

Intensity-modulated Radiation Therapy and Xerostomia

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ABSTRACT

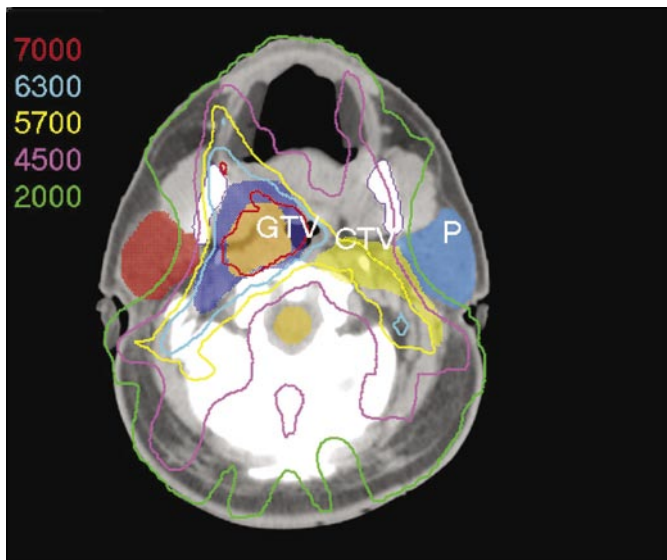
Conformal radiation with intensity-modulated radiation therapy, IMRT, is a radiation technique that potentially can minimize the dose to salivary glands and thereby decrease the incidence of xerostomia. Precise target determination and delineation is most important when using salivary gland-sparing techniques of IMRT. The reduction of xerostomia may be achieved by sparing the salivary glands on the noninvolved oral cavity and keeping the mean parotid gland dose of <26-30 Gy if the treatment of disease is not compromised and parotid function preservation is desired.

Intensity-modulated radiation therapy, IMRT, is commonly used in the treatment of head and neck cancers because of its effectiveness in reducing radiation exposure to major salivary glands, which can result in xerostomia.¹ With IMRT, dose distributions can be designed to conform specifically to a 3-D target, the advantages of which are improved radiation dose uniformity, creation of concave dose patterns exacting to the shape of the tumor, treatment of multiple targets simultaneously, and lowering complication rates.² Studies have shown that

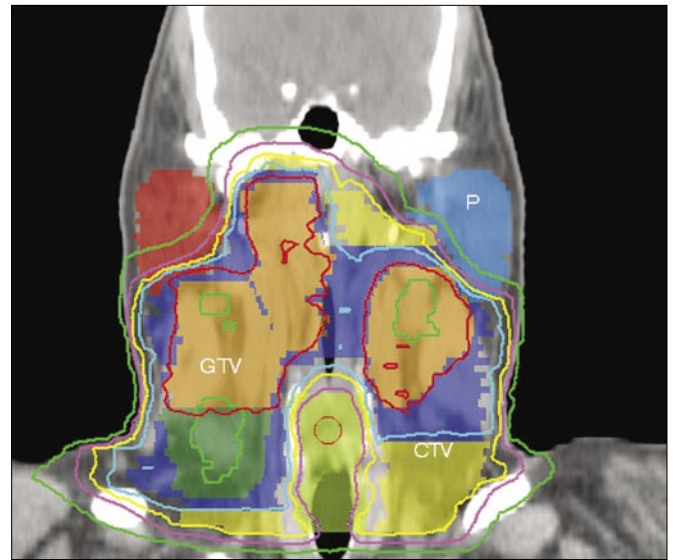


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1a.



1b.

Figures 1a and 1b. Example of parotid-sparing IMRT in a patient with advanced oropharyngeal cancer. In these axial (Figure 1a) and coronal (Figure 1b) sections (treatment planning CT scan) illustrating planned doses, the gross tumor volume (GTV) is 70 Gy and the clinical target volume (CTV) is 57-63 Gy, and the bulk of the superficial parotid (P) region is <20 Gy.

the tight, conformal radiation doses produced by IMRT and the absence of internal organ motion in the head and neck, substantially improve organ sparing and tumor control.^{3,4} As well, other studies have shown that IMRT is dosimetrically (prescribed dose of radiation to the tumor volume) superior to conventional treatment approaches.³⁻⁵ More recently, IMRT has been associated with improvements in tumor coverage, local-regional tumor control, and short-term toxicity in patients with head and neck cancers.⁶ However, there is limited data about the long-term therapeutic benefit and late radiation toxicity associated with IMRT.⁶ Several authors have reported a reduction of radiation-induced xerostomia following IMRT compared with conventional therapies.¹⁻⁷ In this article, the authors review current reports of salivary gland injury following IMRT for head and neck cancer.

