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Early changes in serial CBCT-measured parotid gland biomarkers predict chronic xerostomia after head and neck radiotherapy

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Abstract

Purpose—To determine whether serial cone-beam computed tomography (CBCT) images taken during head and neck radiotherapy (HNR) can improve chronic xerostomia prediction

Methods and Materials—In a retrospective analysis, parotid glands (PGs) were delineated on daily kV CBCT images using deformable image registration (DIR) for 119 HNR patients (60 or 70 Gy in 2 Gy/fraction over 6 or 7 weeks). DIR accuracy for a subset of deformed contours was quantified using the Dice similarity coefficient (DSC) and mean distance-to-agreement (MDA) in comparison to manually drawn contours. Average weekly changes in CBCT-measured mean HU intensity and volume were calculated for each PG relative to week 1. Dose-volume-histogram (DVH) statistics were extracted from each plan, and interactions between dose, volume, and intensity were investigated. Univariable analysis and penalized logistic regression were used to analyze association with observer-rated xerostomia at one year following HNR. Models including CBCT delta imaging features were compared to clinical/DVH-only models using area under the receiver-operating characteristic curve (AUC) for Grade 1 or higher (Grade 1) and for Grade 2 or higher (Grade 2) xerostomia prediction.

Results—All patients experienced end-treatment PG volume reduction with mean (range) ipsilateral and contralateral PG shrinkage of 19.6% (0.9–58.4%) and 17.7% (4.4–56.3%), respectively. Mid-treatment volume change was highly correlated with mean PG dose ($r = -0.318$, $p < 1e-6$). Incidence of Grade 1 and Grade 2 xerostomia was 65% and 16%, respectively. For Grade 1 xerostomia prediction, the delta-imaging model had AUC = 0.719 (95% CI: 0.603–0.830), compared to 0.709 (95% CI: 0.603–0.815) for the dose/clinical model. For Grade 2 xerostomia prediction, the dose/clinical model had AUC = 0.692 (95% CI: 0.615–0.770), and the addition of contralateral PG changes modestly improved predictive performance with AUC = 0.776 (0.643–0.912).

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Conclusions—The rate of CBCT-measured PG image feature changes improves prediction for chronic xerostomia prediction over dose alone. Analysis of CBCT images acquired for treatment positioning may provide an inexpensive monitoring system to support toxicity-reducing adaptive radiotherapy.

Keywords

CBCT; dose response; adaptive radiotherapy; xerostomia prediction

1. Introduction

Xerostomia is a frequent complication following head and neck cancer (HNC) radiotherapy, affecting between 60-90% of patients (1, 2), and can significantly impact long-term quality of life (3, 4). Substantial technical advancements in radiation delivery, such as intensity modulated radiotherapy (IMRT), have lowered the risk of xerostomia by limiting dose to the salivary glands without compromising treatment efficacy (5–7). Despite such advancements, persistent elevated rates of radiation-induced toxicities, often exacerbated by the use of concurrent systemic therapies, have motivated radiotherapy dose de-intensification regimens in specific HNC patient cohorts (8, 9). As treatment regimens become more personalized, it becomes more important to form accurate risk assessments. Additionally, with the establishment of novel streamlined radiotherapy planning and delivery modalities (10–12), the ability to adapt treatments based on physiological changes during the course of treatment is now practical (13, 14). However, existing normal-tissue complication probability (NTCP) models are based on planned biological dose-volume characteristics, which do not adequately address inter-patient or intra-treatment variation.

Advanced imaging techniques, such as diffusion-weighted magnetic resonance (MR) imaging, have demonstrated the ability to non-invasively characterize parotid glands (PGs) before and after radiotherapy, and correlation with physiological function as been shown (15). MR sialography has also been used to directly visualize radiation injury for quantitative xerostomia severity prediction (16). While these studies demonstrate that physiological changes to PGs can be visualized and are important for xerostomia prediction, the clinical utility of such imaging is limited. Specifically, the ideal imaging frequency during the course of radiotherapy has not been established and it is unlikely to be feasible in the general clinical setting, where access to MR scanners remains scarce.

