Published in final edited form as:
Pediatr Blood Cancer. 2014 March ; 61(3): 407–416. doi:10.1002/pbc.24842.

A Systematic Review of Dental Late Effects in Survivors of Childhood Cancer

Prasad L. Gawade, PhD[1], **Melissa M. Hudson, MD**[1,2], **Sue C. Kaste, DO**[2,3,4], **Joseph P. Neglia, MD, MPH**[5], **Louis S. Constine, MD**[6], **Leslie L. Robison, PhD**[1], and **Kirsten K. Ness, PT, PhD**[1]

[1]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN 38105

[2]Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105

[3]Radiological Sciences at St. Jude Children's Research Hospital, Memphis, TN 38105

[4]Department of Radiology, College of Medicine, University of Tennessee Health Science Center, 910 Madison, Suite 1002, Memphis, TN 38163

[5]Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN 55455

[6]Departments of Radiation Oncology and Pediatrics, School of Medicine and Dentistry, University of Rochester Medical Center, 601 Elmwood Ave, Box 647, Rochester, NY 14642

Abstract

Survivors of childhood cancer are at risk for dental late effects. This systematic review summarizes associations between treatment exposures and dental late effects among survivors of childhood cancer. We included investigations with at least 20 study participants conducted for 2 or more years after completion of childhood, adolescent, or young adult cancer therapy. This review suggests both independent and additive effects of radiotherapy and chemotherapy on dental complications, and identifies vulnerable groups with specific host and treatment characteristics. This summary provides information that will assist clinicians to prevent, detect, and facilitate early intervention for dental late effects.

Keywords

pediatrics; tooth abnormalities; radiotherapy; chemotherapy

INTRODUCTION

Five-year survival rates among children diagnosed with malignancies when younger than 19 years of age have improved from 62% in 1977 to almost 84% in 2009 in the United States

Corresponding author: Dr. Kirsten K. Ness, Department of Epidemiology and Cancer Control MSN 735, S-6013, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, USA. kiri.ness@stjude.org, Tel: 901-595-5157, Fax: 901-595-5845.

Conflict of interest disclosures: The authors have no conflicts of interest to declare.

[1]. Successes in surgery, radiotherapy, combination chemotherapy and supportive care are responsible for this increase in survival. However, survivors of childhood cancer remain at risk for radiation [2-4] and chemotherapy [2,5-8] associated dental complications such as caries, and dental developmental abnormalities including agenesis, dental hypoplasia, root stunting, and enamel defects. Survivors also have a higher prevalence of xerostomia, and cariogenic microflora, which have been linked to risk of periodontal disease [9-15]. In the general population, periodontal disease is known to be associated with systemic inflammation and atherogenesis [16,17]. Therefore, preventing dental complications is especially important in childhood cancer survivors at risk for early cardiac morbidity [18] and mortality [19].

Despite their increased risk for dental complications, investigators have reported suboptimal rates of regular dental care among childhood cancer survivors [20]. This is concerning as oral dental health among survivors can be optimized by identifying at-risk childhood cancer survivors and providing timely interventions. Fluoride therapy, chlorhexidine rinses, and dental restorations reduce dental complications in children during [21] and following cancer treatment [12,22]. Although there are multiple reports in the literature that describe dental outcomes among childhood cancer survivors, these data have not been systematically evaluated to better characterize childhood cancer survivors at greatest risk. Here we systematically review and summarize the existing knowledge about the dental late effects of childhood cancer treatment, delineating vulnerable groups according to specific host and treatment characteristics. We also review the potential interactions between radiation and chemotherapy that may have long-term dental consequences among childhood cancer survivors.

METHODS

Inclusion Criteria

We reviewed clinical trials, observational studies, case series, and review articles according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [23]. Our review was limited to studies that discussed dental late effects among survivors of pediatric cancer where follow-up time among survivors was a minimum of 2 years after completion of childhood, adolescent or young adult cancer therapy. Primary outcomes were defined as occurrence of dental complications at least 2 years after completion of childhood cancer therapy. Studies evaluating salivary gland hypofunction [24] have been previously reviewed and were excluded. However, studies evaluating oral late effects at least 2 years after completion of HCT were separately evaluated. In addition, literature reviews were excluded.

Search Strategies

For our initial search of the PubMed database (limits: English, human, and dates: 01/01/1970 to 12/01/2012) for clinical trials, observational studies, case series, and reviews, we used the search terms “tooth abnormalities”, “adverse effects”, “child”, “adolescent”, “adult, young”, “neoplasms”, “survivors”. All abstracts derived from this search were reviewed for relevance. The Web of Science was searched with similar terms to find

additional articles. Reference lists published in review articles and retrieved studies were also reviewed to identify potential manuscripts.

Validity Assessment and Data Extraction

One author (PG) screened all retrieved studies for relevance and validity. The methodological quality of selected studies was independently evaluated by two authors (PG and KN) [25]. Study quality was determined using four criteria: comparability of subjects, clear definition of exposure or intervention, standard outcome measurement and appropriate statistical analysis. Any discrepancy in assessment of validity was resolved by discussion between authors. We extracted information about sample size, age at diagnosis, type of diagnosis, follow-up period, type and details of treatment and dental late effects from the selected studies.

RESULTS

Search Results

Our initial search of the PubMed database identified 2,354 studies; 14 of these were retained. An additional 33 studies that met the inclusion criteria were found in the reference lists of the retained studies (Figure 1). No additional articles were found in the Web of Science. Studies were evaluated according to the predominant anticancer therapy exposure (radiotherapy, chemotherapy, and hematopoietic cell transplant [HCT]) associated with dental effects. Of 47 studies evaluating dental late effects, 12 studies focused on effects of radiotherapy (Table I), 25 on effects of chemotherapy (Table II), and 10 on effects of HCT (Table III). We describe dental late effects in two categories including 1) caries and 2) dental developmental abnormalities, including dental agenesis, dental hypoplasia, root stunting, and enamel hypoplasia.

Study Quality and Risk of Bias

We limited our search to studies with at least 20 participants. All studies included were determined to be valid and had clearly defined exposure and outcome measures. In all studies dental late effects were assessed clinically from medical charts or by self-report. Because most were retrospective and from single institutions, we were not able to compare outcomes across studies. Anticancer therapies varied by institution, cancer type, staging, and era of primary diagnosis. Additionally, because dental care during and following cancer treatment has improved, we were unable to compare rates of dental caries across studies from different eras. The cross-sectional nature of many studies also made them vulnerable to survivor bias. It is possible that patients with the most severe dental effects were not included because of death or inability to participate in follow-up testing.

Dental Late Effects of Radiotherapy in Survivors of Childhood Cancer

Radiation interferes with dental development (odontogenesis) by directly inhibiting mitotic activity of odontoblasts. The abundance of rapidly dividing presecretory odontoblasts in children makes them particularly vulnerable to effects of radiation [26]. In contrast, radiation affects enamel formation (amelogenesis) indirectly by inducing formation of “osteodentin” which replaces normal dentin [27]. Osteodentin has reduced phosphorylated

phosphoprotein which inhibits nucleation of enamel crystals and leads to deficient enamel mineralization [28]. Tooth development is halted by 30 Gray (Gy) and mature ameloblasts are damaged by 10 Gy of direct irradiation [29]. However, dental late effects have been reported in patients treated with radiation doses as low as 4 Gy [30]. This dose spectrum is related to several variables, including patient age, total radiation dose, daily radiation fraction size, exposed tissue volume, interaction with specific chemotherapeutic agents, pre-existing dental health, and presence of chronic graft- vs-host disease in HCT survivors.