Parotid Sparing

An effective way to diminish xerostomia is to spare one major gland from exposure to moderate- to high-dose radiation (Figures 1a and 1b). Traditionally, tonsillar carcinoma, even at an early stage, has been treated with bilateral therapy, which resulted in irradiation of all major glands. It was believed that early-stage carcinomas could be treated only to the involved side. Several large retrospective studies have subsequently demonstrated that ipsilateral radiation was safe. A study reported by O'Sullivan and colleagues described an ipsilateral radiation technique to restrict treatment to only the primary tumor and draining lymphatics of the neck on the same side as the tumor in patients with carcinoma of the tonsillar region.⁸ 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 seven years, the three-year actuarial local control rate was 77 percent and the cause-specific survival rate was 76 percent, with failure in the opposite side of the neck occurring in only eight patients.⁸ 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 computed tomography planning is necessary to ensure adequate target coverage.⁸ However, the authors did not assess for xerostomia, but rather assumed that its incidence would be reduced in this population with the more volume limited technique.

Reddy and colleagues compared the outcomes of patients with cancer of the oral cavity who were treated with a 2-D technique, sparing at least one parotid

gland (n=31) and a bilateral, opposed photon beam technique that included both parotid glands (n=83).⁹ Patients for whom the parotid-sparing technique was used were able to maintain nutritional intake and retained their baseline body weight during and after irradiation. However, those treated with the bilateral technique had poor nutritional intake and lost more than 10 percent of their baseline body weights, and these patients did not regain their body weights within the two years post-treatment.⁹ The primary tumor-control rates, with respect to tumor stage, for patients undergoing the parotid-sparing and bilateral techniques were similar (93 percent and 87 percent, respectively, for early-stage tumors; 42 percent and 36 percent, respectively, for advanced-stage tumors).

The authors noted that it was essential for the physician to consider the risk of contralateral cervical lymph node metastases when selecting patients for whom parotid sparing might provide benefit.⁹

While highly conformal techniques are being developed and used for patients requiring bilateral therapy of the head and neck, with very low doses delivered to the parotid glands, unilateral therapy appears to remain advantageous. Eisbruch and colleagues, comparing the outcomes of unilateral techniques and bilateral conformal techniques (including IMRT), demonstrated that unilateral therapy produced higher rates of salivary flow from the major contralateral glands.² In some cases of unilateral therapy, flow rates in the untreated gland were often higher than the pretreatment rates, suggesting a compensatory mechanism. Additionally, the mean radiation dose in the oral cavity correlated significantly with xerostomia scores, indicating that sparing the noninvolved oral cavity might facilitate further reduction of xerostomia.²

Parotid Doses and Xerostomia

One of the great challenges for radiation oncologists, who must treat all of the major glands, is understanding what dose limits exist to minimize xerostomia. Dreizen et al. in the 1970s, quantified saliva production in patients with head and neck cancer who were treated with radiation therapy.¹⁰ In this study, it was noted that after 10 Gy, patients already developed a 50 percent reduc-

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tion in salivary flow.¹⁰ Furthermore, after receiving 50 Gy, patients had less than 10 percent salivary flow remaining and few patients regained salivary function.¹⁰

In the 1980s, Marks et al. described decreased flow rates seen in the contralateral glands of patients treated with ipsilateral appositional electron beam fields due to the lower doses from the exit of the beam.¹¹ In these patients, the "untreated" gland was receiving <15 Gy. Emami et al. defined the tolerance dose (TD) of the saliva glands to radiation, stating the minimum TD 5/5 (tumor dose causing 5 percent complication rate at five years) as 30 Gy, and the TD 50/5 as 50 Gy.¹² Leslie and Dische described high rates of xerostomia in patients whose parotid glands received 40 Gy, but negligible rates in patients who received <14 Gy.¹³ Thus, the tolerance doses of the glands lies somewhere within this wide range.¹³

Investigators subsequently have tried to determine more precisely what this tolerance dose is through multicenter clinical research.

