INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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PENTEC ORGAN SYSTEM REVIEW

Salivary and Dental Complications in Childhood Cancer Survivors Treated With Radiation Therapy to the Head and Neck: A PENTEC Comprehensive Review

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Received Dec 21, 2020; Accepted for publication Apr 21, 2021

Purpose: Radiation therapy (RT) to the head and neck (H&N) region is critical in the management of various pediatric malignancies; however, it may result in late toxicity. This comprehensive review from the Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative focused on salivary dysfunction and dental abnormalities in survivors who received RT to the H&N region as children.

Materials & Methods: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.

Results: Of the 2,164 articles identified through a literature search, 40 were included in a qualitative synthesis and 3 were included in a quantitative synthesis. The dose-toxicity data regarding salivary function demonstrate that a mean parotid dose of 35 to 40 Gy is associated with a risk of acute and chronic grade ≥2 xerostomia of approximately 32% and 13% to 32%, respectively, in patients treated with chemo-radiation therapy. This risk increases with parotid dose; however, rates of xerostomia after lower dose exposure have not been reported. Dental developmental abnormalities are common after RT to the oral cavity. Risk factors include higher radiation dose to the developing teeth and younger age at RT.

Conclusions: This PENTEC task force considers adoption of salivary gland dose constraints from the adult experience to be a reasonable strategy until more data specific to children become available; thus, we recommend limiting the parotid mean dose to ≤26 Gy. The minimum toxic dose for dental developmental abnormalities is unknown, suggesting that the dose to the teeth

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Disclosures: Paul Gidley is a shareholder of Amgen, Eli Lily, Merck, Medtronic, Novartis, Pfizer, and Roche.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Acknowledgments—The authors would like to thank Dr Lawrence Marks for his assistance with the tables and figures.

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijrobp.2021.04.023.

Int J Radiation Oncol Biol Phys, Vol. 119, No. 2, pp. 467–481, 2024
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2021.04.023

should be kept as low as possible particularly in younger patients, with special effort to keep doses <20 Gy in patients <4 years old.

Introduction

Radiation therapy (RT) to the head and neck (H&N) region is critical in the management of numerous pediatric malignancies. However, it predisposes survivors to complications that may affect quality of life.[1] This comprehensive review from the Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative aims to describe the risk of salivary and dental complications in cancer survivors who were treated with RT to the H&N as children. Although other types of toxicity occur after RT to the H&N region, the task force focused on salivary dysfunction and dental abnormalities, because the most dose-toxicity data are available in published reports for these endpoints.

Clinical Significance

RT is used to treat various pediatric malignancies in the H&N region. Examples include rhabdomyosarcoma, Ewing sarcoma, nonrhabdomyosarcoma soft tissue sarcoma, lymphoma, nasopharyngeal carcinoma, retinoblastoma, juvenile nasopharyngeal angiofibroma, salivary gland tumors, and thyroid malignancies. Additionally, normal tissues of the H&N are exposed to radiation during total body irradiation (TBI) that is used in conditioning regimens for stem cell transplantation (SCT), and the parotid glands are exposed during whole brain RT that may be used for primary brain tumors and leukemias.

Xerostomia (subjective dry mouth) and salivary gland dysfunction (objective reduced saliva production) are common side effects of RT to the H&N region. The major salivary glands are located superficially relative to most H&N tumors and are, therefore, exposed to radiation during H&N RT. In addition, the minor salivary glands in the oral cavity are often exposed, depending on the location of the tumor within the H&N region. Radiation affects the secretory function of the salivary glands, altering the volume, consistency, and pH of the saliva.[1,2] In affected individuals, diminished salivary output predisposes to caries, oral infections, pain, and difficulty eating, swallowing, and speaking.[2] A reduction in salivary function may begin within 1 to 2 weeks of the initiation of RT. Recovery of salivary function may occur up to 36 months after RT.[3,4] The salivary glands are parallel structures, so partial sparing of the parenchyma reduces the probability of xerostomia.[5,6]

Additionally, RT to the H&N may impair dental development in survivors. Irradiation of tooth buds during development is associated with various abnormalities, including dental agenesis/hypoplasia and root stunting,[7] owing to effects on dividing odontoblasts and interference with the signaling network that directs dental development.[7,8] Additionally, exposure of developing teeth to radiation induces the formation of osteodentin, in place of normal dentin, resulting in abnormal mineralization and enamel defects.[9] Dental effects, such as tooth agenesis, microdontia, arrested root development, and enamel dysplasia, may compromise function, cosmesis, and quality-of-life.[10-12] These anomalies become apparent over the years after RT, and the effects are typically permanent. In some cases, surgical and/or orthodontic corrective procedures may be required.[10,13,14]

Endpoints and Toxicity Scoring

Multiple measurements are used to score salivary and dental toxicity. Adverse effects are categorized into "acute" and "late" periods. Typically, toxicity is categorized as "acute" or "early" if it occurs within 3 months of RT, and as "late" or "chronic" if it occurs 3 months or more after the completion of RT.

Salivary gland dysfunction can be graded using various approaches, each of which addresses specific aspects of toxicity, and each of which has strengths and limitations.[15] Xerostomia may be patient- or physician-graded. The major advantage of patient-reported outcomes is that toxicity and its impact on functioning are captured from the survivor's own perspective. Several validated instruments exist to measure children's oral health-related quality of life (OHRQoL).[16] As an example, the Child Oral Health Impact Profile (COHIP) is a validated instrument for measuring OHRQoL in children and adolescents 8 to 15 years of age. An item in this questionnaire is "dry mouth or lips," so the COHIP can be used to assess xerostomia, in addition to other oral health-related concerns.[17] Advantages of physician-assessed toxicity are that it is recorded as a part of routine patient care, and it may be scored using a standardized system (eg, the Common Terminology Criteria for Adverse Events [CTCAE]). However, clinician-based grading may differ from patients' self-reported scores.[18] Furthermore, a limitation of both patient- and physician-assessed scores is that young children may be unable to describe their symptoms accurately.

Measurements of salivary gland function provide additional parameters of toxicity that are quantifiable. Sialometry, the most commonly used assessment, measures the unstimulated and/or stimulated salivary secretion rates (USSR, SSSR). Patients produce as much saliva as possible during a specified period in an unstimulated or stimulated fashion (ie, in response to a salivary stimulant such as chewing paraffin wax) to give the USSR and SSSR, respectively. This test provides quantitative data that are easy to collect. However, measurements may be variable, because salivary

secretion is affected by numerous factors, including time of day, stress level, and time since eating or drinking.[19] Furthermore, sialometry requires patient cooperation. Salivary gland scintigraphy provides an alternative method to assess saliva production, and measurements correlate well with salivary secretion rates in pediatric patients.[20] However, scintigraphy is not readily available, and it involves exposure to ionizing radiation. In addition, because pertechnetate scintigraphy images the water transport component of saliva production, it is subject to the same variability as sialometry.[21,22] Thus, although scintigraphy reveals information regarding the dynamics of salivary secretion, it does not add value for toxicity scoring. The use of other imaging modalities, such as magnetic resonance imaging (MRI),[23,24] computed tomography (CT),[25] and ultrasound,[26] to predict and identify xerostomia is an area of research. These imaging studies do not measure salivary function directly; however, their findings may be associated with clinical toxicity.

The effects of radiation on teeth are identified by physical examination and imaging studies, most commonly panoramic radiographs. Multiple endpoints are used to report dental abnormalities. Caries may be quantified using the Decayed Missing or Filled Teeth (DMF/T) score. In addition, authors may report the number of patients or the number of teeth per patient with specific findings, such as microdontia, abnormal root development, enamel opacities, etc. Alternatively, authors may group various findings together. For example, the Defect Index combines root/crown ratio abnormalities, microdontia, and agenesis.[27] A strength of these methods is that the data are quantitative and objective. However, comparisons across studies are complicated by the large variety of endpoints that have been used.