Dental Caries after Radiotherapy—Impaired dental health due to caries affects cosmesis, functioning, and quality of life of children [31]. Post-radiation salivary gland damage reduces salivary secretion, makes saliva more acidic, and promotes highly cariogenic oral microflora such as streptococci mutans and lactobacilli [9-15]. Early observational studies [2,30,32] describe a direct association between TBI of 10 Gy, cranial radiation of 24 Gy, and total tumor dose of 40 to 60 Gy and dental caries.. Pajari et al. [2] reported a higher average number of new caries per year (1.3 ± 1.4 vs. 0.7 ± 1.4; P <0.05) and higher Decayed Missing Filled Teeth (DMFT) scores (5.9 ± 5.9 vs. 1.7 ± 2.3, P < 0.01) among 45 acute lymphoblastic leukemia (ALL) survivors (mean: age at diagnosis 5.4 years; follow-up 4 years) compared to 45 controls. In addition, the authors found that survivors treated with 24 Gy cranial irradiation or 10 Gy TBI had higher average DMFT scores than survivors treated with chemotherapy alone (7.1 ± 4.6 and 12.0 ±11.5 vs. 3.4 ± 4.4, P < 0.05) [2]. These DMFT scores are higher than those reported among American children between 12 and 15 years of age (1.78 ± 0.08, P < 0.01) [33]. Additionally, Duggal et al. [34] reported higher mean numbers of untreated decayed teeth among 46 long-term survivors of various childhood cancers diagnosed when younger than 10 years of age when compared to their siblings (1.33 ± 0.25 vs. 0.37 ± 0.14, P < 0.001).

Dental Developmental Abnormalities after Radiotherapy—Radiation damages tooth buds at early stages of development and is associated with dental developmental abnormalities including dental agenesis (commonly manifested as partial agenesis or hypodontia), dental hypoplasia, root stunting, and enamel hypoplasia. These abnormalities influence functional and aesthetic outcomes among survivors [35,36]. Children treated with local radiation [3,32,37-42], are at high risk for dental developmental abnormalities later in life. Among 5-year survivors of ALL, Sonis et al. [41] observed severe dental developmental abnormalities (root stunting = 20/20, hypodontia = 5/20, and microdontia = 15/20) among survivors who had received 24 Gy of cranial radiation when younger than 5 years of age. In a study of 22 head and neck rhabdomyosarcoma survivors treated with 34-67 Gy radiation and chemotherapy when younger than 18 years of age, the authors also found severe dental abnormalities (root stunting = 12, hypodontia = 11, and microdontia = 5) [39].

The risk of dental abnormalities after radiotherapy is influenced by both younger age at irradiation [38,41,43], and by higher doses of radiation [32,42]. In a study of 423 ALL survivors, Kaste et al. [43] observed a higher prevalence of dental abnormalities (root stunting, microdontia, hypodontia, taurodontia, and over-retention of primary dentition) in survivors treated when younger than 8 years of age (138/331, 42%) when compared to those

treated when 8 years of age or older (29/92, 32%, $P < 0.05$), and among those who were treated (122/244, 50%) when compared to those not treated (45/179, 25%, $P < 0.01$). Kaste et al. [42], in a multivariable analysis adjusting for chemotherapy, also reported a dose-dependent risk of having at least one dental abnormality (≥ 1 hypodontia, microdontia, enamel hypoplasia, abnormal root development, ≥ 6 missing teeth, denture use, and dental prosthesis) among survivors with jaw radiation exposure when compared to those without jaw radiation exposure (> 0 to < 20 Gy: [OR: 1.3; 95% CI: 1.2-1.5]; ≥ 20 Gy: [OR: 5.6; 95% CI: 3.7-8.5]).

Dental Late Effects of Chemotherapy in Survivors of Childhood Cancer

Because many children treated with chemotherapy also received concomitant radiation, it is difficult to determine the independent effects of chemotherapy on dental outcomes. This is an area in need of future research. Nevertheless, both vincristine [44,45] and alkylating agents [42,46] have been associated with dental abnormalities among survivors of childhood cancer. Two studies have reported prominent incremental lines on the dentine of extracted teeth among survivors of various childhood cancers corresponding to cycles of intravenous chemotherapy including vincristine [44,45]. This effect is likely related to the inhibitory effect of vincristine on the secretion of collagenous dentine matrix by odontoblasts [47,48]. In a multivariable analysis adjusting for radiation to the jaw, Kaste et al. [42] reported a dose-dependent risk of having at least one dental abnormality among survivors treated with alkylating agents when compared to those who received no alkylating agents (alkylating score 1: [OR: 1.4; 95% CI: 1.2-1.6]; alkylating score 2: [OR: 1.7; 95% CI: 1.5-2.0]; alkylating score 3: [OR: 2.0; 95% CI: 1.6-2.4]). Evaluating the risk for individual dental abnormalities, the authors observed dose-dependent association between alkylating agents and ≥ 1 anatomical abnormality, ≥ dental appliance, abnormal roots, abnormal shaped or small teeth, and ≥ 1 missing teeth among survivors diagnosed when younger than 5 years [42]. This study may have underestimated the prevalence of dental abnormalities since data was self-reported by survivors. Another study [46] of 106 survivors of childhood cancer treated at a mean age of 5 years and examined at least 5 years post-treatment reported a dose-dependent association (unadjusted $P_{trend} < 0.001$) between cyclophosphamide and Holtta's Defect Index (HDI) scores which includes hypodontia, microdontia, and root/crown ratios measured using panoramic radiographs [49]. In a multivariable analysis adjusted for age at treatment, sex, HCT, surgery, and radiotherapy, the authors observed that survivors treated with ≥ 7,500 mg/m^2 cyclophosphamide had a 13 point increase (equivalent to at least 2 missing or 3 microdontic teeth) in HDI [49] scores compared to those not exposed to cyclophosphamide ($P = 0.01$) [46].

Dental Caries after Chemotherapy—Dental caries [6,8,30,42,50-54], often reported as a higher number of teeth fillings [8], a higher DMFT score [50,51,55,56], or a higher Decayed, Missing, Filled Surface (DMFS) score [6,51,55], are the most commonly reported dental late effect following chemotherapy. A case-control study reported that 96 survivors of childhood cancer (mean follow-up: 2.5 years) treated with chemotherapy and no radiation to the teeth had lower salivary flow rate (median: 1.2 vs. 1.4 ml/min) and higher cariogenic bacteria such as mutans streptococci and lactobacillus than 96 healthy controls [54]. The authors also reported a higher prevalence of dental caries (82% vs. 54%) and a higher

DMFT score (7.8 ± 4.9 vs. 4.2 ± 3.8) among survivors than among healthy controls. Another case-control study reported a three-fold increase in risk for dental caries and fillings in permanent dentition among 45 survivors of childhood cancer, a mean age at examination of 10 years, treated with chemotherapy alone, when compared to 300 healthy controls [8]. In a case-control study of 45 ALL survivors and 45 healthy controls, Pajari et al. [2] observed a higher proportion of filled anterior permanent tooth-surfaces at the age of twelve years among those treated with chemotherapy alone (7.4%), chemotherapy and cranial radiation (6.6%), and chemotherapy and TBI (29.7%) when compared to controls ($P < 0.001$).

There is evidence to support the use of preventive dental care to improve post-chemotherapy dental outcomes. A Danish population-based study [57] compared the prevalence of caries among 869 cancer survivors diagnosed between the ages of 0 and 6 years with a national sample. The authors observed a decline in risk of dental caries as the age of the follow-up examination increased from 7, 12 and 15 years for children diagnosed when younger than 5 years (OR: 1.05, 1.03 and 0.91) and also for those diagnosed between 5 and 6 years (OR: 1.18, 1.20 and 1.02) of age. The authors proposed that the gradual decline in risk was a result of individualized dental procedures and oral hygiene plans for cancer patients. These findings are supported by previous studies that show a declining risk of dental caries with time from cancer treatment [44,58].

