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Clinical Investigation: Head and Neck Cancer

Reducing Xerostomia After Chemo-IMRT for Head-and-Neck Cancer: Beyond Sparing the Parotid Glands

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Summary

Xerostomia after chemotherapy plus intensity-modulated radiotherapy for head-and-neck cancer improves if, in addition to the parotid glands, the submandibular glands and oral cavity are spared.

Purpose: To assess whether, in addition to sparing the parotid glands (PGs), xerostomia after chemotherapy plus intensity-modulated radiotherapy (chemo-IMRT) for head-and-neck cancer is affected by reducing the dose to the other salivary glands.

Patients and Methods: In a prospective study, 78 patients with Stage III-IV oropharynx/nasopharynx cancer underwent chemo-IMRT, with the aim of sparing the parts of the bilateral PGs, oral cavity (OC) containing the minor salivary glands, and contralateral submandibular gland (SMG) outside the target (when contralateral level I was not a target). Before therapy and periodically for 24 months, validated patient-reported xerostomia questionnaire (XQ) scores and observer-graded xerostomia scores were recorded. Also, the stimulated and unstimulated saliva was measured selectively from each of the PGs and SMGs. The mean OC doses served as surrogates of minor salivary gland dysfunction. Regression models assessed the XQ and observer-graded xerostomia predictors.

Results: Statistically significant predictors of the XQ score on univariate analysis included the OC, PG, and SMG mean doses and the baseline XQ score, time since RT, and both stimulated and unstimulated PG saliva flow rates. Similar factors were statistically significant predictors of observer-graded xerostomia. The OC, PG, and SMG mean doses were moderately intercorrelated ($r = 0.47-0.55$). On multivariate analyses, after adjusting for the PG and SMG doses, the OC mean dose ($p < .0001$), interval from RT ($p < .0001$), and stimulated PG saliva ($p < .0025$) were significant predictors of the XQ scores and the OC mean dose and time for observer-graded xerostomia. Although scatter plots showed no thresholds, an OC mean dose of <40 Gy and contralateral SMG mean dose of <50 Gy were each associated with low patient-reported and observer-rated xerostomia at almost all post-therapy points.

Conclusion: The PG, SMG, and OC mean doses were significant predictors of both patient-reported and observer-rated xerostomia after chemo-IMRT, with OC doses remaining significant

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after adjusting for the PG and SMG doses. These results support efforts to spare all the salivary glands by IMRT, beyond the PGs alone. © 2012 Elsevier Inc.

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Introduction

Reducing xerostomia by sparing the parotid glands (PGs) has been the main rationale of intensity-modulated radiotherapy (IMRT) for head-and-neck cancer, improving xerostomia compared with conventional RT in randomized studies (1−3), with continuous improvement over time (4). However, these achievements are relatively modest. Although salivary output and observer-rated xerostomia such as the Radiation Therapy Oncology Group scale scores have consistently been significantly better using IMRT, a rate of post-IMRT Grade 2 or greater xerostomia as high as 40% at 12 months, reported in one of the randomized studies (3), is typical. It has been even harder to demonstrate significant improvements in patient-reported xerostomia. Kam *et al.* (1) reported no advantage of IMRT compared with two-dimensional RT in patient-reported xerostomia, and Nutting *et al.* (3) reported that the advantage through 12 months after therapy was <10 points on a 0−100 scale, regarded as a less than clinically relevant difference. Thus, IMRT, aiming to spare only the PGs, achieves partial gains in observer-rated, and even smaller gains in patient-reported, xerostomia.