Part of the complexity of this task is to determine precisely where this dose lies, and to appropriately model this dose. The works of Dreizen and subsequently Leslie and Dische were relatively straightforward, as they made assumptions that the entire gland received the dose in question.^{10,13} However, the parotid gland is often thought to be a parallel organ. It consists of multiple functional subunits, with xerostomia (if using a strict categorical definition) occurring only when a sufficient number of units are destroyed. Not only is dose determination and its definition complex, but the definition of xerostomia is also not uniformly accepted. Thus studies may either use subjective scores, or attempt objective measures of salivary flow when assessing xerostomia. Even the latter is fraught with challenges, as many investigators rely on whole saliva, while others will cannulate the specific ducts to obtain clearer measures. Blanco et al. addressed these challenges by studying numerous complex dose-volume models.¹⁴ They concluded that a mean-dose model, which others had used for defining a tolerance dose, was predictive of xerostomia.¹⁴

Eisbruch and colleagues were the first to investigate the dose, volume, and functional relationships in parotid salivary glands following conformal and IMRT treatments for head and neck cancer.¹⁵ They examined 88 patients with head and neck cancer who were irradiated with parotid-sparing conformal and multisegmental IMRT.¹⁵ Unstimulated and stimulated saliva were measured from each parotid gland before radiation therapy (RT) and at 1, 3, 6, and 12 months post-RT. In glands receiving a mean dose below or equal to a thresh-



old less than 25 percent of pretreatment level (24 Gy for unstimulated and 26 Gy for stimulated saliva) demonstrated preservation of the flow rates post-RT and continued to improve over time.¹⁵ The glands that received doses below the threshold had functional recovery over time; whereas, glands receiving higher doses did not recover.^{7,15} Partial volume thresholds were found as well: 67 percent, 45 percent, and 24 percent gland volumes receiving more than 15 Gy, 30 Gy, and 45 Gy of radiation, respectively.¹⁵ Notably, salivary flow rates were not found to be affected by the patient's age, gender, pre-RT surgery, chemotherapy, and certain intercurrent illnesses. The conclusion of Eisbruch et al. was that a parotid gland mean dose of <26 Gy should be planned to substantially spare gland function and reduce overall xerostomia.^{5,15,16} By subjective assessment in Eisbruch's series it was demonstrated that xerostomia has been significantly reduced in patients treated with bilateral neck, parotid-sparing RT as compared to patients with similar disease treated with conventional RT.^{16,17} Twelve months following administration of post-parotid sparing IMRT, statistical significance (positive association) was found between patient-reported xerostomia and four domains of quality of life: eating, communication, pain, and emotion.¹⁷

Chao and colleagues, using mathematical modeling, concluded that the functional outcome of salivary flow using inverse-planning IMRT could be modeled as a function of dose; therefore, making the mean dose to each parotid gland a reasonable indicator for the functional outcome of each gland.¹⁸ The entire parotid volume was used to compute dose-volume histograms in this trial evaluating 41 patients with head and neck cancer. At six months, the stimulated salivary flow rate reduced

exponentially for each gland, independently, at a rate of approximately 4 percent per Gy of mean parotid dose.¹⁸ This work was further developed and reported by Blanco et al.¹⁴ After studying 65 patients, and evaluating six separate models, the mean-dose model remained predictive, thus, the researchers advocated its continued use. They also recommended keeping at least one parotid

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gland below 25.8 Gy; however, with the exponential improvement in flow rates (5 percent per 1 Gy), they suggested that even lower mean doses imply increased late salivary function.¹⁴

An additional finding made by both groups of investigators challenged the conventional wisdom that xerostomia was a permanent irreversible sequela of radiation. Eisbruch and colleagues assessed long-term xerostomia in 84 patients with head and neck cancer who had undergone comprehensive bilateral neck RT using conformal and multisegmental IMRT to spare major salivary glands.² Xerostomia was assessed using a validated eight-item xerostomia-specific questionnaire. The researchers observed that, with these parotid-sparing techniques, xerostomia improved over time (second-year post-RT), with rising salivary production from the spared major salivary glands; thus, a long-term clinical ben-

efit was achieved. This University of Michigan research group also studied the parotid salivary function up to 12 months post-RT in 20 patients receiving bilateral neck parotid-sparing RT to determine whether parotid preservation improved xerostomia-related quality of life.¹⁹ Salivary sampling and a 15-item xerostomia-related quality of life scale were completed by each patient. The salivary flow rate from spared and treated glands decreased significantly at the completion of RT. Post-RT unstimulated and stimulated function increased and did not differ significantly from baseline; therefore, the researchers concluded that with the use of parotid-sparing RT, contralateral glands are preserved at 12-months post-RT with parallel improvement in xerostomia-related quality of life.¹⁹ Similarly, Blanco et al. were able to measure stimulated whole saliva rates at six months (61 patients) and 12 months (31 patients), and demonstrated improvements in rates from six to 12 months after radiation.¹⁴