Dental Developmental Abnormalities after Chemotherapy—There is strong evidence to support the association between chemotherapy and dental developmental abnormalities, including dental agenesis, dental hypoplasia, root stunting, and enamel hypoplasia. Chemotherapy has been reported to impact both odontogenesis and amelogenesis in cohorts of survivors with hematological cancers [59-61], solid tumors [52,62-64], and various childhood cancers [8,44,54]. A case-control study of 56 survivors of ALL treated at a mean age of 5.3 years when compared to 56 age- and sex-matched controls reported a higher prevalence of survivors with hypodontia (28 vs. 9), microdontia (14 vs. 0), and root stunting (12 vs. 0) [59]. In a study of 30 survivors of lymphoma treated with chemotherapy between 4 and 15 years of age, the authors observed higher prevalence of survivors with hypodontia (15 vs. 2), enamel hypoplasia (14 vs. 3), and enamel discoloration (17 vs. 1) when compared to 20 healthy controls [60]. In a cohort of 52 neuroblastoma survivors, most who were treated with chemotherapy alone (8 received radiotherapy), Kaste et al. [52] observed high rates of hypodontia (17%), microdontia (38%), root stunting (17%), enamel hypoplasia (17%), and severe tooth decay (> 4 teeth; 29%). The authors hypothesized that dental abnormalities were a result of inhibitory effect of cyclophosphamide on odontogenesis [48,65]. Avsar et al. [54] observed an association between chemotherapy and dental abnormalities in a case-control study of childhood cancer survivors with various diagnoses treated at mean age of 6.4 years and followed for 2.5 years. Survivors had higher rates of arrested root development with short V-shaped root formation (52.1% vs. 17.7%) and white/cream enamel opacity (49% vs. 13.5%) when compared to 96 controls matched on age, sex, and socioeconomic status [54].

The association between chemotherapy and dental abnormalities is influenced by younger age at chemotherapy [59,66,67] and concomitant radiation [40,59]. The effects of chemotherapy are amplified when the dental cells are rapidly proliferating at a young age

[68]. In a study of 76 ALL survivors, treated at a mean age of 5 years and followed for a mean of 3 years post-treatment, Minicucci et al. [67] reported that younger age at treatment (1 to 6 years vs. 7 to 12 years) was associated with an increased prevalence of dental abnormalities (56.6% vs. 26.3%), including delayed development, microdontia, malformed roots, and enamel hypoplasia. Maciel et al. [59] reported a higher mean number of teeth with abnormalities (agenesis, dental hypoplasia, supernumerary teeth, microdontia, taurodontism, tapering roots, short roots and enlarged pulp chamber) among survivors of ALL treated with chemotherapy, radiotherapy and HCT (n = 8; 15.4 ± 15.1) when compared to those treated with chemotherapy and radiotherapy (n = 18; 5.0 ± 6.1) or chemotherapy alone (n = 30; 3.9 ± 6.2) ($P < 0.05$).

Dental Late Effects of HCT in Survivors of Childhood Cancer

Dental Caries after HCT—The evidence regarding long-term effect of HCT on dental caries is conflicting. Two studies (n = 26, age range 4 - 12 years and n = 19, mean age 6.5 ± 3.5 years) among HCT survivors reported no difference in mean number of decayed and filled surfaces between those conditioned with 10 Gy TBI and cyclophosphamide and controls (2.5 ± 2.9 vs. 3.5 ± 3.9 and 3.5 ± 2.8 vs. 2.7 ± 3.5) [12,15]. These null associations were attributed to the use of fluoride prophylaxis, chlorhexidine rinse and parental training in dental care. However, two other studies [56,69] reported higher DMFT scores among survivors treated with HCT compared to those treated with chemotherapy alone. Hutton et al. [56] observed higher mean DMFT scores for primary teeth among 14 survivors (mean follow-up 52 months) conditioned with high dose chemotherapy prior to HCT compared to 106 survivors whose chemotherapy was less intense (~3 versus <1, no P-value reported). Uderzo et al. [69] also observed higher DMFT scores for permanent teeth when survivors treated with HCT (meadian follow-up 2 years) were compared to survivors treated with chemotherapy alone (11-15 years: 7.6 vs. 4.1 and 16-20 years: 12.4 vs. 8.0, no P-values reported).

Dental Developmental Abnormalities after HCT—Children conditioned with TBI and high-dose chemotherapy before HCT [12,15,69-72], are at high risk for dental developmental abnormalities later in life. Nasman et al. [12] compared dental abnormalities among 1) survivors conditioned with 8-10 Gy of TBI and cyclophosphamide for HCT, 2) survivors of leukemia, lymphoma, sarcomas, central nervous system tumors and neuroblastoma who had received combination chemotherapy but no radiation, and 3) a healthy age- and sex-matched control group. Two years after HCT, survivors treated with TBI had a higher mean number of teeth with arrested root development than those treated with chemotherapy alone (15.9 ± 8.2 vs. 1.2 ± 1.6; $P < 0.001$). Rates of enamel hypoplasia, microdontia, and hypodontia were also higher among those treated with TBI. No dental abnormalities were found in the control group [12].

Younger age at treatment [12,69-71,73,74] and intensive chemotherapy [12,15,69-71,73] increase the risk of long-term dental abnormalities among survivors treated with HCT. Nasman et al. [12] observed a higher number of dental abnormalities such as dental hypoplasia, root growth impairment, and enamel defects among those who had TBI when younger than 6 years of age than among those irradiated when 7 to 12 years of age. In

another study of 55 survivors of hematological cancer conditioned with chemotherapy for HCT, survivors who were younger than 3 years of age at treatment (77%) had a higher prevalence of dental agenesis of permanent teeth (third molars excluded) compared to those between 3 and 5 years (40%) and older than 5 years of age (0%) at treatment (*P*-values < 0.001) [73]. Another study of 39 survivors of hematological malignancies conditioned with high dose cyclophosphamide, busulfan and/or 10 Gy TBI for HCT, observed smaller mean areas of mandibular central incisors (0.75 vs. 0.97) and first (2.35 vs. 2.87) and second molars (1.93 vs. 2.83) when compared to the 78 healthy controls (all *P*-values <0.001) [71]. The authors also reported that the severity of tooth area loss was strongly influenced by younger age at treatment ($P < 0.001$).

CONCLUSION AND FUTURE DIRECTIONS

This systematic review summarizes the literature on treatment-related dental late effects in survivors of childhood cancer. Younger age at treatment, higher radiation dose, and treatment with radiotherapy, chemotherapy, and HCT appear to be associated with an increased risk for dental agenesis, dental hypoplasia, root stunting, and enamel hypoplasia. Fortunately, risk for dental caries among survivors treated with HCT [12,15,72] or chemotherapy [57] has declined over time as regular, individualized preventive dental care has been implemented. In addition to the established risk factors for dental late effects included in the current Children's Oncology Group (COG) long term follow-up guidelines [75], recent studies have reported an age-specific and dose-dependent increased risk for dental abnormalities among those treated with alkylating agents [42,46]. Using this information, health care providers can offer targeted surveillance for early detection and intervention among at-risk survivors. Some of the dental late effects such as caries are preventable and can be managed by following the COG guidelines for dental health [76]. However, survivors at risk for non-preventable late effects such as agenesis or microdontia should regularly follow-up with a dentist or orthodontist experienced in survivorship care [77].

Limitations of studies included in this review should be considered. First, cross-sectional observation of survivors may have resulted in selection bias in many studies. It is possible that children with adverse dental outcomes were more likely to return for evaluation and care which would lead to an inflation of the reported estimates. Conversely, if children who died prior to returning for evaluation were more likely than those who survived to have adverse dental outcome, the reported estimates would be biased toward the null. Family history, hygiene patterns, and socioeconomic status play a crucial role in dental health [78]. However, few studies included in this review attempted to control for these confounders by comparing survivors with their siblings [34,42,44,58]. None of the studies specifically evaluated the effect of preventive oral care, screening, or follow-up with dentist on dental complications. Finally, most studies did not clearly differentiate between dental outcomes in deciduous and permanent dentition.