Conversely, conventional imaging techniques such as computed tomography (CT) and ultrasound have also been shown to provide a physiological assessment of PG changes during radiotherapy (17–21). Using serial CT imaging, Feng et al. (22) and Barker et al. (23) independently showed that Hounsfield unit (HU) changes occur in gross tumor volumes (GTVs) and PGs during the course of radiotherapy. Using weekly diagnostic CT, Belli et al. (24) showed that the rates of PG density and volume change (reduction in both) were correlated with acute onset xerostomia. Further, they showed that these changes occurred early into treatment, which presents an opportunity for adaptive radiotherapy. van Dijk et al. (25) showed that PG surface area changes imaged using diagnostic CT before and 6 weeks following radiotherapy were predictive of chronic xerostomia. Fiorino et al. (26)

demonstrated a significant decrease in parotid gland density (mean 5.6 HU loss) for a majority of patients. It was hypothesized that these changes are a result of acinar cell loss with a replacement of fatty tissue components, leading to average density reduction (24, 26). Still, the addition of extra imaging sessions is not ideal, as it adds cost and time to patient treatments, and the optimal imaging frequency is unknown (i.e., whether the rate of PG change is essential for accurate prediction). Since daily on-board kV cone-beam CT (CBCT) is routinely used for HNC-IMRT patient alignment (27–29), we sought to investigate whether serial CBCT imaging could provide an accurate measure of dose response and improve chronic xerostomia prediction over dose-only models. The primary aims of this study are to 1) assess whether previously shown radiation-induced volume and HU changes can be reproduced using CBCT imaging and 2) whether these features can add value to existing clinical factors for long-term xerostomia prediction. A CBCT-based assessment of dynamic radiation-induced changes is readily implementable and offers a straightforward scheme for adaptive radiotherapy in a wide range of clinical settings, with minimal extra cost. If shown feasible, the use of CBCT for frequent assessment of radiation-induced changes may be possible in a variety of body locations.

2. Materials and Methods

2. A. Patients

This study was approved by an institutional review board (IRB# HUM00119720). Of 128 patients considered, the analyzed cohort consisted of 119 patients treated with HNC volumetric modulated arc therapy (VMAT) with daily CBCT imaging between July 2013 and July 2016. Exclusion criteria included patients who received prior radiotherapy to the head or neck (N=3), the non-availability of CBCT imaging over the full treatment course (N=2), or patients for whom at least 50% of either PG was outside the CBCT field-of-view (N=4). For xerostomia outcome modeling, inclusion criteria further required a record of a follow-up visit within one month of the one-year anniversary of radiotherapy completion, during which salivary function was prospectively graded by the treating physician according to RTOG criteria. The resulting cohort of 105 patients was analyzed.

2. B. Imaging and treatment protocol

Planning CT (pCT) images were acquired using a CT simulator (Big Bore Brilliance 16-slice, Phillips Healthcare Co., Andover, MA). Normal tissue structures contoured for treatment planning, including the right and left PGs, were retrospectively analyzed. All contours and plans were reviewed by a radiation oncologist with over 25 years' experience treating HNCs with radiotherapy (AE). The right and left PG dose-volume histograms (DVHs) were extracted from each patient's 6MV VMAT plan totaling 60 Gy or 70 Gy in 2 Gy fractions over 6 or 7 weeks. Inverse planning objective functions included a mean dose of <22 Gy for each PG. Plan preparation was performed using a commercial treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA), and patients were treated on one of three institutional linear accelerators (C-Series, Varian Medical Systems, Palo Alto, CA) with on-board kV imaging systems (OBI). Daily CBCT images were taken using the Standard Dose Head protocol (100 kV and 20 mA tube current in full-fan mode). All CBCT images had in-plane voxel resolution of 0.65×0.65 mm and 1 mm or 2.5 mm

slice thickness. Patients were aligned using on-board co-registration of the planning CT and kV CBCT images. All CBCT images had been transferred to our ARIA oncology information system (Varian Medical Systems, Palo Alto, CA), where they were subsequently processed and analyzed for the purposes of this work.

