Intensity-modulated Radiotherapy: Is Xerostomia Still Prevalent?

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Conformal radiation with intensity-modulated radiotherapy (IMRT) is a technique that potentially can minimize the dose to salivary glands and thereby decrease the incidence of xerostomia. Precise target determination and delineation is most important when using salivary gland–sparing techniques of IMRT. Reduction of xerostomia can be achieved by sparing the salivary glands on the uninvolved oral cavity and keeping the mean parotid gland dose of less than 26 to 30 Gy as a planning criterion if the treatment of disease is not compromised and parotid function preservation is desired.

Introduction

Xerostomia is a common, debilitating complication of radiotherapy for head and neck cancer [1•]. Recent efforts have focused on the use of conformal radiation or other newer radiotherapy techniques to spare a portion of the major salivary glands (Table 1) [2]. One such system is intensity-modulated radiotherapy (IMRT), which allows for sculpting dose distributions that conform specifically to a three-dimensional shape of the target. The clinical advantages to using IMRT are numerous and include improvement in radiation dose uniformity, creation of concave dose patterns conforming to the shape of the tumor, assignment of weightings to targets and critical structures, treatment of multiple targets simultaneously, and lowering of complication rates. The desire for conformal doses and the lack of internal organ motion make IMRT attractive for patients with head and neck cancer [3,4]. Several studies have demonstrated the significant benefit of IMRT over conventional treatment with respect to dosimetric superiority compared with more conventional approaches [3–5]. Recently, IMRT has been used for treatment of head and neck cancers and studied for improved tumor coverage with resultant increased rates in locoregional control and decreased short-term toxicity [6•]. Longitudinal data on IMRT therapeutic gain are lacking with regard to long-term tumor outcome and late radiation toxicity [6•]; therefore, this paper only presents a review of salivary gland toxicity as it relates to IMRT. A substantial number of studies have documented the reduction of radiation-induced xerostomia following IMRT for pharyngolaryngeal squamous cell carcinomas [1•,2–5,6•,7].

Conventional Parotid Doses and Sparing

Dreizen *et al.* [8] quantified saliva production in patients undergoing radiotherapy for head and neck cancer. In this study, after a dose of 10 Gy, patients had already developed a 50% reduction in salivary flow. After receiving 50 Gy, patients had less than 10% of their salivary flow remaining, and few patients regained salivary function [8]. Emami *et al.* [9] defined the tolerance dose of the saliva glands to radiation, stating the minimum tolerance dose of 5/5 (tumor dose causing 5% complication rate at 5 years) as 30 Gy, and the tolerance dose 50/5 as 50 Gy. Leslie and Dische [10] described high rates of xerostomia in patients whose parotid glands were irradiated with 40 Gy but negligible rates in patients who received less than 14 Gy. Thus, the tolerance doses of the glands lie somewhere within this wide range.

Parotid-sparing Techniques: Oropharynx and Oral Cavity

Reducing the radiation dose to the major salivary glands is achievable with IMRT [7]. Reddy *et al.* [11] investigated the use of parotid-sparing irradiation techniques in patients with cancer of the oral cavity. Thirty-one patients were treated with two-dimensional techniques sparing at least one parotid gland from radiation beams, whereas 83 patients were treated with bilateral opposed photon beams, including both parotid glands [11]. Patients