Further studies are required to characterize dental late effects and associated risk factors among survivors treated with newer salivary gland sparing intensity-modulated radiation [79], targeted chemotherapies [80], and advanced preventive dental care during and after

cancer treatment [81,82]. Studies are also required to evaluate the modification in risk of cardiovascular morbidity and mortality with dental care intervention among survivors. Additional investigations evaluating effects of diet, oral hygiene, psychosocial status, and genetics on dental abnormalities may improve the precision to identify survivors at risk for dental late effects. Educating parents and health care providers in early prevention is vital for minimizing deleterious effects of cancer treatment. Comprehensive survivor clinics and dentists with expertise in survivor care are not accessible for all survivors. However, a reduction in the burden of dental complications among vulnerable survivors is possible with early and regular dental follow-up.

Acknowledgments

Funding source: This work was supported by a Cancer Center Support (CORE) grant CA 21765 from the National Cancer Institute, and by the American Lebanese Syrian Associated Charities (ALSAC).

REFERENCES

1. Howlader, N.; Noone, AM.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975-2010. National Cancer Institute; May 15. 2013 2013<http://seer.cancer.gov/csr/1975_2010/>May 15, 2013
2. Pajari U, Ollila P, Lanning M. Incidence of dental caries in children with acute lymphoblastic leukemia is related to the therapy used. ASDC J Dent Child. 1995; 62:349–352. [PubMed: 8550925]
3. McGinnis JP Jr. Hopkins KP, Thompson EI, et al. Mandibular third molar development after mantle radiation in long-term survivors of childhood Hodgkin's disease. Oral Surg Oral Med Oral Pathol. 1987; 63:630–633. [PubMed: 3473386]
4. Dahllof G. Oral and dental late effects after pediatric stem cell transplantation. Biol Blood Marrow Transplant. 2008; 14:81–83. [PubMed: 18162225]
5. Pajari U, Lanning M, Larmas M. Prevalence and location of enamel opacities in children after anti-neoplastic therapy. Community Dent Oral Epidemiol. 1988; 16:222–226. [PubMed: 3165749]
6. Pajari U, Larmas M, Lanning M. Caries incidence and prevalence in children receiving antineoplastic therapy. Caries Res. 1988; 22:318–320. [PubMed: 3263210]
7. Rosenberg SW, Kolodney H, Wong GY, et al. Altered dental root development in long-term survivors of pediatric acute lymphoblastic leukemia. A review of 17 cases. Cancer. 1987; 59:1640–1648. [PubMed: 3470112]
8. Purdell-Lewis DJ, Stalman MS, Leeuw JA, et al. Long term results of chemotherapy on the developing dentition: caries risk and developmental aspects. Community Dent Oral Epidemiol. 1988; 16:68–71. [PubMed: 3162858]
9. Dreizen S, Brown LR, Handler S, et al. Radiation-induced xerostomia in cancer patients. Effect on salivary and serum electrolytes. Cancer. 1976; 38:273–278. [PubMed: 7352]
10. Cowman RA, Baron SS, Glassman AH, et al. Changes in Protein Composition of Saliva from Radiation-induced Xerostomia Patients and Its Effect on Growth of Oral Streptococci. J Dent Res. 1983; 62:336–340.
11. Makkonen TA, Edelman L, Forsten L. Salivary flow and caries prevention in patients receiving radiotherapy. Proc Finn Dent Soc. 1986; 82:93–100. [PubMed: 3737609]
12. Nasman M, Bjork O, Soderhall S, et al. Disturbances in the oral cavity in pediatric long-term survivors after different forms of antineoplastic therapy. Pediatr Dent. 1994; 16:217–223. [PubMed: 8058547]
13. Brown LR, Dreizen S, Handler S, et al. Effect of radiation-induced xerostomia on human oral microflora. J Dent Res. 1975; 54:740–750. [PubMed: 1099136]

14. Jones LR, Toth BB, Keene HJ. Effects of total body irradiation on salivary gland function and caries-associated oral microflora in bone marrow transplant patients. Oral Surg Oral Med Oral Pathol. 1992; 73:670–676. [PubMed: 1437034]
15. Dahllof G, Bagesund M, Ringden O. Impact of conditioning regimens on salivary function, caries-associated microorganisms and dental caries in children after bone marrow transplantation. A 4-year longitudinal study. Bone Marrow Transplant. 1997; 20:479–483. [PubMed: 9313881]
16. Teles R, Wang CY. Mechanisms involved in the association between periodontal diseases and cardiovascular disease. Oral Dis. 2011; 17:450–461. [PubMed: 21223455]
17. Huck O, Saadi-Thiers K, Tenenbaum H, et al. Evaluating periodontal risk for patients at risk of or suffering from atherosclerosis: recent biological hypotheses and therapeutic consequences. Arch Cardiovasc Dis. 2011; 104:352–358. [PubMed: 21693372]
18. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ. 2009:339.
19. Mertens AC, Liu Q, Neglia JP, et al. Cause-Specific Late Mortality Among 5-Year Survivors of Childhood Cancer: The Childhood Cancer Survivor Study. J Natl Cancer Inst. 2008; 100:1368–1379. [PubMed: 18812549]
20. Yeazel MW, Gurney JG, Oeffinger KC, et al. An examination of the dental utilization practices of adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Public Health Dent. 2004; 64:50–54. [PubMed: 15078062]
21. Hong CH, Napenas JJ, Hodgson BD, et al. A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer. 2010; 18:1007–1021. [PubMed: 20449756]
22. Dahllof G, Barr M, Bolme P, et al. Disturbances in dental development after total body irradiation in bone marrow transplant recipients. Oral Surg Oral Med Oral Pathol. 1988; 65:41–44. [PubMed: 2963247]
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLos Med. 2009:6.
24. Jensen SB, Pedersen AM, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 2010; 18:1039–1060. [PubMed: 20237805]
25. West S, King V, Carey TS, et al. Systems to rate the strength of scientific evidence. Evid Rep Technol Assess (Summ). 2002:1–11. [PubMed: 11979732]
26. Ash, MM.; Nelson, SJ., editors. Wheeler’s dental anatomy, physiology, and occlusion. St. Louis, Missouri: 2002.
27. Collett WK, Thonard JC. The Effect of Fractional Radiation on Dentinogenesis in the Rat. J Dent Res. 1965; 44:84–90. [PubMed: 14245501]
28. Arsenault AL, Robinson BW. The dentino-enamel junction: a structural and microanalytical study of early mineralization. Calcif Tissue Int. 1989; 45:111–121. [PubMed: 2505895]
29. Kaste SC, Hopkins KP, Jenkins JJ 3rd. Abnormal odontogenesis in children treated with radiation and chemotherapy: imaging findings. AJR Am J Roentgenol. 1994; 162:1407–1411. [PubMed: 8192008]
30. Fromm M, Littman P, Raney RB, et al. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. Cancer. 1986; 57:2070–2076. [PubMed: 3955515]
31. Benjamin RM. Oral health: the silent epidemic. Public Health Rep. 2010; 125:158–159. [PubMed: 20297740]
32. Jaffe N, Toth BB, Hoar RE, et al. Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: effects of treatment with chemotherapy and radiation to the head and neck. Pediatrics. 1984; 73:816–823. [PubMed: 6728583]
33. Dye BA, Tan S, Smith V, et al. Trends in oral health status: United States, 1988-1994 and 1999-2004. Vital and health statistics Series 11, Data from the national health survey. 2007:1–92.
34. Duggal MS, Curzon ME, Bailey CC, et al. Dental parameters in the long-term survivors of childhood cancer compared with siblings. Oral Oncol. 1997; 33:348–353. [PubMed: 9415335]