Anatomy and Developmental Dynamics

The major paired salivary glands (parotid, submandibular, and sublingual) and the minor salivary glands of the oral cavity and pharynx begin to develop between the 6th and 10th week of embryogenesis. After birth, the glands gradually increase in size until adulthood.[28]

Typically, primary dentition develops from 6 months to 3 years of age, and permanent dentition erupts from 6 to 12 years of age. The last of the permanent teeth to appear are the "third molars" or "wisdom teeth" that typically erupt between 17 and 21 years of age.

Defining Volumes: Pediatric Imaging Considerations

Organs-at-risk that are relevant to the endpoints of this review include the parotid and submandibular glands, as well as the oral cavity that harbors the minor salivary glands and dentition. Typically, these structures are readily identifiable on noncontrast-enhanced CT scans. However, intravenous contrast and/or MRI may facilitate accurate contouring of the salivary glands by improving their delineation from the surrounding soft tissues.[29] Atlases for contouring H&N structures in adults[29] may be applied to the pediatric population. Additionally, Thompson et al demonstrated the feasibility of contouring the developing primary and permanent teeth in children as young as one year of age.[30]

In an adequately immobilized patient, intrafractional motion of these structures is not a concern; however, salivary glands may shrink during the course of RT,[31-33] which might compromise sparing of the major glands. As advances are made in parotid sparing (eg, if selective sparing of regions within the parotid were incorporated into clinical practice), careful on-treatment imaging may be useful to reveal if the glands shrink after exposure to radiation or shift in location after tumor response.

Review of Dose Volume Response Data and Risk Factors

Methodology

This comprehensive review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.[34] Eligible studies were those that assessed the risk of salivary and dental toxicity after RT to the H&N region in children. On November 6, 2015, a search of the PubMed, Medline, and Cochrane databases was performed for peer-reviewed manuscripts that were written in English and published from 1965 to 2014 (Appendix E1).

As summarized in Fig. 1, the literature search provided 2164 unique references. Two authors (SAM and ACP) reviewed all titles and abstracts and excluded 2082 studies because they were not relevant to this study. Subsequently, the same 2 authors reviewed the full text of articles considered potentially eligible. An additional 50 studies were excluded after review of the full text. The main reasons for exclusion were that patients were adults, radiation information was not provided, and/or articles were reviews or case reports. Eight studies known to the authors that were not included in the initial literature search but met the eligibility criteria were added. Thus, 40 studies were identified that fit the inclusion criteria. For each manuscript that was found to be eligible, data were extracted regarding study design, population characteristics, and outcomes of interest. Bias assessments were performed (Appendix E2).

All 40 studies were included in the qualitative synthesis. Of these, 5 studies provided data regarding the incidence of xerostomia and parotid gland dose. Three of these studies reported the rates of xerostomia and mean dose (D_{mean}) to the parotids. Data from these 3 studies were plotted in Fig. 2, as a quantitative synthesis.

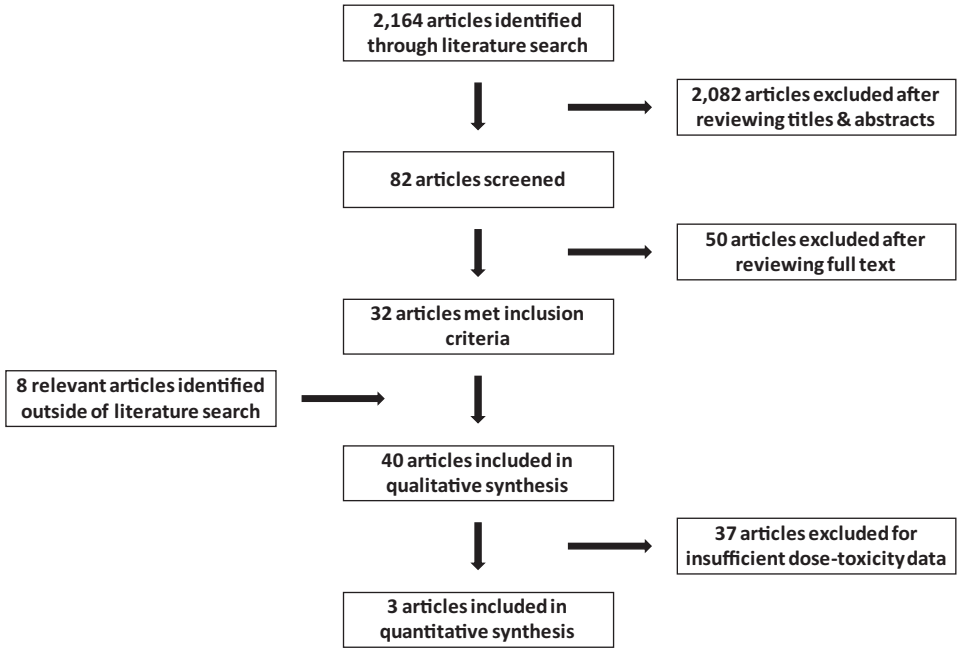

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

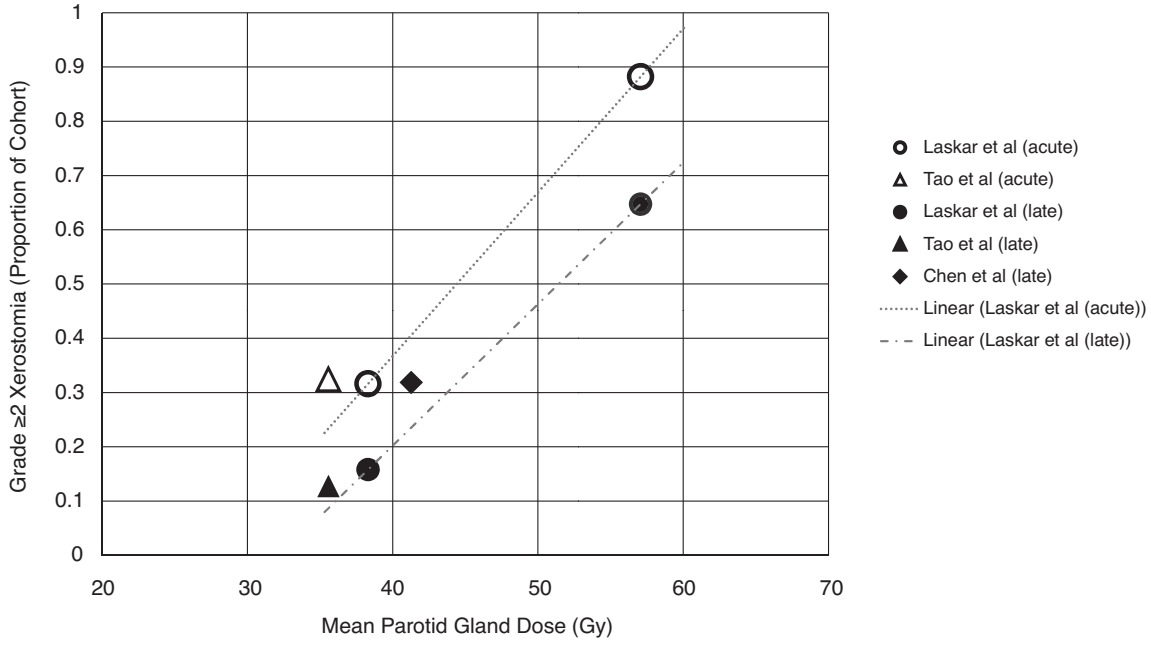

Fig. 2. Incidence of grade ≥2 xerostomia as a function of mean parotid gland dose after chemo-radiation therapy for pediatric nasopharyngeal carcinoma. Acute xerostomia rates are shown with open markers, and late xerostomia rates are shown with solid markers. Dashed lines connect the datapoints reported by Laskar et al for patients treated with intensity modulated radiation therapy (IMRT) versus conventional radiation therapy (RT) (both groups received the same chemotherapy).[36] Acute xerostomia affected 11/34 patients in the series by Tao et al (32%),[39] 6/19 in the IMRT cohort reported by Laskar et al (32%), and 15/17 in the conventional RT cohort reported by Laskar et al (88%). Late xerostomia affected 3/24 patients in the series by Tao et al (13%), 3/19 in the IMRT cohort reported by Laskar et al (16%), 11/17 in the conventional RT cohort reported by Laskar et al (65%), and 43/135 patients in the series by Chen et al (32%).[41]

