the methodological quality of selected studies. Study quality was determined using four criteria:

- comparability of subjects,
- clear definition of exposure or intervention,
- standard outcomes measurement and
- appropriate statistical analysis.

Any discrepancy in the validity assessment was resolved by discussion between authors. The relevant data about sample size, age at diagnosis, type of diagnosis, follow-up period, type and details of treatment, late dental effects, and main endpoints from the selected studies were extracted by researchers using a standardized form.

RESULTS

Data compilation

Our initial research retrieved a total of 117 titles and abstracts. After thorough examination of these abstracts and full-text articles, 105 papers were discarded for not matching the inclusion criteria. Ten papers fulfilled all of the previous established inclusion criteria and were considered in this review. Six of them were cross-sectional studies, two were case-controls, one was a retrospective study and one was a cohort study (Figure 1).

All together, the studies evaluated a total of 423 patients with a mean age of 3 years (range: 4.7–25.9 years). Patients' median age at dental evaluation was 9 years, and, at HSCT, it was 3 years. Follow-up median time was 5 years. The most common onco-hematological malignancy was acute lymphoblastic leukemia (ALL) comprising 45% of the diagnoses (n = 190), followed by acute myeloblastic leukemia (AML; 11%, n = 44), and neuroblastoma (NBL; 10%, n = 43). Other diagnoses comprised 45% of the study population (n = 144; Figure 2).

Total body radiation therapy (TBR) was administered to 25.9% (n = 88) of the patients with a mean dose of 11.5 Gy (range: 6–22 Gy), mainly for ALL treatment (76%; n = 72; Figures 3 and 4). When the authors provided a full description of the chemotherapeutic protocols involved, the most

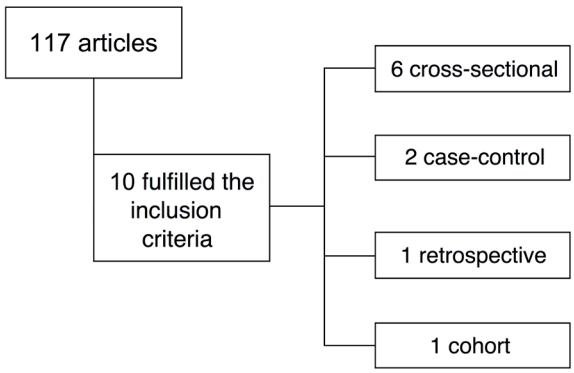

Figure 1 | Paper selection algorithm. The keyword search returned 117 papers. After thorough review, only 10 fulfilled the inclusion criteria. Of these, 6 were cross-sectional studies; 2 were case-control studies; 1 was a retrospective study and 1 was a cohort study.

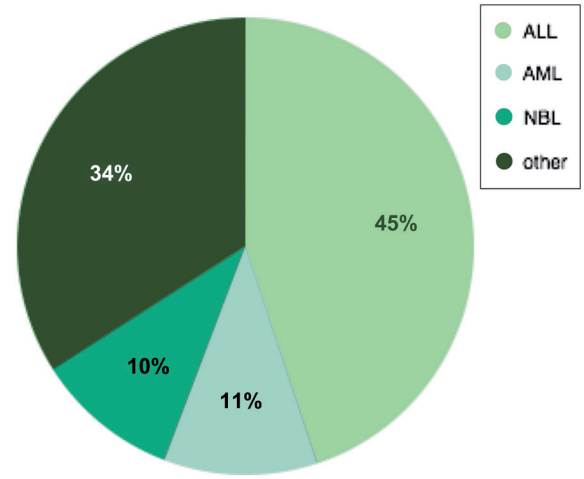

Figure 2 | Descriptive diagnosis distribution. ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; NBL: Neuroblastoma; Other: other onco-hematological malignancies.

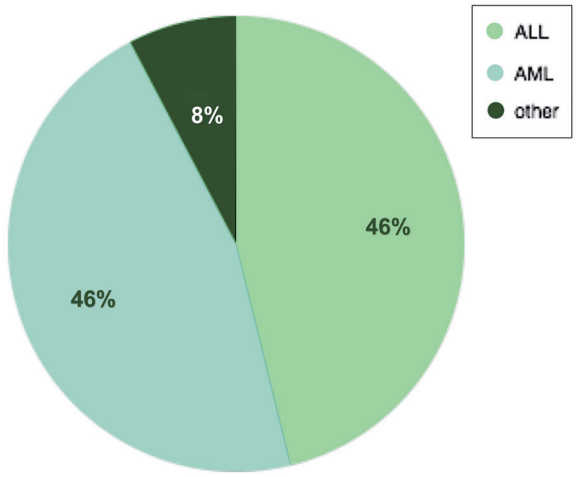

Figure 3 | Total body irradiation (TBI) versus focal radiation therapy (non-TBI; %) disk chart distribution. ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; Other: other onco-hematological malignancies.

