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Oral and dental late effects in survivors of childhood cancer: a Children's Oncology Group report

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Abstract

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Purpose—Multi-modality therapy has resulted in improved survival for childhood malignancies. The *Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* provide practitioners with exposure- and risk-based recommendations for the surveillance and management of asymptomatic survivors who are at least 2 years from completion of therapy. This review outlines the pathophysiology and risks for oral and dental late effects in pediatric cancer survivors and the rationale for oral and dental screening recommended by the Children’s Oncology Group.

Methods—An English literature search for oral and dental complications of childhood cancer treatment was undertaken via MEDLINE and encompassed January 1975 to January 2013. Proposed guideline content based on the literature review was approved by a multi-disciplinary panel of survivorship experts and scored according to a modified version of the National Comprehensive Cancer Network “Categories of Consensus” system.

Results—The Children’s Oncology Group oral-dental panel selected 85 relevant citations. Childhood cancer therapy may impact tooth development, salivary function, craniofacial development, and temporomandibular joint function placing some childhood cancer survivors at an increased risk for poor oral and dental health. Additionally, head and neck radiation and hematopoietic stem cell transplantation increase the risk of subsequent malignant neoplasms in the oral cavity. Survivors require routine dental care to evaluate for potential side effects and initiate early treatment.

Conclusions—Certain childhood cancer survivors are at an increased risk for poor oral and dental health. Early identification of oral and dental morbidity and early interventions can optimize health and quality of life.

Keywords

Pediatric cancer; Oral dental health; Survivorship; Late effects

Introduction

With contemporary multi-modality therapy, the 5-year survival rate for pediatric malignancies exceeds 80 % [1]. This success has produced 379,000 childhood cancer survivors in the USA [1]. As many as 60 to 90 % of these long-term survivors experience adverse health consequences related to cancer or its treatment, which may not manifest until years after therapy completion [2–6]. Among treatment-related sequelae, oral and dental complications are common but often overlooked sources of morbidity and impaired health-related quality of life.

This manuscript reviews the pathophysiology and risks for oral and dental late effects in childhood cancer survivors and the rationale and importance of screening recommended in the *Children’s Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (COG Guidelines; www.survivorshipguidelines.org) [7, 8]. Since routine dental care is not universally accessible in the USA, primary care providers (PCPs), to whom survivors return for care, play key roles in screening and early detection, hygiene recommendations, and referral for preventive and corrective dental interventions. To avoid potential complications of

otherwise routine dental and orthodontic procedures, providers need to recognize late effects impacting tooth development, salivary function, and temporomandibular joint (TMJ) function and risk factors necessitating antibiotic prophylaxis prior to dental intervention. Additionally, PCPs need to be aware of the risk and presentation of oral subsequent malignant neoplasms (SMNs).

Methods

The COG Guidelines represent recommendations for risk-based screening and management of late effects that arise in asymptomatic survivors who are at least 2 years from therapy completion for pediatric and adolescent malignancies [7]. Organ-specific, multi-disciplinary panels within the COG Late Effects Committee ensure that the guidelines reflect current evidence-based research by undertaking biennial reviews of the literature. The COG panel on oral and dental complications includes expertise in pediatric and radiation oncology, pediatric radiology, oral and dental medicine, pediatric oncology nursing, and pediatric hematopoietic stem cell transplantation (HSCT).

The English literature search for oral and dental complications of cancer treatment was undertaken via MEDLINE (National Library of Medicine, Bethesda, MD, USA) and encompassed January 1975 to January 2013. Key search words included “oral health,” “dental,” “dental abnormalities,” “dental development,” “trismus,” “xerostomia,” “osteoradionecrosis,” “graft-versus-host and oral complications,” “prosthodontic chemotherapy,” “oral malignancies,” “dental antibacterial prophylaxis,” “childhood cancer,” “complications,” and “late effects.” Search criteria were then expanded using references cited in the bibliographies of selected articles. A multi-disciplinary panel of survivorship experts qualitatively evaluated each result. Structured criteria for exclusion were not applied due to the paucity of literature on this topic. Proposed guideline content based on the literature review was reviewed and approved by the panel of experts. It was scored according to a modified version of the National Comprehensive Cancer Network “Categories of Consensus” system [9]. “High-level evidence” was derived from high quality case-control or cohort studies, while “lower-level evidence” was derived from non-analytic studies, case reports, case series, and clinical experience. This review presents “Category 1” recommendations and reflects uniform consensus among the oral-dental panel that (1) there is high-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective experience of panel members. The COG Guidelines and their accompanying patient education materials (“Health Links”) are available at <http://www.survivorshipguidelines.org>.