Xerostomia

Review of dose-volume data

Many groups have described the risk of xerostomia after RT to the H&N in pediatric patients (Tables 1 and 2). The largest study with both toxicity and dosimetric information comes from the German "registry for the evaluation of side effects after radiation in childhood and adolescence" (RiSK) database, a prospective registry including children and adolescents with cancer who received RT between 2001 and 2010.[35] Toxicity rates were reported for the subcohort of 114 pediatric patients treated with fields that exposed the salivary glands. Follow-up examinations were scheduled to be performed within 8 weeks after the end of RT to evaluate for acute toxicity and at least 1 year after RT for late toxicity. The median follow-up time was 2.9 years (range, 0.04-9.1 years). The risk of both acute and late xerostomia increased with parotid and submandibular gland dose. In general, grade ≥1 xerostomia was seen in patients receiving a maximum dose (D_{max}) of >20 Gy to the salivary glands. The odds of both acute and late xerostomia were higher in patients who received concurrent chemotherapy, with an odds ratio (OR) for acute xerostomia of 3.64 (95% CI, 1.49-8.89) and for late xerostomia of 5.15 (95% CI, 1.20-22.15) when comparing patients treated with concurrent chemo-RT versus RT alone. Analyses of chemotherapy subgroups were not feasible owing to the broad variety of chemotherapy regimens used.[35]

Several studies have reported specifically on the risk of xerostomia after definitive RT for pediatric nasopharyngeal carcinoma (Table 1).[35−41] Of these, 4 publications provided parotid gland dose-toxicity data. First, Laskar et al compared outcomes of children treated for nasopharyngeal carcinoma with intensity modulated radiation therapy (IMRT) and conventional RT who were followed for a median of 27 months (range, 4-42). The radiation dose to the parotids was lower with IMRT compared with conventional RT (average D_{mean} 39 Gy vs 57 Gy, $P < .001$). Correspondingly, the risk of acute grade ≥2 xerostomia was 32% after IMRT and 88% after conventional RT ($P = .002$). Among patients with late toxicity data, grade ≥2 xerostomia affected 16% after IMRT and 65% after conventional RT.[36] Second, Tao et al reported on 34 patients who were treated with IMRT for nasopharyngeal carcinoma and followed for a median of 52 months (range, 9-111). The average parotid D_{mean} was 35.5 Gy. Acute and late grade ≥2 xerostomia affected 32% and 13% of the population with toxicity data, respectively.[39] Third, Chen et al compared outcomes of adult and pediatric patients treated for nasopharyngeal cancer. In 159 children treated with IMRT, the average parotid D_{mean} was 41 Gy, and late grade ≥2 xerostomia affected 32% of the cohort with a median follow-up of 58.4 months (range, 10.2-182).[41] Lastly, Louis et al reported on 5 patients treated for nasopharyngeal carcinoma with IMRT and followed for a median of 6.3 years (range, 2.5-9.8). The parotid D_{mean} was <26 Gy in all patients. Late grade 2 xerostomia occurred in 1 patient (20% of the cohort), and no patient experienced grade ≥3 xerostomia.[37] The outcomes reported by Laskar et al, Tao et al, and Chen et al are plotted in Fig. 2, as subsequently described. Louis et al did not provide sufficient dosimetric information for their results to be plotted.

Numerous studies have explored the risk of xerostomia in patients treated with TBI as a part of the SCT conditioning regimen (Table 2).[42-46] Patients in these reports have been treated with a narrow range of doses, with almost all patients receiving 10 Gy in a single fraction. Therefore, mathematical modeling to explore a dose-toxicity relationship was not possible, and a qualitative summary of the data was more appropriate. Uniformly, these studies identified salivary toxicity. In the absence of TBI, SCT is associated with salivary gland dysfunction that may be exacerbated by chemotherapy and/or graft-versus-host disease. Some,[43,44] but not all,[46] studies suggest that salivary secretion is affected more significantly by a TBI-containing preparative regimen than by chemotherapy alone. Single-fraction TBI (7.5-10 Gy) has been associated with a greater reduction in salivary secretion than fractionated TBI at 1 year after treatment[45]; however, this difference was not detected at 8 years of follow-up.[46] Each study regarding TBI reported the prescription dose, but none included dose-volume data regarding parotid gland exposure specifically. Given dose inhomogeneities, the TBI prescription dose may not be equivalent to the parotid gland dose. Phantom measurements suggest that the dose to the superficial portion of the parotid during TBI, delivered with AP-PA (anterior-posterior and posterior-anterior) beams, is approximately 10% greater than the prescription dose[47] because the beams enter tangentially and pass through small depths compared with the total AP separation, creating a relative hotspot. This nonrandom misclassification of true parotid dose would likely have led to slight overestimations of the true dose-toxicity risk because an observed effect on salivation would have been attributed to a dose that was lower than the true dose.

Endpoints

Various endpoints have been reported, including physician- and patient-reported xerostomia, USSR, SSSR, and salivary gland scintigraphy (Tables 1 and 2).

Risk factors

After focal RT to the H&N, concurrent chemotherapy increases the risk of acute and late xerostomia; however, data are not available regarding which chemotherapeutic agents are associated with the greatest risk.[35] After TBI-containing regimens, nondosimetric risk factors for xerostomia include female sex, graft-versus-host disease, and seropositivity for 3 to 4 herpesviruses.[43-46] The effect of age at the time of RT is unclear. For example, in a comparison of pediatric and matched adult patients treated for nasopharyngeal

Table 1 Studies of xerostomia in childhood cancer survivors treated with focal radiation therapy to the head and neck*

First author	n†	Median age at RT, y	Sex (M; F)	Median follow-up after RT, y	RT technique	Median RT prescription dose (range), Gy	Parotid dose (range/std dev), Gy‡	Scoring of toxicity	Rates of xerostomia	Notes
Bölling [35]	114	13	69; 64§	3	Photon (79%), proton (20%), electron (1%), cobalt (1%)	36 (18-74)	20 (0-80)	RTOG/EORTC criteria	Acute G2+: 7% Late G2+: 3%	↑Xerostomia with dose to salivary glands ↑Xerostomia with concurrent chemotherapy
Chen[41]	135	15	117; 42§	5	IMRT	68 (60-70)	41 (±6)	CTCAE v 5.0	Late G2+: 32%	↓Xerostomia in pediatric patients vs matched adult patients
Laskar[36]	36	14	28; 8	2	Conventional (47%); IMRT (53%)	70	38 (19-55) IMRT; 57 (23-64) conventional	Sialometry	Acute G2+: 32% IMRT; 88% conventional	↑Xerostomia with conventional RT vs IMRT
Louis[37]	5	14	3; 2	6	IMRT	61-66	<26	CTCAE v 3.0	Acute G3+: 20% Late G2+: 20%	
Shen[38]	42	16	28; 14	5	Conventional	64-74		CTCAE v 3.0	Acute G1+: 95%	
Tao[39]	34	16	24; 10	4	IMRT	64-68	36 (27-42)	RTOG/EORTC criteria	Acute G2+: 32% Late G2+: 13%	
Yan[40]	185	17	132; 53	5	Conventional (66%), IMRT (34%)	68 (39-84)		Difficulty swallowing without water	Late G1+: 47%	↑Xerostomia with radiation prescription dose

Bold text indicates the studies plotted in Fig. 2.