35. Meaney S, Anweigi L, Ziada H, et al. The impact of hypodontia: a qualitative study on the experiences of patients. Eur J Orthodont. 2011
36. Vargas-Ferreira F, Ardenghi TM. Developmental enamel defects and their impact on child oral health-related quality of life. Braz Oral Res. 2011; 25:531–537. [PubMed: 22147234]
37. Laverdière C, Cheung N-KV, Kushner BH, et al. Long-term complications in survivors of advanced stage neuroblastoma. Pediatr Blood Cancer. 2005; 45:324–332. [PubMed: 15714447]
38. McGinnis JP Jr. Hopkins KP, Thompson EI, et al. Tooth root growth impairment after mantle radiation in long-term survivors of Hodgkin's disease. J Am Dent Assoc. 1985; 111:584–588. [PubMed: 3863857]
39. Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. Med Pediatr Oncol. 1995; 25:96–101. [PubMed: 7603407]
40. Cubukcu CE, Sevinir B, Ercan İ. Disturbed dental development of permanent teeth in children with solid tumors and lymphomas. Pediatr Blood Cancer. 2012; 58:80–84. [PubMed: 21254371]
41. Sonis AL, Tarbell N, Valachovic RW, et al. Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. Cancer. 1990; 66:2645–2652. [PubMed: 2249205]
42. Kaste SC, Goodman P, Leisenring W, et al. Impact of Radiation and Chemotherapy on Risk of Dental Abnormalities A Report From the Childhood Cancer Survivor Study. Cancer. 2009; 115:5817–5827. [PubMed: 19834960]
43. Kaste SC, Hopkins KP, Jones D, et al. Dental abnormalities in children treated for acute lymphoblastic leukemia. Leukemia. 1997; 11:792–796. [PubMed: 9177429]
44. Maguire A, Craft AW, Evans RG, et al. The long-term effects of treatment on the dental condition of children surviving malignant disease. Cancer. 1987; 60:2570–2575. [PubMed: 3664436]
45. Macleod RI, Welbury RR, Soames JV. Effects of cytotoxic chemotherapy on dental development. J R Soc Med. 1987; 80:207–209. [PubMed: 3585885]
46. Hsieh SG, Hibbert S, Shaw P, et al. Association of cyclophosphamide use with dental developmental defects and salivary gland dysfunction in recipients of childhood antineoplastic therapy. Cancer. 2011; 117:2219–2227. [PubMed: 21523736]
47. Moskalewski S, Thyberg J, Lohmander S, et al. Influence of colchicine and vinblastine on the golgi complex and matrix deposition in chondrocyte aggregates. An ultrastructural study. Exp Cell Res. 1975; 95:440–454. [PubMed: 1193161]
48. Stene T, Koppang HS. Autoradiographic investigation of dentin production in rat incisors after vincristine administration. Scand J Dent Res. 1980; 88:104–112. [PubMed: 6929558]
49. Holtta P, Alaluusua S, Saarinen-Pihkala UM, et al. 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; 29:121–127. [PubMed: 11850706]
50. Fleming P, Kinirons MJ. Study of the dental health of children in remission from acute lymphoblastic leukaemia in Northern Ireland. Community Dent Oral Epidemiol. 1993; 21:309–312. [PubMed: 8222608]
51. Dens F, Boute P, Otten J, et al. Dental caries, gingival health, and oral hygiene of long term survivors of paediatric malignant diseases. Arch Dis Child. 1995; 72:129–132. [PubMed: 7702374]
52. Kaste SC, Hopkins KP, Bowman LC, et al. Dental abnormalities in children treated for neuroblastoma. Med Pediatr Oncol. 1998; 30:22–27. [PubMed: 9371385]
53. Küpeli S, Varan A, Özyar E, et al. Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. Pediatr Blood Cancer. 2006; 46:454–458. [PubMed: 16200569]
54. Avsar A, Elli M, Darka O, et al. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007; 104:781–789. [PubMed: 17618135]
55. Alberth M, Kovalecz G, Nemes J, et al. Oral health of long-term childhood cancer survivors. Pediatr Blood Cancer. 2004; 43:88–90. [PubMed: 15170898]
56. Hutton A, Bradwell M, English M, et al. The oral health needs of children after treatment for a solid tumour or lymphoma. Int J Paediatr Dent. 2010; 20:15–23. [PubMed: 20059589]

57. Wogelius P, Dahllöf G, Gorst-Rasmussen A, et al. A population-based observational study of dental caries among survivors of childhood cancer. Pediatr Blood Cancer. 2008; 50:1221–1226. [PubMed: 18273868]
58. Nunn JH, Welbury RR, Gordon PH, et al. Dental caries and dental anomalies in children treated by chemotherapy for malignant disease: a study in the north of England. Int J Paediatr Dent. 1991; 1:131–135. [PubMed: 1812966]
59. Maciel JCC, de Castro CG, Brunetto AL, et al. Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. Pediatr Blood Cancer. 2009; 53:361–365. [PubMed: 19484760]
60. Alpaslan G, Alpaslan C, Gogen H, et al. Disturbances in oral and dental structures in patients with pediatric lymphoma after chemotherapy: a preliminary report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999; 87:317–321. [PubMed: 10102592]
61. Oğuz A, Çetiner S, Karadeniz C, et al. Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. Eur J Oral Sci. 2004; 112:8–11. [PubMed: 14871187]
62. Flandin I, Hartmann O, Michon J, et al. Impact of TBI on late effects in children treated by megatherapy for Stage IV neuroblastoma. A study of the French Society of Pediatric oncology. Int J Radiat Oncol Biol Phys. 2006; 64:1424–1431. [PubMed: 16427213]
63. Welbury RR, Craft AW, Murray JJ, et al. Dental health of survivors of malignant disease. Arch Dis Child. 1984; 59:1186–1187. [PubMed: 6524952]
64. Marec-Berard P, Azzi D, Chaux-Bodard AG, et al. Long-term effects of chemotherapy on dental status in children treated for nephroblastoma. Pediatr Hematol Oncol. 2005; 22:581–588. [PubMed: 16166051]
65. Vahlsing HL, Kim SK, Feringa ER. Cyclophosphamide-induced abnormalities in the incisors of the rat. J Dent Res. 1977; 56:809–816. [PubMed: 269161]
66. Pedersen LB, Clausen N, Schroder H, et al. Microdontia and hypodontia of premolars and permanent molars in childhood cancer survivors after chemotherapy. Int J Paediatr Dent. 2012; 22:239–243. [PubMed: 22092748]
67. Minicucci EM, Lopes LF, Crocci AJ. Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. Leuk Res. 2003; 27:45–50. [PubMed: 12479851]
68. Goho C. Chemoradiation therapy: effect on dental development. Pediatr Dent. 1993; 15:6–12. [PubMed: 8233995]
69. Uderzo C, Fraschini D, Balduzzi A, et al. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. Bone Marrow Transplant. 1997; 20:865–869. [PubMed: 9404928]
70. Nasman M, Forsberg CM, Dahllof G. Long-term dental development in children after treatment for malignant disease. Eur J Orthodont. 1997; 19:151–159.
71. Vesterbacka M, Ringden O, Remberger M, et al. Disturbances in dental development and craniofacial growth in children treated with hematopoietic stem cell transplantation. Orthod Craniofac Res. 2012; 15:21–29. [PubMed: 22264324]
72. Vaughan MD, Rowland CC, Tong X, et al. Dental abnormalities after pediatric bone marrow transplantation. Bone Marrow Transplant. 2005; 36:725–729. [PubMed: 16113667]
73. Holtta P, Alaluusua S, Saarinen-Pihkala UM, et al. Agenesis and microdontia of permanent teeth as late adverse effects after stem cell transplantation in young children. Cancer. 2005; 103:181–190. [PubMed: 15540242]
74. van der Pas-van Voskuilen I, Veerkamp J, Raber-Durlacher J, et al. Long-term adverse effects of hematopoietic stem cell transplantation on dental development in children. Support Care Cancer. 2009; 17:1169–1175. [PubMed: 19139926]
75. Landier W, Bhatia S, Eshelman DA, et al. Development of Risk-Based Guidelines for Pediatric Cancer Survivors: The Children's Oncology Group Long-Term Follow-Up Guidelines From the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol. 2004; 22:4979–4990. [PubMed: 15576413]
76. Children's Oncology Group 2008. Dental Health Following Childhood Cancer Treatment. Sep 30. 2013 <http://www.survivorshipguidelines.org/pdf/dentalhealth.pdf>September 30, 2013