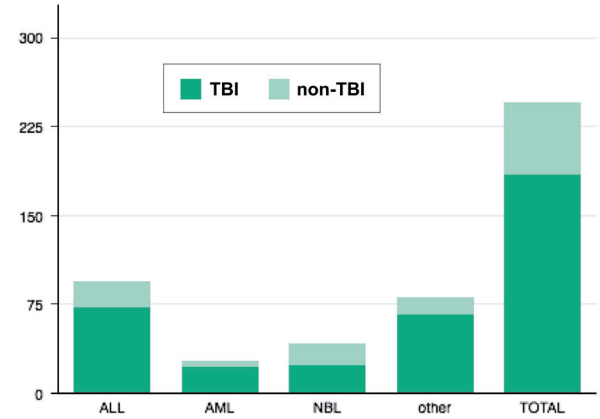

Figure 4 | Total body irradiation (TBI) versus focal radiation therapy (non-TBI; %) column chart comparison. ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; NBL: Neuroblastoma; Other: other onco-hematological malignancies.

common antineoplastic agent was a combination of cyclophosphamide (Cy) or busulfan (Bu) with vincristine (Vin) in association with methotrexate (MTX).

Qualitative comparisons of dental development disturbances

A qualitative evaluation of dental developmental disturbances revealed that the most commonly described dental changes were root stunting, shortened or V-shaped roots, and premature apical closure. The authors also extensively described dental agenesis and microdontia. These alterations were seen in a variable number of patients (33.3%–100%), but most articles concluded that nearly all of the childhood cancer patients submitted to HSCT presented at least one dental development disturbance. The most affected teeth were the first and second premolars and the second molar, with the first molars or anterior teeth rarely being involved. A significant dental development disturbance was found in those patients submitted to radiation therapy as a preparative regimen for HSCT ($p = 0.01$). The studies that presented statistical comparisons between different chemotherapeutic preparative regimens revealed poor statistical significance for differences in chemotherapeutic regimens. Age at HSCT was found to be more relevant in dental development disturbances.

Quantitative comparisons of dental development disturbances

The papers published more recently used panoramic radiography to assess and compare dental developmental disturbances, and these evaluations involved performing tooth-area or crown-root (C:R) ratio measurements with imaging software and then performing statistical comparisons. The authors quantitatively evaluated crown-root proportion alterations and correlated them with administered chemotherapeutic agents, focal or total body radiation therapy, age at HSCT and, in one study, alveolar bone growth and facial development.[5]

The evaluation of tooth area or C:R proportion revealed that nearly 80% (± 3.7) of the HSCT patients showed smaller teeth or C:R alterations with shortened roots. When tooth area or C:R proportions of HSCT patients were compared with matched age and sex pairs, statistically significant

differences were found (p = 0.002). In addition, the most affected teeth were the first and second premolars and the second molars.

Correlation of age with dental development disturbances

There were strong correlations between age at HSCT and risk of developing dental disturbances. The patients that were submitted to HSCT before the age of 4 years showed a significantly higher prevalence of qualitative and quantitative developmental dental disturbances compared to normative data for first and second premolars in both the maxilla and mandible, as well as for second molars in the mandible ($p < 0.001$). In addition, the childhood cancer patients revealed to be at significantly higher risk of presenting precocious apical closure and advanced dental age in comparison with non-HSCT children with matched age and sex ($p < 0.020$). Childhood HSCT radiation therapy appeared to increase the risk of the occurrence of dental development disturbances, although, due to different preparative regimens, no statistical test could be performed to evaluate this risk increase. Different chemotherapeutic agents did not change the risk of developing dental developmental disturbances.

Review considerations

Our reviewers identified several faults in the published articles. First, not all of the studies presented detailed information about the chemotherapeutic preparative regimens used, failing to fully describe the dosages and administration protocols of antineoplastic agents. In addition, poor descriptions were found of the total body radiation therapy, whenever it was employed. Since we believe that dental development is a highly sensitive continuous process, detailed descriptions would seem to be important for identifying, preventing and managing the late effects of dental alterations induced by the chemo-radiotherapy administered for HSCT. The reviewers also identified an inaccurate description of the follow-up time among the published papers. This must be due to the difficulty involved in accompanying childhood-HSCT long-term survivors. Since the survival rates are continually rising, as is the number of patients likely to be included in study groups, we believe that this time issue will be surpassed as further investigations are conducted about the late systemic and local effects of HSCT.