Abbreviations: CTCAE = common toxicity criteria for adverse events; G = grade; IMRT = intensity modulated radiation therapy; RT = radiation therapy; RTOG/EORTC = Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria; v = version.

* All patients treated for nasopharyngeal cancer, with the exception of Bölling et al, who included a variety of tumor types. A variety of chemotherapy regimens were used. Most nasopharyngeal cancer patients received platinum-based chemotherapy.

† Patients treated with RT and with toxicity data.

‡ All studies reported the parotid D_{mean}, except for Bölling et al, who reported $D_{max.}$ All studies reported the mean value for the patient cohort, except for Bölling et al, who reported the median value.

§ Includes total cohort, including patients for whom toxicity data were not available.

Table 2 Studies using sialometry to assess salivary dysfunction in childhood cancer survivors treated with total body irradiation*

First author	n†	Median/mean age at RT (range), y	Sex (M; F)	Median follow-up after RT, y	RT prescription dose (Gy); number of fractions (% of cohort)	Outcome
Bagesund[42]	13	<13	7; 6	7	10; 1 (85%), 8; 1 (15%)	↓USSR and SSSR after transplant with TBI vs pretreatment controls
Dahllof[43]	30	4-12	n/s	1	10; 1	↓SSSR after transplant with TBI vs chemotherapy only
Dahllof[44]	30	7 (2-12)	16; 14	7	10; 1	↓USSR and SSSR after transplant with TBI vs chemotherapy only
Dahllof[63]	14	8 (5-12)	9; 5	4	10; 1	↓SSSR after transplant with TBI vs chemotherapy only
Garming Legert[45]	44	9 (5-13)	30; 14	1	10; 1 (61%); 12; 4 (32%); 6; 2 (7%)	↓In USSR and SSSR greater after single-fraction vs fractionated TBI
Garming-Legert[46]	49	8	26; 23	8	8-10; 1 (71%), 12; 4 (22%), 6; 2 (6%)	=SSSR and USSR after single-fraction vs fractionated TBI
Nasman[64]	19	7	8; 11	5	8-10; 1	↓SSSR after transplant with TBI vs chemotherapy only or no cancer therapy

Abbreviations: SSSR = stimulated salivary secretion rate; TBI = total body irradiation; USSR = unstimulated salivary secretion rate.
* Various diagnoses, most commonly acute leukemia. Various systemic agents used with TBI as part of the preparative regimen, most commonly cyclophosphamide.
† Treated with TBI.

cancer, adults experienced a greater incidence of late xerostomia (pediatric and adult patients were matched according to sex, T-stage, N-stage, overall stage, chemotherapy, and radiation technique).[41] Conversely, in a cohort of pediatric patients, younger age at the time of TBI/SCT was associated with a greater risk of salivary dysfunction.[42] These discrepant findings may be due to a variety of factors, including differences in the radiation doses and other treatments given to these patient populations.

Dose-toxicity effects

We plotted the risk of acute and late grade ≥2 xerostomia in pediatric patients as a function of dose, as observed in the reports by Laskar et al, Tao et al, and Chen et al[36,39,41] (Fig. 2). Although Louis et al and Bölling et al did provide dosimetric data, these reports were not plotted on the same graph because Louis et al did not provide sufficient dosimetric data and Bölling et al reported maximum, rather than mean, parotid doses.[35,37]

For the studies plotted in Fig. 2, an average D_{mean} was used that was derived from the D_{mean} to each gland. We believe it was acceptable to use an average value, because the dose to the right and left parotid glands was similar within each cohort. Specifically, the average D_{mean} (range) to the right and left parotid, respectively, was: 35.33 Gy (30.68-39.42 Gy) and 35.82 Gy (27.31-41.61 Gy) in Tao et al; 37.17 Gy (19.6-55.0 Gy) and 39.44 Gy (19.4-50.0 Gy) in Laskar et al (IMRT); 57.31 Gy (31.1-62.2 Gy) and 56.82 Gy (23.0-63.9 Gy) in Laskar et al (conventional); and 41.14 Gy ± 5.5 Gy and 41.41 Gy ± 6.2 Gy in Chen et al. Also, the target was a midline structure and the bilateral cervical nodes were treated, suggesting that the dose to both glands was similar. However, we cannot exclude the possibility that the dose to each parotid was different at the individual patient level, which would affect rates of xerostomia. Also, because we assumed that the dose to both glands was similar, these data cannot be used to determine xerostomia rates if only 1 parotid was exposed and the other was spared.

Patients in these studies received different chemotherapy regimens that may have influenced toxicity rates. The chemotherapy regimens comprised neoadjuvant and adjuvant cisplatin, bleomycin, and methotrexate (Laskar et al); neoadjuvant cisplatin and 5-fluorouracil and concurrent cisplatin (Tao et al); and various neoadjuvant platinum-based regimens and concurrent cisplatin (Chen et al).

Taken together, the data plotted in Fig. 2 suggest that a D_{mean} of 35 to 40 Gy to both parotids is associated with a risk of acute and late grade ≥2 xerostomia of approximately 32% and 13% to 32%, respectively, in patients treated with chemo-radiation therapy. The risk of salivary dysfunction

Table 3 Dosimetric data quality analysis for articles on xerostomia incidence related to parotid dose

First author	RT prescription dose, Gy	Average mean parotid dose (range), Gy	RT technique	Treatment planning system	Dosimetry grade	Binning grade
Chen[41]	60-70	41 (±6)	IMRT	NA*	3	3
Laskar[36]	70.2	39 (19.4-55) IMRT; 57 (23-63.9) conventional RT	Conventional RT and IMRT	CadPlan, Eclipse	3	3
Tao[39]	64-68	35.5 (27.3-41.6)	IMRT	Peacock	3	3

Dosimetry grading: 1. Prescribed, poor representation of the organ of interest dose. 2. Prescribed, good representation of the organ of interest dose. 3. TPS, modern 3D planning. 4. Measurement based organ of interest dose.
Binning grading: 0, 1 bin (all doses > or < X). 1, 2 to 3 bins. 2, >3 bins. 3, No binning, cite mean and range. 4, Per-patient scatter graph or table.
Abbreviations: IMRT = intensity modulated radiation therapy; RT = radiation therapy.
* Not enough information.

increases with doses greater than 35 Gy. Information is unavailable regarding the risk of xerostomia at lower doses.

Limitations

The task force medical physicist performed a dose accuracy evaluation for each of the investigations of dose-toxicity relationships that was plotted in Fig. 2. This analysis included a categorization of the reported doses, as well as an estimate, when possible, of the accuracy of those doses (Table 3, Appendix E3). All articles reported the use of CT images for planning, detailed target and organ-at-risk (OAR) contouring, and dose-volume histogram (DVH) calculations using modern treatment planning systems (TPS). Several DVH points were reported in most articles. Lack of information regarding the distribution of doses increased the uncertainty in the shape of the dose-response. Because of the location of the parotids and the nature of IMRT treatments (using multiple fields or arcs), the D_{mean} should be accurate (ie, within 5%) for patients treated with IMRT. For treatments that used electrons in patients treated with conventional RT (Laskar et al[36]), higher uncertainty and dose heterogeneity may be expected (ie, 5%-10%). Before 2010, electron calculations were generally based on water percentage depth dose (PDD) and often normalized to a point and prescription isodose line.

Importantly, these articles treated the parotid gland as a uniform organ; however, animal and human data suggest that the radiosensitive stem/progenitor cells reside in the region of the gland containing the major ducts.[48,49] Salivary gland dysfunction has been associated with dose to this specific region during RT.[48] These findings were identified in animal models and adult patients; their applicability to children is unknown. None of the articles explored the clinical significance of regional dose distribution within the salivary glands.

In addition, data are limited regarding the potential impact of submandibular or minor salivary gland dose on the incidence of xerostomia. The study by Bölling et al reported a greater risk of xerostomia in patients who received higher submandibular gland doses ($P = .001$)[35]; however, most studies did not report submandibular gland dose. In addition, no study reported on the potential effect of dose to the minor salivary glands in the oral cavity.