We have previously hypothesized that in addition to sparing the PGs, whose secretions are serous and constitute most of the saliva produced during eating, there is potential benefit in sparing the minor salivary glands and the submandibular/sublingual glands (SMGs). The SMGs, in addition to their important mucinous secretions, are the dominant nonstimulated saliva producers (4). Our previous analysis of the predictors of xerostomia, in a very heterogeneous patient cohort undergoing IMRT or three-dimensional RT, showed that the mean doses delivered to the PGs and SMGs, as well as the doses delivered to the oral cavity (OC), where the minor glands are dispersed, were all statistically significant predictors of patient-reported xerostomia (4). Because of these findings, we have routinely included sparing of the noninvolved OC in the IMRT plans. In addition, after assessing the relationships between the doses to the SMGs and their post-therapy salivary output, we have used these relationships to set the IMRT cost functions for sparing these glands when neck level I was not considered at risk (5).

We have recently assessed prospectively the predictors of xerostomia in patients with Stage III-IV oropharyngeal/nasopharyngeal cancer treated with chemotherapy plus IMRT (chemo-IMRT) in whom the planning goals included sparing parts of all the salivary glands outside the targets. We sought to determine how the xerostomia predictors in these patients differed from those found in our previous study, whose goal was sparing of the contralateral PGs only. Also, although ample data exist regarding the relationships between the PG dose and patient-reported or observer-rated xerostomia (6), very little is known about such dose−effect relationships for the other salivary glands. These potential relationships are presented in this report.

Patients and Methods

The present study was a prospective longitudinal study of IMRT concurrent with chemotherapy for head-and-neck cancer. The institutional review board of the University of Michigan approved the study, and all patients signed study-specific informed consent forms. Eligibility included Stage III-IV squamous cell carcinoma of the oropharynx or nasopharynx requiring bilateral neck treatment, no previous therapy, Karnofsky performance status of ≥ 60, and primary therapy with chemo-RT. The study assessed sparing the swallowing structures, reported elsewhere (7), and sparing the salivary glands. The details of the therapy have been previously published (7). In brief, all patients required treatment of the bilateral neck. The IMRT planning objectives included dosimetric sparing of the parts of the bilateral PGs, contralateral SMGs, and OC that were outside the target. The OC was defined schematically as the surface of the inner lips, buccal mucosa, tongue, base of tongue, floor of mouth, and palate, representing the sites of the minor salivary glands, as reported previously (4). Early in the study, the contralateral SMGs in the cases in which the contralateral level Ib was outside the targets were assigned low weights in the optimization cost function, striving to reduce their mean dose as much as possible (ipsilateral level Ib was a target in all patients). After establishing the dose−response relationships for SMG saliva output, the cost function for these glands was changed to achieve a mean dose of <39 Gy, and its weight was increased, as previously reported (5). Similar cost functions were set to achieve a mean PG dose of <26 Gy bilaterally and a mean OC dose as low as possible. The cost functions for sparing the salivary glands had lower weights than the target doses.

The PG mean dose was calculated as a volume-weighted average of both PGs. Only the contralateral SMG was considered in the analysis, because in all patients, the ipsilateral SMGs resided within the targets, received high doses, and were not expected to produce any saliva. The mean doses were calculated for the whole organs, including the parts overlapping with the targets, and optimization was aimed only at the parts of the organs outside the targets.

The clinical target volumes were each expanded uniformly by 3 mm to yield the planning target volumes (PTVs); 70 Gy was prescribed to PTV1 and 63−56 Gy to PTV2/PTV3, all in 35 fractions. Achieving adequate target doses superseded sparing of any organ, except for the spinal cord. On-line imaging and correction before each treatment were done to ensure a correct setup.

Concurrent carboplatin (area under the curve, 1) and paclitaxel 30 mg/m^2 once weekly were delivered to the oropharyngeal cancer patients and cisplatin 100 mg/m^2 every 3 weeks to the nasopharyngeal cancer patients. No salivary protectors or stimulants were allowed during therapy or the 2-year study follow-up period.

Xerostomia assessment

The patients completed a previously validated, xerostomia-specific questionnaire (XQ), detailed elsewhere (4). In brief, the questionnaire consisted of four items asking about dryness while eating/speaking and four items about dryness while not eating. The subjects rated each symptom on an 11-point ordinal Likert