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Parotid Glands Dose-Effect Relationships Based on Their Actually Delivered Doses: Implications for Adaptive Re-Planning in Radiotherapy of Head and Neck Cancer

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Abstract

Purpose—Doses actually delivered to the parotid glands during radiotherapy often exceed planned doses. We hypothesized that the delivered doses correlate better with parotid salivary output than the planned doses, used in all previous studies, and that determining these correlations will help decisions regarding adaptive re-planning (ART) aimed at reducing the delivered doses.

Methods and Materials—Prospective study: oropharyngeal cancer patients treated definitively with chemo-irradiation underwent daily cone beam CT (CBCT) with clinical set-up alignment based on C2 posterior edge. Parotid glands in the CBCTs were aligned by deformable registration to calculate cumulative delivered doses. Stimulated salivary flow rates were measured separately from each parotid gland pretherapy and periodically posttherapy.

Results—36 parotid glands of 18 patients were analyzed. Average mean planned doses was 32 Gy and differences from planned to delivered mean gland doses were −4.9 to +8.4 Gy, median difference +2.2 Gy in glands whose delivered doses increased relative to planned. Both planned and delivered mean doses were significantly correlated with post-treatment salivary outputs at almost all post-therapy time points, without statistically significant differences in the correlations. Large dispersions [on average, standard deviation (SD) 3.6 Gy] characterized the dose/effect relationships for both. The differences between the cumulative delivered doses and planned doses were evident already at first fraction ($r=0.92$, $p<0.0001$) due to complex set-up deviations, e.g. rotations and neck articulations, uncorrected by the translational clinical alignments.

Conclusions—After daily translational set-up corrections, differences between planned and delivered doses in most glands were small relative to the SDs of the dose/saliva data, suggesting that ART is not likely to gain measurable salivary output improvement in most cases. These differences were observed already at first treatment, indicating potential benefit for more complex

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set-up corrections or adaptive interventions in the minority of patients with large deviations detected very early by CBCT.

Keywords

parotid; head neck cancer; IMRT; IGRT; Adaptive radiotherapy

Introduction

Head and neck cancer patients often undergo significant anatomical changes during the course of therapy due to tumor response and weight loss. Several publications showed a decrease in parotid salivary gland volume and medial displacement during the course of therapy [1-3], associated with increases of the delivered compared with the planned mean parotid doses [3-6]. The changes in the doses to target and organs at risk, especially the parotid glands, prompted recent investigations in adaptive re-planning (ART) during therapy to restore the delivered to the originally planned doses [6-10], including pilot studies describing the clinical outcome of patients treated with an adaptive process [8, 9]. No previous study attempted to measure the potential effect on clinical outcomes of the dosimetric differences between the planned and the actually delivered organ doses.

We hypothesized that the correlation between the post-therapy parotid gland salivary output and the actually delivered mean parotid gland dose would be higher than its correlation with the planned doses. This would explain the large variety in the published dose-effect relationships for the gland, and the relatively large dispersion of the dose-effect data points characteristic of these studies, all of which relied on the simulation CT scans-based planned mean doses [11-14]. Moreover, recommendations regarding re-planning to improve parotid gland doses have thus far been made based on the dosimetric differences between the planned and the delivered doses, without evidence as to how these dosimetric differences may affect post-therapy salivary output. Determining dose-effect relationships based on the actually delivered doses would facilitate a more realistic prediction of parotid gland function after therapy, and help decision-making regarding re-planning during therapy.

To test these hypotheses we prospectively studied the planned and the accumulated actually delivered mean parotid gland doses in oropharyngeal cancer patients and measured the pre-therapy and periodic post-therapy selective salivary output from each of their parotid glands. We have also examined how we might determine early-on which patients could benefit from re-planning.