Table 1. Pivotal intensity-modulated radiotherapy salivary gland–sparing trials

Study	Patients, *n*	Median follow-up	Endpoint(s)	Cancer sites	Findings
Eisbruch *et al.* [2]	84	24 months	Assessment of long-term xerostomia; patient and therapy-related factors	Oropharynx	Sparing of uninvolved oral cavity should be considered planning objective; improvement over time in xerostomia
Henson *et al.* [15]	20	12 months	Assessment of parotid salivary function; if parotid sparing would improve QOL	Head and neck	With use of parotid-sparing RT, contralateral glands are preserved at 1 year post RT
Eisbruch *et al.* [16••].	88	12 months	Determination of 3-D dose distributions in parotid glands	Head and neck	Mean RT dose of ≤26 Gy is threshold for preserved stimulated saliva flow
Lin *et al.* [18•]	36	12 months	Assessment of QOL and predictors after IMRT	Head and neck	After parotid-sparing IMRT, a statistical correlation was found between xerostomia and each of the domains of QOL: eating, communication, pain, and emotion
Lee *et al.* [27•]	67	31 months	Experience with IMRT in treatment of nasopharyngeal carcinoma	Nasopharynx	Xerostomia decreased with time; IMRT allowed delivery of high dose to target with significant sparing of salivary glands
Chao *et al.* [22]	74	33 months	Analysis of impact of primary gross tumor volume and nodal GTV	Oropharynx	GTV and nGTV are important factors predictive of therapeutic outcome
Chao *et al.* [20]	430	3.9 years	Comparison of acute and late toxicity and tumor control between conventional RT and IMRT	Oropharynx	IMRT significantly reduced the incidence of late xerostomia with dosimetric advantage
Chao *et al.* [19••]	41	6 months	Sparing of parotid glands may result in significant objective and subjective improvement in xerostomia	Head and neck	Correlation between parotid mean dose and fractional reduction of stimulated saliva post IMRT; modeling suggests an exponential relationship between saliva flow reduction and mean parotid dose: rate of approximately 4% per Gy of mean parotid dose

3D—three-dimensional; GTV—gross tumor volume; IMRT—intensity-modulated radiotherapy; nGTV—nodal gross tumor volume; QOL—quality of life; RT—radiotherapy.

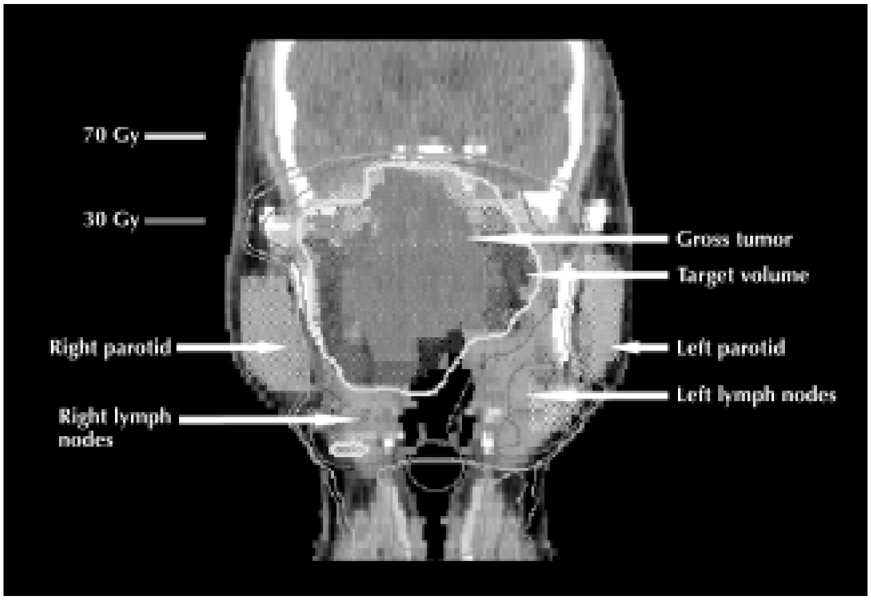

Figure 1. Example of parotid-sparing, intensity-modulated radiotherapy in a patient with advanced cancer of the nasopharynx. In this coronal section, the 30-Gy isodose line is visualized as curving around the parotid glands.

treated with the parotid-sparing technique were able to maintain nutritional intake and baseline body weight during and after irradiation. In contrast, those treated with the bilateral technique had poor nutritional intake and lost more than 10% of body weight, which was not regained during the 2 years after treatment [11]. When analyzed according to tumor stage, primary tumor control rates with the parotid-sparing and bilateral techniques were similar (93% and 87%, respectively, for early-stage tumors; 42% and 36%, respectively, for advanced-stage tumors); therefore, the authors noted that selection of patients who might benefit from this technique requires consideration of the risk of contralateral cervical lymph node metastases [11].