77. Dahllof G, Jonsson A, Ulmner M, et al. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. Am J Orthod Dentofacial Orthop. 2001; 120:459–465. [PubMed: 11709663]

78. Shearer DM, Thomson WM, Caspi A, et al. Family history and oral health: findings from the Dunedin Study. Community Dent Oral Epidemiol. 2012; 40:105–115. [PubMed: 22022823]

79. Kun, LE. General Principles of Radiation Oncology. In: Pizzo, PA.; Poplack, DG., editors. Principles and practice of pediatric oncology. 6th ed.. Wolters Kluwer/Lippincott Williams & Wilkins Health; Philadelphia, PA: 2011. p. 406-425.

80. Pui CH, Mullighan CG, Evans WE, et al. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012; 120:1165–1174. [PubMed: 22730540]

81. Jensen SB, Pedersen AM, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. Support Care Cancer. 2010; 18:1061–1079. [PubMed: 20333412]

82. American Academy on Pediatric Dentistry Clinical Affairs C; American Academy on Pediatric Dentistry Council on Clinical A. Guideline on dental management of pediatric patients receving chemotherapy, hematopoietic cell transplantation, and/or radiation. Pediatr Dent. 2008; 30:219–225. [PubMed: 19216425]

83. Duggal MS. Root surface areas in long-term survivors of childhood cancer. Oral Oncol. 2003; 39:178–183. [PubMed: 12509972]

84. van der Does-van den Berg A, de Vaan GA, van Weerden JF, et al. Late effects among long-term survivors of childhood acute leukemia in The Netherlands: a Dutch Childhood Leukemia Study Group Report. Pediatr Res. 1995; 38:802–807. [PubMed: 8552452]

85. Raney RB, Asmar L, Vassilopoulou-Sellin R, et al. IRS Group of the Children's Cancer Group; Pediatric Oncology Group. Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: A descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and - III. Med Pediatr Oncol. 1999; 33:362–371. [PubMed: 10491544]

86. Holtta P, Hovi L, Saarinen-Pihkala UM, et al. Disturbed root development of permanent teeth after pediatric stem cell transplantation. Dental root development after SCT. Cancer. 2005; 103:1484–1493. [PubMed: 15739206]

87. Treister NS, Woo SB, O'Holleran EW, et al. Oral chronic graft-versus-host disease in pediatric patients after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2005; 11:721–731. [PubMed: 16125643]

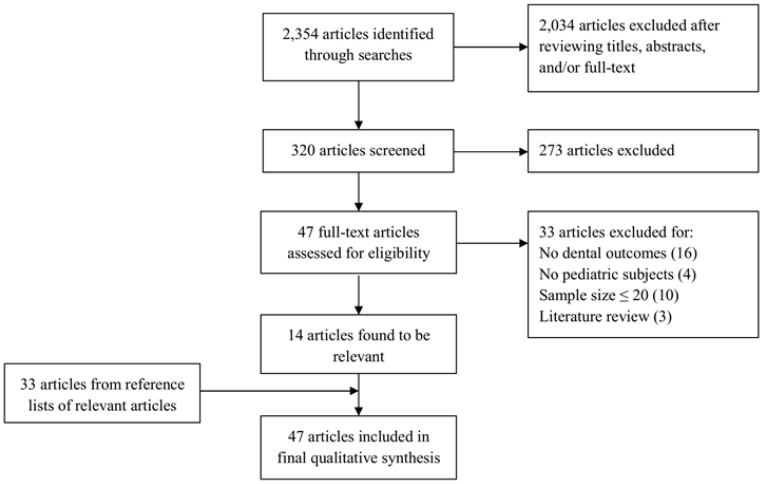

Figure 1.
Flowchart of study selection.

Table I

Summary of 12 reports of radiation-induced dental late effects in long-term survivors of childhood cancer

First Author (Year)	Sample Size (n)	Age at Diagnosis	Diagnosis	Time since Diagnosis	Surgery/ HCT	Chemotherapy Agents	Radiotherapy (RT) and Dose	Dental Late Effects														Additional Risk Factors		
								Caries	High DMFT score	High DMFS score	Agenesis	Hypodontia	Hypoplasia	Microdontia	Impaired root growth	Arrested root growth	Enamel defects/ hypoplasia	Delayed eruption	Gingivitis	Xerostomia/ acidic saliva	Taurodontism	Trismus/ Microstomia	Younger age at RT	RT dosage	Concomitant chemo
Jaffe 1984 [32]	68	Medians 5 y (HL) 5 y (ALL) 7 y (RMS) 4 y (Other)	HL, ALL, RMS, Other	Medians 6 y (HL) 5 y (ALL) 7 y (RMS) 5 y (Other)	NR	chemo only (n=23) chemo and RT (n=43)	Facial RT (n=45) 30 Gy (HL) 24 Gy (ALL) 55 Gy (RMS) 35 Gy (Other)	✓					✓		✓		✓				✓	✓		✓	
McGinnis 1985 [38]	47	4-19 y	HL	long-term survivors	NR	NR	All had RT 35-37 Gy								✓								✓		
Fromm 1986 [30]	20	7 mo-13 y (median 6 y)	Soft tissue sarcomas	2-10 y (median 6 y)	NR	All had chemo: VCR AMD, CPM, ADR	40-60 Gy (median 50 Gy)	✓			✓				✓										
McGinnis 1987 [3]	47 plus 149 controls	4-10.8 y	HL	7-12 y [a]	NR	NR	All had RT 37 Gy				✓		✓	✓	✓								✓		
Sonis 1990 [41]	97	< 10 y	ALL	≥ 5 y	NR	All had chemo	CRT (n=78; MeV) 18 Gy (27) 24 Gy (51)				✓			✓		✓	✓						✓	✓	
Pajari 1995 [2]	45 plus 45 controls	0.5-15 y (mean 5.4 y)	ALL	1-11 y (mean 3.8 y)	HCT (n=4)	chemo (n=45)	CRT (n=19) TBI (n=4; 10 Gy)	✓	✓																
Kaste 1995 [39]	22	0.8- 20.4 y	RMS of head and neck	5-16 y (median 9.4 y)	NR	All had chemo: CPM VCR, ADR, AMD	All had RT 0-67.1 Gy					✓		✓		✓				✓		✓			
Duggal 1997 [34]	46 plus 46 siblings	< 10 y	Various cancers	≥ 5 y	Some had HCT	Some had chemo	Some had RT	✓	×	×			✓	✓			✓		✓						
Kaste 1997 [43]	423	0.6-13 y (median 4.8 y)	ALL	2.4-20.3 y (median 9.5 y)	NR	All had chemo Protocol IX - XII	18-24 Gy (n=243; CRT)						✓	✓		✓		✓			✓		✓		
Duggal 2003 [83]	69 plus 69 controls	< 10 y	Various cancers	≥ 5 y	NR	chemo only (n=24) with CRT (n=25)	16-22 Gy (n=25;CRT) TBI (n=7); Jaw (n=13)								✓										✓
Laverdiere 2005 [37]	63	0.1-23.5 y (median 3 y)	NB stage 3 and 4	Median 7.06 y	All had surgery	MSKCC (n=53) and CCG protocol(n=10)	20.93-21.74 Gy (n=56)							✓		✓	✓								
Cubukcu 2012 [40]	37 plus 37 controls	< 10 y (mean 2.7 y)	Various cancers	6.7 ± 1.5 y	NR	All had chemo.	25-59 Gy (n=10; Head and Neck RT)				✓			✓	✓										✓