2. C. CBCT Quality Assurance and Stability

Institutional QA procedures for ensuring Hounsfield unit (HU) constancy, uniformity, and noise were based on AAPM TG-142 (30) and AAPM TG-179 (31) guidelines and implemented over the time of the cohort's treatments. Specifically, CT imaging quality assurance phantoms (CatPhan, The Phantom Laboratory, Salem, NY) were regularly scanned to ensure that HU measurements of known materials were consistent within manufacturer recommendations. In addition, daily CBCT alignment accuracy was verified by a qualified medical physicist each day a machine was used for patient treatments requiring CBCT imaging. Since the primary intent of these QA procedures is verification of positional accuracy, versus quantitative CT number measurements, the daily CBCT HU measurement reproducibility was further studied. For this purpose, daily CBCT images of an acrylic cube phantom taken over the course of a year, totaling 630 image volumes (212 from OBI 1, 239 from OBI 2, and 179 from OBI 3), were analyzed. Images with acquisition parameters deviating from the institutional QA technique (120 kVp, 80 mA, 1 mm slice thickness) or with inappropriate fan filter were excluded. Mean CT number and standard deviation within a $1 \times 1 \times 1 \text{ cm}^3$ VOI automatically selected inside the $5 \times 5 \times 5 \text{ cm}^3$ phantom were calculated from these image volumes. The standard error and corresponding 95% confidence interval were calculated for global and OBI-specific image metrics to assess the baseline noise of serial CBCT measurements. This noise level estimates CBCT HU stability and the minimum change required to detect a true change in physical density.

2. D. Patient demographics, follow-up and clinical outcomes

Patient characteristics, including age, sex, smoking history, primary tumor site, stage, systemic therapy, relevant surgical history, and neck treatment laterality are tabulated in Table 1. Baseline salivary function was assessed by a physician at the first treatment visit, and no patient had reported baseline xerostomia symptoms. Patients were seen for regular follow-up visits every 3 months after radiotherapy completion. Follow-up documentation taken between 11 and 13 months after radiotherapy was analyzed for information regarding xerostomia, and physician-graded xerostomia was scored using RTOG criteria (Grades 1 to 3). The number of patients with Grade 1, 2, and 3 RTOG xerostomia persistent at one-year was 51 (49%), 15 (14%), and 2 (2%), respectively, for this cohort, which agreed well with historical experience in our institution since the adoption of IMRT for HN cancers.

2. E. Image processing and analysis

2. E.I. Contour propagation—Deformable alignment (SmartAdapt, Varian Medical Systems, Palo Alto, CA) was used to register the pCT to CBCT images. For initial registration, a rigid downhill simplex optimization was used for maximizing mutual information between the two image sets. A “demons”-like deformable image registration (DIR) algorithm was subsequently applied (32). Deformed structure sets, including the right

and left PG contours, were transferred to CBCT images and visually inspected for accuracy. For the majority of patients (N=80) CBCTs from every fraction were used; and for the remaining patients at least 2 fractions were included from each treatment week, totaling 3558 deformed contour propagations.

To evaluate the accuracy of the DIR algorithm used in this study, propagated parotid contours for a representative subset of the patient cohort (N=10) were compared to physician drawn contours. Parotid glands were manually delineated by a physician on CBCT images from three treatment fractions (3rd, 15th, and 30th) for each patient. The structures were propagated using the deformable vector fields, then transferred to a commercial tool (Velocity, v3.2, Varian Medical Systems, Palo Alto CA) for calculation of Dice similarity coefficient (DSC), mean distance-to-agreement (MDA), and standard deviation of the MDA (MDA SD) between the DIR-propagated contours and manually delineated contours, in accordance with AAPM TG-132 (33) recommendations.

2. E. II. Patient CBCT image harmonization—Small but measureable daily and OBI-dependent variation in phantom images was initially observed, motivating development of a CBCT image harmonization strategy. For this purpose, the mean HU within a 4 cc VOI placed in posterior neck muscle (medial nape region) within each patient image was used to linearly re-scale CBCT voxel values (using nominal HU values for air and muscle of −1000 and 40, respectively). The medial nape region was used since its physical density is assumed to remain unchanged over a treatment course due to relatively low dose in typical HN VMAT treatments. The linear transform normalizes each patient image using a stable anatomic landmark and, thus, the image HU better approximates relative physical density. Although a bilinear transform is commonly applied (34, 35), our analysis is limited to parotid tissue with fatty components and mean HU values typically near or slightly less than zero, where CT-to-density conversion is nearly linear.