In another study, O'Sullivan *et al.* [12] used an ipsilateral technique to restrict irradiation to the primary tumor and neck on the same side in patients with carcinoma of the tonsillar region. From 1970 to 1991, these researchers treated 228 of 642 patients with carcinoma of the tonsillar region (mainly T1 and T2, N0 and N1) with this technique. After a mean follow-up of 7 years, the 3-year actuarial local control rate was 77% and the cause-specific survival rate was 76%, with failure in the opposite side of the neck in eight patients [12]. Difficulties with primary coverage early in the study resulted in higher rates of local failure. The researchers concluded that, in appropriately selected patients with tonsillar carcinoma, the risk of failure in the opposite side of the neck is minimal with ipsilateral therapy, but CT planning is necessary to ensure adequate target coverage [12].

The dose-volume-response relationship in the major salivary glands is needed to determine the treatment planning goal and to optimize radiotherapy plans. Eisbruch *et al.* [13] found that mean dose to the gland is correlated with reduced salivary flow; therefore, mean doses between 26 and 39 Gy can cause significant salivary flow reduction.

The emerging parotid-sparing technique, IMRT, involves the manipulation of beam intensity across each treatment field, providing a dose distribution that conforms more accurately to the three-dimensional configuration of the target volume than does conventional three-dimensional conformal radiotherapy (Fig. 1) [1•,6•]. This technique delivers a higher dose to the tumor target without increasing the dose to normal tissues, provides a higher dose per fraction, and offers an improved physical and biologic therapeutic ratio [14]. IMRT has the potential to deliver a lower dose of radiation to the parotid glands compared with conventional beam arrangements, and thus it has the greatest potential for patients with mucosal primary tumors that require bilateral neck irradiation [1•,14].

Eisbruch *et al.* [2] assessed long-term xerostomia in 84 patients with head and neck cancer who had undergone comprehensive bilateral neck irradiation using conformal and multisegmental IMRT to spare major salivary glands. Xerostomia was assessed with a validated eight-item xerostomia-specific questionnaire. With these parotid-sparing techniques, xerostomia improved over time (second year after radiotherapy), with rising salivary production from the spared major salivary glands, thus showing long-term clinical benefit. In addition, the oral cavity mean radiation dose was found to be significantly correlated with xerostomia scores, indicating that it may be beneficial to spare the uninvolved oral cavity to further reduce xerostomia [2]. These University of Michigan researchers also studied the parotid salivary function up to 12 months after radiotherapy in 20 patients undergoing bilateral neck parotid-sparing irradiation to determine if parotid preservation improves xerostomia-related quality of life [15]. Salivary sampling and a 15-item xerostomia-related quality of life scale were completed by each patient. The salivary flow from spared and treated glands significantly decreased at the completion of radiotherapy. After radiotherapy, unstimulated and stimulated function increased and was not significantly different from baseline figures; therefore, these authors concluded that, with the use of parotid-sparing radiotherapy, contralateral glands are preserved 12 months after treatment with parallel improvement in xerostomia-related quality of life [15].

The dose, volume, and functional relationships in parotid salivary glands following conformal and multisegmental IMRT of the head and neck were studied by Eisbruch *et al.* [16••]. Eighty-eight patients with head and neck cancer participated in the study. Unstimulated and stimulated saliva was measured from each parotid gland before radiotherapy and 1, 3, 6, and 12 months afterward. Glands receiving a mean dose below or equal to a threshold of less than 25% of the pretreatment level (24 Gy for unstimulated and 26 Gy for stimulated saliva) revealed preservation of the flow rates after radiotherapy and continued to improve over time [16••]. The glands receiving doses below the threshold had functional recovery over time, whereas glands receiving higher doses did not recover [7,16••]. Partial volume thresholds were found as well: 67%, 45%, and 24% gland volumes received more than 15 Gy, 30 Gy, and 45 Gy, respectively [16••]. Age, sex, preradiotherapy surgery, chemotherapy, and specific intercurrent illnesses were not found to affect the salivary flow rates. Eisbruch *et al.* [5,16••,17] concluded that a parotid gland mean dose of less than 26 Gy should be the planning goal for substantial sparing of gland function. Subjective assessment in the studies by these authors has demonstrated that xerostomia was significantly reduced in patients treated with bilateral neck, parotid-sparing radiotherapy, as compared with patients with similar disease treated with conventional radiotherapy [17,18•]. Twelve months after parotid-sparing IMRT, statistical significance was found between patient-reported xerostomia and four domains of quality of life: eating, communication, pain, and emotion [18•].