Conclusions and future directions

This systematic review summarizes the literature on the long-term effects of treatment-related dental development disturbances in survivors of childhood onco-hematological cancer. Only ten published papers fulfilled the inclusion/exclusion criteria and were evaluated for:

- type of study,
- number of individuals (n),
- preparative regimen therapies,
- qualitative and quantitative dental development disturbances,
- follow-up time, and
- age at HSCT.

In addition, data on the purpose, results, and main conclusions were gathered.

Data assembling suggested that a younger age at transplantation and preparative regimens seemed to be related to a higher risk of developing dental alterations, such as agenesis, dental hypoplasia, root stunting, crown-root proportion alterations, and microdontia. Additionally, total body radiation therapy and high-dose chemotherapy increased the risk of developing dental development disturbances in HSCT children. There was not sufficient evidence to indicate that different chemotherapeutic mieloablative agents can have increased effects on dental development.

There was a positive correlation between pa-

tient age at HSCT and an increased risk of developing dental developmental disturbances. This finding seems reasonable, since tooth formation is a continuous, highly sensitive and complex process led by several cytokines and an intricate interaction between buccal epithelium and underlying ectomesenchyme.[19,20] Tooth development begins just after birth, lasts all childhood, and follows subsequential stages:

- initiation stage,
- bud stage,
- cap stage,
- bell stage, and finally
- maturation.[21]

These physiological processes occur at different moments of life, and any disturbance may interfere with tooth development. At the age of 4 years, a child has already formed the first molars and anterior teeth, while premolars and second molars are developing.[22,23] This chronology may explain why these teeth showed the highest qualitative and quantitative dental alterations.

The limitations of the studies included in this systematic review should be considered. First, the cross-sectional observations of childhood cancer may have resulted in selection bias. It is possible that children with adverse dental outcomes were more likely to return for evaluation and care, which could have inflated report estimates. On the other hand, those patients who did not survive long enough to be included in the study groups may have biased the reported dental outcomes toward the null. Another study shortcoming was related to the small number of survivors, especially when there was no non-HSCT control group with matched age and sex, which may have compromised the data evaluation and led to non-reliable results. Furthermore, some authors failed to present accurate descriptions of the chemical agents, radiation mieloablative therapy and preparative regimens used, whereas others failed to report specific information about the demographic characteristics of the study population and mean follow-up time.[14,15,24] To offset this lack of data, further investigations are warranted to provide more accurate information and help patients and dental care providers to improve the long-term quality of life of HSCT patients, focusing on the late effects involved.

In conclusion, although HSCT has improved the survival rates of childhood cancer patients, this improvement has been accompanied by the occurrence of long-term treatment-related complications such as secondary neoplasms, organ dysfunction and psychosocial and cognitive disturbances[25] that may entail the perception of a poorer quality of life.[18] The dental alterations induced by HSCT include aesthetic and functional impairment, and periodontal bone resorption, resulting in impairment of chewing ability and a greater risk of early tooth loss, thus jeopardizing the long-term maintenance of oral health.[24] In addition, it has been recently suggested that these dental complications could increase the cardiovascular morbidity and mortality rates associated with dental care intervention among survivors. Further studies are required to outline the late dental effects of HSCT among survivors of childhood cancer treatment, contributing with new information about the extension of dental alterations, and with useful evidence to help predict the location of enamel defects. This information would help the dental team to provide improved dental care for these children and more accurate information to patients and parents on the possible long-term sequelae they might experience.