2. E.III. Intensity and DVH metric extraction—Three dimensional image intensity profiles in their native voxel resolution from each CBCT PG and the pCT were extracted for all patients using a batch-processed Eclipse API plugin written in-house, and PG volume was calculated. After harmonization, voxels outside −200 to 0 HU were excluded and the mean HU of remaining voxels within each PG was calculated. This intensity range helps mitigate the effects of contour propagation variation and reduces non-PG tissues, calcifications, and artifacts included in the contour. DVH statistics were extracted for each patient from the initial treatment plan if the patient had a single plan over the full treatment course or from the as-treated plan sum if there were any treatment modifications, such as a re-plan or coned-down treatment boost. Five DVH metrics were used in subsequent analysis for the ipsilateral and contralateral gland: mean physical dose and equivalent dose in 2 Gy fractions (EQD₂) with $\alpha/\beta = 2.5$ Gy, and the volumes receiving at least 15, 30, and 45 Gy (V15, V30 and V45), as these metrics have been shown to correlate with salivary production (36, 37). All DVH metrics were used for investigation of CBCT-measured dose-response and to build a baseline late-xerostomia prediction model.

2.E.IV. Dynamic modeling—To reduce dimensionality for modeling purposes, PG measurements were discretized by averaging over each treatment week. For volume the

percentage change in cc and for mean intensity the absolute HU change was calculated relative to baseline (week 1 mean). In this way, treatment-related changes were determined over time on an average weekly basis, while still incorporating information from each available fraction. An example of dynamic feature profiling is shown in Supplementary material (Item 1) for a representative patient's volume change over the treatment course.

2. F. Statistical analysis

2. F. I. Dose-response characterization—To test the hypothesis that CBCT-measured PG features are influenced by dose, Spearman rank inter-correlation was calculated for all DVH and imaging features. Linear regression was applied to estimate the effect magnitude (slope) of dose on a subset of statistically significant imaging features in pair-wise rank correlation ($p < 0.05$).

2. F. II. Xerostomia prediction—Association between one-year xerostomia of any grade and each of the clinical factors was assessed by Fisher's exact test or two-sample t-test, as appropriate, and any clinical variables with statistically significant association ($p < 0.05$) were saved for further analysis. Univariable association between average weekly HU change and outcome was assessed by two-sample t-test, and test p-values less than 0.05 were considered statistically significant. Because inter-correlation between dose, volume, and mean intensity change was expected, penalized logistic regression using the least absolute shrinkage and selection operator (LASSO) was used on the combination of all measured features for xerostomia prediction. To avoid overfitting, the minimum deviance of 10-fold cross validation was used for lambda selection. Receiver-operating characteristic (ROC) analysis was performed, and the area under the curve (AUC) and 95% confidence intervals from 2000 bootstrap replicates were calculated. Internal validation using bootstrapping was performed to correct for optimism of the apparent model according to TRIPOD guidelines (38). The corrected AUC ($AUC_{corrected}$) was calculated as the difference between the apparent AUC and the average optimism of the 100 bootstrap models. These methods were repeated for DVH and clinical input variables only (DVH/clinical model), and AUCs were compared. These statistical methods were performed separately for Grade 1 or higher (Grade 1) and Grade 2 or higher (Grade 2) one-year xerostomia prediction.

3. Results

3.A. CBCT HU measurement QA and stability

Mean (95% CI, standard deviation) acrylic phantom intensity measurement for all OBI systems combined was 120.0 HU (119.2-120.7 HU, 7.8 HU), indicating rather stable CBCT intensity in standard measurement conditions. Individual metrics for the 3 OBIs were 125.2 HU (124.4-126.0 HU, 5.1 HU), 116.3 HU (115.1-117.5 HU, 6.6 HU), and 115.1 HU (113.5-116.6 HU, 7.8 HU), indicating slight variations in the absolute output due to the particular OBI. Assuming normal distribution, these results indicate a baseline 95% CI of 2 to 3 HU for 15 to 30 serial CBCT images on a random assortment of OBIs. To reduce this potentially confounding effect, we applied a CBCT harmonization strategy using intra-patient normalization and weekly HU averaging described in sections 2. E. II-IV. After

harmonization the standard deviation of the mean global PG intensity distributions and OBI-dependent differences decreased, as shown in Supplementary material (Item 2).

3.B. Contour propagation accuracy

The DIR algorithm demonstrated good performance with population average registration metrics of 0.83 (DSC), 1.7 mm (MDA), and 1.8 mm (MDA SD). Comparison of registration results using a Welch T-test between ipsilateral and contralateral PGs demonstrated slight but significant differences for MDA (0.3 mm, $p = 0.013$) and MDA SD (0.7 mm, $p < 0.01$), but not for DSC (0.04, $p = 0.14$). There were no fraction-dependent trends in DIR metrics. Box plots describing all registration metrics are shown in Supplementary material (Item 3).