Materials and Methods

36 parotid glands were studied in 18 patients with biopsy-proven stage III-IV oropharyngeal cancer treated between 2009 - 2011 with definitive chemoradiation in a prospective study. The study was approved by the local Institutional Review Board and all patients signed an informed consent. Patients were immobilized by a head rest and thermoplastic mask bolted at 5 points to the couch, including the shoulders, and underwent simulation CT scan with IV contrast. Radiation was planned and delivered using IMRT with a prescription dose of 70Gy to the gross primary tumor and involved lymph nodes, 59 Gy to high risk nodal regions and the anatomical compartments around the gross tumor volumes, and 56 Gy to low risk nodal regions, all in 35 fractions. Targets were expanded uniformly by 0.3 cm to obtain planning target volumes (PTVs). Priority was given during planning to spare the major salivary glands, non-involved oral cavity, pharyngeal constrictor muscles, larynx, and esophagus, to minimize toxicity. The full extent of the parotid glands was outlined for dose calculations while only the parts outside the PTVs were taken into account for IMRT optimization. All

patients received weekly chemotherapy with carboplatin ($AUC=1$) and paclitaxel ($30\text{mg}/\text{m}^2$) concurrent with RT. Patients were weighed before and weekly during therapy. Patients underwent daily kilovoltage cone-beam CT (CBCT) scans on the treatment machine immediately prior to each treatment delivery. The CBCT scans were used clinically to align the patients to the second cervical vertebral body (C2) with translational corrections triggered by 3 mm set-up difference at any axis.

The planned radiation doses were derived from the clinical treatment plan calculated on the simulation CT scan. The delivered radiation doses were estimated using the patient's daily CBCT scans and an in-house dose-to-date (DTD) infrastructure. Each analyzed weekly CBCT scan was aligned with the simulation CT scan by translational alignment to match the posterior aspect of the body of C2 to reflect the treated configuration of the patient for the given fraction. The planning CT and translated CBCT images were then registered using an in-house deformable registration program based on B-spline coefficients, optimized on passes through multiple resolutions, and using mutual information as a cost function as previously detailed [15-16]. Verification of the registration was performed by transforming the parotid gland surfaces back from the deformed version of the simulation CT to the original CBCT, and verifying qualitatively (by the participating radiation oncologists) the accuracy of gland overlap. If verification found a mis-match of 2 mm or more, registration was repeated until found satisfactory. The deformation map from this registration was used to generate a deformed version of the simulation CT based on the anatomical configuration of the associated CBCT (to provide a complete electron density map for dose calculation at the time of treatment).

The delivered dose was calculated on each of these generated scans and summed over multiple treatment fractions using DTD. The cumulative delivered dose over the entire treatment course was estimated from the sum of the seven weekly CBCT scans. The targets and organs at risk were mapped onto the final scan (generated CT scan based on the CBCT scan from the last day of treatment) by using a deformation vector field from registration between the 35th CBCT scan and the simulation CT scan. Delivered doses were then evaluated on this scan using the accumulated dose information from the intermediary weekly scans.

Stimulated saliva measurements were performed pretreatment and at 3, 6, 12, 18, and 24 months post-treatment. Separate measurements from each parotid gland used Leshley suction cups attached to the mucosa around the opening of each Stensen's duct orifice, as previously detailed, with stimulated saliva measured after applying 2% citric acid to the dorsum of the tongue followed by a two-minute collection period during which gustatory stimulation was maintained, as previously detailed [12,17]. No patient received radiation protectors or prescribed salivary stimulants during therapy or during the 2-year study follow-up period.

Statistical analysis

At each time point Spearman rank based correlation coefficients were calculated for the association between saliva flow rate and the planned (delivered) mean parotid doses, denoted as $r_1(r_2)$. To test if there is difference between the two correlations (i.e. $r_1 - r_2$) the standard error of the difference was calculated using the bootstrap method. The null hypothesis was that the correlations between saliva and either of the mean gland doses (planned or actually delivered) were the same; hence every bootstrap sample of doses was drawn from the combined values of both the doses with replacement. The correlation between saliva output and these bootstrapped samples was estimated and the difference of these correlations was noted. This process was repeated 2000 times and the standard error for all these differences was used in testing the above hypothesis.

Based on the plots of the saliva flow rate and the two doses (planned and delivered) it was noticed that the variability about the mean was proportional to the mean. An exponential model was used to model the mean of the saliva flow as a function of planned dose as follows, Expected saliva flow (mean) = $\exp(\beta_0 + \beta_1 \text{planned dose})$. A Normal distribution was used to model the variance as a function of this mean (i.e. Variance (saliva flow) = $\text{mean}^2 \cdot \sigma^2$). The same was repeated for the actual dose at each of the time points. All analysis was done using SAS and R statistical software.