Results

Due to the lack of randomized controlled trials, results are derived largely from observational studies. The COG oral-dental panel selected 85 citations that were the most current and relevant from the several hundred retrieved via MEDLINE. These include a large retrospective cohort of 5-year childhood cancer survivors with longitudinal follow-up (Childhood Cancer Survivor Study [CCSS]), cross-sectional studies that evaluated survivors with and without controls, retrospective cohort studies, review articles, and clinical

guidelines. Case series were included for completeness, although considered as anecdotal. Literature regarding late effects in adult cancer survivors was incorporated to extrapolate experiences, since there are few high-level evidence pediatric investigations on oral and dental late effects. The quality of current evidence is sometimes constrained by the use of convenience cohorts; retrospective data collection; small sample size; and heterogeneity in treatment approach, time since treatment, and method of ascertaining late effects.

Oral cavity development

Dental development is a complex process influenced by intense genetic signaling and controlled by a network of activators and inhibitors [10]. Primary central incisors develop as early as 6 months with most children having complete primary dentition by 3 years. Formation and eruption of permanent dentition occurs from approximately 6 to 12 years [11]. The temporal disruption or modifications of this network by cancer therapy administered during stages of tooth development can cause dental anomalies [12, 13] (Figs. 1, 2, and 3).

Impact of cancer therapy on tooth development

Structural anomalies of teeth, including hypodontia, microdontia, enamel hypoplasia, and root malformation, are increasingly recognized after childhood cancer treatment [12, 13]. The prevalence of hypodontia, which may alter craniofacial development and lead to malocclusion [14, 15], has ranged from 8.5 to 50 % depending on age at diagnosis, treatment modality, and study ascertainment methods [16–18]. In a CCSS report, childhood cancer survivors self-reported enamel hypoplasia more than twice as often as sibling controls (11.7 % versus 5.3 %) and were at higher risk for reporting root anomalies than siblings (odds ratio [OR]=3.0 [2.2–4.0]) [19]. A retrospective evaluation of dental records and panoramic radiographs in 52 neuroblastoma survivors with a median age of 1.5 years at treatment reported hypodontia in 17 %, microdontia in 38 %, enamel hypoplasia in 17 %, and root stunting in 17 %. All of these patients received chemotherapy, and eight patients received head and neck radiation [17].

Several therapeutic exposures have been associated with dental anomalies due to the disruption of ameloblast and odontoblast activity early in life [12] (Table 1). Risk increases with treatment age younger than 5 years and higher doses of alkylating agents, especially cyclophosphamide [19–22]. Radiation involving the oral cavity also increases the risk of dental anomalies since ameloblasts can be permanently damaged by doses as low as 10 Gy [12, 19]. HSCT conditioning regimens, especially those containing total body irradiation (TBI), are cytotoxic and may lead to tooth agenesis and root anomalies [23–27]. In a study of long-term childhood cancer survivors treated before age 10 years, children who underwent HSCT with TBI had smaller root areas compared to children treated with other modalities [28].

Complications associated with dental anomalies can influence quality of life. Many childhood cancer survivors have white/cream-colored and yellow/brown opacities in the enamel and develop grooves or pits [29]. Survivors with enamel hypoplasia may have colonization with *Streptococcus mutans* and other bacteria, leading to an increased rate of

caries formation [30, 31] (Figs. 1, 2, and 3). A population-based study from Denmark, which has universal childhood dental care, reported that caries were increased in 12-year-old children diagnosed with cancer at 5 or 6 years of age, but not in older teenage survivors [32]. This underscores the importance of routine care with biannual dental exams and yearly oral exams to ensure early intervention and treatment (Table 1). Root development should be evaluated with panoramic radiographs prior to any dental or orthodontic procedure in order to prevent complications. In a case series, five of eight orthodontists modified their treatment choice in pediatric HSCT survivors due to the extent of dental disturbances [33]. Additionally, PCPs should encourage good oral hygiene with brushing, use of fluoride toothpaste, flossing, and limitation of sweets [34].