3.C. Dose-response modeling

All patients experienced PG volume loss by the end of radiotherapy, with median (min-max) ipsilateral and contralateral shrinkage of 19.6 % (0.9 – 58.4%) and 17.7 % (4.4 – 56.3%), respectively. Loss of mid-treatment CT density was evident in most patients, with mean (95% CI) ipsilateral and contralateral loss of 3.3 HU (1.8 – 4.8 HU) and 4.6 HU (2.8 – 6.5 HU), respectively. A heat map indicating statistically significant Spearman rank correlations (R_s) for all features is shown in Supplementary material (Item 4). All ipsilateral DVH metrics were correlated with week 3 and 4 ipsilateral volume change, with the strongest correlation found between ipsilateral mean dose and week 3 volume change ($R_s = -0.35$, $p < 6e-4$). Most of the contralateral dose metrics were correlated with contralateral volume changes at any week, with contralateral V45 most strongly correlated with week 3 volume change ($R_s = -0.44$, $p < 2e-6$). Ipsilateral DVH metrics were weakly correlated with ipsilateral intensity change, with strongest correlation between mean dose and week 2 intensity change ($R_s = -0.29$, $p = 0.02$). Contralateral dose was generally not correlated with intensity changes. Using linear regression with mean PG dose, the magnitude of week 3 ipsilateral and contralateral volume loss was 0.31 %/Gy (95%CI: 0.19-0.43 %/Gy) and 0.31 %/Gy (95%CI: 0.15-0.46 %/Gy), respectively. For all parotid glands combined, the magnitude was 0.26 %/Gy (95%CI: 0.18-0.35 %/Gy). For ipsilateral intensity loss, the dose effect magnitude was 0.09 HU/Gy (95%CI: 0.02-0.18 HU/Gy). Regression plots and fit statistics are shown in Figure 1.

3.D. Xerostomia outcome prediction

3.D.I Imaging findings—Figure 2 shows the average weekly contralateral HU measurement for all patients, stratified by whether or not they experienced Grade 1 or Grade 2 toxicity. Similar plots for ipsilateral HU and bilateral volume are shown in Supplementary material (Item 5). Example CBCT PG images taken from fractions 1 and 10 (end of week 2) are shown in Figure 3 for a representative patient with chronic (1-year) xerostomia, showing regions with marked density loss.

3.D.II Univariable analysis—The incidence of chronic Grade 1 and Grade 2 xerostomia at one year was 65% and 16%, respectively. The single clinical variable that reached statistical significance was the primary site of oropharyngeal cancer (OPC) with $p < 0.001$ and $p < 0.002$ in Fisher's exact test for Grade 1 and Grade 2, respectively. For Grade 1, all ipsilateral DVH features were significant, but none of the DVH metrics were

associated with Grade 2. Volume change was also not independently associated with either clinical endpoint. Week 4, 5, and 6 contralateral mean intensity loss were all associated with Grade 2 ($p=0.006$, 0.022 , and 0.030 , respectively). Week 3 ipsilateral and week 4 contralateral intensity loss trended toward but did not reach statistical significance for Grade 1 ($p=0.086$ and 0.101 , respectively). Detailed univariable results are shown for mean intensity changes in Table 2 and for all tested variables in Supplementary material (Item 6).

3.D.III Penalized logistic regression models—Using LASSO regularized regression with only DVH and clinical inputs, OPC and V30 were retained for the Grade 1 model with an AUC of 0.709 (0.603–0.815) ($AUC_{corrected} = 0.643$). When imaging features were included, OPC, week 5 ipsilateral volume, and week 3 intensity change were selected, with an AUC of 0.719 (0.603–0.830) ($AUC_{corrected} = 0.649$). For Grade 2 xerostomia, the optimal LASSO model contained only OPC with AUC of 0.692 (0.615–0.770) ($AUC_{corrected} = 0.607$). Adding imaging variables to the LASSO search produced an optimal model containing OPC, week 4 contralateral intensity change and week 6 ipsilateral volume change with an AUC of 0.776 (0.643–0.912) ($AUC_{corrected} = 0.688$). Plots of the ROC curve and corresponding 95% CI are shown in Supplementary material (Item 7), and model details are shown in Table 3, for both Grade 1 and Grade 2 xerostomia prediction.