Dental developmental effects

Review of data

Numerous publications describe the dental developmental effects of RT to the H&N in children (Tables 4 and 5). However, multiple endpoints have been used. Furthermore, radiation dose-volume parameters for the teeth were rarely provided. Therefore, we concluded that mathematical modeling was inappropriate and chose to provide a qualitative description of the data instead.

Numerous dental developmental abnormalities have been identified after RT, including dental agenesis/hypoplasia, root malformations, altered dental eruption patterns, and enamel defects. Depending on the patient population, cancer treatment, and dental endpoint, up to 100% of survivors may be affected.[11,12,50-53] The largest cohort is from the Childhood Cancer Survivor Study (CCSS). In this group, adult long-term survivors of pediatric cancers treated between 1970 and 1986 were more likely than their siblings to have self-reported dental developmental abnormalities, and RT to the jaw significantly increased the incidence in a dose-dependent manner with an odds ratio (OR) of 1.32 for dose >0 and <20 Gy and an OR of 5.6 for dose ≥20 Gy. Children who were younger at the time of RT were more prone to toxicity: doses <20 Gy increased the risk of dental anomalies only in children who were <10 years at the time of RT, whereas doses ≥20 Gy increased the risk in children of all ages (Fig. 3).[54]

Thompson et al was the only group from our search that reported detailed dose-volume data for late dental complications. In their study, the dose to each tooth was determined in pediatric patients who were treated with spot-scanning proton therapy at a median age of 4 years. Developing primary teeth and permanent incisors, canines, premolars, and first and second molars were identifiable on CT scans in all

Table 4 Studies of dental developmental abnormalities* in childhood cancer survivors treated with focal radiation therapy to the head and neck†

First author	n‡	Median age at RT, y	Diagnoses	Median follow-up time after RT, y	Radiation technique	Median radiation prescription dose (range), Gy/CGE	Outcome, % of cohort affected					
							≥1 Dental abnormality	Dental agenesis	Microdontia	Root abnormalities	Enamel abnormalities	Delayed eruption
Childs[66]	10	3	RMS	5	Passive scatter proton	50.4 (50.4-56)		30				
Çubukçu[27]	10	3	Solid tumors and lymphoma	n/s	n/s	25-59	100					
Duggal[76]	38	<10	Various	n/s	Cranial RT (66%); "jaw RT" (34%)	n/s				↑In survivors vs noncancer controls		
Estilo[67]	9	4	RMS	12	n/s	54 (50-61)	89	44		56	44	33
Fromm[11]	15	6	STS	6	Conventional	50 (40-60)	93 (100‖)	100‖		100‖		
Jaffe[57]	45	5	Various	6	Conventional	36 (18-65)	82					
Kaste[13]	22	5	RMS	10	n/s	45 (34-67)	77	50	23	68		
Kaste	244	5	ALL	2	Cranial RT	18-24	50					
Kaste[54]	143	6	Various	22	n/s	≥20	OR 5.6§					
	5198					1-20	OR 1.3§					
Lockney[77]	30	7	RMS	8	IMRT	50.4 (36-50.4)	33			7		3
Maciel[73]	18	5	ALL	7	Cranial RT	24	Mean of 5 affected teeth/ patient					
McGinnis[78]	47	7	HL	n/s	Conventional, mantle RT	37		↑In survivors vs noncancer controls				
McGinnis[59]	47	4-19	HL	n/s	Conventional, mantle RT	35-37				↑In patients treated with RT at the youngest ages		
Pajari[74]	19	4	ALL	n/s	cranial RT	24				↑After RT vs chemotherapy or no cancer therapy	Mean of 7 affected teeth/ patient	
Paulino[10]	7	6	RMS	20	2D-RT	50.4 (41.4-65)	100	43	57	43		
Raney[14]	213	5	STS	7	n/s	46 (38-68)	29					
Sonis[53]	78	<10	ALL	>5	Cranial RT	18 (35%), 24 (65%)	100	6	27	94	35	
Thompson[30]	10	4	Various	5	Spot-scanning proton	46-66	60					10

Abbreviations: ALL = acute lymphoblastic leukemia; HL = Hodgkin lymphoma; n/s = not stated; OR = odds ratio; RMS = rhabdomyosarcoma; RT = radiation therapy; STS = soft tissue sarcoma.

* All toxicity data were based on dental evaluations, except Raney et al used study flowsheet data and Kaste et al used patient self-reports.

† Various multiagent chemotherapy regimens used.

‡ Treated with RT with dental follow-up.

§ Odds ratio for ≥1 dental abnormality for those with RT to the jaw, relative to 0 Gy to the jaw.

‖ With teeth in RT field.

Table 5 Studies of dental developmental abnormalities* in childhood cancer survivors treated with total body irradiation†

First author	n‡	Median age at TBI, y	Median follow-up time after RT, y	Radiation prescription dose (Gy); number of fractions	Outcome, % of cohort affected					
					≥1 Dental abnormality	Dental agenesis	Microdontia	Root abnormalities	Enamel abnormalities	Ectopic eruption of first molars
Dahllof[50]	13	8	6	10; 1 (+24-25 Gy cranial RT in 23%)	100		31	100	23	
Duggal[76]	7	<10	n/s	various				↑After TBI vs cranial RT, jaw RT, no cancer therapy		
Holtta[79]	10	3	8	10-12	100	100	80	100		
Holtta[56]	18	4	9	10-12		72	41			
Ko[58]	20	6	n/s	10; 3						15
Maciel[73]	8	5	7	12 (+24 Gy cranial in 25%)	Mean of 15 affected teeth/ patient					
Nasman[64]	19	7	5	8-10; 1	100	58	68	95	42	
Nishimura[52]	6	<10	n/s	12	70§	6§	9§	55§		
Pajari[74]	4	4	n/s	10; 1				↑After TBI vs chemotherapy, no cancer therapy	Mean of 3 affected teeth/ patient	
Uderzo[80]	25	9	2	12; 3 (+18 Gy cranial RT in 44%)	63	11		33		

Abbreviation: TBI = total body irradiation.

* All toxicity data were based on dental evaluations.

† Various diagnoses, most commonly acute leukemia. Various systemic agents used with TBI as part of the preparative regimen, most commonly cyclophosphamide.

‡ Treated with TBI with dental follow-up.

§ Percent of teeth.