Using mathematical modeling, Chao *et al.* [19••] concluded that the functional outcome of salivary flow using inverse-planning IMRT could be modeled as a function of dose, and therefore the mean dose to each parotid gland is a reasonable indicator for the functional outcome of each gland. The entire parotid volume was used to compute dose-volume histograms in this trial evaluating 41 patients with head and neck cancer. Stimulated saliva, at 6 months, reduced exponentially for each gland independently at a rate of approximately 4% per Gy of mean parotid dose [19••].

In another study by the same authors, acute toxicity, late toxicity, and tumor control were retrospectively compared in 430 patients with oropharyngeal cancer who underwent radiotherapy with a conventional beam arrangement or IMRT [20]. These investigators concluded that the dosimetric advantage of IMRT translated into significant reduction of late salivary toxicity, with no adverse impact on tumor control or disease-free survival [20,21]. After IMRT, only 17% to 30% of patients had late grade 2 xerostomia. Although the majority had moderate to severe dry mouth during therapy, the spared salivary glands showed recovery over time. The dosimetric conformity of IMRT for normal tissue sparing in patients with oropharyngeal cancer was studied by Chao *et al.* [22] in assessing the therapeutic outcomes of IMRT as it relates to the impact on gross tumor volume (GTV) and nodal gross tumor volume (nGTV). A multivariate analysis revealed that GTV and nGTV were important independent risk factors predictive of therapeutic outcome for definitive treatment of oropharyngeal IMRT [22].

In delineating the target volume for radiation in parotid gland–sparing techniques, Eisbruch *et al.* [23] recently published results of a longitudinal clinical investigation assessing patients treated with parotid-sparing IMRT for non-nasopharyngeal head and neck squamous cell carcinomas; furthermore, patients were examined for locoregional failures near the base of the skull and their relationships to the target delineation in the high neck. The results reported in this study confirmed defining level II delineation in the contralateral node-negative neck so that the targets included the subdigastric nodes, yet not extend as cranial as in conventional radiotherapy, allowing substantial sparing of the contralateral parotid glands, and hence, reducing salivary dysfunction. Another study evaluating the radiotherapy target volume and organs at risk in oropharyngeal carcinoma defined the lowering of the cranial border of the level II lymph nodes from C1 to C2 in bilateral cervical radiotherapy and found reduced toxic effects on major salivary gland tissue, as proposed by Astreinidou *et al.* [24]. The lowering of the cranial border to C2 with IMRT could be considered on the contralateral side if the risk of metastasis on that side is significantly low, thus reducing the average mean dose to the contralateral parotid gland. Astreinidou *et al.* [24] calculated that the reduction of the normal tissue complication probability for xerostomia 1 year after radiotherapy could be up to 68% (lowering the cranial border to C2), compared with conventional radiotherapy when treating C1.

Munter *et al.* [25] evaluated salivary gland function after IMRT for head and neck cancer using quantitative pertechnetate scintigraphy. The mean dose to the primary planning target volume was 61.5 Gy, and the median follow-up was 23 months. This study revealed that it was possible to protect the parotid glands and reduce the incidence of xerostomia in patients with head and neck cancer if mean parotid doses were less than 30 Gy.