Impact of cancer therapy on salivary gland function

Xerostomia, the subjective sensation of dry mouth, is a potential side effect following head and neck radiation or HSCT (Table 1) that can severely impact quality of life [35]. Consequences of decreased salivary secretion include increased caries (Figs. 1, 2, and 3), susceptibility to oral infections, sleep disturbances, and difficulties with chewing, swallowing, and speaking [35].

The prevalence of salivary gland dysfunction after cancer treatment varies based on measurement techniques (patient report versus stimulated or unstimulated salivary secretion rates) [36]. A review of 79 studies reported an 83.5 % prevalence of self-reported xerostomia 2 years after radiation for head and neck cancer in adults [35]. However, a study of childhood rhabdomyosarcoma survivors who received head and neck radiation showed a prevalence of only 12 % at a median follow-up of 7 years [37]. In a CCSS study, the prevalence of self-reported xerostomia in survivors was 2.8 % compared to 0.3 % in siblings, with an increased risk in survivors older than 30 years of age [19]. The discordance in xerostomia reporting between adults and children may be due to the higher doses of radiation used in adult head and neck cancers, increased co-morbidities in adult patients, or underreporting of symptoms by children [38].

The largest risk factor for xerostomia is exposure to radiation. Unlike most non-dividing tissues, salivary glands are exquisitely radiosensitive [39]. Due to their location, the salivary glands are often included in the radiation field for head and neck malignancies, i.e., nasopharyngeal carcinoma, rhabdomyosarcoma, and Hodgkin lymphoma [40]. Adult oncology data suggest that long-term severe xerostomia can usually be avoided if one parotid gland is spared to a mean dose less than 20 Gy or both glands are spared to a mean dose less than 25 Gy [41]. Additionally, risk is reduced if submandibular glands are spared [41]. Development of intensity-modulated radiotherapy (IMRT) has allowed dosimetric sparing of the parotid gland, with a hope of improved salivary function [42]. The long-term outcomes of these new modalities remain to be determined.

The association of chemotherapy alone with xerostomia is controversial [35]. One study of pediatric patients treated for a variety of tumors showed that cyclophosphamide was associated with an excess risk (OR=12.32 [2.1–74.4]) of decreased stimulated saliva flow rates; however, no increased dental caries were noted, and patient-reported xerostomia was not evaluated [21].

In HSCT recipients, salivary gland dysfunction occurs as a result of toxicity from conditioning regimens or can be an early symptom of chronic graft-versus-host disease (cGVHD) [43, 44]. In a study of pediatric HSCT survivors, 60 % of those exposed to a conditioning regimen with cyclophosphamide and 10-Gy single-dose TBI had decreased salivary secretion rates compared to 26 % in those who received cyclophosphamide and busulfan [45]. However, another study reported no difference in the percentage of long-term survivors with decreased salivary secretion based on conditioning regimen (single-dose TBI 47 %, fractionated TBI 47 %, busulfan 42 %) [46].

In order to assess for xerostomia and determine if further testing or intervention is warranted, PCPs should ask survivors about trouble eating dry foods, problems swallowing, or the need to drink water frequently. Treatment focuses on relieving xerostomia symptoms. Pilocarpine is approved for radiation-induced xerostomia in adults and is effective in increasing salivary secretion rates as well as improving symptoms [47]. Acupuncture and saliva substitutes may also provide temporary relief. Many individuals prefer frequent sips of water to these treatments [47]. There have been no intervention trials for xerostomia in children.

Craniofacial abnormalities associated with radiation

Craniofacial abnormalities, which may impact the oral cavity, occur in 35 to 90 % of children who receive high-dose radiotherapy to the head and neck [20, 37, 48–50]. Such abnormalities are often associated with oral cavity sequelae such as dental anomalies, xerostomia, and trismus [50]. Cosmetic deformities and the requirement for multiple surgical reconstructions can deeply impact quality of life in long-term survivors [50]. Younger age at treatment and increased radiotherapy volume and dose (> 30 Gy) contribute to the extent and severity of bone and soft-tissue deformity [50] (Table 1). Since craniofacial reconstruction techniques have flourished in the last decade, cases are best managed in an individualized manner by a multi-specialty team with extensive pre-operative planning [51]. Resources for survivors with craniofacial abnormalities include FACES: The National Craniofacial Association (www.faces-cranio.org).