Results

Thirty-six parotid glands were evaluable from 18 patients at baseline, 34 at 3-6 months and 32 at 12 months. Patient characteristics as well as weight and parotid gland volume changes during treatment are detailed in Table 1.

The median of the mean planned parotid doses was 31.9 Gy (range 24.5-61.7; median 28 Gy to contralateral and 38 Gy to ipsilateral glands) and the median of the mean delivered parotid doses was 32.4Gy (range 23.2-63.2). The median delivered mean parotid dose increased by 0.92 Gy (range -4.9 Gy to +8.4 Gy) over the median planned mean dose. The dose change for each gland is shown in Figure 1. Twenty-three glands had an increase in mean delivered total parotid mean dose compared to the planned mean dose (median increase 2.2 Gy, range 0.4-8.4 Gy), of which four had an increase of ≥ 4 Gy. Eleven glands had a decrease (median decrease 2.0 Gy, range 0.6-4.9 Gy), and two glands were unchanged (change ≤ 0.1 Gy). In nearly all cases where cumulative delivered mean parotid dose decreased compared to the planned dose, the other parotid gland in the same patient showed an increase compared with the planned dose.

Stimulated selective parotid salivary flow rates before and after therapy are detailed in Table 2. Both mean planned parotid gland doses and accumulated delivered mean parotid doses were statistically significantly (negatively) correlated with the selective parotid salivary output at almost all post-therapy time point (Table 3). The mean decreases in parotid salivary flow per unit of dose increase (Gy) based on the planned or the delivered parotid mean doses were best modeled as exponential relationships and are shown in Fig 2. Analysis comparing the abilities of the planned or the delivered doses to predict the post-therapy salivary output did not show any statistically significant differences between their correlation coefficients (Table 3 and On-line Appendix Table 1) or in the percent decrease per Gy in the salivary output (Fig 2) at any time point. Furthermore, no statistically significant differences were noted for the 23 glands whose delivered doses increased (by median 2.2 Gy) compared with planned doses.

Large dispersion was noted in the dose/saliva data points at each mean dose level (Fig 2), manifested as relatively large standard deviations (SDs). At 3, 6, and 12 months, the average of the mean doses causing 50% reduction in salivary output from pre-therapy (TD_{50}) and their SDs were, for the planned doses, 31(3.1), 34.5 (2.1), and 35 (2.7) Gy, respectively, and for the delivered doses, 32 (4.8), 35 (2.4), and 39 (6.4) Gy, respectively. These SDs (on average, 3.6 Gy) were larger than the differences between the delivered and the planned doses in most individual glands (28/36; 78%) (Fig 1).

The clinical factors listed in Table 1, including weight loss during therapy and multiple dosimetric variables, were not statistically significantly predictive of the changes from planned to delivered doses. The only factor found to be statistically significant predictor of the differences from total planned to total delivered doses was the difference between the delivered dose and the planned dose in the first treatment fraction ($r=0.92$, $p<0.001$), with all glands receiving excess cumulative delivered doses ≥ 4 Gy compared with the cumulative

planned doses demonstrating excess dose on Day 1 = 0.1 Gy (Figure 3). The differences in the cumulative delivered versus the planned gland doses were in part due to complex set-up deviations, such as head rotations, which were not addressed by the daily translational set-up corrections. These deviations from the planning CT were observed already on the Day 1 CBCT (Fig 1, on-line Appendix).

Discussion

In this study, the first to correlate the actually delivered parotid gland doses with their salivary output, the major findings were that contrary to our initial hypothesis, no statistically significant differences were observed in the ability of the planned or the actually delivered mean parotid gland doses to predict post-therapy salivary output, and that using actually delivered doses did not reduce the dispersion of the dose-saliva data points compared to using the planned doses. Another notable finding was that the differences in the total planned versus delivered doses could be predicted already from the first fraction of treatment. These findings are relevant for decisions as to whether or not adaptive re-planning, or other corrections, should be done during therapy to offset an increase in parotid gland doses, and what may be the best timing for such corrections.