4. Discussion

To our knowledge, this is the first report on the quantitative use of CBCT image analysis for modeling normal tissue changes during the course of radiotherapy for the purpose of toxicity prediction in HNC. Other investigators have shown that imaging-based changes measured using in-room CT (18, 23), or within additional MR (15) or CT imaging sessions (20, 24, 39), are descriptive of PG changes and may quantify xerostomia risk. However, the method presented here can be readily applied in a number of centers already employing on-board kV CBCT. Additionally, our findings could be prospectively incorporated into personalized radiotherapy trials where intensity changes in the parotid may be used to further limit dose to the affected glands in oropharynx response-adapted trials.

Our characterization of CBCT voxel intensity showed that under standard measurement conditions, the CBCT stability is on the order of a few HUs. Although patient imaging invariably increases image noise, the use of serial images (weekly averaging) and anatomical normalization can mitigate the effect of slight variations in absolute HU measurements. Further, since the relative location of the parotid glands and the normalization regions are highly similar among patients, the effects of geometric CBCT intensity variation due to inter-patient scatter differences (40, 41) are likely minimal.

Our population average DIR metrics of 0.83 (DSC) and 1.9 (MDA) are consistent with previous investigations of deformable PG contour propagation to CBCTs (42–44). These metrics have been shown to be representative of inter-observer variability of CT-based PG contouring (45). Further, these fall within the suggested tolerances of AAPM TG-132 [Table III in ref. (33)] of 0.8 (DSC) and 3 mm (MDA), which demonstrates confidence in using this DIR method for automated PG delineation on CBCT imaging. The use of deformable registration for PG contour propagation has shown to be adequate in

previous work (42, 46, 47), and we believe this study provides preliminary validation for its use in a novel application of serial CBCT imaging for xerostomia prediction.

Nearly all patients experienced PG volume and density loss during the course of radiotherapy, but the response dynamics and characteristics varied among patients. In agreement with other investigations, a correlation between dose and volume change was found (18, 19). Further, the magnitude of volume and HU changes over the course of radiotherapy were in agreement with previous CT imaging studies (22, 26), which indicates coherence between imaging modalities for measuring in-vivo density changes. In the context of previous during-treatment imaging studies, it was somewhat surprising that no volumetric features were directly associated with chronic xerostomia though they were strongly associated with dose. In their study on the use of weekly diagnostic CT imaging to predict xerostomia, Belli et al. (24), reported that early rates of PG volume and density change are important predictors of xerostomia. However, the investigators used acute xerostomia as the endpoint. As such, it is possible that volume changes are more temporary and recoverable over time than severe changes in internal gland anatomy, possibly quantified by the rate of density change. Further investigation is warranted to substantiate this claim.

Although most patients experienced loss of density for both PGs over the treatment course, Grade 2 or higher xerostomia was marked by a higher rate of intensity loss of the contralateral PG specifically. However, contralateral intensity changes had little association with dose, which suggests that patient-specific PG radiation sensitivity may play a role in late-xerostomia. This finding would be in accordance with other studies which indicate that preservation of a single PG reduces the risk of xerostomia (48, 49). In a result that is well-suited for adaptive radiotherapy, the Grade 2-associated features are derived early during radiotherapy.

The Grade 1 model with imaging had only marginal performance improvement over the clinical/DVH-only model. This could have been due to the relatively low number of patients with no xerostomia in addition to the presence of two variables (OPC and ipsilateral dose) directly associated with this endpoint. Further investigation with a larger, more controlled cohort is warranted. However, the clinical relevance of Grade 1 toxicity prediction should also be considered. In accordance with Gabry et al (50), no association between PG dose and late Grade 2 xerostomia was observed, limiting the discriminative performance of the clinical/DVH-only model. The modest improvement in Grade 2 prediction by including mean intensity loss is thought to reflect a measured increase in fatty (i.e., non-functional) parotid tissue, which would be in accordance with the observations of previous investigators (21, 24, 26, 39). Since ipsilateral parotid dose was independently predictive of low-grade xerostomia, it is expected that dose adaptation (i.e., further PG dose reduction) based on CBCT-derived imaging characteristics would reduce the risk for chronic xerostomia on a patient-specific level. A prospective study which includes serial multi-modality imaging (e.g., fan-beam CT, multi-parametric MRI, or ¹⁸FDG-PET (51)) in conjunction with CBCT is warranted to test these hypotheses and help inform the roles of CBCT and deformable registration in quantitative imaging. As on-board imaging becomes more refined and commonplace, a plethora of high-quality image data is likely to be available at a large

number of radiotherapy centers. Such data facilitates rapid external validation and center-specific xerostomia model calibration.