Radiation-induced trismus

Trismus is associated with radiotherapy effects on the TMJ, mandible, or muscles of mastication. Its prevalence ranges from 7 to 27 % in childhood nasopharyngeal carcinoma survivors [52–54]. Functional sequelae include compromised oral hygiene, poor nutrition, impaired dental care, and difficulties with speech [55–57]. Additionally, chronic pain with mouth opening can impair quality of life. While no studies in children have evaluated the radiation dose associated with trismus, an adult series reported that for each 10 Gy over 40 Gy of radiation to the pterygoid muscle, the probability of trismus increased by 24 % [58]. Adult survivors who received head and neck radiation greater than 50 Gy have the highest risk of trismus [59], and children with nasopharyngeal carcinoma typically receive doses greater than 50 Gy [52–54]. Involvement of the muscles of mastication by head and neck tumors can also increase the risk due to late fibrosis. Early intervention with prophylactic jaw-stretching exercises is crucial for patients receiving radiotherapy to the head and neck to

prevent progressive fibrosis [60]. Survivors may benefit from jaw motion devices, such as TheraBite®, or trismus-release surgery [54, 61, 62].

Osteoradionecrosis (ORN) of facial bones

Oral cavity ORN is defined by the breakdown of the overlying oral mucosa for a minimum of 6 months resulting in the exposure of necrotic bone, usually the mandible, and ultimate mechanical failure of the TMJ [63]. While cohorts treated in the 1950s had ORN rates as high as 37 % [64], the incidence in adults with head and neck malignancies treated with contemporary radiation techniques is 3 to 7 % [63, 65]. ORN typically occurs within 1 to 5 years after head and neck radiation [66]; however, there are reports decades after exposure [67].

There is a paucity of ORN literature in children. In adults, ORN has been associated with radiation exposures of 40 to 50 Gy [68–70] and higher [63, 66, 71]. Increased risk due to concurrent radiation and chemotherapy [63] or radiation fractionation schedule is controversial [72, 73]. Poor pre-radiotherapy dental and periodontal status increases ORN risk [70]. Invasive dental therapy, such as the extraction of teeth included in the radiation field or periodontal surgical procedures that involve the manipulation of bone, is a potential contributing factor [65].

The use of newer radiation techniques, such as IMRT or proton beam, to reduce the mandibular dose may decrease the risk of ORN [68]. Additionally, improving pre-treatment dental hygiene is thought to enhance outcomes [71]. If oral cavity surgery is necessary after radiation, dentists and radiation oncologists should discuss the risk of ORN based on the dose and fields of radiation. Prophylactic hyperbaric oxygen therapy (HBO) before dental surgery [74, 75] and the use of prophylactic antibiotics remain controversial and have not proven to be effective in adults [63, 65]. Treatment of ORN depends on stage, with lower-grade disease being amenable to conservative measures and HBO, while advanced disease requires surgical intervention [69, 75–77].

Oral graft-versus-host disease (GVHD)

GVHD is a serious condition limited to survivors of allogeneic HSCT [43]. cGVHD typically presents 100 days or more after HSCT. Most cases manifest by 1 year, and almost all begin within 2 to 3 years [43, 78]. While the oral cavity is the second most commonly affected organ by cGVHD in adults, 9 to 45 % of children are affected [43, 79–81]. Oral cGVHD may be the primary or only indicator of cGVHD in HSCT survivors.

Signs and symptoms of oral cGVHD are similar to auto-immune disorders such as scleroderma and Sjögren syndrome [78]. They include pain, food sensitivities, taste alteration, xerostomia, and restricted mobility of the tongue or mouth [43]. Children are less likely to report these symptoms; therefore, asking directed questions is necessary. Trismus may result from skin fibrosis or musculoskeletal involvement with cGVHD. According to the National Institute of Health consensus criteria guidelines, diagnostic signs of oral cGVHD include lichenoid changes, leukoplakia, and oral range of motion difficulties [82]. Distinctive signs include mucosal ulceration or atrophy, multiple mucocelles (rare in children), pseudomembrane formation, and xerostomia or salivary gland dysfunction [82].