The lack of superiority of the delivered doses in modeling parotid salivary output compared with the planned doses can be explained by these data. At a median difference of 0.9 Gy between the planned and the actually delivered doses for all glands, and even the median difference of 2.2 Gy in the 23 glands whose delivered doses increased relative to the planned doses, these differences were not large enough to affect the dose-response relationships, due to the substantial dispersion of the salivary output values at each mean dose level for both planned and delivered doses. This dispersion is demonstrated in Fig 2 and is manifested in relatively high SDs for both planned and delivered dose vs. saliva data. At an average SD of 3.6 Gy, it is unlikely that smaller differences between planned and delivered doses would result in better modeling of the dose-saliva data. More importantly, it is unlikely that improving the mean parotid doses by less than these SDs (the “noise” in the data) would result in a measurable improvement in the salivary output. Thus, these data suggest that adaptive re-planning for the sake of overcoming the rise in parotid gland doses during therapy may only be justified in the minority of patients whose cumulative delivered mean dose is expected to rise substantially, more than the SD in the dose-effect data (e.g. 4 Gy), compared with the planned mean dose. Moreover, the relationship between parotid salivary output and patient-reported xerostomia is not strong, as xerostomia is also dependent on submandibular and minor salivary gland function [17,18], suggesting that gains in symptoms would be even less likely following small improvements in parotid gland doses.

Similar dispersion of the dose-response data points was found in our and others’ previous, larger studies of dose-effect relationships for the parotid glands based on the planned doses and selective measurements of parotid gland salivary flows [12-14, 17]. Similar wide dispersion also characterizes other methods measuring salivary gland function, including whole mouth saliva [19], selective submandibular gland saliva [20], or parotid gland scintigraphy [21], with SDs approximating 4 Gy based on provided confidence intervals, similar to the SDs found in our study [14, 19-21]. The current study shows that the dispersion of the dose/saliva data points using the actually delivered doses is no less than the dispersion observed in all previous studies which relied on the planned doses. This “noise” in the data relates to several factors which are not diminished by using the actually delivered doses. There are uncertainties in the measurements of the salivary output related to its diurnal variation and other factors that are only partly addressed by standardization of measurements [12]. Importantly, factors besides doses, such as age, hydration status, medications affecting salivary output, and others, confound strict dose-effect relationships

[18]. Also, some uncertainties in estimating the delivered doses, due to uncertainties in estimates of the deformation aligning the daily CBCT image with the planning CT, likely existed in our as well as other studies of delivered doses [15, 16]. Additional limitations in our, as well as other related studies, include using weekly rather than daily CBCTs, and parotid contouring reproducibility uncertainties (22).

Daily set-up imaging and on-line position correction, performed routinely at our department and in this study, was reported to reduce delivered parotid doses by a median of 2 Gy compared to less frequent imaging [4]. However, an increase in the delivered compared with the planned parotid doses has still been observed, by a median of 1-2 Gy in our study and in O'Daniel et al [4]. Using ART, Schwartz et al reported further improvements in parotid mean doses beyond those gained by daily imaging and set-up corrections: a single mid-course ART achieved average reductions of 0.6 Gy and 1.3 Gy in the contralateral and ipsilateral parotid glands, respectively, and two re-plans reduced by 1.3 Gy and 4.1 Gy, respectively [8]. Only the latter improvement would be expected to result in measurable difference in the salivary output, taking into account the results of the present study. Castadot et al found on average no difference between the cumulated parotid mean doses and the doses expected to be achieved by re-planning, indicating that only selected patients, those with large GTVs and significant tumor shrinkage during RT, could benefit from an adaptive strategy [10]. An even further improvement in parotid mean delivered doses compared to the planned doses may be achieved if ART fully addresses all set-up uncertainties and obviates the need for PTV expansions, suggested by some [6-9]. For example, Wu et al suggested combined benefit of 10% in mean doses if at mid-course PTV margins are reduced from 3 to 0 mm and one re-planning is performed, translating to a mean dose reduction of 2-4 Gy [6]. However, whether or not all set-up errors are indeed eliminated by ART requires further clinical validation. We were unable to find any clinical or pre-treatment dosimetric factor that predicted which patients were at highest risk for large changes from planned to delivered parotid doses, likely due to small patient number. We postulate that dose changes during treatment result from a combination of anatomic changes and complex set-up variations, including rotations, which were not corrected by our translational alignment for treatment. Notably, head and neck rotations explain the fact that in all patients with decreased parotid doses, the contralateral parotid had increased doses. Detailed examination of the exact nature of these complex set-up deviations will be the subject of a separate study. Importantly, the trend for change in delivered doses relative to the planned doses was already observed in the first treatment fraction. If reproduced by others, this provides an avenue for prompt correction in patients whose CBCT on the first treatment day shows a dose deviation predicting a large eventual deviation in cumulated delivered dose. Such correction may be performed when a substantial rotational set-up error is detected, by using a couch which facilitates rotational errors corrections [23], or by re-planning.