Intensity-modulated Radiotherapy Technique

Nasopharynx

Sultanem *et al.* [26] treated 35 patients with nasopharyngeal cancer of various stages between 1995 and 1998. IMRT of the primary tumor was delivered by manually cut partial transmission blocks, a computer-controlled autosequencing static multileaf collimator, or a Peacock system (Nomos, Sewickley, PA) using a dynamic multivane intensity-modulating multileaf collimator. A forward three-dimensional planning system was used for the first two methods, and inverse treatment planning was used for the third method [26]. Some patients also underwent brachytherapy, and most received chemotherapy. After a mean follow-up of 21.8 months, the 4-year locoregional progression-free rate, estimated with the Kaplan-Meier method, was 100%, the 4-year overall survival rate was 94%, and the distant metastasis–free rate was 57% [26]. The most frequent acute toxicities were mucositis and pharyngitis, and the most common late effect was xerostomia. After 3 months, 65% of evaluated patients had Radiation Therapy Oncology Group (RTOG) grade 2 xerostomia, and 35% had grade 1 xerostomia; however, after 24 months, 50% had grade 1 xerostomia, and 50% had no xerostomia. These researchers concluded that three-dimensional IMRT provided improved target volume coverage and increased dose to the gross tumor, with significant sparing of the salivary glands and other critical structures, achieving good locoregional control [26].

Lee *et al.* [27•] continued to follow the patients initially studied by Sultanem *et al.* [26] at the University of California, San Francisco and analyzed the results of IMRT in the treatment of 67 patients with nasopharynx cancer. Although the goal was improved tumor coverage with delivery of high dosing to the target, a significant finding was that lower doses to the parotid glands were demonstrated, and the group described a low incidence of RTOG grade 2 or greater xerostomia. Three months after IMRT, 64% of the patients had RTOG grade 2 xerostomia, 28% had grade 1, and 8% had grade 0 xerostomia [27•]. In the study by Lee *et al.* [27•], xerostomia was found to decrease with time. Cheng *et al.* [28] studied target volume coverage and normal tissue sparing of IMRT for nasopharyngeal carcinoma, compared with conventional treatment. They concluded that fixed-field IMRT, as compared with serial tomotherapy, had the best parotid-sparing effect. The RTOG is now testing IMRT for nasopharyngeal cancer in a multi-institutional setting (RTOG 0225) [1•].

Larynx

In reviewing the benefit of IMRT with salivary gland function in patients with node-negative laryngeal cancer, Braaksma *et al.* [29] evaluated parotid gland sparing using three-dimensional conformal radiotherapy. IMRT treatment plans were generated for the 26 patients enrolled in this trial, and dose-volume histograms of three-dimensional conformal radiotherapy and IMRT were compared. Dose distributions of the major salivary glands were correlated with stimulated whole salivary flow and subjective assessment. The questionnaires reached their nadir at 3 months after radiotherapy, and the whole stimulated salivary flow reached its nadir 6 months after radiotherapy; therefore, the authors concluded that the three-dimensional conformal radiotherapy salivary gland–sparing technique is inadequate for fully preserving salivary gland function [29].

Conclusions

Emerging data indicate that IMRT and other new parotid-sparing techniques hold promise for the treatment of head and neck cancer, potentially offering reduced severity of xerostomia without compromised tumor control for appropriately selected patients [6•,30]. Target determination and delineation are paramount when using salivary gland–sparing techniques in IMRT [7]. The extent to which the clinical benefits of parotid gland sparing are detectable depends on the volume of salivary tissues receiving subthreshold doses. Phase III trials using RTOG guidelines to assess IMRT in multicenter approaches or in cooperative groups will further validate the acute and longitudinal effects on salivary gland toxicity.

Disclosures

Dr. Chambers has reported a financial interest/relationship with Daiichi Pharmaceutical Corporation and RxKinetix as an investigator. Dr. Garden has reported a financial interest/relationship with Daiichi Pharmaceutical Corporation as an investigator. Dr. Rosenthal has reported a financial interest/relationship with MGI Pharma, Inc. and MedImmune. Dr. Schwartz has reported research support from RxKinetix and Intrabiotics, and with the Advisory Board/Speakers Bureau at MedImmune. Dr. Weber has reported a financial interest/relationship with Daiichi Pharmaceutical Corporation as an investigator.

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- •• Of major importance

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Relationships between dose, volume, and function in the parotid glands are characterized by dose and volume thresholds, steep dose-response relationships when the thresholds are reached, and a maximal volume dependence parameter in the normal tissue complication probability model. A parotid gland mean dose of 26 Gy or less should be a planning goal if substantial sparing of the gland function is desired.

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