Gingivitis and mucosal erythema may also be seen [43, 78, 82]. Additionally, oral cGVHD can result in dental caries, difficulty in maintaining oral hygiene, or opportunistic infections [78]. Severe manifestations may impair oral intake or speech. Malignant transformation is a long-term concern [83].

Treatment of cGVHD is often challenging and typically takes months to years to control, with up to 40 % of cases unresponsive to intervention [78, 84]. Physicians should biopsy suspicious oral lesions, particularly if no other manifestations of cGVHD are present. Testing for infection should include herpes simplex virus and candida, which can co-occur with cGVHD. Erythematous and ulcerative oral lesions typically require therapy, while reticular lesions often do not. Treatment directed specifically towards oral cGVHD usually involves oral steroid rinses such as budesonide or dexamethasone [78]. Topical calcineurin inhibitors, such as cyclosporine and tacrolimus, and phototherapy have been used less commonly either individually or in combination with steroids. Topical anesthetics may be of benefit if symptoms are severe. A mouth-opening device for physical therapy may be required in the setting of trismus. Systemic immunosuppression is often required if other organs are affected [84]. When oral cGVHD is suspected or has been diagnosed, follow-up with a dental professional with experience in oral medicine every 4 to 6 months is advised [34].

SMNs associated with HSCT and radiation

Oral SMNs are well-recognized treatment-related sequelae [85]. While mucoepidermoid carcinoma of the parotid gland and oral carcinomas are uncommon in childhood, they develop at increased rates in survivors of childhood cancer, particularly after radiotherapy and HSCT [86–88]. Squamous cell carcinoma accounts for approximately one-third of solid SMNs after HSCT, with 50 % occurring in the oral cavity [89]. The CCSS reported childhood cancer survivors had a significantly higher risk of head and neck carcinoma compared to the general population (standardized incidence ratio [SIR] 13.6 [8.9–20.9]) with a prevalence of 0.2 % [87]. Like other solid SMNs, these tumors typically develop 5 to 20 years after treatment [83, 85, 87–90].

Survivors of acute lymphoblastic leukemia, neuroblastoma, soft tissue sarcomas, and Hodgkin lymphoma are at an increased risk for oral SMNs, which are usually associated with head and neck radiotherapy [87, 88]. CCSS participants who received radiation had an increased risk of head and neck SMNs compared to those who did not (SIR 18.5 versus 2.3), and 17 of 20 participants who received radiation and developed an oral SMN developed the carcinoma in a previous radiation field [87]. In HSCT survivors, conditioning regimens including TBI or limited field radiation are associated with an increased risk for oral carcinomas, with higher radiation doses (10 Gy single-dose or 13 Gy fractionated TBI) portending the largest risk [85, 86, 90, 91]. Additionally, survivors with cGVHD are at an increased risk for developing oral SMNs [85, 90]. Oral cGVHD was present in 23 of 26 individuals aged 14 to 67 years with oral epithelial dysplasia or squamous cell carcinoma following HSCT [89]. Host risk factors associated with an increased risk of oral cancer include younger age at HSCT and underlying cancer predisposition syndromes, such as

Fanconi anemia and dyskeratosis congenita [85, 87, 88, 92, 93]. Alcohol or tobacco use also increases the risk of oral SMNs [83, 87].

PCPs and dentists should monitor survivors who received head or neck radiation therapy or HSCT annually for oral SMNs. Masses, atypical plaques, chronic ulcerations, and induration of the mucosa should be evaluated with adequate lighting. Due to the concurrent and sometimes difficult distinction between cGVHD and oral SMNs, practitioners should have a low threshold for performing a biopsy on suspicious lesions [78]. There is no evidence to support tissue autofluorescence or screening biopsies in the absence of clinical signs or symptoms [93]. Survivors should be counseled to avoid carcinogenic exposures such as tobacco use, excessive alcohol, and excessive sun exposure, which increase the risk of oral and lip cancers [94] (Table 1).

Dental antibacterial prophylaxis

Normal oral flora may enter the bloodstream with chewing, toothbrushing, and dental procedures [95]. Regular dental exams are a key element of maintaining good oral hygiene; however, transient bacteremia places some survivors at risk for serious infections. Discussion between oncologists and dentists is important to determine when antibacterial prophylaxis is necessary prior to dental procedures.