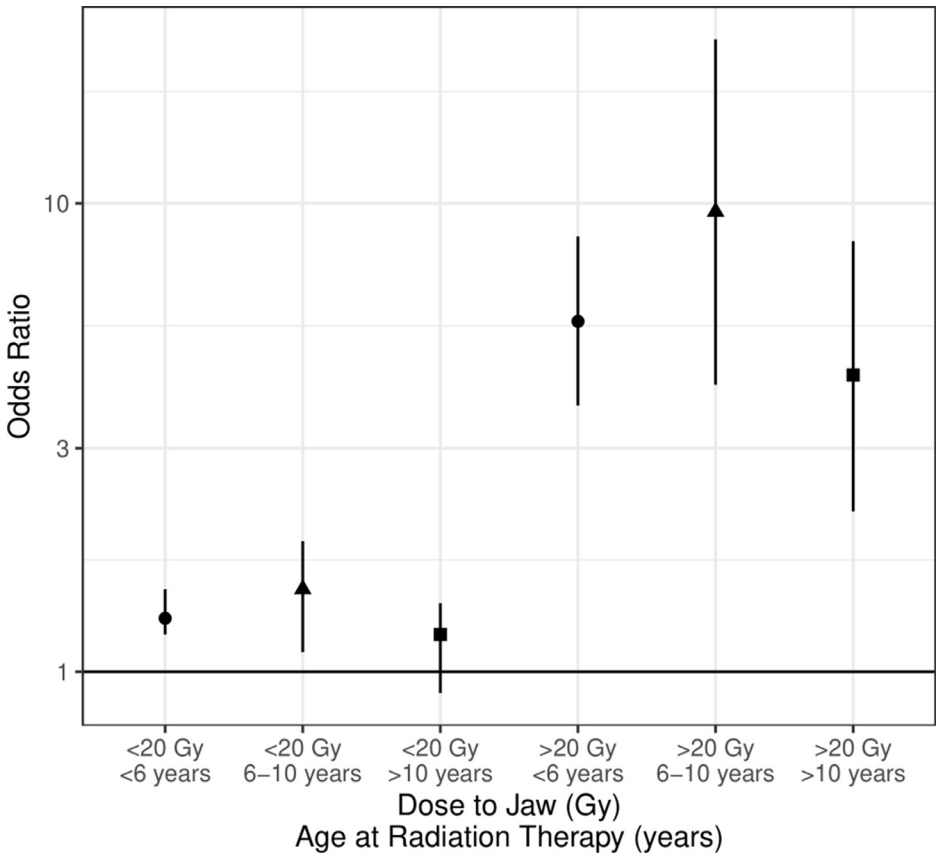

Fig. 3. Odds ratio of ≥1 dental abnormality in survivors treated with head and neck radiation therapy (RT) compared with their siblings as a function of dose to the teeth and age at RT. A childhood cancer survivor study by Kaste et al reported the odds ratio of ≥1 self-reported dental abnormality in survivors compared with their siblings.[54] The comparison group, the survivors' siblings, did not have a history of cancer or radiation. Radiation to the teeth significantly increased the risk of dental abnormalities in a dose-dependent manner. This dose-dependent risk was present within all age strata, except for those survivors who were the oldest at diagnosis (>10 years) and received the lowest doses (>0 to <20 Gy).

patients as early as 1 year of age. To be eligible for this study, each patient must have had ≥1 developing permanent teeth that received a D_{max} of >20 Gy (RBE) (the physical dose was multiplied by the proton relative biological effectiveness, so the D_{max} was the equivalent of >20 Gy with photons[55]). Patients were followed for a median of 5 years after treatment (range, 17-90 months), with 10 having seen a dentist at least once during that time. Among these 10 patients with dental follow-up, 2 had abnormal or missing teeth, and 1 had asymmetrically delayed permanent tooth eruption. The patients with the most severe dental developmental abnormalities were those who had received the highest doses at the youngest ages. It is unclear if factors such as the length of follow-up and frequency of dental evaluations were similar for these patients and the remainder of the cohort. Nonetheless, these limited data suggested that developmental abnormalities occurred only in teeth that received a dose of >20 to 30 Gy (RBE) in children <4 years. No dental developmental abnormalities were observed in children who were ≥4 years at the time of RT, despite doses in excess of 48 Gy (RBE).[30] Despite the small size of the cohort, the dosimetric information in this study was the most detailed, with accurate data at the level of each individual tooth.

Other data suggest that lower doses may be associated with dental abnormalities. Fromm et al reported on 20 children who were treated with conventional RT for soft tissue sarcomas of the H&N at a median age of 6 years and were followed with dental evaluations for a median of 6 years (range, 2-10 years). Among the 11 patients who had developing teeth in the RT field and long-term dental follow-up, root abnormalities were identified in all 11 (100%) and crown defects in 9 (82%). The authors reported that the dose to the developing dentition ranged from 4 to 60 Gy in these affected patients. Thus, they conclude that developing teeth exposed to a dose as low as 4 Gy may show some abnormality.[11] It must be noted, however, that the dose to the teeth was estimated based on "isodose plans, simulation films, and treatment set-up photographs," but not based on CT images, detailed OAR contouring, and DVH calculations using modern TPS as in the work by Thompson et al previously described. This methodological difference is one factor that may contribute to the discrepant findings betweenthese studies.

Risk factors

Several nondosimetric risk factors have been identified for dental developmental abnormalities, including younger age at the time of RT[30,51,53,54,56-60] and chemotherapy,[61] specifically alkylating agents.[54]

Caries

Review of data

In addition to developmental abnormalities, there may be an increased risk of dental caries after RT to the H&N in childhood. Some,[60,62] but not all,[63-65] studies have identified a higher incidence of caries in long-term childhood cancer survivors, not all of whom received RT, compared with matched controls. Additionally, some,[62] but not all,[63,64] studies have shown that individuals who received RT to the H&N had a greater risk of caries than other survivors. Series of patients treated with H&N RT as children for various malignancies have reported rates of dental caries that range from 7% to 60%.[10,11,14,30,37,38,66-71] The variation in these results may be related to differences in the patient cohorts, treatment regimens, radiation dosimetry, or dental follow-up care.

Caries are attributed to decreased salivary flow and changes in salivary composition, rather than a direct effect of radiation on the teeth. Concordantly, in the study by Thompson et al, the presence of caries during follow-up was independent of the dose to the affected teeth.[30]

Recommended Dose-Volume Constraints

Dose-toxicity data regarding the salivary glands and teeth in children are limited, complicating the identification of specific dose-volume constraints.

Most available data concern the parotids and show that if both glands receive a D_{mean} of 35 to 40 Gy, the risk of acute and chronic grade ≥2 xerostomia is approximately 32% and 13% to 32%, respectively, in patients receiving chemo-RT, and the risk is greater with increasing parotid dose (Fig. 2). The data are insufficient to predict rates of xerostomia after lower parotid doses. Additionally, Bölling et al demonstrated an increased risk of xerostomia associated with higher dose to the submandibular glands.[35] However, parotid and submandibular gland dose constraints specific to children cannot be provided based on these limited data. The dose-toxicity relationship may be similar to that in the 2010 QUANTEC review,[3] although the data are insufficient for statistical comparisons.

We conclude that a parotid D_{mean} of 35 to 40 Gy is associated with clinically significant xerostomia in a substantial proportion of childhood cancer survivors, so a lower dose constraint is recommended. However, the data regarding rates of xerostomia after lower dose exposure in children are insufficient to identify an acceptable constraint. Therefore, this PENTEC task force considers adoption of salivary gland dose constraints from the adult experience, where there are more abundant low-dose data, to be a reasonable strategy until more dose-toxicity information specific to children becomes available. Current clinical trials in adult H&N cancer (NRG HN001, HN004, HN005) recommend limiting the parotid gland D_{mean} to ≤26 Gy. We recommend using this constraint for the pediatric population, as well. In the setting of unilateral parotid exposure, it is possible that the exposed gland could be treated to a higher dose because salivary function will be maintained in the contralateral, spared gland. Nonetheless, we recommend limiting the parotid D_{mean} to ≤26 Gy, even in this setting, to be cautious, given the lack of data regarding the dose-toxicity relationship after unilateral parotid irradiation in children.

Although it is not clear whether the parotid and submandibular glands have the same dose−volume response characteristics, this task force recommends limiting the submandibular gland D_{mean} to ≤26 Gy whenever possible. If this constraint cannot be achieved, higher doses may be acceptable, but sparing the submandibular gland to modest mean doses (eg, <35 Gy) might reduce the risk of xerostomia.[3]

Regarding dental developmental abnormalities, the minimum toxic dose is unknown. The nature and severity of dental abnormalities is inversely related to the patient's age and stage of tooth development at the time of RT.[13,30,52-54,56-59,72-74] The dose should be minimized, with attention paid to the developing tooth buds, particularly in younger patients. In children <4 years, special effort should be made to keep doses <20 Gy.[30]

Caries have been attributed to salivary dysfunction, rather than direct effects of radiation on the teeth. No association has been identified between the risk of caries and the dose to the individual affected teeth.[30] To reduce the risk of caries, dose to the salivary glands should be minimized, as previously described.

In all cases, the contribution of RT to disease control should be weighed against its potential toxicity. Higher doses to the salivary glands and oral cavity may be acceptable, if they are necessary for a favorable oncologic outcome.