The current methodology is not without limitations. First, underlying CBCT image quality is reduced relative to diagnostic CT imaging. CBCT image quality improvement is an active area of research, and substantial advancements have recently been made (52–55). We believe that the frequent imaging, harmonization, and use of relative HU changes associated with our methodology helped alleviate underlying image quality issues. Yet, even after harmonization, slight differences in absolute HU measurements across OBIs were apparent, which suggests that future work is warranted to characterize these differences and to prospectively harmonize machine parameters (e.g., absolute HU calibration). Second, it is well-known that non-PG tissues, such as the submandibular glands and oral cavity, contribute to salivary function and play a role in radiation-induced xerostomia (56, 57). The higher association between OPC and xerostomia, relative to other primary tumor sites, is consistent with the fact that the OPC patients in our cohort were more likely to receive prescription doses to the retropharyngeal nodes, likely increasing nearby salivary gland doses. Further, a recent study by Miah et al. (58) suggests that dose to specific PG sub-volumes (lobes) may play a significant role in xerostomia prediction. In both cases, we believe that this work presents a framework for CBCT-based normal tissue characterization which can be adapted for other body sites or for clinically relevant sub-volumes. An extension of our study might include daily dose re-calculation using the daily image information as density input, which may improve DVH-only prediction of late xerostomia. Third, since a secondary goal of this work was to demonstrate feasibility for the use of CBCT-measured changes in an adaptive radiotherapy platform, clinical workflows and clinically released software were used whenever possible. As such, the DIR process was laborious and time-consuming, as each image pair required manual selection and initial coarse alignment. These issues have been addressed by the AAPM TG-132 (33), and we expect that better integration into clinical systems will arise as DIR becomes more widely used. Such advancements may offer efficient and accurate daily dose calculation, by incorporating daily changes in patient positioning and anatomy, which may improve DVH-based NTCP models (59). Further, apart from visual inspection and subset analysis, high-throughput quality control of propagated contours was limited. The use of deformable registration algorithms for CBCT is an active area of research, and significant variation in accuracy may be achieved, depending on the specific algorithms and regions-of-interest considered (42). Finally, physician reported xerostomia was used in our analysis, which we have previously shown to underestimate patient reported xerostomia quality of life (QOL) (60). It is possible that our results may have been more significant if patient-reported QOL was available for all patients in our cohort.

5. Conclusions

A methodology for the use of on-board CBCT to quantify treatment-related PG changes during the course of HNC radiotherapy has been presented. Early treatment CBCT-measured PG density changes were shown to be associated with long-term xerostomia and improved predictions over PG dose alone. Moreover, the CBCT analysis may be performed with

minimal extra cost, which is attractive for a clinically feasibly adaptive radiotherapy platform.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Week 3 CBCT-measured change in volume (left) and intensity (right) as a function of dose and associated linear regression fits, indicating a moderate correlation of dose with volume change and weak correlation with intensity changes

Figure 2:

Mean contralateral intensity (HU) over time across all patients stratified by (left) Grade 1 (+N=68, -N=37) and (right) Grade 2 (+N=88, -N=17) one-year xerostomia. Error bars represent 1 standard deviation of the mean.

Figure 3:

Example coronal CBCT ipsilateral parotid gland images for a representative patient with 1-year chronic xerostomia on the same color window (−300 to 400 HU). Note loss of high density regions between fraction 1 (left) and fraction 10 (right) which would be in accordance with mean intensity loss

Table 1:

Patient Characteristics (N = 108). SD = standard deviation. Patients were staged according to the 7th Edition of the American Joint Committee on Cancer Staging Manual.