The American Heart Association (AHA), American Dental Association (ADA), and American Academy of Pediatric Dentistry (AAPD) have developed guidelines for the use of prophylactic antibiotics prior to dental procedures in certain high-risk individuals. For survivors with a history of infective endocarditis, cardiac transplant with valvulopathy, or prosthetic heart valves, antibiotics are recommended prior to procedures that involve the perforation of the mucosa or manipulation of gingival tissue or periapical region of the teeth [96]. Brain tumor survivors with ventriculoatrial, ventriculocardiac, or ventriculovenous shunts for hydrocephalus also require prophylaxis; however, it is not recommended for those with ventriculoperitoneal shunts or non-valvular devices [97]. There are no evidence-based guidelines for antibiotic prophylaxis prior to dental procedures in asplenic individuals, those with cGVHD, or other immunosuppressed survivors; hence, current use is based on individual physician practice [98, 99].

The ADA and American Academy of Orthopedic Surgeons (AAOS) published a joint evidence-based guideline in 2012 on the prevention of orthopedic implant infections in those undergoing dental procedures. The review found no clear evidence of prosthetic infections due to bacteremia after dental procedures, leading to the new limited recommendation that prophylactic antibiotics prior to dental procedures are not needed for those with hip or knee implants [100]. This may apply to survivors with various orthopedic appliances. Since this is a limited guideline, dentists, orthopedic surgeons, and PCPs should discuss risks associated with procedures on an individual basis. These updated recommendations will be reflected in the next version of the COG Guidelines.

Discussion

As the population of childhood cancer survivors expands and ages, it is important for PCPs to be aware of oral and dental treatment-related sequelae in order to facilitate early detection and interventions to optimize health and quality of life. Ideally, oral and dental health should be evaluated at initial cancer diagnosis to anticipate the potential impact of planned cancer treatment on acute and chronic problems and to stabilize existing dental disease. Maintenance of oral hygiene throughout treatment and survivorship is key. Oral and dental disturbances following childhood cancer therapy can be associated with oral infections, speech delay, poor nutrition, sleep disturbances, or facial cosmetic concerns with resultant poor quality of life.

Childhood cancer survivors are at an increased risk for oral and dental complications due to the disruption of dental developmental networks, especially when treated at a younger age. Table 1 outlines the recommendations for screening and dental care in childhood cancer survivors. PCPs should educate survivors in good general dental care, including brushing, use of fluoride toothpaste, flossing, limitation of sweets, and avoidance of tobacco products [34, 101]. Survivors should also undergo routine biannual dental exams with yearly oral exams and be referred to specialists based on the specific risks outlined herein. Life-long screening for oral SMNs is crucial in those who received head and neck radiation or underwent HSCT. Baseline panoramic radiographs should be performed prior to any dental or orthodontic care in survivors to evaluate root development. Fluoride applications are important for enamel mineralization to prevent dental caries. PCPs should monitor for xerostomia and consider saliva substitutes or moistening agents to relieve symptoms. Survivors with health conditions predisposing to bacterial endocarditis should receive antibiotic prophylaxis prior to any dental procedure as outlined above.

While these recommended dental examinations are congruent with good healthcare for all individuals, childhood cancer survivors are at a high risk for unmet oral care needs. Despite childhood cancer survivors' risk of oral and dental sequelae, Kaste et al. reported that 28.3 % of survivors had not visited the dentist and 32.6 % had not received a dental cleaning in the previous year [19]. Lower rates of dental care are reported in uninsured and publicly insured survivors compared to those with private insurance [102]. Current lack of universal dental coverage in the USA is one reason many survivors neglect their oral health needs. However, those with dental insurance may also have difficulty finding providers equipped to treat high-risk populations. PCPs play key roles in facilitating referrals and may benefit from collaboration with local dental schools.

Additionally, survivors may be unaware of their oral and dental risks and depend on PCPs for education. Therefore, communication between PCPs, radiation oncologists, oncologists, and dentists is crucial to ensure proper care of these patients. Both PCPs and dentists benefit from having a cancer treatment summary and understanding the therapies imparting dental risk received by survivors prior to delivering care.