In conclusion, this study demonstrates that the wide dispersion in the dose/effect data points for the parotid glands, noted for the planned doses, are also noted for the actually delivered doses, with SDs on average near 4 Gy. It suggests that reducing mean parotid doses by smaller amounts using ART is unlikely to result in a measurable improvement in salivary output. These results also suggest that deviations in the total delivered parotid doses from the planned doses may be predicted from deviations noted in the first fraction, implying that corrective measures can be implemented very early in the course of therapy if a large cumulated deviation is predicted. These findings need to be validated by additional, independent studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Relationships between delivered parotid mean doses and their salivary output were statistically significant but with large dispersion of the data points, suggesting that small adaptive improvements are not likely to yield measurable salivary output improvement. Determinants of the differences between planned and actually delivered doses included complex set-up deviations detected very early in treatment.

Figure 1.
Difference between Planned and Delivered Mean Parotid Dose for Each Patient.

Figure 2. Relationship of Planned or Delivered Parotid Doses with 6 and 12 months A. Salivary Parotid Output (upper 2 panels) and B. % baseline output (lower panels).

Figure 3.
Plot of the difference (Gy) between planned and delivered doses over the entire treatment versus the difference between planned and delivered doses on first treatment day.

Table 1

Patient Characteristics

	Demographic
Age	Median 57 years (range 50-76 years)
Sex	Male: 16 patients (89%) Female: 2 patients (11%)
Disease Site	Base of Tongue: 9 patients (50%) Tonsil: 9 patients (50%)
T Stage	T1: 2 patients (11%) T2: 10 patients (56%) T3: 5 patients (28%) T4: 1 patient (6%)
N Stage	N0: 1 patient (6%) N1: 0 N2a: 1 patient (6%) N2b: 10 patients (56%) N2c: 4 patients (22%) N3: 2 patients (11%)
Pre-treatment Weight	Median 203lbs (range 105-308 lbs)
Weight Change During Treatment	Median 13 lbs lost (range -41 to +2 lbs)
% Weight Change During Treatment	Median 6.5% lost (range -18.7% to +1.9%)
Pre-treatment Parotid Volume	Median 32.3 cc (range 17.2-57.5 cc)
Change in Parotid Volume During Therapy	Median -4.3cc (range +2 to -16.8 cc)
Smoking Status	Current Smoker: 3 patients (17%) Former Smoker: 11 patients (61%) Never Smoker: 4 patients (22%)

Table 2

Stimulated Selective Parotid Gland Salivary Output (flow rates: cc/min)

Time Point	Mean (STD)	Median (Range)	Number of Glands
Baseline	0.41 (0.438)	0.30 (0-2.0)	36
3 months	0.19 (0.339)	0.04 (0-1.46)	34
6 months	0.22 (0.361)	0.05 (0-1.56)	34
12 months	0.16 (0.165)	0.15 (0-0.54)	32
18 months	0.22 (0.323)	0.08 (0-1.33)	20
24 months	0.17 (0.159)	0.15 (0-0.42)	8

Table 3

Correlation Between Parotid Mean Doses and the Salivary Output at each time point. The P values tested whether the correlation for each measurement at each time point was statistically significant.

Time Point	Planned Mean Parotid	Delivered Mean Parotid	Number of parotid glands with saliva data
	Dose: Correlation	Dose: Correlation	
	Coefficients (p-values)	Coefficients (p-values)	
Baseline	−0.23 (0.18)	−0.26 (0.12)	36
3 months	−0.30 (0.08)	−0.42 (0.01)	34
6 months	−0.55 (0.0007)	−0.57 (0.0004)	34
12 months	−0.39 (0.03)	−0.35 (0.05)	32
18 months	−0.52 (0.02)	−0.42 (0.06)	20
24 months	−0.86 (0.007)	−0.60 (0.12)	8