[a] = age at study; ✓ = reported late effect or risk factor; x = no significant difference in DMFT and DMFS between survivors and controls **Abbreviations: ALL**: Acute Lymphoblastic Leukemia; **ADR**: Adriamycin; **AMD**: Actinomycin-D; **CCG**: Children's Cancer Group; **CPM**: Cyclophosphamide; **CRT**: Cranial Radiotherapy; **DMFT**: Decayed, Missing, Filled Teeth; **DMFS**: Decayed, Missing, Filled Surface; **Gy**: Gray; **HL**: Hodgkin lymphoma; **MSKCC**: Memorial Sloan Kettering Cancer Center; **NR**: Not reported; **NB**: Neuroblastoma; **RMS**: Rhabdomyosarcoma; **TBI**: Total Body Irradiation; **VCR**: Vincristine; **y**: years

Table II

Summary of 25 reports of chemotherapy-induced dental late effects in long-term survivors of childhood cancer

First Author (Year)	Sample Size (n)	Age at Diagnosis	Diagnosis	Time since Diagnosis	Surgery/ HCT	Chemotherapy Agents	Radiotherapy (RT) and Dose	Late Effects															Additional Risk Factors				
								Caries	DMFT score	DMFS score	Agenesis	Hypodontia	Hypoplasia	Microdontia	Impaired root growth	Arrested root growth	Enamel defects/ hypoplasia	Impaired dentinogenesis	Delayed eruption	Malformed teeth	Malocclusion	Taurodontism 1	Trismus/ Microstomia	Younger age at treatment	Vincristine	Alkylating agents/CPM	Intensive chemotherapy	Concomitant RT
Welbury 1984 [63]	64	NR	Leukemia and solid tumors	3-20 y [a]	NR	All had chemo	CRT for ALL					✓	✓					✓										
Maguire 1987 [44]	82 plus 49 siblings	NR	Leukemia and solid tumors	3-22 y [a]	NR	All had chemo	24 Gy (CRT)	×	×	×			✓		✓		✓				✓			✓	✓			
Pajari 1988a [6]	37 plus 74 controls	1-15 y (mean 5.7 y)	ALL and Others	3-13 y [a]	NR	All had chemo	24 Gy (CRT) (n=17)	✓		✓																		
Pajari 1988b [5]	37 plus 37 controls	1-15 y (mean 5.7 y)	ALL and Others	1-8 y	NR	All had chemo	24 Gy (CRT) (n=17)										✓											
Purdell- Lewis 1988 [8]	45 plus 300 controls	NR	ALL and Others	7-13 y (mean 10.1 y) [a]	NR	VCR, MTX, CPM,6-MP, cytarabine, bleomycin	25 Gy (CRT)	✓								✓	✓		✓	✓				✓				
Nunn 1991 [58]	52 plus 41 sibling	NR	Various cancers	57-291 mo (mean 144 mo) [a]	NR	All had chemo	CRT for leukemia	×	×	×				✓	✓		✓					✓						
Fleming 1993 [50]	54 plus 54 controls	3.8-19.8 y (mean 10.5 y)	ALL	5 mo-13.5 y (mean 4.8 y)	NR	UK MRC's protocol for ALL	NR		✓																			
Dens 1995 [51]	52 plus 60 control	0-10 y	Various cancers	2-17 y [a]	NR	All had chemo	NR	✓	✓	✓																		
Van der Does- Van den Berg 1995 [84]	273	< 2 y (n=36) 2-10 (n=206) >10 (n=31)	ALL (n=263) ANLL (n=4) AUL (n=6)	≥ 6 y	NR	ALL I -V, ANLL 80 and AUL protocol	NR	✓							✓													
Kaste 1998 [52]	52	3 d-7.2 y (median 1.5 y)	NB	1.9-19.3y (median 5 y)	NR	DOXO, CPM, CPL, CSPL, VP-16 (n=52)	NR	✓				✓		✓		✓	✓							✓		✓		
Algan1an 1999 [60]	30 plus 20 controls	4-15 y	Lymphoma	Long-term remission	NR	BFM-90, LSA2-L2, COPP or ABVD (n=30)	NR		×		✓		✓				✓							✓				
Raney 1999 [85]	213	Median 5 y	Non-orbital RMS	Median 7 y	NR	Intergroup RMS II and III protocol	40-55 Gy (n=210; local)	✓												✓								
Minicucci 2003 [67]	76	1-12 y (mean 5.1 y)	ALL	0.6-9 y (mean 2.9 y)		Brazilian protocol or BFM-86 protocol	CRT for high risk				✓		✓	✓	✓				✓	✓				✓			✓	
Alberth 2004 [55]	45 plus 45 controls	1-22 y (mean 6.9 y)	Leukemia and solid tumors	1- 14 y (mean 5.9 y)	NR	Hungarian Pediatric Oncology Protocol	12-18 Gy (n=13) 18-40 Gy (n=11)	✓	✓	✓																		
Ogut 2004 [61]	36 plus 36 controls	3.2-15 y (mean 7.1 y)	NHL	1-6.2 y (mean 2.6)	NR	BFM-90 B cell LSA2-L2, LMT-89	NR								✓					✓							
Maree- Beaard 2005 [64]	27 plus 78 controls	0.8-8.6 y (median 3.6y)	WT	3-12.7 y (median 7.5 y) [a]	NR	SIOP-93 protocol VCR, AMD, DOXO	NR					✓		✓	✓		✓					✓						
Flandin 2006 [62]	62	Mean 3.1 y	NB stage IV	Mean 12 y	NR	NB-87 protocol	4.5-12 Gy (TBI) 25-36 Gy (local)				✓			✓		✓												
Kupelli 2006 [53]	84	7-17 y (median 13 y)	NPC	Median 9 y	NR	All had CPM,VCR,EPIR, AMD, CSPL, MTX, FU	All had RT	✓															✓					
Avsar 2007 [54]	96 plus 96 controls	2.9-13.1 y (mean 6.4 y)	NHL, WT, HL, OS, RMS	0.5-7.2 y (mean 2.5 y)	NR	All had chemo	NR	✓							✓	✓	✓			✓								
Wogelius 2008 [57]	1273 plus 914817 controls	650/1273 diagnosed at < 5 y	Various cancers	288 (age 7 y) [a] 459 (age 12 y) [a] 526 (age 15 y) [a]	NR	Danish protocols	NR	✓																				
Kaste 2009 [42]	8522 plus 2831 siblings	0-20 y (median 6 y)	Various cancers	15-34 y (median 22 y)	Surgery (0.2%)	chemo only (25.4%) chemo and RT (51.8%)	RT only (12.5%)	✓				✓		✓	✓		✓							✓		✓	✓	✓
Maciel 2009 [59]	56 plus 56 controls	5.3 ± 2.6 y	ALL	11.8 ± 4.2 y [a]	HCT (n=8)	All had chemo chemo only (n=30)	TBI (n=8);chemo and RT (n=18)				✓			✓	✓					✓				✓				✓
Hutton 2010 [56]	120	0-17 y	NB, WT, RMS, HL, NHL, other	Mean 51.9 ± 40.3 mo	HCT (n=14)	Alkylating agents, Anthracyclines, CSPL	NR		✓															✓			✓	
Hsieh 2011 [46]	106	Mean 4.9 ± 3.6 y	Various cancers	Mean 15.8 ± 5.1 y [a]	Surgery (n=11)	CPM, DOXO, AMD, VCR, MTX (n=105)	TBI (8), Head and neck (19), both (5)					✓		✓	✓											✓		