Toxicity Scoring Recommendations

This task force recommends patient-reported toxicity scoring. As previously stated, several validated instruments exist to measure OHRQoL in children.[16] One comprehensive assessment is the COHIP that includes 34 total items within the domains: "Oral Health−Wellbeing," "Functional Well-being," "Social/Emotional Wellbeing," "School Environment," and "Self-Image." Example items include "had pain in your teeth/toothache," "had dry mouth or lips," "had difficulty eating the foods you would like because of your teeth, mouth, or face," "been unhappy or sad because of your teeth, mouth, or face," and "missed school for any reason because of your teeth, mouth, or face." This validated instrument has been used in diverse patient populations and is

available in multiple languages.[17] To the best of our knowledge, it has not been used in survivors of childhood cancer who received RT to the H&N region. However, it captures data that are important for this patient population. Therefore, we recommend use of this instrument in future studies.

Patient-reported OHRQoL may be supplemented with other objective measures. For salivary function, we recommend measuring the USSR and SSSR. For effects on dental development, we recommend reporting the incidence of each type of abnormality separately (ie, tooth agenesis, shortened roots, enamel defects, etc). For caries, we recommend reporting the DMF/T, a commonly used, quantitative scoring method.

Data Reporting Standards

It is vital that published data sets conform to rigorous reporting standards, so their results can be compared and/or pooled. Authors should report:

- Patient sex
- Age at the time of RT
- Cancer diagnosis
- RT dose and fractionation
- RT technique
- Salivary gland and oral cavity exposure in the form of dose-volume histograms for each individual major salivary gland, the oral cavity, and the teeth/tooth buds
- Chemotherapy information (agents and timing)
- Dental follow-up care
- Thorough description of the toxicity scoring system used
- Timing of the outcome assessment relative to the completion of RT and attained age of the patient

Future Investigations

The overarching goal of future investigations is to develop validated predictive models for salivary and dental toxicity. These models would contribute to the reduction in risk by treatment optimization, as well as accurate identification of high-risk individuals who may benefit from interventions to prevent late adverse events. As one example, patients at the highest risk of salivary gland dysfunction may be selected for intensive dental follow-up care to reduce the risk of caries. Multiple topics warrant future investigation:

1. Obtain dose distributions and prospectively measured toxicity outcomes in larger cohorts of patients to allow the identification of dosimetric risk factors specific to children.
2. Evaluate the role of age and sex in the development of toxicity by identifying rates of each endpoint in boys and girls across the spectrum of ages.
3. Assess the risk of toxicity associated with various chemotherapeutic agents, given concomitantly and sequentially with RT.
4. Investigate how parotid, submandibular, and minor salivary gland doses each should be incorporated into predictive salivary function models, and if the dose to any other organ-at-risk should be included.
5. Determine whether patients with acute xerostomia are more likely to develop late xerostomia.
6. Explore whether variability in radiosensitivity exists throughout organs-at-risk. As one example, detailed dosimetric analyses may reveal if the parotids of children, similar to those of adults,[48] contain regions of greater radiosensitivity. Similarly, when sparing the whole parotid gland is not possible, sparing at least 1 portion of the gland may reduce the risk of salivary dysfunction in children, as it does in adults.[6] Modern RT planning/delivery systems can create highly nonuniform doses, so a better understanding of the regional dose-response may help to guide RT planning decisions to reduce the risk of xerostomia.
7. Study the role of radioprotective agents in children.[75]

References

1. Effinger KE, Migliorati CA, Hudson MM, et al. Oral and dental late effects in survivors of childhood cancer: A Children's Oncology Group report. *Support Care Cancer* 2014;22:2009-2019.
2. 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.
3. Deasy JO, Moiseenko V, Marks L, et al. Radiotherapy dose-volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys* 2010;76 (suppl 3):S58-S63.
4. Gupta T, Hotwani C, Kannan S, et al. Prospective longitudinal assessment of parotid gland function using dynamic quantitative pertechnate scintigraphy and estimation of dose-response relationship of parotid-sparing radiotherapy in head-neck cancers. *Radiat Oncol* 2015;10:67.
5. Dijkema T, Raaijmakers CP, Ten Haken RK, et al. Parotid gland function after radiotherapy: The combined Michigan and Utrecht experience. *Int J Radiat Oncol Biol Phys* 2010;78:449-453.
6. Nevens D, Nuyts S. Can sparing of the superficial contralateral parotid lobe reduce xerostomia following radiotherapy for head and neck cancer? *Br J Radiol* 2017;90 20170596.
7. Gawade PL, Hudson MM, Kaste SC, et al. A systematic review of dental late effects in survivors of childhood cancer. *Pediatr Blood Cancer* 2014;61:407-416.
8. Bei M. Molecular genetics of tooth development. *Curr Opin Genet Dev* 2009;19:504-510.
9. Collett WK, Thonard JC. The effect of fractional radiation on dentinogenesis in the rat. *J Dent Res* 1965;44:84-90.
10. Paulino AC, Simon JH, Zhen W, et al. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys* 2000;48:1489-1495.
11. 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.
12. 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.
13. Kaste SC, Hopkins KP, Bowman LC. Dental abnormalities in long-term survivors of head and neck rhabdomyosarcoma. *Med Pediatr Oncol* 1995;25:96-101.
14. Raney RB, Asmar L, Vassilopoulou-Sellin R, et al. 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. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. *Med Pediatr Oncol* 1999;33:362-371.
15. Cheng SC, Wu VW, Kwong DL, et al. Assessment of post-radiotherapy salivary glands. *Br J Radiol* 2011;84:393-402.
16. Genderson MW, Sischo L, Markowitz K, et al. An overview of children's oral health-related quality of life assessment: From scale development to measuring outcomes. *Caries Res* 2013;47(suppl 1):13-21.
17. Broder HL, Wilson-Genderson M. Reliability and convergent and discriminant validity of the Child Oral Health Impact Profile (COHIP Child's version). *Community Dent Oral Epidemiol* 2007;35(suppl 1):20-31.
18. Meirovitz A, Murdoch-Kinch CA, Schipper M, et al. Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2006;66:445-453.
19. Proctor GB. The physiology of salivary secretion. *Periodontol 2000* 2016;70:11-25.
20. Bagesund M, Richter S, Agren B, et al. Correlation between quantitative salivary gland scintigraphy and salivary secretion rates in children and young adults treated for hematological, malignant and metabolic diseases. *Dentomaxillofac Radiol* 2000;29:264-271.
21. van Acker F, Flamen P, Lambin P, et al. The utility of SPECT in determining the relationship between radiation dose and salivary gland dysfunction after radiotherapy. *Nucl Med Commun* 2001;22:225-231.
22. Fox PC, Bodner L, Bowers MR, et al. Uptake and secretion of technetium pertechnetate by the rat parotid gland. *Comp Biochem Physiol A Comp Physiol* 1986;83:579-584.
23. Astreinidou E, Roesink JM, Raaijmakers CP, et al. 3D MR sialography as a tool to investigate radiation-induced xerostomia: Feasibility study. *Int J Radiat Oncol Biol Phys* 2007;68:1310-1319.
24. van Dijk LV, Thor M, Steenbakkers R, et al. Parotid gland fat related magnetic resonance image biomarkers improve prediction of late radiation-induced xerostomia. *Radiother Oncol* 2018;128:459-466.
25. van Dijk LV, Brouwer CL, van der Schaaf A, et al. CT image biomarkers to improve patient-specific prediction of radiation-induced xerostomia and sticky saliva. *Radiother Oncol* 2017;122:185-191.
26. Imanimoghaddam M, Rahrooh M, Tafakhori Z, et al. Changes of parotid and submandibular glands caused by radiotherapy—An ultrasound evaluation. *Dentomaxillofac Radiol* 2012;41:379-384.
27. Cubukcu CE, Sevinir B, Ercan I. Disturbed dental development of permanent teeth in children with solid tumors and lymphomas. *Pediatr Blood Cancer* 2012;58:80-84.
28. Iro H, Zenk J. Salivary gland diseases in children. *GMS Curr Top Otorhinolaryngol Head Neck Surg* 2014;13:Doc06.
29. Brouwer CL, Steenbakkers RJHM, Bourhis J, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. *Radiother Oncol* 2015;117:83-90.
30. Thompson RF, Schneider RA, Albertini F, et al. Dose to the developing dentition during therapeutic irradiation: Organ at risk determination and clinical implications. *Int J Radiat Oncol Biol Phys* 2013;86:108-113.
31. Robar JL, Day A, Clancey J, et al. Spatial and dosimetric variability of organs at risk in head-and-neck intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1121-1130.
32. Barker Jr JL, Garden AS, Ang KK, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys* 2004;59:960-970.
33. Wang ZH, Yan C, Zhang ZY, et al. Radiation-induced volume changes in parotid and submandibular glands in patients with head and neck cancer receiving postoperative radiotherapy: A longitudinal study. *Laryngoscope* 2009;119:1966-1974.
34. 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. *J Clin Epidemiol* 2009;62:e1-e34.
35. Bolling T, Weege J, Eich HT, et al. Acute and late side effects to salivary glands and oral mucosa after head and neck radiotherapy in children and adolescents. Results of the "Registry for the evaluation of side effects after radiotherapy in childhood and adolescence. *Head Neck* 2015;37:1137-1141.
36. Laskar S, Bahl G, Muckaden M, et al. Nasopharyngeal carcinoma in children: Comparison of conventional and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:728-736.
37. Louis CU, Paulino AC, Gottschalk S, et al. A single institution experience with pediatric nasopharyngeal carcinoma: High incidence of toxicity associated with platinum-based chemotherapy plus IMRT. *J Pediatr Hematol Oncol* 2007;29:500-505.
38. Shen C, Gao Y, Xu T, et al. Carcinoma of the nasopharynx in young patients: A single institution experience. *Clin Oncol (R Coll Radiol)* 2009;21:617-622.
39. Tao CJ, Liu X, Tang LL, et al. Long-term outcome and late toxicities of simultaneous integrated boost-intensity modulated radiotherapy in pediatric and adolescent nasopharyngeal carcinoma. *Chin J Cancer* 2013;32:525-532.
40. Yan Z, Xia L, Huang Y, et al. Nasopharyngeal carcinoma in children and adolescents in an endemic area: A report of 185 cases. *Int J Pediatr Otorhinolaryngol* 2013;77:1454-1460.
41. Chen BB, Lu SY, Peng H, et al. Comparison of long-term outcomes and sequelae between children and adult nasopharyngeal carcinoma treated with intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2020;106:848-856.
42. Bagesund M, Richter S, Agren B, et al. Scintigraphic study of the major salivary glands in pediatric bone marrow transplant recipients. *Bone Marrow Transplant* 2000;26:775-779.
43. Dahllof G, Bagesund M, Remberger M, et al. Risk factors for salivary dysfunction in children 1 year after bone marrow transplantation. *Oral Oncol* 1997;33:327-331.
44. Dahllof G, Wondimu B, Barr-Agholme M, et al. Xerostomia in children and adolescents after stem cell transplantation conditioned with total body irradiation or busulfan. *Oral Oncol* 2011;47:915-919.
45. Garming Legert K, Remberger M, Ringden O, et al. Salivary secretion in children after fractionated or single-dose TBI. *Bone Marrow Transplant* 2012;47:404-410.
46. Garming-Legert K, Remberger M, Ringden O, et al. Long-term salivary function after conditioning with busulfan, fractionated or single-dose TBI. *Oral Dis* 2011;17:670-676.
47. Bagesund M, Tilikidis A, Dahllof G. Absorbed doses in the head and oral cavity during total body irradiation. *Oral Oncol* 1998;34:72-74.
48. van Luijk P, Pringle S, Deasy JO, et al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. *Sci Transl Med* 2015;7:305ra147.
49. Konings AW, Cotteleer F, Faber H, et al. Volume effects and region-dependent radiosensitivity of the parotid gland. *Int J Radiat Oncol Biol Phys* 2005;62:1090-1095.
50. 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.
51. Dahllof G, Heimdahl A, Bolme P, et al. Oral condition in children treated with bone marrow transplantation. *Bone Marrow Transplant* 1988;3:43-51.
52. Nishimura S, Inada H, Sawa Y, et al. Risk factors to cause tooth formation anomalies in chemotherapy of paediatric cancers. *Eur J Cancer Care (Engl)* 2013;22:353-360.