Oral and dental health is important for proper nutrition and quality of life; however, it is an area in which many providers receive little training. Compounding limited training, few

prospective studies or randomized trials of dental intervention have been reported in childhood cancer survivors. Most knowledge of oral late effects is extrapolated from adult data, especially the epidemiology of trismus and osteoradionecrosis. Additionally, most of the literature focuses on survivors treated in the 1960s to 1990s, limiting the generalizability to survivors managed with contemporary treatment approaches. In the future, large, prospective trials evaluating oral and dental late effects and preventative or ameliorating interventions are needed to fully evaluate the risks in this population.

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Fig. 1.

Hypodontia (*yellow stars*) and root malformation (*red arrows*) in a 5-year old treated for sinus rhabdomyosarcoma with chemotherapy and radiation at age 2 years with recurrence 1 year later. Dental caries (*blue arrows*) are on non-occlusal surfaces, which is rare in healthy individuals. (Photograph courtesy of Dr. Kaste)

Fig. 2. Multiple dental caries (requiring crowns) with granuloma formation (*blue arrows*) and root malformation (*red arrows*) in a 14-year old treated for right infratemporal sinus rhabdomyosarcoma with surgery, chemotherapy, and radiation at age 8 years. The patient required tooth extraction and was edentulous 2 years later. (Photograph courtesy of Dr. Kaste)

Fig. 3. Dental caries (*yellow arrows*) secondary to enamel hypoplasia and xerostomia in a 20-year old treated with chemotherapy and mantle radiation for Hodgkin lymphoma stage IIIb at age 8 years. Multiple periapical lucencies (*blue arrows*) indicate granuloma formation after prolonged infection. (Photograph courtesy of Dr. Kaste)

Table 1

Oral-dental late effects associated with cancer therapy in survivors of childhood and adolescent cancers [8]

Potential late effect	Predisposing therapy	Modifying factors	Recommended screening/care considerations
Altered tooth development <ul style="list-style-type: none"> • Tooth/root agenesis • Root thinning/shortening • Enamel dysplasia • Microdontia 	Any chemotherapy Head and neck radiation HSCT	Lack of permanent dentition at time of therapy Age <5 years at treatment Alkylating agents (especially cyclophosphamide) Radiation involving oral cavity or salivary glands History of dry mouth	Dental cleaning, exam, and fluoride application: every 6 months Oral exam: yearly Panorex to evaluate root development: baseline prior to dental procedure
Xerostomia/salivary gland dysfunction	Head and neck radiation HSCT	Radiation involving parotid glands Chronic GVHD	Dental cleaning, exam, and fluoride application: every 6 months Xerostomia inquiry: yearly Treatment with saliva substitutes, moistening agents, and sialogogues
Craniofacial abnormalities	Head and neck radiation	Age <5 years at treatment	Psychosocial assessment: yearly Craniofacial exam: yearly
Trismus/temporomandibular joint dysfunction	Head and neck radiation HSCT	Age <5 years at treatment Chronic GVHD	Jaw stretching exercises Use of jaw motion devices
Osteoradionecrosis	Head and neck radiation	Poor pre-radiation dental and periodontal status	Imaging studies (x-ray, CT scan, and/or MRI) or surgical biopsy as needed Treatment with hyperbaric oxygen or surgical intervention
Oral GVHD	HSCT	Allogeneic HSCT Unrelated donor HLA mismatch donor Peripheral blood stem cell source History of acute GVHD Conditioning regimen with TBI Increased donor age Female donor with male recipient	Dental exam: every 4–6 months Referral for biopsy of suspicious lesions Treatment with topical steroids or systemic immunosuppression if multi-system involvement
Subsequent oral malignancy	Head and neck radiation HSCT	Allogeneic HSCT Acute/chronic GVHD Familial cancer predisposing mutations Tobacco use (smoking cigars, cigarettes, or pipes; dipping; chewing) Alcohol abuse Excessive sun exposure (increases risk of cancer of lower lip)	Inspection and palpation of oral cavity, skin, and soft tissues: yearly Referral for biopsy of suspicious lesions

All recommendations are consensus “Category 1” recommendations based upon a modified version of the National Comprehensive Cancer Network “Categories of Consensus” system [9]. “Category 1” recommendations reflect uniform consensus that (1) there is high-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective experience of members of a multi-disciplinary panel

HSCT hematopoietic stem cell transplantation, *GVHD* graft-versus-host disease, *TBI* total body irradiation