In a longitudinal trial, Munter and colleagues, using quantitative pertechnetate scintigraphy, evaluated salivary gland function following IMRT for head and neck cancer.²⁰ The mean dose to the primary planning target volume was 61.5 Gy and median follow-up was 23 months. In their study, it was concluded that it was possible to protect the parotid glands and reduce the incidence of xerostomia in head and neck cancer patients if mean parotid doses were <30 Gy.²⁰

Bussels et al. used salivary gland scintigraphy and single photon emission computed tomography in 16 patients treated with a conformal parotid-sparing technique.²¹ These researchers concluded that 22.5 Gy of RT resulted in a 50 percent loss of the excretion fraction of the functional subunit.²¹

Clinical Results of IMRT and Xerostomia

Further study by Chao and colleagues, compared the outcomes of conventional-beam RT and IMRT in patients treated for oropharyngeal cancer (n=430).²² Specifically, the acute toxicity, late toxicity, and tumor control associated with these treatments were retrospectively reviewed. The dosimetric advantage of IMRT resulted in a significant reduction of late salivary toxicity, with no adverse impact on tumor control or disease-free survival.^{22,23} After IMRT, only 17 percent to 30 percent of patients had late-grade 2 xerostomia (Common Terminology Criteria for Adverse Events v3.0: Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min).

Although the majority had moderate to severe dry mouth during therapy, the spared salivary glands showed recovery over time. Chao et al. also evaluated the dosimetric conformity of IMRT for normal tissue-sparing in patients with oropharyngeal cancer by assessing the therapeutic outcomes of IMRT treatment as it relates to the impact on gross tumor volume (GTV) and nodal gross tumor volume (nGTV).²⁴ The results of a multivariate analysis showed that GTV and nGTV were important independent risk factors predictive of therapeutic outcome for definitive therapy for patients undergoing IMRT for oropharyngeal cancer.²⁴

Recently, Eisbruch and colleagues conducted a longitudinal clinical trial in delineating the RT target volume in a parotid gland-sparing technique.²⁵ The researchers assessed patients treated with parotid-sparing IMRT for non-nasopharyngeal head and neck squamous cell carcinomas. Patients were assessed for the occurrence of local-regional failure near the base of skull and their relation-

ships to the target delineation in the high neck.²⁵ The results reported in this study confirmed defining level II delineation in the contralateral node-negative neck so that the targets would include the subdiaphragmatic nodes, and not defining them as cranial as in conventional RT, allowing for substantial sparing of the contralateral parotid glands; hence, reduced salivary dysfunction.²⁵

Although the majority had moderate to severe dry mouth during therapy, the spared salivary glands showed recovery over time.

Another study evaluating the RT 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 RT in order to reduce the toxic effects on major salivary gland tissue as proposed by Astreinidou et al.²⁶ Lowering 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.²⁶ Astreinidou reported a reduction of up to 68 percent in the normal tissue complication probability for xerostomia one year following RT (lowering the cranial border to C2) compared to conventional RT when treating C1.

Lee and colleagues analyzed the results of IMRT in the treatment of 67 patients with nasopharynx cancer.²⁷ Although the goal of the technique

was improved tumor coverage with delivery of high dosing to the target, it is notable that lower doses to the parotid glands were demonstrated, and a low incidence of RTOG grade 2 or greater xerostomia. At three months post-IMRT, 64 percent of the patients had RTOG grade 2; 28 percent had grade 1; and 8 percent had grade 0 xerostomia.²⁷ In agreement with previous studies, Lee showed that the incidence of xerostomia decreased over time.²⁷ Wolden et al. recently updated previously reported findings from a study in which patients with nasopharyngeal cancer (n=74) treated with IMRT at Memorial Sloan-Kettering Cancer Center were found to have low rates of xerostomia in 59 patients with >one-year follow-up.²⁸ The rates of xerostomia were as follows: 26 percent none; 42 percent grade 1; and 32 percent grade 2.²⁸ The Radiation Therapy Oncology Group, RTOG, is now testing IMRT for treatment of nasopharyngeal cancer in a multi-institutional setting (RTOG 0225).¹

Conclusions

IMRT and parotid-sparing techniques, in appropriately selected patients, hold promise for the treatment of head and neck cancer, potentially offering reduced severity of xerostomia without compromised tumor control.^{6,29} Target determination and delineation is most important when planning salivary gland-sparing techniques of 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 clinical trials using RTOG guidelines and assessing IMRT in multicenter approaches or in cooperative groups will further validate the acute and longitudinal effects on salivary gland toxicity and oral sequelae. ■■■■

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