53. 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.
54. 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.
55. International Commission on Radiation Units & Measurements. Available at: https://icru.org/home/reports/prescribing-recording-and-reporting-proton-beam-therapy-icru-report-78. Accessed May 5, 2021.
56. 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.
57. 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.
58. Ko Y, Park K, Kim JY. Effect of anticancer therapy on ectopic eruption of permanent first molars. *Pediatr Dent* 2013;35:530-533.
59. McGinnis Jr JP, 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.
60. 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.
61. Minicucci EM, Lopes LF, Crocci AJ. Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. *Leuk Res* 2003;27:45-50.
62. Cubukcu CE, Sevinir B. Dental health indices of long-term childhood cancer survivors who had oral supervision during treatment: A case-control study. *Pediatr Hematol Oncol* 2008;25:638-646.
63. 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.
64. 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.
65. Sonis AL, Waber DP, Sallan S, et al. The oral health of long-term survivors of acute lymphoblastic leukaemia: A comparison of three treatment modalities. *Eur J Cancer B Oral Oncol* 1995;31B:250-252.
66. Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: Clinical outcomes and late effects. *Int J Radiat Oncol Biol Phys* 2012;82:635-642.
67. Estilo CL, Huryn JM, Kraus DH, et al. Effects of therapy on dentofacial development in long-term survivors of head and neck rhabdomyosarcoma: The Memorial Sloan-Kettering Cancer Center experience. *J Pediatr Hematol Oncol* 2003;25:215-222.
68. Fields JN, Halverson KJ, Devineni VR, et al. Juvenile nasopharyngeal angiofibroma: Efficacy of radiation therapy. *Radiology* 1990;176:263-265.
69. Kupeli S, Varan A, Ozyar E, et al. Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. *Pediatr Blood Cancer* 2006;46:454-458.
70. Kupferman ME, de la Garza GO, Santillan AA, et al. Outcomes of pediatric patients with malignancies of the major salivary glands. *Ann Surg Oncol* 2010;17:3301-3307.
71. Laskar S, Sanghavi V, Muckaden MA, et al. Nasopharyngeal carcinoma in children: Ten years' experience at the Tata Memorial Hospital, Mumbai. *Int J Radiat Oncol Biol Phys* 2004;58:189-195.
72. Kaste SC, Hopkins KP, Jones D, et al. Dental abnormalities in children treated for acute lymphoblastic leukemia. *Leukemia* 1997;11:792-796.
73. Maciel JC, de Castro Jr 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.
74. Pajari U, Lanning M. Developmental defects of teeth in survivors of childhood ALL are related to the therapy and age at diagnosis. *Med Pediatr Oncol* 1995;24:310-314.
75. Anacak Y, Kamer S, Haydaroglu A. Daily subcutaneous amifostine administration during irradiation of pediatric head and neck cancers. *Pediatr Blood Cancer* 2007;48:579-581.
76. Duggal MS. Root surface areas in long-term survivors of childhood cancer. *Oral Oncology* 2003;39:178-183.
77. Lockney A Natalie. Late Toxicities of Intensity-Modulated Radiation Therapy for Head and Neck Rhabdomyosarcoma. *Pediatr Blood Cancer* 2016;63:1608-1614.
78. McGinnis JP. Mandibular third molar development after mantle radiation in long-term survivors of childhood Hodgkin's disease. *Oral Surg* 1987;63:630-633.
79. Holtta P. 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.
80. Uderzo C. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. *Bone Marrow Transplant* 1997;20:685-689.