First Author (Year)	Sample Size (n)	Age at Diagnosis	Diagnosis	Time since Diagnosis	Surgery/ HCT	Chemotherapy Agents	Radiotherapy (RT) and Dose	Late Effects																Additional Risk Factors				
								Caries	DMFT score	DMFS score	Agenesis	Hypodontia	Hypoplasia	Microdontia	Impaired root growth	Arrested root growth	Enamel defects/ hypoplasia	Impaired dentinogenesis	Delayed eruption	Malformed teeth	Malocclusion	Taurodontism 1	Trismus/ Microstomia	Younger age at treatment	Vincristine	Alkylating agents/CPM	Intensive chemotherapy	Concomitant RT
Pedersen 2012 [66]	150 plus 193 controls	0-7 y	Various cancers	12-18 y [a]	NR	chemo as per Danish protocol	NR					✓		✓										✓				

[a] = age at study; ✓ = reported late effect or risk factor; x=higher prevalence of caries were reported but were not associated with chemotherapy and/or TBI conditioning **Abbreviations: ABVD**: Adriamycin, Bleomycin, Vinblastine and Dacarbazine; **ALL**: Acute Lymphoblastic Leukemia; **ADR**: Adriamycin; **AMD**: Actinomycin-D; **ANLL**: Acute Non-Lymphoblastic Leukemia; **AUL**: Acute Undifferentiated Leukemia; **BFM**: Berlin-Frankfurt-Munster; **BVD**: Bleomycin, Vinblastine and Dacarbazine; **CCG**: Children's Cancer Group; **CPL**: Carboplatin; **CPM**: Cyclophosphamide; **CML**; Chronic Myeloid Leukemia; **CRT**: Cranial Radiotherapy; **CSPL**: Cisplatin; **CSRT**: Craniospinal Radiotherapy; **DMFT**: Decayed, Missing, Filled Teeth; **DMFS**: Decayed, Missing, Filled Surface; **DOXO**: Doxorubicin; **EPIR**: Epirubicin; **Gy**: Gray; **HL**: Hodgkin lymphoma; **HLH**: Hemophagocytic Lymphohistiocytosis; **HCT**: Hematopoietic Cell Transplant **JMML**: Juvenile Myelomonocytic Leukemia; **mo**: months; **MB**: Medulloblastoma; **MDS**: Myelodysplastic syndrome; **MP**: Mercaptopurine; **MRC**: Medical Research Council; **MTX**: Methotrexate; **NR**: Not reported; **NB**: Neuroblastoma; **NHL**: non-Hodgkin Lymphoma; **NWTS**: National Wilms Tumor Study; **NPC**: Nasopharyngeal carcinoma; **PRED**: Prednisone; **RMS**: Rhabdomyosarcoma; **SIOP**: International Society of Pediatric Oncology; **VP-16**: Etoposide; **TBI**: Total Body Irradiation; **VCR**: Vincristine; **WT**: Wilm's tumor; **y**: year

Table III

Summary of 10 reports of dental late effects in long-term survivors of childhood cancer treated with hematopoietic stem cell transplant

First Author (Year)	Sample Size (n)	Age at Diagnosis	Diagnosis	Time since Diagnosis	HCT	Chemotherapy Agents	Radiotherapy (RT) and Dose	Dental Late Effects																Additional Risk Factors		
								Caries	High DMFT score	Agenesis	Hypodontia	Hypoplasia	Microdontia	Impaired root growth	Arrested root growth	Enamel defects/ hypoplasia	Delayed eruption	Malformed teeth	Gingivitis	Xerostomia\acidic saliva	Trismus/ Microstomia	Mucosal lesions	Atrophic glossitis	Younger age at treatment	RT dosage	Intensive chemo
Näsman 1994 [12]	76	5.1 y for chemo 6.5 y for HCT	Hematological cancer	6 y for chemo 5.4 y for HCT	HCT (n=19)	chemo (n=57)	8-10 Gy (n=19; TBI)	×		✓			✓	✓	✓	✓				✓				✓		✓
Nasman 1997 [70]	68; HCT (n=16) chemo (n=52)	6.3 ± 3.5 y for HCT group 5.1 ± 3.3 y for chemo group	Hematological cancer (n=44), solid tumors (n=24)	3.0-8.6 y for HCT group 3.0-17.5 y for chemo group	HCT (n=16)	All had CPM in HCT group. All had multiagent therapy in chemo group	10 Gy (n=16; TBI) 18-24 Gy (n=13;CRT)						✓	✓										✓		✓
Dahllöf 1997 [15]	26 plus 26 controls	4-12 y	Hematological cancers (n=17)	4 y	All had HCT	CPM and or BU in TBI group (n=14)	10 Gy (n=14; TBI)	×												✓					✓	✓
Uderzo 1997 [69]	27	0.7-14.7 y (median 6.6 y)	Hematological cancers	4.5-19.9 y[a] (median 11.6 y)	All had HCT	High-dose VCR and CPM	12 Gy (n=25; TBI) 18 Gy (n=11; CRT)		✓	✓		✓		✓	✓		✓		✓		✓			✓		✓
Höltä 2005a[73]	55	1-9.4 y (mean 4.3 y)	Leukemia, Lymphoma and WT	1-20.6 y (mean 7.4 y)	All had HCT	Nordic protocols and NWTS protocol	10-12 Gy (n=39; TBI)			✓			✓											✓		
Höltä 2005b[86]	52	1-9.4 y (mean 4.4 y)	Leukemia, Lymphoma and WT	1-20.6 y (mean 7.2 y)	All had HCT	Nordic protocols and NWTS protocol	10-12 Gy (n=38; TBI)							✓												✓
Treister [87]	49	1-20 y (median 8.5 y)	Hematological cancers	0.3- 9 y (median 2 y)	All had HCT	CPM and/BU and /Fludarabine/VP-16	TBI (n=36)	✓															✓	✓			
Vaughan 2005 [72]	99	3.4-25.9 y (median 13.5 y)	Hematological cancers	0.17-9.04 y (median 3.1 y)	All had HCT	St. Jude Institutional Protocols	TBI	×							✓												
Van der Pas-Van Voskuilen 2009 [74]	40	0.2-9 y (mean 3.7 y)	ALL, AML CML, HLH JMML, MDS	1.9-14 y (mean 8.1 y)	All had HCT	All had chemo as per Dutch protocol	7-12 Gy (n=16; TBI)			✓				✓				✓						✓		
Vesterbacka 2012 [71]	39 plus 78 controls	1.5-12.4 y (mean 6.8 y)	Hematological cancers	mean 9.4 y	All had HCT	High dose CPM or Busulfan	10 Gy (n=25; TBI)					✓	✓											✓		✓

✓ = reported late effect or risk factor; x=higher prevalence of caries were reported but were not associated with chemotherapy and/or TBI conditioning; **Abbreviations: ALL**: Acute Lymphoblastic Leukemia; **BU**: Busulphan; **CPM**: Cyclophosphamide; **CML**; Chronic Myeloid Leukemia; **CRT**: Cranial Radiotherapy; **DMFT**: Decayed, Missing, Filled Teeth; **DMFS**: Decayed, Missing, Filled Surface; **Gy**: Gray; **HLH**: Hemophagocytic Lymphohistiocytosis; **HCT**: Hematopoietic Cell Transplant **JMML**: Juvenile Myelomonocytic Leukemia; **MDS**: Myelodysplastic syndrome; **NWTS**: National Wilms Tumor Study **TBI**: Total Body Irradiation; **VCR**: Vincristine; **VP-16**: Etoposide; **WT**: Wilm's tumor; **y**=year