REFERENCES

1. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. J Clin Oncol. 2012 May;30(14):1663-9. doi: 10.1200/JCO.2011.37.8018.
2. Passweg JR, Halter J, Bucher C, Gerull S, Heim D, Rovó A, et al. Hematopoietic stem cell transplantation: a review and recommendations for follow-up care for the general practitioner. Swiss Med Wkly. 2012 Oct 15;142:w13696. doi: 10.4414/smw.2012.13696.
3. Pui C-H, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008 Mar;371(9617):1030-43. doi: 10.1016/S0140-6736(08)60457-2.
4. Mariotto AB, Rowland JH, Yabroff KR, Scoppa S, Hachey M, Ries L, et al. Long-term survivors of childhood cancers in the United States. Cancer Epidemiol Biomarkers Prev. 2009 Apr;18(4):1033-40. doi: 10.1158/1055-9965.EPI-08-0988.
5. Vesterbacka M, Ringdén O, Remberger M, Huggare J, Dahllöf G. Disturbances in dental development and craniofacial growth in children treated with hematopoietic stem cell transplantation. Orthod Craniofac Res. 2012 Feb;15(1):21-9. doi: 10.1111/j.1601-6343.2011.01533.x.
6. Haupt R, Jankovic M, Hjorth L, Skinner R. Late effects in childhood cancer survivors and survivorship issues. Epidemiol Prev. 2013 Jan-Feb;37(1) suppl 1:266-73.
7. Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA. 2007 Jun;297(24):2705-15. doi:10.1001/jama.297.24.2705.
8. Brennan BM, Shalet SM. Endocrine late effects after bone marrow transplant. Br J Haematol. 2002 Jul;118(1):58-66. doi: 10.1046/j.1365-2141.2002.03527.x.
9. Leiper AD. Non-endocrine late complications of bone marrow transplantation in childhood: part II. Br J Haematol. 2002 Jul;118(1):23-43. doi: 10.1046/j.1365-2141.2002.03471.x.
10. Leiper AD. Non-endocrine late complications of bone marrow transplantation in childhood: part I. Br J Haematol. 2002 Jul;118(1):3-22. doi: 10.1046/j.1365-2141.2002.03470.x
11. Minicucci EM, Lopes LF, Crocci AJ. Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. Leuk Res. 2003 Jan;27(1):45-50. doi: 10.1016/S0145-2126(02)00080-2.
12. Oğuz A, Cetiner S, Karadeniz C, Alpaslan G, Alpaslan C, Pinarli G. Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. Eur J Oral Sci. 2004 Feb;112(1):8-11. doi: 10.1111/j.0909-8836.2004.00094.x.
13. Cubukcu CE, Sevinir B, Ercan I. Disturbed dental development of permanent teeth in children with solid tumors and lymphomas. Pediatr Blood Cancer. 2012 Jan;58(1):80-4. doi: 10.1002/pbc.22902.
14. Nishimura S, Inada H, Sawa Y, Ishikawa H. Risk factors to cause tooth formation anomalies in chemotherapy of paediatric cancers. Eur J Cancer Care (Engl). 2013 May;22(3):353-60. doi: 10.1111/ecc.12038.
15. Hölttä P, Alaluusua S, Saarinen-Pihkala UM, Wolf J, Nyström M, Hovi L. Long-term adverse effects on dentition in children with poor-risk neuroblastoma treated with high-dose chemotherapy and autologous stem cell transplantation with or without total body irradiation. Bone Marrow Transplant. 2002 Jan;29(2):121-7. doi: 10.1038/sj/bmt/1703330.
16. Hölttä P, Alaluusua S, Saarinen-Pihkala UM, Peltola J, Hovi L. Agenesis and microdontia of permanent teeth as late adverse effects after stem cell transplantation in young children. Cancer. 2005 Jan 1;103(1):181-90. doi: 10.1002/cncr.20762.
17. van der Pas-van Voskuilen IG, Veerkamp JS, Raber-Durlacher JE, Bresters D, van Wijk AJ, Barasch A, et al. Long-term adverse effects of hematopoietic stem cell transplantation on dental development in children. Support Care Cancer. 2009 Sep;17(9):1169-75. doi: 10.1007/s00520-008-0567-1.
18. Tanzi EM. Health-related quality of life of hematopoietic stem cell transplant childhood survivors: state of the science. J Pediatr Oncol Nurs. 2011 Jul-Aug;28(4):191-202. doi: 10.1177/1043454211408100.
19. Abe R, Endo T, Shimooka S. Maxillary first molar agenesis and other dental anomalies. Angle Orthod. 2010 Nov;80(6):1002-9. doi: 10.2319/020210-69.1.
20. Harada H, Kettunen P, Jung HS, Mustonen T, Wang YA, Thesleff I. Localization of putative stem cells in dental epithelium and their association with Notch and FGF signaling. J Cell Biol. 1999 Oct 4;147(1):105-20. doi: 10.1083/jcb.147.1.105.
21. Thesleff I, Järvinen E, Suomalainen M. Affecting tooth morphology and renewal by fine-tuning the signals mediating cell and tissue interactions. Novartis Found Symp. 2007;284:142-53; discussion 153-63.

22. Brook AH. Multilevel complex interactions between genetic, epigenetic and environmental factors in the aetiology of anomalies of dental development. Arch Oral Biol. 2009 Dec;54 Suppl 1:S3-17. doi: 10.1016/j.archoralbio.2009.09.005.
23. Nanci A. Ten Cate's oral histology. 8th ed. St. Louis: Elsevier; 2013. p. 70-94.
24. Duggal MS. Root surface areas in long-term survivors of childhood cancer. Oral Oncol. 2003 Feb;39(2):178-83. doi: 10.1016/S1368-8375(02)00089-1.
25. Bhatia S, Davies SM, Scott Baker K, Pulsipher MA, Hansen JA. NCI, NHLBI first international consensus conference on late effects after pediatric hematopoietic cell transplantation: etiology and pathogenesis of late effects after HCT performed in childhood - methodologic challenges. Biol Blood Marrow Transplant. 2011 Oct;17(10):1428-35. doi: 10.1016/j.bbmt.2011.07.005.