Age at diagnosis, years	
Mean (SD)	58.6 (8.8)
Median (range)	57 (39-84)
Female sex	19 (17.6%)
Smoking history	
Never	45 (41.7%)
Former *	32 (29.6%)
Current	31 (28.7%)
Mean pack years (SD)	20.6 (26.9)
Median pack years (range)	10 (0-150)
Primary tumor site	
Oropharynx	65 (60.2%)
Oral cavity	16 (14.8%)
Larynx	16 (14.8%)
Hypopharynx	4 (3.7%)
Nasopharynx	3 (2.8%)
Unknown primary	3 (2.8%)
Synchronous oropharynx and larynx	1 (0.9%)
T classification	
x	3 (2.8%)
is	1 (0.9%)
1	23 (21.3%)
2	31 (28.7%)
3	14 (13.0%)
4	36 (33.3%)
N classification	
0	14 (13.0%)
1	12 (11.1%)
2	59 (54.6%)
3	23 (21.3%)
Group stage	
0	1 (0.9%)
I	1 (0.9%)
II	5 (4.6%)
III	12 (11.1%)
IV	89 (82.4%)

Concurrent systemic therapy **	
Yes	90 (83.3%)
Head and neck surgery	
Prior to RT or within 1 year of RT	34 (31.5%)
Prior to RT with removal of major salivary gland	11 (10.2%)
Within 1 year of RT with removal of major salivary gland	0
Bilateral neck treatment	
Yes	98 (90.7%)

* Former smoking status defined as having quit smoking at least 1 year prior to cancer diagnosis.

** Concurrent systemic therapy refers to cytotoxic chemotherapy and cetuximab.

Weekly averaged ipsilateral and contralateral parotid gland mean change in CBCT-measured HU (relative to week 1) and t-test p-value for grade 1 and grade 2 xerostomia with significance level $p < 0.05$

Week	Ipsilateral Mean HU				Contralateral Mean HU							
	Grade<1 (N=37)	Grade 1 (N=68)	p	Grade<2 (N=88)	Grade 1 (N=68)	p	Grade<2 (N=88)	p				
2	-1.40	-2.13	0.469	-2.02	-1.20	0.525	-1.49	-1.31	0.858	-1.22	-2.17	0.437
3	-1.90	-4.20	0.086	-3.59	-2.35	0.474	-1.23	-2.90	0.239	-1.96	-4.02	0.257
4	-2.32	-3.73	0.410	-3.54	-1.77	0.416	-1.88	-4.58	0.101	-2.70	-8.43	0.006
5	-2.88	-3.57	0.666	-3.24	-3.73	0.812	-3.33	-5.38	0.297	-3.70	-9.39	0.022
6	-3.18	-2.92	0.875	-3.11	-2.54	0.785	-4.70	-5.82	0.552	-4.57	-9.72	0.030
7	-4.53	-3.81	0.706	-3.99	-4.40	0.860	-4.11	-6.23	0.340	-4.59	-9.64	0.064

Table 3:

Model characteristics for 1 yr. xerostomia prediction

LASSO Model	Origin	WK	Feature	Normalized Coefficient	AUC (95% CI)	AUC _{corrected}
<i>1 yr. Grade 1 xerostomia</i>						
DVH/Clinical	I	0	V30	0.137	0.709 (0.603-0.815)	0.643
	n/a	0	OPC	0.378		
DVH/Clinical + Imaging	I	3	Mean HU	−0.412	0.719 (0.603-0.830)	0.649
	I	5	Volume	0.368		
	n/a	0	OPC	0.357		
<i>1 yr. Grade 2 xerostomia</i>						
DVH/Clinical	n/a	0	OPC	0.782	0.692 (0.615-0.770)	0.607
	C	4	Mean HU	−0.297		
DVH/Clinical + Imaging	I	6	Volume	0.148	0.776 (0.643-0.912)	0.688
	n/a	0	OPC	0.455		

OPC = Oropharyngeal primary tumor. AUC_{corrected} = AUC corrected for optimism using internal bootstrap validation

Imaging for head and neck radiotherapy (HNR) normal tissue treatment response typically requires advanced techniques and/or extra sessions, limiting wide adoption and clinical utility. Parotid glands were delineated on daily CBCT images during the course of HNR for 105 patients who had xerostomia grade scored at one year following treatment. CBCT-measured dynamic intensity changes were associated with chronic xerostomia, with improved prediction over dose alone, which may have profound implications for adaptive radiotherapy.